THE AFIB REPORT

Your Premier Information Resource for Lone Atrial Fibrillation!

NUMBER 62 **SEPTEMBER 2006** **6th YEAR**

The main feature of this issue is an extensive research report on the problems confronting afibbers who have to take warfarin (Coumadin). Although warfarin is not recommended for afibbers with no underlying cardiovascular disease or other risk factors for stroke, it is still considered mandatory for afibbers with serious risk factors such as a history of stroke or TIA, prosthetic heart valves, and mitral stenosis. Afibbers with a combination of any two moderate risk factors such as age over 75 years, diabetes, hypertension, and heart failure may also face the need to consider lifelong warfarin therapy. Unfortunately, while warfarin is indeed an effective anticoagulant, it has many serious adverse effects. How to eliminate, or at least minimize, these side effects is the topic of our feature report "Living with Warfarin".

Also in this issue we report that the prevalence of AF in the United States is twice as high as previously estimated and could reach over 15 million by 2050. As well, blood viscosity and red blood cell deformability are important, modifiable risk factors for stroke, and high fibrinogen have been linked to an increased risk of developing atrial fibrillation. Both of these newly discovered risk factors can be minimized by an adequate daily water intake.

On a completely different note altogether, Bill Ware and I have just completed our 440-page book "The Prostate and Its Problems". For more on this book please see http://www.yourhealthbase.com/prostate/book.htm

Last, but not least, if you need to restock your supplements, please remember that by ordering through my on-line vitamin store you will be helping to defray the cost of maintaining the web site and bulletin board. You can find the store at http://www.afibbers.org/vitamins.htm Your continuing support is very much appreciated.

Wishing you good health and lots of NSR,

Hans

Highlights

AF prevalence higher than expected

ROCHESTER, MINNESOTA. A 2001 study by Kaiser Permanente researchers estimated the number of afibbers in the United States at 2.3 million rising to 5.6 million in 2050. Mayo Clinic researchers now report that these estimates are likely to be low by a factor of two to three. The Mayo study determined the incidence (first AF episode documented by an electrocardiogram) of atrial fibrillation in Olmsted County, MN. They found that the number of new afib cases in 1980 was 4.09 per 1000 person-years for men and 2.36 per 1000 person-years for women. By the year 2000, the incidence had increased to 4.89 per 1000 person-years for men and 2.80 per 1000 person-years for women. This corresponds to an overall increase of 12.6% over 21 years. Applying their data to the entire US population, the researchers estimate that 5.1 million Americans were suffering from AF in 2000. The prevalence in 2006 would be about 6 million and by 2050 it would be 15.9 million assuming the growth rate observed over the period 1980-2000 continues.

The Mayo researchers point out that the prevalence of obesity (BMI of 30 or more) increased from 10% in 1980 to 25% in 2000 and suggest that about 60% of the observed increase in AF cases could be due to the increase in obesity.

Miyasaka, Y, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. **Circulation**, *Vol. 114, July 11, 2006, pp. 119-25*

Editor's comment: It is quite possible that even the Mayo Clinic numbers for afib incidence and prevalence are low. Less than 20% of Olmsted County residents had an ECG in any one year and some presumably never had one. Whatever the real prevalence is, it is obviously high and growing. It is to be hoped that this new reminder of the seriousness of the AF epidemic will result in more research being directed toward finding the cause(s).

Fibrinogen level linked to afib

COPENHAGEN, DENMARK. An elevated level of the blood coagulation factor fibrinogen has been linked to inflammation and in increased risk of heart disease, stroke, and periodontal (gum) disease. Danish researchers now report an association between high fibrinogen levels and an increased risk of developing atrial fibrillation. Their study involved 8870 men and women free of cardiovascular disease who were enrolled in the Copenhagen City Heart Study. During an average 7.5 years of follow-up, 286 of the participants developed AF (4.3 cases per 1000 person-years).

The researchers observed that men with a plasma fibrinogen level above 353 grams/L had twice the risk of developing AF than did those with a level below 243 grams/L. Among women, those with a fibrinogen level above 360 grams/L had a 2.14 times higher risk of AF than did those with a level below 250 grams/L. There was also a clear correlation between a low level of serum albumin in women and an increased risk of AF. No such correlation was observed for the men.

Both an elevated level of fibrinogen and a low level of albumin are markers of inflammation. The Danish researchers conclude that their findings support the hypothesis that inflammation contributes to the etiology of atrial fibrillation.

Mukamal, KJ, et al. Fibrinogen and albumin levels and risk of atrial fibrillation in men and women (the Copenhagen City Heart Study). **American Journal of Cardiology**, *Vol. 98, July 1, 2006, pp. 75-81*

Editor's comment: High fibrinogen levels are also an important risk factor for stroke. An increased water intake and supplementation with fish oils and niacin have been found to lower fibrinogen levels.

Blood viscosity and stroke risk

FIRENZE, ITALY. There is evidence that a high blood viscosity (thick blood) may increase the risk of ischemic stroke. Blood viscosity, as a whole, affects the ease of general circulation, while erythrocyte (red blood cell) deformability affects circulation through the capillaries. Because red blood cells can only flow through a capillary (the smallest diameter blood vessels involved in nutrient and waste exchange with individual cells) one at a time and even then must be elongated to do so, it is clearly advantageous to have a high erythrocyte deformability index. Research has shown that endurance athletes have significantly higher erythrocyte deformability indices than do sedentary people. The main reason for this is that red blood cells in endurance athletes tend to be replaced quicker than they are in sedentary people, thus creating a population of younger, more deformable cells.

Italian researchers have just reported on a study to determine if afibbers and afibbers who have suffered a stroke or TIA ("mini-stroke") have higher blood viscosity and lower erythrocyte deformability than does a control population of non-afibbers without cardiovascular disease. Their study involved 42 afibbers who had suffered an ischemic stroke, 20 who had suffered a TIA, 94 afibbers who had not suffered a stroke or TIA, and 130 age- and gender-matched healthy volunteers. About 60% of the afibbers were hypertensive and about 25% had coronary artery disease and/or left ventricular dysfunction. Average age of the study participants was 73 years and all afibbers were on oral anticoagulation.

After adjusting for gender, age, hypertension, left ventricular dysfunction, coronary artery disease, diabetes, elevated cholesterol level, smoking, hematocrit, fibrinogen, and C-reactive protein levels

(hs-CRP), the researchers concluded that healthy controls had a significantly lower whole blood viscosity (at a shear rate of 94.5 seconds^{-1}) and a significantly higher erythrocyte deformability index than did afibbers who had not suffered a stroke. Afibbers who had not suffered a stroke, in turn, had a lower blood viscosity and higher erythrocyte deformability than did those afibbers who had suffered a stroke or TIA.

The researchers also noted a correlation between hypertension and reduced erythrocyte deformability, but observed no effect of ACE inhibitors, beta-blockers, diuretics, and calcium channel blockers on deformability. This would indicate that treating hypertension does not reduce the stroke risk attributable to reduced erythrocyte deformability. The researchers speculate that reduced erythrocyte deformability may be partly caused by a lack of nitric oxide availability and perhaps by inflammation or oxidative stress resulting in "premature aging" of red blood cells. They also suggest that adding a small dose of aspirin to oral anticoagulants in high-risk patients may be beneficial since aspirin has been found to improve erythrocyte deformability.

