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Secondary Prophylaxis with Simvastatin and Lovastatin:
Additional Insights from the XVIIIth Congress of the European Society of Cardiology

Reported and discussed by: Shaun Goodman, MD

Numerous epidemiological studies have demonstrated a continuous relationship between serum cholesterol levels and coronary artery disease. It is now well established that a 10% reduction in cholesterol level over a period of several decades is associated with a 30% reduction in coronary artery disease incidence.[1] Despite the overall suggestion that earlier lipid lowering therapies (e.g., clofibrate, gemfibrozil, cholestyramine) reduced deaths related to coronary artery disease, there was no improvement in overall survival, in part due to an apparent increase in non-cardiac mortality, including cancer and violent deaths.

The first generation of lipid lowering trials utilized drugs that lower cholesterol only modestly (approximately 10%). However, with the availability of 3-hydroxy-3 methyl glutaryl coenzyme A (HMG CoA) reductase inhibitors, the degree of cholesterol lowering is about 25%. In November, l994, the landmark Scandinavian Simvastatin Survival Study (4S) was published.[2] This trial demonstrated a 30% reduction in the risk of death (p = 0.0003) over a median of 5.4 years in patients with coronary heart disease with the use of simvastatin 20-40 mg daily compared with placebo. The reduction in overall mortality was explained by a 42% reduction in the risk of coronary death with simvastatin therapy, which produced a long term 35% mean reduction in low density lipoprotein (LDL) cholesterol, accompanied by a mean increase in high density lipoprotein (HDL) cholesterol of 8%. Based on these results, the addition of simvastatin 20-40 mg daily to the treatment regimens of 100 coronary heart disease patients could be expected to yield the following approximate benefits over the first 6 years of treatment: preservation of the lives of 4 of 9 patients who otherwise would die from coronary heart disease, prevention of non-fatal infarction in 7 of an expected 21 patients, and avoidance of myocardial revascularization procedures (bypass surgery and/or coronary angioplasty) in 6 of the 19 anticipated patients.

Cost effectiveness

Dr. Terje Pedersen, 4S Co-ordinator, presented additional information regarding the remarkable safety profile and cost effectiveness of long term simvastatin therapy on

St. Michael's Hospital
30 Bond St., Suite 701A
Toronto, Ontario M5B 1W8
Fax: (416) 864-5330

August 25, l996 at the XVIIIth Congress of the European Society of Cardiology. Dr. Pedersen discussed the results of a 4S substudy designed to evaluate the impact of simvastatin on healthcare resource utilization. Prospectively collected data from hospital admissions were used to perform a cost minimization analysis,[3] which quantified the direct economic impact of simvastatin during a treatment period that was equal to the trial duration. Cost minimization analyses do not consider the potential benefits of therapy in comparison with the cost of therapy; rather, they consider the healthcare utilization costs and assume that the clinical effects are equivalent to the alternative treatment strategy.

In the placebo group (n = 2,223), 937 patients had 1,905 hospitalizations for acute cardiovascular events or coronary revascularization procedures. In the simvastatin group (n = 2,221), 720 patients had 1,403 such hospitalizations ($p < 0.0001$). The cost of cardiovascular hospitalizations was estimated by use of diagnosis – related group (DRG) – based costs per case in the United States. Simvastatin therapy reduced the costs for total cardiovascular disease over the median 5.4 years of follow-up by 31%, or US $3,872 per randomized patient. In the United States, the mean daily cost of simvastatin in the dosages used in 4S is US $2.30. Thus, the effective cost of simvastatin would be reduced by 88% to US $0.28 per day through the reduced need of healthcare resources resulting from therapy. In other words, the drug costs of treatment are largely offset by savings that result from fewer hospitalizations from myocardial infarction, unstable angina, or revascularization procedures.

Dr. Pedersen also described an analysis of cost effectiveness of simvastatin as used in the 4S. This type of analysis quantifies the cost of simvastatin treatment against the cost of hospitalization and procedures avoided due to simvastatin treatment and "converts" the observed benefit into life years saved. By placing a dollar value on clinical effects, one can arrive at a reproducible method of calculating the total cost of treatment in a way that can be used for comparative purposes against other standard medical treatments. A cost-effective analysis model of survival over the next 20 years following completion of the trial was added to the observed benefit seen during the double blind period of 5.4 years.[4] In this analysis, the cost per life year saved was US $9,300. This calculation is comparable to the estimates by Goldman et al[5] indicating that in secondary prevention with 20 mg per day of lovastatin given patients with serum cholesterol > 6.4 mmol/L, the cost per life year saved is $25,000. Compared with other cost effective analyses of a variety of commonly accepted treatments (e.g., treatment of mild hypertension, US $17,000 – 25,000), this estimate is very favourable.

Dr. Pedersen concluded by commenting on the remarkable safety profile of long term simvastatin therapy.[6] Detailed clinical and laboratory safety data collected during the study revealed that the only clearly drug-related serious adverse event was a single reversible case of myopathy. Minor elevations of hepatic transaminases among patients in the simvastatin group were also noted, but the frequency of persistent elevations above 3 times the upper limit of normal was not significantly different from placebo. There were no significant differences in adverse events in any body system between simvastatin and placebo. Importantly, 94% of patients in both the simvastatin and placebo treated groups maintained their study drug over the course of the trial (median 5.4 years).

