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Scientific Update™

Future Directions of Statin Therapy

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Coronary heart disease (CHD) and stroke remain leading causes of death in North American men and women. Consequently, the atherosclerotic process that affects the coronary, cerebral, and peripheral vascular circulation has been studied extensively in the last decade. It is now well-established that lipid-lowering therapy reduces cardiac death. Newer data suggest that the incidence of stroke is also decreased with HMG-CoA reductase inhibitor (statin) therapy in CHD patients. Recent trials with statins have "pushed the envelope" by assessing patients with moderate and even normal lipid values. A dilemma now exists as to which patients should be started on lipid-lowering therapy, and how aggressive that therapy should be.

The science of statins

The majority of coronary and cerebrovascular events result from unstable atheroma which can rupture, erode, and form thrombi. These are "soft" plaques that are prone to rupture, in contrast to "hard" fixed plaques that have a decreased risk of rupture. The transition from a chronic stable atherosclerotic plaque to one that is unstable is a complex, nonlinear process that is sporadic in nature. The process involves the endothelial wall interacting with many systems, including the hematopoetic and inflammatory systems. Current concepts about the mechanisms of statins include their ability to stabilize plaque and improve endothelial function.

Lipid-lowering diets in animals[1] have demonstrated a decrease in both macrophage accumulation and matrix metalloproteinase activity (MMPI), the latter allowing for increased collagen synthesis, increased plaque stabilization, and prevention of rupture.

The endothelium is a vital and active "organ" in the atherosclerotic process. Many intermediates of cholesterol synthesis are important in endothelial and cellular function. Nitric oxide synthase (eNOS type III) is important in vasodilation and statins have been shown *in vivo* to increase the bioavailability of NO.[2] New animal research suggests that the stroke protection seen with statins may be mediated by increased NOS and that this appears to be a class effect of these drugs. Thus, statins may have a pleiotropic cardiac effect that is independent of their effect on serum cholesterol levels.

Stroke studies

Stroke is the leading cause of long-term disability in the aged. Prior to the statin era, trials did not show a consistent benefit in stroke reduction. However, there was a 20% relative risk reduction in stroke with decreased LDL cholesterol levels in patients in the 4S Study, a 31% decreased risk (p=0.03) in the CARE trial, and a 19% decrease in stroke rates (p=0.048) in a CAD population in the LIPID study. A recent meta-analysis of 28 trials demonstrated a 24% risk reduction (95% CI, 0.062-0.92) of non-fatal and fatal stroke with statin therapy in this patient group.[3]

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Table 1: NCEP II with risk assessment

Positive

- age: male ≥45
- age: female ≥55 or premature menopause without ERT
- smoking
- hypertension
- HDL <0.9 mmol/L
- diabetes
- negative HDL >1.6 mmol/L

NCEP Guidelines: Past, present, and future (Table 1 and 2)

The Expert Panel of the National Cholesterol Education Program (NCEP) Guidelines have evolved over the last 10 years. The NCEP II Guidelines were published in 1993 and new Guidelines are in preparation that will hopefully be ready in one to two years. There are several issues to consider.

In NCEP I, the major target of treatment of high blood cholesterol in adults focused on LDL; however, they set barriers to drug treatment. Major emphasis was on primary prevention with lifestyle changes that are still appropriate today.

In NCEP II, Guidelines focused more on the absolute risk of an event. The goal for LDL was <2.6 mmol/L for secondary prevention.[4] Dietary and lifestyle intervention was suggested prior to any drug treatment initiation.

The future: When to treat, who to treat, how to treat

Recent clinical trials of primary and secondary prevention in CHD (4S, CARE, WOSCOPS, AFCAPS-TexCAPS,[5] LIPID) have implications for the selection of patients for therapy that need to be addressed in future NCEP guidelines. Cardiac events were decreased in 4S by 34%, in CARE by 24%, and in LIPID by 27%. In the subgroup analysis of LIPID of patients with LDL <3.5 mmol/L, there was a 16% reduction in events, however, confidence intervals overlap unity. In addition, follow-up in the large observational MRFIT cohort (over 350,000 patients) suggests no evidence for a threshold level of LDL and CAD risk (Figure 1).[10] These studies strongly support the NCEP approach of adjusting the intensity of cholesterol-lowering therapy to absolute risk, and confirm that drugs are indicated for many high-risk patients in both primary and secondary prevention. Although, according to Dr. Grundy, it may make sense to initiate statin therapy in patients with LDL levels of 2.6 to 3.3 mmol/L – given the curvilinear relationship between serum cholesterol levels and CAD risk – more analysis is needed. Data to-date is based on sub-group analysis, which can be fraught with danger.