Cecchi, E, et al. Hyperviscosity as a possible risk factor for cerebral ischemic complications in atrial fibrillation patients. **American Journal of Cardiology**, *Vol. 97, June 15, 2006, pp. 1745-48*

Editor's comment: A large epidemiological study has shown that drinking 5 or more glasses of water every day cuts the risk of coronary artery disease in half as compared to drinking only 2 or fewer glasses of water every day. It is likely that this beneficial effect of adequate water intake is closely linked to the fact that water, but not necessarily other fluids, reduces blood viscosity. It is also of interest that NO-ASA, a recently developed nitrogen oxide-releasing version of aspirin, has been found to reduce thrombosis (blood clotting).

New RF ablation approach in persistent and permanent afib

ROME, ITALY. It is now clear that performing a successful ablation in afibbers with persistent (episodes longer than 7 days, but amenable to cardioversion) and permanent afib is far more difficult than doing so in afibbers with paroxysmal (intermittent, self-terminating) episodes. The problem is that, while the source of paroxysmal afib initiation is largely in the pulmonary veins, the origin of persistent and permanent afib can be in several other areas of both the left and right atrium. Thus, while just isolating the pulmonary veins using the Haissaguerre (electrophysiological mapping), Natale (electrophysiological mapping), or Pappone (electroanatomical mapping) method will often suffice for paroxysmal afib, it is much less likely to be successful for the persistent and permanent varieties. The problem with sources other than the pulmonary veins is particularly serious in the case of the Pappone method, which is based on ablating fixed anatomical features located via CARTO mapping rather than on ablating specific, abnormal electrical potentials located through electrophysiological mapping.

A team of Italian electrophysiologists now reports that ablating certain specific anatomical features in the left atrium combined with ablation of other features in the right atrium is more likely to restore normal sinus rhythm in persistent and permanent afibbers than is left atrial ablation alone. Their clinical trial involved 52 men and 28 women between the ages of 50 and 68 years. Forty-three of the patients had persistent afib, while the remaining 37 had permanent afib. All patients had failed at least three antiarrhythmic drugs and 84% had structural heart disease. Most of the patients (53%) were on amiodarone before, during, and 6 months after the procedure; the rest of the patients were on sotalol (21%), flecainide or propafenone.

The patients were divided into two groups. Group I underwent just left atrial ablation (circumferential pulmonary vein isolation plus a line from the lesion encircling the left inferior pulmonary vein to the mitral annulus). Group II underwent left atrial ablation plus several specific ablations in the right atrium including the electrical disconnection of the superior vena cava from the right atrium. Total average procedure time for group I was 2 hours and 44 minutes compared to 3 hours and 48 minutes for group II. All patients were in afib at the beginning of the procedure, but afib was terminated in 85% of group II patients and in 24% of group I patients at the end of the procedure.

The study participants were followed for a total of 14 months after the procedure and remained on antiarrhythmic drugs for the first 6 months after the procedure. Success rates at the end of the follow-up period were as follows:

	Group I Left atrium ablation	Group II Left and right atrium ablation
Persistent afibbers		
Afib-free without antiarrhythmics	21%	47%
Afib-free with antiarrhythmics	46%	42%
Still in afib	33%	11%
Permanent afibbers		
Afib-free without antiarrhythmics	12%	35%
Afib-free with antiarrhythmics	41%	45%
Still in afib	47%	20%

Thus, the overall complete success rate (no drugs) was 17% for left atrium ablation only and 41% for biatrial ablation.

Calo, L, et al. Left atrial ablation versus biatrial ablation for persistent and permanent atrial fibrillation. **Journal of the American College of Cardiology**, *Vol. 47, June 20, 2006, pp. 2504-12*

Editor's comment: The complete success rate (no antiarrhythmics) for this new "improved" ablation procedure was only 41% and a dismal 17% for the standard left atrium ablation. This clearly shows (again) that the Pappone method (circumferential anatomical pulmonary vein isolation) using the CARTO mapping system is vastly inferior to the Haissaguerre and Natale methods, especially when

it comes to persistent and permanent afib. The Haissaguerre team in Bordeaux recently reported a complete success rate of 87% (95% after a follow-up ablation) in a group of persistent and permanent afibbers using extensive electrophysiologically guided mapping and ablation.[1-3] The superiority of the Haissaguerre method would probably apply to any afibbers who have ever experienced episodes lasting 24 hours or longer.

[1] Haissaguerre, M, et al. Catheter ablation of long-lasting persistent atrial fibrillation: Critical structures for termination. Journal of Cardiovascular Electrophysiology, Vol. 16, November 2005, pp. 1125-37

[2] Haissaguerre, M, et al. Catheter ablation of long-lasting persistent atrial fibrillation: Clinical outcome and mechanisms of subsequent arrhythmias. Journal of Cardiovascular Electrophysiology, Vol. 16, November 2005, pp. 1138-47

[3] Tse, Hung-Fat and Lau, Chu-Pak. Catheter ablation for persistent atrial fibrillation: Are we ready for "prime time"? Journal of Cardiovascular Electrophysiology, Vol. 16, November 2005, pp. 1148-49

RESEARCH REPORT

Living with Warfarin

by Hans R. Larsen

Anticoagulation with warfarin is not recommended for afibbers with no underlying heart disease or other risk factors for stroke.[1,2] However, in patients with a history of prior stroke or TIA (transient ischemic attack) and in those with prosthetic (artificial) heart valves the use of warfarin is likely to be beneficial overall. Many patients with less serious stroke risk factors such as hypertension and diabetes are also prescribed warfarin although it is somewhat doubtful whether the reduction in ischemic stroke risk outweighs the increase in the risk of serious bleeding and hemorrhagic stroke. A recent study of atrial fibrillation patients on warfarin found that the risk of major bleeding was 2.5% a year in the case of uncontrolled hypertension. [3] This compares to an ischemic stroke risk of 1.5-2.8% a year when not on warfarin.[4,5] This is not a significant difference.

The study, involving 1604 afibbers released from hospital on warfarin, found that most of the major bleeding events occurred in the gastrointestinal tract (67.3%). Hemorrhagic strokes accounted for 15.3% of the bleeding events, and the remaining 17.3% were in other locations. The seriousness of the bleeds can be judged by the fact that 21.6% of the patients admitted for warfarin-induced bleeding died within 30 days. In comparison, only 6-10% of patients admitted to hospital for ischemic stroke die while in hospital, most of them through errors in the administration of thrombolytic agents.[6]

While it is thus not at all clear that anticoagulation with warfarin produces an overall benefit in the majority of patients, it is nevertheless widely prescribed and many patients need to live with it for the remainder of their lives. For those patients it is clearly important to know what the adverse effects of warfarin are, and how to protect against them.

ADVERSE EFFECTS

The most serious adverse effect of warfarin is the potential for major gastrointestinal bleeding and hemorrhagic stroke or bleeding in the brain. A recent study of 1604 afibbers released from hospital on warfarin observed a 5% a year risk of a major bleed and a 21.6% chance of dying from this bleed within 30 days.[3] Warfarin usage has also been linked to arterial calcification (atherosclerosis) and long-term use to an increased risk of osteoporosis. Other less common adverse effects include skin necrosis sometimes requiring amputation, and ocular (eye-related) bleeding.

