Nutrition in Stroke Prevention

J David Spence, MD, FRCPC, FAHA

Professor of Neurology and Clinical Pharmacology, Stroke Prevention & Atherosclerosis Research Centre, Robarts Research Institute, University of Western Ontario, London, Ontario, Canada

Abstract

Nutrition is far more important than most physicians and patients recognize. Maintaining a healthy weight, reducing dietary cholesterol, avoiding egg yolks, and consuming a Cretan Mediterranean diet substantially reduce the risk for stroke. Besides the very high cholesterol content of egg yolks (more than the recommended daily intake of 200 mg of cholesterol in a single large egg yolk), it is now apparent that phosphatidylcholine (lecithin, 250 mg per egg yolk) is converted by intestinal bacteria to trimethylamine, which in turn is oxidized in the liver to trimethylamine n-oxide (TMAO), which is pro-atherosclerotic in animal models and increases the risk for cardiovascular events in patients at risk for coronary disease. Unrecognized metabolic deficiency of vitamin B12 is very common, and frequently missed, because a 'normal' serum B12 is not a reliable test for adequacy of B12. Besides neuropathy, myelopathy, and dementia, B12 deficiency increases the risk for stroke by raising levels of total homocysteine (tHcy). Despite widespread misunderstanding of the complex issues, it is increasingly clear that B vitamin therapy to reduce homocysteine does reduce the risk for stroke. However adequacy of B12 dosing and renal impairment determine the response to B vitamin therapy: cyanocobalamin is beneficial in patients with normal kidney function, but harmful in those with renal impairment (GFR<50). Methylcobalamin should be used in patients with renal impairment.

Keywords

Nutrition, diet, cholesterol, egg yolk, homocysteine, vitamin B12

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Correspondence: J David Spence, MD, FRCPC, FAHA, Stroke Prevention & Atherosclerosis Research Centre, Robarts Research Institute, University of Western Ontario, 1400 Western Road, London, ON, Canada N6G 2V2. E: dspence@robarts.ca

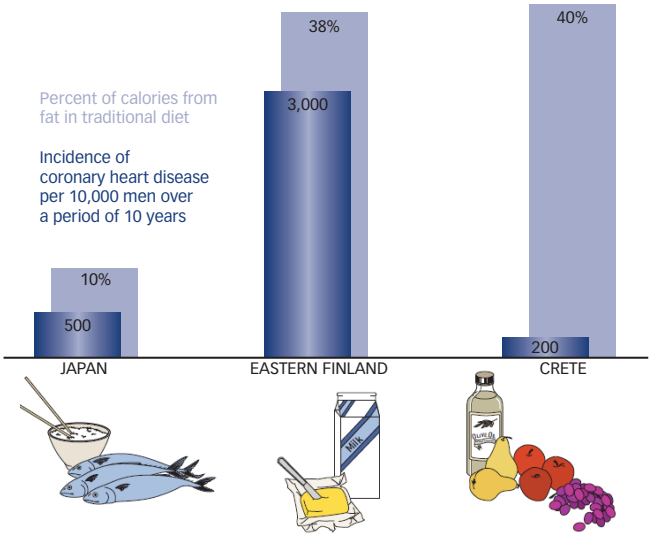
The importance of nutrition to stroke prevention is vastly under-appreciated. Many physicians and patients think that if they are taking a statin, they can eat whatever they want. Few concepts could be further from the truth. An analysis[1] of the Nurses' Health Study and the US Health Professionals study showed the importance of lifestyle in general: among 43,685 men and 71, 243 women, adhering to all five healthy lifestyle choices reduced risk for stroke by 80 %. The healthy lifestyles were not smoking, a healthy weight (BMI <25 kg/m^2), moderate activity for at least 30 minutes per day, modest alcohol consumption, and scoring within the top 40 % of a healthy diet score. The US Centers for Disease Control estimated in 2004 that half of all deaths were attributable to unhealthy behaviors.[2]

The diet that is best for stroke prevention is the Mediterranean diet: not Italian food, but the diet from Crete. Besides diet, it is increasingly clear that metabolic B12 deficiency is far commoner than is usually recognized, that B12 deficiency is the leading cause of elevated homocysteine, and that B vitamin therapy to lower homocysteine does reduce the risk for stroke, if not of myocardial infarction. In this review I will address maintenance of a healthy weight, the Cretan Mediterranean diet, the importance of dietary cholesterol and egg yolk consumption, metabolic B12 deficiency, mechanisms by which elevated levels of total homocysteine (tHcy) increase the risk for stroke, and B vitamin supplementation to reduce the risk for stroke.

