DYSLIPIDEMIA GUIDELINES

2012 Update

DYSLIPIDEMIA

Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult

For more information, please see the CCS Dyslipidemia Guidelines at www.ccsguidelineprograms.ca.

Canadian Cardiovascular Society
Leadership. Knowledge. Community.

DYSLIPIDEMIA GUIDELINES

About This Pocket Guide

This pocket guide is a quick-reference tool that features essential diagnostic and treatment recommendations based on the 2009 CCS Dyslipidemia Guidelines and the 2012 CCS Dyslipidemia Guidelines Update.

These recommendations are intended to provide a reasonable and practical approach to care for specialists and allied health professionals with the duty of bestowing optimal care to patients and families. They are subject to change as scientific knowledge and technology advance and practice patterns evolve. The guidelines are not intended to be a substitute for physicians using their judgement in managing clinical care in consultation with the patient, with appropriate regard to the individual circumstances of the patient, diagnostic and treatment options and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

For the complete CCS Guidelines for the Diagnosis and Treatment of Dyslipidemia, or for additional resources, please visit our guidelines website at www.ccsguidelineprograms.ca.

2012 Update of the Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult

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Major Changes Since 2009 Guidelines

2012 Update

• Use of GRADE system for scoring grading recommendations	
• Introduction of the concept of cardiovascular age	(pages 10, 12-15)
• Recommendation for more frequent monitoring in patients with FRS ≥5%	(page 9)
• Apo B or non-HDL-C as alternate lipid markers	(pages 17-19)
• Chronic kidney disease as a high-risk feature	(page 18)
• Reduced age for treatment in diabetes	(page 18)
• Specific recommendations on health behaviours	(page 24)
• New recommendation on statin adverse effects	(page 28)

Apo B: apolipoprotein B; FRS: Framingham Risk Score; GRADE: Grading of Recommendations Assessment, Development and Evaluation; non-HDL-C: non-high-density lipoprotein cholesterol.

Guiding Principles

Who to Screen

- Men ≥40 years of age
- Women ≥50 years of age or postmenopausal
- Consider earlier in ethnic groups at increased risk

- All patients with the following conditions, regardless of age:
  - Current cigarette smoking
  - Diabetes
  - Arterial hypertension
  - Family history of premature CVD
  - Family history of hyperlipidemia
  - Erectile dysfunction
  - CKD
  - Inflammatory disease
  - HIV infection
  - COPD
  - Clinical evidence of atherosclerosis or abdominal aneurysm
  - Clinical manifestations of hyperlipidemia
  - Obesity (BMI >27 kg/m^2)

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How to Screen (every 3-5 years, or every year for adjusted FRS 5-10%)

- For all:
  - History and examination
  - Non-HDL (will be calculated from profile: TC - HDL=non-HDL)
  - LDL
  - HDL
  - TG
  - Glucose
  - eGFR
- Optional:
  - Apo B (instead of standard lipid panel)
  - Urine ACR (if eGFR <60 mL/min/1.73m^2, hypertension or diabetes)

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Stratify by Risk Features
FRS & Cardiovascular Age

See Pages 10-15

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

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Initiate therapy if:
- LDL-C ≥5.0 mmol/L
- OR genetic dyslipidemia

Primary ***target***:
- 50% ↓ in LDL-C

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

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Initiate therapy if:
- LDL-C ≥3.5 mmol/L
- OR apo B ≥1.2 g/L or non-HDL-C ≥4.3 mmol/L

Primary ***target***:
- LDL-C ≤2 mmol/L or 50% ↓

Alternate ***target***:
- Apo B ≤0.8 g/L
- Non-HDL-C ≤2.6 mmol/L

High-Risk FRS ≥20% or:
- Clinical atherosclerosis
- Abdominal aortic aneurysm
- CKD
- High-risk hypertension
- Diabetes* and:
  - Age ≥40
  - OR >15 years duration and age ≥30
  - OR microvascular disease

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- Consider treatment in all

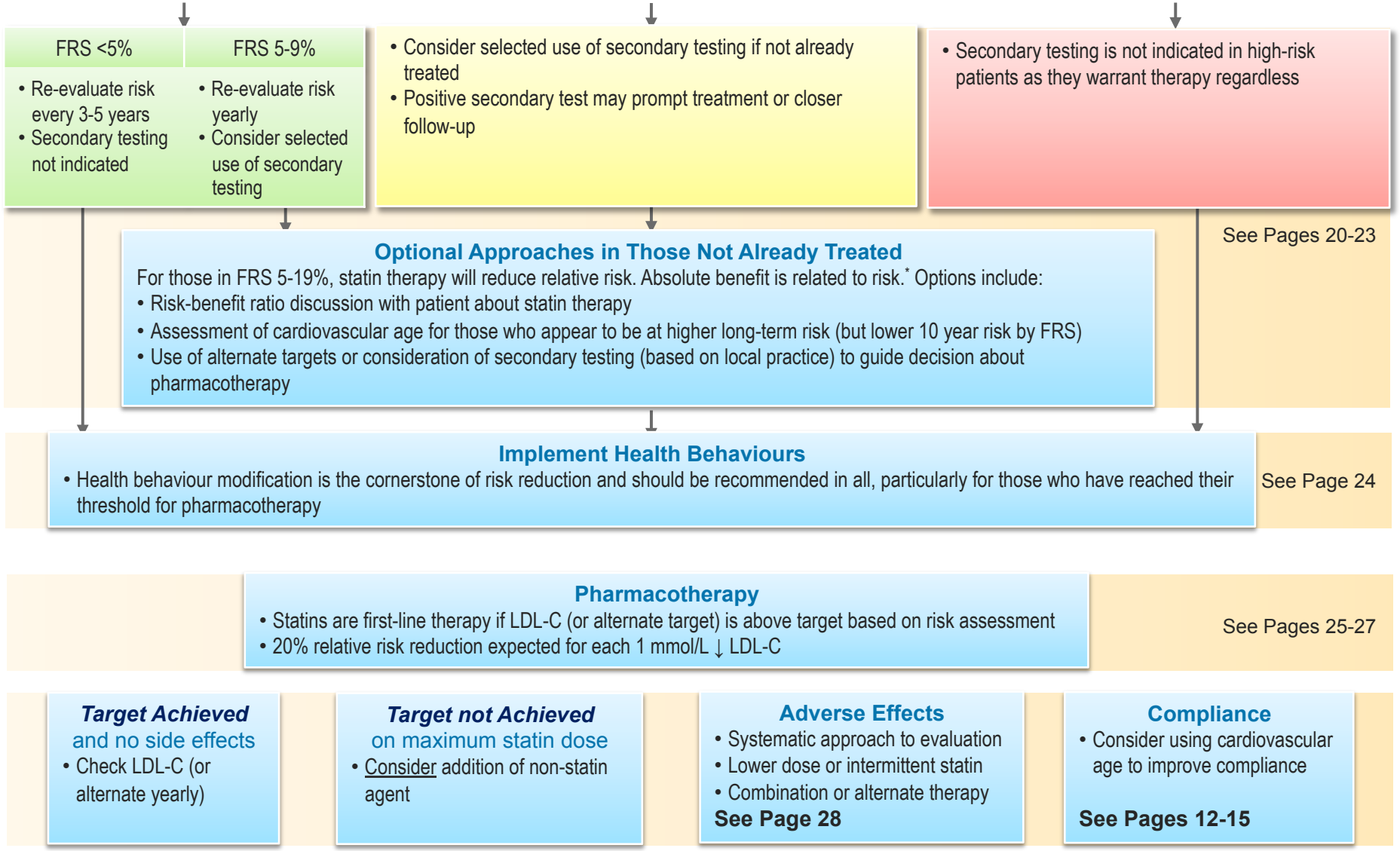
Primary ***target***:
- LDL-C ≤2 mmol/L or 50% ↓

