Complete Summary

GUIDELINE TITLE

Drug treatment for hyperlipidaemias.

BIBLIOGRAPHIC SOURCE(S)

Finnish Medical Society Duodecim. Drug treatment for hyperlipidaemias. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2008 Jan 3 [Various]. [3 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: 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]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Primary hyperlipidemia
- Secondary hyperlipidaemia

GUIDELINE CATEGORY

Evaluation
Risk Assessment
Treatment

CLINICAL SPECIALTY

Cardiology
Endocrinology
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

Individuals with hyperlipidaemia, especially those with atherosclerotic disease or diabetes

INTERVENTIONS AND PRACTICES CONSIDERED

Drug Therapy

1. Antihyperlipidemic agents
    - Statins (hydroxy-methylglutaryl-coenzyme A [HMG-CoA] reductase inhibitors), such as lovastatin, pravastatin, simvastatin, atorvastatin, fluvastatin, rosuvastatin
    - Resins, such as cholestyramine, colestipol
    - Guar gum
    - Fibrates, such as gemfibrozil, bezafibrate, fenofibrate
    - Ezetimibe
2. Follow-up
    - Lipid levels
    - Patients on statins: alanine aminotransferase (ALT), creatine kinase in patients with myalgia
    - Patients on fibrates: ALT, creatine kinase in patients with myalgia
    - Referral for specialist consultation

MAJOR OUTCOMES CONSIDERED

- Reduction in lipid levels
- Incidence of myopathy and other side effects

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

Classification of the Quality of Evidence

Code	Quality of Evidence	Definition
A	**High**	Further research is very unlikely to change our confidence in the estimate of effect. • Several high-quality studies with consistent results • In special cases: one large, high-quality multi-centre trial
B	**Moderate**	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. • One high-quality study • Several studies with some limitations
C	**Low**	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. • One or more studies with severe limitations
D	**Very Low**	Any estimate of effect is very uncertain.

Code	Quality of Evidence	Definition
		• Expert opinion • No direct research evidence • One or more studies with very severe limitations

GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group 2007 (modified by the EBM Guidelines Editorial Team).

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

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

Basic Principles

- 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 the patient as if he 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; Ross et al., 1999) **[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, cholestyramine, gemfibrozil, simvastatin, pravastatin, lovastatin, atorvastatin, fluvastatin and fenofibrate have been tested in randomized double-blind trials lasting at least 3 years (Scandinavian Simvastatin Survival Study Group, 1994) [**A**].
- A statin is the drug of choice [**A**] unless the main abnormality is hypertriglyceridaemia or a low HDL cholesterol concentration. In these cases, even a fibrate may be considered.
- 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 (pheno)type	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 triglycerides <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 (Bucher, Griffith, & Guyatt, 1999; Ross et al., 1999) [**A**]

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 ezetimibe or resins (Schectman & Hiatt, 1996) [**C**] results in additive effects.

Adverse Effects

- Statins are usually well tolerated, even by elderly patients.
- Serum aminotransferase concentrations rise in about 2% of the patients. The clinical significance of this is unclear because the patients often have other factors that may increase the transaminase concentrations. There is no conclusive evidence that statin therapy would cause significant liver damage.
- 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

- Adjust the dose (Illingworth & Tobert, 1994; Hsu, Spinler, & Johnson, 1995) [**A**] according to response. Doubling the dose provides a further decrease of serum cholesterol by 7%.
- Atorvastatin:10 to 80 mg/day
- Fluvastatin: (20) to 40 to 80 mg/day
- Lovastatin: 20 to 80 mg
- Pravastatin: 20 to 40 mg/day
- Simvastatin: 10 to 80 mg
- Rosuvastatin: 10 to 40 mg/day

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

- Cholestyramine 16 to 32 g/day
- Cholestipol 20 to 40 g/day

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% to 15%. 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

- 5 g 2 to 5 times a day

Adverse Effects

- About 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

- Gemfibrozil: 600 to 1200 mg/day divided into 2 to 3 doses
- Bezafibrate: 400 mg x 1 at lunch
- Fenofibrate: 200 mg x 1 with meal

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

- 10 mg/day

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 1 to 2 months after the onset of therapy and thereafter usually once a year.
    - Concentrations greater than twice the upper limit of the reference range are clinically significant. A slight increase in serum ALT concentration is an indication for follow-up, not necessarily for discontinuation of the drug.
- If unexplained myalgia occurs, serum creatine kinase should be determined if necessary.

Fibrates

- Serum ALT is 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 (when combined with a fibrate, the statin dosage should be only half of the normal).
- 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 Resources

Refer to the original guideline document for related evidence, including Cochrane reviews and other evidence summaries.

Definitions:

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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 hyperlipidemia

POTENTIAL HARMS

Adverse Effects of Statins

- Serum aminotransferase concentrations rise in about 2% of the patients. The clinical significance of this is unclear because the patients often have other factors that may increase the transaminase concentrations. There is no conclusive evidence that statin therapy would cause significant liver damage.
- 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.

Adverse Effects of Resins

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

Adverse Effects of Guar Gum

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

Adverse Effects of Fibrates

- 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.

CONTRAINDICATIONS

CONTRAINDICATIONS

The use of fibrates is contraindicated in patients 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

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Finnish Medical Society Duodecim. Drug treatment for hyperlipidaemias. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2008 Jan 3 [Various]. [3 references]

ADAPTATION

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

DATE RELEASED

2001 Apr 4 (revised 2008 Jan 3)

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

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This guideline updates a previous version: 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 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

None available

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). This summary was updated by ECRI Institute on September 25, 2008.

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