BRIDGING THE CARE GAP IN DYSLIPIDEMIA

Cardiovascular disease remains the number one cause of mortality in men and women in Canada. Dyslipidemia is one of the major risk factors for the development of atherosclerotic disease. Recent evidence has shown that the highest risk patients are being treated sub-optimally or not being treated at all. Bridging the care gap in dyslipidemia management remains a significant challenge. The lost benefit due to undertreatment contributes to the rising cardiovascular disease burden. In addition to diet, exercise and lifestyle interventions new strategies are needed to optimize current vascular disease management. The translation, transfer and utilization of knowledge remains the singular failure of our health care system.

In order to bridge the care gap we must:

- Identify and treat more of the high risk patient population (untreated 50-75%)
- Achieve evidence based targets (published LDL target 2.5 mmol/L achievement 40-72%; LDL target 1.8-2.0 mmol/L achievement 19-22%)
- Follow patients long term and feedback results to ensure compliance and adherence
- Develop strategies which adapt to evolving dyslipidemia targets
- Involve our patients in their disease management through novel and efficient educational tools and strategies

The Lipid Optimization Tool has been developed and utilized at the Ottawa Cardiovascular Centre in response to a documented need to improve LDL targeting and dyslipidemia control. This tool has been utilized to manage approximately 10,400 patients with dyslipidemia. With a simple dosing strategy based on evidence, efficacy and cost, we have been able to achieve control rates of 87% to an LDL of 2.5 mmol/L, 72% to an LDL of 2.0 mmol/L and 57% to an LDL of 1.8 mmol/L for all patients and 92%, 77% and 61% to LDL targets of 2.5, 2.0 and 1.8 mmol/L in statin-treated patients. This matches or betters the best control rates seen in the world literature. The tool incorporates a simple categorical risk assessment strategy, reminder checklists for metabolic syndrome diagnostic criteria, secondary causes of dyslipidemia and indications for treatment. Dosing selection is based on percent LDL reduction needed to achieve targets (easily derived from integrated tables) and selection of the most cost effective agent to achieve target (derived from the Cost Efficacy Grid). Lipid results are tracked on a flowsheet as one would follow an INR, and the results are communicated to the patient by nursing or clerical staff to ensure compliance.

Recent adverse publicity pertaining to statins may have a negative impact on patient compliance. Misrepresentation of the safety and dangers of hypolipidemic therapy may lead to inappropriate discontinuation of effective pharmacotherapy, placing patients at increased risk for cardiovascular events. In response to patient concerns we have developed the **Statin Advisory** and **Statin Risk Benefit** pages included in this mail-out. We believe that statin therapy is safe and effective and that in properly selected patients **the benefit of statin therapy far outweighs the risk**. As LDL targets are revised downwards, higher doses of statins and combination therapies will be necessary to reach target. Side effects will inevitably occur. The challenge is to identify those patients at increased risk for statin adverse effects and make the appropriate statin dose reductions in these patients.

Patients at risk for statin myopathy and other complications include the elderly, Oriental and Asian populations and patients with: chronic kidney disease, hypothyroidism, previous muscle problems with statins, family history of muscular disorders, or history of alcohol abuse. The potential for **drug interactions** particularly with gemfibrozil, niacin, cyclosporine, azole anti-fungals, macrolide antibiotics, HIV protease inhibitors, nefazodone, verapamil, diltiazem, amiodarone, and grapefrut juice > 1 qt/day requires careful attention. By taking appropriate precautions through judicious dose selection and monitoring, this safe and effective therapy has the potential to produce huge reductions in cardiovascular event rates in our at-risk populations.

