AACE Clinical Practice Guideline on Pharmacological Management of Persons with Dyslipidemia (High Cholesterol and Triglycerides)

PATIENT SUMMARY

American Association of Clinical Endocrinology

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Abbreviations

LDL, low-density lipoprotein; HDL, high-density lipoprotein; ApoB, apolipoprotein B; Lp(a), lipoprotein a; FDA, Food and Drug Administration

Patient Summary

Background

Heart disease is a leading cause of death worldwide. In the U.S. alone, almost 700,000 people died from heart disease in 2021.[1] Major risk factors for heart disease include high cholesterol (LDL-C), high blood pressure, diabetes, obesity, smoking, and history of heart disease (CDC).[2]

Dyslipidemia and hypertriglyceridemia are terms used when the levels of fat (lipids) in your blood are not in a healthy range. Usually, these terms refer to when either cholesterol or other fats called triglycerides are too high, but sometimes good blood fats (HDL) can be too low. High levels of LDL-C, or "bad" cholesterol, in your blood can build up as a fatty substance called plaque, leading to atherosclerosis, which is when the inside walls of your arteries become hard or thick, reducing blood flow. Some people have genetic conditions that make their blood fat levels high; this is called familial hypercholesterolemia (FH).

High levels of triglycerides can be linked with diabetes and liver issues (fatty liver), and very high levels are linked to pancreatitis, which is inflammation of the pancreas.

Lowering bad cholesterol and triglycerides can decrease the risk of heart disease. Along with changes in nutrition and physical activity, medications may be prescribed to help.

What information is included in this guideline?

Questions and recommendations in this guideline focus on the following specific information related to the care of people with dyslipidemia.

Patients

- Adults with dyslipidemia, including those with increased blood levels of cholesterol and/or triglycerides.
- Recommendations for the use of medications added to statins and lifestyle changes are specific for people with high cholesterol or triglycerides who already have heart disease or are at increased risk of heart disease.

Interventions

- Newer non-statin medications FDA-approved to reduce cholesterol and triglycerides.
- Nutrition, physical activity, and statins are important first steps in the treatment of high cholesterol and triglycerides but as standards of care were not included in this guideline.

Comparison Interventions

Usual (standard of) care which can include:

- No medication
- Nutrition and physical activity
- Other medications like statins or statins + ezetimibe

Outcomes Important to Patients Who Are Prescribed or Use Medications to Treat Dyslipidemia

- Death (mortality), heart attacks, stroke, surgery for blocked arteries (bypass), peripheral vascular disease or decreased circulation in arms and legs (e.g. limb ischemia, amputation), inflammation in the pancreas (pancreatitis), and discontinuation of treatment due to side effects.
- Outcomes were evaluated individually, and the absolute risk (number of people affected per 1,000 participants) was calculated for each outcome.

What is the purpose of this guideline?

This AACE guideline was developed by a group of health care professionals who are experts in endocrinology, lipid research, family medicine, pharmacy, and the study of research methods to provide recommendations for the use of medications to prevent heart disease in adults with dyslipidemia. [3]

Why should I trust these recommendations?

Recommendations were made after a careful search of the medical literature and review of the evidence. The strength of the recommendation was based on several things: the certainty or confidence in the evidence, different patient values and preferences, and the balance of desirable and undesirable effects. For this guideline, desirable effects included lower risk of heart disease events and undesirable effects included the number of people stopping the medications because of side effects.

Overall, only small benefits were observed in some of the outcomes and the confidence for the evidence was low or moderate leading to conditional recommendations for treatment options based on shared decision-making with patients.

What medications are recommended to treat dyslipidemia in this guideline?

- **In adults who have elevated LDL-C** ("bad" cholesterol) **and cardiovascular disease (heart disease) or are at increased risk for cardiovascular disease**:
  - AACE suggests adding alirocumab or evolocumab to usual care if not at goal LDL-C
    Conditional recommendation / Moderate certainty of evidence
  - AACE suggests the use of bempedoic acid in addition to usual care if statin intolerant
    Conditional recommendation / Moderate certainty of evidence
  - No recommendation for or against use of inclisiran
    No recommendation / Insufficient evidence
  - AACE suggests treating to a goal of less than 70 mg/dL LDL-C
    Conditional recommendation / Low certainty of evidence

- **In adults who have elevated LDL-C without cardiovascular disease and can tolerate other lipid-lowering medications:**
  - AACE suggests against the use of alirocumab, evolocumab, or bempedoic acid.
    Conditional recommendation / Moderate certainty of evidence

- **In adults who have elevated triglycerides and cardiovascular disease or are at ncreased risk for cardiovascular disease**:
  - AACE suggests the use of EPA in addition to usual care
    Conditional recommendation / Low certainty of evidence
  - AACE suggests against the use of EPA+DHA
    Conditional recommendation / Low certainty of evidence

- AACE recommends against the use of niacin
  Strong recommendation / Low certainty of evidence

What should I expect during my health care visits?

- To better understand your risk of heart disease, your health care professional will ask about your medical history and order some routine blood tests.
- Your doctor should calculate your risk using a specific calculator to determine your risk for future heart disease events.
- Your doctor may recommend additional tests measuring other types of lipids (ApoB or Lp[a]) or imaging for calcium buildup in the arteries of your heart (also called coronary artery calcium); however, evidence supports that these tests do not provide substantial improvement in the calculation of risk for heart disease.

How should I select treatment for my dyslipidemia with my health care professional?

