

ACC/AHA Guidelines for Cholesterol Management and Considerations for Newer and Emerging Therapies

Nathan D. Wong PhD, FACC, FAHA, FNLA

From the Heart Disease Prevention Program, Division of Cardiology, University of California, Irvine, CA, USA

Abstract

The American College of Cardiology/American Heart Association in 2013 issued revolutionary guidelines for blood cholesterol management, accompanied by guidelines on cardiovascular risk assessment, lifestyle management, and obesity management. The use of an atherosclerotic cardiovascular disease (ASCVD) risk calculator was the foundation of the risk assessment guideline and the lifestyle management guideline focused on recommending an evidence-based dietary pattern and regular physical activity. The blood cholesterol management guideline identified four groups of patients shown to benefit from moderate or high intensity statin therapy and removed the use of specific low density lipoprotein (LDL)-cholesterol goals due to lack of evidence for specific targets. Rigorous evidence from randomized clinical trials formed the rationale for moderate and high intensity statin therapy. Updated guidance has since provided recommendations for newer non-statin therapies, including cholesterol absorption inhibitors and proprotein convertase subtilisin kexin type 9 (PCSK9) monoclonal antibody (mAb) therapy when additional LDL-C lowering is needed beyond that provided by maximum tolerated statin therapy. Novel RNA interference therapy for PCSK9 synthesis is also currently in development. The recent development and application of PCSK9 mAb therapies have resulted in remarkable reductions in LDL-C beyond statin therapy that are well-tolerated and with promising outcome data demonstrating ASCVD event reductions beyond statin therapy.

Key words: Cholesterol, statins, risk assessment, prevention, cardiovascular disease.

Introduction

In November 2013, the American College of Cardiology (ACC) and American Heart Association (AHA) issued four bold guidelines for atherosclerotic cardiovascular disease (ASCVD) prevention including ones on cardiovascular risk assessment¹, lifestyle management², obesity management³, and blood cholesterol management⁴. These guidelines were based nearly exclusively on higher quality randomized controlled clinical trials or systematic reviews and meta-analyses, and deemphasized the use of expert opinion in their development. They were also designed to answer specific critical questions rather than to address all aspects of a particular topic (e.g. dyslipidemia management). This paper provides an overview of the ACC/AHA Guideline for Blood Cholesterol Management⁴ including new and emerging non-statin therapies, as well as the supporting role provided by the risk assessment, lifestyle management, and obesity management guidelines. These guidelines form the foundation of practice in preventive cardiology. The evidence and role for cholesterol absorption inhibitor and PCSK9 monoclonal antibody (mAb) therapy, as well as emerging RNA interference therapy for inhibiting PCSK9 synthesis are also discussed.

Cardiovascular risk assessment, lifestyle, and obesity management guidelines as a foundation for preventive cardiology


The foundation of preventive cardiology is an assessment of a patient's global risk for ASCVD for appropriate targeting of the intensity of lipid and other preventive therapies. As early as 1976, former Framingham Heart Study director Dr. William B. Kannel noted that such risk functions provide an "economic and efficient method for identifying persons at high cardiovascular risk who need preventive treatment"⁵. Some 20 years later the ACC Bethesda Conference noted that the intensity of treatment should match a person's risk⁶. In addition, such risk assessment can help communicate to patients their risk of ASCVD and to motivate adherence to lifestyle and other therapies, promoting improved outcomes⁷. The ACC/AHA Cardiovascular Risk Assessment working group¹ developed a new risk calculator based on the broader endpoint of ASCVD (including coronary heart disease [CHD] death, nonfatal myocardial infarction [MI] and fatal and nonfatal stroke). In contrast to many older calculators that have primarily focused on the prediction of CHD events and based on the predominantly Caucasian population of Framingham, Massachusetts, the new Pooled Cohort Risk Calculator was

The ACC and the American Heart Association (AHA), in collaboration with the National Heart, Lung, and Blood Institute and other specialty societies, have released four guidelines focused on the assessment of cardiovascular risk, lifestyle modifications to reduce cardiovascular risk and management of elevated blood cholesterol and body weight in adults.