Alternate ***target***:
- Apo B ≤0.8 g/L
- Non-HDL-C ≤2.6 mmol/L

*Not all subjects with diabetes are at high 10-year risk, included for treatment based on randomized studies and high long-term risk.

ACR: albumin:creatinine ratio; Apo B: apolipoprotein B; BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; FRS: Framingham Risk Score; HDL: high-density lipoprotein; HIV: human immunodeficiency virus; LDL: low-density lipoprotein; LDL-C: low-density lipoprotein cholesterol; non-HDL: non-high-density lipoprotein; non-HDL-C: non-high-density lipoprotein; cholesterol TC: total cholesterol; TG: triglycerides.

Guiding Principles



*Greater benefit for those at higher risk.
FRS: Framingham Risk Score; LDL-C: low-density lipoprotein cholesterol.

Target Patients for Lipid Screening

Who to Screen

- Men ≥40 years of age
- Women ≥50 years of age, or who are postmenopausal

Consider screening earlier in ethnic groups at increased risk (South Asian or First Nations individuals)

- 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
  - Erectile dysfunction
  - Chronic kidney disease†
  - Inflammatory disease‡
  - HIV infection
  - Chronic obstructive pulmonary disease
  - Clinical evidence of atherosclerosis or abdominal aneurysm
  - Clinical manifestation of hyperlipidemia‖
  - Obesity (body mass index >27 kg/m^2¶)

*First-degree relative aged <55 years in men and <65 years in women;
†eGFR ≤60 mL/min/1.73m^2 or urinary ACR ≥3 mg/mmol;
‡Such as: rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, ankylosing spondylitis and inflammatory bowel disease;
‖Xanthomas, xanthelasmas or premature arcus cornealis;
¶Or metabolic syndrome, pre-diabetes or polycystic ovarian syndrome.
ACR: albumin:creatinine ratio; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; HIV: human immunodeficiency virus.

Lipid Screening

How to Screen

For all patients

- History and examination
- LDL
- HDL
- TG
- Non-HDL (will be calculated from profile: TC - HDL=non-HDL)
- Glucose
- eGFR

Optional

- Apo B (instead of standard lipid panel)
- Urine albumin:creatinine ratio (if eGFR <60 mL/min/1.73m^2, hypertension or diabetes)

Framingham Risk Score <5%

Repeat every 3-5 years

2012 Update — Framingham Risk Score ≥5%

Repeat every year

Apo B: apolipoprotein B; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; Non-HDL: non-high-density lipoprotein; TC: total cholesterol; TG: triglyceride.

Risk Assessment

Recommendations

Framingham Risk Score (FRS), using "10-Year Risk"

- Every 3-5 years
  - Men aged 40-75
  - Women aged 50-75
- Double percent risk for family history of premature CVD (i.e. first-degree relative aged <55 for men or <65 for women) - a.k.a. modified FRS
- Risk assessment might also be completed whenever a patient's expected risk status changes
- Younger individuals with one or more risk factors for premature CVD might also benefit from a risk assessment to motivate them to improve their lifestyle

Strong Recommendation, Moderate-quality Evidence

Practical tip:

- For patients >75 years of age, the FRS is not well validated
- Clinical judgement is required in consultation with the patient to determine the value of pharmacotherapy
- One approach is extrapolation of modified FRS – identifies most subjects as intermediate- to high-risk, based on age

2012 Update

Cardiovascular age

- Calculate and discuss a patient's Cardiovascular Age to improve the likelihood they will reach lipid targets and that poorly controlled hypertension will be treated

Strong Recommendation, High-quality Evidence

Values and preferences

- Primary evaluation of risk is modified 10-year FRS
- Simultaneous evaluation of cardiometabolic risk for diabetes might be useful to motivate lifestyle changes (considering the overlap in risk factors with FRS)
- 10-year risk does not fully account for risk in younger individuals – calculation of Cardiovascular Age has been shown to motivate subjects to achieve risk factor targets

CVD: cardiovascular disease.

