Journal of Clinical Lipidology (2017) 11, 880–890

Journal of Clinical Lipidology

Original Articles

Update on the use of PCSK9 inhibitors in adults: Recommendations from an Expert Panel of the National Lipid Association

Carl E. Orringer, MD, (Chair)*, Terry A. Jacobson, MD, (Co-Chair), Joseph J. Saseen, PharmD, Alan S. Brown, MD, Antonio M. Gotto, MD, DPhil, Joyce L. Ross, MSN, CRNP, James A. Underberg, MD, MS

Cardiovascular Division, Department of Medicine, University of Miami Miller School of Medicine, Miami, FL, USA (Dr Orringer); Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA (Dr Jacobson); University of Colorado Anschutz Medical Campus, Aurora, CO, USA (Dr Saseen); Division of Cardiology, Advocate Lutheran General Hospital, Park Ridge, IL, USA (Dr Brown); Cardiac Disease Prevention, Weill Cornell Medical College, New York, NY, USA (Dr Gotto); University of Pennsylvania Health System, Philadelphia, PA, USA (Ms Ross); and NYU School of Medicine & NYU Center for Prevention of Cardiovascular Disease, New York, NY, USA (Dr Underberg)

KEYWORDS:
PCSK9 inhibitors;
Evolocumab;
Alirocumab;
Dyslipidemia;
Hypercholesterolemia;
Familial hypercholesterolemia;
Statin intolerance;
Lipid treatment guidelines

Abstract: An Expert Panel convened by the National Lipid Association was charged with updating the recommendations on the use of proprotein convertase subtilisin/kexin type 9 (PCSK9) antibody therapy that were provided by the 2015 National Lipid Association Recommendations for the Patient-Centered Management of Dyslipidemia: Part 2. Recent studies have demonstrated the efficacy of these agents in reducing low-density lipoprotein cholesterol and non–high-density lipoprotein cholesterol and have confirmed their excellent safety profile. A cardiovascular outcomes study has shown that these agents reduce incident atherosclerotic cardiovascular disease (ASCVD) events in patents with stable ASCVD and concomitant risk factors. The current update provides the Expert Panel's evidence-based recommendations on the clinical utility of PCSK9 inhibitors in patients with stable ASCVD, progressive ASCVD, LDL-C ≥ 190 mg/dL (including polygenic hypercholesterolemia, heterozygous familial hypercholesterolemia and the homozygous familial hypercholesterolemia phenotype) and very-high-risk patients with statin intolerance.

Introduction

Subcutaneously administered human monoclonal proprotein convertase subtilisin/kexin type 9 (PCSK9) antibody therapy reduces intrahepatic lysosomal degradation of internalized low-density lipoprotein (LDL) receptors, resulting in increased hepatic expression of LDL receptors (LDLRs) and a reduced concentration of circulating LDL cholesterol (LDL-C). The clinical use of these agents has

* Corresponding author. Department of Medicine, University of Miami Miller School of Medicine, 1120 NW 14th Street, Miami, FL 33136, USA.
E-mail address: carl.orringer@gmail.com
Submitted May 2, 2017. Accepted for publication May 2, 2017.

http://dx.doi.org/10.1016/j.jacl.2017.05.001

been demonstrated to result in marked reduction in circulating LDL-C when given as monotherapy, or as additive therapy to statins, with or without concomitant ezetimibe therapy. Along with other evidence, 2 major PCSK9 inhibitor safety and efficacy studies published in 2015 were used to support the National Lipid Association's (NLA) Part 2 Recommendations on the use of PCSK9 inhibitors. Since that time, 1 study in 2016 evaluating percent atheroma volume and plaque regression by intravascular ultrasound and 1 cardiovascular disease outcomes study in 2017 demonstrated that currently available PCSK9 inhibitors are safe, efficacious in lowering LDL-C, reduce percent atheroma volume, induce plaque regression, and reduce the incidence of adverse cardiovascular outcomes. Additional studies have confirmed their safety and efficacy in lowering atherogenic lipoproteins in patients with LDL-C $\geq$ 190 mg/dL, a group with high or very high atherosclerotic cardiovascular disease (ASCVD) risk. Based on these results, the NLA now provides an update of our recommendations for the clinical use of these medications.

Methodology

A Writing Committee representing original authors of the NLA Recommendations for the Patient-Centered Management of Dyslipidemia: Part 2 (C.E.O., T.A.J., J.L.R., and J.A.U.) and others in the leadership of the NLA was assembled with the objective to update the organization's position on the clinical use of PCSK9 inhibitors. The article was written with contributions from 3 authors (C.E.O., T.A.J., and J.J.S.) and a review for content and suggestions for revision was provided by 4 authors (A.S.B., A.M.G., J.L.R., and J.A.U.). The completed article was then submitted to the NLA Board of Directors, which approved the content of this update.

Grading of the strength of recommendations was made in accordance with the grading system used in the NLA Recommendations for the Patient-Centered Management of Dyslipidemia: Part 2.[1]

The NLA 2015 recommendations for PCSK9 inhibitor therapy: The evidence base

In addition to available mechanistic data,[2,3] the NLA Recommendations for the Patient-Centered Management of Dyslipidemia: Part 2 used 2 major safety and efficacy studies to inform our advice on the early clinical use of these agents. These studies are summarized below.

In 2015, a safety and efficacy trial of the PCSK9 inhibitor, alirocumab (ODYSSEY LONG TERM), enrolled 2341 adult subjects aged $\geq$18 years at high risk for cardiovascular events based on the presence of heterozygous FH (HeFH), established coronary heart disease (CHD), or coronary risk equivalent states.[4] A coronary risk equivalent state was defined as peripheral arterial disease, ischemic stroke, moderate chronic kidney disease (estimated glomerular filtration rate, 30 to <60 mL/min/1.73 m^2 or diabetes mellitus plus 2 or more additional risk factors [hypertension; ankle–brachial index of $\leq$0.90; microalbuminuria, macroalbuminuria, or a urinary dipstick result of >2+ protein; preproliferative or proliferative retinopathy or laser treatment for retinopathy, or a family history of premature CHD]). These subjects had LDL-C levels $\geq$70 mg/dL and were receiving statin therapies at the maximum-tolerated dose associated with an acceptable side effect profile, with or without additional lipid-lowering therapy. They were randomly allocated to receive alirocumab 150 mg subcutaneously or placebo every 2 weeks by subcutaneous injection for 78 weeks.

Subjects were a mean 60 years of age, 60% were male, and 93% were self-identified as "White." The mean body mass index was slightly >30 kg/m^2. Approximately, 18% had HeFH using World Health Organization-Simon Broome diagnostic criteria and or genotyping and 69% had CHD. Coronary risk equivalent states were identified in 41%, type II diabetes in 34%, and 21% were smokers. 99% were on statin therapy, 47% on 40 to 80 mg of atorvastatin, 20 to 40 mg of rosuvastatin, or 80 mg of simvastatin daily. Ezetimibe was taken by about 14%. The median baseline LDL-C was 122 mg/dL.