Maintaining a Healthy Weight

The high intake of fat and carbohydrates that lead to obesity increase the risk for diabetes and of vascular disease through effects independent of obesity per se. However, obesity is an independent risk factor for stroke.[3,4,5] Although heredity undoubtedly plays an important role in obesity, 'genes are not destiny'. People with an inherited tendency to obesity may need to maintain a lower caloric intake and/or a higher level of activity to maintain a healthy weight. The arithmetic of weight maintenance is simple (and simpler with imperial units than with metric units): to maintain a given weight, the average caloric intake is approximately 10 calories (kilocalories) per pound. Assuming a normal level of (in)activity for sedentary office workers, a person who weighs 250 pounds has been consuming approximately 2,500 calories per day. One pound of fat represents 3,500 stored calories and a mile of walking only burns off 100 calories. Thus to lose a pound, one would need to walk 35 miles, or reduce caloric intake by 500 calories per day for a week. (It takes more than a year to lose 50 pounds at that rate, because of metabolic adjustments to caloric restriction).

Figure 1: Cardiovascular Risk and Fat Intake



International comparisons reveal that total fat intake is a poor indicator of heart disease risk. What is important is the type of fat consumed. In regions where saturated fats traditionally made up much of the diet (for example, eastern Finland), rates of heart disease were much higher than in areas where monounsaturated fats were prevalent (such as the Greek island of Crete). Crete's Mediterranean diet, based on olive oil, was even better for the heart than the low-fat traditional diet of Japan.
Source: Reproduced by permission of Cornelia Blik from: Willett and Stampfer, 2003.[9]

To achieve this, obese people must learn to eat more low-calorie food and less high-calorie food. They need to know the calorie values of the foods they are eating, and when they are about to eat something, need to ask themselves if the item they are about to consume is worth that many calories to them. A single potato chip is 10 calories; a peanut seven, a cashew 15, a large order of French fries 600 calories (consisting of 200 calories of potato and 400 calories of absorbed fat). A serving of meat is around 400 calories, so a useful maneuver, which also helps adherence to the Mediterranean diet discussed below, is to consume meat (the flesh of any animal: anything with eyes, a face or a mother) every other day. To make this successful it is important to think in terms of having fun learning how to make a healthy diet tasty and enjoyable.[6]

Although the public media tout the advantages of a low-carbohydrate diet for weight loss, in the long term it is balance of caloric intake and caloric expenditure that determines weight.[7] The Israeli diet study of Shai et al.,[8] one of the best dietary studies ever conducted, in that it achieved much higher compliance than most dietary studies, showed that weight loss was virtually identical on the Mediterranean or low-carbohydrate diet, and both were significantly better than the low-fat diet. As discussed below, that study also showed that the Mediterranean diet was the best for diabetes and pre-diabetes.

The Cretan Mediterranean Diet

As pointed out by Stampfer and Willett,[9] the low-fat diet recommended by the National Cholesterol Education Program (NCEP) was drawn from thin air, by a group of experts trying to imagine the diet that would be most effective for reduction of fasting LDL cholesterol levels. It is not the proportion of calories from fat that determines cardiovascular risk, but the type of fat. As shown in *Figure 1*, the Mediterranean diet from Crete contains nearly the same proportion of calories from fat (40 %) as the diet of Eastern Finland, but has only 1/15th the cardiovascular risk for the Finnish diet and only 40 % of the risk for the low-fat diet of Japan, where only 15 % of calories were from fat.

