Complete Summary

GUIDELINE TITLE

Drug treatment for hyperlipidaemias.

BIBLIOGRAPHIC SOURCE(S)

Strandberg T, Vanhanen H. Drug treatment for hyperlipidaemias. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2004 Apr 22 [various]. [18 references]

GUIDELINE STATUS

Note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
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SCOPE

DISEASE/CONDITION(S)

Hyperlipidaemia

GUIDELINE CATEGORY

Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine

INTENDED USERS

Health Care Providers
Physicians

GUIDELINE OBJECTIVE(S)

Evidence-Based Medicine Guidelines collect, summarize, and update the core clinical knowledge essential in general practice. The guidelines also describe the scientific evidence underlying the given recommendations.

TARGET POPULATION

Patients with hyperlipidaemia, especially those with atherosclerotic disease or diabetes

INTERVENTIONS AND PRACTICES CONSIDERED

Drug Therapy

1. Statins (hydroxy-methylglutaryl-coenzyme A [HMG-CoA] reductase), such as lovastatin, pravastatin, simvastatin, atorvastatin, fluvastatin, rosuvastatin*
2. Resins, such as cholestyramine, colestipol
3. Guar gum
4. Fibrates, such as gemfibrozil, bezafibrate, fenofibrate
5. Ezetimibe

***Note from the National Guideline Clearinghouse**: On March 2, 2005, the U.S. Food and Drug Administration (FDA) issued a public health advisory describing revisions to the WARNINGS, DOSAGE AND ADMINISTRATION, CLINICAL PHARMACOLOGY, and PRECAUTIONS sections of the labeling for the drug Crestor (rosuvastatin calcium). The revisions include results from a Phase 4 pharmacokinetic study in Asian-Americans and highlight important information on the safe use of Crestor to reduce the risk for serious muscle toxicity (myopathy/rhabdomyolysis), especially at the highest approved dose of 40 mg. At this time, the FDA is also making statements about the muscle and kidney safety of Crestor based on extensive review of available information. See the FDA Web site for more information.

MAJOR OUTCOMES CONSIDERED

- Total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentration, cardiovascular events, cardiovascular and all cause mortality
- Adverse effects
- Cost-effectiveness
- Reduction in risk of ischaemic heart disease

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The evidence reviewed was collected from the Cochrane database of systematic reviews and the Database of Abstracts of Reviews of Effectiveness (DARE). In addition, the Cochrane Library and medical journals were searched specifically for original publications.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

A. Strong research-based evidence. Multiple relevant, high-quality scientific studies with homogenic results.
B. Moderate research-based evidence. At least one relevant, high-quality study or multiple adequate studies.
C. Limited research-based evidence. At least one adequate scientific study.
D. No research-based evidence. Expert panel evaluation of other information.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not applicable

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A systematic review including 124 studies (83 randomized controlled trials [RCTs] with a total of 25,157 subjects) was abstracted in Database of Abstracts of Reviews of Effectiveness (DARE). The results of the cost-effectiveness analysis were presented using the decrease in total cholesterol/high-density lipoprotein (HDL) ratio per dollar of daily drug cost. The most cost-effective drugs in the class with highest potency (greater than 30% decrease in the ratio) were fluvastatin (60 mg/day, 1.80 dollars), micronized fenofibrate (200 mg/day, 1.73 dollars), and simvastatin (20 mg/day, 2.20 dollars). The analysis is sensitive to changes in the cost of the drugs.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary. The recommendations that follow are based on the previous version of the guideline.

The levels of evidence [A-D] supporting the recommendations are defined at the end of the "Major Recommendations" field.

Basic Rules

- Make sure that an effective diet has been implemented, and start drug therapy without delay, if clearly indicated.
- People with atherosclerotic disease or diabetes are the most important target groups.
- Determine serum cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol, and calculate serum low-density lipoprotein (LDL) cholesterol according to the Friedewald equation before commencing drug treatment.
- Rule out secondary hypercholesterolaemia. If the cause of secondary hypercholesterolaemia cannot be managed, treat as if the patient had primary hypercholesterolaemia.
- Identify patients with familial hypercholesterolaemia (serum cholesterol usually above 8 mmol/L, xanthomas, family history) in order to screen family members.
- If an increased serum LDL cholesterol concentration is the most important lipid abnormality, a statin is the drug of choice (Bucher, Griffith, & Guyatt, 1999; The Database of Abstracts of Reviews of Effectiveness (DARE)-993524, 2000; Ross et al., 1999; DARE-999402, 2002) **[A]**.

