TREATMENT OF LDL CHOLESTEROL, HDL CHOLESTEROL AND TRIGLYCERIDES IN THE PREVENTION OF CORONARY HEART DISEASE AND ISCHEMIC STROKE

(1/28/04) (lipids-stroke-therapy)

I- BACKGROUND:

* Coronary artery disease and stroke are the major killers in the United States. A majority of strokes are ischemic. With better national control of blood pressure, hemorrhagic stroke has become less common. According to the latest statistics, around 1 million Americans will have a heart attack this year. National Health And Nutrition Surveys that rely on self-reported myocardial infarction (MI) and angina probably underestimate the actual prevalence of advanced CHD. These data suggest that 13.7 million persons in the United States have CHD, half of whom have MI's and half angina. The actual numbers may be higher as 75% cases of ischemic heart disease may be brought to light by electrocardiographic changes on an exercise test or by ambulatory 24 hour EKG monitoring (Third National Health and Nutrition Examination Survey - Public use data).

** Stroke is the second leading cause of mortality world-wide. It is estimated to be responsible for 9.5% of all deaths and 5.1 million of the 16.7 million cardiovascular disease deaths. Throughout the world, unfavorable trends in stroke risk factor profile, lack of prevention programs, misapplication or underutilization of stroke preventative portend high stroke rates and serve to widen the stroke prevention gap. This is unfortunate because stroke is well suited for prevention since it has a high prevalence and economic cost, well-defined modifiable risk factors, and effective prevention measures.

*** The major risk factors for both coronary artery disease and ischemic strokes have already been established. Among them one of the most important is hyperlipidemia. A large number of studies have proven the beneficial effects of lowering LDL-C on the incidence of coronary events but the effect of LDL lowering on ischemic stroke has been uncertain, until recently, when a number of studies like the 4S study, CARE and Lipid Trial have shown significant reduction in the incidence of Strokes and TIA. The purpose of this brief review is to shed some light on the importance of appropriate cholesterol and triglyceride management in the primary and secondary prevention of Strokes and Coronary Heart disease.

**** The Cholesterol Center of the Jewish Hospital of Cincinnati, ABC Building, 3200 Burnet Avenue, Cincinnati OH, 45229 (phone 513-924-8250), Fax (513-924-8273), email (glueckch@healthall.com) is very expert in the diagnosis and treatment of reversible risk factors for ischemic stroke, including atherosclerotic and thrombotic. Outpatient appointments can be scheduled through 513-924-8250.

II- STUDIES:  

i. Reduction of new coronary events and new atherothrombotic brain infarction in older persons with diabetes mellitus, prior myocardial infarction, and serum low-density lipoprotein cholesterol >/=125 mg/dl treated with statins.¹

A prospective study in which 529 diabetics, mean age 79+/- 9 years with no morbidities as mentioned above were divided into 2 groups; one treated with statins and the other with no lipid lowering drug. After a follow up of 29 +/- 18 months it was observed that the use of statins was associated with a 37% significant, independent reduction in the incidence of new coronary events and with a 47% significant, independent reduction in the incidence of new atherothrombotic brain infarction. And thus it was concluded that elderly diabetics with prior MI and increased LDL-C should especially be treated with statins.
ii. **ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness.**²
   This was a single center, randomized clinical trial of 161 patients with mean age of 60 years and 46% with known cardiovascular disease. The effects of atorvastatin 80 mg/d and pravastatin 40 mg/d on CIMT were compared. Baseline CIMT and other characteristics were similar in both groups. After 12 months of follow up it was found that the LDL-C was around 76 +/- 23 and 110 +/- 30 mg/dl in the atorvastatin and pravastatin group respectively. There was a regression in the CIMT of -0.034 +/- 0.021 mm in the atorvastatin group whereas the CIMT remained stable in the pravastatin group. It was concluded that marked LDL reduction (<100 mg/dl) provides superior efficacy for atherosclerosis regression at 1 year.

iii. **The Anglo-Scandinavian Cardiac Outcomes Trial lipid-lowering arm: significant lipid and coronary heart disease effects.**³
   Of the 19,342 patients randomized to one of the two antihypertensive regimens 10,305 were further randomly assigned atorvastatin 10 mg daily or placebo to form the lipid lowering arm of the study. Mean age of participants was 63 years and baseline blood pressure and lipid subtraction values were identical in the 2 groups. The study was stopped prematurely after median 3.3 years of follow up. Compared with placebo there was a 35% relative reduction of LDL-C in the atorvastatin group. The primary end point of the study (non fatal MI and a fatal Coronary Heart disease ) was significantly lower by 36 % in the statin group than in the placebo group. There were also significant reductions in secondary endpoints such as total coronary events by 29% and especially fatal and non-fatal strokes by 27%.
   Previous randomized trials of statin use for lowering cholesterol have shown, on average, significant reduction in strokes in both primary and secondary prevention of about 15 to 30%. Hence the 27% reduction in stroke incidence is in keeping with the prior observations.