The Cretan Mediterranean diet is clearly the best diet for prevention of stroke or myocardial infarction, and also the best diet for diabetes. In the Lyon Diet Heart Study, a secondary prevention trial in which patients who had survived a myocardial infarction, the Mediterranean diet was compared to a 'prudent Western Diet', which was a low-fat diet equivalent to the Step 1 diet promoted then by the National Cholesterol Education Program (NCEP). In the Mediterranean diet, canola margarine was substituted for butter. It contained less than 300 mg/day of cholesterol and aimed for a low intake of fat. The daily cholesterol intake in the Western diet was around 300 mg/day, versus 200 for the Mediterranean diet; the intake of beneficial oils was much higher in the Mediterranean diet, the intake of saturated fat lower, and importantly, the intake of alcohol (mainly from red wine, this being a French study) was not different. The French paradox is not about red wine; it is about the entire dietary portfolio.

The result of the study was a 70 % reduction of cardiovascular events in 4 years; event rates are shown in *Table 1*. Thus the effect of diet was approximately twice that of simvastatin in the Scandinavian Simvastatin Survival Study,[10] carried out at the same time, with a 40 % reduction of cardiovascular events in 6 years.

Many experts were skeptical of the results of the Lyon Diet Heart Study, which was the first randomized trial to show that the Mediterranean diet was far superior to the low-fat diet recommended by NCEP and the American Heart Association at the time. One objection was that 'it was a margarine study, not a diet study'. The skepticism was largely due to the failure of the Mediterranean diet to reduce fasting levels of cholesterol. However, diet is not about the fasting lipids; it is about the post-prandial state.[11]

Recently, a Spanish study showed in primary prevention that a Mediterranean diet was superior to a low-fat diet. A total of 7,447 participants, 57 % women, who were at high cardiovascular risk, but with no cardiovascular disease at enrollment, were randomized to either a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a low-fat diet. Mean age was ~67 years, and ~14 % were smokers; ~half were diabetic, ~80 % hypertensive, ~70 % dyslipidemic, and ~22 % had a family history of premature vascular disease. Compared to the low-fat diet, the Mediterranean diet with supplemental olive oil reduced stroke by 34 %, and the Mediterranean diet supplemented with nuts reduced stroke by 46 %; myocardial infarction was reduced by 20 and 26 % respectively. In Britain, a vegetarian diet reduced ischemic heart disease by approximately 30 %,[12] but there were too few strokes to detect an effect on stroke reduction. Furthermore, a Mediterranean diet is more palatable to most patients. There should now be no residual doubt that the Cretan Mediterranean diet is the best diet for preventing stroke and myocardial infarction.

The Cretan diet is also the best diet for diabetes. This was shown in the Israeli diet study,[8] which achieved unprecedented adherence by providing color-coded meals in the cafeteria to residents of a large institution. That study clearly showed that compared to either a low-fat diet or a low-carbohydrate diet, the Mediterranean diet achieved the greatest

reduction of blood glucose, insulin and insulin resistance, among overweight diabetics. Weight loss was similar on the low-carb and Mediterranean diet, and both were more successful in maintaining weight reduction than the low-fat diet. Regression of carotid arterial volume measured by 3D ultrasound was similar on the three diets, and was proportional to blood pressure reduction with weight loss.[13]

Ancel Keys, leader of the seven Countries Study that first recognized the benefits of the Cretan diet, described 'the good Mediterranean diet' in a retrospective article[14] as follows: "The heart of this diet is mainly vegetarian, and differs from American and northern European diets in that it is much lower in meat and dairy products and uses fruit for dessert." This diet is both high in beneficial foods, and low in harmful ones. It is not a low-fat diet; it is high in olive oil and canola oil, high in whole grains, fruits, vegetables, lentils, beans, nuts, and low in cholesterol and saturated fat. It favors fish, limits red meats to once a week or less, and has a much lower quantity of animal flesh than the North American diet. For most North Americans, a serving of only 2–3 ounces of chicken, fish, beef or other animal flesh ('anything with eyes, a face or a mother') is not sufficient to make a meal. We tend to name the meal by the meat: 'What's for dinner tonight? Chicken', with potatoes and compulsory boring vegetables on the side (what I call 'heated groceries', as opposed to cuisine) because our mother told us we had to eat them. For this reason I encourage my patients to alternate vegetarian days with days on which the intake of animal flesh is kept to a serving the size of the palm of the hand, but not as thick as the thenar eminence—more like the thickness of a hamburger patty. Patients at risk for stroke should avoid egg yolks, as discussed below. They may get a bit of cholesterol in a piece of cake, but they should never eat an egg yolk or a whole egg on a plate, or in a sandwich or salad. This is a big change in lifestyle, so to accomplish this I encourage them to think of the meatless day every other day as their gourmet cooking class day, have fun learning how to make this tasty and enjoyable, and provide them with recipes for meatless chili, pastas, curries, stir-fries, and an omelette and a frittata made with egg substitutes such as Egg Beaters or Better 'N Eggs. These recipes are in my book for the public, *How to Prevent Your Stroke*.[6] The reasons for using egg whites or egg-white-based egg substitutes are discussed next.

