Antilipidemics: Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitor Subclass

Executive Summary

- **For the MTF Formulary Management Document with the formulary recommendation from the November 2016 P&T Committee meeting, see http://www.health.mil/DoDPTResources.**
- The PCSK9 inhibitors alirocumab (Praluent) and evolocumab (Repatha) provide an additional adjunctive therapy for LDL-lowering in the management of hyperlipidemia, and are indicated for a specific subset of patients at high cardiovascular risk.
- Dyslipidemia treatment guidelines have been in flux, with an overall shift from LDL-lowering targets to a focus on addressing risk reduction.
- Statins have wide support as an initial lipid management choice, and intolerance continues to be ill-defined in theory and poorly validated in practice.
- Alirocumab and evolocumab are indicated as adjunctive therapies for LDL lowering beyond that achieved by statins for those populations with heterozygous familial hypercholesterolemia (HeFH) and atherosclerotic cardiovascular disease (ASCVD). Evolocumab has an additional indication for homozygous familial hypercholesterolemia (HoFH).
- IMPROVE-IT, a recently completed outcomes trial, revealed marginal benefit for the non-statin ezetimibe when added to statins.
- While the LDL hypothesis connects LDL lowering with improved cardiovascular outcomes, large trials are in progress to address what specific benefit these two new PCSK9 inhibitors provide beyond statins.
- At this time, there are no direct head-to-head trials between alirocumab and evolocumab. They both appear to be equally effective in lowering LDL with similar side effect profiles, but several long-term cardiovascular outcomes and safety concerns have yet to be resolved.

Background and P&T Committee Actions (see Table 1 for drugs in the class)

- The PCSK9 inhibitors are a subclass of the Antilipidemics-1 (LIP-1s) Drug Class and have not previously been reviewed.
  - At the time of the November 2016 P&T Committee meeting, alirocumab was designated with Uniform Formulary (UF) status, as it had been FDA-approved and added to the UF prior to implementation of the Innovator Rule on August 25, 2016, which requires newly-approved innovator drugs to be designated nonformulary (NF). Manual prior authorization (PA) criteria were recommended by the P&T Committee in August 2015.
  - Evolocumab was FDA-approved on August 27, 2015, and designated NF as newly-approved innovator in November 2015. Manual PA criteria also apply to evolocumab, with acknowledgement of the HoFH indication unique to this drug.
- PA criteria were recommended when the PCSK9 inhibitors were FDA-approved, to ensure appropriate patient selection due to limited efficacy and safety data. The limited patient years of experience and their relatively high cost when compared to well-studied and readily accessible alternative LDL-lowering strategies (statins) significantly limit PCSK9 inhibitor acceptance by providers as an appropriate first-line choice.
- Quantity limits also apply to the class.
- While statins are not part of this P&T Committee review, efficacy data and recently updated guidelines and their role in lipid management are discussed to ensure appropriate maximization of this well-studied therapy.

Table 1: Drugs in the Class

PCSK9 Inhibitor Subclass		
Generic	**alirocumab**	**evolocumab**
Brand	**Praluent**	**Repatha**
Manufacturer	Sanofi/Regeneron	Amgen
Approval Mo/Yr	Jul 2015	Aug 2015
Dose/ Dosing Frequency	Initial 75 mg SC q 2wks; max 150 mg q 2wks	140 mg SC q 2wks; 420 mg q 4wks (limited to HoFH patients)

Generic Name	**alirocumab**	**evolocumab**
Formulation	• 75 mg/1 mL or 150 mg/1 mL single-dose prefilled pen • 75 mg/1mL or 150 mg/1 mL single-dose prefilled syringe	• 140 mg/ 1 mL single-use prefilled syringe or autoinjector • 420 mg/3.5 mL Pushtronex prefilled cartridge with on-body infusion device, given over 9 minutes q month
Indication	• Adjunct to diet and maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of LDL • Effect on CV morbidity/mortality not determined for either drug • Evolocumab also approved as an addition to statins, ezetimibe, LDL apheresis in homozygous familial hypercholesterolemia (HoFH) (age ≥13 yo)	

