



Controversies in the Management of High Cholesterol

Final Background and Scope

Background:

Cardiovascular disease (CVD) is the most common cause of death in the United States and approximately one third of American adults have CVD.¹ Low density lipoprotein cholesterol (LDL) is a major modifiable risk factor for myocardial infarction, stroke, and death from cardiovascular disease.¹ The use of statins to decrease LDL has contributed to the marked decline in death from CVD since 1950, but some patients are not able to tolerate statins and others have inadequate reductions in LDL.² In June 2015, the FDA advisory panel voted to recommend approval of two human monoclonal antibodies that target proprotein convertase subtilisin/kexin type 9 (PCSK9) in the blood and markedly reduce LDL cholesterol levels.

Project Aim:

The focus for this assessment will be on the use of PCSK9 inhibitors for individuals with elevated LDL cholesterol. We will assess the evidence on comparative effectiveness and value of the drugs across relevant populations including: 1) patients with familial hypercholesterolemia 2) patients with established cardiovascular disease, and 3) patients at elevated risk for cardiovascular disease.

Scope of the Assessment:

The proposed scope for this assessment is described below using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, Settings) framework. The evidence review will primarily be based on the systematic review and meta-analysis published electronically in the *Annals of Internal Medicine* on 4/28/15.³ We will update their systematic review to identify any additional randomized trials with particular attention paid to abstracting data from the five trials that were only available as presentation slides for the original review. We will also add the results from any newly completed trials. If there are changes in the data, the meta-analyses will be updated. Additional meta-analyses will be performed in subgroups not reported in the published meta-analysis.

Population

The populations of interest will include:

- Adults (age 18+) individuals with familial hypercholesterolemia (FH) who have inadequate control of their cholesterol
- Adults with known CVD who are intolerant of statins or who have inadequate control of their cholesterol
- Adults who are at high risk for CVD who are intolerant of statins or who have inadequate control of their cholesterol

Interventions

The interventions will be limited to the PCSK9 inhibitors likely to be approved by the FDA in 2015.

Medications

- Alirocumab (Praluent™)
- Evolocumab (Repatha™)

Comparators

The studies will compare an intervention of interest to usual care (i.e., statin therapy, lifestyle and dietary changes), placebo, and/or other medications that lower LDL such as ezetimibe.

Outcomes

Outcomes of interest will include the impact of cholesterol-lowering interventions on:

- Mortality
- CVD mortality
- CVD events (myocardial infarction, stroke, unstable angina, revascularization)
- LDL reduction as an intermediate marker
- Measures of pain, function, health-related quality of life, and/or patient satisfaction
- Short- and long-term complications and adverse events including neurocognitive events, hemorrhagic strokes, myalgias, hemolytic anemia, and local injection site reactions
- Economic outcomes, including payer costs, patient productivity, and cost-effectiveness

We will assess the evidence on an overall basis as well as stratified by important patient subgroups.

Timing

Evidence on intervention effectiveness will be limited to phase 2 or 3 comparative studies with at least two months of follow-up for LDL reduction. Evidence on cardiovascular outcomes and harms will be derived from comparative studies of any duration.

Settings

All relevant settings will be considered, including inpatient, clinic, and outpatient settings.

References:

1. Mozaffarian D, Benjamin EJ, Go AS, et al: Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation* 131:e29-322, 2015
2. Dadu RT, Ballantyne CM: Lipid lowering with PCSK9 inhibitors. *Nat Rev Cardiol* 11:563-75, 2014
3. Navarese EP, Kolodziejczak M, Schulze V, et al: Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia: A Systematic Review and Meta-analysis. *Ann Intern Med*, 2015