Lipid Lowering Agents
Evidence, Questions & Comparisons

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The **RxFiles**

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The pharmacological management of dyslipidemia has become an important topic in lowering cardiovascular risk. Several recent articles discuss current evidence, guidelines and perspectives:

CMAJ 2000;162(10)1441-7. (**Canadian** Dyslipidemia Guidelines)[1]
JAMA 2001;285(19):2486-97. (American-**ATP III** Guidelines)[2]
NEJM 1999;341(7)498-511. (Review: Drug treatment of Dyslipidemia)[3]
Drugs 2001;61(2):197-206. (Safety Profiles for HMG-CoA's)[4]
WJM 2001;175:246-250 & 396-401. (Hyperlipidemia – Best Practice)[5,6]
Medical Letter 2001;43(1105):43-48. (Review: Choice of Lipid Agents)[7]

OVERVIEW OF LIPID LOWERING AGENTS

STATINS (HMG-COA Reductase Inhibitors)

Statins inhibit HMG-CoA reductase which catalyzes the rate-limiting step in cholesterol synthesis. Low density lipoprotein cholesterol (LDL) levels are lowered by inhibiting synthesis and up-regulating LDL receptors. Statins may also lower triglycerides (TGs) and raise high density lipoprotein (HDL). Studies have demonstrated their ability to prevent coronary events and reduce mortality. **Those at highest risk benefit the most**!

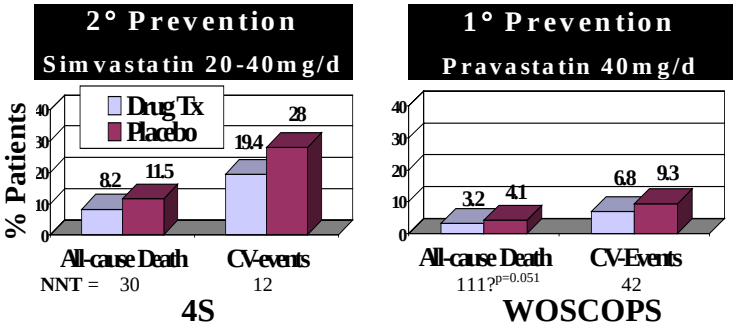
Secondary (2°) Prevention with Statins

The benefits of statin therapy are greatest in patients who already have heart disease (2° prevention). Reductions in coronary events, the primary endpoint for most studies, have been consistently observed. The Scandinavian Simvastatin Survival Study (4S)[8] showed that treatment with **simvastatin** *ZOCOR* 20-40mg/day for 5.4 years reduced both all-cause mortality and major coronary events (See Figure 1). For every **30** coronary artery disease (CAD) patients treated, one death was prevented and for every **12** patients treated one major coronary event was prevented. Reductions in all-cause mortality have also been observed for **pravastatin** *PRAVACHOL* in the LIPID[9] trial (Figure 3). The 4S was the only study where all-cause mortality was the primary endpoint.

Primary (1°) Prevention

Statins have demonstrated efficacy in reducing coronary events in two 1° prevention studies (WOSCOPS[10]& AFCAPS/TexCAPS[11]). The WOSCOPS study evaluated the use of **pravastatin** in middle age men with high cholesterol. This study looked at 1° prevention in a high risk population since 44% were smokers and 16% had a prior history of vascular disease. Coronary event rates were reduced, but to a lesser extent than in 2° prevention studies. For every **42** men treated with pravastatin 40mg/day for 4.9 years, one major coronary event was prevented. A reduction in all-cause mortality approached statistical significance (p=0.051) suggesting that for every **111** men treated, 1 death was prevented. In the AFCAPS trial, **lovastatin** *MEVACOR* 20-40mg/day for 5.2 years was effective in preventing the first cardiovascular event; however all-cause mortality was non-significantly higher in the lovastatin group due to an increase in non-cardiovascular deaths.

Figure 1: Outcome Data - All Cause Death & Coronary (CV) Events



NNT= Number of patients needed to treat to prevent one event (based on absolute risk reduction)

FIBRATES (Fibric Acid Derivatives)

Fibrates increase HDL, decrease TGs and have modest effect on LDL (LDL may even increase if baseline TGs are highly elevated). They cause a shift in distribution of LDL to larger, less dense, less atherogenic particles. Fibrates may benefit patients who have high TGs, low HDL and low LDL. Studies show reductions in coronary event rates (See Figure 3); however no fibrate trial has reduced all-cause mortality.

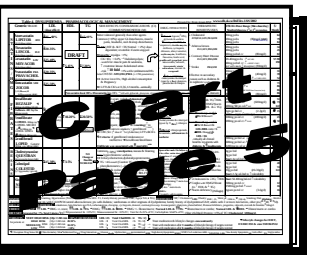
RESINS (Bile Acid Sequestrants)

Resins bind bile acids in the gut and block their entero-hepatic recirculation. They decrease LDL and raise HDL. They may cause TGs to increase and are contraindicated in those whose TGs are already elevated. In one 7-year, 1° prevention study cholestyramine reduced cardiovascular events in men with primary hypercholesterolemia.[12] Reductions in all-cause mortality have not been observed.

NIACIN (Nicotinic Acid)

Niacin has the most potent effect on increasing HDL of any antihyperlipidemic. It also decreases both LDL and TGs. Plain niacin has more favorable effects on HDL and TGs than slow release preparations. (Nicotinamide is not effective!) To prevent flushing, giving 325mg regular ASA 30 minutes prior is useful when initiating therapy or increasing dosage. In a secondary prevention study (CDP), niacin 3g/day was effective in preventing coronary events.[13] An observational follow-up showed a 6.2% absolute reduction in mortality 9 years later.[14]

Also in this issue



QUESTIONS & ANSWERS

Which lipid lowering agents have outcome evidence for reductions in rates of all-cause mortality?