GASTROINTESTINAL BLEEDING AND HEMORRHAGIC STROKE

Warfarin was originally developed as a rat poison. It works in two ways – in effective doses it increases the permeability of the capillaries (smallest blood vessels) thus allowing blood to seep out of the vessels and into the organs and surrounding body cavity. Secondly, it prevents the vitamin K-dependent clotting activity, which would normally stop the leak until it can be repaired. If nothing is done the animal (or human) will eventually die

from loss of blood.[7-9] To understand the intricacies of this process and find possible ways of preventing it, it is necessary to develop a basic understanding of the function and construction of blood vessels.

Blood vessels

Blood is "the river of life". It carries nutrients to and receives waste from each individual cell in the body. It begins its journey in the main arteries emanating from the heart's left ventricle. As it flows through smaller and smaller arteries it eventually reaches the arterioles, which control the flow of blood to the tissues. Each arteriole, in turn, can serve hundreds of the smallest blood vessel of all, the capillary. The diameter of a capillary is so small that red blood cells can only pass through one at a time. About 10 billion capillaries lace all body tissues bringing blood to within reach of every cell. Capillary walls are highly permeable and while they will not, in normal circumstances, allow the passage of blood itself, they readily allow the transfer of oxygen, nutrients, hormones, carbon dioxide, and waste products between the cell and the blood flowing through the capillary. After the exchange with the cell has taken place the capillaries become part of the venous system with the blood flowing through venules and veins before returning to the right atrium.

In order to achieve the required permeability, the walls of the capillaries are, of necessity, very thin. As a matter of fact, they consist of just one layer of epithelial (lining) cells held in place by a "skeleton" of cross-linked collagen fibers embedded in a matrix of laminin which "glues" the lining cells to the collagen "net". The collagen/laminin structure supporting the single layer of epithelial cells is also known as the basement membrane and is a component of all blood vessels whether large or small.[10,11]

Research involving snake venom and matrix metalloproteinases has clearly shown that hemorrhage (blood seeping out of blood vessels) is caused by destruction of the collagen fibers forming the backbone of the basement membranes.[12] In other words, for red blood cells to be able to get through the collagen "net" it must first be broken. Although I am not aware of any specific research concerning the mechanism by which warfarin causes hemorrhage, it would have to do so by degrading the collagen network and perhaps the laminin matrix as well. Thus, an obvious way of preventing warfarin-induced bleeding would be to strengthen the basement membrane and ensure that the raw materials for repairing it are readily at hand.

Prevention of hemorrhage

Perhaps the most "famous" disease involving internal bleeding is scurvy. Scurvy is now known to be caused by a vitamin C deficiency, but before this was understood scurvy epidemics devastated the ancient populations in Egypt, Greece and Rome, and until the 18th Century caused numerous deaths in Europe as well. In 1536 when the French explorer Jacques Cartier arrived in Newfoundland native Indians advised him to give his men, who were dying from scurvy, a potion made from spruce tree needles. This potion would have been very high in vitamin C and actually cured most of Cartier's crew. In 1742 British naval commander James Lind described the miraculous effects of citrus juice on sailors suffering from scurvy and by the late 1700s all British navy ships carried citrus fruits (especially limes from which the term "limey" originates) to avoid scurvy outbreaks.

There is now substantial evidence that vitamin C works its bleeding preventing magic by promoting the synthesis and deposition of both collagen and laminin.[13-15] There is also direct evidence that vitamin C helps prevent gastrointestinal bleeding resulting from regular aspirin use. German researchers found that combining aspirin (acetylsalicylic acid) with vitamin C (ascorbic acid) significantly reduces the number of microscopic blood leaks normally observed in the stomach when taking aspirin.[16] Another group of German researchers found that aspirin causes gastric mucosal damage and micro-bleeding both before and after *H. pylori* eradication. Buffering the aspirin with vitamin C resulted in significantly less stomach lining damage and bleeding both before and especially after *H. pylori* eradication.[17]

Thus, it would appear that ensuring an adequate daily intake of vitamin C is an important step in reducing and quickly repairing warfarin-induced breakdown of the basement membrane. Since vitamin C is used up and excreted fairly quickly, taking three or four doses of 500 mg of vitamin C throughout the day is the ideal way to ensure a constant and adequate level in the blood stream. Patients with hemochromatosis (iron overload) should only supplement with vitamin C under the supervision of a competent health care provider and should probably limit their intake to 200 mg three or four times daily.

Collagen is the most abundant protein in the human body so it is clearly important to also ensure an adequate intake of the amino acids (lysine, alanine, and proline) that make up the collagen structure. Cheese, eggs, lima beans, potatoes, milk, meat, and brewer's yeast are good sources of lysine, and meats are good sources of proline, which can also be synthesized in the liver from other amino acids. Alanine can be obtained from meat, poultry, fish, eggs, avocado, and dairy products. Lysine, proline and alanine are also available as individual supplements.

Mathias Rath MD, a former associate of the late Linus Pauling, has formulated a supplement specifically designed to ensure optimum collagen production and repair.[18] The formula contains vitamin C and other dietary antioxidants and minerals as well as proline and lysine. Dr. Rath reports that it is effective in preventing and reversing atherosclerosis, but I am not aware of any research that has studied its possible effects in preventing warfarin-induced bleeding.

Green tea and grapeseed extract have also been found to inhibit the collagen-destroying action of metalloproteinases, and green tea on its own has been found to significantly reduce the risk of a certain type of hemorrhagic stroke involving bleeding on the surface of the brain (subarachnoid hemorrhage).[19,20]

There is also some, still controversial evidence, that supplementation with the amino acid arginine may enhance collagen synthesis and deposition.[21-23]

It would thus appear that the risk of warfarin-induced bleeding and hemorrhagic stroke can be materially reduced by supplementing with vitamin C and the amino acids proline and lysine. Green tea may also be helpful because of its significant content of vitamin K, but large amounts should not be consumed without appropriate monitoring of INR.[24,25] There is no evidence that vitamin C interferes with the anticoagulation effect of warfarin.[26] As a matter of fact, low blood levels of vitamin C have been associated with a substantially increased risk of both ischemic and hemorrhagic stroke. Finnish researchers have found that men with a plasma vitamin C level below 28.4 micromol/L have twice the risk of experiencing a stroke (hemorrhagic or ischemic) when compared to men with a level above 65 micromol/L. The association was particularly pronounced among hypertensive men where low vitamin C levels were associated with a 2.6 times higher risk and among overweight men where low levels were associated with a 2.7-fold risk increase.[27] Tissue saturation with vitamin C (about 70 micromol/L in plasma) can be achieved by supplementing with 300-500 mg of vitamin C three times daily.

