# Guidelines

# For The Management of

# Dyslipidemia

By

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Setting Clinical and Professional Excellence

**Major changes for the new Guidelines for the management of dyslipidemia**
Introduction of the concept of cardiovascular age
Recommending more frequent monitoring of patients with FRS ≥ 5%
Using apolipoprotein B or non-HDL-C as alternate lipid markers
Addition of chronic kidney disease as a high-risk feature
Reduced age for treatment in diabetes
Specific recommendations about health behaviours
New recommendation about statin adverse effects
Use of GRADE recommendations and process

*ApoB:* apolipoprotein B*;   FRS:*Framingham Risk Score*;*
*GRADE:***G**rading of **R**ecommendations **A**ssessment, **D**evelopment and **E**valuation*;*

**Who to screen**
-Men ≥ 40 years of age, and women ≥ 50 years of age or postmenopausal
-All patients with any of the following conditions, regardless of age
*Current cigarette smoking •Diabetes •Arterial hypertension •Family history of premature CVD •Family history of hyperlipidemia • Clinical manifestation of hyperlipidemia •Clinical evidence of atherosclerosis or abdominal aneurysm •Obesity (body mass index > 27) •Erectile dysfunction •Chronic kidney disease• HIV infection •Chronic obstructive pulmonary disease •Inflammatory disease (rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel diseases.).*
It is recommended that a cardiovascular risk assessment, using the "10-Year Risk" provided by the FRS (Framingham Risk Score) be completed every 3-5 years for men age 40-75, and women age 50-75 years. This should be modified (percent risk doubled) when family history of premature CVD (first-degree relative <55 years for men and <65 years of age for women).
A risk assessment might also be completed whenever a patient's expected risk status changes. Younger individuals with at least 1 risk factor for premature CVD might also benefit from a risk assessment to motivate them to improve their lifestyle.

 It is recommended calculating and discussing a patient's Cardiovascular Age (*calculated as the patient's age minus the difference between his or her estimated remaining life expectancy {adjusted for coronary and stroke risk} and the average remaining life expectancy*) calculated concurrently with the adjusted FRS at [www.chiprehab.com](www.chiprehab.com) to improve the likelihood that patients will reach lipid targets and that poorly controlled hypertension will be treated.
For patients older than 75 years of age, the Framingham model is not well validated as clinical judgment is required in consultation with the patient to determine the value of pharmacotherapy.

**How to screen**

*For all*: History and examination, LDL, HDL, TG, non-HDL, glucose & HbA$_1$c, eGFR

*Optional*:  ApoB.

.                 Urine {albumin:creatinine} ratio (if eGFR < 60, hypertension, diabetes)

**\*Calculate non-HDL-C (total cholesterol minus HDL-C) in patients with triglycerides (200-500 mg/dL), diabetes mellitus, established CAD or if insulin resistance is suspected; as non HDL-C calculation will provide better risk assessment than LDL-C alone when triglycerides are  200 - 500 mg/dL.**

Triglyceride levels ≥200 mg/dL may indicate a substantial increase in CAD risk. Triglycerides levels that are even moderately elevated (**>150 mg/dL**) may identify individuals at risk for the insulin resistance syndrome.

**\*Optimal apo B levels for patients at risk of CAD, including those with diabetes, are less than 90 mg/dL, while patients with established CAD or diabetes who have 1 or more additional risk factor(s) should have an apo B goal of less than 80 mg/dL(Apo B reflects LDL particle number, which may be elevated in patients at or below LDL-C goal).**

**\* No recommendation for routine measurement of homocysteine, uric acid, plasminogen activator inhibitor 1, or other inflammatory markers because of unclear benefit of doing so.**

**\*Noninvasive measures of atherosclerosis such as *Graded exercise stress testing, Carotid ultrasound imaging, Ankle brachial index, Coronary artery calcium* should not be performed routinely, but may be used in certain conditions as adjuncts to standard CVD risk factors in an attempt to refine risk stratification and the need for more aggressive preventive strategies**

**Screening recommendations**

Screen for dyslipidemia in all adults up to age 75 years regardless of CAD risk status, and in adults older than age 75 years who have multiple CAD risk factors:

Framingham Risk Score < 5%   Repeat every 3-5 year

Framingham Risk Score ≥ 5%   Repeat every year

*Young Adults (≥20 Years of Age)*

Should be screened every 5 years as part of a global risk assessment.