Framingham Risk Score Estimation of 10-year Cardiovascular Disease Risk

Step 1 In the "points" column enter the appropriate value according to the patient's age, HDL-C, total cholesterol, systolic blood pressure and if they smoke or have diabetes. Calculate the total points.

Step 2 Using the total points from Step 1, determine the 10-year CVD risk %.

Step 3 For subjects between 30 and 59 years – double cardiovascular disease risk percentage if cardiovascular disease is present in a first degree relative before 55 years of age for men and 65 years of age for women.

Step 1

Risk factor		Risk points				Points
		Men		Women		
Age						
30-34		0		0		
35-39		2		2		
40-44		5		4		
45-49		6		5		
50-54		8		7		
55-59		10		8		
60-64		11		9		
65-69		12		10		
70-74		14		11		
75+		15		12		
HDL-C (mmol/L)						
>1.6		-2		-2		
1.3-1.6		-1		-1		
1.2-1.3		0		0		
0.9-1.2		1		1		
<0.9		2		2		
Total cholesterol (mmol/L)						
<4.1		0		0		
4.1-5.2		1		1		
5.2-6.2		2		3		
6.2-7.2		3		4		
>7.2		4		5		
Systolic blood pressure (mmHg)		**Not treated**	**Treated**	**Not treated**	**Treated**	
<120		-2	0	-3	-1	
120-129		0	2	0	2	
130-139		1	3	1	3	
140-149		2	4	2	5	
150-159		2	4	4	6	
160+		3	5	5	7	
Diabetes	Yes	3		4		
	No	0		0		
Smoker	Yes	4		3		
	No	0		0		
Total points						

Step 2

Total points	10-year CVD risk (%)	
	Men	Women
-3 or less	<1.0	<1.0
-2	1.1	<1.0
-1	1.4	1.0
0	1.6	1.2
1	1.9	1.5
2	2.3	1.7
3	2.8	2.0
4	3.3	2.4
5	3.9	2.8
6	4.7	3.3
7	5.6	3.9
8	6.7	4.5
9	7.9	5.3
10	9.4	6.3
11	11.2	7.3
12	13.3	8.6
13	15.6	10.0
14	18.4	11.7
15	21.6	13.7
16	25.3	15.9
17	29.4	18.51
18	>30	21.5
19	>30	24.8
20	>30	27.5
21+	>30	>30

Can be calculated concurrently with adjusted Cardiovascular Age at: www.chiprehab.com

For mobile device applications from the CCS, please visit: www.ccsguidelineprograms.ca or www.ccs.ca

HDL-C: high-density lipoprotein cholesterol.

Cardiovascular Age – Males Without Diabetes

2012 Update

Blood pressure (mmHg)	Non-smokers Total cholesterol:HDL ratio						Smokers Total cholesterol:HDL ratio						Blood pressure (mmHg)
	3	4	5	6	7		3	4	5	6	7		
120/80	28.1	28.4	28.9	29.5	30.2	Age 30	33.1	33.7	34.7	35.7	36.8	120/80	
130/85	29.1	29.4	30.0	30.8	31.5		34.2	34.9	36.0	37.1	38.3	130/85	
140/90	30.0	30.4	31.2	32.0	32.9		35.3	36.0	37.3	38.5	39.7	140/90	
150/95	31.0	31.4	32.3	33.2	34.2		36.4	37.2	38.5	39.8	41.1	150/95	
120/80	37.3	37.6	38.1	38.8	38.5	Age 40	42.2	42.8	43.8	44.8	45.9	120/80	
130/85	38.2	38.6	39.2	40.0	40.8		43.3	43.9	45.1	46.2	47.3	130/85	
140/90	39.2	39.6	40.3	41.2	42.1		44.3	45.1	46.3	47.5	48.7	140/90	
150/95	40.1	40.6	41.5	42.4	43.4		45.4	46.2	47.5	48.8	50.0	150/95	
120/80	47.1	47.3	47.9	48.5	49.2	Age 50	51.7	52.3	53.2	54.2	55.1	120/80	
130/85	47.9	48.3	48.9	49.6	50.4		52.7	53.3	54.4	56.4	56.4	130/85	
140/90	48.8	49.2	50.0	50.8	51.7		53.7	54.4	55.5	56.6	57.6	140/90	
150/95	49.7	50.2	51.0	51.9	52.9		54.6	55.4	56.6	57.7	58.7	150/95	
120/80	57.4	57.6	58.1	58.6	59.2	Age 60	61.5	62.0	62.7	63.5	64.3	120/80	
130/85	58.2	58.5	59.0	59.6	60.3		62.4	62.9	63.7	64.5	65.3	130/85	
140/90	59.0	59.3	60.0	60.6	61.4		63.2	63.8	64.6	65.4	66.2	140/90	
150/95	59.8	60.2	60.9	61.6	62.4		64.0	64.6	65.5	66.2	66.9	150/95	
120/80	68.2	68.4	68.7	69.1	69.5	Age 70	71.4	71.7	72.2	72.7	73.2	120/80	
130/85	68.8	69.0	69.4	69.9	70.3		72.1	72.4	72.9	73.4	73.9	130/85	
140/90	69.5	69.7	70.1	70.6	71.1		72.7	73.0	73.6	74.0	74.4	140/90	
150/95	70.1	70.4	70.8	71.3	71.8		73.3	73.6	74.1	74.5	74.9	150/95	

Cardiovascular Age= Patient's Age – (Estimated Remaining Life Expectancy* – Canadian† Average Remaining Life Expectancy)

Can be calculated concurrently with adjusted FRS at: www.chiprehab.com

Legend	
	≤Actual age
	>Actual age & <Actual age + 5 years
	≥Actual age + 5 years

*Adjusted for coronary and stroke risk;
†For Canadians of the same age and sex as the patient.
FRS: Framingham Risk Score;
HDL: high-density lipoprotein.