In order to support the implementation of these guidelines the ACC and AHA have jointly published a new mobile application (app).

The ASCVD Risk Estimator application helps health care providers and patients estimate 10-year and lifetime risks for atherosclerotic cardiovascular disease (ASCVD) using the Pooled Cohort Equations and lifetime risk prediction tools. The ASCVD Risk Estimator provides easy access to recommendations specific to calculated risk estimates. Additionally, the app includes readily accessible guideline reference information for both providers and patients related to therapy, monitoring, and lifestyle.


The app is available on both iTunes (iPhones, iPads) and Google Play (Galaxy, Nexus, other Android devices). Use the links below from your mobile device to download the app.



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Estimator	Clinicians	Patients	About
ASCVD Risk Estimator*			
<p>10-Year ASCVD Risk</p> <p><small>This calculator only provides 10-year risk estimates for individuals 40 to 79 years of age.</small></p>	<p>Lifetime ASCVD Risk</p> <p style="font-size: 2em; font-weight: bold; text-align: center;">50%</p> <p style="text-align: center;"><small>calculated risk</small></p> <p style="text-align: center;"><small>5% risk with optimal risk factors</small></p>		
Gender	<input checked="" type="radio"/> M <input type="radio"/> F	Age	<input type="text" value="35"/>
Race	<input checked="" type="radio"/> White <input type="radio"/> African American <input type="radio"/> Other	Total Cholesterol (mg/dL)	<input type="text" value="220"/>
Systolic Blood Pressure	<input type="text" value="130"/>	HDL - Cholesterol (mg/dL)	<input type="text" value="38"/>
Diabetes	<input type="radio"/> Y <input checked="" type="radio"/> N	Treatment for Hypertension	<input type="radio"/> Y <input checked="" type="radio"/> N
		Smoker	<input checked="" type="radio"/> Y <input type="radio"/> N

Figure 1. 2013 ASCVD Risk Estimator. Adapted from the ACC/AHA Risk Assessment Guideline¹.

developed from four major cohorts: the Atherosclerosis Risk in Communities (ARIC), Cardiovascular Health Study (CHS), Coronary Artery Risk Development in Young Adults (CARDIA), and Framingham Original and Offspring Study, which all had at least 10 years of follow-up when developed. It calculates both the 10-year (among those aged 40-74 years) and lifetime ASCVD risk (among those aged 20-59 years) and can be downloaded onto most smartphones, tablets, and computers (Figure 1). When the treatment decision based on initial risk assessment using the Pooled Cohort Risk Calculator, is uncertain, the assessment of other measures (see below in ACC/AHA 2014 Guideline for Cholesterol Management) can be recommended to further inform treatment decision making.

The ACC/AHA Lifestyle Management Guideline² recommends for adults who would benefit from LDL-cholesterol or blood pressure (BP) lowering, a dietary pattern focusing on intake of vegetables, fruits, and whole grains, low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils and nuts, and limited intake of sweets, sugar-sweetened beverages, and red meats (Class I, level of evidence A recommendation). Such a dietary pattern should also include 5% to 6% calories from saturated fat, with a reduction in calories from trans-fat and no more than 2,400 mg of sodium daily (or a reduction of sodium intake of at least 1,000 mg per day). Moreover, moderate to vigorous aerobic physical activity is recommended 3-4 times per week for ~40 minutes per session. The ACC/AHA/The Obesity Society Guideline for the Management of Overweight and Obesity in Adults³ provides a key message that only modest weight loss of 3% to 5% of body weight is need to result in clinically meaningful benefits for several cardiometabolic risk factors, including triglycerides, blood glucose, glycated hemoglobin, and development of type 2 diabetes. Importantly, it is advised that overweight and obese individuals participate for at least 6 months in a comprehensive lifestyle program adhering to a reduced calorie diet and increased physical activity as well as high-intensity (≥ 14 sessions in 6 months) comprehensive weight loss interventions prescribed by a trained professional (e.g., dietitian or exercise physiologist).

