

# Cholesterol Lowering, Nutrition and Stroke Prevention

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In this issue of CJNS, Kim et al<sup>1</sup> report that statins halt or reverse progression of intracranial stenosis. In a related paper from a trial of the antiplatelet agent cilostazol<sup>2</sup>, progression of intracranial stenosis was shown to be related to the HDL cholesterol levels and to the ratio of ApoB to Apo A1 (similar to the ratio of LDL to HDL cholesterol).

Intracranial stenosis is a difficult problem for physicians seeking to reduce the risk of stroke. It can be hard to diagnose, and it is very hard to treat. It carries a high risk, anticoagulants provide only limited if any benefit<sup>3</sup> (with the possible exception of basilar stenosis<sup>4</sup>), and stenting carries a higher risk than does intensive medical therapy<sup>5</sup>. The key lesson from the Stenting versus aggressive medical therapy for intracranial arterial stenosis (SAMMPRIS) trial<sup>5</sup> was that medical therapy needs to be very intensive.

Clues to the diagnosis may include repeated and frequent TIA's in the territory of the same artery (particularly TIA's in the territory of a carotid branch, without proximal stenosis), and a "string of pearls" distribution of strokes in watershed distribution<sup>6</sup>. Risk factors include hypertension, diabetes, hyperlipidemia<sup>6</sup> and smoking<sup>7</sup>. Intracranial stenosis is surprisingly common; in a paper submitted for publication we found stenosis of a middle cerebral artery in a third of patients with asymptomatic carotid stenosis, and it was bilateral in a quarter of those cases.

Combination antiplatelet therapy with aspirin and clopidogrel is more effective in reducing microemboli distal to intracranial stenosis<sup>8</sup>, and is probably indicated. There was no difference found in outcomes of patients with intracranial stenosis randomized to aspirin and clopidogrel versus aspirin and cilostazol<sup>9</sup>.

Statins do reduce the risk of stroke<sup>10</sup>, and more so in patients with large artery disease. Although the overall reduction of stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial<sup>11</sup> was only 16%, this is a major underestimate of the benefit of statins for patients with strokes from atherosclerosis. In the subgroup with large artery disease in SPARCL<sup>12</sup> the reduction of stroke was 33%, and the reduction of coronary events was 43%. However, as I have pointed out<sup>13</sup>, even this is an important underestimate of the benefit, because in SPARCL there were serious problems with noncompliance, and 24.5% of patients randomized to placebo crossed over to statin during the trial. This calls for an intent-to-treat analysis to fully understand the potential of lipid lowering in stroke prevention.

In patients with asymptomatic carotid stenosis, we found that intensive medical therapy based on an approach that I call "treating arteries instead of treating risk factors"<sup>14</sup> (using measurement of carotid plaque to assess response to therapy and intensify therapy in non-responders) markedly reduced risk<sup>15</sup>. Microemboli, which strongly predict risk in asymptomatic

carotid stenosis<sup>16,17</sup>, were reduced by that approach from 12.6% to 3.7% of patients<sup>15</sup>. More importantly, the two-year risk of stroke declined from 8.8% to 1%, and the two-year risk of myocardial infarction declined from 7.7% to 1%<sup>15</sup>.

There are some problems with high-dose statins, including aggravation of diabetes<sup>18</sup>, and myopathy. It is likely that both these problems are due to mitochondrial dysfunction due to depletion of CoQ10, and some evidence that supplementation with CoQ10 and L-carnitine (which is needed by mitochondria for fatty acid entry) may improve both problems<sup>13</sup>. Another important approach is to use moderate doses of statin in combination with ezetimibe. This combination is synergistic; 10mg of atorvastatin or 5mg of rosuvastatin, when combined with 10mg of ezetimibe, lowers the LDL by as much as does 80mg of atorvastatin. The notion that ezetimibe may be harmful to the arteries was based on studies of intima-media thickness, which is not atherosclerosis<sup>19</sup>. We found<sup>20</sup> that addition of ezetimibe regressed carotid plaque in patients with plaque progression despite statin therapy.

However, it is crucial to recognize that "intensive medical therapy" does not just mean intensifying antiplatelet therapy or adding a statin. Smoking cessation, exercise, control of diabetes, control of blood pressure (preferably with an angiotensin converting inhibitor or angiotensin receptor blocker unless other therapy is indicated) and a Cretan Mediterranean diet are all important<sup>21</sup>. Indeed when ranked in importance, smoking cessation and a Mediterranean diet (things that patients must do for themselves) are at or near the top. (It is for that reason that I wrote a book for the public<sup>22</sup>). Perhaps the most underestimated is the importance of nutrition<sup>23</sup>.

A Cretan Mediterranean diet reduced stroke and myocardial infarction by over 60%, compared to a low-fat diet that was equivalent to the NCEP Step 1 diet<sup>24</sup>. It is also the best diet for diabetics<sup>25</sup>. That diet is high in beneficial oils such as olive and canola, high in whole grains, fruits, vegetables, lentils, beans and nuts, and low in saturated fats, trans fats and cholesterol. For North Americans to reduce their intake of animal flesh to the quantities consumed in the Cretan diet, it is probably easier to eat about four ounces of animal flesh every other day<sup>22,23</sup>; fish should be favoured. A single large egg yolk contains ~237mg of cholesterol, more than the 210 mg in a Hardee's Monster Thickburger, with 2/3 of a pound of beef. It is a myth that dietary cholesterol is unimportant, and a myth that egg yolks can be safely consumed by patients at risk of vascular disease<sup>26</sup>. Another nutritional myth is that vitamin therapy for homocysteine does not prevent stroke; it does<sup>27</sup>. The apparent lack of benefit probably resulted from lumping together patients with good and bad renal function<sup>28</sup>. It turns out that high-dose cyanocobalamin leads to accumulation of cyanide in patients with renal failure, so cyanocobalamin is harmful in patients with renal impairment (a GFR<50), but beneficial in patients with

good renal function. Another key issue is underdiagnosis of B12 deficiency; serum B12 is a poor way to diagnose B12 deficiency, because only 6-20% of total B12 is active; to exclude metabolic B12 deficiency the serum B12 needs to be above 400pmol/L. Within the “normal range” of 160-600 pmol/L that is commonly used, are many patients with metabolic B12 deficiency; among my patients age >71, it is 30%. However, it is now increasingly clear that for those with renal impairment we should be using methylcobalamin rather than cyanocobalamin.

Statin therapy, as observed by Kim et al<sup>1</sup>, is good for patients with intracranial stenosis – but there is much more to be done for them.

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