Cardiovascular Age – Males With Diabetes

2012 Update

Blood pressure (mmHg)	Non-smokers Total cholesterol:HDL ratio						Smokers Total cholesterol:HDL ratio						Blood pressure (mmHg)
	3	4	5	6	7		3	4	5	6	7		
120/80	33.3	33.7	34.3	35.0	35.8	Age 30	38.4	39.1	40.1	41.1	42.1	120/80	
130/85	34.3	34.7	35.4	36.2	37.1		39.5	40.2	41.3	42.4	43.4	130/85	
140/90	35.3	35.7	36.6	37.5	38.4		40.6	41.3	42.5	43.6	44.7	140/90	
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120/80	61.6	61.9	62.4	62.9	63.5	Age 60	65.4	65.9	66.5	67.1	67.6	120/80	
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140/90	63.1	63.5	64.1	64.7	65.4		66.9	67.3	67.9	68.5	69.0	140/90	
150/95	63.8	64.2	64.9	65.6	66.2		67.5	67.9	68.5	69.1	69.6	150/95	
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130/85	72.1	72.4	72.7	73.1	73.5		74.9	75.1	75.5	75.8	76.1	130/85	
140/90	72.7	72.9	73.3	73.7	74.1		75.3	75.5	75.9	76.2	76.5	140/90	
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Cardiovascular Age – Females Without Diabetes

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150/95	30.9	31.2	31.7	32.2	32.8		35.0	35.9	36.9	38.1	39.4	150/95	
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Cardiovascular Age – Females With Diabetes

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140/90	39.8	40.4	41.2	42.2	43.2		44.5	45.9	47.5	49.1	50.7	140/90	
150/95	40.6	41.3	42.3	43.4	44.5		45.5	47.1	48.8	50.5	52.0	150/95	
120/80	47.2	47.6	48.2	48.9	49.6	Age 40	51.3	52.4	53.6	54.8	56.2	120/80	
130/85	47.9	48.5	49.2	50.0	50.9		52.3	53.5	54.9	56.3	57.7	130/85	
140/90	48.7	49.4	50.2	51.1	52.1		53.2	54.6	56.2	57.7	59.3	140/90	
150/95	49.5	50.2	51.2	52.3	53.4		54.2	55.8	57.5	59.1	60.5	150/95	
120/80	56.3	56.7	57.2	57.8	58.4	Age 50	60.0	60.9	61.9	62.9	64.0	120/80	
130/85	57.0	57.4	58.1	58.8	59.5		60.8	61.9	63.0	64.1	65.3	130/85	
140/90	57.6	58.2	59.0	59.8	60.7		61.7	62.8	64.1	65.3	66.5	140/90	
150/95	58.4	59.0	59.9	60.8	61.8		62.5	63.8	65.1	66.4	67.5	150/95	
120/80	65.3	65.6	66.0	66.4	66.9	Age 60	68.4	69.0	69.6	70.3	71.0	120/80	
130/85	65.9	66.2	66.7	67.2	67.8		69.0	69.7	70.4	71.1	71.8	130/85	
140/90	66.5	66.9	67.4	68.0	68.6		69.7	70.4	71.2	71.9	72.6	140/90	
150/95	67.1	67.6	68.1	68.8	69.4		70.3	71.1	71.9	72.6	73.3	150/95	
120/80	74.3	74.4	74.6	74.9	75.2	Age 70	76.5	76.8	77.1	77.5	77.8	120/80	
130/85	74.7	74.9	75.2	75.4	75.7		76.9	77.3	77.6	78.0	78.3	130/85	
140/90	75.1	75.4	75.7	76.0	76.3		77.4	77.7	78.1	78.4	78.7	140/90	
150/95	75.6	75.8	76.1	76.5	76.8		77.8	78.1	78.5	78.8	79.1	150/95	

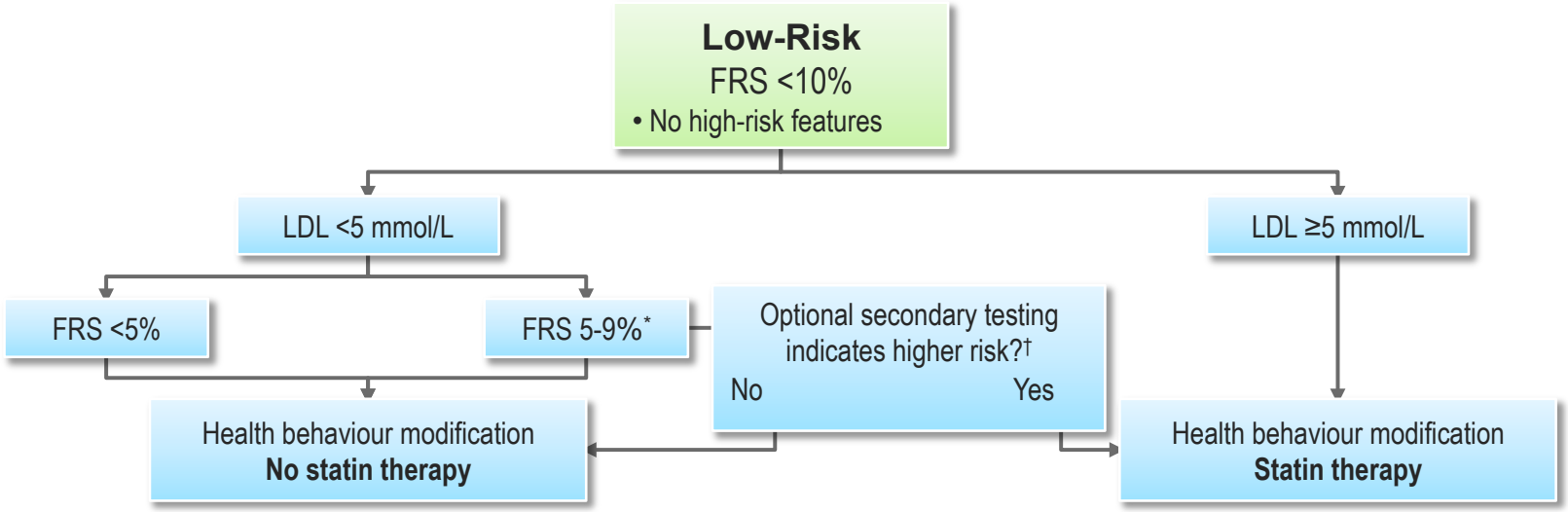
Cardiovascular Age= Patient's Age – (Estimated Remaining Life Expectancy* – Canadian† Average Remaining Life Expectancy)

Can be calculated concurrently with adjusted FRS at: www.chiprehab.com

Legend	
	≤Actual age
	>Actual age & <Actual age + 5 years
	≥Actual age + 5 years

*Adjusted for coronary and stroke risk;
†For Canadians of the same age and sex as the patient.
FRS: Framingham Risk Score;
HDL: high-density lipoprotein.