The primary efficacy endpoint was the change in calculated LDL-C at week 24. Alirocumab therapy was associated with a mean reduction in LDL-C from 122.8 $\pm$ 42.7 mg/dL to 48.3 $\pm$ 0.9 mg/dL, least squares mean percentage reduction from baseline -61.9 ± 1.3, (95% confidence interval [CI], -64.3 to -59.4, $P < .001$), compared with placebo. In the alirocumab group compared with placebo, there were more injection site reactions (5.9 vs 4.2%), myalgia (5.4 vs 2.9%), neurocognitive events (1.2% vs 0.5%), and ophthalmologic events (2.9% vs 1.9%). A post-hoc analysis at 78 weeks showed a lower incidence of major cardiovascular events (CHD death, nonfatal myocardial infarction (MI), fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization) 1.7% vs 3.3%, hazard ratio 0.52 (95% CI, 0.31–0.90; nominal $P = .02$).

A second safety and efficacy study simultaneously published in 2015 reported the results of 2 extension studies (OSLER-1 and OSLER-2) evaluating the PSCK9 inhibitor, evolocumab.[5] A total of 4465 subjects who had completed 1 of 12 phase 2 or 3 randomized trials were enrolled and were randomly assigned in a 2:1 ratio to receive either evolocumab, 140 mg every 2 weeks or 420 mg monthly plus standard therapy or standard therapy alone. These subjects were followed for a median of 11.1 months for lipid levels, safety and adjudicated cardiovascular events, including death, MI, unstable angina, coronary revascularization, stroke, transient ischemic attack, and heart failure. The data from the 2 trials were then combined and reported.

Subjects in this study had completed 1 of the parent studies and were further selected because they did not have an adverse event that led to discontinuation of the study drug

during the parent trial, did not have an unstable medical condition, and were not expected to need unblinded lipid measurements or adjustment of background lipid therapy during the first 12 weeks of participation in the parent trials.

Their mean age was 58 years and the subjects were evenly divided between males and females, and approximately 86% were self-identified as "White." Ethnic representation included 47% North Americans, 40.5% Europeans, and 12% from Asia Pacific or South African descent. Examining cardiovascular risk factors, 52% were hypertensive, 13% diabetic, about 34% had the metabolic syndrome, 15% were current cigarette smokers, 24% had a first-degree male relative with coronary artery disease at age ≤65 years in a female or ≤55 years in a male, and 10% had FH. Approximately 20% had established coronary artery disease and 9% cerebrovascular or peripheral arterial disease. As this patient population included some individuals with statin intolerance, 70% were treated with any statin, 27% high-intensity, and 35% moderate-intensity statin. Approximately 14% were treated with ezetimibe. The median baseline LDL-C level was 120 mg/dL.

Evolocumab, compared with standard therapy, was associated with a 61% reduction in LDL-C, from a median of 120 mg/dL to 48 mg/dL ($P < .001$). There was a 7.5% incidence of serious adverse events reported in both the evolocumab and placebo groups, resulting in discontinuation of the study drug in 2.4% of subjects taking evolocumab. Compared with those receiving standard care, 4.3% of those receiving evolocumab had injection site reactions. A greater percentage of subjects receiving evolocumab experienced neurocognitive events, including delirium and/or confusion, cognitive and attention disorders, dementia and amnestic conditions, disturbances in thinking and perception, and mental impairment disorders (0.9% vs 0.3%), arthralgia (4.6% vs 3.2%), headache (3.6% vs 2.1%), limb pain (3.3% vs 2.1%), and fatigue (2.8% vs 1.0%). Neither transaminase elevations nor creatine kinase elevations were reported more often in those taking evolocumab. Using Kaplan–Meier estimates at 1 year, prospectively adjudicated cardiovascular events occurred less frequently in those receiving evolocumab than in those in the standard therapy group (0.95% vs 2.18%, respectively; hazard ratio 0.47; 95% CI, 0.28–0.78; $P = .003$).

Based on these data, the 2015 recommendations on the clinical use of PCSK9 inhibitors are shown in Table 1.

The 2017 NLA Expert Panel's updated recommendations on the use of PCSK9 inhibitors: The evidence base

The 2017 NLA Expert Panel Recommendations on treatment with PCSK9 inhibitors build on the 2015 NLA Part 2 Recommendations and are informed by new randomized controlled trial (RCT) data showing that PCSK9 inhibitor monoclonal antibody therapy reduces atheroma volume, induces atheroma regression, and most importantly, improves ASCVD outcomes on top of maximally-tolerated statin therapy. Studies using FDA-approved monoclonal antibodies to PCSK9 have demonstrated no major safety issues and no evidence of declining LDL-C lowering efficacy over time. Newer genetic, observational, epidemiologic, and mechanistic studies have increased our appreciation of the heterogeneity of the FH phenotype and the natural history of the severe hypercholesterolemia phenotype. These studies add to the evidence base that supports the clinical value of additional LDL-C reduction with PCSK9 inhibitor therapy. The new recommendations of the NLA Expert Panel are based on the totality of the cited evidence, supplemented with clinical judgment.

The new PCSK9 inhibitor therapy recommendations made in this document apply to the following ASCVD risk and disease categories: (1) stable ASCVD; (2) progressive ASCVD; (3) LDL-C ≥ 190 mg/dL (including polygenic hypercholesterolemia, heterozygous familial hypercholesterolemia [FH] and the homozygous FH phenotype); and (4) very-high-risk patients with statin intolerance. The key studies informing these recommendations are summarized below.

Table 1 2015 NLA Part II recommendations for the use of PCSK9 inhibitors

1. Until cardiovascular outcomes trials are completed with PCSK9 inhibitors, these drugs should be considered primarily in (1) patients with ASCVD who have LDL-C ≥ 100 mg/dL (non–HDL-C ≥130 mg/dL) while on maximally tolerated statin (±ezetimibe) therapy; and (2) heterozygous hypercholesterolemia (FH) patients without ASCVD who have LDL-C ≥130 mg/dL (non–HDL-C ≥160 mg/dL) while on maximally tolerated statin (±ezetimibe) therapy. Strength: B, Quality: Moderate
2. PCSK9 inhibitor use may be considered for selected high-risk patients with ASCVD (eg, recurrent ASCVD events) who have atherogenic cholesterol levels below the specified values, but above their treatment goals (ie, LDL-C ≥ 70 mg/dL [non–HDL-C ≥100 mg/dL]). Such use would be based on clinical judgment, weighing the potential benefits relative to the ASCVD event risk and the risks and costs of therapy. Strength C, Quality: Low
3. PCSK9 inhibitor use may also be considered in selected high or very-high-risk patients who meet the definition of statin intolerance (as previously defined by the NLA Statin Expert Panel) and who require substantial additional atherogenic cholesterol lowering, despite the use of other lipid-lowering therapies. Such use would be based on clinical judgment, weighing the potential benefits relative to the ASCVD event risk and the risks and costs of therapy. Strength C, Quality: Low

ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NLA, National Lipid Association; PCSK9, proprotein convertase subtilisin/kexin type 9.