- If an increased triglyceride concentration (>4.5 mmol/L) and a low HDL cholesterol concentration are the most important abnormalities a fibrate may be the drug of choice.

General Principles on the Choice of Drug

- Of the drugs in common use, pravastatin, simvastatin, lovastatin, cholestyramine, and gemfibrozil have been tested in randomized double-blind trials lasting at least 5 years ("Randomised trial of cholesterol lowering," 1994) **[A]**. There are long lasting trials on atorvastatin and fluvastatin, as well.
- A statin is the drug of choice (Bucher, Griffith, & Guyatt, 1999; DARE-993524, 2000; Ross et al., 1999; DARE-999402, 2002) **[A]** unless the main abnormality is hypertriglyceridaemia in combination with a low HDL cholesterol concentration.
- Resins and guar gum are safe during pregnancy and in children because they are not absorbed from the intestine. Their adverse effects may cause problems.

Choice of Drug According to the Type of Hyperlipidaemia

Table. Selection of Lipid Lowering Drug According to the Type of Hyperlipidaemia

Dyslipidaemic (phenotype)	Drug of choice
Hypercholesterolaemia alone (familial hypercholesterolaemia)	Statin or a combination of a statin and ezetimibe or a combination of a statin and a resin (the dose of resin <20 g to avoid adverse effects).
Both cholesterol and triglycerides increased	Statin if serum triglyceride <4.5 mmol/L. Fibrate plus statin if increasing the dose of statin is not sufficient (the need for combination treatment should be evaluated by a specialist).
Pure hypertriglyceridaemia	Reducing weight and limiting alcohol consumption is essential before drug treatment is considered. Control of diabetes should be improved. Fibrate.
Hypothyroidism	Thyroxine substitution normalizes the lipid abnormality if it is caused by

hypothyroidism.

Statins

The most important group of antihyperlipidaemic agents.

Mechanism of Action

Based on the inhibition of the hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase resulting in the inhibition of cholesterol synthesis in hepatocytes. The number of LDL receptors on hepatocytes is increased, and the elimination of LDL from the blood is enhanced. Part of the action may be through very low-density lipoprotein (VLDL) or even other mechanisms.

Effectiveness

- LDL is decreased by 30 to 40%.
- HDL is increased by 5 to 15%.
- Triglycerides are decreased by 10 to 30%.
- Combining statins with resins results in additive effects (Schectman & Hiatt, 1996; DARE-978010, 1999) **[C]**.

Adverse Effects

- Statins are usually well tolerated, even by elderly patients.
- Serum aminotransferase concentrations rise in about 2% of the patients.
- Serum creatine kinase need not be determined routinely. The test is indicated if the patient has unexplained myalgias or muscular symptoms. Concentrations 10 times above the upper limit of the reference value are significant. The incidence of myopathy is about 0.5%.
- The incidence of notable muscular side effects is <0.1%.
- The risk of myopathy is increased by:
    - simultaneous cyclosporine, fibrate, macrolide, or conazole medication.
    - very high age
    - multiple diseases
    - operations
    - hypothyroidism
- Individual cases of polyneuropathy have been described in connection with statin treatment.

Dosage

Dosage recommendations can be found in the original guideline document.

Resins (Cholestyramine, Colestipol)

Mechanism of Action

- The resins absorb bile acids in the intestine, prevent their reabsorption, and increase their excretion in the faeces.

- They do not increase the excretion of neutral steroids or cause fat malabsorption.
- The enhanced excretion of bile acids results in increased metabolism of cholesterol into bile acids and further in an increase in the number of LDL receptors and intake of cholesterol into hepatocytes.

Effectiveness

- Serum total and LDL cholesterol concentration decrease by 15 to 30%.
- Serum triglyceride concentration may increase slightly.

Dosage

Dosage recommendations can be found in the original guideline document.

Adverse Effects

- Bowel symptoms: constipation, flatulence, nausea, epigastric pain
- Deficiency of fat-soluble vitamins and folic acid

Interactions

- The absorption of the following drugs may be affected. These drugs should be taken at least 1 hour before or 4 hours after the resin.
    - Digoxin
    - Thyroxine
    - Warfarin
    - Thiazide diuretics

Guar Gum

Mechanism of Action

Guar gum is an unabsorbable dietary fibre, galactomannan. The mechanism of action is similar to that of resins. Guar gum also increases the excretion of neutral steroids in the faeces.