ACC/AHA 2014 Guideline for cholesterol management

The recent ACC/AHA cholesterol guideline⁴ identified four groups of patients proven from clinical trials to benefit from statin therapy: those with 1) clinical ASCVD, 2) LDL-C ≥ 190 mg/dl and aged ≥ 21 years, 3) diabetes and aged 40-75 years with LDL-C 70-189 mg/dl, and 4) primary prevention without diabetes with a $\geq 7.5\%$ 10-year ASCVD risk, aged 40-75 years, and LDL-C 70-189 mg/dl. Patients in each of these groups are indicated for either moderate intensity statin therapy to reduce LDL-C 30% to $<50\%$ or high intensity statin therapy intended to reduce LDL-C $\geq 50\%$ from baseline. Moreover, in primary prevention, there is also consideration for a moderate intensity statin even in those at lower risk (5 to $<7.5\%$ 10-year risk). These intended percentage reductions in LDL-C are now the intended "therapeutic goals" rather than the use of specific LDL-C goals (e.g., <70 mg/dl for very high risk persons) since the guideline committee determined that there was a lack of randomized clinical trial evidence to support titration of drug therapy to specific LDL-C and/or non-HDL-C goals. However, given the wealth of clinical trial data on higher versus lower intensity statin therapy⁸, there was strong evidence that the appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit. Therefore, the guideline took the bold step of abandoning specific LDL-C goal levels that have been the principal therapeutic target in lipid management for decades. In addition, there is emphasis on evaluation of net clinical benefit, in which potential harms must be weighed against potential benefits. For example, the $\geq 7.5\%$ cutpoint for consideration of high intensity statin therapy in primary prevention is consistent with the level of risk where the number needed to treat (NNT) to prevent an ASCVD event is lower (favorable) compared to the number needed to harm (NNH) based on the projected incidence of statin side effects (most of which are incident diabetes, despite its relatively small rate and somewhat arbitrary definition). Net clinical benefit can similarly be demonstrated for a moderate intensity statin when the 10-year ASCVD risk $\geq 5\%$.

While the above statin eligible groups indicate where the evidence is clear regarding those who would benefit from statin therapy for ASCVD risk reduction based on the clinical trial data, it is emphasized that these guidelines are not a “point and shoot” approach of prescribing statin therapy exclusively on calculated ASCVD risk, but one that is based on conducting a careful clinician-patient discussion before starting statin therapy, especially in primary prevention. This includes discussing with patients their estimated 10-year ASCVD risk and reviewing other risk factors and strategies for their control, including the potential for benefit from a heart-healthy lifestyle and consideration of referral to a dietitian and/or exercise physiologist. Further, the potential benefit vs. adverse effects of therapy should always be discussed, as well as patient preferences. These are important concepts of shared decision making in which the patient is an equal partner in decisions regarding appropriate care rather than a one-sided “doctor prescribes and tells the patient what to do” approach. Strategies for shared decision making are an important focus of recently released guidance from the ACC/AHA in lipid management⁹.

For patients in the statin eligible groups and those not explicitly in these groups (e.g., those aged <40 or >75 with diabetes or candidates for primary prevention) or when the treatment decision is otherwise uncertain (perhaps due to patient and/or provider reluctance or preference), the guideline indicates specific factors that may inform the decision. These include a family history of premature ASCVD, elevated lifetime risk of ASCVD, LDL-C ≥ 160 mg/dl, hs-CRP ≥ 2.0 mg/dl, coronary artery calcium score ≥ 300 or ankle brachial index <0.9. These findings can be used to inform management decisions between the clinician and patient. Finally, while specific LDL-C targets were removed from the ACC/AHA guidelines, this document continues to 1) emphasize adherence to medication and lifestyle and 2) promote assessment of therapeutic response to statin therapy and safety. The latter of course requires monitoring of fasting lipids 4-12 wk after initiating therapy and every 3-12 months thereafter to monitor therapeutic response. Safety laboratory data should be obtained as clinically indicated.

