### Exclusion Criteria

**If ANY box is checked below, the patient should NOT receive alirocumab or evolocumab**

- **Contraindication:**
  - History of a serious hypersensitivity reaction to alirocumab or evolocumab
  - Patient has NYHA* Class III or IV Congestive Heart Failure
  - Patient has severe renal insufficiency (e.g., eGFR <30 ml/min/1.73m²)
  - Patient is on dialysis
  - Patient has severe comorbid non-cardiovascular condition that is expected to limit life expectancy to <3 years
  - Patient is pregnant
  - Patient is lactating

*NYHA=New York Heart Association

eGFR=estimated glomerular filtration rate

### Inclusion Criteria (Alirocumab [Praluent] is the preferred PCSK9 inhibitor in VHA)

**TO RECEIVE ALIROCUMAB OR EVOLOCUMAB:**

Patient has one of the following indications:

- **PATIENTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HEFH):**
  - Patient meets criteria for definite HeFH according to Simon-Broome, Dutch Lipid Network or US (MEDPED) diagnostic criteria.³ When the diagnosis of HeFH is uncertain, consultation with local experts is advised.

  **AND**

  - Maximally tolerated statin plus ezetimibe has not resulted in at least a 50% reduction in LDL from untreated baseline OR LDL remains > 100 mg/dL despite confirmed adherence to treatment with maximally tolerated statin plus ezetimibe.

- **OR**

- **PATIENTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HOFH):**
  - Patient meets one or more of the following clinical or laboratory diagnostic criteria for homozygous familial hypercholesterolemia (HoFH):

    - Confirmation with genetic testing (mutation in LDL receptor: true homozygote or double heterozygote).
Untreated LDL of >500 mg/dL

OR

LDL >300mg/dL despite maximally tolerated, clinically indicated lipid-lowering therapy (e.g., statins, ezetimibe) and LDL remains >300 mg/dL (adherence is confirmed), AND

Presence of any of the following physical findings including: tendon xanthomas at any age, arcus corneae in patients <45 years or tuberous xanthomas or xanthelasma in patients <20 years.

OR

PATIENTS WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) AT VERY HIGH RISK ON MAXIMALLY TOLERATED STATIN PLUS EZETIMIBE AND MEETS ONE OF THE FOLLOWING:

Patient with an established diagnosis of ASCVD (history acute coronary syndrome [ACS], MI, ischemic stroke [secondary to atherosclerosis] or symptomatic peripheral arterial disease [PAD] - with confirmatory testing for PAD) and with a subsequent ASCVD event (ACS, new MI, ischemic stroke or unstable angina) while receiving maximally tolerated statin plus ezetimibe (with confirmed adherence to statin and ezetimibe).

OR

Patient with an established diagnosis of ASCVD (history of ACS, MI, ischemic stroke [secondary to atherosclerosis] or symptomatic peripheral arterial disease [PAD] - with confirmatory testing for PAD) considered to be at very high risk (history of recurrent ASCVD events, recent ACS and/or multiple uncontrolled risk factors or high risk conditions) and LDL remains >100 mg/dL on maximally tolerated statin plus ezetimibe (with confirmed adherence to statin and ezetimibe). (Refer to Appendix for evidence summary)

OR

This selection requires that the patient is receiving care from a VA authorized Cardiologist, Lipid Specialist, Endocrinologist or locally designated VA expert for approval who must engage in shared-decision making with the patient:

Patient with an established diagnosis of ASCVD (history of ACS, MI, ischemic stroke [secondary to atherosclerosis] or symptomatic peripheral arterial disease [PAD] - with confirmatory testing for PAD) considered to be at very high risk (history of recurrent ASCVD events, recent ACS and/or multiple uncontrolled risk factors or high risk conditions) and LDL remains 70-99 mg/dL on maximally tolerated statin plus ezetimibe (with confirmed adherence to statin and ezetimibe) and is considered to require additional LDL lowering based upon CV risk.

PATIENTS WITH STATIN INTOLERANCE (See Appendix for Evidence/Discussion)

Alirocumab and evolocumab were specifically not approved for use in the “statin intolerant” patient population because the FDA and its advisory committee were concerned that providers and patients may “bypass” statin therapy or use less intense regimens in favor of using PCSK9 inhibitors. At this time, there is no evidence supporting a reduced risk for adverse cardiovascular disease events with PCSK9 inhibitors alone (in the absence of statins) and therefore statins remain the treatment of choice for improving CV outcomes. Additionally, statins augment the LDL lowering capability of PCSK9 inhibitors since statins upregulate LDL receptors while PCSK9 inhibitors block degradation of the LDL receptor. These actions result in a greater number of LDL receptors available to clear circulating LDL. Additionally, statins are believed to be associated with pleiotropic effects (e.g. lowering hsCRP in contrast to PCSK9 inhibitors), benefitting patients beyond LDL lowering.

The following applies to patients with HeFH, HoFH or those with established ASCVD at high risk for recurrent events and with documented “statin intolerance”:

1. Intolerance to statins should be documented and in practical terms is defined as a trial of at least 3 statins which resulted in intolerable unexplained skeletal muscle-related complaints including pain or ache, weakness or muscle cramping that starts or worsens during treatment with statins and resolves when the statin is stopped.