LDL-Lowering Hypothesis and Cardiovascular Risk

- Hypercholesterolemia treatment guidelines have evolved over time with an acknowledgement that LDL and cholesterol values are among several factors that drive cardiovascular risk. Prior recommendations focused on specific LDL targets, but more recent guidance has noted that the older recommendations lacked evidence to directly connect specific targets to improved outcomes. While many studies have shown a benefit from LDL lowering, many of these have used statins as the driving force for that achievement without necessarily connecting outcomes to a specific LDL endpoint. Several guidelines have migrated towards encouraging patients and providers to choose the appropriate statin dose in line with level of cardiovascular risk, in order to achieve the greatest degree of LDL lowering in those patients at greatest risk. Some guidelines have developed a hybrid model looking at risk, target LDL levels, and achievement of expected LDL reductions.
- Studies that have evaluated non-statin agents have not always borne out positive cardiovascular outcomes for all patient populations, in spite of achieving statistically significant LDL reductions. Most recently, the IMPROVE-IT trial showed marginal improvement in cardiovascular outcomes in patients with high cardiovascular risk (post-acute coronary syndrome), with much of the benefit accruing from non-fatal myocardial infarctions in patients where ezetimibe was added on to a moderate intensity simvastatin dose, compared to the group receiving simvastatin alone. The study results showed that ezetimibe lowered LDL by 24% when added to simvastatin and was able to contribute to a 2% absolute risk reduction in the primary endpoint, which included CV death, nonfatal myocardial infarction/stroke, rehospitalization for unstable angina, and coronary revascularization.
- There are certain populations who may not achieve optimal LDL lowering either from a risk reduction or specific LDL target point of view. These include patients with a history of ASCVD, HeFH, or HoFH who require additional lipid-lowering therapy despite having maximally dosed statin therapies as part of treatment regimens.
- Intolerance to statins is often cited when patients fail to reach LDL target goals or achieve cardiovascular risk reduction. Available literature suggests 5% to 20% of patients may be statin intolerant. Statin intolerant patients are difficult to quantify and validate. As an example, one of the studies performed with alirocumab (that was not part of the FDA approval package), actually re-exposed previously identified “statin intolerant” patients and found over 70% of patients were subsequently able to tolerate a high intensity statin for 12 weeks.
- While some suggest that intolerance can be identified after exposure to as little as one or two statins, a majority of Military Health System providers surveyed felt exposure to three or more statins would be appropriate, prior to eliminating the class as a therapeutic option for a patient who has tolerance issues with selected statins.
- Beyond lifestyle changes, studies to support the use of bile acid sequestrants, fibrates, and niacin provide at best an incremental benefit and at worst no benefit with attendant side effects. The cardiovascular benefit is often driven by whether the non-statin agent was used as primary prevention or secondary prevention and also by the baseline cardiovascular risk levels of the population studied.

Clinical Practice Guidelines

- PCSK9 inhibitor discovery, development, clinical trials, and FDA approval of alirocumab and evolocumab in 2015 occurred when hypercholesterolemia treatment guidelines were undergoing significant revisions.
- In the years prior to PCSK9 inhibitor marketplace introduction, several organizations, including the U.S. Department of Veterans Affairs (VA)/Department of Defense (DoD), American College of Cardiology/American Heart Association (ACC/AHA), and the National Lipid Association (NLA), produced guidelines for lipid management that were widely regarded as transitions from prior recommendations and significant departures from widely-held practices.

- Guidance from major stakeholders, such as the ACC/AHA and VA/DoD, shifted away from the original Adult Treatment Panel III (ATPIII) recommendations of specific LDL goals, to a risk reduction evaluation and approach. These organizations also acknowledged that many lipid-lowering agents lacked evidence-based support, and encouraged use of statins over alternative lipid-lowering approaches (e.g., bile acid sequestrants, ezetimibe, fibrates, and niacin). The VA/DoD acknowledged that many of the studies only developed LDL-specific targets based on post hoc analyses, and that few studies were driven by a treat-to-target strategy, although this concept had become widely practiced and ingrained in the minds of providers and patients.
- Today, the overall trend is a shift away from, or entire elimination of, specific treat-to-target goals. The guidance shifted towards assessing risk based on a defined population subset or via a risk calculator. Often certain subgroups, such as those with coronary vascular disease or diabetes, were identified as requiring more intense LDL-lowering therapies. Consistent among the guidelines is an approach to encourage use of moderate to high intensity statins for those at greatest risk.
- Since approval of the PCSK9 inhibitors, a few organizations have provided updates that mainly rely on expert recommendations and reference the ongoing but yet-to-be-completed large cardiovascular outcome trials as keys to wider acceptance of these agents. These trials will likely drive the role that PCSK9 inhibitors will play in the discussion of their appropriate use in achieving significantly lowered LDL levels compared to that obtained with current therapies.
- While providers await these seminal trials, consistent among the guideline recommendations is an approach that includes maximizing statin use before considering PCSK9 inhibitors for selected high-risk patients who are unable to achieve goals of either expected percentage LDL reduction or achievement of a stated LDL target. Some guidance goes so far as to ensure that the patient is simply receiving a tolerated statin, and does not require follow-up lipid or liver panel monitoring to assess for level of LDL lowering or rare liver side effects.