Table 2: NCEP II treatment decisions based on LDL cholesterol.

	Initial level	LDL Goal
Dietary treatment		
Without CHD, <2 risks	4.1 mmol/L	4.4 mmol/L
Without CHD, ≥2 risks	3.4 mmol/L	3.4 mmol/L
With CHD	2.6 mmol/L	2.6 mmol/L
Drug treatment		
Without CHD, <2 risks	4.9 mmol/L	4.1 mmol/L
Without CHD, ≥2 risks	4.1 mmol/L	3.4 mmol/L
With CHD	3.4 mmol/L	2.6 mmol/L

Special groups

Future Guidelines will also need to address special groups such as patients with high triglycerides, diabetes, the elderly, women, and those with low HDL.

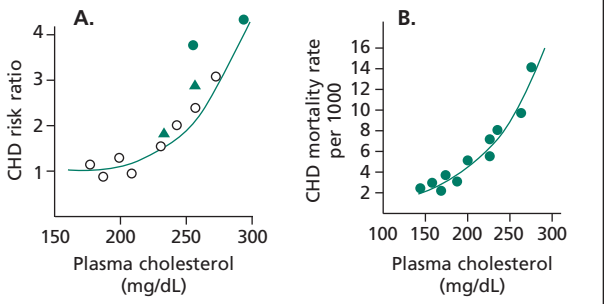
Diabetic patients: New NCEP guidelines will also address the high-risk diabetic patient. Recent data suggest that patients with diabetes may have as high a risk for coronary events as non-diabetics with established CAD.

The elderly: Age should not be a factor regarding secondary prevention CAD in the elderly. Ongoing trials for primary prevention are underway. The SAME study – fluvastatin versus placebo for primary prevention of CAD in patients aged 70-85 years and total cholesterol >6.4 mmol/L – is now underway.

Postmenopausal women: NCEP II Guidelines suggest estrogen as an alternative to statin therapy in the postmenopausal woman with CAD and hyperlipidemia. Although estrogen may have other uses in some patients, the recent HERS[11] study showed a lack of benefit of combination HRT on cardiac events despite reducing LDL levels. These results will focus future emphasis on therapy with statins in post-menopausal women. Recent primary and secondary prevention trials (TexCAPS and LIPID) have shown a clear benefit of statins in the female population.

Patients with low HDL: A recent unpublished report from the VA-HIT trial assessing gemfibrozil in men with low HDL (mean 0.8 mmol/L) and low LDL (2.9 mmol/L) found a 22% relative risk reduction in cardiac events (P=0.006), despite only small changes in HDL and no change in LDL. This suggests that patients with low HDL alone may benefit

Figure 1: Relationship between serum cholesterol levels and CHD in male subjects without established CHD at entrance into prospective study. Figure 1A relates serum cholesterol levels to relative risk (risk ratio) for developing clinical CHD in earlier prospective studies: Framingham Heart Study[6] (●), Pooling Project[7] (▲), and Israeli Prospective Study[8] (○). These surveys suggest a threshold relationship. Figure 1B plots association between serum cholesterol levels and CHD mortality for 356,222 male screenees of MRFIT.[9] A curvilinear relationship was observed.[10]



from lipid-lowering therapy. Patients in the primary prevention AFCAPS/TexCAPS study had HDL levels of <0.9 mmol/L. Lowering LDL attenuated the baseline low HDL.

When to initiate therapy: This will also require future thought. The ongoing MIRACL study is assessing atorvastatin versus placebo, 24 to 96 hours after a cardiac event. Current Guidelines suggest initially waiting until after a trial of diet therapy. Data from this trial are not yet complete.

TNT (Treating to New Targets): An ongoing study

There are no definitive trials addressing how low to go with LDL cholesterol in patients with CAD. An international randomized trial is currently underway that will hopefully address this important question. The Treating to New Targets (TNT) study is measuring the additional benefits of very aggressive lipid-lowering. This study will compare atorvastatin, 80 mg versus 10 mg PO OD, after a two-month run-in phase (over 5 years) of the 10 mg dose. At entry into TNT, the mean LDL of patients is expected to be 4.2 mmol/L, and it is expected that each treatment arm will achieve an LDL of 2.6 versus 1.8 mmol/L, respectively. Thus, the range of LDL cholesterol on which treatment will be based in some TNT Study patients is similar to that used as a treatment target in other studies (eg, CARE). Over 8500 patients will enter the study and recruitment is one-third complete. Men and women aged 35 to 75, with CAD and LDL levels of 3.4 to 6.5 mmol/L are eligible. The primary endpoint of TNT is nonfatal MI or CAD death.