Low-Risk



Recommendations

- Initiate pharmacotherapy in low-risk individuals with LDL-C ≥5 mmol/L, or if there is evidence of genetic dyslipidemia (such as familial hypercholesterolemia)
  Strong Recommendation, Moderate-quality Evidence

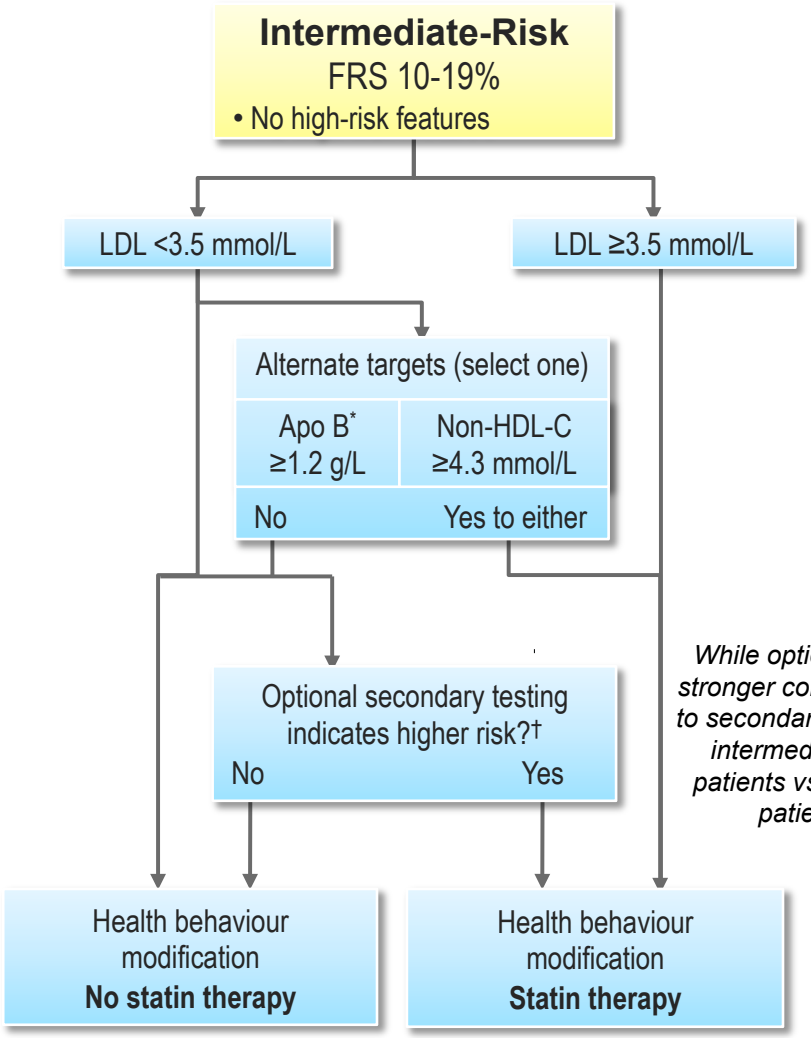
- Target ≥50% reduction of LDL-C in low-risk individuals for whom treatment is initiated
  Strong Recommendation, Moderate-quality Evidence

Values and preferences

- Less clinical trial evidence in this group of subjects
- Individual practice will vary dependant on wishes of the patient and evaluation of the treating clinician
- Subjects with risk in the higher end of this category can have the risks/benefits of statin therapy discussed and might be offered statin therapy based on their wishes and/or the judicious use of secondary testing
- In low-risk individuals with LDL-C <5 mmol/L and FRS 5-9% monitor patients annually

*More frequent, yearly assessment, judicious use of secondary testing, and encouragement for aggressive nonpharmacological risk factor modification; †See pages 20-23.
FRS: Framingham Risk Score; LDL" low-density lipoprotein; LDL-C: low-density lipoprotein cholesterol.

Intermediate-Risk



While optional, give stronger consideration to secondary testing in intermediate-risk patients vs. low-risk patients.

Recommendations

- Includes individuals with adjusted FRS ≥10% and <20%
  Strong Recommendation, Moderate-quality Evidence

- Treat individuals with LDL-C ≥3.5 mmol/L
  Strong Recommendation, Moderate-quality Evidence

2012 Update

- In individuals with LDL-C <3.5 mmol/L, either apo B ≥1.2 g/L or non-HDL-C ≥4.3 mmol/L are suggested to identify patients who might benefit from pharmacotherapy
  Strong Recommendation, Moderate-quality Evidence