Dietary Cholesterol and Egg Yolk

The myth that dietary cholesterol is harmless because it does not increase levels of fasting LDL cholesterol by much is responsible for much of the misunderstanding in this field. It has been well known for many years that dietary cholesterol increased cardiovascular risk, and that feeding of cholesterol causes atherosclerosis in animal models. These issues were reviewed in 2010.[15] There are good reasons for guidelines recommending that dietary cholesterol be limited to less than 200 mg/day.[16,17]

Egg Marketing Propaganda

The propaganda of the egg industry rests on a red herring and a half-truth. The red herring is the emphasis on fasting lipids; the half-truth is the slogan 'eggs can be part of a healthy diet for healthy people', based on failure to show harm from egg consumption among people who remained healthy during follow-up, in two large observational studies.[18,19]

The Red Herring

Diet is not about fasting lipids; it is about the post-prandial state.[11] The level of LDL cholesterol we wake up with is mainly determined by how much cholesterol our liver puts out during the night, and this is mainly determined by heredity. For about 4 hours after a high-cholesterol meal, there is inflammation in the arteries, an increase in oxidative stress, impaired endothelial function and an increase in oxidation of LDL cholesterol by nearly 40 %.[15]

Table 1: Cardiovascular Outcomes in the Lyon Diet Heart Study[70]

423 MI survivors; 4-year follow-up			
	Mediterranean	Western	p value
Cardiac death	14	44	0.0001
+ Non-fatal MI			
Above plus	27	90	0.0002
Unstable angina, stroke, CHF, PE or systemic embolism			

CHF = congestive heart failure; MI = myocardial infarction; PE = pulmonary embolism. Source: By permission of Lippincott, Williams and Wilkins.[70]

The Half-truth

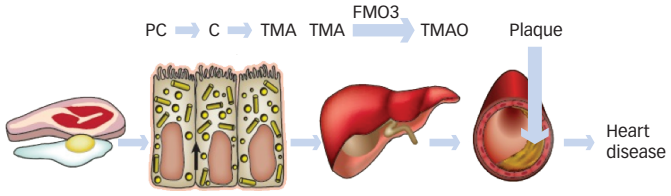
Both of the observational studies referred to above showed that among participants who remained healthy during follow-up, no harm could be shown from egg yolks. However, in both studies, an egg a day doubled coronary risk among those who became diabetic during follow-up.[18,19] A recent meta-analysis[20] confirmed that finding, and also showed that eggs significantly increase the risk for diabetes. The likely reason for failure to show harm among participants who remained healthy was lack of statistical power: participants were too young and not followed long enough to have enough events; diabetics have a higher risk for cardiovascular events, so harm could be shown in that subgroup. The Greek study in diabetics[21] showed that each 10 g of egg per day increased coronary risk by half; an egg a day increased coronary risk fivefold.