DYSLIPIDEMIA

LIPID OPTIMIZATION TOOL

Patient: _____ Pharmacy: _____

Responsible for Lipid Management: ❍ Family Physician ❍ Cardiologist ❍ Endocrinologist

LIPID FLOW SHEET[1] – Use the following Table to Guide Intervention: NB*: UPPER STRATUM Exceeds

CCS Guidelines for the Dx and Tx of Dyslipidemia for the Prevention CVD 2012 / NCEP ATP III Guidelines 2004

Risk Level	10 year CHD Risk	No. Of Risk Factors		Targets 1°	2°	2°	3°	Initiation of Lipid Lowering Therapy
Count risk factors or use **Framingham tables, Reynolds Risk Score or European SCORECARD** to calculate 10 year risk of hard CHD/CVD endpoints.				LDL <	Apo-B	Non-HDL Cholesterol	Ratio	
* CAD, PCI, CABG, TIA/CVA, PVD/bruits, DM[2], CKD[3]				1.8	≤ 0.8	≤ 2.6	3/1	Immediately
High	> 20%	3	Rx to <	2.0	≤ 0.8	≤ 2.6	4/1	Immediately
Moderate	10-20%	2	Rx if ≥	3.5	1.2	4.3	5/1	Diet/Lifestyle 3 months
Low	< 10%	≤1	Rx if ≥	5.0			6/1	Diet/Lifestyle 6 months

1) **Count Risk Factors:**
   ❍ Age M > 45 F > 55 ❍ Family Hx CAD ❍ Smoking ❍ HPT ❍ DM ❍ LVH ❍ HDL < 0.9 mmol/l
2) **Identify Metabolic Syndrome (> 3 parameters):**
   ❍ Abdominal obesity (Waist circumference: Male >94 cm (37 in.) / Female > 80 cm (91.5 in.) ❍ TG > 1.7 mmol/L
   ❍ HDL < 1 mmol/L (male)/< 1. 3 mmol/L (female) ❍ BP > 130/85 ❍ FBG 6.2-7 mmol/L
3) **Identify secondary causes:** ❍ Diabetes ❍ Hypothyroidism ❍ Renal disease ❍ Liver disease ❍ Drugs & Alcohol
4) **Record Indication:** ❍ Risk Factors ❍ CAD: _ angina, _ post MI, _ post PTCA, _ post CABG ❍ TIA ❍ CVD ❍ PVD/AAA
5) **Risk Modifiers elevate risk one level:** +FH, Ethnicity-South Asian/Aboriginal, Metabolic syndrome, ↑CRP, ↑Lp(a), ↑A1C, ↑MAU, +GXT, ↑CIMT, ↓ABI, ↑CAC, Rheumatologic Disorders: RA/SLE/PSS/AnkSpond/Psoriatic Arthritis, IBD, AAA, CKD, COPD, HIV-HAART, Erectile Dysfunction

Date	TC	TG	HDL	LDL	Non HDL Chol	TC/ HDL	ALT	CK	Medication Rx Adjustment Addition	Next Test	Req. Sent ✓	Patient Called (Initial)

1 Monitor lipid profile, ALT and CK at baseline, 2 months then every 6 to 12 months
2 Diabetes carries the same CV risk as manifest CAD. DM+CAD impart much higher risk for subsequent CV events.
3 Chronic Kidney Disease

Secondary Prevention: % LDL (mmol/L) change to reach LDL target by risk category.

ATP III Very High Risk		
Initial	Target	% Change
LDL	LDL <	LDL
5.00	1.8	-64%
4.80	1.8	-63%
4.60	1.8	-61%
4.40	1.8	-59%
4.20	1.8	-57%
4.00	1.8	-55%
3.80	1.8	-53%
3.60	1.8	-50%
3.40	1.8	-47%
3.20	1.8	-44%
3.00	1.8	-40%

CCS High Risk		
Initial	Target	% Change
LDL	LDL <	Min. ↓ 50%
5.0	2.0	-60%
4.8	2.0	-58%
4.6	2.0	-57%
4.4	2.0	-55%
4.2	2.0	-52%
4.0	2.0	-50%
3.8	1.9	-50%
3.6	1.8	-50%
3.4	1.7	-50%
3.2	1.6	-50%
3.0	1.5	-50%

Moderate Risk		
Initial	Target	% Change
LDL	LDL <	Min. ↓ 40%
5.00	3.0	-40%
4.80	2.9	-40%
4.60	2.8	-40%
4.40	2.6	-40%
4.20	2.5	-40%
4.00	2.4	-40%
3.80	2.3	-40%
3.60	2.2	-40%
3.40	2.0	-40%
3.20	1.9	-40%
3.00	1.8	-40%