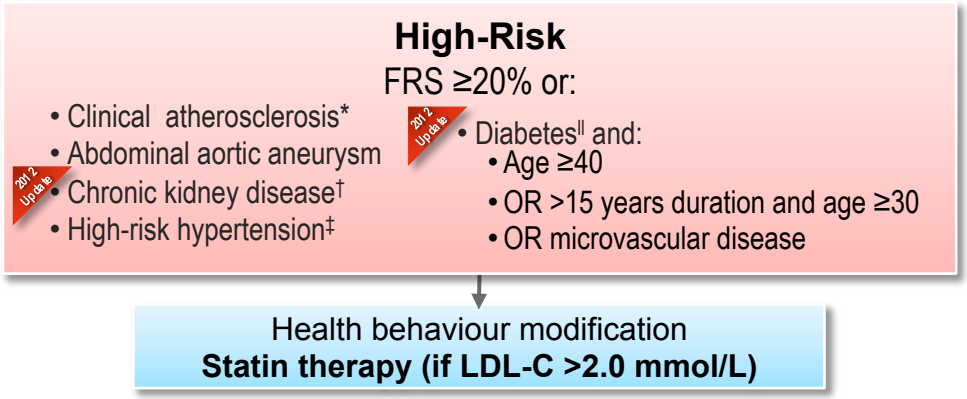
- Target LDL-C ≤2.0 mmol/L or ≥50% reduction in LDL-C for intermediate-risk individuals in whom treatment is initiated
  Strong Recommendation, Moderate-quality Evidence
- Alternate target variables: apo B ≤0.8 g/L or non-HDL-C ≤2.6 mmol/L
  Strong Recommendation, Moderate-quality Evidence

Values and preferences

- Non-HDL-C is available without additional cost or testing and there are increasing data to demonstrate its potential value
- Non-HDL-C is particularly useful where apo B is not available and in patients whose triglyceride level is >1.5 mmol/L
- Non-HDL-C, like apo B, also has the advantage of being applicable in a nonfasting state

*Not yet uniformly available as a funded laboratory test;
†See pages 20-23.
Apo B: apolipoprotein B; FRS: Framingham Risk Score; LDL: low-density lipoprotein; LDL-C: low-density lipoprotein cholesterol; Non-HDL-C: non-high-density lipoprotein cholesterol.

High-Risk



Recommendations

- High-risk defined as: clinical atherosclerosis,* abdominal aortic aneurysm, or an adjusted FRS of ≥20%
  Strong Recommendation, High-quality Evidence
- Definition also includes: diabetes >15 years duration and age ≥30 years, diabetes with age ≥40 years, or the presence of microvascular disease,‖ high-risk kidney disease† or high-risk hypertension‡
  Strong Recommendation, Moderate-quality Evidence

- Target LCL-C ≤2.0 mmol/L or ≥50% reduction of LDL-C for high-risk individuals in whom treatment is initiated
  Strong Recommendation, Moderate-quality Evidence

2012 Update
- Apo B ≤0.80 g/L or non-HDL-C ≤2.6 mmol/L may be considered as alternative treatment targets for optimal risk reduction
  Strong Recommendation, Moderate-quality Evidence

Values and preferences

- Addition of chronic kidney disease to high-risk category was based on significant emerging epidemiologic data and recently published SHARP data
- Treatment of dyslipidemia in subjects on hemodialysis remains controversial and individual judgment is required

*Clinical coronary, cerebrovascular or peripheral vascular disease; †GFR ≤45 mL/min/1.73m^2 or ACR ≥30 mg/mmol or GFR ≤60 mL/min/1.73m^2 and ACR ≥3 mg/mmol; ‡Hypertension plus three 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 abnormalities, or microalbuminuria;‖Not all subjects with diabetes are at high 10-year risk; included for treatment based on randomized studies and high long-term risk. ACR: albumin:creatinine ratio; Apo B: apolipoprotein B; FRS: Framingham Risk Score; GFR: glomerular filtration rate; LDL-C: low-density lipoprotein cholesterol; non-LDL-C: non-high-density lipoprotein cholesterol.

Targets of Therapy

Risk level	Initiate therapy if:	Primary target (LDL-C)	2012 Update Alternate target
High FRS ≥20%	• Consider treatment in all *(Strong, High)*	• ≤2 mmol/L or ≥50% decrease in LDL-C *(Strong, High)*	• Apo B ≤0.8 g/L or • Non-HDL-C ≤2.6 mmol/L *(Strong, High)*

Intermediate
FRS 10-19%
	• LDL-C ≥3.5 mmol/L
	(Strong, Moderate)
	• For LDL-C <3.5 mmol/L consider if:
	  • Apo B ≥1.2 g/L
	  • OR Non-HDL-C ≥4.3 mmol/L
	(Strong, Moderate)
		• ≤2 mmol/L or ≥50% decrease in LDL-C
		(Strong, Moderate)
			• Apo B ≤0.8 g/L or
			• Non-HDL-C ≤2.6 mmol/L
			(Strong, Moderate)

Low FRS <10%	• LDL-C ≥5.0 mmol/L • Familial hypercholesterolemia *(Strong, Moderate)*	• ≥50% decrease in LDL-C *(Strong, Moderate)*	N/A

Practical tip:

- LDL-C remains the primary target in the guidelines
- Physicians are encouraged to be familiar with LDL-C and one of the two alternate targets
- We are not advocating for using all three indices regularly or testing for both LDL-C and apo B in subjects
- For clinicians who have apo B available and are comfortable using it, there are advantages

Apo B: apolipoprotein B; FRS: Framingham Risk Score; LDL-C: low-density lipoprotein cholesterol; Non-LDL-C: non-low-density lipoprotein cholesterol.

When to Use Secondary Testing in Risk Stratification

- Should only be used if results will alter therapy – usually addition of pharmacotherapy
- Left to the discretion of the clinician in consultation with the patient – type of testing reflects local availability and expertise (cost and expected yield should be considered)
- Multiple tests should not be routinely undertaken
- Annual or repeated assessment is not advocated
- Each test outlined provides incremental predictive value to FRS in terms of risk stratification
- A "positive" test indicates that the calculated FRS may be erroneously low – treatment should be considered
- With the exception of hsCRP, or eGFR, the benefits of initiating statin therapy based on this approach has not yet been tested and thus has not yet been proven to improve CV outcomes

CV: cardiovascular; eGFR: estimated glomerular filtration rate; FRS: Framingham Risk Score; hsCRP: high-sensitivity C-reactive protein.