Most statins have strong outcome evidence for reducing coronary event rates; however only **simvastatin** and **pravastatin** have reduced all-cause mortality (2° prevention trials). A follow-up of patients in the 4S trial showed that simvastatin continued to show survival benefit for up to 8 years.[15] Figure 3 summarizes all-cause mortality data from major lipid trials. When evaluating this data the following should be noted:

- only the 4S trial had all-cause mortality as a primary endpoint; not all trials had enough patients to evaluate this endpoint.
- benefits in cardiovascular endpoints do not always produce reductions in all-cause mortality (e.g. BIP, AFCAPS, HHS)
- all-cause mortality data can be found for all studies and is important in evaluating overall safety as well as efficacy.

Which agent has the most potent LDL-lowering effect?

Atorvastatin *LIPITOR* currently has the greatest effect on LDL (but lacks evidence for long-term clinical outcome benefit).

Which statin is least likely to cause drug interactions?

Pravastatin has the least potential for CYP450 mediated drug interactions; but has some other drug interactions (Table 3).[16,17]

What does the recent Heart Protection Study (HPS) add?

Preliminary data from the yet unpublished HPS confirms the benefits of **simvastatin** $_{\textbf{40mg od}}$ in 2° prevention and 1° prevention in high risk patients.[18] The trial included a broad group of high risk patients (e.g. **diabetes**, **age ≤80**, hypertension, previous stroke) whose average LDL was only $3.3_{mmol/L}$. All-cause mortality data suggests that for every **59** patients treated for 5 years, 1 death could be prevented. The study also found that vitamins E, C, and beta-carotene did not provide any benefit. **Further analysis awaits full publication of the data.**

When should statins and fibrates be co-administered?

Combinations of lipid lowering agents may be considered in severe dyslipidemia when a single drug fails to achieve targets. **These combinations have not been well studied. Potential benefits must be weighed against increased risks!** For statins and fibrates, the risk of myopathy is of particular concern.[17] Twelve of 31 deaths[USA] in patients on cerivastatin *BAYCOL* occurred in patients also taking gemfibrozil.[19] Patients should be advised to report any unusual symptoms such as unexplained muscle pain, tenderness or weakness. (Table 1.)

Table 1. COMBINATION THERAPY

statin +fibrate low-mid dose	↓LDL,↓TGs,↑HDL; **↑↑ risk of myopathy*** if used, pravastatin least likely to cause DI's
statin +niacin	↓LDL,↓TGs ,↑HDL; lovastatin ↑risk myopathy?* (lovastatin+ SR niacin *ADVICOR* - recent FDA approval) simvastatin & pravastatin also studied & appear safe
statin + resin	↓LDL,↑HDL; safe; may ↓CHD risk by ≥50% [3]
niacin +resin	option in statin intolerance (ie. hepatic/muscle)
niacin +fibrate	↓TGs; ↑HDL
niacin +fish oil	↓TGs; questionable efficacy

***MYOPATHY RISK** is dose-dependant; ↑ risk in small-framed, older & impaired **renal** function patients; furosemide & probenecid may ↑ risk in **nephrotic syndrome** patients on fibrates[20]; **DI**= drug interaction

Does statin therapy work as well in smokers?

Observations from the landmark trials show that statins reduce risk in smokers; however benefit is markedly reduced.[21] Event rates in treated smokers were similar to those in untreated non-smokers. (Smoking also ↓'s HDL)

Can LDL be lowered too much?

The currently recommended target LDL levels vary from $<2.5_{mmol/L}$ in very high risk patients to $<5_{mmol/L}$ in those at low risk. Although it is generally thought that "lower is better", the results from the CARE trial raised some question as to what the ideal LDL target should be. In this trial there was no benefit for those post-MI patients whose initial LDL was less than $3.2_{mmol/L}$.[22] This finding has not been confirmed in other trials. Factors yet to be fully evaluated include the safety of very high doses (see below) and the risk versus benefit in the very elderly. The HPS should provide additional information.

What evidence supports high dose statins?

Recent studies have evaluated the safety and efficacy of high dose statins in very high risk patient groups. The **Post-CABG** (coronary artery bypass graft) trial compared moderate versus aggressive lowering of LDL using various doses of lovastatin +/- cholestyramine.[23] This study of 1,351 patients found that an aggressive LDL target of $<2.6_{mmol/L}$ was beneficial, resulting in fewer new occlusions and a lower rate of revascularization. Apart from poor tolerance to cholestyramine, the regimen was safe and well tolerated over the 4.3 years of the study.