Recommendations for consideration of non-statins

Importantly, the ACC/AHA Cholesterol Guideline indicates that in those at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy (which may be no therapy in a statin intolerant individual), the addition of a non-statin cholesterol lowering drug with proven efficacy may be considered if the ASCVD risk reduction benefits outweigh the potential for adverse effects.¹⁴ Further guidance to this effect is provided by the ACC/AHA 2016 Expert Consensus Decision Pathway on Role for Non-Statin Therapies in LDL-C Lowering¹⁰ as an update to the 2014 guideline statement. This statement notes that non-statin therapies (ezetimibe first, PCSK9 mAb second) may be used in selected high risk patients if at least a 50% LDL-C reduction is not achieved on maximal tolerated statin therapy. These therapies may also

serve as alternatives for those with 1) LDL-C <70 mg/dL and ASCVD and other comorbidities, 2) LDL-C ≥ 190 mg/dl or <100 mg/dl in those with ASCVD without comorbidities, or 3) without ASCVD but LDL-C ≥ 190 mg/dl. For patients with diabetes (without ASCVD) or in primary prevention patients with 10-year ASCVD risk $\geq 7.5\%$, additional therapies may include ezetimibe followed by a bile acid sequestrant if $\geq 50\%$ LDL-C lowering on maximal statin therapy or LDL-C <100 mg/dl is not achieved. Moreover, the recently released National Lipid Association Recommendations Part II also provide guidance for considering the use of PCSK9 mAb therapy, specifically indicating their use when LDL-C targets of <100 mg/dl in those with ASCVD or <130 mg/dl in those with familial hypercholesterolemia (FH) are not reached¹¹. We recently reported from statin-treated U.S. adults in the National Health and Nutrition Examination Survey (NHANES) 2009-2010 showed that only 27% of those with coronary heart disease (CHD) were at LDL-C <70 mg/dL and those not at goal averaged 34 mg/dL above this cutpoint¹². While it is unclear how many of these persons were on recommended moderate or high-intensity therapy, these data do suggest a significant opportunity for consideration of newer therapies, such as PCSK9 mAb, when reasonable targets cannot be reached.

The Improve-IT trial and implications for cholesterol management

The recent results of the IMPROVE-IT trial¹³ in acute coronary syndrome patients with the addition of ezetimibe confirm the value of additional LDL-C lowering with non-statin therapy. Benefits were seen after 7 years of accrual included a significant (albeit modest) 6% relative risk reduction (HR=0.94, p=0.016) and number needed to treat [NNT] of 50 for the primary endpoint of CVD death, myocardial infarction, hospital admission for unstable angina, coronary revascularization, or stroke. Patients in this trial were very high risk randomized shortly (within 10 days) after their ACS and many of the events occurred within the first year of the trial so it is uncertain whether the results can be generalized to lower risk patients. While ezetimibe offers an additional 15-20% LDL-C reduction (on-trial LDL-C in IMPROVE-IT was 53 mg/dl in those receiving ezetimibe vs. 70 mg/dl in the placebo group), those with more severe LDL-C elevations despite statin therapy may need additional therapy beyond ezetimibe.

PCSK9 monoclonal antibody therapy: safety and efficacy

Among the most significant advances in cardiology in the past decade is the development of proprotein convertase subtilisin kexin type 9 (PCSK9) mAb therapy. Alirocumab (Praluent™) and evolocumab (Repatha™) (both fully human mAb) were approved by the US Food and Drug Administration (FDA) in July-August 2015. A third PCSK9 mAb product, bococizumab (RN316) (a humanized mAb product), however, was discontinued

