CHOLESTEROL THERAPY

Who should be screened for hyperlipidemia? [1,7]

- Healthy men >40 years old and women >50 years old or postmenopausal should be screened every 5 years
- Patients with diabetes, especially >30 years old should be screened annually
- Patients with vascular disease (ie. carotid, peripheral and coronary atherosclerosis) should be screened annually
- Patients with genetic dyslipidemias, signs of hyperlipidemia or a strong family history of premature cardiovascular disease may be screened earlier at the physician's discretion
- Patients can be screened at any age at the physician's discretion, especially when lifestyle changes are needed

Cholesterol Targets [1]

Risk Category	LDL (mmol/L)	Total Cholesterol:HDL Ratio
High Risk (10 yr CAD risk of ≥ 20%, or history of diabetes mellitus or any atherosclerotic disease)	<2.5	<4.0
Moderate Risk (10 yr CAD risk of 11-19%)	<3.5	<5.0
Low Risk (10yr CAD risk of ≤ 10%)	<4.5	<6.0

Calculating 10 year Risk of Coronary Heart Disease in a Patient without Diabetes Mellitus or Clinically Evident CVA [2]

Part A: Global Risk Assessment Scoring

Risk Factor	Men	Women	Score
Age (years)			
<34	-1	-9	
35-39	0	-4	
40-44	1	0	
45-49	2	3	
50-54	3	6	_____
55-59	4	7	
60-64	5	8	
65-69	6	8	
70-74	7	8	
Total Cholesterol (mmol/L)			
<4.14	-3	-2	
1.15-5.17	0	0	
5.18-6.21	1	1	_____
6.22-7.24	2	2	
>or equal to 7.25	3	3	
HDL cholesterol (mmol/L)			
<0.09	2	5	
0.91-1.16	1	2	
1.17-1.29	0	1	_____
1.30-1.55	0	0	
>or equal to 1.56	-2	-3	
Systolic blood pressure (mmHg)			
<120	0	-3	
120-129	0	0	
130-139	1	1	_____
140-159	2	2	
>or equal to 160	3	3	
Smoker			
No	0	0	_____
Yes	2	2	
		TOTAL RISK POINTS	☐

Part B: Calculate 10 year absolute risk for total CVD end points estimated from Framingham data

Risk Points:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
CVD Risk: Men	3%	4%	5%	7%	8%	10%	13%	16%	20%	25%	31%	37%	45%	>52%			
Women	2%	3%	3%	4%	4%	5%	6%	7%	8%	10%	11%	13%	15%	18%	20%	24%	>27%

Primary vs Secondary Prevention

Primary Prevention:

- Aggressive cholesterol therapy for primary prevention in patients ≥ 75 years old is not supported[5]
- Examples of primary prevention using statins:[5]
  - **DM**, high risk, but no CHD need to treat **23 patients*** (HPS Study)
  - type 2 **DM**, no CHD, male, $62yo_{ave}$, LDL 3.0_{ave} need to treat **25 patients*** (CARDS)
  - male, $55yo_{ave}$, 44% smoke, LDL 5.0_{ave} need to treat **41 patients*** (WOSCOPS)
  - male, 63 yo_{ave}, no CHD**, hypertension +3 risk factors**, LDL 3.4_{ave} need to treat **60 patients*** (ASCOT)

Secondary Prevention:

- Statins are most effective in patients who are already at high risk[5]
- **Studies support use of statins in patients who are at high risk, not just patients with high TC or LDL**[3]
- CARDS study which looked at patients with type 2 DM and ≥ 1 risk factor, showed that there is benefit in using a statin even if LDL is <2[3]
- LIPID and 4S studies showed reduced mortality due to secondary prevention in patients ≥ 65 years old[5]
- Examples of secondary prevention using statins:[5]
  - **CVD or diabetes,** LDL 4.9_{ave}, $59yo_{ave}$ need to treat **10 patients*** (4S Study)
  - **history of MI or angina,** LDL 4.9_{ave}, $59yo_{ave}$ need to treat **13 patients*** (4S)
  - **acute coronary syndrome,** LDL 2.7_{ave}, 58 yo_{ave} need to treat **15 patients*** (PROVE-IT)
  - **DM, CHD,** or other **CVD,** BP $148/82_{ave}$, BMI 28.6_{ave} need to treat **17 patients*** (HPS)
  - **high risk with or without history of CHD,** LDL 3.9_{ave} need to treat **19 patients*** (HPS)