The **AVERT** trial studied 341 patients with non-acute ischemic heart disease or stable angina over 18 months. Patients were randomized to receive either atorvastatin 80mg/day or angioplasty.[24] Ischemic events were 13% in the atorvastatin group compared to 21% in the angioplasty group (p=0.048; not statistically significant after adjustment for interim analysis). High dose atorvastatin appeared at least as effective as angioplasty in reducing the incidence of ischemic events in low-risk patients. {One reviewer noted that these patients were such low risk that they would not have been offered angioplasty in Canada and that anginal events were significantly less in the angioplasty group.}

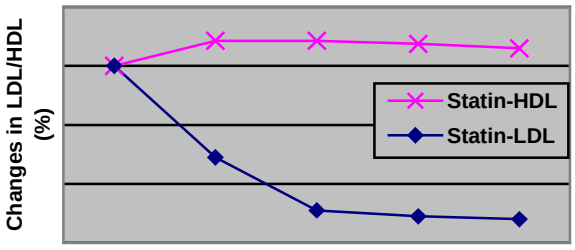
The **MIRACL** study of 3,086 patients evaluated the role of atorvastatin 80mg/day given within 96hours post-MI.[25] Over 16 weeks, the atorvastatin group had less recurrent symptomatic ischemia requiring rehospitalization. The results of the study have been called into question due to eleven patients lost to follow-up.[26] The rate of **liver enzyme elevation** was **2.5%** in the atorvastatin 80mg group and there were three cases of hepatitis. Rates of liver enzyme elevation for lower doses have commonly been in the 0.2-0.6% range.[27]

The results of these three trials show that high dose statin therapy is effective in reducing coronary events in select high risk groups. **Caution is warranted** due to increased toxicity and limited data on long term use. Ongoing studies (SEARCH, TNT, SPARCL and PROVE IT) will provide more information on the relative efficacy and safety of high versus low dose therapy.[28] *Related question on next page (Dose-response to Statins).*

How does doubling the dose affect response to a statin?

A doubling of the dose above the minimal effective dose does not achieve a doubling of the LDL lowering effect.[3,29] Beneficial increases in HDL appear to peak at lower doses and decline slightly thereafter (Figure 2). Whether high doses provide better morbidity/mortality outcomes is not yet studied.

Figure 2: Dose-response for Statins [3,29]



Lab results: At what point should treatment be stopped?

- **aminotransferase (AST/ALT):** Discontinue drug if greater than 3X normal or if less than 3X normal and symptomatic.
- **CK: Routine monitoring is unnecessary**; check in symptomatic patients (muscle pain or weakness). If no improvement on discontinuing suspect drug(s), evaluate for other causes eg. toxic, endocrine, neurologic etc.

Which herbs may effectively lower cholesterol?

Several herbs have been suggested to lower cholesterol and a few may be effective. **None have evidence** for lowering mortality. There are **some concerns** regarding long-term safety, drug interactions and purity of some products. See Table 2.

Table 2. HERBAL OPTIONS for DYSLIPIDEMIA[3,30]

- **Likely safe & effective:** Avocado, Flaxseed[a], Guar gum, Niacin, Oat bran, Pectin, Psyllium, Red Yeast[b], Sitostanol, Soy
- **Possibly safe/effective:** Guggal/Guggulipids[c], Garlic?

[a] **Flaxseed:** Usual dose 1 tablespoon of whole seed with 150ml liquid 2-3X/day; lack of adequate liquid causes intestinal blockage; can impair drug absorption

[b] **Red Yeast:** 2400mg/day actually contains 7.2mg **lovastatin**

[c] **Guggulipids:** (Commiphora mukul)**:** a gum resin (from India) may lower serum cholesterol & triglycerides. It has thyroid stimulating activity & may interfere with thyroid disorders. Side effects: GI – nausea, burping, hiccups; headache. Drug interactions (potential ↓ bioavailability). Usual dose 100-500mg/day.

Dietary measures are encouraged recognizing that they are modestly effective in lowering total cholesterol and LDL levels.

Recommend in diet! [5]	**Avoid/minimize in diet!**
whole grain bread, cereal, rice & pasta	fried foods
fruits and vegetables	high-fat meats
legumes (beans, peas, lentils) & nuts some	high-fat dairy products
fish, skinless chicken, lean meat	stick/hydrogenated margarine
olive & canola oils; peanut oil	commercial baked goods
skim milk/low fat dairy products	

Very aggressive dietary measures may lower LDL at the expense of lower HDL levels. The American Heart Association Step II diet (AHA-II)[2] recommends the following:

Saturated fat <7% of **Total Calories** (**TCal**);
Polyunsaturated fat <10% TCal; Monounsaturated fat <20% TCal;
Total fat 25-35% TCal; Carbohydrate 50-60% TCal; **Fiber** 20-30g/d;
Protein ~15% TCal; **Cholesterol <200mg/d.**
(Consider: plant **stanols/sterols** – e.g. *Becel Pro-activ*® $$)

DYSLIPIDEMIA: SPECIAL CONSIDERATIONS

The Very Elderly

This is an area of some controversy. The following should be considered in assessing risk versus benefit:

- Published studies only include age **≤75**; HPS will include ≤80
- Subanalysis of 4S & LIPID suggests benefit for 2° prevention was greater for older patients (≥ age 65).[31]
- The risk vs benefit of lowering cholesterol in the very old is not well established. One study in men aged 71-93 found that mortality rates may actually increase with lower cholesterol levels.[32] Another study of those aged 85 and older found that those with a higher total cholesterol level had a lower rate of all-cause mortality.[33] LDL may be a better predictor.
- Risk of myopathy increases with age & ↓ renal function.
- Aggressive lipid lowering for 1° prevention in age ≥75years is not supported in the literature. Encourage lifestyle change!
- Consideration should be given to concomitant illness, general health status and social issues such as the patient's values.