"Standard" medical therapy: A moving target

Although patients with stable angina and good exercise tolerance have relatively low event rates (MI or death <5%/year), trials such as ACME, MASS, and RITA that compared PTCA to medical therapy have shown improvement in symptoms and exercise tolerance with angioplasty. However, standard therapy in previous studies did not include intensive cholesterol lowering.

The AVERT Trial

The Atorvastatin VErsus Revascularization and Treatments Trial (AVERT) randomized 341 patients referred for angioplasty to treatment with either atorvastatin 80 mg/day or percutaneous transluminal coronary angioplasty (PTCA), followed by usual care.[12] Included were patients with at least one coronary stenosis of ≥50%, an LDL cholesterol >3.0 mmol/L, and the ability to exercise ≥4 min. Patients were followed for 18 months. This is an intriguing study, but it should be mentioned that 15% of the patients who entered the trial were asymptomatic. Because Canada is a country that is less revascularization-based, these patients might not have been offered angioplasty and therefore, they risked procedure-related events. LDL decreased to 3.2 mmol/L (an 18% reduction) in the PTCA group and to 2.0 mmol/L (a 46% reduction) in the atorvastatin group. There was a lower incidence of combined CV events 13% (N=22) in the medical treatment group than in the PTCA treatment group 21% (N=37). This represents a 36% reduction in events with medical therapy. A substudy of exercise time[13] suggests that among patients with exercise-induced ST depression, ischemic events occurred at least as infrequently in the medical group (6/70 or 8.6%) as in the PTCA group (17/88 or 19%).

The overall safety of aggressive LDL reduction in the medical therapy group was good, with only four patients (2.4%) experiencing transaminase elevations of greater than three times the upper limits of normal. There were no clinically significant differences in adverse event rates between the two treatment groups.

The COURAGE Study (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) sponsored by the Canadian government, the NIH, and industry, will address aggressive medical therapy versus revascularization in the future with 3200 patients targeted for this ambitious trial.

Forest for the trees; Trying to reach current targets

Although an interesting academic debate has evolved around such issues as "how low to go" with lipid-lowering therapy, there is a larger and probably more important issue

that is often ignored. The medical community as a whole is often remiss in not treating patients to *current* target levels. Schrott et al recently published baseline lipid values and rates of adherence to NCEP treatment goals in the HERS study cohort.[14] This study included a well-treated, well-educated group of women with established heart disease – over 85% had undergone coronary angioplasty or bypass surgery within six months of entering the trial – in a randomized, controlled trial carried out at major centres in North America. Usually such patients receive "more ideal" treatment than those not entered into big trials. However, at baseline, only 47% of the women were taking lipid-lowering drugs. In this group, 63% were not meeting the 1988 target LDL-C of <3.4 mmol/L, and astonishingly, 91% were not meeting the 1993 target LDL-C of <2.6 mmol/L.

The PREVENT study was a cardiac drug trial that included a large group of patients with established coronary disease who were treated from 1994-1996; women made up 20% of the study group. An oral presentation of PREVENT revealed that 48% of men, compared to 29% of women, had LDL-C levels <3.4 mmol/L ($p<0.05$), and that 31% of men, compared to 12% of women, had LDL-C levels <2.6 mmol/L ($p<0.05$). This and other data suggest that both men and women are not being treated as aggressively as is warranted regarding lipid-lowering. In addition, women are being treated sub-optimally compared to men.

Given this apparent gender discrepancy, one might ask if treating to targets in women is feasible. The Women's Atorvastatin Trial on Cholesterol (WATCH) study[15] evaluated 318 women with coronary disease (n=198) or risk factors for coronary disease (n=120) in a 16-week open-label study evaluating atorvastatin in treating to target LDL-C levels that included: <2.6 mmol/L in patients with CHD, <3.4 mmol/L in those with ≥2 risks, and <4.1 mmol/L in those with <2 risks. Over 50% of the women with established CHD achieved NCEP II target LDL-C with 10-20 mg/day of atorvastatin. Only 18% of this cohort could not reach target LCL-C levels. One can conclude that in the female population, target LDL-C levels are achievable on drug therapy. These results are interesting when juxtaposed against data presented above that suggests poor treatment of female (and male) patients.

Conclusion

In an era of proven benefit of statin therapy in CAD patients, new trials will address lower targets for LDL levels and include a broader range of patients to start lipid-lowering drugs. Cholesterol guidelines may need to be refined given the implications of recent trials. Treatment strategies contrasting revascularization with aggressive and comprehensive medical therapy will be explored as we enter the next millennium. More important perhaps is the recognition that many patients currently are undertreated based on recommendations from relatively conservative contemporary guidelines.

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