2. In addition, one of the statins causing muscle complaints should have been tried at the lowest approved dose.
3. Consider checking Vitamin D levels and replacing Vitamin D if levels are low (e.g., <15-20 ng/mL). Preliminary evidence suggests a higher risk of statin intolerance in patients with low Vitamin D levels and an increased ability to tolerate statin rechallenge after replacement. Close follow up of replacement vitamin D levels and of statin related muscle symptoms is recommended.

4. Those on lower than optimal statin doses should receive other oral lipid-lowering therapies (e.g., ezetimibe) as necessary as second line treatment.

5. For those who are on lower than optimal statin dosing (including use of alternate day statin dosing) and are on other applicable oral lipid-lowering therapy (e.g., ezetimibe, bile acid sequestrants (BAS)), if the LDL reduction from untreated baseline is <50%, despite confirmed adherence to treatment, consideration can be given to using alirocumab or evolocumab.

6. Finally, if a patient is completely intolerant of statin therapy (i.e., no statin can be used) and other applicable lipid-lowering therapy (e.g., ezetimibe, BAS, niacin or fibrates) have not or are not expected to reduce LDL at least 50% from untreated baseline, use of alirocumab or evolocumab can be considered.

*Family history of premature ASCVD: Onset in men <55 years and women <65 years, in first-degree relative. ASCVD: acute coronary syndrome, myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, stable coronary heart disease, cerebrovascular accident or transient ischemic attack or atherosclerotic peripheral vascular disease.

+See Appendix for discussion of PCSK9 inhibitors in HoFH

### Dosage and Administration (Refer to the manufacturers prescribing information for detailed information)

In order to ensure proper injection technique and to prevent wastage of product, patients must be adequately trained on the proper storage, handling and administration of alirocumab or evolocumab.

### Monitoring

- To assess response to alirocumab or evolocumab, LDL should be measured within 3 months of treatment initiation and after dose titration. If LDL reduction is <40%, consider increasing the dose of alirocumab to 150 mg every 2 weeks. If monthly dosing had been used, then switch to every 2 week dosing.

- If LDL is <15 mg/dL on at least 2 occasions, consider reducing the dose of the PCSK9 inhibitor or discontinuing therapy.

- To ensure prolonged LDL reduction with alirocumab or evolocumab, LDL should be checked periodically (e.g., every 6 months)
  - To confirm adherence to treatment with alirocumab or evolocumab and other lipid-lowering treatments.
  - To confirm continued response to therapy. The presence of anti-drug antibodies or neutralizing antibodies has been observed in clinical trials and some patients have experienced loss of efficacy and an increased incidence of adverse events. However, the clinical significance of these antibodies has not been fully elucidated.

### Issues for Consideration (REFER TO APPENDIX FOR ADDITIONAL EVIDENCE/DISCUSSION INFORMATION)

**ALIROCUMAB (PRALUENT) IS THE PREFERRED PCSK9 INHIBITOR IN VHA**

- Patients should be educated to follow a lipid-lowering diet and counseled to adopt healthy lifestyle changes to reduce cardiovascular risk, including tobacco cessation, maintaining a healthy weight and optimizing physical activity.

- Molecular genetic testing should be reserved for those patients in whom a clinical diagnosis cannot be made (i.e., according to published criteria) but whose serum lipids or clinical profile is suggestive of Familial Hypercholesterolemia.\(^1\)\(^-\)\(^3\)\(^,\)\(^10\) The patient should be referred for (or offered) genetic consultation PRIOR to genetic testing.

- Alirocumab or evolocumab are not recommended in patients with New York Heart Association III-IV congestive heart failure or in those patients on dialysis since clinical evidence is lacking in these patients.

**ACTIVE CIGARETTE SMOKING:**

- Patients with established CV disease who were able to stop smoking had a 36% lower relative risk of mortality compared to those patients unable to quit (RR 0.64, 0.58-0.71). The reduction in mortality risk appeared to be consistent across age, sex, index cardiac event, country of origin and year of study initiation.\(^24\) Because of robust clinical benefits with smoking cessation in patients with ASCVD, including a mortality benefit, all efforts should be made to have patients enter into a clinically...
meaningful smoking cessation effort which involves both pharmacologic and behavioral therapy. There is no confirmed mortality benefit with alirocumab or evolocumab overall in the ODYSSEY OUTCOMES or FOURIER trials.

- If a patient is making a reasonable attempt to quit smoking (actively participating in a smoking cessation program involving pharmacologic and behavioral treatment), consideration can be given to adding alirocumab or evolocumab to maximally tolerated dose of statin plus ezetimibe for those meeting all other inclusion criteria, on a case by case basis. (Refer to the Appendix for additional evidence of the cardiovascular (CV) benefits of smoking cessation.)

**PLACE IN THERAPY:**

Because of limited long-term safety (<3 years) and modest clinical efficacy data with alirocumab (prespecified hierarchical statistical testing plan prevented confirmation of mortality benefit) or evolocumab (no mortality benefit), use of these agents should be limited to the following groups at highest risk for ASCVD events:

- Patients with a diagnosis of HeFH who have not achieved at least a 50% reduction in LDL from untreated baseline or LDL remains ≥ 100 mg/dL despite treatment with and confirmed adherence to maximum dose statins plus ezetimibe.