Patients With Diabetes [1,2,34,35,36]

- Prevalence of hypercholesterolemia is similar in patients with and without diabetes; however, the CHD risk is much higher. Patients with diabetes without MI history are at an **equal 7 year risk** of acute MI as patients without diabetes who have had a previous MI.[37] Thus, patients with diabetes over age 30 years are classified as **"very high risk"** for CAD. Aggressive lifestyle measures and drug treatment is recommended.
- Diabetic dyslipidemia (↑TG; ↓HDL; small dense LDL particles, often only borderline high) is part of the ***metabolic syndrome*** consisting of several risk factors: abdominal obesity, hypertension, insulin resistance & a procoagulant state. ATP III Guidelines consider lowering **LDL to be a primary target** of therapy.[2] Other factors contributing to the metabolic syndrome (e.g. obesity, physical inactivity & other dyslipidemia) are 2° targets.
- **Statins** are **first-line therapy when LDL is above target** especially given clinical trial evidence for reducing cardiac events and overall mortality.[38] Higher doses will also lower TGs. Some literature suggests atorvastatin may be preferred when both LDL and TGs are highly elevated; however outcome data is stronger for simvastatin and pravastatin.
- For patients with **predominant hypertriglyceridemia**, initial therapy should include diet, weight loss, physical activity and moderation of alcohol intake. Improving **glucose control** is effective although high TG levels may not be adequately controlled with diet alone; **treatment with fibrates may be useful.** Patients with TG levels >5.65mmol/L are also at high risk of acute pancreatitis.[6] Note: if TG levels are very high, fibrate treatment may ↑ LDL.
- Caution with **Niacin**; high doses may cause insulin resistance.
- Caution with **Resins**; (e.g. cholestyramine) can ↑ TG levels.

HIV Patients on Protease Inhibitors [39]

- Treatment requires special considerations that are beyond the scope of this publication - reader should be aware of the need for screening; consider consultation to specialist.

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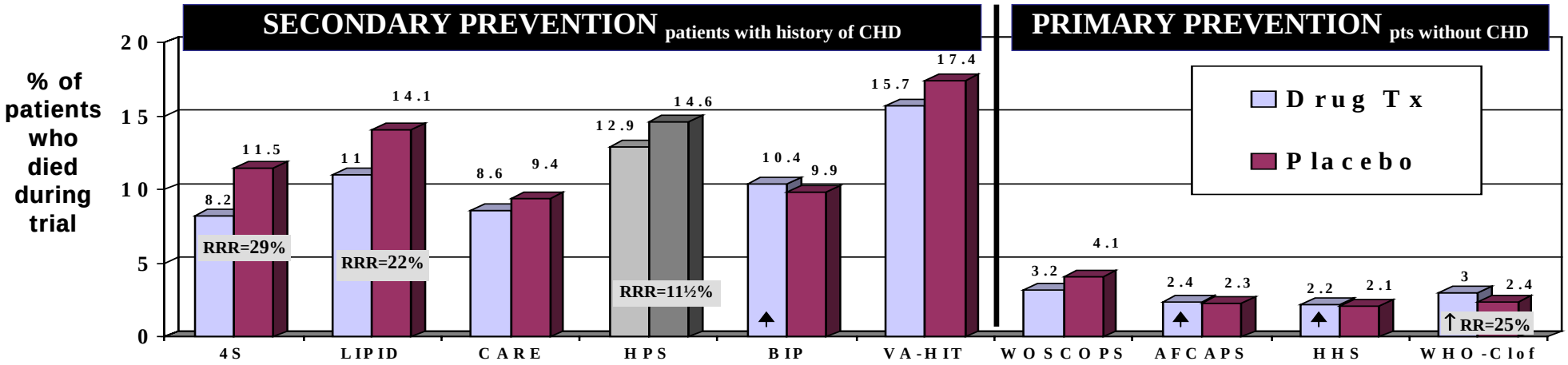
Loren Regier BSP,BA & Brent Jensen BSP