* *Number of patients needed to treat for 5 years to prevent one CV event*

Dyslipidemia Therapy

High Risk Patients: treat with drug therapy and lifestyle changes[3]
Low Risk Patients: begin with lifestyle changes and if targets are not met in 3-6 months, treat with medications[3]

	First Choice	Alternative	Notes
LDL	**Statin**[1]	If target not achieved with statin, may add **Resin** or **Ezetimibe**[1]	- most patients can be controlled with statin monotherapy[1] - LDL is the primary target in patients with metabolic syndrome[1] - statin + resin/ezetimibe combinations can ↓ LDL by an extra 10-20%[1] - ezetimibe is better tolerated than a resin[1]
TC:HDL ratio	**Statin + Niacin**[1]	**Statin + Fibrate**[1]	- niacin is able to ↑ HDL most, but has more s/e including flushing, may ↓ insulin sensitivity, and is taken BID-TID (fenofibrate is OD and gemfibrozil is BID)[1,3] - combination therapy is not well studied[6] - carefully monitor statin when using with niacin or fibrate (*see statin monitoring*); advise patient to report unexplained symptoms such as muscle pain, tenderness or weakness[1,3,6] - fenofibrate is a better choice than gemfibrozil for combination because it has fewer myotoxic effects[1] - evidence shows that pravastatin or simvastatin may be fairly safe to use with fenofibrate[1] - also may need to ↓ TG to reach TC:HDL goal[1]
TG (generally, target is <1.7mmol/L)[1]	For dyslipidemia that is mainly ↑ TG, use initial therapy of **diet**, **weight loss**, **exercise**, and **moderation of alcohol intake**[5]	**Fibrate** (if TG are very ↑, fibrate may ↑ TG initially), **Niacin,** or **Fish oil** (less evidence for fish oils)[3]	- TG itself, is not stated as a treatment goal, but to reach TC:HDL ratio goal, you may need to ↓ TG[1] - for moderate ↑ TG, may add salmon oil (1-3g TID) to statin[1] - higher doses of **statins** will ↓ TG (some evidence shows atorvastatin is best statin choice if LDL and TG ↑, but outcome evidence is better for pravastatin and simvastatin)[5]

References:
1. J Genest, J Frohlich, G Fodor, Ruth McPherson. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease; 2003 update. Appendix to CMAJ 2003; 168(9):921-4
2. Grey, J. Therapeutic Choices. 4th ed. Canadian Pharmacists Association. 2003
3. Rx files: Drug Comparison Chart Sept 2004
4. Rx files: Monitoring of CK in patients on Statin Therapy March 2002
5 Rx files: Lipid Lowering Agents Feb 2002
6. Rx files: Q&A: Update on Statins Nov 2004
7. Curnew, G. In the Know: Canadian Guidelines for Dyslipidemia, 2003. www.stacommunications.ca/journals/cardiology/2004/september/pdfs/032.pdf