- Patients with a diagnosis of HoFH on maximum lipid lowering therapy (e.g., statins, ezetimibe) and who require additional LDL lowering.

- Patients with an established diagnosis of ASCVD (history of prior MI, ischemic stroke [secondary to atherosclerosis] or symptomatic peripheral artery disease [PAD] with confirmatory testing for PAD) and with a subsequent ASCVD event (e.g., ACS, new MI, ischemic stroke or unstable angina) while receiving maximum dose statins plus ezetimibe or considered to be at very high risk (history of multiple/recurrent ASCVD events, recent ACS and/or multiple uncontrolled risk factors or high risk conditions) and LDL remains > 100 mg/dL while receiving maximally tolerated statins plus ezetimibe (with confirmed adherence statin and ezetimibe). (See Appendix for evidence discussing further lowering of LDL levels when the LDL level is ≥ 100 mg/dL).

- Alternatively, in very high risk patients with LDL 70-99 mg/dL on maximum tolerated statin + ezetimibe (with confirmed adherence to treatment) and considered to require additional lipid lowering therapy based upon CV risk, addition of a PCSK9 inhibitor can be considered. Approval for use in this group requires the patient is receiving care from a VA authorized Cardiologist, Lipid Specialist, Endocrinologist or locally designated VA expert who must engage in shared-decision making with patients.

- A prompt reconsideration of all lipid-lowering treatments is recommended for all patients initiated on and tolerating treatment with alirocumab or evolocumab (e.g., possible discontinuation or dose adjustment of nonstatin medications)
  - If LDL decreases to <15 mg/dL during treatment with PCSK9 inhibitors, consider lowering the dose of or discontinuing the PCSK9 inhibitor and continuing statin therapy.
  - Statins augment the LDL lowering capability of PCSK9 inhibitors since statins upregulate LDL receptors while PCSK9 inhibitors block degradation of the LDL receptor. These actions result in a greater number of LDL receptors available to clear circulating LDL. Additionally, statins are believed to be associated with pleiotropic effects, benefitting patients beyond LDL lowering.27

**SAFETY** (Refer to the Appendix for more detailed information)

- Both alirocumab and evolocumab have been associated with severe hypersensitivity reactions, patients and caregivers should be informed to seek immediate medical attention if signs and symptoms of an allergic reaction occur.

- The long-term safety (>3 years) of very low LDL levels for a prolonged duration is uncertain since both FOURIER and ODYSSEY OUTCOMES followed patients for a median duration of less than 3 years. The FOURIER open-label extension trial, involving 1600 patients, may help address long-term safety but results are not expected until 2022 or 2023.34

**Renewal Criteria** *(All must be met prior to renewal of alirocumab)*

- Patient is tolerating alirocumab or evolocumab and is adherent to therapy.

- Patient has achieved a reduction in LDL of at least 40% from baseline (4-8 weeks after initiation or dose titration of alirocumab or evolocumab).
- Patient continues to have a significant reduction in LDL (with continuation of alirocumab or evolocumab) of at least 40% from baseline since initiation of PCSK9 inhibitor. LDL should be checked periodically with continued treatment with PCSK9 inhibitors (e.g., every 6 months).
- If LDL is <15 mg/dL while on alirocumab or evolocumab on at least 2 occasions, consider reducing the dose of the PCSK9 inhibitor or discontinuing therapy.


REFER TO APPENDIX FOR ALL REFERENCES
APPENDIX (Summary of details and/or of supporting evidence and references)

I. SAFETY

- Both alirocumab and evolocumab have been associated with severe hypersensitivity reactions, patients and caregivers should be informed to seek immediate medical attention if signs and symptoms of an allergic reaction occur.
- In the FOURIER trial, there was a higher incidence of injection site reactions in the evolocumab vs. placebo group, 2.1% vs. 1.6%, respectively. Most reactions were mild and only 0.1% in each group discontinued therapy due to these reactions. There were no differences in cataract formation, new diabetes, neurocognitive events, muscle-related events or hemorrhagic stroke between groups.11
- Because the FOURIER trial was stopped earlier than anticipated, the long-term safety of LDL levels <25 mg/dL remains unclear. Even though there were no neurocognitive or other signals in FOURIER, experts suggest caution when PCSK9 inhibitors are used long term due to the potential for neurocognitive events, cataract formation and development of diabetes.
- The EBBINGHAUS trial involved a subgroup of 1204 patients from the FOURIER trial who were followed for a median of 19 months to determine the effect of evolocumab on neurocognitive function. The primary endpoint was the score on the spatial working memory strategy index of executive function and secondary endpoints included scores for working memory, episodic memory and psychomotor speed. After a median period of 19 months, the mean change from baseline in spatial working memory strategy index for executive function was -0.21 in the evolocumab group vs. -0.29 for placebo (p<0.001 for noninferiority and p=0.85 for superiority). There were also no differences in the secondary endpoints between groups. The authors concluded no significant differences in neurocognitive function between groups.33
- The ODYSSEY OUTCOMES trial demonstrated no differences in adverse events between addition of alirocumab or placebo to maximal statin therapy. The only difference was in local injection site reactions which were higher in the alirocumab group vs. placebo (3.8% vs. 2.1%, respectively). Patients with LDL-C measurements of <15 mg/dL on 2 consecutive visits had their PCSK9 inhibitor dose reduced or substituted with placebo for the duration of the trial (N=730 or 7.7% of patients switching to placebo due to sustained LDL <15 mg/dL).26
- The long-term safety (>3 years) of very low LDL levels for a prolonged duration is uncertain since both FOURIER and ODYSSEY OUTCOMES followed patients for a median duration of less than 3 years. The FOURIER open-label extension trial, involving 1600 patients, may help address long-term safety but results are not expected until 2022 or 2023.34