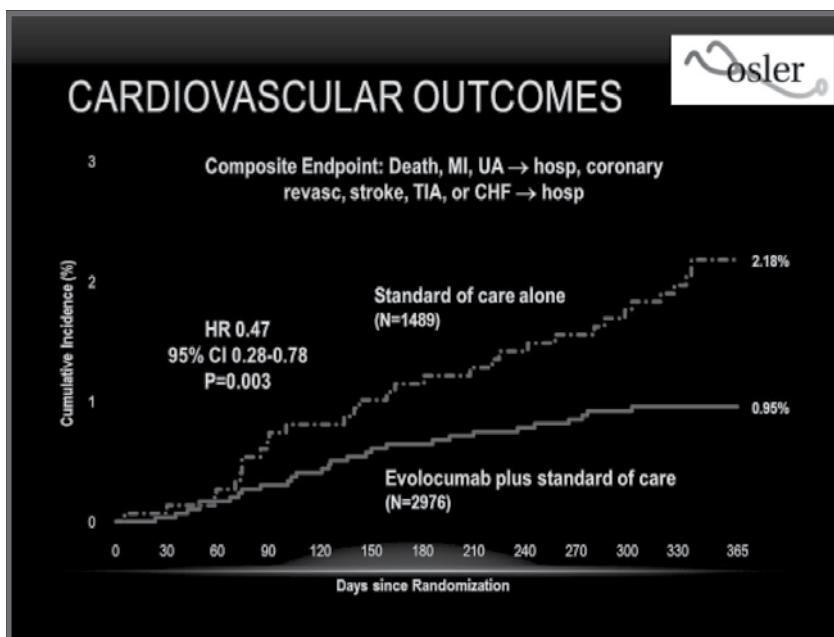
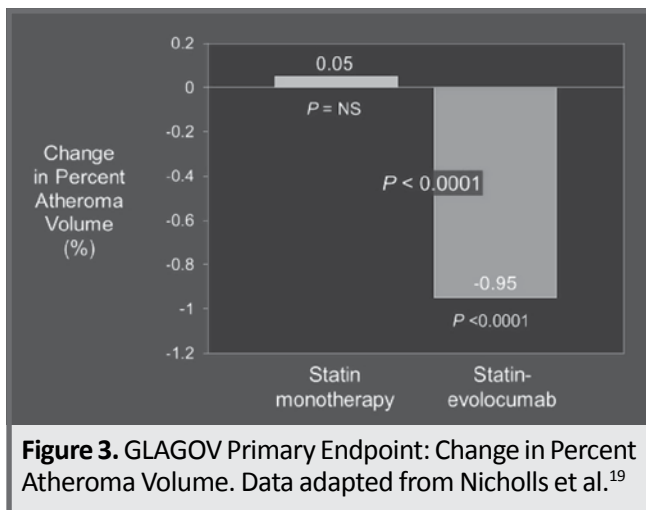


Figure 2. Cumulative incidence of cardiovascular events from two open-label randomized trials (OSLER 1 and OSLER 2) of evolocumab. Kaplan-Meier 1 year event rate. Adapted from Sabatine et al.¹⁷

from further clinical development in November 2016 due to increase immunogenicity and decreased LDL-C efficacy. PCSK9 is a 692 amino acid mature protein mainly expressed as a secreted protease in the liver, intestines, and kidneys. This molecule forms a complex with the hepatic LDL receptor, which undergoes endocytosis and destruction of the LDL receptor complex. This process reduces the number of LDL receptors available to continue to process LDL, thereby resulting in increased circulating plasma LDL-C particles.¹⁴⁻¹⁵ PCSK9 mAbs bind to PCSK9, which prevents the association of PCSK9 and the LDL receptor. This action inhibits the deleterious effects of PCSK9, maintaining the LDL receptors and promoting continued clearance of LDL particles resulting in lowered LDL-C levels. Multiple phase II and III trials which have examined the efficacy and safety of alirocumab, evolocumab and bococizumab have shown LDL-C reductions averaging 50-60 percent in statin-treated or statin-intolerant patients with or without documented ASCVD. Observed effects on lipid fractions include 25-39% decrease in LDL-C in patients with homozygous FH (HoFH), ~50% reduction in non-HDL-C and apolipoprotein B, and 25% lowering of lipoprotein(a).¹⁵