References available on request or online @ www.sdh.sk.ca/RxFiles

Figure 3. ALL-CAUSE MORTALITY OUTCOMES from MAJOR LIPID TRIALS

Prepared by: Loren Regier – www.sdh.sk.ca/RxFiles –Feb/02



Drug & dose used	Simvastatin 20-40mg/day [8]	Pravastatin 40mg/day [9]	Pravastatin 40mg/day [40]	Simvastatin 40mg/day [18,41]	Bezafibrate 400mg/day [42]	Gemfibrozil 600mg BID [43]	Pravastatin 40mg/day [10]	Lovastatin 20-40mg/day [11]	Gemfibrozil 600mg BID [44]	Clofibrate 1.6g/day [45]
ARR mortality	**3.3%** p=0.0003	**3.1%** p<0.001	**NS**	1.7% p<0.001	**NS**	**NS**	**0.9% p=0.051**	**NS**	**NS**	**(-0.6%)** p <0.05
NNT mortality	30	32	**NS**	59	**NS**	**NS**	**111 (p=0.051)**	**NS**	**NS**	**NNH=167**
Tx Duration	5.4 yrs	6.1 yrs	5 yrs	5 yrs	6.2 yrs	5.1 yrs	4.9 yrs	5.2 yrs	5 yrs	5.3 yrs
All-cause mortality in *plain English* based on NNT for study	**Treat 30 patients for 5.4 years to prevent 1 death**	**Treat 32 patients for 6.1 years to prevent 1 death**	No statistical difference in all-cause mortality	**Treat 59 patients for 5 years to prevent 1 death**	No statistical difference in all-cause mortality	No statistical difference in all-cause mortality	**Trend: 1 death prevented per 111 patients over 4.9yrs**	No statistical difference in all-cause mortality	No statistical difference in all-cause mortality	Treating **167** patients for 5.3yrs **caused 1 extra death**
n= (♂+♀) *publication year*	3617+827 *1994*	7498+1516 *1998*	3583+576 *1996*	15454♂+5082♀ *2002?*	2825♂ *2000*	2531♂ *1998*	6595♂ *1995*	5608+997 *1998*	4081♂ *1987*	15745♂ *1978*
Patients studied	pts with angina or previous MI & TC >5.5 age 35-70	recent hx of acute MI or unstable angina; age 31-75	recent hx of acute MI & average LDL; age 21-75	High risk patients: MI, CHD, PVD, PVD, DM, HTN; TC ≥3.5; age 40-80	recent hx of MI or stable angina; age 45-74	♂ with CHD, low HDL & normal LDL; age <74	♂ with cholesterol ≥7; (44% smokers) age 45-64	↓**HDL** but normal LDL & TC; ♂ 45-73yr & ♀ 55-73yrs	♂ with high levels of non-HDL cholesterol age 40-55	♂ with normal or high TC ; age 30-59
LDL (average) initial⇨achieved	**4.9⇨3.2**	3.9⇨2.9	3.6⇨2.5 ✝	3.3⇨2.3	3.9⇨3.6	2.9;↔LDL	5⇨4.1	3.9⇨3.0	4.9⇨4.5	not available
1° Endpoint Placebo/Drug	**↓ total mortality 11.5% / 8.2%**	**↓ death CHD 8.3% / 6.4%**	**↓ MI / death CHD 13.2% / 10.2%**	mortality from: all cause/CHD/other	**MI** or **death** sudden **NS** 15% / 13.6%	**↓ MI / death CHD 21.7% / 17.3%**	**↓MI /death CHD 7.9% / 5.5%**	**↓ 1st CV event 10.9 / 6.8%**	**↓ MI / death CHD 41.4% / 27.3%**	**↓ heart disease**
Comments	impact began at ~ 1 year		benefit most in ♀ & high LDL baseline	awaiting publication	benefit only in pts with *TG* >2.3	some benefit in ↑HDL & ↓TGs	higher risk pts	Serious adverse outcome events 34% in **both** groups	↑ in non-CHD mortality?	NOTE: ↑ death & ↑ liver/GI risk
	STATINS				**FIBRATES**		**STATINS**		**FIBRATES**	

ARR= % absolute risk reduction **CHD**= coronary heart disease **CV**= cardiovascular **CVD**= cardiovascular death **DM**= diabetes **GI**= gastrointestinal **hx**= history **MI**= myocardial infarction **MI NF** =nonfatal MI **NNH**= # needed to harm one **NNT**= # needed to treat to benefit one (e.g. in 4S trial, treating 30patients for 5.4yr would prevent 1 death) **NS**= not statistically significant **pts**=patients **RRR**= relative risk reduction **Tx**= treatment ✝ in the CARE trial pts with initial LDL **<** 3.2 did not receive CV benefit from pravastatin; **Lipid values in mmol/L** (**HDL**= high density lipoprotein **LDL**= low density lipoprotein **TC**= total cholesterol **TG**= triglycerides)
NOTE: This collection of data is from different studies of varying patient groups and with varying methodology; it presents data and demonstrates overall trends but can not be used for direct quantitative comparison.

Summary of All-Cause Mortality Evidence

{ many studies not powered to evaluate this endpoint ; of published trials, only the 4S had this as the primary (1°) endpoint }

- **Statins**: good evidence for 2° prevention; some evidence for 1° prevention of middle-age male patients at ↑'d risk of CHD; lack evidence for 1° prevention in low risk patients
- **Fibrates**: **no** evidence yet for reductions in 1° or 2° all-cause mortality; possible benefit in subset of patients with low HDL, TG's >2.3 &/or patients with diabetes
- lack of published data to evaluate risk vs benefit in **age ≥75**; all-cause mortality risk vs benefit of **aggressive pursuit of targets** (e.g. high dose/combinations) is **not studied**