PCSK9 inhibitor therapy for patients with stable ASCVD

Intravascular ultrasound trial

In 2016, a double-blind, placebo-controlled randomized angiographic intravascular ultrasound trial (GLAGOV) was conducted at 197 academic and community hospitals in North and South America, Asia, Australia, and South Africa.[6] A total of 968 subjects were randomized to receive monthly subcutaneous injections of evolocumab 420 mg or placebo. The primary efficacy measure was nominal change in percent atheroma volume from baseline to week 78, and the secondary efficacy measures were the nominal change in normalized total atheroma volume and percentage of patients showing plaque regression.

Subjects were aged ≥18 years and had to have at least 1 epicardial coronary artery with a stenosis of ≥20% on clinically indicated coronary arteriography and had a target vessel suitable for imaging with ≤50% visual obstruction. Treatment with a stable statin dose for a minimum of 4 weeks and an LDL-C ≥80 mg/dL, or between 60 and 80 mg/dL with 1 major or 3 minor cardiovascular risk factors were inclusion criteria. Major risk factors were noncoronary atherosclerotic vascular disease, MI, or hospitalization for unstable angina during the preceding 2 years or type II diabetes. Minor risk factors were current cigarette smoking, hypertension, low high-density lipoprotein cholesterol (HDL-C) levels, a family history of premature CHD, high-sensitivity C-reactive protein (hs-CRP) ≥2 mg/L, age ≥50 years for men and ≥55 years for women. Exclusion criteria included uncontrolled diabetes or hypertension, heart failure, renal dysfunction, or liver disease.

Baseline characteristics included mean age 60 years, 72% men, 94% White, body mass index 29.4 kg/m^2, approximately 84% had hypertension, 39% had a previous percutaneous intervention, 35% had a previous MI, 23% were smokers, and 22% had diabetes. Approximately 60% were treated with high-intensity statins and 38% with moderate-intensity statins. Approximately 2% were treated with ezetimibe.

During the 76-week treatment period, the time weighted mean LDL-C level was 93 mg/dL in the placebo group and 36.6 mg/dL in the evolocumab group (mean difference: −56.5 mg/dL [95% CI, −59.7 to −53.4, $P < .001$]). The primary efficacy measure, the percent atheroma volume, decreased by 0.95% in the evolocumab group and did not change in the placebo group ($P < .001$ compared with baseline; between group difference −1.0% [95% CI, −1.8 to −0.64%]; $P < .001$). Total atheroma volume, the secondary efficacy measure, did not change in the placebo group and decreased by 5.8 mm^3 in the evolocumab group ($P < .001$ compared with baseline, between group difference −4.9 mm^3 [95% CI, −7.3 to −2.5]; $P < .001$). A greater percentage of evolocumab-treated subjects demonstrated percent atheroma regression (64.3% vs 47.3%, $P < .001$) and total atheroma volume regression (61.5% vs 48.9%, $P < .001$). Of note, a post-hoc analysis demonstrated that percent atheroma regression was observed in >80% of subjects receiving evolocumab and with baseline LDL-C <70 mg/dL. Additional post-hoc analysis suggested that the benefit may extend to levels of LDL-C as low as 20 mg/dL.

Cardiovascular outcomes study

The first large cardiovascular outcome study using PCSK9 inhibitor therapy was published online in March 2017. Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) was a randomized, double-blind placebo-controlled trial of 27,564 subjects with ASCVD and LDL-C levels ≥70 mg/dL while on maximally tolerated statin therapy.[7] The subjects were randomly assigned to receive subcutaneously administered evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo. The primary endpoint of the study was the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary endpoint was the composite of cardiovascular death, MI, or stroke. Subjects were followed up for a median duration of 2.2 years.

Entry criteria included diagnosis of MI or nonhemorrhagic stroke or symptomatic peripheral arterial disease (PAD) as evidenced by intermittent claudication with ankle brachial index <0.85 or peripheral arterial revascularization procedure or amputation due to atherosclerotic disease. In addition, subjects had to have at least 1 major risk factor or at least 2 minor risk factors as listed below. Major risk factors included diabetes (type I or type II); age ≥65 years at randomization (and ≤85 years at the time of informed consent); MI or nonhemorrhagic stroke within 6 months of screening; additional diagnosis or MI or nonhemorrhagic stroke excluding qualifying MI or nonhemorrhagic stroke; current daily cigarette smoking; or history of symptomatic PAD if eligible by MI or stroke history. Minor risk factors include history of non–MI-related coronary revascularization, residual coronary artery disease with ≥40% stenosis in ≥2 large vessels, most recent HDL-C <40 mg/dL for men and <50 mg/dL in women; most recent hs-CRP >2.0 mg/L; most recent LDL-C ≥130 mg/dL or non-HDL-C ≥160 mg/dL before randomization; or the presence of the metabolic syndrome. In addition, all participants had to have their most recent fasting LDL-C ≥70 mg/dL or non–HDL-C ≥100 mg/dL, after 2 weeks of stable lipid-lowering therapy; and their most recent fasting triglycerides ≤400 mg/dL before randomization.

The mean age of the subjects was 63 years, 75% were male, and 85% White. Geographical representation included 62.9% from Europe, 16.6% from North America, 13.0% from Asia Pacific and South Africa, and 6.6% from Latin America. Atherosclerotic manifestations included MI in 81% (with a median time from the most recent MI 3.4 years [interquartile range, 1–7.4 years]). Approximately 19% had suffered a nonhemorrhagic stroke (with a median time from the most recent stroke 3.2 years [interquartile

range, 1.1–7.1 years]). Approximately 13% had PAD. Regarding ASCVD risk factors, 80% had arterial hypertension, 37% were diabetic, and 28% were current cigarette smokers. At baseline, high-intensity statin use was reported in 69.5% moderate-intensity statin use in 30.2% and low-intensity statin use in 0.3%. Ezetimibe therapy was added to statin therapy in 5.3% of subjects.