II. SELECTED ISSUES:

ACTIVE CIGARETTE SMOKING:

- Daily cigarette smoking is one of the most preventable causes of cardiovascular (CV) disease. When tobacco use is combined with other cardiovascular risk factors, the risk of myocardial infarction (MI), sudden cardiac death, stroke, peripheral vascular disease (PVD), etc. can increase dramatically. Even limited exposure to tobacco smoke can trigger adverse CV events, therefore complete cessation of tobacco use and avoidance of second-hand smoke is extremely important especially in those patients with established CV disease.24
- Patients with established CV disease who were able to stop smoking had a 36% lower relative risk of mortality compared to those patients unable to quit (RR 0.64, 0.58-0.71). The reduction in mortality risk appeared to be consistent across age, sex, index cardiac event, country of origin and year of study initiation.25 Because of robust clinical benefits with smoking cessation in patients with ASCVD, including a mortality benefit, all efforts should be made to have patients enter into a clinically meaningful smoking cessation effort which involves both pharmacologic and behavioral therapy.
- A recent meta-analysis of CV mortality in current, former and never smokers (ages 60 years and older) found that cigarette smoking is a substantial risk factor for CV events and mortality. For current smokers, the hazard ratio for CV mortality was 2.07 (95% CI 1.82-2.36) and 1.37 (95% CI 1.25-1.49) for prior smokers compared to people who never smoked cigarettes. Current smoking was found to accelerate the risk of dying from CV disease by 5.5 years. The risk for CV events and stroke was also 2-fold and 1.5-fold higher in smokers, respectively, compared to never smokers. These CV risks were higher with heavier cigarette smoking. The higher risk for CV events and CV mortality seen in former smokers decreased over time. Evidence from this meta-analysis supports that there is a significant benefit in reducing CV events (MI and stroke) as well as CV mortality in patients who quit smoking.26
- Smoking cessation in VA:
  - Patient is actively participating in a smoking cessation program which involves both pharmacologic treatment and behavioral therapy for smoking cessation.
HISTORY OF HEMORRHAGIC STROKE:

- Patients with a history of a hemorrhagic stroke at any time in their past were excluded from the Further Cardiovascular Outcomes Research in Subjects with Elevated Risk (FOURIER) and Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome (ODYSSEY OUTCOMES) trials. As a result, it is unknown if patients with a prior history of hemorrhagic stroke may be at a greater risk for a subsequent hemorrhagic stroke while receiving a PCSK9 inhibitor. In FOURIER, rates of hemorrhagic stroke were low and not significantly different between groups (evolocumab 0.21% vs. placebo 0.18%, HR 1.16, 95% CI 0.68-1.98).

- In ODYSSEY OUTCOMES, rates of hemorrhagic stroke were also low (alirocumab <0.1% vs. placebo 0.2%, no statistics provided).

III. CLINICAL OUTCOME EVIDENCE-MAXIMIZING STATINS OR ADDING NONSTATINS TO STATIN THERAPY:

CLINICAL OUTCOMES:

- In the ODYSSEY OUTCOMES study, alirocumab added to maximally tolerated statins in patients 1-12 months after an acute coronary syndrome (ACS) reduced the primary outcome (Composite: CHD death, nonfatal MI, fatal or nonfatal ischemic stroke or unstable angina requiring hospitalization) by 1.6% (9.5% vs. 11.1%, RRR 15%, NNT 62.5) compared to maximally tolerated statins alone over a median follow up period of 2.8 years. Outcomes were analyzed according to a pre-specified hierarchical testing plan and therefore testing for statistical significance was stopped after the first nonsignificant p value (CHD death).

- Because of the testing plan, as well as not testing for multiplicity, an effect of treatment on the following individual components of the primary endpoint cannot be inferred: CHD death, CV death, all cause death, etc. (Refer to table 2 in the publication).

- Prespecified subgroup analysis of baseline LDL and effect on the relative risk reduction of the primary endpoint demonstrated that patients with a baseline LDL of >100 mg/dL experienced the greatest benefit from treatment with alirocumab (RRR 24%, ARR 3.4% NNT 29 over 2.8 years); however testing for interaction was not statistically different (p=0.09). Although not prespecified, analysis of baseline LDL and effect on absolute risk reduction in the primary endpoint showed that patients with baseline LDL >100 mg/dL experienced the most benefit from treatment (ARR 3.4%, NNT 16 patients over 4 years vs. overall group RRR 1.6%, NNT 49 over 4 years) including the most benefit on secondary endpoints as well. Overall, NNT 63 to prevent 1 event over 2.8 years vs. NNT 29 to prevent 1 event over 2.8 years in the baseline LDL >100 mg/dL.