ARTERIAL CALCIFICATION

Arterial calcification is commonly associated with atherosclerosis and involves the deposition of calcium phosphate (hydroxyapatite) on artery walls. Atherosclerosis is a major risk factor for ischemic stroke so it is indeed ironic that warfarin has been implicated in the formation of arterial calcification. Australian researchers have reported that rats treated with warfarin develop extensive arterial calcification and concluded that, "It is likely that humans on long-term warfarin treatment have extrahepatic vitamin K deficiency and hence are potentially at increased risk of developing arterial calcification."[28] US doctors recently reported the case of an otherwise healthy man who developed extensive calcification of the coronary arteries after long-term warfarin treatment. They conclude, "that physicians prescribing long-term warfarin treatment should consider arterial calcification as one of its potential consequences."[29] Dutch researchers have confirmed that a vitamin K deficiency, such as would be induced by warfarin treatment, increases the risk of arterial calcification and conclude that the current RDA for vitamin K is too low.[30]

Unfortunately, the common advice given by physicians to their warfarin-treated patients is to avoid dark green leafy vegetables (the major dietary source of vitamin K) and to strictly avoid vitamin K-containing supplements – thus guaranteeing a vitamin K deficiency.

Fortunately, this advice may be about to become obsolete. British researchers recently reported that minimizing vitamin K intake while on warfarin might be precisely the wrong thing to do. Their study involved 26 patients (stable) whose INR had remained within the therapeutic range for at least 6 months without a change in warfarin dosage. The daily vitamin K intake of these patients was compared to that of 26 patients (unstable) whose INR

had been varying considerably (standard deviation of INR values greater than 0.5) over a 6-month period and thus requiring continuous adjustment of warfarin dosage. All participants carefully weighed their food intake for two 7-day periods and completed detailed food diaries. Analysis of the data showed that the unstable patients had a significantly lower average daily intake of vitamin K (K_1) than did stable patients (29 versus 76 micrograms/day). As a matter of fact, the daily vitamin K intake of the unstable patients was significantly lower than the daily intake of 60-80 micrograms estimated for the general UK population. The researchers conclude that INR levels can be stabilized by increasing daily vitamin K intake. They point out that even a daily increase in vitamin K intake of 100 micrograms has comparatively little effect on INR (reduction of about 0.2). While it would be theoretically possible to improve the consistency of daily vitamin K intake through a strictly controlled diet, it is unlikely that this would be a viable solution. The researchers conclude their report with the statement, "Daily supplementation with vitamin K could be an alternative method in stabilizing anticoagulation control, lessening the impact of variable dietary vitamin K intake. We are currently evaluating this possibility."[31]

Johannes Oldenburg, a German medical researcher, concurs and suggests that a continuous low-dose intake of vitamin K may stabilize the INR and subsequently reduce risk of bleeding complications.[32]

Natural vitamin K comes in two forms – phylloquinone (vitamin K1) and menaquinone (vitamin K2). Phylloquinone is found in dark green vegetables like spinach, broccoli and kale. Green, but not black tea is also a rich source of phylloquinone. Menaquinone is found in meats, butter, cheese and fermented foods (especially natto) and can also be produced by conversion of vitamin K1 in the intestinal tract. This conversion, however, is compromised after a course of antibiotics. The RDA for total vitamin K intake is 90 micrograms/day for women and 120 micrograms/day for men, and is essentially the amount required for the synthesis of coagulation factors in the liver. The RDA does not consider that vitamin K (especially K2) is also required outside of the liver (extrahepatic), particularly to ensure healthy bones and blood vessels.[30]

The main role of vitamin K is to act as a cofactor for the conversion of glutamate into gamma-carboxyglutamate. Matrix Gla protein (MGP) is derived from gamma-carboxyglutamic acid residues and is a powerful inhibitor of arterial calcification.[30,31] There is evidence that oxidative stress and warfarin inhibit the synthesis of MGP.[33]

Dutch researchers have observed that vitamin K1 tends to accumulate in the liver where it is used in the synthesis of coagulation factors, whereas K2 preferentially accumulates in the artery walls where it participates in the production of MGP which, in turn, inhibits arterial calcification. Unfortunately, warfarin inhibits the intestinal conversion of K1 to K2, thus explaining why warfarin promotes arterial calcification. The researchers also observed that menaquinone, but not phylloquinone supplementation prevented warfarin-induced arterial calcification in rats.[31]

Another group of researchers from Maastricht University in the Netherlands has reported that a high intake of menaquinone (vitamin K2), but not phylloquinone (vitamin K1) is associated with a significantly reduced risk of arterial (aortic) calcification and coronary heart disease (CHD). The epidemiological study included 4800 participants in the Rotterdam Study. The researchers found that the average daily intake of vitamin K1 was 250 micrograms, while that of vitamin K2 was only about 29 micrograms. Study participants with a vitamin K2 intake of more than 32.7 micrograms/day had a 41% reduced risk of CHD, a 57% reduced risk of dying from CHD, and a 26% reduction in overall mortality when compared to those with an intake below 21.6 micrograms/day. Participants with a high menaquinone intake also had a 52% reduced risk of severe arterial calcification. Phylloquinone intake was not associated with decreased risk of CHD, CHD mortality, overall mortality or arterial calcification.[35]

University of Wisconsin researchers have found that, while warfarin is highly effective in blocking the recycling of vitamin K1, it has little effect on the activity of vitamin K2.[36]

Considering the above findings it is tempting to conclude that daily supplementation with menaquinone (vitamin K2) would be highly beneficial in reducing arterial calcification (whether warfarin-induced or not), CHD, and overall mortality without impacting on warfarin's role in reducing the level of coagulation factors. In other words, supplementing with moderate amounts of vitamin K2 should not affect INR levels. Clinical trials, of course, should and hopefully will be carried out to substantiate or negate this hypothesis.

Vitamin D may also play a role in the prevention of arterial calcification. Researchers at the UCLA School of Medicine have reported that the degree of vascular calcification observed in a group of patients at moderate risk for CHD was inversely proportional to the blood level of 1,25-dihydroxyvitamin D, the active metabolite of vitamin D. They suggest that this form of vitamin D may play a role in inhibiting vascular calcification.[37] Dutch researchers support this observation with their finding that supplementation with vitamin D and vitamin K1 has a beneficial effect on the elastic properties of the arterial vessel wall.[38]

Other researchers have, however, found that very large (20 million IU/day or more) doses of vitamin D may actually induce arterial calcification (at least in rats).[39,40] Thus, it may be best to avoid supplementing with more than the dose known to be free of adverse events (2000 IU/day).

A magnesium deficiency, especially if combined with a high exposure to trans-fatty acids, has been found to increase the risk of arterial calcification in cell culture experiments [41] and supplementation with a combination of magnesium and potassium citrate has been found to reduce arterial calcification in rats.[42]

It would thus appear that supplementation with vitamin K, vitamin D and magnesium and potassium citrate can materially reduce the risk of warfarin-induced arterial calcification. It is, of course, necessary to monitor INR very closely if embarking on vitamin K2 prophylactic therapy and it would also appear wise to limit daily vitamin D intake to 2000 IU or less. The most effective form of vitamin K for prevention of arterial calcification is menaquinone (vitamin K2). However, in view of the finding that supplementing with vitamin K (vitamin K1) may help stabilize INR levels, it may be advisable for warfarin-treated patients to use a 50:50 mixture.