At 48 weeks, the least squares mean percentage reduction in LDL-C in those receiving evolocumab, compared with placebo, was 59%, from a median baseline of 92 mg/dL to 30 mg/dL ($P < .001$). Relative to placebo, evolocumab significantly reduced the risk of the primary endpoint (1344 subjects [9.8%] vs 1563 subjects [11.3%]; hazard ratio 0.85; 95% CI, 0.79–0.92; $P < .001$) and the key secondary endpoint (816 [5.9%] vs 1013 [7.4%]; hazard ratio 0.80; 95% CI, 0.73–0.88; $P < .001$), with consistent results across key subgroups, including those with the lowest baseline LDL-C (median, 74 mg/dL). Injection site reactions were more common in those receiving evolocumab (2.1% vs 1.6%) than placebo.

In FOURIER, there was a 1.5% absolute risk reduction in both the primary and key secondary endpoints at 48 weeks, translating into a number needed to treat (NNT) to prevent 1 event of 67 over 2 years. The authors noted that the magnitude of risk reduction increased over time from 12% (95% CI, 3–20) in the first year to 19% (95% CI, 11–27) beyond the first year. However, evolocumab had no effect on total mortality (hazard ratio 1.04; 95% CI, 0.91–1.19; $P = .54$) or cardiovascular mortality (hazard ratio 1.05; 95% CI, 0.88–1.25; $P = .62$).

Safety of PCSK9 inhibitor therapy

In FOURIER and other PCSK9 inhibitor trials, the addition of PCSK9 inhibitors to statin-based therapy is not associated with an increased likelihood of major adverse events, including new-onset diabetes and neurocognitive events. A sub-study of the FOURIER trial, Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects (EBBINGHAUS) examined cognitive function in 1974 subjects using a validated cognitive instrument. There was no significant difference in cognitive function between evolocumab and placebo after a mean of 19 months, regardless of the LDL-C level achieved.[8]

Use of evolocumab or alirocumab is associated with a higher incidence of injection site reactions. An increased risk of cataracts has been noted in pooled alirocumab studies in patients with post-treatment LDL-C levels <25 mg/dL.[9] However, no difference in cataract incidence was noted when comparing alirocumab with control groups. The increased incidence of cataracts in those with low LDL-C may be due to confounding. In FOURIER, there was no increased risk of cataracts with evolocumab, but the data were not broken down by posttreatment LDL-C levels.[7] Longer-term analyses are currently ongoing to confirm safety findings. Collectively, these data should address concerns about the safety of very low LDL-C levels in patients PCSK9 inhibitors.

Summary of new recommendation for PCSK9 inhibitors for patients with stable ASCVD

Results from the previously mentioned studies indicate that therapy with PCSK9 inhibitors effectively and safely lowers LDL-C in subjects taking statins and that evolocumab, compared with placebo, reduces atheroma volume, induces atheroma regression, and reduces the incidence of ASCVD events. These data support the recommendation that PCSK9 inhibitor therapy should be considered for ASCVD risk reduction in patients with stable ASCVD, especially in the presence of additional risk factors.

Recommendation 1: PCSK9 inhibitor therapy should be considered for ASCVD risk reduction in patients with stable ASCVD, particularly in those with additional ASCVD risk factors, on maximally-tolerated statin therapy ± ezetimibe, with on-treatment LDL-C ≥70 mg/dL or non–HDL-C ≥100 mg/dL. Strength A, Quality: High.

Summary of new recommendation for PCSK9 inhibitors for patients with progressive ASCVD

The presence of progressive ASCVD was not an entry criterion in FOURIER, although some patients had an additional diagnosis of MI or nonhemorrhagic stroke excluding the qualifying MI or nonhemorrhagic stroke.[7] Such patient are more likely to have uncontrolled risk factors, and in some cases, additional genetic influences that predispose them to ASCVD disease progression. Thus, the Panel felt that the application of similar recommendations, but with a lower level of evidence, was reasonable for those with progressive ASCVD.

Recommendation 2: PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients with progressive ASCVD on maximally-tolerated statin therapy ± ezetimibe, and on-treatment LDL-C ≥70 mg/dL or non–HDL-C ≥100 mg/dL. Strength B, Quality: Moderate.

PCSK9 inhibitor therapy for patients with LDL-C ≥ 190 mg/dL, including polygenic hypercholesterolemia, heterozygous FH and the homozygous FH phenotype.

Polygenic hypercholesterolemia and HeFH

PCSK9 inhibitors have US Food and Drug Administration approval for treatment of patients with FH as adjuncts to diet and maximally-tolerated statin therapy for those who

require additional LDL-C lowering. Because there is no universally recognized definition of FH, clinicians often confront the issue of trying to determine which patients among those with LDL-C ≥ 190 mg/dL should be considered for additive therapies to statins.

The prevalence of severe hypercholesterolemia, defined as LDL-C ≥ 190 mg/dL, is estimated to be approximately 7% in the U.S. population.[10] The great majority of these patients have polygenic hypercholesterolemia, contributed to by atherogenic diets and multiple less well-defined genetic factors. FH is far less common than the polygenic disorder, estimated in US and European population cohort gene sequencing studies to represent only 1.7% of those with LDL-C ≥190 mg/dL.[10] The prevalence of pathogenic mutations in LDLR, APOB, and PCSK9 can be determined in those countries using genetic screening from birth, but these data cannot be readily applied to the US population where such screening is not done. The issue is further complicated, in the absence of universal FH genetic testing, by the overlap in the LDL-C values between polygenic hypercholesterolemia and FH and by only moderately elevated LDL-C levels in some patients with pathogenic FH-causing mutations related to incomplete genetic penetrance or the presence of competing LDL-C lowering polymorphisms.[11]

Regardless of whether the finding of an LDL-C ≥ 190 mg/dL is due to a defined mutation, the long-term risk for ASCVD in these patients is high. Pooled data from 6 large US epidemiologic studies of individuals at index ages 20 to 79 years demonstrated increased ASCVD risk for those with LDL-C ≥190 mg/dL compared with those with LDL-C <130 (hazard ratio 5.0 for CHD and 4.1 for ASCVD), resulting in an accelerated risk for CHD of 10 to 20 years in men and 20 to 30 years in women.[12] The prognostic value of adding genetic information was demonstrated in a gene sequencing study done in 26,025 participants from 7 case control and 5 prospective cohort studies. This study showed that those with an LDL-C ≥190 mg/dL and no FH mutation had a 6-fold higher odds for CAD (hazard ratio 6.0; 95% CI, 5.2–6.9), whereas those with defined mutations of LDLR, APOB, and PCSK9 had a 22-fold higher odds (hazard ratio 22.3; 95% CI, 10.7–53.2) compared with CAD-free controls.[10] The 10-year risk of ASCVD in genetic FH also depends on the age at which time the diagnosis is made. The risk is estimated to be about 30% in those between the ages or 40 and 80 years, but <10% in those <40 years of age.[13]