- In the FOURIER study, evolocumab added to maximized statins (with or without ezetimibe) in patients with known ASCVD reduced the primary outcome (Composite: CV death, MI, stroke, hospitalization for USA or coronary revascularization) by 1.5% (9.8% vs. 11.3%, RRR 15%, NNT 74) compared to maximized statins +/-ezetimibe alone over a median follow up of 2.2 years. Although there were reductions in MI, stroke and coronary revascularizations which appeared to increase with time, there was no difference in CV death and a negative trend was noted between years 1 and 2 (Year1: HR 0.96, 95% CI 0.74-1.25/Year2: HR 1.12, 95 CI 0.88-1.42). There was also no difference in hospitalization for unstable angina or CV death + hospitalization for worsening heart failure. Differences were limited to nonfatal events. NNT=74 to prevent 1 event over 2.2 years.

- In the IMPROVE-IT study, addition of ezetimibe or placebo to moderate dose simvastatin in patients with recent ACS (time to randomization was about 5 days) reduced the occurrence of having a primary endpoint event (Composite: CV death, major coronary event [nonfatal MI, USA requiring hospitalization or coronary revascularization- at least 30 days after randomization] or nonfatal stroke) by 2% (32.7% vs. 34.7%, RRR 6%, NNT 50) after a median of 6 years of follow up. Differences were limited to nonfatal events. NNT=50 to prevent 1 event over 6 years.

- In secondary prevention, the evidence supports a reduction in all-cause mortality, nonfatal myocardial infarction (MI), coronary heart disease (CHD) death, fatal and nonfatal stroke with moderate dose statins (reducing LDL-C by 30-50%). In 5 studies comparing high versus moderate dose statins, improvement in the primary outcome of major cardiovascular events was observed in only two of the five trials (PROVE-IT TIMI 22 ARR=3.9%, RRR 16%, NNT=26 Patients with ACS to prevent 1 event over 2 years. TNT ARR=2.2%, RRR 22%, NNT 45 patients with stable CAD to prevent 1 event over 4.9 years). The primary composite outcome measures in these five trials were similar to FOURIER and IMPROVE-IT and the differences observed...
were limited to a reduction in nonfatal events. Although there was a difference in death from any cause in the ODYSSEY OUTCOMES trial in favor of alirocumab, the hierarchical statistical testing plan prevents confirmation of a mortality benefit.

- Although there are no direct comparisons between interventions added to statins (PCSK9 inhibitors or ezetimibe) or use of higher versus moderate dose statins in higher risk patients, all interventions appear to modestly reduce the incidence of nonfatal events. Although components of the primary composite outcome measures were similar between studies, populations differ as well as the duration of follow up. Evidence is lacking to determine the optimal intervention (addition of ezetimibe or PCSK9 inhibitors to maximized statin therapy or use of maximum dose statins in patients able to tolerate maximum doses) for reducing recurrent ASCVD events in patients on moderate or high dose statins. (Refer to table below)

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Intervention/Population (Maximize statin or addition of nonstatin)</th>
<th>Primary Composite Endpoint results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODYSSEY OUTCOMES&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Alirocumab added to maximum dose statin in patients 1-12 months after ACS</td>
<td>9.5% vs. 11.1% ARR 1.6%, RRR 15%, NNT 62.6 over 2.8 years</td>
</tr>
<tr>
<td>FOURIER&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Evolocumab added to maximum dose statins with or without ezetimibe in patients with known ASCVD</td>
<td>9.8% vs. 11.3% ARR 1.5%, RRR 15%, NNT 74 over 2.2 years</td>
</tr>
<tr>
<td>IMPROVE-IT&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Ezetimibe added to moderate dose statins in patients after ACS</td>
<td>32.7% vs. 34.7% ARR 2%, RRR 6%, NNT 50 over 6 years</td>
</tr>
<tr>
<td>PROVE-IT TIMI 22&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Moderate dose (pravastatin 40 mg) vs. high dose statin (atorvastatin 80 mg) in patients with ACS</td>
<td>22.4% vs. 26.3% ARR 3.9%, RRR 16%, NNT 26 over 24 months</td>
</tr>
<tr>
<td>TNT&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Moderate dose of atorvastatin (10 mg) vs. high dose (80 mg) in patients with stable CAD</td>
<td>8.7% vs. 10.9% ARR 2.2%, RRR 22%, NNT 45 over 4.9 years</td>
</tr>
</tbody>
</table>