Persistent benefits of cholesterol lowering

An additional abstract from the 4S researchers was presented on August 27th. Kjekshus et al[7] described the subsequent coronary mortality and coronary event rate among the 757 patients who sustained one or more hospital verified non-fatal myocardial infarctions during the study (n = 300 in the simvastatin group, n = 457 in the placebo group; risk reduction of 37%). Not surprisingly, patients who sustained a non-fatal infarction and were receiving simvastatin had fewer subsequent coronary heart disease deaths (10.1% vs 15%), non-fatal reinfarctions (18.3% vs 23.0%), revascularizations (30.3% vs 37.2%), and atherosclerosis-related events (51.7% vs 63.7%) when

compared to the placebo group. Together with the original trial results, this presentation suggests that cholesterol lowering with simvastatin was effective in not only preventing recurrent infarction in the first place, but was also effective in reducing subsequent coronary heart disease mortality and the risk of coronary heart disease /atherosclerotic events in patients who sustained a non-fatal myocardial infarction during treatment. Kjekshus et al[7] concluded that therapy should be continued in such patients in order to provide maximal benefit from simvastatin.

In his address on medical therapy for primary and secondary prevention (as part of an independent symposium on implications of clinical trials of lipid lowering therapy), Dr. G.D. Smith (Professor of Clinical Epidemiology, Bristol, United Kingdom) indicated that multivariate analysis of the available data reveal a strong relationship ($p < 0.001$) between pretreatment cholesterol elevation and cost-effectiveness of its treatment. Furthermore, in lowering coronary heart disease mortality, there is a direct relationship ($p = 0.02$) to the extent of cholesterol lowering, suggesting that more potent lipid lowering medication may be most appropriate and cost-effective.

Lipid lowering post-CABG

On August 25, l996, Dr. Lucien Campeau from the Montreal Heart Institute discussed the results of the NHLBI-sponsored Post-CABG (Coronary Artery Bypass Grafting) trial.[8] Saphenous vein graft (SVG) occlusion approaches 40-50% at 10 years and is related to accelerated atherosclerosis. While several traditional risk factors for coronary artery disease (hyperlipidemia, diabetes, and smoking) are also found to be more frequently associated with SVG disease, only lipid lowering therapy has clearly been shown to delay the development of late graft obstructive changes.

Post-CABG was a multicenter, double blind controlled trial designed to answer two major questions regarding the optimal care of patients after CABG: 1) Is an aggressive cholesterol lowering regimen better than a moderate one for improving outcome? and 2) Can a low dose anticoagulant regimen that uses warfarin affect outcome? A total of 1,351 patients who had undergone bypass surgery 1-11 years previously were enrolled between March l989 and August l991. To qualify, patients had to have an LDL level between 3.4 and 4.5 and a triglyceride level of < 4. Qualifying patients aged 21-76 were randomized in a factorial design to: 1) aggressive cholesterol reduction with lovastatin (40-80 mg per day) +/- cholestyramine (8 gm) vs moderate cholesterol reduction with lovastatin (2.5-5 mg per day) +/- cholestyramine (8 gm), or 2) low dose warfarin (target INR of l.8-2) vs placebo. All patients received 80 mg of ASA.

Quantitative angiography was performed at baseline and after 4-5 years of follow-up (achieved in 88% of enrolled patients). The primary end point of the study was the percentage of patients in each group that showed substantial angiographic progression (decrease in the minimal luminal diameter by ≥0.6mm). In the aggressive cholesterol reduction group (utilizing a mean lovastatin dose of 76 mg, and with 30% of patients also requiring 8 gm of cholestyramine), 27.9% of patients showed substantial angiographic progression compared with 38.8% in the moderate cholesterol reduction group (mean dose of lovastatin 4 mg, only 5% of patients also on cholestyramine), a 29% relative decrease ($p < 0.0001$). In contrast, 34.2% of the warfarin treated group and 32.5% of the placebo treated group showed substantial progression ($p = NS$). There was a trend toward fewer clinical events in the aggressive cholesterol reduction group (12.6% vs 15.3%: $p = 0.09$), although the study was not powered to detect a difference in clinical events.

New lesions were found in the saphenous vein grafts of 10% of patients treated with aggressive cholesterol reduction compared with 20% in the moderate cholesterol reduction group ($p < 0.001$), a 50% risk reduction. The mean reduction of graft minimal luminal diameter was 0.2 mm with aggressive lowering compared with 0.37 mm ($p < 0.0001$) luminal loss in moderate cholesterol reduction group, a 16% risk reduction. Re-operation or angioplasty was necessary in 6.3% of patients treated

with aggressive cholesterol reduction compared with 9.2% of patients treated with moderate cholesterol reduction ($p < 0.02$), a 30% risk reduction.

Dr. Campeau concluded that aggressive cholesterol reduction using full dose lovastatin ± cholestyramine is more effective than moderate cholesterol reduction in preventing disease progression in coronary artery bypass grafts.

Secondary prophylaxis

Another recently published secondary prevention trial (CARE)[9] enrolled 4,159 post myocardial infarction patients with even lower baseline cholesterol levels (mean total 5.9 mmol/L, LDL 4.0 mmol/L) at initial screening. Despite a more modest reduction (20%) in total cholesterol with pravastatin, there was a 24% reduction in cardiovascular death and myocardial infarction after 5 years ($p = 0.003$).

Conclusion

Collectively, these secondary prevention trials demonstrate that cholesterol lowering therapies (in particular, the HMG Co-A reductase inhibitors) result in a 20-25% reduction in total cholesterol. This in turn produces dramatic reductions in cardiovascular events in patients with pre-existing coronary artery disease across a broad range of cholesterol values within the relatively short time frame of 5 years. The "statins" are extremely well tolerated agents which are clearly cost effective in secondary prevention. The results from these trials indicate that any patient with established coronary artery disease with a total cholesterol above approximately 5.0 and/or an LDL above 3.2 despite dietary and other lifestyle modifications should strongly be considered for therapy.

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