Table 3. DYSLIPIDEMIA – PHARMACOLOGICAL MANAGEMENT

Prepared by: Brent Jensen BSP **www.sdh.sk.ca/RxFiles** **FEB/02**

	Generic/TRADE	LDL[2,7] (dose effect)	HDL[2]	TG[2]	SIDE EFFECTS /CONTRAINDICATIONS (CI) /COMMENTS/MONITOR (M)	DRUG INTERACTIONS	THERAPEUTIC BENEFITS/USES	USUAL Dose Range (Max dose/day) Studied doses in 1° or 2° prevention	$ / Year
STATINS/HMG	**Atorvastatin** LIPITOR ATO (10,20,40,80$_{elipitcal}$mg tablet)	↓ 35 - 60%	↑ 5-15%	↓ 7-30%	**SE≤10%**;Generally better tolerated than other agents Common: upper **GI disturbances**, muscle pains, **headache**, rash & sleep disturbances Rare: peripheral neuropathy, lupus like Sx, impotence[46] ↑ **LFT** (AST & ALT >3X Normal in < 2%)[4,7]; **dose** dependent; reversible if statin stopped **Myopathy**: <1%; rhabdomyolysis <0.2%[6] (CK>10x) -watch for muscle pain & weakness, ↑ creatinine kinase (CK) & darkened urine. -risk ↑ **10 fold**[17] with combinations/DI's (<1%) ↓ CNS SE: **ATO,FLU,PRA** due to↓ CNS penetration **CI**: Active Liver Disease, High alcohol consumption & Pregnancy **M**: LFT:0,3,6,12 months→annually.(CK if indicated)	↑ **effect of:** digoxin[ATO]↑20%, warfarin[FLU,LOV,SIM] **FOR: LOV, SIM, ATO**[less effect] ↑ **toxicity with HMG &:** amprenavir, **clarithromycin**, clofibrate, cyclosporin, diltiazem, ethinyl estradiol, **erythromycin**, fenofibrate, fluoxetine, fusidic acid, **gemfibrozil**, **grapefruit juice**, ketoconazole, indinavir, **itraconazole**, **niacin**, **nefazodone**, ritonavir & **verapamil**. ↓ **effect of HMG by:** cholestyramine & colestipol (space by ≥ **2hrs**); carbamazepine, phenytoin, phenobarbital & rifampin.	↓ Cholesterol ATO,FLU,LOV,PRA,SIM ↓ Atherosclerosis FLU,LOV,PRA,SIM ↓ Coronary Heart Disease FLU,LOV,PRA,SIM ↓ Stroke PRA,SIM Effective in secondary causes such as diabetes & in nephrotic syndrome	10mg po hs 20mg po hs (80mg/d **$1,008**) AVERT,MIRACL 40mg po hs	771 943 1,008
	Fluvastatin LESCOL FLU (20 & 40mg capsule)	↓ 20-35%						20mg po hs 40mg po hs 40mg po bid cc (80mg/d)	406 535 986
	Lovastatin LOV MEVACOR (**20**$_{scored}$ & 40mg tablet)	↓ 25-40%						20-40mg po hs 1° AFCAPS 40mg po bid cc → 40-80mg/d POST CABG (**cc**=with meals ↑ absorption) (80mg/d)	679-1,182 2,279
	Pravastatin PRA PRAVACHOL (10,20 & 40mg tablet)	↓ 20-35%		ATO & SIM may ↓ TGs most [3,29]				20mg po hs (80mg/d) 40mg po hs 1° WOSCOPS; 2° → CARE,LIPID {Adjust dose for severe **renal** impairment [7]}	467 653
	Simvastatin SIM ZOCOR (5,10,20,40 & 80$_{rectangle}$ mg tablet)	↓ 25-50%						10mg po hs 20-40mg po hs 2° 4S 40mg po hs 2° MRC/BHP: HPS 80mg po hs (80mg/d)	849 1,029 1,029 1,029
	Pravastatin least DIs-some transplant meds &GEM. Fluvastatin less DIs→ still with glyburide, phenytoin, rifampin & warfarin. **Atorvastatin similar** DIs but less dramatic. {**Primary Mechanisms**[3,17] **of DI**: **PRA⇨sulfation**; **ATO/LOV/SIM⇨CYP-3A4**; **FLU⇨CYP-2C9**}								
FIBRATES	**Bezafibrate** BEZALIP BEZ (200mg tab;400mg SR tab)	LDL shifts to larger more buoyant forms[3]	↑ 10-20%	↓ 20-50%	Common: GI upset, rash & **abdominal pain** Less common: headache, pruritis, loss of libido, drowsiness, dizzy, arthralgia, ↑ glucose, sleep disorders & blurred vision Rare: ↓ renal fx, anemia, ↑ LFT's, **myopathy,** reversible impotence & **gallstones** ↑ by 1-2%[3] **CI**: severe hepatic & renal Dx & ?**smoking** (↑ in cardiac events in smokers + gemfibrozil[VA-HIT]) **M**: CBC,Scr (↓ dose if ↑ Scr),Glucose, LFT's (?CK's) **Criteria**: if gemfibrozil/fenofibrate intolerance or ineffective ➜ bezafibrate **Clofibrate was associated with ↑ mortality**[WHO]	↑ **toxicity/levels with**: cyclosporin, furosemide, MAOI's, probenecid & **statins**. ↓ **effect by** : cholestyramine & colestipol (space by ≥ **2hrs**); rifampin ↑ **effect of**: chlorpropamide, furosemide, **sulfonylureas** & **warfarin**.	✔↓Cholesterol & ↓TG; ↑HDL ✔Combo with HMG/Niacin (to ↑ HDL & ↓ TG) ↓ Atherosclerosis ✔**Type III** dyslipidemia May be useful if : ♦**TG >2.3**mmol/l BIP, HHS -virtually **all** clinical benefits in patients with **diabetes & ↑ insulinemia**[7] -to date, lack evidence for all-cause mortality benefit	200mg po bid cc 200mg po tid cc (600mg/d) 400mg SR po od 2° BIP	615 881 771
	Clofibrate -D/C by Co 500mg capsule	↓ 5-20% (LDL may ↑ if **TG very high** initially)						1gm po bid cc (2-3g/d) WHO 1° - 1.6g/d; 2° CDP 1.8g/d	✘ 186
	Fenofibrate LIPIDIL 100mg cap ✘ LIPIDIL MICRO 67✘ & 200mg cap LIPIDIL SUPRA (✘→ 100 & 160mg tab)	-fenofibrate may ↓ LDL & ↓TG more than GEM [3,7] -current outcome evidence best with gemfibrozil						2 x100mg LIPIDIL od cc (400mg/d) 200mg MICRO po od cc DAIS (200mg/d)	✘ 456 604
	Gemfibrozil LOPID GEM (300mg cap, 600mg tablet)							300mg po bid ac (**ac**=before meals) 600mg po bid ac 1° HHS, 2° VA-HIT (1500mg/d)	211 260 260
RESINS	**Cholestyramine** QUESTRAN CME (4gram regular,4gram **light**)	Option: mix with metamucil & orangejuice/lemonade the night before; refrigerate & give next day, ½ before breakfast & ½ before supper (shake well)			Common(<30%): **constipation**, nausea & bloating Rare:hyperchloremic acidosis[CME] in peds/↓renal fx [3] **CI**: biliary obstruction, dysbetalipoproteinemia, **TG >4.6** mmol/l (Caution TG >2.3 mmol/l); phenylketonurics ("light" & "orange granules") ↑ fluid & bulk in diet→ **metamucil** may be required **Mix** →**juice**/milk/water/applesauce **M**:LFT's,TGs	**Space other meds** (by ≥ **2hrs**) with **resins since ↓ absorption** of: amiodarone, cyclosporin, digoxin, diuretics, fat soluble vitamins (A,D,E,K), folate, **HMG's**, levothyroxine, methotrexate, mycophenolate, NSAIDS, propranolol, steroids, sulfonylureas, valproate, **warfarin**.	✔↓ Cholesterol & ↓ LDL (esp. pregnancy & age >2yrs) ✔Combo with HMG (to ↓ LDL) ✔Pruritus esp. with certain biliary/liver dx ✔Bile acid induced diarrhea	4g po bid ac → +/- 8g/day POST CABG 8g po bid ac (16-24g/d) **Start** 4g od-bid to ↑ tolerability	635 1,185
	Colestipol COLESTID (5g granules; 7.5g **orange** granules; 1gm tab)	↓ 15-30%	↑ 3-5%	NO Change or Possible INCREASE				2g po bid ac 4g po bid ac 10g po bid ac (20-30g/d) **Start** 2-5g od-bid to ↑ tolerability	485 886 1,491
	Nicotinic acid NIACIN (50,100 & 500mg tablet) **SR products** non-prescription in Canada: less effective; ? better tolerated but ↑ hepatic SE	↓5-25% -shifts to larger buoyant forms[3]	↑ 15-35%	↓ 20-50%	**Flushing** (↓ by **ASA 1/2hr pre**),dry eyes, pruritus, headache,GI upset,↑ LFT's,↑uric acid & ↑ **glucose** **CI**: severe peptic ulcer Dx, chronic liver Dx, overt diabetes & severe gout **M**: LFT's, glucose, uric acid	♦Low dose or 325mg/d **ASA**: useful on initiating/↑ niacin dose to ↓ flushing; some pretreat X3d. ASA may also ↑ niacin levels. **HMG's**: ? ↑ myopathy if with lovastatin[47]	✔↓Cholesterol & ↓TG; ↑HDL ✔Combo with HMG/Fibrate (to ↑ HDL & ↓ TG) ✔Niacin deficiency (Pellagra)	**Start 50-100mg bid-tid (↑ tolerability) (increase weekly by ~100mg/week)** 500mg po tid **with meals** 1500mg po bid 1° ADMIT 1g po tid cc 2° CDP (3-6g/d)	144 191 191
	~**2g niacin/day** helps **HDL & TG**, but **only** higher doses affect **LDL**[3,7] **NICOTINAMIDE-NOT EFFECTIVE !!**								