Statin therapy reduces ASCVD risk in those with LDL-C ≥ 190 mg/dL, likely related to a reduction in circulating atherogenic lipoproteins. The impact of statin treatment on primary ASCVD prevention in Dutch patients was examined in an FH screening program between 1994 and 2013.[14] The identified patients were age ≥18 years, who were genetically determined carriers of deleterious mutations associated with HeFH. Hospital, pharmacy, and mortality records between 1995 and 2015 were examined. The primary outcome was the composite of MI, coronary revascularization, and death from any cause. The time-varying effect of statins was examined using a Cox proportional hazard model, correcting for the use of other lipid medication, thrombocyte aggregation inhibitors, and antihypertensive and anti-diabetic medication. The 2 most commonly prescribed statins in this cohort were simvastatin 40 mg daily (23.1%) and atorvastatin 40 mg daily (22.8%). Statin users (n = 1041) had 89 CAD events and 17 deaths during 11,674 person-years of follow-up vs statin never-users (n = 518), who had 22 CAD events and 9 deaths during 4892 person-years (combined rates 8.8 vs 5.3 per 1000 person-years, respectively; $P < .001$). After using inverse probability of treatment weighting and adjusting for other medication intake, the hazard ratio for CAD and all-cause mortality was 0.56 in those receiving statins (95% CI, 0.33–0.96).

The ASCVD risk reduction benefit of statins in patients with established ASCVD has been widely recognized and is the basis for recommending statin therapy in such patients in multiple guideline documents. Despite statin therapy, there is evidence that statin-treated patients with clinically-defined FH have a greater likelihood of recurrent CHD events after MI than do their family members without FH. A multicenter, prospective cohort study[15] was done of 4534 Swiss patients who had initially been screened for FH based on 3 different definitions and who had acute coronary syndromes. The study used Cox proportional models to assess 1-year risk of first recurrent coronary death or MI with multivariable adjustment. Depending on which FH definition was used, between 94.5% and 99.1% of patients who had initially been screened for FH based on 3 different definitions with FH were discharged on statins, with 74.0% to 82.3% on high-intensity statins. Despite such treatment, the mean achieved LDL-C was 119 mg/dL, only 49.1% achieved an LDL-C ≤ 100 mg/dL and 8.8% an LDL-C ≤70 mg/dL. At 1-year follow-up, 153 patients (3.4%) died, 104 of fatal MI. A total of 113 patients (2.5%) had a nonfatal MI. After multivariable analysis that included age, the risk of recurrent coronary events was greater in those with FH compared with those without, with an adjusted hazard ratio of 2.46 (95% CI, 1.07–5.65; $P = .034$) using the American Heart Association definition, 2.73 (95% CI, 1.46–5.65; $P = .034$) using the Simon-Broome definition and 3.53 (95% CI, 1.26–9.94; $P = .017$) using the Dutch Lipid Clinic definition.

A recent study analyzed systematic reviews of subgroup analyses from randomized trials and observational studies of statin-treated patients to help to identify high- and very-high-risk patients who might benefit from the addition of a nonstatin to maximally tolerated statin therapy.[13] Relative risk reduction for the addition of a nonstatin to lower LDL-C was used to determine the NNT to prevent 1 ASCVD event over 5 years for each patient group. Adding a PCSK9 inhibitor to lower LDL-C by an additional increment of ≥50% was estimated to provide a NNT ≤50 for very-high-risk (≥30% 10-year ASCVD risk) and

high-risk patients (20%–29% 10-year ASCVD risk, including those with HeFH without additional risk factors) with an LDL-C ≥70 mg/dL, and an NNT ≤30 for very-high-risk or high-risk patients with LDL-C ≥130 mg/dL. The accuracy of these estimates as demonstrated in long-term outcomes studies of PCSK9 inhibitors remains to be determined.

Although no ASCVD outcomes data are currently available in statin-treated patients with LDL-C ≥ 190 mg/dL who receive PCSK9 inhibitors, both alirocumab[16] and evolocumab[17] have been demonstrated to safely and effectively provide significant additional LDL-C reduction in such patients, and alirocumab has been shown to reduce the frequency of required LDL apheresis treatments in patients with severe HeFH.[18] Another PCSK9 inhibitor, bococizumab, effectively lowered LDL-C and reduced ASCVD events in a mixed secondary and primary prevention cohort with a baseline LDL-C ≥100 mg/dL. However, bococizumab is a humanized monoclonal antibody, which is different than alirocumab and evolocumab, which are fully human monoclonal antibodies. The bococizumab drug development program was terminated by the manufacturer, at least in part because of more injection site reactions, and the development of anti-drug antibodies and reduced LDL-C lowering efficacy over time.[19]

Regardless of genetic factors that may impact prognosis in these patients or pharmacologic therapies used, guideline documents and consensus statements have recognized the importance of addressing nonlipid risk factors to further reduce ASCVD risk.[11] The presence of key additional markers of increased risk, including uncontrolled ASCVD risk factors, a family history of premature ASCVD, elevated Lp(a), elevated hs-CRP concentration, the presence of coronary calcium or CKD may identify particularly high-risk individuals who merit more aggressive prevention strategies.

Based on the previous data, the Expert Panel advised consideration of PCSK9 inhibitor therapy in those with LDL-C ≥ 190 mg/dL and advised different cut-points for treatment intensity in accordance with the presence of concomitant ASCVD risk factors, key additional ASCVD risk markers, or genetic confirmation of FH.

Recommendation 3a: PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients aged 40 to 79 years with LDL-C ≥ 190 mg/dL, no uncontrolled ASCVD risk factors, or other key additional-high risk markers, and on-treatment LDL-C ≥100 mg/dL or non–HDL-C ≥130 mg/dL on maximally-tolerated statin therapy ± ezetimibe. Strength B, Quality: Moderate.

Recommendation 3b: PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients aged 40 to 79 years with LDL-C ≥ 190 mg/dL, and the presence of either uncontrolled ASCVD risk factors, key additional high-risk markers, or genetic confirmation of FH, and on-treatment LDL-C ≥70 mg/dL or non–HDL-C ≥100 mg/dL on maximally-tolerated statin ± ezetimibe. Strength: B, Quality: Moderate.

The optimal management of LDL-C ≥ 190 mg/dL in patients aged 18 to 39 years taking maximally-tolerated statin ± ezetimibe remains unclear. Although their short-term risk of an ASCVD event is low, their long-term risk places them at high to very-high risk, especially those with defined pathogenic genetic mutations of LDLR, APOB, or PCSK9 and/or poorly controlled ASCVD risk factors or other key additional high-risk markers. Although patients in this age range have been enrolled in safety and efficacy studies of PCSK9 inhibitors, there are no currently available age-specific outcomes data. In addition, the potential harms of long-term PCSK9 inhibitor therapy begun in patients in this age group are unknown. With these limitations in mind, the consensus of the authors of this update is that consideration of PCSK9 therapy in this group is reasonable, given the available safety and efficacy data in other patient groups.