PCSK9 Inhibitors

Mechanism of Action

- Alirocumab and evolocumab are human monoclonal antibodies that bind to PCSK9. Their development resulted from a combination of population genomics, sequencing of genes, identifying families with specific mutations, and a novel discovery of a gene responsible for disease. Found on chromosome 13, initially PCSK9 was believed to be an enzyme, but upon further analysis was identified as the low-density lipoprotein receptor (LDLR) regulator.
- Typically, PCSK9 binds to the LDLR on the surface of hepatocytes to promote LDLR degradation within the liver. LDLR is the primary receptor that clears circulating LDL, therefore the decrease in LDLR levels by PCSK9 results in higher blood levels of LDL-C. By inhibiting the binding of PCSK9 to LDLR, alirocumab and evolocumab increase the number of LDLRs available to clear LDL, thereby lowering LDL cholesterol levels.
- PCSK9 expression results from an interplay of factors that include additional regulatory proteins, as well as dietary intake of cholesterol. While PCSK9 inhibitors have been shown to lower LDL levels, it is interesting to note that statins, while lowering LDL, actually cause increases in PCSK9 levels.

Efficacy

- There are no head-to-head trials comparing alirocumab to evolocumab in terms of LDL lowering or cardiovascular outcomes.
- Available meta-analyses suggest that alirocumab and evolocumab effectively lower LDL whether used as monotherapy, when compared to ezetimibe, or when used as add-on therapy to standard care. Given recent changes in guidance, the treatment approaches for the completed studies have not always been consistent. For example, in both short- and long-term PCSK9 inhibitor studies, there are significant numbers of patients who are not receiving any lipid-lowering regimen, let alone a high intensity statin, as several guidelines suggest should be standard.
- Nine efficacy studies evaluating LDL reductions were part of the FDA approval package for alirocumab and evolocumab. Two relatively long-term trials have been published, ODYSSEY Long Term (for alirocumab) and OSLER 1/2 (for evolocumab). These two studies reported LDL lowering approached or exceeded 50% for both alirocumab and evolocumab over the short-term (12 to 24 weeks) and longer periods (up to 52 weeks). Most studies allowed the use of standard available lipid-lowering therapies (e.g., statins) and some compared the individual PCSK9 inhibitor to ezetimibe.
- Both the ODYSSEY and OSLER 1/2 long-term trials, which were published in the New England Journal of Medicine, had similar demographics with regards to age, race, sex, and LDL baseline level. In the alirocumab trial, 99% of patients were receiving a statin with 46% of patients on a high intensity dose, while in the evolocumab trial, 70% of patients were on a statin, with 26% on a high dose. The percentage of patients with pre-existing coronary heart disease ranged from 19% of patients in the evolocumab trial to 68% in the alirocumab trial. These examples of a demographically mixed population from a cardiovascular risk population profile will likely limit assessment of benefit from a cardiovascular perspective once the outcome trial results do become available. Nevertheless, when examined from a LDL-lowering perspective, the benefit as viewed from a pure effect on

LDL has been consistent between the agents. Table 2 provides details of the demographic differences between the PCSK9 inhibitors from their long-term clinical trials.

- ODYSSEY Long Term was a randomized, double-blinded, placebo-controlled trial that enrolled 2,341 patients to an alirocumab arm or a placebo arm in a two-to-one fashion. LDL change from baseline at 24 weeks was assessed as the primary endpoint and also was also examined at 78 weeks. LDL percent change from baseline was a 61.9% reduction at 24 weeks for the alirocumab arm, which was maintained at 78 weeks at a 56% reduction with alirocumab. As for actual LDL values, there was an improvement of LDL from 122 mg/dL at baseline to 48 mg/dL at 24 weeks with alirocumab treatment.

- OSLER 1/2 was an open label trial whereby 4,465 patients who had already been exposed to evolocumab via shorter term phase 2 and phase 3 trials were re-randomized to receive evolocumab or standard of care. Interestingly, in what could be argued was a heavily prescreened population from a safety perspective, the primary endpoint for the trial was adverse event incidence. An additional secondary endpoint was LDL percent change at 52 weeks, which was a 50.1% reduction in the evolocumab arm. As for actual LDL values, there was an improvement of LDL from 121 mg/dL at baseline to 50 mg/dL at 24 weeks.