Dose response to Medication (statins & fibrates) % LDL Reduction

Drug mg.	5	10	20	40	80	200	400	900
Lovastatin			24-28%	28-34%	39-42%			
Pravastatin		18-25%	21-28%	27-33%				
Simvastatin	23-30%	27-32%	30-40%	36-43%	45-47%			
Fluvastatin	13%	13%	19%	29%	36%			
Atorvastatin		38-41%	44-46%	50-51%	54-61%			
Rosuvastatin	42-46%	52%	55%	63%				
Gemfibrozil	† Avoid in patients with renal impairment							12-16%
Fenofibrate	† Avoid in patients with renal impairment					21-32%		
Bezafibrate	† Avoid in patients with renal impairment						2-15%	
Ezetimibe		19%	(Co-administration with statin yields incremental 21% LDL reduction)					

Protocol: Initiate lipid lowering immediately in high-risk patients (concomitant with dietary/therapeutic lifestyle modification).

1) Target initial medication dose to ↓ LDL by 50% to minimum of < 2.0 mmol/L for all risk levels. Consider target LDL < 1.8mmol/L for ATP III Very High Risk patients.
   Initiate therapy with dose required to achieve target LDL. Initiate therapy with dose required to achieve target LDL.
   - NB: Initiate rosuvastatin at 10-20 mg (5 mg in Asians/CKD). *40 mg. contraindicted in Asian population.
   - NB: Caution with simvastatin 80 mg. A to Z Trial and max dose statin in populations at risk for myositis.
2) If initial LDL at target, raise HDL and lower triglycerides to target values with appropriate intervention: diet, exercise, weight loss, refined carbohydrate restriction, moderate alcohol intake or medication: fibrate, Niaspan® or salmon oil/omega-3 supplements (1gm OD-TID).
3) If LDL and triglycerides high and HDL-C low, consider combination therapy (fibrate or Niaspan®).
4) If unable to raise HDL sufficiently, lower LDL to achieve Non-HDL Chol < 2.6 mmol/L or Apo B < 0.8 g/L, TC/HDL< 4 and/or LDL/HDL< 3.
5) If initial lipid profile normal look at other risk factors (LPa, homocysteine, apo-B and hs-CRP).
6) Follow Total cholesterol, LDL, non-HDL chol., HDL, triglycerides, CK and ALT in 2 months then every 6 months.
7) If LDL not at target increase statin dose to achieve target or switch to more potent statin. If LDL target not achievable on monotherapy add cholesterol absorption inhibitor (ezetimibe) or bile acid sequestrant (cholestyramine or colesevelam). Doubling statin dose adds ~ 6% LDL. Adding ezetimibe to statin therapy provides additional LDL lowering up to 20% reduction. See Statin Cost Efficacy Grid.
8) Feedback results to patent to improve compliance.

STATIN RISK BENEFIT

Statin medications have previously received adverse publicity regarding the risk of muscle problems including rhabdomyolysis. (See Statin Advisory) The risks of these side effects are low and are far outweighed by the proven benefits of this class of medication. Such publicity is unfortunate in that it generates fear and uncertainty, undermines risk reduction strategies and may lead to discontinuation or under-dosing of statin medications. Such a response may result in adverse cardiovascular and cerebrovascular outcomes due to **lost benefit**. As with all drugs the pros and cons of therapy need to be weighed carefully. Based on the available data, the NLA Statin Safety Task Force has concluded that all currently marketed statins are safe and share a low risk of serious adverse effects (AEs). Any possible risks are greatly outweighed by their protective effects against thromboembolic stroke and CAD.

The risk of serious myopathy or rhabdomyolysis with use of stains is low:

Drug	Reported Cases of Fatal Rhabdomyolysis per 1,000,000 US prescriptions since launch [1]
Cerivastatin[1]	3.16
Lovastatin[1]	0.19
Simvastatin[1]	0.12
Pravastatin[1]	0.04
Atorvastatin[1]	0.04
Fluvastatin[1]	0.00
Rosuvastatin[2]	0.00

Risk: To put risk and benefit in a clearer perspective, for every 100,000 patients with statins in large secondary outcome trials 4 will suffer rhabdomyolysis and 33 will suffer myositis

Benefit: Extrapolated to 100,000 patients, the benefits of statin therapy are:

4S Trial (6 years): prevention of 4000 deaths, 7000 nonfatal heart attacks and 6000 myocardial revascularization procedures.