When to Use Secondary Testing in Risk Stratification

Recommendations

- Secondary testing should be considered for further risk assessment in intermediate-risk patients (10-19% FRS after adjustment for family history) who are not candidates for lipid treatment based on conventional risk factors or for whom treatment decisions are uncertain
  Strong Recommendation, Moderate-quality Evidence

- Secondary testing should be considered for a subset of low- to intermediate-risk patients (5-9% FRS after adjustment for family history for whom further risk assessment is indicated [e.g. strong family history of premature CAD, abdominal obesity, South Asian ancestry or impaired glucose tolerance])
  Weak/Conditional Recommendation, Low-quality Evidence

Values and preferences

- Use of these tests is optional; they are only to be used where decision-making will be directly affected (i.e. not in high- or lower-risk patients [FRS <5%])
- Choice of test depends on clinical situation and local expertise
- In appropriate situations, A1C, urine ACR and hsCRP can be helpful, safe and inexpensive, and should be considered
- For noninvasive testing:
  - Clinical suspicion of peripheral vascular disease should prompt ABI
  - Individuals who have been inactive and wish to exercise could be given an exercise stress test
  - Recent evidence suggests CAC testing with computed tomography is superior to carotid ultrasound — however, given its expense and radiation exposure it cannot be widely advocated until further data are available

ABI: ankle brachial index; ACR: albumin:creatinine ratio; CAC: coronary artery calcium; CAD: coronary artery disease; FRS: Framingham Risk Score; hsCRP: high-sensitivity C-reactive protein.

Optional Biomarkers for Risk Stratification

Biomarker	Indications for testing	Frequency of testing	Normal range
Lp(a) (mg/L)	• Further risk assessment particularly in individuals with a family history of premature CVD	• Genetically determined risk factor • Repeat testing not required	• <300 mg/L*
hsCRP (g/L)	• Men >50 years of age and women >60 years of age who are not candidates for statin Rx based on conventional risk factors	• Every 3 years from age 50 (males) and age 60 (females) • If >2.0 mg/L, repeat in 2-4 weeks, use lower value for risk assessment	• Lowest risk <1.0 • Increased risk† >2.0 • High-risk >3.0
A1C (%)	• Further risk assessment in selected subjects with FPG >5.6 mmol/L	• Every 1-5 years • More frequently if weight gain or increased FBG	• Low-risk <5.5% • Mid-risk 5.5-5.9% • High-risk‡ 6.0-6.4% • Diabetes >6.5%
Urinary ACR (mg/mmol)	• Type 2 diabetes • Poorly controlled hypertension • Selected patients who are not candidates for statin Rx based on conventional risk factors	• Every year for patients with type 2 diabetes or poorly controlled hypertension	• <3.0 mg/mmol

*Lp(a) 300-700 mg/L confers ~1.3X increased risk, >800 mg/L ~1.5X increased CVD risk;
†hsCRP >2 mg/L is associated with ~1.5-2.0X increased CVD risk;
‡HbA1C 6.0-6.5% is associated with ~1.5-1.8X increased CVD risk.
ACR: albumin:creatinine ratio; CVD: cardiovascular disease; FBG: fasting blood glucose; FPG: fasting plasma glucose; hsCRP: high-sensitivity C-reactive protein; Lp(a): lipoprotein (a).

Optional Noninvasive Testing for Risk Stratification

Noninvasive test	Indications for testing	Frequency of testing	Normal range
Graded exercise stress test	• Selected asymptomatic adults with CVD risk factors especially those who are embarking on a vigorous exercise program • Selected adults in the intermediate-risk category	• If symptoms develop	Duke Score* • Low-risk ≥+5 • Moderate-risk -10 to +4 • High-risk ≤-11
Carotid ultrasound imaging	• Selected asymptomatic adults not candidates for statin Rx based on conventional risk factors • Only in centres with clear expertise	• Every 5-10 years as indicated for reassessment of risk	• CIMT <1.0 mm • No visible plaque†
Ankle brachial index (ABI)	• Selected asymptomatic adults not candidates for statin Rx based on conventional risk factors (particularly smokers, patients with diabetes)	• Every 5-10 years as indicated for reassessment of risk or if symptoms develop	• ABI 1.0-1.3‡
Coronary artery calcium (CAC)	• Selected asymptomatic adults who are not candidates for statin Rx based on conventional risk factors	• CAC=0, every 10 years where clinically indicated • CAC=0-100, every 3-5 years if Rx is deferred	• Low-risk 0 • Increased risk 0-99 • High-risk 100-299‖ • Very high-risk >300¶

*CAD risk is also increased in subjects with low exercise capacity (<6 METS achieved on GXT);
†Each 0.1 mm increase in CIMT is associated with a 10% increased risk for MI and a 13% increased risk for stroke – visible arterial wall plaques defined as a CIMT ≥1.5 mm or in the absence of plaque, CIMT values >75% for age and sex are considered as evidence of subclinical atherosIcerosis – a CIMT ≥1.5 mm is an indication for statin therapy;
‡An ABI <0.90 is associated with at least a 50% stenosis in a peripheral artery and a high probability of concomitant coronary artery disease and is an indication for intensive statin therapy;
‖CAC >100 is generally considered high-risk;
¶CAC >300 places patients in very high-risk category (10 year risk of MI/CV death=28%).
ABI: ankle brachial index; CAC: coronary artery calcium; CAD: coronary artery disease; CIMT: carotid intimal media thickness; CV: cardiovascular; CVD: cardiovascular disease; GXT: graded exercise stress test; MI: myocardial infarction; METS: metabolic equivalents.