OSTEOPOROSIS

Osteoporosis is characterized by a decrease in bone mass and density, causing bones to become fragile and increasing the risk of fractures. In the United States 26% of women 65 years or older, and more than 50% of women 85 years or older have osteoporosis. Over 1.5 million fractures, requiring about 500,000 hospitalizations and costing the health care system about 12 billion dollars, occur every year as a result of osteoporosis.[43] Men are not immune to osteoporosis, but the incidence is significantly lower than among women.[44]

Vitamin K is a crucial element in the process of bone formation, so it is relevant to ask the question, “Is long-term use of warfarin associated with an increased risk of osteoporotic fractures?” A team of researchers from Washington University School of Medicine and the NYU Medical Center recently investigated the association between osteoporotic fractures and warfarin usage in over 14,000 Medicare beneficiaries who were hospitalized with atrial fibrillation. Most of the study participants (70%) had hypertension, 48% had heart failure, and 35% had a history of stroke. A total of 1005 of the study participants (6.9%) experienced an osteoporotic fracture during the 3-year study period. The researchers found that men who had been taking warfarin for a year or more had a 63% higher relative risk of experiencing an osteoporotic fracture when compared to men not taking warfarin. Hip fractures were most common (65% of all fractures) and were associated with a 30-day mortality of 39%. Men using warfarin for less than a year did not have an increased risk of osteoporotic fractures. Osteoporosis risk was not increased in women irrespective of duration of warfarin usage.

The researchers point out that patients taking warfarin are often advised to limit their intake of vitamin K rich green vegetables. They believe this may be poor advice and that ensuring an adequate intake of vitamin K-1 (found especially in green vegetables) and vitamin K-2 (present in fermented dairy and soy products, fish, meat, liver and eggs) would be more appropriate. They also caution that avoiding green vegetables may lead to a folic acid deficiency and subsequent high levels of homocysteine, a known promoter of atherosclerosis.[45]

Although this study did not find an increased risk of osteoporosis among female warfarin users, it is possible that an association still exists, but is masked by other, more important, risk factors such as loss of estrogen production after menopause. This hypothesis is supported by the recent finding by Australian researchers that children on long-term warfarin therapy also experience a marked reduction in bone density.[46]

To better understand the role of vitamin K in osteoporosis and to suggest ways of preventing it, it is necessary to first gain a broad understanding of the process of bone formation.

Bone formation
Bones consist of a matrix of hydroxyapatite (calcium phosphate) and other minerals embedded in a cross-linked collagen matrix. The formation and maintenance of the bone structure is an ongoing, dynamic process. Up until the age of about 30 years the process involves mainly bone formation, but after this bone formation and bone resorption develop a delicate balance, which if bone resorption becomes dominant can lead to osteopenia (a forerunner of osteoporosis) and osteoporosis. There are two main types of cells involved in the process – osteoblasts which promote the formation of new bone structure by increasing calcium content, and osteoclasts which promote the resorption (demineralization of old bone) by releasing calcium into the blood circulation. Bone formation and resorption are also known as bone remodelling and take place continuously in the entire skeleton. The concentration of calcium in the blood is maintained within very narrow limits using the bone structure as a reservoir. The hormone calcitonin promotes the transfer of calcium into the bones, while parathyroid hormone (PTH) promotes the release of calcium from the bones.

Vitamin D is important in controlling PTH level with a deficiency leading to higher PTH concentration and subsequent demineralization. There is some evidence that an estrogen deficiency makes the osteoclasts more sensitive to PTH. Vitamin K is important in the synthesis of the gamma-carboxylated protein, osteocalcin. A deficiency of osteocalcin is associated with impaired bone formation (remineralization). Calcium, magnesium, boron, and zinc are all important constituents of the bone matrix with calcium being needed in by far the greatest amounts.

The main effect of warfarin as far as osteoporosis is concerned is that its long-term use leads to impaired remineralization due to its interference with the vitamin K-dependent synthesis of osteocalcin. Thus, the main players in the “osteoporosis drama” are calcium, vitamin D, vitamin K, magnesium, boron, and zinc. Maintaining appropriate levels of these components can go a long way in preventing osteoporosis in both men and women whether on warfarin or not.

Prevention of osteoporosis
Due to the devastating nature of osteoporosis and its enormous cost to the health care system, a great deal of research has gone into finding ways of preventing it. The standard medical approach to osteoporosis prevention and treatment involves the life-long use of bisphosphonates such as etidronate (Didronel), alendronate (Fosamax), and raloxifene (Evista) interspersed with calcium and vitamin D supplementation. These drugs work primarily by decreasing bone resorption, in orders words, they result in “old bones”. Bisphosphonate therapy is usually effective, but carries the risk of significant side effects, among them necrosis (rotting) of the jaw bone.[47] Merck & Co., the manufacturer of Fosamax is currently facing several class action suits launched by Fosamax users who developed severe necrosis after undergoing dental work.[48]

Fortunately, it is eminently possible to achieve effective and safe osteoporosis prevention through exercise, proper food choices, and supplementation with natural products.

Exercise
There is little doubt that physical inactivity leads to loss of bone mass – even in highly fit astronauts. There is also evidence that a structured program of load-bearing exercise such as regular walking can help prevent osteopenia and its progression to osteoporosis, especially if accompanied by supplementation with calcium and vitamin D.[49,50] Just recently Dr. Rittweger of the Institute for Biophysical and Clinical Research into Human Movement in the UK suggested that high strain rate exercises (weightlifting), while being beneficial in the prevention of osteopenia, may actually increase the risk of fractures in full-blown osteoporosis.[51] So, while high strain rate exercises may be appropriate for younger people, a more moderate program such as regular walking may be better suited to older people. In any case, the program to be effective needs to be accompanied by a proper diet, judicious supplementation, and avoidance of coffee, alcohol, smoking, and soft drinks (colas) which have all been proven to increase the risk of osteoporosis.[52]

Vitamin D
Several studies have shown that vitamin D deficiency is widespread. Researchers at Boston University School of Medicine found that 52% of postmenopausal women with osteoporosis had abnormally low vitamin D (25-hydroxyvitamin D) levels and commensurate high levels of PTH.[53] Vitamin D deficiency was more prevalent in

women whose daily intake of dietary vitamin D was less than 400 IU. Swiss researchers recently reported that 64% of postmenopausal women with osteoporosis had a vitamin D deficiency and elevated PTH.[54]

The connection between vitamin D deficiency and osteoporosis was first reported by Meryl LeBoff and colleagues at Brigham and Women's Hospital in Boston. Their 1999 study found that 50% of women admitted with acute osteoporosis-related hip fracture were vitamin D deficient. They suggested that supplementation with vitamin D and accompanying suppression of PTH may reduce future fracture risk and help the healing of existing fractures. They concluded that vitamin D deficiency among the elderly is entirely preventable and recommended supplementation with calcium and 800 IU/day of vitamin D.[55]

Australian researchers have observed that vitamin D deficiency is also a major cause of osteoporosis and hip fractures among men. Their study involved 41 men (60 years and older) who were admitted with hip fractures. Known risk factors for osteoporosis and hip fracture were determined and compared to those of two control groups – one a group of 41 inpatients, the other a group of 41 outpatients all without hip fractures and aged 60 years or older. The researchers found that men in the hip fracture group had significantly lower blood levels of vitamin D (25-hydroxyvitamin D) than did men in the control group. Sixty-three per cent of the men in the hip fracture group had a subclinical vitamin D deficiency (<50 nmol/L serum 25- hydroxyvitamin D) as compared to only 25 per cent in the control group. The researchers also noted that men with hip fractures and hospital in-patients had lower levels of calcium and testosterone than did the out-patient controls. About 89 per cent of the men with hip fractures and the in-patients were diagnosed with hypogonadism (low testosterone levels). The researchers conclude that a vitamin D deficiency is a major cause of hip fractures in elderly men.[56]