Pooled data from relatively short-term safety and efficacy open-label studies were published in spring 2015, providing significant additional insight into safety and preliminary outcomes of treatment of PCSK9 mAbs. The Long-Term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG-TERM) placebo-controlled trial¹⁶ evaluated 2,341 patients with hyperlipidemia on maximally tolerated statins who were at high risk for CHD (69% with prior CHD and 35% with diabetes). Alirocumab (150 mg biweekly) reduced LDL-C 62% at 24 weeks compared to placebo; mean LDL-C was 48 mg/dL in the ali-

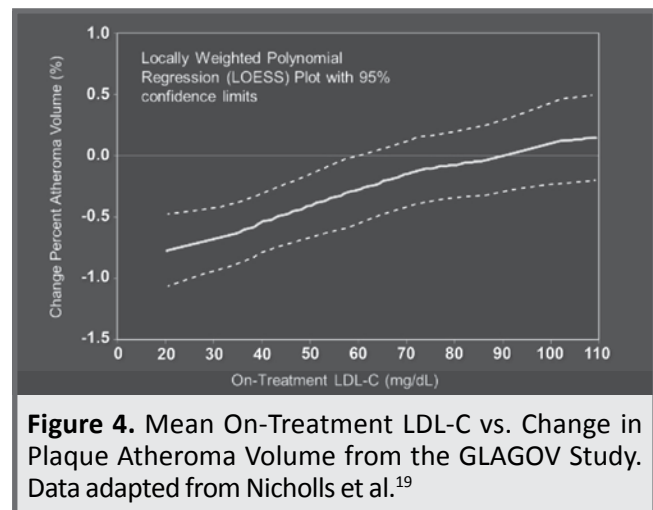
rocumab group compared to 119 mg/dL in placebo patients. Among the alirocumab group, 79% achieved an LDL-C <70 mg/dL at week 24, compared to only 8% in the placebo group. Certain adverse events were higher in the alirocumab group compared to placebo: injection site reactions 5.9 percent vs. 4.2 percent, myalgia 5.4 percent vs. 2.9 percent, neurocognitive events 1.2 percent vs. 0.5 percent, and ophthalmologic events 2.9 percent vs. 1.9 percent. Of particular interest, the post-hoc analysis of the composite of cardiovascular events over 78 weeks — including CHD death, myocardial infarction, ischemic stroke and unstable angina requiring hospitalization — showed those in the alirocumab group compared to placebo had a 48% reduced risk of such events (1.7% vs. 3.3%, HR=0.52, 95% CI=0.31-0.60). A similar study of evolocumab (Open-Label Study of Long-Term Evaluation Against LDL-Cholesterol [OSLER])¹⁷ included a pre-specified combined analysis of 4,465 patients who completed one of 12 Phase 2 or 3 studies of evolocumab. These subjects were randomized either to evolocumab 420 mg every 4 weeks plus standard of care vs. standard of care alone in an open-label extension study averaging 11 months. The evolocumab group showed a 61% reduction in LDL-C, from 120 to 48 mg/dL (a 72 mg/dL between-group LDL-C difference) at 12 weeks. There was no difference in the rate of serious adverse events (7.5% in each group). The OSLER study reported a 53% reduction in the incidence of the pre-specified composite endpoint of death, MI, hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack and hospitalization for heart failure (0.95 percent vs. 2.18 percent, HR=0.47, 95 percent CI=0.28-0.78). This can be considered a promising outcome in a short time despite a limited number of events (n=60) (Figure 2). Large Phase 3 trials involving >70,000 patients will provide definitive data on reduction in cardiovascular outcomes.