More frequent assessments are warranted for those with CAD risk factors or a family history of premature CAD (definite MI or sudden death before age 55 years in father or other first-degree male relative, or before age 65 years in mother or other first-degree female relative). All young adults with diabetes should be screened annually.

*Middle-Aged Adults (Men ≥45 Years of Age; Women ≥55 Years of Age)*

Should be screened every 1-2 years even when no CAD risk factors are present.

More frequent lipid testing is recommended when multiple CAD risk factors are present.

All patients with diabetes should be screened at least annually.

*Older Adults (65 Years of Age, both sexes)*
Those with 0 -1 CAD risk factor should be screened annually.
More frequent lipid assessment should be done if they have risk factors other than age.
Treatment to lower lipid levels and attenuate atherosclerosis may potentially decrease stroke and transient ischemic attack incidence in this population.

*Children and Adolescents*
Fasting lipid profile should be offered to children older than 2 years who have:
- CAD risk factors (besity -central adiposity and/or elevated body mass index, insulin resistance, diabetes, hypertension, cigarette smoking)
- Family history of CAD or dyslipidemia
- Children for whom family history is not known;
these patients should be rescreened every 3-5 years.
In all adolescents older than 16 years, screening should be repeated every 5 years or more frequently for patients with CAD risk factors or a family history of CAD.
Important points considered when interpreting lipid profiles in children & adolescents:
• Lipid levels fluctuate during childhood and adolescence. While plasma cholesterol levels normally peak before puberty (age 8-11 years), they often decline profoundly during puberty, along with HDL-C values
• Low HDL-C may not have the same implications in children as it does in adults.
More than 50% of children with low HDL-C levels have normal HDL-C levels as adults. Furthermore, low HDL-C values do not constitute a hallmark of the insulin resistance syndrome as obesity & hypertriglyceridemia are the best predictors of this condition in children
• Lipid levels vary by sex. Throughout childhood and adolescence, plasma cholesterol levels tend to be higher in girls than in boys
• Intervention is indicated for those with borderline (110-129 mg/dL) or high (≥130 mg/dL) LDL-C values, abnormal pediatric HDL-C and triglyceride levels as less than 35 mg/dL and greater than 150 mg/dL, respectively
• Lifestyle changes be implemented for at least 6-12 months before considering drug therapy
• Pharmacotherapy to achieve LDL-C levels less than 130 mg/dL for children ≥8 years who do not respond sufficiently to lifestyle modification, if they have:
  ➢ LDL-C ≥190 mg/dL or
  ➢ LDL-C ≥160 mg/dL and
        ♦ 2 or more cardiovascular risk factors, even after vigorous intervention or
        ♦ A family history of premature CAD (before 55 years of age) or
        ♦ Overweight, obese, or other elements of the insulin resistance syndrome

**Levels of Risk**

*Low Risk   LR*

Involves individuals with a adujusted FRS <10%

Pharmacologic treatment is recommended if they have severe dyslipidemia
(LDL-C > 5.0 mmol/L: 195mg/dL) or if there is evidence of genetic dyslipidemia .

The goal is to have ≥ 50% reduction of LDL-C as this 50% reduction (which is achievable with single-agent therapy with moderate to high doses of the most widely prescribed statins) is associated with approximately a 40% reduction in major cardiovascular events.

*Intermediate risk   IR*

Involves individuals with adjusted FRS ≥ 10% -20%

The main lipid trigger for treatment is LDL-C ≥ 3.5 mmol/L:136.5mg/dL.

Every 1.0 mmol/L: 39mg/dL reduction in LDL-C is associated with a corresponding 20-25% reduction in CVD mortality and nonfatal myocardial infarction (MI).

Pharmacologic therapy is recommended after initiation and compliance with health behaviour modifications among individuals with LDL-C that remains ≥ 3.5 mmol/L:136.5mg/dL

Pharmacologic therapy for IR patients with LDL-C <3.5 mmol/L:136.5mg/dL is not routinely recommended because of the smaller estimated absolute benefit of therapy, unless there is  atherogenic dyslipidemia as reflected by high plasma apo B ≥ 120 mg/dL &/or non-HDL-C  ≥ 4.3 mmol/L:167.7.5mg/dL as they have increased CVD risk.