Recommendation 3c: PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients aged 18 to 39 years with LDL-C ≥ 190 mg/dL and the presence of either uncontrolled ASCVD risk factors, key additional high-risk markers or genetic confirmation of FH and on-treatment LDL-C ≥100 mg/dL or non–HDL-C ≥ 130 mg/dL on maximally-tolerated statin ± ezetimibe. Strength: E, Quality: Low.

Homozygous FH phenotype

The 2015 NLA Part 2 Recommendations for the Patient-Centered Management of Dyslipidemia: Part 2 did not address the use of PCSK9 inhibitors in patients with homozygous FH (HoFH). The potential value of evolocumab in HoFH was assessed in a randomized double-blind phase 3 clinical trial performed at 17 sites in 10 countries in North America, Europe, the Middle East and South Africa in which patients, aged ≥ 12 years on stable lipid-lowering therapy for at least 4 weeks and not undergoing lipoprotein apheresis, were randomly allocated in a 2:1 ratio to receive subcutaneous evolocumab 420 mg or placebo every 4 weeks for 12 weeks.[20] The diagnosis of HoFH was made either by genetic analysis or by clinical criteria (history of untreated LDL-C >500 mg/dL plus either xanthomas before age 10 years or the presence of HeFH in both parents). All patients underwent genetic analysis as part of the protocol and 92% had deleterious mutations in LDLR, 4% APOB mutations and 1% had autosomal recessive hypercholesterolemia. The primary endpoint was percent change from baseline in LDL-C by ultracentrifugation at week 12 compared with placebo, analyzed by intention to treat. The sample used for analysis was taken 4 weeks after the last dose of the medication was given. A total of 49 patients received the study drug and completed the study (16 in the placebo group and 33 in the evolocumab group). Compared with those receiving placebo, evolocumab significantly

reduced LDL-C at 12 weeks by 30.9% (95% CI, −43.9% to −18.0%, $P < .0001$). Of note is that both the patient who was LDLR negative and the patient who had autosomal recessive hypercholesterolemia did not respond to evolocumab; LDL-C increased slightly in both patients. There were no serious clinical or laboratory adverse events and no anti-evolocumab antibody development was identified during the study. The US Food and Drug Administration approved the use of evolocumab for patients with HoFH in August 2015.

The very-high risk of premature ASCVD in patients with phenotypic HoFH is well-recognized. Because of their life-long exposure to high concentrations of LDL-C, every effort must be made to initiate effective LDL-C lowering treatments, beginning at a young age. Because of the presence of defective or absent LDLRs in the great majority of these patients, the use of even high-intensity statins is often associated with only a 10% to 25% reduction in LDL-C.[11] Although other agents such as mipomersen and lomitapide have been approved for treatment of patients with HoFH, the use of these agents is associated with significant side effects. The manufacturers of both drugs were required by the US Food and Drug Administration to submit a Risk Evaluation and Mitigation Strategy to demonstrate that the benefits of these drugs outweigh the risks.

Based on this information, the previously mentioned study, and the safety data on PCSK9 inhibitor therapy, the Expert Panel advised consideration of PCSK9 inhibitor therapy in HoFH patients of either unknown genotype, or those known to be LDLR defective. LDL-C treatment goals for patients with HoFH are controversial, but European guidelines have suggested goals of <100 mg/dL in adults in the absence of clinical ASCVD and <70 mg/dL in those with ASCVD.[21] Although such goals are extremely difficult to achieve, a sequential strategy of maximally tolerated statin, ezetimibe, and PCSK9 inhibitor therapy before consideration of lomitapide, mipomersen, and LDL apheresis is reasonable.

Recommendation 3d: PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients with HoFH, either of unknown genotype, or those known to be LDLR defective, on maximally-tolerated statin therapy ± ezetimibe with LDL-C ≥70 mg/dL or non–HDL-C ≥100 mg/dL. Strength B, Quality: Moderate.

Summary of new recommendations for PCSK9 inhibitors for patients with LDL-C ≥ 190 mg/dL

Results from the previously mentioned studies indicate that PCSK9 inhibitors safely and effectively lower LDL-C in patients with LDL-C ≥ 190 mg/dL in those taking evidence-based statin ± ezetimibe therapy. Such therapy is most effective in those with polygenic and HeFH, less effective in those with receptor-defective HoFH, and apparently ineffective in LDLR-negative HoFH patients. Those with polygenic hypercholesterolemia or HeFH, in the absence of poorly controlled ASCVD risk factors or key high-risk markers, may be considered for PCSK9 inhibitor therapy when their on-treatment LDL-C is ≥100 mg/dL, or non–HDL-C ≥130 mg/dL. Those polygenic patients with multiple risk factors and key high-risk markers, or HeFH patients with genetic confirmation of deleterious FH-related mutations or additional poorly controlled ASCVD risk factors, especially in the 40- to 80-year-old age group, are at very-high risk for ASCVD events and should be considered for treatment with PCSK9 inhibitors when their on treatment LDL-C is ≥70 mg/dL or non–HDL-C ≥100 mg/dL. The Expert Panel also recommended for those patients aged 18 to 39 years with LDL-C ≥ 190 mg/dL, especially in the presence of confirmed deleterious FH mutations, poorly controlled ASCVD risk factors or other key additional high-risk markers, consideration of treatment with PCSK9 inhibitor therapy when their LDL-C is ≥100 mg/dL or non–HDL-C ≥130 mg/dL. HoFH patients who are known to be receptor defective should be considered for therapy with evolocumab for additional LDL-C lowering. It is reasonable to consider the use of this agent before the use of lomitapide or mipomersen because of relative equivalency of LDL-C lowering and lower potential for adverse side effects. In those who do not respond adequately to pharmacotherapy, LDL apheresis is a therapeutic option.