Most recently, it was announced that the FOURIER trial had met both its primary composite endpoint (including cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina or coronary revascularization) and the even more rigorous key secondary composite endpoint (cardiovascular death, non-fatal MI or non-fatal stroke) and that the important FOURIER substudy, the EBBINGHAUS cognitive function trial, also achieved its primary endpoint, demonstrating that evolocumab was non-inferior to placebo for the effect on cognitive function. The details for both of these studies are due to be released March 2017 at the American College of Cardiology Scientific Sessions.¹⁸

Impact of combined PCSK9 mAb therapy on regression of atherosclerosis

To assess the impact of PCSK9 inhibitors on ASCVD burden, the GLAGOV (Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound) multicenter, double-blind, placebo-controlled randomized clinical trial, Nicholls et al.¹⁹ studied 968 patients with angiographic coronary disease, 98% of whom were already on statin therapies. These patients were randomized to a monthly injection of evolocumab (420 mg) or placebo on a background of statin therapy, and examined as the primary endpoint the percent atheroma volume (PAV) over a 84 week treatment period. Compared with placebo, the evolocumab group achieved lower mean, time-weighted LDL-C levels (93.0 vs 36.6 mg/dL; difference, -56.5 mg/dL [95%CI, -59.7 to -53.4]; $P < .001$). Furthermore, despite a history of prior statin therapy (duration of use not reported), PAV increased 0.05% in those assigned to placebo, compared to a decrease of 0.95% in those assigned to evolocumab; between-group difference of -1.0% [95% CI, -1.8% to -0.64%]; $P < .0001$ (Figure 3). Moreover, evolocumab induced plaque regression in 64.3% of patients, compared to 47.3% in those on placebo, in addition to statin ($p < 0.001$). In addition, an exploratory pre-specified post hoc analysis showed a linear relationship between achieved LDL-C level and change in PAV with further “regression” in PAV down to LDL-C levels as low as 20 mg/dl, without any evidence

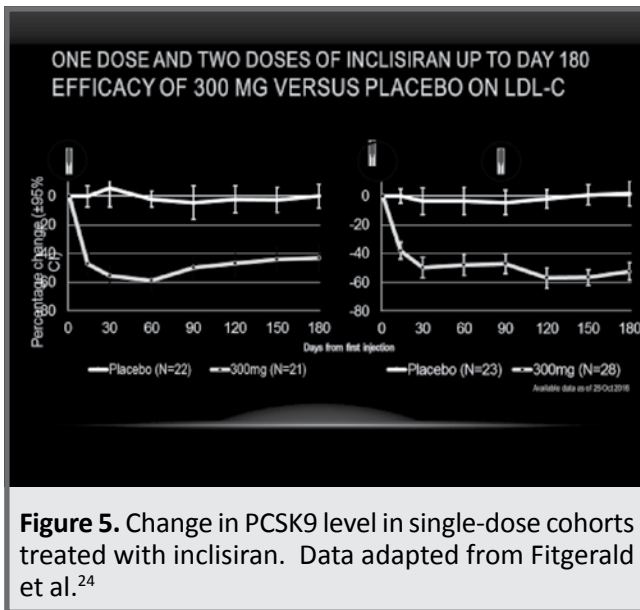


of a threshold effect (Figure 4). Finally, MACE occurred in 74 patients (15.3%) on placebo and 59 patients (12.2%) on evolocumab and while not powered to evaluate clinical outcomes, the 20.3% relative and 3.1% absolute risk reduction translates to a very acceptable NNT of 32 in the relatively short 18-month duration trial.