iv. **Prevention of stroke and dementia with statins: Effects beyond lipid lowering.**⁴
   The epidemiological association between elevated serum cholesterol and stroke risk is controversial. However, recent secondary prevention studies with statins have demonstrated a significant reduction in ischemic stroke. Statins probably reduce stroke by a variety of mechanisms, including modulation of precerebral atherothrombosis, thus preventing plaque disruption and artery to artery thromboembolism. They also provide endothelial homeostasis, and in experimental models have shown to decrease brain infarct size and neurological outcomes. Further studies are needed to fully address the role of statins and thus cholesterol lowering in the prevention of stroke in patients without established vascular disease.

v. **Reducing the risk of coronary events: evidence from the Scandinavian Simvastatin Survival Study (4S).**⁵
   Patients with pre-existing CAD had a reduced risk of any coronary event of 27% on Zocor compared with placebo. Looking at actual LDL-C levels achieved, the 4 year event rate was:
   1. -10.8% with LDL-C level of 58 to 104 mg/dl
   2. - 3.3% with LDL-C level of 105 to 126 mg/dl
   3. -18.9% with LDL-C level of 127 to 266 mg/dl.
   This analysis shows a near linear relationship between LDL-C achieved and the rate of coronary events.

vi. **Reduction in stroke with gemfibrozil in men with coronary heart disease and low HDL cholesterol: The Veterans Affairs HDL Intervention Trial (VA-HIT).**⁶
   This was a placebo-controlled, randomized trial conducted in 20 Veterans Affairs medical centers. A total of 2531 men with coronary heart disease, mean HDL cholesterol 31.5 mg/dl and mean LDL cholesterol 111 mg/dl, were randomized to gemfibrozil 1200 mg/d or placebo and were followed up for 5 years. In the VA-HIT study Gemfibrozil resulted in 6 % higher value of HDL cholesterol, 4 % lower for total cholesterol and 31% lower for the triglycerides compared with placebo. There were 134 confirmed strokes, 90%of which were ischemic. 76 occurred in the placebo group and 58 in the gemfibrozil group, for a relative risk reduction of 31%. This beneficial effect of increasing HDL , lowering triglycerides and total cholesterol was observed only with atherothrombotic type of stroke. The incidences of lacunar or cardioembolic strokes were similar in the two groups. Gemfibrozil treatment was also associated with a 59
% reduction in TIA's and 65% reduction in carotid endarterctomies. Important point to note is that all these beneficial effects were noted in the first 6 to 12 months of initiating therapy compared with statin therapy in which the lag time is 3.5 years. This study brought the role of HDL cholesterol and triglyceride in the prevention of ischemic strokes.

vii. Effects of lowering average of below-average cholesterol levels on the progression of carotid atherosclerosis: results of the LIPID Atherosclerosis Substudy. LIPID Trial Research Group. ⁷
In this study, 522 patients with a history of myocardial infarction or unstable angina and with baseline levels of total cholesterol between 4 to 7 mmol/L (average to below average values) were randomized to treatment with a low fat diet plus pravastatin (40 mg daily) or to a low fat diet plus placebo. The Primary study outcome was the change from baseline in Carotid Wall Thickness after 2 and 4 years of follow up. Carotid atherosclerosis is not only a marker of CHD risk, it is also a marker of the risks of stroke and ischemic cerebrovascular disease. Treatment with pravastatin had the following effects:

- Total cholesterol decreased by 19%
- LDL cholesterol reduced by 27%
- Triglycerides by 13%
- Apolipoprotein B decreased by 19%
- HDL cholesterol increased by

After 2 years of follow up, the mean CWT increased by 0.039 mm in the placebo group and was essentially unchanged in the pravastatin group. After 4 years of follow up, the mean CWT had increased by a total of 0.048 mm in the placebo group and had DECLINED by 0.014 mm in the pravastatin group. Thus the finding here and in previous studies of a marked effect of cholesterol lowering on the carotid atherosclerosis (which as mentioned earlier is considered to be a marker of CHD and ischemic stroke risk), suggest that such treatment might be expected to lower the risks of having such events.