When treatment is initiated in IR patients, the primary target is LDL-C ≤ 2.0 mmol/L: 78mg/dL or ≥ 50% reduction of LDL-C from untreated baseline.

Alternate targets include apo B ≤ 80 mg/dL or non-HDL-C ≤ 2.6 mmol/L: 101.4 mg/dL.

Though high-sensitivity C-reactive protein (hsCRP) is not believed to be causative in the development of atherosclerosis but any man > 50 years and women > 60 years of age & CRP ≥ 2 mg/L & LDL <3.5 mmol/L:136.5mg/dL could be considered for treatment.

*High risk   HR*

Individuals are considered to be at high risk of major ischemic cardiovascular events and thus to have principle greatest absolute benefit from pharmacotherapy with statins if they have FRS of  ≥ 20% or regardless FRS level and having:

1. Clinical evidence of atherosclerosis, previous MI, coronary revascularization by (PCI or CABG) or other arterial revascularization procedures.

2. Cerebrovascular disease including transient ischemic attack, or peripheral arterial disease.

3. Abdominal aortic aneurysm (because atherosclerosis is the primary aetiology of this type of aneurysm).Thoracic aortic aneurysm is more frequently associated with medial degeneration than atherosclerosis, and risk estimation in this type of aneurysm should be based on the presence of other risk modifiers rather than the aneurysm itself.

4. Type 1 or type 2 diabetes mellitus in any patient older than 40 years of age, or younger

patients with diabetes of more than 15 years duration or with documented silent or clinically apparent CVD or microvascular complications.

5. Chronic renal disease:  eGFR ≤ 45 mL/min/1.73 m$^2$ or albumin:creatinine ratio (ACR) of ≥ 30 mg/mmol (≥ 300 mg/day).

Those with an eGFR ≤ 60 mL/min/1.73 m$^2$ and an ACR of ≥ 3 mg/mmol are also at risk.

6. Hypertension plus 3 of the following risk factors:

male, age > 55 years, smoking, total cholesterol/HDL-C ratio > 6, left ventricular hypertrophy, family history of premature CVD, electrocardiogram (ECG) abnormalities, or microalbuminuria.

## Secondary Testing in Risk Stratification

For patients who do not exhibit significant dyslipidemia (LDL-C <3.5 mmol/L:136.5mg/dL,  apo B <120 mg/dL, or non-HDL-C <4.3 mmol/L:167.7mg/dL); it might be unclear whether to offer or withhold therapy when the adjusted FRS falls between 5%-19%.

Secondary testing might be considered in such patients to help decision-making regarding the need for lipid lowering agents.

Secondary testing is not recommended in patients with FRS risk >20% or risk <5%.

## Health Behaviours

1. Moderate caloric intake to achieve and maintain a healthy body weight

2. Emphasize a diet rich in vegetables, fruit, whole-grain cereals, polyunsaturated and monounsaturated oils, including Ω-3 fatty acids particularly from fish

3. Avoid trans fats, limit cholesterol intake to 200 mg daily, limit saturated and total fats to <7% and <30% of daily total caloric intake, respectively & increase vegetable oils and nut.

4. Increase daily fiber intake to > 30 g.

6. Adults should accumulate at least 150 minutes of moderate-to-vigorous intensity aerobic physical activity per week, in bouts of 10 minutes or more to reduce CVD risk

7. Smoking cessation and limiting alcohol intake to 30 g or less per day (1-2 drinks).

## Pharmacologic Therapy

- Statins as the drug of choice for LDL-C reduction
- Fibrates for treatment of severe hypertriglyceridemia (triglycerides >500 mg/dL)
- 2-4 g of omega 3 fish oil can be used to achieve satisfactory triglyceride lowering.

## Combination therapy

Considered in the following circumstances:

• Cholesterol level is markedly increased and monotherapy does not achieve targets.

• When mixed dyslipidemia is present

• To reduce the risk of dosage-related adverse effects

**Pharmacologic therapy in young age**

*Statins ( atorvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin) are considered safe and effective medication for the treatment of dyslipidemia in pediatric patients & have been approved for the treatment of familial hypercholesterolemia in patients 10 years or older with no significant effects on growth, hormonal, or nutritional status.