Egg yolks are very high in cholesterol: a single large egg yolk contains more than the recommended daily intake of cholesterol; a jumbo egg yolk contains 237 mg of cholesterol, more than a Hardee's Monster Thickburger®, which contains 12 ounces of beef, three slices of cheese and four strips of bacon.[22] Yes, the burger is more harmful than an egg, because it also contains saturated fat, but a little-known fact is that dietary cholesterol is permissive of the harmful effect of saturated fat.[23] Replacing eggs with egg-white-based egg substitutes improves endothelial function.[24]

In 2012, egg yolk consumption was found to be approximately 60 % as harmful as smoking, with regard to development of carotid atherosclerosis.[25] The effect of egg yolks and smoking was additive: egg yolks alone increased carotid total plaque area (TPA) 1.77-fold, smoking alone increased TPA 2.22-fold, and the combination of smoking and egg consumption increased TPA 3.09-fold (all significant after adjustment for age).[26]

It turns out that the harmful effect of egg yolk is not all due to the very high cholesterol content. Phosphatidylcholine (lecithin) in egg yolks is converted by intestinal bacteria to trimethylamine, which in turn is oxidized in the liver to trimethylamine n-oxide (TMAO)[27,28] (see *Figure 2*). TMAO is pro-atherosclerotic in animal models,[27] and in patients referred for coronary angiography, using a test dose of two hard-boiled eggs, patients in the top quartile of TMAO levels had a 2.5-fold increase in risk for major cardiovascular events, after adjusting for all the traditional

Figure 2: Egg Yolks, Intestinal Microbiome, and Vascular Disease



Meat and egg yolks are rich in the lipid phosphatidylcholine (PC) and its metabolite choline (C). Intestinal bacteria convert C to trimethylamine n-oxide (TMA). In the liver, the enzyme FMO3 processes TMA to TMAO—a metabolite that makes its way into the blood. Wang and colleagues show that circulating TMAO may contribute to greater plaque development in the arteries, and so to heart disease. Source: Reproduced by permission of Nature *from Rak and Rader, 2011.[28]*

coronary risk factors.[29] A growing awareness of the importance of the intestinal microbiome is changing our understanding of dietary issues.[30]

Patients at risk for cardiovascular disease, including stroke, should limit their intake of dietary cholesterol, and should avoid egg yolks. They should learn to make a Cretan Mediterranean diet tasty and enjoyable, reduce their intake of animal flesh to a serving the size of the palm of their hand every other, day, and learn to make a tasty omelette or frittata using egg whites or (what I think is tastier) egg-white-based substitutes such as Egg Beaters or Better 'N Eggs.[6,11]

Metabolic B12 Deficiency

There is an important problem with underestimation of the prevalence of B12 deficiency in the elderly. This issue is of particular importance to neurologists, because besides increasing the risk for stroke via increases in levels of homocysteine. As discussed below, B12 deficiency causes neuropathy, myelopathy, and dementia.

Much of unrecognized metabolic B12 deficiency results from failure to understand that a 'normal' serum B12 does not define adequacy of B12. Only ~20 % of serum B12 is in the active form,[31] so serum B12 is not sensitive for B12 deficiency. In Europe measurement of holotranscobalamin[32] is used for diagnosing B12 deficiency.

Metabolic B12 deficiency is specifically defined by elevation of methylmalonic acid levels (or in folate-replete subjects by elevation of plasma homocysteine).[33] It is present in 20 % of the elderly,[34] so the 'normal' range (the 95 % of the population within two standard deviations of the mean) includes, in the elderly, quite a few people with B12 deficiency (about 17.5 % of those in the normal range).

Helga Refsum, at Oxford, and colleagues showed in 2009[35] that to be 95 % confident that metabolic B12 deficiency can be excluded, serum B12 needs to be above 400 pmol/L. That inflection point coincides with the serum B12 below which levels of tHcy increased in the NHANES study.[36]

A typical 'normal' range in a hospital lab would be around 160–600 pmol/L. In my vascular patients, metabolic B12 deficiency is present in 12 % below age 50, 13 % age 50–71, and 30 % over age 70.[37] *Figure 3* shows the 'normal' distribution of serum B12 among my patients; it can be seen that it is clearly not adequate.

B12 deficiency raises levels of homocysteine,[33] which is a clotting factor that increases the risk for deep vein thrombosis, retinal vein thrombosis and cerebral vein thrombosis, and quadruples the risk for stroke in patients with atrial fibrillation.[38] This is probably why reduction of homocysteine is important in stroke prevention, even though it has not reduced myocardial infarction.[39]

Just as with folate deficiency, B12 deficiency can cause atrophy of intestinal villi,[40] preventing absorption of oral B12. This can be restored in many (or maybe most) patients with a couple of injections of B12, so that thereafter B12 can be absorbed from tablets.