Table 2: PCSK9 Inhibitors Long-Term Studies: Patient Characteristics

	Alirocumab (Praluent) (N=1,553)	Placebo (N=788)	Standard care (N=1,489)	Evolocumab (Repatha) (N=2,976)
Mean Age (years)	60.4	60.6	58.2	57.8
Male	63.3%	60.2%	51.4%	50.1%
White	92.8%	92.6%	86.0%	85.1%
CV risk factors:				
BMI	30.2	30.5	--	--
Heterozygous FH	17.8%	17.6%	10.1%	9.7%
CHD	67.9%	70.1%	20.6%	19.8%
Type 2 DM	34.9%	33.9%	13.9%	10.4%
Current smoker	20.9%	20.2%	15.9%	15.6%
Lipid medications:				
Any statin	>99.9%	99.9%	70.9%	69.7%
High intensity	46.8%	46.7%	26.7%	27.9%
Baseline LDL-C (mg/dL)	122.7	121.9	121	122
Triglycerides (mg/dL)	132.0	135.0	119	120
HDL-C (md/DL)	49.8	50.0	51	51

- Evolocumab and alirocumab had numerous phase 2 and phase 3 trials that were focused on a variety of subpopulations as part of their respective PROFICIO or ODYSSEY trial programs. These included patients with or without HeFH or ASCVD, and the treatments included statin with or without ezetimibe, or monotherapy with the PCSK9 inhibitor. The phase 2 and phase 3 trials lasted from 12 to 120 weeks.
- Alirocumab included ODYSSEY Long Term as part of the pivotal trial data set, which included a diverse mix demographically with regards to HeFH, ASCVD, or statin status. The FHI, FHII, and High FH trials included patients who were all identified as having HeFH. A large majority of the trials included statins as part of the treatment regimen. Overall 36% of patients were identified as having HeFH and 54% had ASCVD in the trials that were part of the alirocumab pivotal data set.
- Alirocumab treatment achieved baseline LDL lowering ranging from 27% to 31% beyond that achieved with ezetimibe in the 24 to 52 week trials, and from 39% to 58% when compared to standard of care at the 52-week endpoint.
- Evolocumab treatment achieved baseline LDL lowering ranging from 41% to 75% at 12 weeks and from 49% to 57% at 52 weeks in the demographically mixed population. Evolocumab was also approved for the HoFH population down to age 13 as a result of the TESLA Part B trial, which examined 49 patients with the condition. Ten adolescents ranging in age from 13 to 17 years, 7 of whom received evolocumab, were part of this study subpopulation, and allowed for the pediatric indication.
- The effect of the PCSK9 inhibitors on cardiovascular outcomes is unknown, and this fact is stated in both package inserts. Pre-specified exploratory analysis and post hoc analysis have suggested a positive benefit, but these results are limited by the study designs.

- Alirocumab is being evaluated in the ODYSSEY Outcomes trial underway that enrolled 18,600 patients experiencing acute coronary syndrome in the past year. Endpoints include time to first coronary heart disease (CHD) event, major CHD event, any cardiovascular (CV) event, and composite of all-cause mortality/nonfatal myocardial infarction (MI), nonfatal ischemic stroke, and all-cause mortality. Results are expected in late 2017.
- Evolocumab has a FOURIER outcomes trial that enrolled 27,564 patients with established cardiovascular disease. Endpoints include time to CV death, MI, hospitalization for unstable angina, stroke, or coronary revascularization. Results are expected in late 2017.
- Some of the study design differences between the ODYSSEY Outcomes trial and FOURIER trials may limit ability to directly compare the outcomes for alirocumab and evolocumab. However, there is a high likelihood that the outcome benefits for one agent will apply for the class.

Safety

- In regards to safety, adverse events were similar between alirocumab and evolocumab in the clinical trials. Safety issues for both products include injection site reactions, which are expected, given their subcutaneous delivery route. There are slightly more concerns with regard to antibody development with alirocumab that is not currently found in the evolocumab data. Neutralizing antibodies can significantly impact clinical efficacy, but have not occurred to any noticeable degree in either product when examining the available safety data set.
- The FDA is requiring long-term monitoring for possible neurocognitive effects given the initial safety data set that was available at the time of review. The labels for both products do not differ significantly in regard to neurocognitive effects.
- Published long-term trials suggest there are slightly more reports of dementia, confusion, and delirium in patients receiving PCSK9 inhibitor treatment versus control therapy. Given the long-term treatment required for hyperlipidemia these concerns will require close monitoring. The long-term outcomes trials currently underway are evaluating for neurocognitive changes.