CARE (5 years): prevention of 15000 cardiovascular events in unselected patients, 20700 cardiovascular events in patients > age 60 and 22800 cardiovascular events in women.

LIPID (6.1 years): prevention of 3000 deaths, 2800 non-fatal heart attacks, 900 strokes, 2300 bypass surgeries, 2000 angioplasties and 8200 admissions for unstable angina.

HPS (5 years): prevention of 7000-10000 heart attacks, stroke or revascularization procedures.

PROVE-IT (18-36 months-mean 24 months) high dose versus moderate dose statin in patients with acute coronary syndromes demonstrates an incremental benefit of 3.9 % absolute and 16% relative risk reduction in the primary end-point - a composite of death from any cause, myocardial infarction, documented unstable angina requiring re-hospitalization, revascularization (performed at least 30 days after randomization), and stroke. For 100,000 patients treated this means the prevention of 3900 further events.

TNT (4.9 years) high dose vs low dose statin in a chronic CHD population showed similar incremental benefits on combined cardiovascular endpoints (death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest or fatal or nonfatal stroke). The incremental benefit was 2.2 % absolute and relative risk reduction of 22%. For 100,000 patients treated this means the prevention of 3400 major cardiovascular events.

In summary:

- **The risk of serious muscle problems with statins is low.**
- **The benefits of statin therapy significantly outweigh any risk.**
- **Higher dosing of statins or use of a more potent statin provides incremental benefits in high risk patients.**
- **Fear of statin adverse effects should not prevent appropriate lipid lowering therapy.**

Statin Risk Benefit References:

1. Staffa JS, Chang J, Green L. Cerivastatin and Reports of Fatal Rhabdomyolysis, N Engl J Med;2002:346(7):539-540.

2. Olsson GO. Safety and efficacy of rosuvastatin. www.thelancet.com Vol 354 July 10, 2004.

3. McKenney JM, Davidson, MH, Jacobson TA, et al. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. AM J Cardiol. 2006;97 (suppl 8A0:89C-94C.

STATIN ADVISORY

Statins are potent cholesterol lowering medications which lower the LDL or “bad cholesterol” to a predictable degree and raise the HDL or “good cholesterol” slightly. All medications have side effects and their use must weigh the potential benefits of the medication with those side effects. Common (2-10%) side effects with statins include:

- Central nervous system: Headache, fatigue, dizziness, weakness
- Cardiovascular: Chest pain
- Dermatologic: Rash
- Gastrointestinal: Nausea/vomiting, diarrhea, heartburn
- Hepatic: Increased transaminases (>3x normal on two occasions)
- Neuromuscular & skeletal: Muscle pains/neuropathy
- Respiratory: Cough
- Miscellaneous: Influenza Headache

Ongoing adverse media reporting has raised patient concerns regarding the risk of myopathy and rhabdomyolysis with statins in general. The risk of serious muscle complications with any of the currently available statins is very rare (<1:10000) and equivalent amongst the statins. Discontinuation of statins in patients at risk could result in increased cardiovascular event rates for stroke or heart attack which far outweigh the risk of muscle complications. Fe**ar of appropriate statin use is causing more harm than good.** However, the use of the maximum doses of any of the statins should be cautioned, particularly in the high risk patient groups detailed below.

Muscle problems with statins include:

1. Myalgias: muscle pains or weakness with or without elevation of CK, a muscle enzyme as measured in the blood. This occurs in 2-10% of patients on statins and is completely reversible.
2. Myositis: myalgias with increases in creatine kinase (CK) values >10 times upper limit of normal.This occurs rarely in patients on statins.
3. Rhabdomyolysis: A more severe breakdown of skeletal muscle associated with a rise in the blood level of CK muscle enzyme above 10,000 U/L may be associated with kidney damage due to the excretion of myoglobin in the urine. Rhabdomyolysis is usually reversible with appropriate medical therapy and discontinuation of the causative medication.
4. The risk of this occurring with statins is rare (< 0.10% or < 1/1000).
5. Rhabdomyolysis is usually associated with other predisposing conditions in which maximum dose statins should be avoided:
   - pre-existing kidney impairment
   - advanced age
   - under-active thyroid
   - family history of muscular disorders
   - previous muscular toxicity with other statins
   - alcohol abuse
   - situations where increased blood levels of statins can occur such as in Japanese, Chinese or Asian populations
   - combination therapy with other cholesterol lowering medications such as gemfibrozil