It is clear that vitamin D deficiency, irrespective of calcium status, is critical risk factor for osteoporosis and associated bone fractures. Thus, it is fortunate that several clinical trials have concluded that vitamin D supplementation is effective in fracture prevention. Researchers at Harvard School of Public Health, after evaluating 14 reliable studies of oral vitamin D supplementation, concluded that daily supplementation with 700-800 IU of vitamin D reduced hip fracture risk by 26% and overall non-vertebral fracture rate by 23%. No benefit was observed with a daily dose of 400 IU (current RDA for women under the age of 70 years).[57]

A group of researchers at Harvard Medical School studied over 72,000 postmenopausal nurses for 18 years and found that those whose daily vitamin D intake exceeded 500 IU had a 37% lower risk of hip fracture than did women whose intake was less than 140 IU/day. They found no benefit of a high daily intake of milk or calcium on its own. The researchers point out that about 60% of the women in the survey had vitamin D intakes below those recommended by the Food and Nutrition Board (400 IU for women between the ages of 51 and 70 years and 600 IU for women older than 70 years). They also point out that the amount of vitamin-D produced by exposure to sunlight decreases significantly with age (due to thinning of the skin) and the use of sunscreens. They further suggest that the reason why milk showed no significant protective effect may be due to its content of vitamin A which recently has come under scrutiny in regard to its possible role as a negative factor in bone health. The researchers conclude that women should ensure an adequate daily intake of vitamin D either through the use of supplements or through increased consumption of fish such as salmon or sardines.[58]

The importance of daily supplementation with vitamin D is becoming increasingly clear. A team of American and Swiss researchers recently concluded that a daily intake of at least 1000 IU is required in order to achieve reasonable protection against the risk of osteoporosis, fractures, falls, and colon cancer. They suggest that an increase in the current RDA is warranted.[59] Dr. Reinhold Vieth and colleagues of the University of Toronto go even further. They found that 62% of supposedly healthy Canadians were deficient in vitamin D and that a daily intake of 4000 IU (100 micrograms/day) was needed to bring their level of 25(OH)D, the active metabolite of vitamin D, to the desirable level of 75 nmol/L. The researchers conclude that 4000 IU/day of vitamin D3 is a safe and desirable intake, but very specifically caution that their findings regarding vitamin D3 (cholecalciferol) cannot be applied to the synthetic version of vitamin D2 (ergocalciferol), the form most often used in North America. Vitamin D2 is far more toxic than vitamin D3 and produces unique metabolites not generated by D3. The researchers are very "down" on vitamin D2 and say, "It is an anachronism to regard vitamin D2 as a vitamin."[60]

Vitamin D and calcium

An adequate intake of calcium is clearly essential in achieving and maintaining sufficient bone mass due to the simple fact that calcium, in the form of hydroxyapatite, constitutes the major part of the bone structure. In

combination with vitamin D it is effective in preventing bone loss and fractures. Ten years ago French researchers discovered that daily supplementation with 1200 mg of calcium and 800 IU of vitamin D3 (cholecalciferol) for 3 years reduced the number of hip fractures in a group of 3270 elderly women by 23%. The researches also noted that the bone density in calcium/vitamin D supplemented women increased by 2.7% over an 18-month period, while it decreased by 4.6% in the placebo group.[61] Since 1996 several other studies have verified the benefits of supplementation with calcium and vitamin D. In 1998 researchers at Johns Hopkins Medical School concluded that, "Optimal intakes of both calcium and vitamin D are relatively cost-effective, safe, and easily implemented approaches to maintain existing bone mass and assist in the prevention of fractures."[62]

Dutch researchers report that 1000-1200 mg/day of calcium (elemental) plus 800 IU/day of vitamin D is effective in the prevention and treatment of osteoporosis.[63] German researchers, after evaluating several randomized, prospective, placebo-controlled clinical trials, conclude that supplementation with 800-1500 mg/day of calcium plus 400-1200 IU/day of vitamin D reduces the risk of falls and fall-related fractures in the elderly.[64] Indeed, the evidence that supplementation with calcium and vitamin D is beneficial in preventing and treating osteoporosis is incontrovertible.

It is, however, becoming increasing clear that a supposedly adequate calcium intake does not guarantee the absence of osteoporosis. The calcium must not only be ingested, it must also be absorbed and its excretion minimized. In other words, it is not the calcium intake per se that is important, but rather how much of it is actually retained in the body. Researchers at the University of Pittsburgh have found that the intake of fat and fiber significantly influences calcium absorption. Their study involved 142 healthy pre-menopausal white women who had enrolled in the Women's Healthy Lifestyle Project in 1995-96. The women had blood samples drawn three hours after consuming apple juice containing labeled (isotope) calcium. The blood samples were analyzed for calcium, 1,25 dihydroxyvitamin D (the active from of vitamin D), and PTH. The researchers found that about 35% (17-58%) of the labeled calcium had been absorbed. It was clear that women with a higher fat intake and a lower intake of fiber absorbed significantly more calcium than did women with less fat and more fiber in their diet. Women with high blood levels of vitamin D also showed increased absorption while women who consumed alcohol had decreased absorption. There is also some indication that a higher total calcium intake is associated with a lower rate of absorption. The researchers caution that it may only be certain types of fiber (eg. wheat bran) that inhibit calcium absorption. Fiber found in green leafy vegetables such as kale, broccoli, and bok choy may not be detrimental to absorption. They found no indication that genetic differences among the women were in any way related to calcium absorption. The researchers express the hope that their findings will encourage a second look at the current standard recommendation to emphasize a low-fat, high-fiber diet.[65]

The rate of excretion of calcium is also an important factor in determining its effectiveness in osteoporosis prevention. Dr. Christopher Nordin of Australia's Institute of Medical and Veterinary Science points out that is not the total calcium intake which determines bone strength (density), but rather the difference between what is taken in and what is excreted. Research has shown that for each gram of animal protein consumed one milligram of calcium is lost in the urine. This means that a 40-gram reduction in animal protein intake reduces the urinary calcium loss by 40 mg which, in turn, corresponds to a reduction in calcium requirements of 200 mg (assuming an absorption of 20%). A reduction in sodium (salt) intake of 2.3 grams also reduces urinary calcium loss by 40 mg lowering requirements by another 200 mg. So a person with a low intake of protein and salt might have half the calcium requirements of a person eating a typical North American diet. This and the fact that developing countries generally get more sunshine (vitamin D) than developed countries go a long way towards explaining the difference in the incidence of osteoporosis and bone fractures between different cultures and individuals. Dr. Nordin concludes that there is no single, universal calcium requirement, only a requirement linked to the intake of other nutrients especially animal protein and sodium.[66]