MAJOR RISK FACTORS[1,2]: **Diabetes,** Smoking, Hypertension (≥140/90/BP meds), Low HDL ≤ 1, Family History premature (Age: ♂ <55, ♀ <65) CHD, Age (♂ ≥45, ♀ ≥55); **MODIFIABLE** ↑BP,↑ Cholesterol/**LDL**,Obesity: BMI > 25, Waist (♂ >100cm, ♀ >90cm), Smoking, Diet, Alcohol & sedentary lifestyle. **Screen:** pts with CAD/PVD/carotid atherosclerosis, diabetes, xanthomata or other stigmata of dyslipidemia; family history of dyslipidemia/CAD; adults with 2 or more risk factors; other pts (♂ ≥40, ♀ ≥50).

DRUG INDUCED HYPERLIPIDEMIA[48,49]: amiodarone, beta-blockers non ISA, carbamazepine, clozapine, cyclosporin, danazol, contraceptives esp. levonorgestrel, phenytoin, phenobarbital, protease inhibitors, progestins, retinoids, steroids & thiazides≥50mg/d.

CHOICE OF AGENT: **↑↑ LDL** ⇨HMG +/- resin; **↑↑ LDL & ↑TG** ⇨HMG; **↑↑ LDL & ↓HDL** ⇨HMG +/- fibrate/niacin; **Normal LDL & ↑↑TG** ⇨fibrate/niacin or combo; **Normal LDL & ↓HDL** ⇨fibrate/niacin or combo

TARGETS[1]:

for patients at:						
See Tables 4&5	**VERY HIGH RISK** (10yr CAD risk **>30%**	LDL **<2.5**	Total Chol/HDL **<4**	TG **<2**)	{**Very high risk** includes ALL patients with **CAD / DIABETES age 30+ / CVD / PVD**}	***Highest risk benefit most!***
	HIGH RISK (10yr CAD risk **20-30%**	LDL **<3**	Total Chol/HDL **<5**	TG **<2**)	May treat **medication & lifestyle** changes **concomitantly**	
	MODERATE RISK (10yr CAD risk **10-20%**	LDL **<4**	Total Chol/HDL **<6**	TG **<2**)	→ May treat with medication **after 3 months** of lifestyle therapy if targets not met	♦ **Lifestyle changes for DIET, EXERCISE, moderate alcohol use & stop SMOKING!**
	LOW RISK (10yr CAD risk **<10%**:	LDL **<5**	Total Chol/HDL **<7**	TG **<3**)	→ May treat with medication **after 6 months** of lifestyle therapy if targets not met	