Treatment: Health Behaviours

2012 Update

Nutrition therapy

Encourage individuals to adopt healthy eating habits to lower their CVD risk

1. Moderate energy (caloric) intake to achieve and maintain a healthy bodyweight
2. Emphasize a diet rich in vegetables, fruit, whole-grain cereals, and polyunsaturated and monounsaturated oils, including omega-3 fatty acids particular from fish
3. Avoid trans fats, limit saturated and total fat to <7% and <30% of daily and total energy (caloric) intake, respectively
4. Increase daily fibre intake to >30 g
5. Limit cholesterol intake to 200 mg daily for individuals with dyslipidemia or at an increased CVD risk
   Conditional Recommendation, Moderate-quality Evidence

- Mediterranean, Portfolio, or Dietary Approach to Stop Hypertension (DASH) diets to improve lipid profiles or decrease CVD risk
  Strong Recommendation, High-quality Evidence
- For cholesterol lowering, consider increasing phytosterols, soluble fibre, soy and nut intake

Exercise

- 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
  Strong Recommendation, High-quality Evidence

Smoking/alcohol

- Smoking cessation
  Strong Recommendation, Moderate-quality Evidence
- Limit alcohol intake to 30 g or less per day (1-2 drinks)
  Conditional Recommendation, Moderate-quality Evidence

Practical tip:

- Some groups suggest a 0-5-30 approach to counselling patients
  - 0 → cigarettes
  - 5 → serving of fruits/vegetables
  - 30 → minutes of exercise daily

CVD: cardiovascular disease.

Treatment: Pharmacotherapy

Lipid Lowering Medications	
Generic name	**Recommended dose range (daily)**
Statins	
Atorvastatin	10 mg-80 mg
Fluvastatin	20 mg-80 mg
Lovastatin	20 mg-80 mg
Pravastatin	10 mg-40 mg
Rosuvastatin	5 mg-40 mg
Simvastatin	10 mg-80 mg*
Bile acid and/or cholesterol absorption inhibitors	
Cholestyramine	2 g-24 g
Colestipol	5 g-30 g
Colesevelam	2.5 g-3.75 g
Ezetimibe	10 mg
Fibrates	
Benzafibrate	400 mg
Fenofibrate†	48 mg-200 mg
Gemfibrozil†‡	600 mg-1200 mg
Niacin	
Nicotinic acid	1 g-3 g / 0.5 g-2 g

Note: The topic of nonstatin pharmacotherapy was not reviewed in detail and thus no new formal recommendations were presented in the 2012 guidelines.
*Increased myopathy on 80 mg;
†Reduce dose or avoid in renal impairment;
‡Should not be used with a statin because of an increased risk of rhabdomyolysis.

Treatment: Pharmacotherapy

LDL-C

- The majority of patients will achieve target LDL-C levels on statin monotherapy
- A minority of patients may require combination therapy with:
  - Ezetimibe (inhibits cholesterol absorption)
  - Cholestyramine, colestipol or colesevelam (inhibit bile acid reabsorption)
  - Niacin

HDL-C

- Low HDL-C may pose no risk, depending on genetic type
- Impact of medications on HDL-C:
  - Statins have little effect
  - Fibrates can modestly raise HDL-C (5% to 10%)
  - Niacin can increase HDL-C 15% to 25%
  - *Medications may not increase HDL-C to a clinically significant extent*
- Smoking cessation, weight loss, exercise and moderate alcohol intake all increase HDL-C

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

Treatment: Pharmacotherapy

Triglycerides

- Lower triglyceride levels are associated with decreased CVD risk
- For hypertriglyceridemia, health behaviour interventions are first-line:
  - Dietary therapy
  - Exercise
  - Weight loss (focus on restriction of refined carbohydrates)
  - Reduced alcohol intake
  - Increased intake of omega-3 fatty acids
- Fibrates may prevent pancreatitis in patients with extreme hypertriglyceridemia (>10 mmol/L)

Combination Therapy

- Statin with niacin
  - Effective in patients with combined dyslipidemia and low HDL-C
- Statin with a fibrate
  - May be used with close patient follow-up
- Statin with omega-3 fatty acids
  - May lower triglycerides and help achieve TC:HDL-C ratio target in patients with moderate hypertriglyceridemia

CVD: cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol.

Statin Intolerance and Adverse Effects

2012 Update

Recommendations

- Overall risk/benefit ratio favours therapy in patients meeting criteria for lipid lowering therapy and cardiovascular risk reduction
  - Despite concerns about a variety of other possible adverse effects, all purported statin-associated symptoms should be evaluated systematically, incorporating observation during cessation, reinitiation (same or different statin, same or lower potency, same or decreased frequency of dosing) to identify a tolerated, statin-based therapy for chronic use
    Strong Recommendation, Very Low-quality Evidence
  - Statins should not be withheld on the basis of a potential, small-risk of new-onset diabetes mellitus emerging during long-term therapy
    Strong Recommendation, Very Low-quality Evidence

- Vitamins, minerals or supplements for symptoms of myalgia perceived to be statin-associated are not recommended
  Strong Recommendation, Very Low-quality Evidence

Practical tip:

- Advise patients to stop taking statin therapy and contact the prescribing healthcare provider if worrisome symptoms develop
- The effort spent persevering with statin therapy in subjects with adverse effects should be directly related to the level of risk for the individual patient
  - In highest-risk patients
    - All options should be exercised before changing to alternate lipid lowering therapy or withdrawing all lipid lowering treatment
    - Lower-dose combination therapy remains an option for these patients
    - Strong emphasis should be put on a more aggressive nonpharmacological approach, such as diet modulation and exercise
  - For lower-risk patients
    - A re-evaluation of the need for lipid lowering therapy should preceded a change to alternative therapy because outcome studies are not robust

Follow-up and Referral to Specialist Clinics

Follow-up

- Most lipid lowering medications are well-tolerated
- Serum transaminases should be checked within first 3 months
- Creatinine kinase can be checked if myalgias develop
- Routine testing of ALT or CK is not required thereafter

Referral May be Warranted in the Following Cases

- Unexplained atherosclerosis
- Severe dyslipidemias
- Genetic lipoprotein disorders
- Patients refractory to pharmacological treatment

ALT: alanine aminotransferase; CK: creatinine kinase.

DYSLIPIDEMIA GUIDELINES

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