If the serum B12 is not above 400 pmol/L with high doses of oral B12 (such as 1,200 mcg slow release), it may be necessary to give several B12 injections (e.g. 1,000 mcg subcutaneously on four occasions at weekly intervals) to restore the intestinal villi. After that is done, if the serum B12 remains above 400 pmol/L, then B12 shots will not be needed.

Monthly injections are usually not adequate to maintain serum B12 levels above 400 (because it is water-soluble and excreted in the urine); injections may need to be more frequent, so for most patients daily B12, 1,200 mcg extended release once or twice a day, is better. Stabler recently reviewed B12 deficiency.[31]

Homocysteine and Risk for Stroke

Despite media reports following the publication of HOPE-2[41] and NORVIT[42] in 2006, homocysteine is not dead, at least for stroke prevention. Elevated levels of plasma total homocysteine (tHcy) are a strong, independent and graded risk factor for vascular disease.[42,43] The biological plausibility is overwhelming. Elevated levels of total homocysteine (tHcy) impair endothelial function, and this is reversible with vitamin therapy.[44] Homocysteine increases oxidative stress,[45] increases hepatic synthesis of cholesterol,[46] increases levels of asymmetric dimethylarginine (ADMA), a nitric oxide antagonist,[47] appears to be causal in Mendelian randomization studies,[48,49,] and is causal in animal models.[50,51] In an analysis of the National Health and Nutrition Examination Survey (NHANES) and the Multi-Ethnic Study of Atherosclerosis (MESA) study, tHcy resulted in a net reclassification of cardiovascular risk by 20 %.[52]

Elevated levels of total homocysteine increase deep vein thrombosis, retinal vein thrombosis, and cerebral vein thrombosis, and markedly increase the risk for stroke in atrial fibrillation.[53,54] It is by far the commonest clotting factor: elevated tHcy is present in 20 % of the population, and increases with age because of impaired renal function and unrecognized metabolic B12 deficiency. In the author's stroke prevention clinic, patients tHcy >14 micromol/L increases gradually with age to 40 % of those over age 80.[55]

B Vitamin Supplementation to Reduce the Risk for Stroke

Given all the foregoing, it is somewhat surprising that the notion that vitamin therapy does not reduce the risk for stroke is so prevalent. One reason is that two of the large clinical trials early in this story (VISP[56] and NORVIT[42]) did not show benefit of vitamin therapy, and the study that did show a significant reduction of stroke, HOPE-2,[41] was interpreted by the authors in a way that turns out to have been incorrect. (It should be noted,

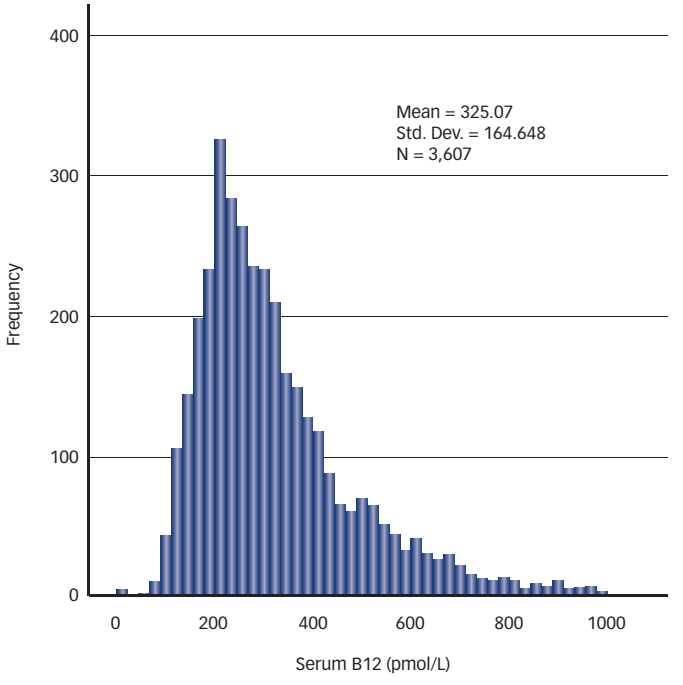
in view of issues discussed below, that HOPE-2 was the only one of the large vitamin studies for lowering homocysteine that used an adequate dose of cyanocobalamin—1,000 mcg daily.) The authors said "we could not think of a biological difference between stroke and myocardial infarction, so we concluded that the reduction of stroke was a chance finding". After the publication of the NHANES/MESA finding referred to above, Rimm and Stampfer commented[57] on the 'spinal reflex' that leads to "automatic rejection of observational data when they appear to be discrepant from trials." However, stroke and myocardial infarction are very different, and there are important problems with interpretation of the clinical trials that need clarification.[39]