- The 2018 ACC/AHA Task Force Guideline on the Management of Blood Cholesterol considers the following high-risk patients for consideration of a PCSK9 inhibitor:<sup>20</sup>
  - In very high-risk patients with known ASCVD, use a LDL-C threshold of 70 mg/dL to consider addition of nonstatins to statin therapy. Very high risk individuals are those with a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. In these patients at very high-risk, it is reasonable to add ezetimibe to maximally tolerated statins when the LDL remains ≥70 mg/dL. Furthermore, in patients at very high-risk whose LDL remains ≥70 m/dL or non-HDL-C of ≥100 mg/dL on maximally tolerated statins plus ezetimibe, adding a PCSK9 inhibitor is reasonable, although long-term safety (>3 years) is uncertain and cost-effectiveness is low at mid 2018 pricing. [Strength of recommendation Ila (moderate-is reasonable); Level of recommendation A based upon evidence from more than 1 randomized controlled trial (RCT) or high-quality meta-analysis of high-quality RCTs]
  - In patients with HeFH and with a LDL level of 100 mg/dL or > while taking a maximally tolerated statin plus ezetimibe, the addition of a PCSK9 inhibitor may be considered. [Strength of recommendation Iib (weak-may be reasonable); Level of recommendation B-R based upon moderate quality evidence from 1 or more RCT or meta-analysis of moderate quality RCTs]
  - Guideline authors indicate that a clinician-patient discussion should take place regarding the net benefit, safety and cost of PCSK9 inhibitor therapy.

- Patient centered decision making must be used to inform patients of the modest reduction in nonfatal events in patients with ASCVD regardless of which intervention is selected (addition of ezetimibe or PCSK9 inhibitors or statin increased to maximum dose) along with a discussion of the associated risks (PCSK9 inhibitors=risk for allergic reactions, injection site reactions and unknown long-term safety or high dose statins=increased risk for liver function test abnormalities, muscle related complaints, small risk for diabetes, etc.).<sup>35</sup>

- Evidence to support treatment to a specific LDL target for reducing CV outcomes is lacking in most populations, including those with HeFH. Therefore, the LDL value that will result in the greatest reduction in CV risk is unknown. However, several studies and meta-analyses do support the greatest reduction in risk, including a potential for reduction in death, is observed in patients with a baseline LDL level of ≥ 100 mg/dL.<sup>28-32</sup>
IV. PCSK9 INHIBITOR PLACE IN THERAPY:

Evidence for use in HoFH:

- There are no clinical trials evaluating alirocumab in patients with homozygous familial hypercholesterolemia (HoFH). However, there is some preliminary in-vitro evidence that alirocumab may also reduce LDL in this population of high risk patients with receptor defective HoFH.4
- There are 2 completed trials evaluating the efficacy and safety of evolocumab in patients with HoFH. The LDL lowering response in these patients was less than that observed in patients with HeFH or those at high CV risk (approximately 23% vs. 50+%, respectively) in indirect studies. Patients who are LDL receptor negative had no response to evolocumab.5-6

Evidence to support further lowering LDL when LDL is 100 mg/dl or >:

- A prespecified subgroup analysis of baseline LDL and relative risk reduction of the primary endpoint in the ODYSSEY OUTCOMES trial showed that only those patients whose baseline LDL (after prerandomization run-in phase) was ≥100 mg/dl had a statistically significant reduction in the composite primary endpoint (RRR 24%, HR 0.76, 95% CI 0.65-0.87) in the alirocumab group vs. placebo. However, testing for interaction did not show a statistical difference between baseline LDL and treatment effect (p=0.09). Although not prespecified, effect of baseline LDL on absolute risk reduction for the primary endpoint showed the greatest benefit was in those with baseline LDL ≥ 100 mg/dl (testing for interaction p<0.001). Absolute risk reduction for secondary endpoints was also not prespecified but showed that statistically significant differences were observed only in those patients whose baseline LDL was ≥100 mg/dl, including CHD death, CV death and all-cause death. Overall, a 15% relative risk reduction in the primary endpoint was observed vs. 24% in patients with a higher baseline LDL. The authors estimate that 49 patients would need to be treat for 4 years to prevent one event in the overall group vs. 16 patients whose baseline LDL was ≥ 100 mg/dl.28-29

- A systematic review and meta-analysis was conducted to determine whether there is an association between baseline LDL and total and CV mortality after LDL lowering. There were 34 trials included in the meta-analysis and comparison groups were categorized as more intensive (n=136,299) or less intensive (n=133,989) depending upon the intensity of the treatment or intervention. Primary endpoints were total mortality and CV mortality and secondary endpoints were major adverse cardiac events (MACE). Random effects meta-regression and meta-analyses were used to examine the association of baseline LDL and events. The authors found that more intense vs. less intense therapy was associated with a lower all-cause mortality (7.08% vs. 7.70%, ARR 0.62, rate ratio [RR] 0.92, 95% CI 0.88-0.96) but varied depending upon baseline LDL level. Meta-regression showed more intense treatment reduced all-cause mortality but only when baseline LDL was 100 mg/dl or > in a meta-analysis. Meta-analysis of all-cause mortality did not find an association with LDL level achieved. Cardiovascular mortality was also lower for more vs. less intense treatment (3.48% vs. 4.07%, ARR 0.59, RR 0.84, 95% CI 0.79-0.89) but varied by baseline LDL level. Use of meta-regression in a meta-analysis showed CV mortality was reduced greater in the more intense group but only when baseline LDL was 100 mg/dl or >. With regard to MACE, more vs. less intense treatment was associated with greater reductions in MACE regardless of baseline LDL. However, reductions in MACE of greater magnitude were observed in those groups with higher LDL levels at baseline. [Limitations: trial level data was used and data from ODYSSEY Outcomes was not yet available].30-31

