

## HMG-CoA Reductase Inhibitors (Statins)

### Key Questions and Inclusion Criteria

#### *Update #5*

#### **Key Questions**

1. How do statins and fixed-dose combination products containing a statin and another lipid lowering drug compare in their ability to reduce LDL-c?
  - a. Are there doses for each statin or fixed-dose combination product containing a statin and another lipid lowering drug that produce similar percent reduction in LDL-c between statins?
  - b. Is there a difference in the ability of a statin or fixed-dose combination product containing a statin and another lipid lowering drug to achieve National Cholesterol Education Panel goals?
2. How do statins and fixed-dose combination products containing a statin and another lipid lowering drug compare in their ability to raise HDL-c?
  - a. Are there doses for each statin or fixed-dose combination product containing a statin and another lipid lowering drug that produce similar percent increase in HDL-c between statins?
  - b. Is there a difference in the ability of a statin or fixed-dose combination product containing a statin and another lipid lowering drug to achieve National Cholesterol Education Panel goals?
3. How do statins and fixed-dose combination products containing a statin and another lipid lowering drug compare in their ability to reduce the risk of nonfatal myocardial infarction, coronary heart disease (angina), coronary heart disease mortality, all-cause mortality, stroke, hospitalization for unstable angina, or need for revascularization (coronary artery bypass graft, angioplasty, or stenting)?
4. Are there differences in effectiveness of statins and fixed-dose combination products containing a statin and another lipid lowering drug in different demographic groups or in patients with comorbid conditions (e.g., diabetes, obesity)?
5. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid lowering drug when used in the general population of children or adults?
6. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid lowering drug when used in special populations or with other medications (drug-drug interactions)? In addressing this question, we will focus on the following populations:
  - a. Patients with HIV
  - b. Organ transplant recipients

- c. Patients at high risk for myotoxicity (e.g., patients with a history of statin-associated muscle-related harms due to drug-drug/drug-food interactions, patients co-administered fibrates, patients taking potent 3A4 inhibitors, elderly patients, especially elderly females)
- d. Patients at high risk for hepatotoxicity
- e. Patients using fibrates (gemfibrozil, fenofibrate, fenofibric acid) or niacin
- f. Children with nephrotic syndrome

## **Inclusion Criteria**

### Populations

- Outpatients targeted for primary or secondary prevention of coronary heart disease or non-coronary forms of atherosclerotic disease with or without hypercholesterolemia.
- Inpatients with acute coronary syndrome or undergoing revascularization (if the statin was continued after hospital discharge and if health outcomes were reported).
- Both children and adults will be included.
  - Children with familial hypercholesterolemia (homozygous or heterozygous) will be included.
- Exclusions: Adults with rare, severe forms of hypercholesterolemia (LDL-c  $\geq$ 250mg/dl).

### Interventions

**Table 1. Individual statins**

| <b>Active ingredient</b>     | <b>Brand name</b> |
|------------------------------|-------------------|
| Atorvastatin                 | Lipitor           |
| Fluvastatin                  | Lescol            |
| Fluvastatin extended release | Lescol XL         |
| Lovastatin                   | Mevacor           |
| Lovastatin extended release  | Altoprev*         |
| Pravastatin                  | Pravachol         |
| Rosuvastatin                 | Crestor           |
| Simvastatin                  | Zocor             |

**Table 2. Fixed-dose combination products containing a statin**

| <b>Active ingredients</b>            | <b>Brand name</b> |
|--------------------------------------|-------------------|
| Lovastatin; niacin extended release  | Advicor           |
| Simvastatin; ezetimibe               | Vytorin*          |
| Simvastatin; niacin extended release | Simcor*           |

\*Not available in Canada

*Exclusions: Caduet (atorvastatin; amlodipine)*

### Study designs

- For assessment of effectiveness, controlled clinical trials and systematic reviews.
- For assessment of harms, controlled clinical trials, observational studies, and systematic reviews.

### Comparators: Effectiveness and harms of individual statins

- For Key Questions 1 and 2, head-to-head trials comparing one statin to another.

- For other key questions, trials comparing a statin to placebo or another active comparator.

Comparators: Effectiveness and harms of fixed-dose combination products containing a statin

- Head-to-head trials comparing one fixed-dose combination product to another.
- Trials comparing a fixed-dose combination product to an individual statin, placebo, or another active comparator.

*Exclusions: Trials comparing a fixed-dose combination product to the product's individual components given separately (co-administration).*

Effectiveness outcomes

- Reduction in nonfatal MI, CHD, mortality (CHD and all-cause), stroke, and need for revascularization (including coronary artery bypass grafting, angioplasty and coronary stents)
- LDL-c lowering ability
- HDL-c raising ability

Harms outcomes

- Overall adverse events
- Withdrawals due to adverse events
- Serious adverse events
- Specific adverse events (including, but not limited to, hepatotoxicity, myopathy, rhabdomyolysis, renal toxicity, myalgia)