Virtually all myocardial infarctions are caused by rupture of a coronary plaque, with coronary occlusion. Although platelet aggregates may play a role in the occlusion of the artery, the formation of red thrombus (fibrin polymer with entrapped red cells, which forms in the setting of stasis) probably is secondary to the occlusion. Except for lacunar infarction from small vessel disease, most strokes are embolic—either atheroembolic (platelet aggregates or plaque fragments) or cardioembolic. Cardioembolic strokes are due to embolization of red thrombus, either originating in the heart (the left atrial appendage, dyskinetic segments), or passing through the heart via a right-to-left shunt such as a patent foramen ovale or atrial or ventricular septal defect. Thus thrombosis plays a bigger role in stroke, particularly since the proportion of strokes of cardioembolic origin is increasing.

After the publication of the VISP trial,[56] some of my colleagues and I realized that there were many factors limiting our ability to detect an effect of vitamin therapy: folic acid fortification of the grain supply in North America coincided with the initiation of the trial, we used a dose of cyanocobalamin, 400 mcg, that was not high enough for elderly persons in the lowest quartile of serum B12, who require 1,000 mcg daily,[58] and we gave injections of cyanocobalamin to participants with serum B12 levels below the reference range, thereby negating the potential benefit of cyanocobalamin in the very participants most likely to benefit. We therefore designed a hypothesis-driven subgroup analysis[59] from which we excluded participants who received injections of cyanocobalamin, and for a reason that in retrospect turns out to have been mistaken, also excluded participants in the lowest 10 % of estimated glomerular filtration rate (GFR), which was <47. The mistaken reason was the expectation that vitamin therapy would not be effective, because I had previously shown with my nephrology colleagues[60] that 5 mg daily of folic acid was no more effective than 1 mg daily in dialysis patients. We never dreamed that the high-dose B vitamins would be harmful in patients with renal failure.

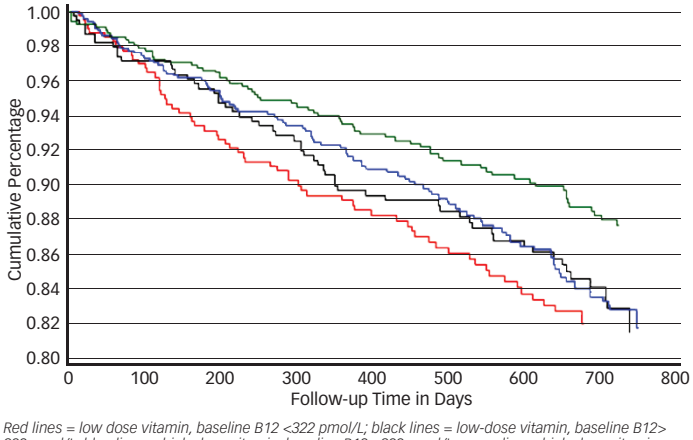
What we found in that subgroup analysis was that high dose B vitamins (folic acid 5 mg, pyridoxine 25 mg and cyanocobalamin 0.4 mg) significantly reduced the risk for stroke, death or myocardial infarction, compared to low-dose vitamins. When participants who entered the study with a serum B12 above the median of 322 pmol/L who received high-dose vitamins were compared with those who had a baseline serum B12 below the median and received low-dose vitamins, the reduction of cardiovascular events was 34 % (see *Figure 4*). This finding was largely ignored, perhaps because of a similar 'spinal reflex' to reject subgroup analysis.[39]