- Shared decision-making means that you and your health care professional make decisions about your care together, based on your values and preferences, your doctor's experience, and evidence-based information.[4]
- These recommendations can support shared decision-making discussions with your health care professional to determine the right medication for you and to understand your risk of developing heart disease.
- This approach will be especially helpful when there is more than one option for screening, testing, or treatment, and no option has a clear advantage. It is also important when the possible benefits and harms of each option may affect a person differently.
- Below is a table (**Table 1**) showing how different treatments affect the risk of different outcomes. The potential risks are shown as the number of people experiencing that outcome per 1,000 individuals based on information from clinical trials. Talking about the difference risk of each outcome with your health care professional can help you decide on a treatment.

TABLE 1: CHANGE IN HEART DISEASE RISK WITH MEDICATIONS COMPARED TO STANDARD OF CARE

	Mortality (death), stroke, coronary revascularization (bypass surgery)	Heart attack	Limb ischemia/amputation (PVD events)	Discontinuation of medication due to side effects
Evolocumab	No difference	11 fewer heart attacks per 1,000 participants *(small decrease)*	No difference	No difference
Alirocumab	No difference	18 fewer heart attacks per 1,000 participants *(small decrease)*	5 fewer PVD events per 1,000 participants *(trivial decrease)*	No difference
Inclisiran	No difference	No difference	No difference	No difference
Bempedoic acid	No difference	11 fewer heart attacks per 1,000 participants *(small decrease)*	6 fewer PVD events per 1,000 participants *(trivial decrease)*	21 more people stopped treatment per 1,000 participants *(moderate increase)*
EPA	No difference	8 fewer heart attacks per 1,000 participants *(small decrease)*	Not reported	No difference
EPA + DHA	No difference	No difference		27 more people stopped treatment per 1,000 participants *(moderate increase)*
Niacin	No difference	6 fewer heart attacks per 1,000 participants *(trivial decrease)*		98 more people stopped treatment per 1,000 participants *(moderate-large increase)*

- Standard of care could include other medications like statins and statins + ezetimibe, lifestyle changes, or no treatment.
- The minimally important difference for heart attack, PVD events, and treatment discontinuation was set at 5 per 1,000 participants.
- **DHA** = docosahexaenoic acid, a type of omega-3 fat; **EPA** = eicosapentaneoic acid, a type of omega-3 fat; **LDL-C** = low-density lipoprotein-cholesterol; **PVD** = peripheral vascular disease

What medications other than statins may lower my cholesterol?

- Alirocumab and evolocumab are injectable medications that probably provide a small decrease in the risk for heart attack with minimal side effects (injection site reactions). However, the costs of these treatments can be high and vary depending on insurance coverage. See **Table 1** for more information on outcomes.
- At this time, there is not enough information from clinical trials on patient-important outcomes to make a recommendation for or against using inclisiran. However, for some people with very high cholesterol, inclisiran may be an option if they can afford the treatment and have access to receive it in a health care setting. Potential side effects with use of inclisiran included injection site reactions, lung infections, and joint pain.
- Bempedoic acid may be an option for people who have side effects with statins, as it probably provides a small decrease in risk of heart attack and a trivial decrease in limb ischemia and amputation (see **Table 1**). However, there can be side effects with this medication, including skin flushing (redness and heat) and stomach and intestinal issues. Studies reported a moderate increase in the number of people who stopped taking bempedoic acid due to side effects compared with those taking evolocumab and alirocumab.

What medications other than statins may lower my triglycerides?

- Different types and amounts of omega-3 fatty acids (fish oil) are available by prescription. EPA alone (icosapent ethyl) may result in a small decrease in the risk of heart attacks but can also increase the risk of certain adverse events like bleeding and heart arrythmia (irregular heartbeat).
- The combination of EPA+DHA and niacin were not observed to provide a reduction in cardiovascular events but may increase the numbers of people stopping treatment due to side effects. Similar to EPA alone, the combination of EPA+DHA can increase the risk of an irregular heartbeat (arrythmia) and bleeding along with impaired taste and indigestion.
- Niacin is not recommended to reduce the risk of heart disease as it may not lower the risk of heart disease and death and probably increases the risk of hospitalization due to high blood sugar in people with diabetes, higher rates of infection, and bleeding. There is currently no information on the use of niacin in people with extremely high levels of triglycerides or in preventing pancreatitis.

How low should my cholesterol (LDL-C) be with treatment?

- There is limited information to set a specific goal for cholesterol level with treatment.
- However, it is important to lower your cholesterol if it is really high (greater than 130 mg/dL for most people and greater than 70 mg/dL for people with heart disease). Many studies have shown that lowering cholesterol from above 100 mg/dL to below 100 mg/dL decreases a person's risk of future heart disease.

- When comparing patients who reached different cholesterol (LDL-C) levels after taking medications, people whose cholesterol was less than 70 mg/dL had a small decrease in the risk of heart attack and a trivial or slight decrease in the risk of death **(see Table 2**).
- There is not enough information on patient-important outcomes to support a goal of less than 55 mg/dL LDL-C for most people.

TABLE 2: TREATMENT GOALS: CHANGE IN RISK OF HEART DISEASE ACHIEVING ‹70 mg/dL LDL-C COMPARED WITH ≥70 mg/dL LDL-C

Specific Heart Disease Event or Outcome	Treating to ‹70 mg/dL LDL-C
Mortality (death) includes death from any cause and death related to heart disease	5 fewer deaths per 1,000 participants (trivial decrease)
Heart attack	11 fewer heart attacks per 1,000 participants (small decrease)
Stroke or coronary revascularization (bypass surgery)	No difference
Limb ischemia/amputation (PVD events)	Not reported
Discontinuation of medication due to side effects	0.1% risk difference in the number of individuals who discontinued medication (trivial increase)

- The minimally important difference for mortality and heart attack was set at 5 fewer per 1,000 participants. The minimally important difference for treatment discontinuation was set at 5 more per 1,000 participants.
- **LDL-C** = low-density lipoprotein-cholesterol; **PVD** = peripheral vascular disease

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