Uses of PCSK9 mAb Therapy

The current indications for both alirocumab and evolocumab, as approved by the US FDA, involve their use as adjuncts to diet and maximally tolerated statin therapy for adults with heterozygous FH or clinical ASCVD who require additional LDL-C lowering^{20,21}. Evolocumab is also indicated for such individuals with homozygous FH who require additional LDL-C lowering²¹. There also is an indication for use by adults and adolescents ages ≥ 12 years with homozygous FH in combination with other lipid-lowering therapies. In Europe, the European Medicines Association²² approved a broader indication for evolocumab in which usage can be considered for adults with primary hypercholesterolaemia (HeFH and non-familial) or mixed dyslipidemia. It can be an adjunct to diet in combination with a statin or with a statin with other lipid-lowering therapies in patients unable to reach LDL C goals via the maximum tolerated dose of a statin or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contra-indicated. There also is an indication for use by adults and adolescents ages 12 years and older with HoFH in combination with other lipid-lowering therapies. However, both products clearly state in their labeling that the effects on cardiovascular outcomes have not been determined.

The wider inclusion of these therapies in future clinical practice guidelines as well as optimal cost negotiations with payers (given current list pricing of approximately \$1200 per month) will be important for accessibility of these agents by patients. It has been recently estimated that annual drug costs per patient would need to be reduced to \$4,536 to be cost-effective at the accepted $< \$100,000$ per quality adjusted life year (QALY).²³ Broader indications for PCSK9 mAb therapy may be possible once further data become available in certain patient subgroups, cost-effectiveness is better



documented, and most importantly, an improvement in clinical outcomes has been demonstrated. Presently, the use of these PCSK-9 inhibitors require a detailed prior authorization. It is the responsibility of the health care provider to document that the approved indications have been carefully documented in order to limit denials by payers for these expensive newer therapies.

Novel RNA interference therapy for inhibition of PCSK9 synthesis

Administration of 'small interfering RNA' (siRNA) molecules has been recently identified as a novel means to inhibit synthesis of PCSK9 levels, thereby reducing LDL-C levels. These siRNA molecules bind intracellularly to the RNA-induced silencing complex (RISC) enabling it to cleave messenger RNA (mRNA) molecules that encode PCSK9. This cleaved mRNA is degraded and thus not available for protein translation, resulting in decreased levels of PCSK9. Inclisiran (ALN-PCSsc) is a long-acting, subcutaneously delivered, synthetic siRNA directed against PCSK9 that is taken up specifically by hepatocytes. Fitzgerald and colleagues²⁴ recently demonstrated in a phase 1 trial involving randomization of healthy volunteers to inclisiran or placebo, that a single 300 mg dose of inclisiran was able to reduce the PCSK9 level by 75% and LDL-C levels of 51% for 6 months or longer (Figure 5), with two dosages reducing LDL-C by 57% at 6 months. This product appeared to be very well-tolerated and offers the potential for bi- or tri-annual dosing. Given the positive results, phase 3 outcomes trials are now being planned.

Conclusions

The ACC/AHA Guideline for Blood Cholesterol Management focuses on the identification of four major statin eligible groups and has as its foundation appropriate ASCVD risk assessment for appropriate targeting of therapy in primary prevention. It also promotes appropriate lifestyle and treatment of obesity as the basis of preventive cardiology and lipid management. While many patients will

achieve adequate therapeutic response from the prescription of moderate or high intensity statin therapy, some patients, particularly those who cannot tolerate statins or have very high baseline LDL-C (e.g., FH) will require addition of non-statin therapy. The IMPROVE-IT trial provides a potential role for cholesterol absorption inhibitor therapy in combination with a statin in patients with acute coronary syndrome, whereas the remarkable LDL-C lowering achievable by PCSK9 mAb is potentially a valuable approach to further address residual ASCVD risk. Recent data show such therapy can also promote regression of atherosclerosis beyond statin therapy. Confirmation of the utility of PCSK9mAb treatment as a viable strategy to reduce ASCVD residual risk will depend on the results of large scale trials of the unique class of PCSK9 mAb currently in progress (the first of these was recently reported to be positive) as well as further demonstration of cost-effectiveness. Clinical practice guidelines have already adopted PCSK9 mAbs, but they are currently reserved for those at highest risk. Moreover, newer therapies in development, such as mRNA interference therapies targeting PCSK9 may hold further promise in providing more sustained reductions in LDL-C and addressing ASCVD residual risk.

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