Dairy products like milk, cheese and yogurt are the richest sources of calcium followed by collards, spinach, beans, sardines and canned salmon. There is some indication that milk may not be an optimum source of calcium for older people. Researchers at the Boston University School of Medicine have studied the effectiveness of various sources of supplemental calcium in preventing bone loss in older women. Their study involved 60 postmenopausal women aged 65 years or older who did not suffer from osteoporosis and whose daily calcium intake from their regular diet was less than 800 mg/day. The women were randomly assigned to three groups. Group 1 supplemented with four 8-ounce glasses of vitamin D-fortified milk per day, group 2 took

a 500 mg calcium carbonate supplement twice a day with meals, and group 3 took a placebo twice a day with meals. Bone density measurements of the spine (L2-L4) and thighbone (greater trochanter[GT]) were done at six-month intervals for a two-year period. After two years women in the placebo group (average daily calcium intake was 683 mg) had lost an average of 3% of their baseline bone mineral density in the trochanter area. This loss occurred exclusively during the winter months. Women in the milk group had an average daily calcium intake of 1028 mg and lost 1.5% of their bone density in the GT area. Women who supplemented with calcium carbonate tablets increased their daily intake to 1633 mg and suffered no bone loss in the GT area. The women in the supplement group also increased the bone density in their spine and femoral neck area by about 3%, while the placebo group women lost about 0.3%, and the milk group about 1.8%. The researchers conclude that 1000 mg/day of supplemental calcium is required in order to prevent bone loss in older women living in northern latitudes. They also point out that an adequate vitamin D intake (600-700 IU/day) is essential in order to prevent bone loss during the winter.[67]

Other researchers, however, have found that calcium is equally well absorbed from skim milk, calcium-fortified orange juice, and calcium carbonate tablets.[68] The most commonly used calcium supplements are calcium carbonate and calcium citrate. A comprehensive study comparing the bioavailability of calcium carbonate and calcium citrate found that calcium citrate was consistently better absorbed whether taken on an empty stomach or with a meal.[69] Other research has shown that calcium carbonate is extremely poorly absorbed by people with low stomach acid even if taken with meals.[52] Inasmuch as low stomach acid (achlorhydria) is a common condition among older people, calcium citrate, calcium malate or calcium fumarate are all much better choices than calcium carbonate. Natural oyster shell calcium, dolomite, and bone-meal products should be avoided due to the potential for lead contamination and poor absorbability.[52]

As an added bonus, supplementation with vitamin D and calcium has also been found to reduce systolic blood pressure by about 10%.[70] Calcium citrate supplementation is also effective in reducing LDL cholesterol (the "bad" kind) and increase HDL cholesterol (the "good" kind").[71] LAF Survey 3 observed that some vagal afibbers who supplemented with calcium experienced longer episodes than average.[72] Thus, vagal afibbers may have to experiment with calcium sources and dosages to find a protocol that works for them.

Calcium

The evidence that calcium supplementation on its own (without vitamin D) increases bone mass and helps prevent osteoporosis is somewhat sparser and more controversial. A 1998 study at the Boston University School of Medicine concluded that 2 x 500 mg of calcium carbonate taken with meals for two years improved bone density in the spine and femoral neck area by about 3%.[67] However, researchers at the Harvard Medical School found no benefit of calcium supplementation on its own.[52] It is quite likely that vitamin D status could explain the differences and also quite conceivable that an adequate vitamin D intake is actually more important than an increased calcium intake. However, as far as I know, no clinical trials have addressed this question.

In any case, there would seem to be little advantage in consuming more than the RDA (1200 mg/day) of calcium and a great advantage in ensuring that this intake is accompanied by a vitamin D3 intake of at least 1000 IU/day.

Magnesium

Magnesium is a hugely important mineral, especially for afibbers. Its many vital functions have been discussed in detail in Conference Room Sessions 14 and 14A and will not be repeated here.[73,74] Suffice it to say that calcium and magnesium are intimately linked and that a high calcium to magnesium ratio can be detrimental and lead to hypertension and other conditions involving the cardiovascular system.[75]

Legumes, tofu, seeds, nuts, whole grains, and green leafy vegetables are good sources of magnesium. Magnesium glycinate (chelated magnesium) is the most bioavailable and best tolerated supplement. Magnesium citrate is also highly available, but may cause loose stools. The common form of magnesium used in supplements, magnesium oxide, is essentially useless in that only about 4% of the ingested amount is actually absorbed.[76]

About half of the body's magnesium stores can be found in bones, so it is clearly a very important mineral as far as osteoporosis prevention is concerned. Magnesium deficiency is, unfortunately, very common. A recent study found that 74% of a cohort of 2000 elderly men and women did not consume the recommended 400 mg/day.

This same study also concluded that a high magnesium intake is associated with a significantly higher bone density in older white men and women. Every 100 mg/day extra intake of magnesium was found to correspond to a 2% increase in whole-body bone mass. This compares to an approximate 2% increase per 400-mg/day increase in calcium consumption. It is thought that magnesium may act as a buffer for the acid produced by the typical Western diet and may also replace calcium in the hydroxyapatite part of bone, thus resulting in a stronger structure.[77] There is also evidence that magnesium suppresses bone resorption (demineralization) at least in younger people.[78]

Other minerals
A high salt diet has been found to significantly increase urinary calcium excretion and bone loss. Supplementing with 90 mmol/day of ***potassium*** citrate (3500 mg of elemental potassium) will prevent this detrimental effect.[79]

Boron is also a very important mineral in osteoporosis prevention. Researchers at the U.S. Department of Agriculture found that women who supplemented with 3 mg of boron daily reduced the amount of calcium excreted in their urine by 44%. The conclusion of the study was that boron improves the metabolism of calcium and magnesium.[80]

A low dietary intake of ***zinc*** and accompanying low blood levels has been associated with an increased risk of osteoporosis in women. Researchers at the University of California have found that an adequate zinc intake is equally important for men. Their study involved 396 men aged between 45 and 92 years who had their bone mineral density (BMD) measured at baseline (in 1988-1992) and 4 years later. Plasma zinc level correlated well with the total intake from diet and supplements. The average daily intake was 11.2 mg and the mean plasma zinc concentration was 12.7 micromol/L. The researchers observed that men with a low zinc intake and plasma concentration were significantly more likely to have osteoporosis of the hip and spine.[81]

Vitamin K
Vitamin K is essential in the synthesis of osteocalcin, the hormone that promotes bone formation. Several epidemiological studies have concluded that a vitamin K deficiency (such as would be induced by warfarin therapy) causes reductions in bone mineral density and increases the risk of fractures. Other studies have shown that the concurrent use of menaquinone (vitamin K2) and vitamin D substantially reduces bone loss. There is evidence that the average dietary intake of vitamin K is insufficient to ensure optimum osteocalcin production and that the RDA should be increased.[82] Supplementation with vitamin K (preferably K2) would, thus, be important for afibbers on warfarin.

Conclusion
Osteoporosis is widespread and of particular concern for afibbers on warfarin. It is clear that moderate exercise combined with an appropriate intake of vitamin D, calcium, magnesium, boron, zinc, and vitamin K can substantially reduce the risk of bone loss and fractures.