*Cholestyramine is currently approved for the treatment of hypercholesterolemia in children. The efficacy and safety of colestipol and colesevelam have not yet been established in pediatric populations. However, colesevelam is approved for children older than 8 years. Therapy should be initiated at low dosages (<8 g daily of cholestyramine or <10 g daily of colestipol) regardless of body weight. Because bile acid sequestrant treatment may lead to nutrient depletion (eg, folic acid and cholecalciferol) in children, multivitamin supplementation should be used.

*Fibrates may be useful in children with severely elevated triglyceride levels and an increased risk of pancreatitis

*Ezetimibe may be prescribed in patients 10-18 years of age BUT not recommended for children younger than 10 years

*Niacin must be used cautiously in pediatric populations because of a lack of safety and tolerance data and the potential for adverse effects.

**Statins**

1. Statins are not contraindicated in patients with mild to moderate elevations in ALT because of hepatic steatosis, chronic hepatitis C, or primary biliary cirrhosis.

2. It is recommended that practitioners no longer use the simvastatin 80 mg dose because of the increased risk of myopathy. Most of this risk has been seen with concomitant use of amiodarone, diltiazem, and amlodipine. With amlodipine, simvastatin should not exceed 20 mg; and it should not exceed 10 mg if amiodarone, verapamil, or diltiazem are being used. Simvastatin should not be used at all with antifungal agents, gemfibrozil, cyclosporine, or the macrolide antibiotics.

3. Vitamin D deficiency is a cause of myopathy and unrecognized, mild deficiencies might represent a rare but potentially reversible cause of statin-associated myalgia or myositis.

4. Alternate day statin therapy can sometimes be useful to reduce side effects and increase compliance.

5. Statins are known to be teratogenic (pregnancy category X); however other medications such as fibrates (pregnancy category C) or colesevelam (pregnancy category B) may be more appropriate

**Target of treatment**

*Current evidence indicates that LDL-C can be aggressively lowered with statin therapy regardless of baseline levels and suggests that there is no threshold below which LDL-C

lowering ceases to be effective.

*The target for most high risk individuals: LDL-C of ≤2.0 mmol/L: 78mg/dL or in patients in whom therapy is limited by drug intolerance and who fail to achieve this level, a 50% or greater reduction of LDL-C from baseline is recommended.

In some individuals with recurrent vascular disease or very high risk on the basis of established vascular disease and multiple major coronary risk factors, an LDL-C target of <1.8 mmol/L:70.2 mg/dL is justified.

*It is recommended for those using the alternate targets for high risk patients is that pharmacotherapy be used to achieve non-HDL-C ≤2.6 mmol/L:101.4mg/dL & apo B ≤ 80 mg/dL.

*Patients for whom aggressive therapy is recommended:
• Patients undergoing coronary artery bypass graft.
• Patients with acute coronary syndrome.
• Certain healthy and functional older patients at high risk who may be appropriate candidates.


**Follow-up and Monitoring**

Reassessing patients' lipid status 6 weeks after therapy initiation and again at 6-week intervals until the treatment goal is achieved, thereafter; patients are tested at 6-12month intervals.

The specific interval should depend on patient adherence to therapy and lipid profile consistency. If adherence is a concern or the lipid profile is unstable, the patient will probably benefit from biannual assessment.

More frequent lipid status evaluation in the following clinical circumstances:
• Deterioration of diabetes control.
• The use of a new drug known to affect lipid levels.
• Progression of atherothrombotic disease.
• Considerable weight gain.
• An unexpected adverse change in any lipid parameter.
• Development of a new CAD risk factor.
• Convincing new clinical trial evidence or guidelines that suggest stricter lipid goals.


Liver transaminase level be measured before and 3 months after statin & fibric acid treatment initiation, because most liver abnormalities occur within 3 months of treatment initiation. This test be repeated periodically (eg, semiannually).

Patients taking niacin have transaminase levels measured at baseline and every 3 months thereafter *for the first year*, followed by periodic (eg, semiannual) assessment.

Liver transaminase level assessment should be repeated at these intervals whenever lipid-altering therapy is restarted, increased, changed, or combined.

Assessment of creatine kinase levels whenever a patient reports clinically significant myalgias or muscle weaknes.