Recommendations for PCSK9 inhibitors for very-high-risk patients with statin intolerance

The optimal approach to lipid management of the statin-intolerant patient with ASCVD remains controversial because there is no universally accepted definition of statin intolerance and because RCTs have not demonstrated a statistically significantly higher risk of statin-related muscle side effects compared with those on placebo. Confirmation of the existence of statin intolerance, in at least some patients, was provided in an RCT evaluating the efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance (Goal Achievement after Utilizing an anti-PSCK9 antibody in Statin-intolerant Subjects).[22] These patients had persistently elevated LDL-C levels and a history of intolerance to 2 or more statins. During the first phase of the study, 491 subjects received atorvastatin 20 mg daily or placebo, with subsequent crossover to the other treatment group. After a 2-week washout period, they entered the second phase of the study, in which they were randomized to receive ezetimibe or evolocumab for 24 weeks. During the initial phase, 26.5% of patients had muscle side effects on placebo, but not atorvastatin and 42.6% had muscle side effects on atorvastatin and not placebo. The diagnosis of statin-related muscle side-effects was confirmed, at least in those patients with

Table 2 2017 Recommendations of the NLA Expert Panel on treatment with PCSK9 inhibitors

ASCVD

1. PCSK9 inhibitor therapy should be considered for ASCVD risk reduction in patients with stable atherosclerotic cardiovascular disease, particularly in those with additional ASCVD risk factors, on maximally-tolerated statin therapy ± ezetimibe, with on-treatment LDL-C ≥70 mg/dL or non–HDL-C ≥100 mg/dL. Strength A, Quality: High
2. PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients with progressive atherosclerotic cardiovascular disease on maximally-tolerated statin therapy ± ezetimibe, and on-treatment LDL-C ≥70 mg/dL or non–HDL-C ≥100 mg/dL. Strength B, Quality: Moderate

LDL-C ≥ 190 mg/dL (including polygenic hypercholesterolemia, heterozygous FH and the homozygous FH phenotype)

3a PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients ages 40 to 79 years with pre-treatment LDL-C ≥ 190 mg/dL, no uncontrolled ASCVD risk factors, or other key additional high-risk markers*, and on-treatment LDL-C ≥100 mg/dL or non–HDL-C ≥130 mg/dL on maximally-tolerated statin therapy ± ezetimibe. Strength B, Quality: Moderate

3b PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients aged 40 to 79 years with pre-treatment LDL-C ≥ 190 mg/dL, and the presence of either uncontrolled ASCVD risk factors, key additional high-risk markers*, or genetic confirmation of FH, and on-treatment LDL-C ≥70 mg/dL or non–HDL-C ≥100 mg/dL on maximally-tolerated statin ± ezetimibe. Strength: B, Quality: Moderate

3c PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients aged 18 to 39 years with pre-treatment LDL-C ≥ 190 mg/dL, and the presence of either uncontrolled ASCVD risk factors, key additional high-risk markers*, or genetic confirmation of FH, and on-treatment LDL-C ≥100 mg/dL or non–HDL-C ≥130 mg/dL on maximally-tolerated statin ± ezetimibe. Strength: E, Quality: Low

3d PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients with homozygous familial hypercholesterolemia, either of unknown genotype, or those known to be LDL receptor defective, on maximally-tolerated statin therapy ± ezetimibe with LDL-C ≥70 mg/dL or non–HDL-C ≥100 mg/dL. Strength B, Quality: Moderate

Very-high-risk/statin intolerance

4. PCSK9 inhibitor therapy may be considered to further reduce LDL-C in selected very-high-risk patients who meet the definition of statin intolerance (as previously defined by the NLA Statin Expert Panel) and who require substantial additional atherogenic cholesterol lowering, despite the use of other lipid-lowering therapies. Strength C, Quality: Low

ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NLA, National Lipid Association; PCSK9, proprotein convertase subtilisin/kexin type 9.

*Including history of uncontrolled high blood pressure, diabetes, current cigarette smoking, or family history of premature ASCVD; or additional high-risk markers (coronary calcium ≥300 Agatston units [or ≥75th percentile for the patient's age, gender, and ethnicity]; Lp(a) ≥ 50 mg/dL using an isoform insensitive assay, hs-CRP ≥ 2 mg/L or CKD including albumin/creatinine ratio ≥ 30 mg/g).

Note: All patients considered for PCSK9 therapy should have updated screening for secondary causes of hypercholesterolemia, particularly hypothyroidism, nephrotic syndrome, obstructive liver disease and drug therapy.

previous intolerance to 2 statins and recurrent muscle-related side effects on atorvastatin rechallenge.

Statin intolerance in individuals with a history of ASCVD is a therapeutic challenge to the clinician. A retrospective cohort study used data from all Medicare beneficiaries hospitalized for MI between January 1, 2007 and December 31, 2013.[23] The analysis was restricted to individuals aged ≥66 and ≤110 years with an overnight hospitalization for MI and a stay ≤30 days. These patients were not taking lipid-lowering medication prior their MI and had an index prescription filled for a high- or moderate-intensity statin within 30 days of discharge. Statin intolerance was defined using several criteria: (1) down-titrating of statins and initiation of ezetimibe therapy; (2) switching from statins to ezetimibe monotherapy; (3) having International Classification of Diseases, Ninth revision, diagnostic codes for rhabdomyolysis or an antihyperlipidemic drug adverse event followed by statin down-titration or discontinuation, or switching among ≥3 statins within 1 year of initiation. High-statin adherence was defined in the year after discharge as proportion of days covered ≥80%. The incidence of recurrent MI, CHD events (recurrent MI or coronary revascularization), and mortality were examined from 1 year after hospital discharge through December 2014.

A total of 1741 patients (1.65%) had statin intolerance, and 55,567 patients (52.8%) had high statin adherence. During a median of 1.9 to 2.3 years of follow-up, there were 4450 recurrent MIs, 6250 CHD events, and 14,311 deaths. The multivariable hazard ratios comparing those with statin intolerance to those with high statin adherence were 1.50 (95% CI, 1.30–1.73) for recurrent MI, 1.51 (95% CI, 1.34–1.70) for CHD events, and 0.96 (95% CI, 0.87–1.06) for all-cause mortality.

Summary of new recommendations for PCSK9 inhibitors for patients with statin intolerance

Recognizing the increased ASCVD risk observed in statin-intolerant patients with previous MI, the Panel

recommends consideration of the use of PCSK9 inhibitors for very-high-risk statin-intolerant patients, such as those who had previous ASCVD events in the presence of additional risk factors and require substantial additional LDL-C lowering despite the use of other LDL-C–lowering therapies. The Panel has chosen to maintain our previous recommendation for such patients with the same strength and quality of evidence as in the 2015 document.

Recommendation 4: PCSK9 inhibitor therapy may be considered to further reduce LDL-C in selected very-high-risk patients who meet the definition of statin intolerance (as previously defined by the NLA Statin Expert Panel) and who require substantial additional atherogenic cholesterol lowering, despite the use of other lipid-lowering therapies. Strength C, Quality: Low.

The NLA's Expert Panel's updated recommendations for the use of PCSK9 inhibitors are provided in Table 2 and summarized in Table 3.

A thorough provider-patent discussion should be undertaken whenever the use of PCSK9 inhibitor therapy is considered. Such discussion should include consideration of the NNT to benefit the patient, cost (including the need to obtain prior authorization), need for subcutaneous injection, and importance of follow-up lipid monitoring. The clinician must continue to emphasize at each visit the importance of adherence to evidence-based statin therapy and attention to lifestyle therapy. The presence of nonlipid ASCVD risk factors must be repetitively considered and, when present, effectively addressed. Careful consideration must also be given to the impact of patient characteristics, concomitant medical conditions, and patient preferences.