Effectiveness

- Serum total cholesterol and LDL cholesterol are decreased by 10 to15%. HDL and triglyceride concentration remain unchanged.
- Guar gum is a suitable alternative in hypercholesterolaemia associated with diabetes as a supplement to diet or in severe hypercholesterolaemia in combination with statins or fibrates.

Dosage

Dosage recommendations can be found in the original guideline document.

Adverse Effects

- Almost 30% of the patients have adverse effects.
- Abdominal distention, flatulence, diarrhoea

Fibrates (Gemfibrozil, Bezafibrate, and Fenofibrate)

Mechanism of Action

Fibrates act through the nuclear peroxisome proliferator-activated receptor (PPAR) system that regulates lipid metabolism.

Effectiveness

- Triglyceride concentration is decreased by 20 to 70%.
- HDL cholesterol is increased by 10 to 25%.
- LDL cholesterol is decreased if the initial concentration is high.

Adverse Effects

- Mild abdominal and bowel irritation
- Myalgia and an increase in serum creatine kinase concentration
- Possible formation of gallstones
- Increase in serum transaminase levels
- Retention of water, growth of mammary tissue, and impotence are rare.

Interactions

Protein-bound drugs are released and their concentrations are increased (warfarin, sulphonylureas).

Contraindications

Severe renal or hepatic dysfunction, diseases of the gallbladder

Dosage

Dosage recommendations can be found in the original guideline document.

Ezetimibe

For patients whose hypercholesterolemia cannot be treated with statin or when the effect is insufficient, ezetimibe is a good choice.

Mechanism of Action

- Prevents cholesterol from being absorbed in the small intestine.
- Effect is additive to statins which prevent cholesterol synthesis.

Effectiveness

- Alone diminishes the concentration of LDL cholesterol 18 to 19 %, triglycerides 4 to 11% and increases the concentration of HDL cholesterol 2 to 3%
- Combining ezetimibe with statin is additive and equals a large dose of statin in reducing cholesterol level.

Dosage

Dosage recommendations can be found in the original guideline document.

Side Effects

The studies conducted so far show little side effects.

Follow-up of a Patient on Cholesterol-lowering Drugs

- Lipid concentrations should be controlled after 1 to 2 months, then after 3 to 6 months, and thereafter annually, if necessary.
- Before changing the drug, wait for the effect for 3 to 6 months.
- Make sure that the target lipid levels are achieved (see the Finnish Medical Society Duodecim guideline "Treatment of Hyperlipidaemia: Aims and Selection").

Laboratory Tests

- Statins: serum alanine aminotransferase (ALT) should be determined after 1 to 2 months. A slight increase (ad 2 x) in serum ALT concentration is an indication for follow-up, not necessarily for discontinuation of the drug. If unexplained myalgia occurs, determine serum creatine kinase.
- Fibrates: ALT or aspartate aminotransferase (AST) and alkaline phosphatase are determined after 1 to 2 months, and thereafter at 6 to 12 month intervals. If used in combination with statins, ALT should be determined at 3 to 4 month intervals. If myalgia occurs, serum creatine kinase should always be examined.

Indications for Specialist Consultation

- Need for a drug combination
- A lipid disorder associated with another complicated disease
- Serum triglyceride concentration is primarily above 10 mmol/L or remains above 5 mmol/L despite treatments.
- Very high serum cholesterol concentration (above 15 mmol/L)
- Ischaemic heart disease or xanthomas occur in childhood or in adolescents or young adults.

Related Evidence

- There is little reduction in risk of ischaemic heart disease in the first two years after lowering cholesterol. Lowering serum cholesterol by 10% decreased the risk of coronary heart disease (CHD) by 54% at the age of 40, by 39% at the

age of 50, 27% at the age of 60, 20% at the age of 70, and 19% at the age of 80 (Law, Wald, & Thompson, 1994; DARE-948027, 1999) **[A]**.
- Lipid lowering by drugs, especially beta-hydroxy-beta-methylglutaryl-coenzyme A (HMG-CoA) inhibitors, is effective in patients with renal disease (Massy et al., 1995; DARE-951884, 1999) **[C]**.
- According to one systematic review, fluvastatin, micronized fenofibrate, and simvastatin were the most cost-effective drugs in reducing the total cholesterol/HDL ratio (Lacour, Derderian, & Lelolier, 1998; DARE-980618, 2000) **[C]**. However, the analysis is sensitive to changes in the cost of the drugs.
- Fenofibrate reduces serum triglycerides, total cholesterol, and LDL cholesterol (Guay, 1999; DARE-992121, 2002) **[A]**.
- Garlic appears to have small short-term benefits on lipid-lowering and antiplatelet factors (Ackermann et al, 2001; DARE-20018130, 2002; Agency for Healthcare Research & Quality (AHRQ), 2000; Health Technology Assessment Database: HTA-20010948, 2004) **[B]**.