Figure 3: Distribution of Serum B12 Among Patients Referred to a Stroke Prevention Clinic



Patients with high levels of serum B12 above 700 pmol/L were probably taking supplements. The "normal" distribution of serum B12 is usually regarded as approximately 160–600 pmol/L, so clearly many patients referrred for stroke prevention do not have adequate levels of serum B12. Because only ~60–20 % of serum B12 is active, a total serum B12 level is not a good way to identify adequacy of vitamin B12. Many patients with a serum B12 below 400 pmol/L have metabolic B12 deficiency, and a measurement of plasma methylmalonic acid or total homocysteine is necessary to determine if the patient is deficient in vitamin B12. Measurement of holotranscobalamin is probably preferable for diagnosis of B12 deficiency.

Figure 4: Efficacy Analysis of the VISP Trial—Kaplan-Meier Analysis of Survival Free of Stroke, Vascular Death or Myocardial Infarction[59]



Red lines = low dose vitamin, baseline B12 <322 pmol/L; black lines = low-dose vitamin, baseline B12> 322 pmol/L; blue lines = high-dose vitamin, baseline B12 <322 pmol/L; green line = high-dose vitamins, baseline B12 >322 pmol/L. The overall value for the logrank comparison of all four groups was significant, p=0.02. Participants who entered the trial with a serum B12 above the median and received high-dose vitamins had a 34 % reduction of events compared with those who entered the trial with serum B12 below the median and received low-dose vitamins. Source: by permission of Lippincott, Williams and Wilkins, 2005.[59]

Since then, however, the meaning of all this has become apparent. In 2010, my colleagues and I found in a randomized trial of high-dose B vitamins, with 1,000 mcg of cyancobalamin, that despite a significant reduction of tHcy, the high-dose vitamins actually accelerated the decline of GFR, and

doubled cardiovascular events.[61] All the events occurred in participants with a GFR <50, raising the question of how B vitamins could be harmful in patients with renal failure. Possible reasons included an increase in ADMA from high-dose folic acid, as suggested by Loscalzo,[62] and accumulation of cyanide from cyanocobalamin, as reported by Koyama et al.[63] Koyama et al. also showed that administration of methylcobalamin, as opposed to cyanocobalamin, significantly reduced levels of ADMA as well as levels of tHcy. A possible mechanism for harmful vascular effects of low-level cyanide toxicity might include interference with hydrogen sulfide,[39] the 'new nitric oxide'.[64,65]

Since the publication of the earlier trials, the French SuFolOM3 trial[66] showed a significant reduction of stroke, and the subgroup analysis of VITATOPS from which participants taking antiplatelet agents were excluded[67] also showed a significant reduction of stroke.

It is now increasingly clear that B vitamins to lower homocysteine do reduce the risk for stroke; however in future we should probably be using methylcobalamin rather than cyanocobalamin. In patients on dialysis, daily nocturnal dialysis normalizes tHcy,[68] and is probably to be preferred, especially in dialysis patients who have experienced a stroke or TIA. Other approaches to lowering homocysteine levels in dialysis patients include administration of thiols such as mesna, but an optimal regimen has not yet been worked out. In renal failure patients, besides tHcy, it is probably also important to consider ADMA, and in view of the recent findings regarding intestinal bacteria and egg yolks,[27,29,69] limit egg yolks and other sources of phosphatidylcholine, and consider approaches to lowering levels of trimethylamine.

Summary

Nutrition is very important in stroke prevention. Maintaining a healthy weight, a Mediterranean diet, limiting intake of dietary cholesterol and egg yolks, diagnosing and treating unrecognized metabolic deficiency of vitamin B12, and therapies to lower homocysteine, including use of methylcobalamin instead of cyanocobalamin, are all aspects of stroke prevention deserving attention of neurologists.

When some of my colleagues say "that's not my job", because they regard it as the job of the dietitian, the internist, or the primary care physician, my response is that if we do not do it, it will not happen. ■

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