Drug Information

Generic Drugs	Brand Name	LDL (%)[3]	HDL (%)[3]	TG (%)[3]	Monitoring	Notes
Resins (Bile Sequestrate Agents)						
Cholestyramine Colestipol	Questran Cholestid	↓ 15-30	↑ 3-5	no Δ or may ↑	• **LFT**, TG[3]	• **s/e**: Common: GI, constipation, bloating[3] • **CI:** biliary obstruction, TG >4.6mmol/L (caution TG >2.3 mmol/L), phenylketonurics[3]
Statins						
Atorvastatin	Liptor	↓ 35-**60**	↑ 5-15 **ros** & **sim** may ↑ most ↑HDL effect peaks at lower doses	↓ 7-30 **ato**, **ros** & **sim** may ↓ most	• routine monitoring of LFT & CK not needed for all patients [3,4] • monitor **LFT** at 0,3,6,12 months and annually if high dose/combo or at risk[3]* ○ **d/c if AST/ALT >3X normal or <3X normal and symptomatic**[3,4] • stop statin and check **CK** if unexplained weakness, muscle aches or soreness[3,4] ○ if no symptoms and minor CK ↑, often continue therapy[4] ○ if severe symptoms, may d/c even if only small CK ↑[4]	• **s/e**: Common: myopathy(0.1-0.5% with statin monotherapy[4]),upper GI, headache, rash, sleep disturbance Rare: peripheral neuropathy, impotence, lupus like symptoms[3] • ato/fluv/pravastatin have ↓ CNS s/e[3] • **CI**: liver disease, pregnancy, ↑ alcohol[3] • **caution:** CYP inhibitors, fibrate, niacin[3]* • **metabolism**: prav (sulfation), ato/lov/sim (CYP 3A4), fluvastatin (CYP2C9)[3] • pravastatin and rosuvastatin have ↓ DI[3] • rosuvastatin appears to ↑ HDL even at ↑ doses[3] STATINS PROVEN TO BE EFFECTIVE:[3] ↓ cholesterol: all statins ↓ atherosclerosis and coronary heart disease: all except rosuvastatin ↓ stroke: pravastatin and simvastatin
Pravastatin	Pravachol	↓ 20-35				
Rosuvastatin	Crestor	↓ 40-**65**				
Simvastatin	Zocor	↓ 35-**50**				
Fibrates						
Bezafibrate Fenofibrate Gemfibrozil	Bezalip Lipidil Lopid	↓ 5-20 may ↑ initially if TG very ↑	↑ 10-20	↓ 20-**50**	• CBC, Scr (↓ dose if ↑Scr), glucose, **LFT**, (CK??)[3]	• **s/e:** Common: GI upset, rash, abd pain Less Common: headache, pruritis, ↓ libido, dizzy, drowsy, ↑ glucose, sleep/vision changes Rare: ↓ renal function, anemia, ↑ LFT, myopathy, gallstones, reversible impotence[3] • **CI**: severe liver and renal disease[3] • fenofibrate may ↓ LDL and ↓ TG more than gemfibrozil[3] • outcome evidence better with gemfibrozil[3] • gemfibrozil has more myotoxic effect, so not recommended to use with statin • **DI:** increased levels with statin, furosemide, MOAI, probenecid, cyclosporin; increased effect of chlorpropamide, furosemide, repaglinide, rosiglitazone, sulfonylurea, warfarin[3]
Others						
Ezetimibe	Ezetrol	↓ 17	↑ 1.3	↓ 6	• **LFT**[3]	• **CI:** hepatic impairment[3] • levels ↑ with fibrates and resins, interfere with absorbtion[3]
Nicotinic acid	Niacin	↓ 5-25	↑ 15-**35**	↓ 20-**50**	• **LFT,** glucose, UA[3]	• **s/e:** flushing (pretreat with NSAID), dry eyes, pruritis, headache, GI, increased LFT, increased glucose, ↑ uric acid (UA)[3] • **CI:** chronic liver disease, severe gout[3] • **caution**: diabetes (can cause insulin resistance), peptic ulcer disease,↑ uric acid • plain niacin ↑HDL & ↓TG more than sustained release[5] • nicotinamide is not effective[3] • can ↑ TG when used with resins[5]

Tips on LFT

ALP: in liver and bones; levels are fairly sensitive to partial or mild biliary obstruction (ie. stone in bile duct)
ALT: mostly in the liver; more specific, but less sensitive than AST; ↑ in severe liver damage
AST: mostly in the heart and liver; ↑ significantly with acute hepatitis and only small ↑ with cirrhosis; also ↑ with liver congestion (ie. CHF) or heart damage

Almost all benefit is in patients with **diabetes** and high insulinemia (↑↑ insulin in blood)[3]

* Risk factors for rhabdomyolysis or myopathy:[3,4]

- high dose of statin
- concomitant therapy with fibrate, niacin, or other CYP3A4 inhibitors such as cyclosporin, macrolide antibiotics, azole antifungals, calcium channel blockers (verapamil, diltiazem), and grapefruit juice **(myopathy/rhabdomyolysis increases 10X when given with drugs that are metabolized by the same path)**[3]
- small framed older patients
- patients with reduced renal function