In conclusion, new cardiovascular outcomes data on therapy with monoclonal antibodies to PCSK9 provide an additional evidence-based option for safe LDL-C lowering and reduction in adverse ASCVD outcomes. This update by an NLA Expert Panel incorporates these new data and provides evidence-based recommendations that may aid in clinical decision-making.

Acknowledgments

The authors would like to acknowledge Dr. Peter Jones for his thoughtful scientific review of the article and Mr. Ryan Essegian and Mr. Brian Hart for their administrative assistance in preparation of these recommendations.

Authors' contributions: Each author made substantial contributions to the article conception and design, analysis, and/or interpretation of data, drafted or revised the article intellectual content, and approved the final version.

Financial disclosures

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

C.E.O. has nothing to disclose. T.A.J. has received consulting fees from Amarin, Amgen, AstraZeneca, Merck and Co, and Sanofi Regeneron. J.J.S. has nothing to disclose. A.S.B. has received honoraria from Akcea, Amarin, Amgen, AstraZeneca, Merck and Co, Pfizer, Regeneron, and Sanofi. A.M.G. is on the Board of Directors with Aegerion Pharmaceuticals, Arisaph Pharmaceuticals, and Esperion Therapeutics, a member of the Data Safety Monitoring Board for Ionis Pharmaceuticals, and received consulting fees from Kowa Pharmaceuticals, Merck and Co, Pfizer, and Vatera Capital. J.L.R. has received honoraria from AbbVie, Akcea, Amarin, Amgen, Kaneka America, Kastle Therapeutics, Kowa Pharmaceuticals, Practice Point, Regeneron, and Sanofi. J.A.U. received honoraria from Akcea, Alexion, Amarin, Amgen, Invitae, Sanofi, Regeneron, and True Health Diagnostics, consulting fees from Amarin and Amgen, and research grants from Aegerion and Sanofi.

Table 3 2017 NLA expert panel PCSK9 inhibitor recommendations

Disorder	LDL-C/Non-HDL-C Threshold for Rx mg/dL	Strength of evidence	Quality of evidence
ASCVD + additional risk factors	≥ 70 / ≥ 100	A	High
Progressive ASCVD	≥ 70 / ≥ 100	B	Moderate
LDL-C ≥ 190, age 40-79 No uncontrolled RF or key additional risk markers	≥ 100 / ≥ 130	B	Moderate
LDL-C ≥ 190, age 40-79 Uncontrolled RF or key additional risk markers	≥ 70 / ≥ 100	B	Moderate
LDL-C ≥ 190, age 18-39 Uncontrolled RF or key additional risk markers or FH causing mutation	≥ 100 / ≥ 130	E	Low
Homozygous FH phenotype	≥ 70 / ≥ 100	B	Moderate
ASCVD + Statin intolerance	Clinical judgment	C	Low

References

1. Jacobson TA, Maki KC, Orringer CE, et al. National Lipid Association Recommendations for the Patient-Centered Management of Dyslipidemia: Part 2. *J Clin Lipidol*. 2015;9:S1–S122.
2. Tavori H, Fan D, Blakemore JL, et al. Serum proprotein convertase subtilisin/kexin type 9 and cell surface low-density lipoprotein receptor: evidence for a reciprocal regulation. *Circulation*. 2013;127:2403–2413.
3. Urban D, Poss J, Bohm M, et al. Targeting the proprotein convertase subtilisin/kexin type 9 for the treatment of dyslipidemia and atherosclerosis. *J Am Coll Cardiol*. 2013;62:1401–1408.
4. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372:1489–1499.
5. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372:1500–1509.
6. Nicholls SJ, Puri R, Anderson T, et al. Effect of evolocumab on progression of coronary disease in statin-treated patients. The GLAGOV randomized clinical trial. *JAMA*. 2016;316:2373–2384.
7. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722.
8. Gugliano RP, Mach F, Zavitz K, et al. Primary results of EBBINGHAUS, a cognitive study of patients enrolled in the FOURIER trial. American College of Cardiology 2017 Scientific Sessions; March 18, 2017; Washington DC. Abstract 17-LB-16161-AC.
9. Robinson JG, Rosenson RS, Farnier M, et al. Safety of very low density lipoprotein cholesterol values with alirocumab. *J Am Coll Cardiol*. 2017;69:471–482.
10. Khera AV, Won HH, Peloso GM, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. *J Am Coll Cardiol*. 2016;67:2578–2589.
11. Gidding SS, Champagne MA, deFerranti SD, et al. The agenda for familial hypercholesterolemia. A statement from the American Heart Association. *Circulation*. 2015;132:2167–2192.
12. Perak AM, Ning H, de Ferranti SD, et al. Long-term risk of atherosclerotic cardiovascular disease in US adults with familial hypercholesterolemia phenotype. *Circulation*. 2016;134:9–19.
13. Robinson JG, Huijgen R, Ray K, et al. Determining when to add nonstatin therapy. *J Am Coll Cardiol*. 2016;68:2412–2421.
14. Besseling J, Hovingh K, Hujjgen R, et al. Statins in familial hypercholesterolemia. Consequences for coronary artery disease and all-cause mortality. *J Am Coll Cardiol*. 2016;68:252–260.
15. Nanchen D, Gencer B, Muller O, et al. Prognosis of patients with familial hypercholesterolemia after acute coronary syndromes. *Circulation*. 2016;134:698–709.
16. Kastelein JP, Ginsberg HN, Langslet G, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolemia. *Eur Heart J*. 2015;36:2996–3003.
17. Raal FJ, Stein EA, Dufour R, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolemia (RUTHERFORD-2): a randomised double-blind, placebo-controlled trial. *Lancet*. 2015;385:331–340.
18. Moriarty PM, Parhofer KG, Babirak SP, et al. Alirocumab in patients with heterozygous familial hypercholesterolemia undergoing lipoprotein apheresis: the ODYSSEY ESCAPE trial. *Eur Heart J*. 2016;37:3588–3595.
19. Ridker PM, Revkin J, Amerenco P, et al. Cardiovascular efficacy and safety of bococizumab in high-risk patients. *N Engl J Med*. 2017;376:1527–1539.
20. Raal FJ, Honarpour N, Blom DJ, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolemia (TESLA Part B): a randomized, double-blind, placebo-controlled trial. *Lancet*. 2015;381:341–350.
21. Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolemia of the European Atherosclerosis Society. *Eur Heart J*. 2014;35:2146–2157.
22. Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance. The GAUSS-3 randomized clinical trial. *JAMA*. 2016;315(15):1580–1590.
23. Serban M-C, Colantonio LD, Manthripragada AD, et al. Statin intolerance and risk of coronary heart events and all-cause mortality following myocardial infarction. *J Am Coll Cardiol*. 2017;69:1386–1395.