viii. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. ⁸
The primary objective of this large study of 4159 patients was to determine whether pravastatin reduces the frequency of coronary events in people who have already had one myocardial infarction yet who had average cholesterol levels (average total cholesterol of 209 mg/dL and average LDL of 139 mg/dL). The patients received either 40mg of pravastain per day or placebo for five years. The primary endpoint was a fatal coronary event or a non-fatal myocardial infarction. The frequency of the primary endpoint was 10.2% in the pravastatin group and 13.2% in the placebo group (p=.003). This difference corresponds to a 24% reduction in coronary events. The pravastatin group also showed a 31% decrease (p=.03) in the incidence of stroke compared to the placebo group. Frequencies of coronary bypass and angioplasty were also significantly lower in the pravastatin group. Patients with higher pretreatment LDL cholesterol demonstrated greater benefit from pravastatin treatment; women benefited more than men in terms of reduction of coronary events. There were no differences in overall mortality or non-coronary-related mortality between the two groups. These results show that patients with a history of coronary disease and average cholesterol levels do benefit from cholesterol-lowering therapy.

ix. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. ⁹
This was a study of 20,536 patients in the UK with the goal to determine whether simvastatin conferred any benefits to patients with a history of coronary disease, other occlusive arterial disease, or diabetes and who had a range of cholesterol levels. Patients were followed for five years taking 40mg of simvastatin or placebo. Among the findings was that patients taking at least simvastatin (some were taking additional lipid-lowering drugs) showed a reduction in non-fatal or fatal stroke (444 [4.3%] vs 585 [5.7%]; p<0.0001). The researchers concluded that the benefit of lipid therapy depends more on the overall risk for a vascular event than on the blood lipid concentrations alone.

III- RECOMMENDATIONS FOR DIAGNOSIS AND TREATMENT :
Risk evaluation:
ATP III (adult treatment panel III from the National cholesterol education program- NCEP)\(^1\) puts more emphasis on risk assessment for proper treatment of hyperlipidemia.

Absolute Risk is the likelihood for developing CHD in a given amount of time. It is further characterized as high, intermediate and low. The high risk includes:

- patients with Coronary heart disease
- patients with Coronary heart disease equivalents who are diabetics
- atherosclerotic peripheral arterial disease
- atherosclerotic abdominal aortic aneurysm
- symptomatic carotid artery disease and multiple (2+) risk factors with 10 year risk of CHD> 20%.

Other risk factors which might fall in the intermediate and low risk categories are age (males >45 years and females >5 years), Family history of premature myocardial infarction, current cigarette smoking, hypertension (BP greater than or equal to 140/90 mmhg or on anti hypertensive medications, low HDL cholesterol ( < 40mg/dl).

Lipid risk factors include triglycerides, lipoprotein (a), LDL particles, Total cholesterol/HDL ratio and nonlipid risk factors include Homocysteine, impaired fasting glucose etc.

ATP III makes a fundamental division of risk categories into,

- multiple (2+) risk factors,
  - 10 year risk for CHD >20% (CHD risk Equivalent)
  - 10 year risk for CHD 10-20%
  - 10 year risk for CHD<10%
- 0-1 risk factors

Treatment is based on the risk evaluation and will be discussed later.

## Diagnoses and desired levels.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Desired Target</th>
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<tbody>
<tr>
<td>LDL cholesterol</td>
<td>&lt;100 to &lt;130mg/dl depending on risks</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>&lt;200 mg/dl</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>&lt;250 mg/dl</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>&gt;35 mg/dl</td>
</tr>
<tr>
<td>Lipoprotein (a)</td>
<td>&lt;35 mg/dl</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>&lt;13.1 (\mu\text{mol/L})</td>
</tr>
<tr>
<td>Methylmalonic acid</td>
<td>&lt;250 nmol/L</td>
</tr>
<tr>
<td>TSH, T4 levels</td>
<td></td>
</tr>
</tbody>
</table>

## Treatment.

<table>
<thead>
<tr>
<th>Risk category</th>
<th>LDL-C goal (mg/dl)</th>
<th>LDL level to initiate therapeutic lifestyle changes (mg/dl)</th>
<th>LDL level to consider drug therapy (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD equivalents. 2+ risk factor with 10yr mortality &gt;20%</td>
<td>&lt;100</td>
<td>³100</td>
<td>³130, 100-129 drug optional</td>
</tr>
</tbody>
</table>
IV- CONCLUSION:

Ischemic stroke and coronary artery disease share similar underlying mechanisms, likely explaining much of the therapeutic benefit from statins. Current research is directed at further determining groups of patients most likely to benefit from lipid reduction in stroke prevention. There is very limited information on the role of LDL in stroke compared with CHD. One of the most interesting study, currently going on is the SPARCL study11 (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) which focuses on the effect of statins on the recurrence rate of cerebrovascular events in patients with no history of coronary heart disease and is the first trial to evaluate the benefits of treatment with statin in this population. Although more research is required to fill in the gaps, our existing knowledge of the interplay between stoke, CHD, cholesterol and triglycerides strongly suggests that patients with established CHD and stroke should be treated with lipid lowering medicine to cut down on their risk of having another event and thus reducing morbidity and mortality.

References:


E-mail: glueckch@healthall.com
or glueck@fuse.net
Fax: 513-924-8273