Other Factors

- There are differences between the agents with regards to dosing. While both alirocumab and evolocumab are dosed via subcutaneous injection every two weeks, evolocumab is the sole agent to offer monthly dosing at the time of this review. Alirocumab can be titrated from 75 mg to a higher 150 mg dose if additional LDL lowering is needed. Sanofi, the manufacturer of alirocumab, is also planning a monthly dosing regimen of 300 mg. For evolocumab, dosing every two weeks is appropriate for HeFH and ASCVD patients, but once monthly dosing should be limited to patients with HoFH per the FDA label. Evolocumab also allows for the monthly dosing to be delivered via an on-body infusor device.
- Litigation issues are a non-clinical factor that may significantly impact this class. Amgen, evolocumab's sponsor, recently won a patent infringement claim that may limit the ability of Sanofi to market alirocumab. The outcomes of this ongoing litigation may range from an injunction, resulting in market withdrawal of alirocumab, to a profit sharing settlement between Amgen and Sanofi. A verdict is expected in the next four to eight months. Whatever the result, it would not preclude further litigation.
- A third investigational PCSK9 inhibitor, bococizumab, also has a large ongoing outcomes trial (SPIRE) that is examining 27,600 patients. However, as of November 1, 2016, the manufacturer has discontinued further testing of this product.

Conclusion

- While providers and patients have historically focused on LDL targets, the transition to a risk-based evaluation calls into question the benefit of approaching patients from a pure LDL number perspective. Risk factor evaluations are consistently part of many guideline recommendations.
- Statins have a solid supporting evidence base for cardiovascular risk reduction, particularly in those populations at greatest risk. It is not clear if the PCSK9 inhibitors will have a similar impact on cardiovascular event reduction beyond what the statins and ezetimibe currently provide.
- Overall the PCSK9 inhibitors provide an additional LDL-lowering option but should be limited to populations of greatest need. This limited place in therapy stems from their still yet-to-be-determined cardiovascular outcome benefit and long-term safety issues that may not have been apparent in the short marketing period for alirocumab and evolocumab.
- A refocus on LDL targets may be premature, when the evidence to date does not suggest this approach is appropriate for the vast majority of patients who require cardiovascular risk reduction. For those who remain at high risk, despite expected statin LDL reductions and who have failed the addition of ezetimibe, PCSK9 inhibitors may be considered. Cardiovascular outcomes trials for alirocumab and evolocumab are ongoing.
- Experts have yet to find convincing evidence to suggest that current approaches focusing on maximizing statins as a primary treatment option should be upended. Assuming that the PCSK9 inhibitor outcomes trials are not prematurely stopped due to overwhelming efficacy, the likelihood increases that PCSK9 inhibitor therapy will provide only a modest benefit over statins for reducing cardiovascular events.

- Significant long-term PCSK9 inhibitor concerns include, but are not limited to, their effect on cognition, potential negative long-term effects of very low LDL levels, ability of patients to adhere to injectable therapies for a silent disease, and significant cost and budget impact over the span of this lifelong diagnosis that may see patients using these agents for 30 to 50 years.
- The results from the PCSK9 inhibitor outcome trials may add disarray to divergent approaches that have developed in the current guidelines. Alternatively, the PCSK9 inhibitors may not provide significant benefit to a large majority of patients. For those patients who are truly statin intolerant and maximally managed from a cardiovascular risk standpoint with the currently available pharmacotherapeutic armamentarium, PCSK9 inhibitor treatment will cause a significantly unsustainable financial cost in the setting of a likely modest cardiovascular benefit and unknown long-term side effects.
- Patients with ASCVD, HeFH, and HoFH present high risk populations who have limited additional options beyond statin therapy, even if these patients can tolerate statin-containing regimens. The IMPROVE-IT trial does provide evidence to support addition of ezetimibe, albeit a marginal benefit. Overall, safety concerns and lack of cardiovascular outcomes are likely outweighed by the potential LDL-lowering benefits achieved in these high-risk populations when patients are truly statin intolerant and have maximized all other available LDL-lowering therapies.

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Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
ASCVD	atherosclerotic cardiovascular disease
ATP III	Adult Treatment Panel III
CHD	coronary heart disease
CV	cardiovascular
FH	familial hypercholesterolemia
HeFH	heterozygous familial hypercholesterolemia
HoFH	homozygous familial hypercholesterolemia
LDL	low-density lipoprotein
LDLR	low-density lipoprotein receptor
MI	myocardial infarction
NLA	National Lipid Association
PCSK9	proprotein convertase subtilisin/kexin type 9 inhibitor
VA/DoD	U.S. Department of Veterans Affairs/Department of Defense