Definitions:

Levels of Evidence

A. Strong research-based evidence. Multiple relevant, high-quality scientific studies with homogenic results.
B. Moderate research-based evidence. At least one relevant, high-quality study or multiple adequate studies.
C. Limited research-based evidence. At least one adequate scientific study.
D. No research-based evidence. Expert panel evaluation of other information.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Concise summaries of scientific evidence attached to the individual guidelines are the unique feature of the Evidence-Based Medicine Guidelines. The evidence summaries allow the clinician to judge how well-founded the treatment recommendations are. The type of supporting evidence is identified and graded for select recommendations (see the "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

General Potential Benefits

- Appropriate drug selection for the treatment of hyperlipidaemia
- Reduction of hyperlipidaemias
- Reduction in risk of death and major cardiovascular events

Specific Potential Benefits

- Statins are the most effective cholesterol-lowering agents for reducing cardiovascular and all-cause mortality. The greater effect of statins is likely due to the large reduction in cholesterol. Statin treatments for hypercholesterolemia reduce the risk of death and major cardiovascular events by 20 to 30%.
- Thyroid substitution in patients with subclinical hypothyroidism results in a modest (0.4 mmol/L) decrease in serum cholesterol level.

POTENTIAL HARMS

- *Statins*. Statins are usually well tolerated, even by elderly patients. Serum aminotransferase concentrations rise in about 2% of the patients. About 0.5% of patients who use statins develop myopathy. The risk of myopathy is increased by simultaneous treatment with cyclosporine, gemfibrozil, or nicotinic acid.
- *Resins*. Adverse effects include bowel symptoms (constipation, flatulence, nausea, epigastric pain) and deficiency of fat-soluble vitamins and folic acid. Interactions. The absorption of digoxin, thyroxine, warfarin, and thiazide diuretics may be affected. These drugs should be taken at least one hour before or four hours after the resin.
- *Guar gum*. Almost 30% of the patients have adverse effects, including abdominal distention, flatulence, and diarrhoea.
- *Fibrates*. Adverse effects include mild abdominal and bowel irritation, myalgia and an increase in serum creatine kinase concentration, eventual formation of gallstones, and an increase in serum transaminase levels. Retention of water, growth of mammary tissue, and impotence are rare.
  Interactions. Protein-bound drugs are released and their concentrations are increased (warfarin, sulphonylureas).

CONTRAINDICATIONS

CONTRAINDICATIONS

The use of fibrates is contraindicated for those with severe renal or hepatic dysfunction and diseases of the gall bladder.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Strandberg T, Vanhanen H. Drug treatment for hyperlipidaemias. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2004 Apr 22 [various]. [18 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2001 Apr 4 (revised 2004 Apr 22)

GUIDELINE DEVELOPER(S)

Finnish Medical Society Duodecim - Professional Association

SOURCE(S) OF FUNDING

Finnish Medical Society Duodecim

GUIDELINE COMMITTEE

Editorial Team of EBM Guidelines

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: Timo Strandberg; Hannu Vanhanen

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

Note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

GUIDELINE AVAILABILITY

This guideline is included in "EBM Guidelines. Evidence-Based Medicine" available from Duodecim Medical Publications, Ltd, PO Box 713, 00101 Helsinki, Finland; e-mail: info@ebm-guidelines.com; Web site: www.ebm-guidelines.com.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- EBM guidelines. Evidence-based medicine. Helsinki, Finland: Duodecim Medical Publications, Ltd. 2004. [CD-ROM]
- EBM guidelines. Web site: www.ebm-guidelines.com.

Available from: Duodecim Medical Publications, Ltd, PO Box 713, 00101 Helsinki, Finland; e-mail: info@ebm-guidelines.com; Web site: www.ebm-guidelines.com.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on March 16, 2001. The information was verified by the guideline developer as of June 15, 2001. The summary was updated by ECRI on August 17, 2001, December 9, 2002, December 29, 2003, and July 15, 2004. This summary was updated by ECRI on March 4, 2005, following the release of a public health advisory from the U.S. Food and Drug Administration regarding the use of revised labeling for the drug Crestor (rosuvastatin calcium).

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