- In an observational cohort population study, patients 30-84 years with a history of ischemic heart disease were examined using a large healthcare database in Israel to determine the relationship between LDL level achieved with statin adherence and MACE. Patients known to be at least 80% adherent to statin treatment were included (n=31,619). The LDL level recorded/achieved after at least one year of treatment (index LDL) was classified as low (< 70 mg/dL), moderate (70.01-100 mg/dL) or high (100.1-130 mg/dL). MACE included MI, unstable angina, stroke, angioplasty, bypass surgery or all-cause mortality. Over a mean of 1.6 years of follow-up, 9035 patients had a major adverse cardiac event (6.7 per 1000 persons per year). There were no differences in MACE between patients with low and moderate achieved LDL level (HR 1.02, 95% CI 0.97-1.07, p=0.54). MACE was lower in patients with moderate vs. high LDL level achieved (HR 0.89, 95% CI 0.84-0.94, p<0.001). Among patients with at least 50% adherence to statins (n=54,884) there was a higher risk for MACE between low and moderate (HR 1.06, 95% CI 1.02-1.10, P=0.001) but lower in the moderate vs. high groups (HR 0.87, 95% CI 0.84-0.91, p=0.01). The authors concluded that patients with LDL levels of 70-100 mg/dL taking statins had a lower risk of MACE vs. those who achieved LDL levels of 100-130 mg/dL. Reducing LDL below 70 mg/dL did not add greater benefit. Authors commented that their findings do not support treatment guidelines recommending very low LDL for all patients with preexisting heart disease. [Limitations: observational study].32
• **Option to consider PCSK9 Inhibitors in patients at very high risk with LDL 70-99 mg/dL on maximally tolerated statin + ezetimibe and considered to need additional LDL reduction to reduce CV risk in shared decision-making. Patients must be receiving care from a VA authorized Cardiologist, Lipid Specialist, Endocrinologist or locally designated VA expert for approval:**

  - The 2018 ACC/AHA Task Force Guideline on the Management of Blood Cholesterol considers the following high-risk patients for consideration of a PCSK9 inhibitor:

  - In very high-risk patients with known ASCVD, use a LDL-C threshold of 70 mg/dL to consider addition of nonstatins to statin therapy. Very high risk individuals are those with a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. In these patients at very high-risk, it is reasonable to add ezetimibe to maximally tolerated statins when the LDL remains ≥70 mg/dL. Furthermore, in patients at very high-risk whose LDL remains ≥70 mg/dL or non-HDL-C of ≥100 mg/dL on maximally tolerated statins plus ezetimibe, adding a PCSK9 inhibitor is reasonable. **Although long-term safety (>3 years) is uncertain and cost-effectiveness is low at mid 2018 pricing.** [Strength of recommendation Ila (moderate-is reasonable); Level of recommendation A based upon evidence from more than 1 randomized controlled trial (RCT) or high-quality meta-analysis of high-quality RCTs]

  - The Institute for Clinical and Economic Review (ICER) reviewed the evidence from ODYSSEY outcomes and recognized that the prespecified subgroup analysis of relative risk reduction in the primary endpoint by baseline LDL was not found to be statistically significant when testing for interaction (p<0.09), but express that this does not exclude the possibility of a difference. They also note that a post-hoc finding of a statistically significant difference (p<0.001) in absolute risk reduction in the primary endpoint when testing for interaction by baseline LDL, patients with a baseline LDL of ≥100 mg/dL had the greatest absolute benefit. The value-based pricing for alirocumab considering these findings are as follows:

    - $2,300-3,500 per year if used to treat all patients meeting eligibility criteria for ODYSSEY and $2,700-4,000 per year if only used to treat higher-risk patients with LDL ≥100 mg/dL despite intensive statin therapy.

    - ICER included a scenario analysis in which they created a “scenario analysis” assuming a statistically significant difference between baseline LDL and the primary endpoint. In those with a recent MI and LDL ≥100 mg/dL, value based pricing was assigned as $4,928-7,417 per year of treatment.

    - **ICER defines value-based pricing as the price that would yield cost-effectiveness ratios between $100,000 and $150,000 per quality adjusted life year (QALY) gained. To be clear, higher value-based pricing is applied to a drug with greater health outcome benefits and is considered to be worth a higher cost since the treatment is offering higher value in terms of reducing important outcomes.**

**V. STATIN INTOLERANCE:**

At this time, there is no evidence supporting a reduced risk for adverse cardiovascular disease events with PCSK9 inhibitors alone (in the absence of statins) and therefore statins remain the treatment of choice for improving CV outcomes.