SKIN NECROSIS

Warfarin-induced skin necrosis is a rare, but serious disorder which primarily affects middle-aged, obese women. The disorder has a prevalence of less than 0.1%. Skin necrosis usually appears in breast, buttocks or thighs of women and on the penis of men. If it is going to occur it would usually do so within the first 3 to 6 days after starting warfarin therapy. It is thought to be associated with a sharp drop in protein C and factor VII experienced in some patients following initiation of therapy. The disorder manifests itself by large bleeding skin eruptions and may require extensive surgery and even amputation. The risk of skin necrosis can be reduced by avoiding large initial doses of warfarin and by increasing dosages slowly. In some cases, it is possible to reverse the condition with rapid intervention with vitamin K infusions. Skin necrosis is a serious condition and its symptoms and the symptom of its close cousin, “purple toes” should not be ignored.[83]

EYE DAMAGE

Massive bleeding in the eye in patients with age-related macular degeneration (AMD) is a devastating event. Dutch researchers have found that warfarin treatment increases the risk of serious bleeding in AMD patients and recommend that warfarin therapy for such patients only be prescribed when absolutely essential.[84]

WARFARIN INTERACTIONS

The efficacy and safety of warfarin therapy depends on maintaining a reasonably constant INR (International Normalized Ratio) between 2.0 and 3.0. An INR below 2.0 is less effective in preventing ischemic stroke and at an INR of 3.0 or higher the risk of a hemorrhagic stroke outweighs the risk of an ischemic stroke.[2] Numerous drugs, herbs, and foods affect the action of warfarin by either increasing or decreasing its anticoagulation effect. It is clearly important to be aware of these interactions so as to avoid large swings in INR and the accompanying risks of over- or under-coagulation. Warfarin interacts with at least 90 common drugs and several herbs. A list of the most significant interactions is given below.

Interactions that **potentiate** warfarin's effect

Highly probable

Drugs	Foods & Herbs
Acetaminophen (Tylenol)	Boldo/fenugreek mixture
Ciprofloxacin	Fish oil
Citalopram	Mango
Diltiazem	Quilinggao
Entacapone	
Fenofibrate	
Miconazole	
Sertraline	
Voriconazole	
Zileuton	

Probable

Amoxicillin	Danshen
NSAIDs	Dong quai
COX-2 inhibitors	Grapefruit juice
Fluorouracil	
Fluvastatin	
Fluvoxamine	
Gemcitabine	

Interactions that **inhibit** warfarin's effect

Highly probable

Drugs	Foods & Herbs
Cholestyramine	
Mercaptopurine	
Mesalamine	
Ribavirin	
Trazodone	

Probable

Azathioprine	Ginseng
Bosentan	
Dicloxacillin	
Ritonavir	

There are no credible studies supporting an interaction between warfarin and the following drugs and food – alcohol, antacids, atenolol, clopidogrel, fluoxetine (Prozac), metoprolol, naproxen, psyllium, ranitidine, vitamin E, atorvastatin (Lipitor), coenzyme Q10, ginkgo biloba, ibuprofen, and influenza vaccine.[85] However, it is a good idea to maintain a reasonably steady intake of coenzyme Q10 and vitamin E since the literature supporting a lack of interactions is not entirely consistent.

The Canadian researchers who compiled the listing point out that there are now so many potential interactions between warfarin and other drugs that it would be impossible for a physician or pharmacist to remember them all. They recommend that doctors prescribing other drugs to patients on warfarin keep in mind that many drugs in the following groups can increase or inhibit the effect of warfarin:[85]

- Antibiotics and antifungal agents
- Cardiovascular drugs (including propafenone, amiodarone, and cholesterol-reducing drugs)
- Painkillers
- Anti-inflammatories
- Central nervous system drugs (citalopram, sertraline)
- Gastrointestinal drugs (cimetidine, omeprazole)
- Anabolic steroids

A team of researchers from Germany, Sweden and Switzerland studied 4152 afib patients who were on warfarin therapy for non-valvular atrial fibrillation. During follow-up (for an average of 11 months) 133 patients died from internal bleeding and another 432 were hospitalized with serious bleeding. This corresponds to a warfarin-associated mortality rate of 3.5% a year and a serious bleeding rate of 12% a year. The researchers observed that 58% of all patients on warfarin had also been prescribed one or more of 88 specific drugs that are known to interact with warfarin. They also found that patients who were taking potentially interacting drugs experienced a 3.4-fold increased risk of serious bleeding. The use of a combination of warfarin and aspirin (75-325 mg/day) was associated with a 4.5-fold risk increase, while the concomitant use of acetaminophen (Tylenol, Paracetamol) was associated with a 3.8-fold increased risk at doses between 885-2900 mg/day taken for at least 4 weeks. Other particularly detrimental drugs were allopurinol (Zyloprim), amiodarone (Cordarone), levothyroxine (Synthroid), Metronidazole, Miconazole, and omeprazole (Prilosec). Taking Metronidazole or Miconazole during warfarin therapy was associated with a 40-fold increase in the risk of a serious bleeding event.

The researchers conclude that drug interactions are an independent risk factor for serious bleeding in patients on long-term warfarin therapy. They also point out that the practice of prescribing potentially interacting drugs is widespread.[86]

INR CONTROL

An obvious way of improving the safety and efficacy of warfarin therapy is to control the INR within close limits. Doing this, by going to a clinic or medical laboratory weekly or more frequently, is clearly inconvenient, time-consuming and expensive. Fortunately, there are now several home testing kits that provide quick and accurate results for INR and prothrombin time. *INRatio* by HemoSense is probably the most reliable and accurate. It must be prescribed by a physician and its cost may be reimbursed by Medicare in the US (http://www.hemosense.com).

SUMMARY

Warfarin (Coumadin) is an effective anticoagulant, but has the potential for serious adverse effects – notably internal bleeding, hemorrhagic stroke, arterial calcification, osteoporosis, and skin necrosis. Fortunately, as detailed in this report, it is possible to greatly reduce the risk of adverse events by judicious supplementation, avoidance of drugs and herbs that interact with warfarin, and maintaining close control of INR through monitoring at home.

The most important supplements for patients on long-term warfarin therapy are:

Supplement	Suggested intake
Vitamin C	500 mg 3-4 times daily with meals
Vitamin D3(1)	1000-2000 IU daily
Vitamin K*(2)	100 micrograms daily
Magnesium (elemental)(3)	100-200 mg 3 times daily
Calcium (elemental)(4)	200 mg 3 times daily
Potassium (elemental)(5)	2-3 grams daily
Boron	3 mg daily
Zinc	15 mg daily
Proline	500 mg daily[18]
Lysine	500 mg daily[18]
Green tea*(6)	4-6 cups daily

* These supplements should only be taken with a doctor's approval and require close INR monitoring.

(1) Please note that many supplements such as multivitamins, calcium, magnesium and vitamin K also contain vitamin D. Total intake from all sources should not exceed 2000 IU/day.
(2) The preferred form of vitamin K is vitamin K2 (menaquinone). However, if the intake of green leafy vegetables is low and INR is fluctuating significantly then a mixture of vitamin K1 (phylloquinone) and vitamin K2 is preferable.
(3) Taurine (3 x 1000 mg/day) may be helpful in ensuring optimum efficacy of magnesium. Magnesium supplementation is not advised in patients with kidney failure.
(4) Total daily calcium intake from diet and supplements should not exceed 1200-1500 mg.
(5) This amount can be obtained from 6-7 daily servings of fruits and vegetables. Supplementation is not advised in patients with kidney failure.
(6) It is likely, but not proven, that a similar benefit can be obtained through supplementing with green tea extract in capsules.

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