=Exception Drug Status SK ✘=Non-formulary SK ✔Indication/Use **DI**=Drug Interaction **Dx**=disease **dysfx**=dysfunction **GI**=gastrointestinal **HDL**=high density lipoprotein **HMG**=HMG CoA reductase inhib→**STATINS** **LDL**=low density lipoprotein **SE**=side effect **TG**=triglycerides

Table 4. CDN Working Group[1] -10yr risk of CAD in patients without diabetes or clinically evident heart disease Framingham data·

RISK*	MEN									WOMEN								
AGE	20-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	20-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74
Age Points	-1	0	1	2	3	4	5	6	7	-9	-4	0	3	6	7	8	8	8
TOTAL CHOL	<4.14 mmol/l		4.15-5.17 mmol/l		5.18-6.21 mmol/l		6.22-7.24 mmol/l		≥7.25 mmol/l	<4.14 mmol/l		4.15-5.17 mmol/l		5.18-6.21 mmol/l		6.22-7.24 mmol/l		≥7.25 mmol/l
	-3		0		1		2		3	-2		0		1		2		3
HDL	<0.9 mmol/l		0.91-1.16 mmol/l		1.17-1.29 mmol/l		1.3-1.55 mmol/l		≥1.56 mmol/l	<0.9 mmol/l		0.91-1.16 mmol/l		1.17-1.29 mmol/l		1.3-1.55 mmol/l		≥1.56 mmol/l
	2		1		0		0		-2	5		2		1		0		-3
SYSTOLIC BP	<120 mmHg		120-129mmHg		130-139mmHg		140-159mmHg		≥160 mm Hg	<120 mmHg		120-129mmHg		130-139mmHg		140-159mmHg		≥160 mm Hg
	0		0		1		2		3	-3		0		1		2		3
Smoker	Yes = add 2 No = 0									Smoker	Yes = add 2 No = 0							
TOTAL POINTS:																		

POINTS	MEN: actual 10yr CAD risk %	Comparative risk for MALE of same age	Avr risk	Low risk
1	3	30-34	3	2
2	4	35-39	5	3
3	5	40-44	7	4
4	7	45-49	11	4
5	8	50-54	14	6
6	10	55-59	16	7
7	13	60-64	21	9
8	16	65-69	25	11
9	20	70-74	30	14
10	25			
11	31			
12	37			
13	45			
14	≥53			

CAUTION: Risk Tables only a tool; some parameters variable. Identification of patient specific risk factors (see bottom Table 3) may be more valuable in some cases! Specialist opinion.

POINTS	WOMEN actual 10yr CAD risk %	Comparative risk for FEMALE of same age	Avr risk	Low risk
1	2	30-34	<1	<1
2-3	3	35-39	<1	<1
4-5	4	40-44	2	2
6	5	45-49	5	3
7	6	50-54	8	5
8	7	55-59	12	7
9	8	60-64	12	8
10	10	65-69	13	8
11	11	70-74	14	8
12	13			
13	15			
14	18			
15	20			
16	24			
17	>27			

RISK CATEGORIES ♂&♀	10yr CAD Risk
VERY HIGH RISK	>30%
HIGH RISK	20-30%
MODERATE RISK	10-20%
LOW RISK	<10%:

Table 5. USA-NCEP Working Group[2] -10yr risk of CAD in patients without diabetes or clinically evident heart disease.

RISK*	MEN										WOMEN									
AGE	20-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	20-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
Age points	-9	-4	0	3	6	8	10	11	12	13	-7	-3	0	3	6	8	10	12	14	16
TOTAL CHOL																				
<4.13 mmol/l	0		0		0		0		0		0		0		0		0		0	
4.14-5.15	4		3		2		1		0		4		3		2		1		1	
5.16-6.19	7		5		3		1		0		8		6		4		2		1	
6.2-7.23	9		6		4		2		1		11		8		5		3		2	
≥ 7.24	11		8		5		3		1		13		10		7		4		2	
HDL mmol/l	<1.03		1.04-1.28		1.29-1.54		>1.55				<1.03		1.04-1.28		1.29-1.54		>1.55			
	+2		+1		0		-1				+2		+1		0		-1			
				Not Treated	Treated									Not Treated	Treated					
SYSTOLIC BP mmHg	<120			0	0						<120			0	0					
	120-129			0	1						120-129			1	3					
	130-139			1	2						130-139			2	4					
	140-159			1	2						140-159			3	5					
	>160			2	3						>160			4	6					
SMOKER																				
No	0		0		0		0		0		0		0		0		0		0	
Yes	8		5		3		1		1		9		7		4		2		1	
TOTAL POINTS																				

POINTS	MEN: actual 10yr CAD risk %												
<0-4	5-6	7	8	9	10	11	12	13	14	15	16	≥17
1	2	3	4	5	6	8	10	12	16	20	25	≥30

POINTS	WOMEN actual 10yr CAD risk %													
<9	9-12	13-14	15	16	17	18	19	20	21	22	23	24	≥25
<1	1	2	3	4	5	6	8	11	14	17	22	27	≥30

*Risk assessments based on Framingham data; other risk factors such as family history of CAD should also be considered. **For suggested lipid targets, see bottom of Table 3.**

Patients with clinical **CAD, CVD, PVD, and DIABETES age 30+** are **"very high risk"** regardless of risk score. **Cardiac Risk Tools:** 1) www.statcoder.com 2) www.nhlbi.nih.gov/guidelines

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