- Patients with a documented intolerance to statins:
  - Alirocumab and evolocumab were specifically not approved for use in the “statin intolerant” patient population because the FDA and its advisory committee were concerned that providers and patients may “bypass” statin therapy or use less intense regimens in favor of using PCSK9 inhibitors. Statins have the most evidence supporting improved cardiovascular outcomes, including all-cause mortality, and remain first-line; while the PCSK9 inhibitors (despite lowering LDL) do not have evidence to support improved outcomes in the absence of statins and have more limited safety data compared to statins.7

  - In a study of 341 patients (non-HeFH) with a documented intolerance to statins, nearly 75% of patients (63 pts were randomized to atorvastatin) were able to tolerate blinded atorvastatin 20 mg daily. In this study, statin intolerance was defined as: The inability to tolerate at least 2 different statins due to unexplained skeletal muscle-related complaints including pain or ache, weakness or muscle cramping that starts or worsens during treatment with statins and resolves when the statin is stopped. One of the two statins causing muscle complaints was required to have been administered at the lowest approved dose.8
• In a study of 307 patients with self-reported statin intolerance who were randomized to evolocumab or ezetimibe, 8-13% of patients withdrew due to adverse events. Eighteen percent of patients were on at least a low statin dose throughout the study. None of the patients were re-challenged with the same statin prior to randomization to determine true intolerance and the study lasted only 12 weeks.9

• In very high-risk patients with HeFH, HoFH or those with ASCVD at high risk for recurrent events and documented statin intolerance, consider re-challenging them with at least a low to moderate dose statin. Alternate-day statin dosing reduces LDL but there is a lack of evidence that this dosing strategy reduces ASCVD events. Statins should remain as first-line therapy in primary and secondary prevention and use of alternate-day statins may be considered in patients unable to tolerate daily statins.

• The 2016 American College of Cardiology Consensus Update of Non-Statin Lipid Lowering Therapies supports stopping statin temporarily, lower statin dosing, re-challenge with 2-3 statins of differing metabolic pathways and/or use of alternative day dosing 1-3 times per week with statins having longer half-lives.19 The 2018 ACC/AHA Task Force Guideline on the Management of Blood Cholesterol also considers statin safety and adverse events. Their guidance in this area is similar to the 2016 consensus update but supports the use of “statin associated side effects” as opposed to “statin intolerance” since most patients can tolerate statin rechallenge.20

• A recently published observational study in Medicare beneficiaries compared the risks of coronary heart disease (CHD) events in patients that were “statin intolerant” versus those who were highly adherent to statin therapy after being hospitalized for a myocardial infarction between 2007-2013. Statin intolerant patients were defined as those patients that had their statin dose reduced or discontinued or switched between three or more statins within a year after statin initiation. Highly adherent statin users were those defined as the proportion of days covered (≥ 80% of the time with statins in possession) in the year after hospitalization. In the study, 105,329 users of moderate or high dose statins were followed over a median of 1.9-2.3 years. Statin intolerance was identified in 1,741 (1.65%) and high statin adherence in 55,567 (52.8%) patients. In comparison to those patients that were highly adherent to statins, statin intolerant patients had a 36% higher rate of recurrent MI (HR 1.5, 95% CI 1.3-1.73), 43% higher rate of CHD events (HR 1.51, 95% CI 1.34-1.7) but no statistical difference in all-cause mortality (HR 0.96, 95% CI 0.87-1.06). The authors conclude that their findings reinforce the importance of high adherence to statin therapy in reducing CHD events and cites studies in which patients with statin intolerance were successfully re-challenged with statins.21

• The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA) trial, conducted between 1998 and 2005, included both a double-blind and open-label phase. A new analysis showed that during the open label phase of the trial, an increase in the rate of muscle-related adverse events was apparent only when patients and their providers were aware that they were being treated with statins. In the double-blind phase of ASCOT-LLA, there was not an increase in the rate of muscle events reported between statin and placebo recipients. The authors of the analysis are suggesting that something called the “nocebo” effect may explain the increased incidence of muscle complaints during the open-label phase. The “nocebo” effect may occur when doctors make their patients aware of potential adverse events from treatments they are taking and then patients develop the side effect. In this case, patients are warned to monitor and report muscle complaints associated with the use of statins.22-23

• Negative statin-related news stories reported by the media may be responsible for patients stopping therapy early with statins based upon findings from a nationwide prospective cohort of Danish patients.21 Other factors were also noted for early statin discontinuation including calendar year, statin dose, male gender, living in cities, etc. Statin persistence was higher with positive statin-related new stories, baseline cardiovascular disease and diabetes. In patients with early withdrawal from statins, the risk for myocardial infarction (HR 1.26, 1.21-1.3) and cardiovascular death (HR 1.18, 1.14-1.23) was increased compared to those patients continuing statins.18

• Preliminary evidence suggests that patients deficient in Vitamin D may be at higher risk of being statin intolerant and replacement may increase patients ability to tolerate statins upon rechallenge.36-38 Therefore, close monitoring of vitamin D replacement levels and statin associated muscle complaints is recommended.

• In HeFH, HoFH or those with established ASCVD at high risk for recurrent events and with a documented intolerance to statins (defined as: a trial of at least 3 statins which resulted in unexplained skeletal muscle-related complaints including pain or ache, weakness or muscle cramping that starts or worsens during treatment with statins and resolves
when the statin is stopped. And, one of the statins causing muscle complaints was administered at the lowest approved dose), who are receiving other randomized controlled trial (RCT) proven lipid-lowering therapy (e.g., ezetimibe, BAS, niacin or gemfibrozil) and LDL reduction from untreated baseline is <50%, despite confirmed adherence to treatment, consideration can be given to a trial of alirocumab or evolocumab. If the patient is unable to tolerate any statin after trialing at least 3 statins, and other applicable RCT proven lipid-lowering agents have not or are not expected to reduce LDL at least 50% from untreated baseline, use of alirocumab or evolocumab may be considered.

VI. REFERENCES