The extrapolation of clinical trial evidence supporting the use of maximum dose statins, to population groups not included in these trials, places those patients at risk for statin induced myopathy. Great caution should be exercised in prescribing simvastatin (Zocor®) 80 mg, atorvastatin (Lipitor®) 80 mg or rosuvastatin (Crestor®) 40 mg to the elderly (> 75 years of age), patients of South Asian ethnicity or patients with renal failure (Cr > 200 Ìmol/L) or patients on dialysis. Appropriate dosing reductions should be made in these cases.

Patients should report unexplained muscle pains, tenderness or weakness particularly if associated with fever or malaise.

Statin Advisory References:

1. Thompson P, Clarkson P, Karas R.H. Statin-associated Myopathy. JAMA. 2003;289:1681-1690.

2. Cholesterol and Statin review. Bandolier EBM Website.

3. Olsson GO. Safety and efficacy of rosuvastatin. www.thelancet.com Vol 3654 July 10, 2004.

STATIN COST EFFICACY GRID

The **Statin Cost Efficacy Grid** details the cost and LDL lowering efficacy of all currently available statins. Statins and doses are highlighted based on evidence or cost efficacy. The green column highlights the minimum therapeutic bar for treatment of low and moderate risk patients. The orange column highlights the minimum therapeutic bar to halt atherosclerotic progression. The pink column highlights the minimum therapeutic bar for treatment of high risk patients or patients with atherosclerotic risk equivalents. The bright orange column highlights the minimum therapeutic bar to induce atherosclerotic regression. See the **Lipid Optimization Tool** for the therapeutic protocol.

STATIN	Dose	Cost/tab$	%LDL Red	%LDL Red Law	%LDL Red Stellar	%LDL Reduction						
						30%	35%	40%	45%	50%	55%	60%
Lovastatin	20mg	0.49	26	29								
(generic)	40mg	0.90	31	37		0.9						
Pravastatin	10mg	0.41	22	20	20							
(generic)	20mg	0.48	25	24	24							
	40mg	0.58	30	29	30	0.58						
Simvastatin	5mg	0.26	27	23								
(generic)	10mg	0.51	30	27	28	0.51						
	20mg	0.63	35	32	35		0.63					
	40mg	0.63	40	37	39			0.63				
	80mg	0.63	46	42	46				0.63			
Fluvastatin	20mg	0.85	19	21								
(generic)	40mg	1.19	29	27		1.19						
	XL 80mg	1.44	36	33			1.44					
Atorvastatin	10mg	0.42	40	37	37	0.42	0.42	0.42				
	20mg	0.52	45	43	43				0.52			
	40mg	0.56	51	49	48					0.56		
	80mg	0.56	58	55	51						0.56	
Rosuvastatin	5mg	0.32	42	38				0.32				
	10mg	0.34	52	43	46				0.34			
	20mg	0.43	55	48	52					0.43		
	40mg	0.45	63	53	55						0.45	

* Average % reduction: Use to estimate initial statin dose. Actual response varies by patient and subgroup (age and gender).

Cost based on Ontario ODB pricing-updated November 2012. For cost to patient, add 10% plus prescribing fee.

Select Statin based on efficacy, safety, evidence and cost.

Revised November 2012

EVIDENCE

COST

HPS/ASCOT/CARDS | **REVERSAL** | **PROVE-IT/TNT/IDEAL/AtoZ/SPARCL** | **ASTEROID**

The 2012 CCS/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascuar disease in the adult (http://www.ccsguidelineprograms.ca) recommends targeting LDL reduction to ≥ 50% when treating any level of cardiovascular risk with pharmacotherapy. Initiation thresholds vary depending on level of risk and presence of risk modifiers.

Prepared by Dr. J. Niznick