*To convert mmol/l of total cholesterol, HDL or LDL cholesterol to mg/dl, multiply by 39*
*To convert mmol/l of triglycerides to mg/dl, multiply by 89*

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**Who to screen**

Men ≥ 40 years of age, and women ≥ 50 years of age or postmenopausal
Or
All patients with any of the following conditions, regardless of age:

| | |
|---|---|
| • Current cigarette smoking<br>• Diabetes<br>• Arterial hypertension<br>• Family history of premature CVD<br>• Family history of hyperlipidemia<br>• Erectile dysfunction<br>• Chronic kidney disease | • Inflammatory disease<br>• HIV infection<br>• Chronic obstructive pulmonary disease<br>• Clinical evidence of atherosclerosis or abdominal aneurysm<br>• Clinical manifestation of hyperlipidemia<br>• Obesity (body mass index > 27 |

**How to screen**

**For all:**
history and examination,
LDL, HDL, TG, non-HDL (Will be calculated from profile), glucose, eGFR

**Optional:**
apoB (instead of standard lipid panel),
urine albumin: creatinine ratio (if eGFR<60, hypertension, diabetes)

Framingham Risk score <5%
Repeat every 3-5 years

Framingham Risk score >5%
Repeat every year
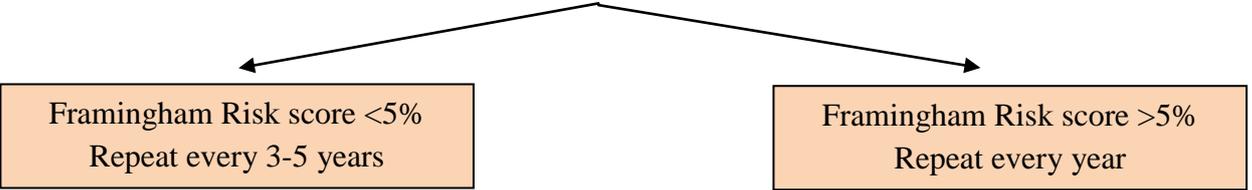
**Target Levels for Treatment**

| Risk level | Initiate therapy if | Primary target LDL C | Alternate target |
|---|---|---|---|
| High<br>FRS $\geq$ 20% | Consider treatment in all | $\leq$ 2 mmoI/L   or<br>$\geq$ 50% decrease in LDL-C | Apo B $\leq$ 80 mg/dL<br>No HDL-C $\leq$ 2.6 mmol/L |
| Intermediate<br><br>FRS<br>10%-19% | LDL-C $\geq$ 3.5 mmol/L<br>For LDL-C < 3.5 mmol/L consider if:<br> Apo B $\geq$ 120 mg/dL or<br>Non-HDL-C$\geq$ 4.3 mmol/L | $\leq$ 2 mmol/L or $\geq$ 50% decrease in LDL-C | Apo B $\leq$ 80 mg/dL<br>Non HDL-C $\leq$ 2.6 mmol/L |
| Low<br>FRS < 10% | LDL-C $\geq$ 5.0 mmol/L<br>Familial hypercholesterolemia | $\geq$ 50% reduction in LDL-C | |

Stratify by Risk

**Low Risk**
- No high risk features
- FRS <10%

**Intermediate Risk**
- No high risk features
- FRS 10%-19%

**High Risk**
- FRS ≥ 20%
- Clinical vascular disease
- Abdominal Aortic Aneurysm
- Diabetes and age ≥40 yrs or > 15yrs duration and age≥30 yrs or microvascular disease*
- Chronic kidney disease
- High risk hypertension

LDL< 5 mmol/L

LDL ≥ 5 mmol/L

FRS < 5%

FRS 5% -90

Health behavior modification
No statin therapy

Optional secondary testing
Indicates higher risk
NO          YES

Health behavior modification
Statin therapy

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                    ┌─────────────────────────┐
                    │  Intermediate Risk      │
                    │  • No high risk features│
                    │  • FRS 10-19%           │
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| | |
|---|---|
| LDL ≥ 3.5 mmol/L | LDL < 3.5 mmol/L |

| Apo B ≥ 1.2 g/L | Non-HDL-C ≥ 4.3 |
|---|---|

| Health behaviour modification | If yes to either | If no |
|---|---|---|
| statin therapy | | |

| Optional secondary testing Indicates higher risk | Health behaviour modification |
|---|---|
| Yes                    No | No statin therapy |