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## REPORT

### Vitamin K & Warfarin

#### Stabilizing Anticoagulant Therapy—While Protecting Cardiovascular and Bone Health

By Laurie Barclay, MD



By preventing the blood clots that trigger heart attack and stroke, the anticoagulant drug warfarin (Coumadin®) saves countless lives. Doctors must regularly monitor patients' blood levels in order to prescribe a high enough dose of warfarin to prevent deadly blood clots, but not an excessive dose that could lead to fatal hemorrhage. Since many factors—including diet, genetic differences, and medication use—influence how much warfarin an individual needs, achieving and maintaining optimal anticoagulation therapy is difficult at best.

Traditionally, patients taking warfarin have been advised to avoid vitamin K to prevent excess clotting. Surprisingly, scientists have now discovered that regular consumption of a modest amount of vitamin K actually helps stabilize the anticoagulant effects of warfarin. Vitamin K

intake may thus help individuals using warfarin achieve the therapeutic benefits of the drug—without danger of clots or bleeding. Vitamin K is attracting attention for its benefits of protecting cardiovascular health and promoting strong bones, making its inclusion in a warfarin user's daily program that much more important.

Here, we examine why those using blood-thinning medications should speak with their physician on how to best incorporate low-dose vitamin K as part of their prevention regimen.

Vitamin K is one of the key factors that allow our blood to clot. It is commonly found in green leafy vegetables. Clotting is a lifesaving process that prevents us from bleeding to death if we are wounded or the skin is punctured. However, for those at risk of stroke, blood clots can ultimately be lethal. For this reason, physicians prescribe blood-thinning medications such as warfarin (Coumadin®) to patients at high risk for developing a clot (thrombus) inside their blood vessels. This includes patients with mechanical heart valves, atrial fibrillation, and pro-thrombotic clotting factors in their blood. Warfarin reduces the risk that a blood clot (thrombus) will form in a blood vessel and then move to vessels in the brain or lungs where it can cause lethal complications. Warfarin interferes with the body's natural clotting cycle by antagonizing the actions of vitamin K. While warfarin may prevent stroke and pulmonary embolism, it could also set the stage for complications associated with low vitamin K levels, such as advanced osteoporosis, bone fractures, and calcification of our arteries.<sup>1</sup>

#### A DELICATE BALANCE

Patients taking warfarin must be regularly screened by their physician to make sure that their INR (international normalized ratio, a measure of how quickly blood coagulates, or clots) remains within a safe range.<sup>2</sup> This delicate balance is difficult to obtain, because one's INR can change due to alterations in one's diet or other medications. Too many green vegetables at one meal can upset one's INR. Great care must be taken by those on warfarin in order to achieve INR stability. Usually those on warfarin must dutifully report to their physician's office every two to three weeks for a standard blood test to make sure that they are in the safe range. Too high or too low an INR reading can quickly lead to complications. For example, when the warfarin dose is too low (and the INR is below the reference range), blood is apt to clot within blood vessels, choking off blood supply to vital organs such as the lungs, heart muscle, or brain. But when the dose is too high (i.e., the INR is above the reference range), excessively reduced clotting capability of the blood may result in bruising and dangerous bleeding—into the gastrointestinal tract, urine, and even the brain—that can be lethal.<sup>3,4</sup> To obtain the greatest benefits of treatment, the patient's INR must be ideally maintained within a therapeutic range, usually 2-3.



#### VITAMIN K MAY REDUCE FLUCTUATIONS IN WARFARIN ANTICOAGULATION

Several recent studies, both in the US and Britain, have found that supplementing with low-dose vitamin K (50-150 mcg/day) may help stabilize the daily fluctuations in INR that occur due to varying dietary intakes of vitamin K.<sup>5</sup> If necessary, the physician can

slightly increase the patient's warfarin dose to counteract vitamin K's tendency to increase blood clotting. A study at the prestigious Massachusetts General Hospital in Boston looked at the effect of varying dietary vitamin K intake on the INR in patients receiving anticoagulation therapy with warfarin.<sup>6</sup> During the five-week study, 60 adults taking warfarin recorded the amounts of all food items and medications consumed, while the scientists recorded week-to-week changes in vitamin K intake, warfarin dose, and INR. Interestingly, as vitamin K intake increased, INR became more consistent and stable. In contrast, as vitamin K intake decreased, INR became more variable and fluctuated to a greater extent. "Patients taking warfarin and consuming markedly changing amounts of vitamin K may have a variable weekly INR with potentially unstable anticoagulant outcomes," the researchers wrote.<sup>6</sup> Similarly, a British study comparing the dietary habits of 26 patients with and 26 patients without stable control of anticoagulation on warfarin showed that the mean daily intake of vitamin K in patients with unstable control was more than 2.5 times lower than that for patients with stable control during the two-week study. "Daily supplementation with oral vitamin K in unstable patients could lead to a more stable anti-coagulation response to warfarin," the scientists concluded.<sup>5</sup>

## MEASURING YOUR INR (INTERNATIONAL NORMALIZED RATIO)

Because warfarin powerfully thins the blood, its dosage must be carefully regulated. Physicians routinely monitor warfarin therapy by checking the patient's INR (international normalized ratio), a measure of how quickly blood coagulates, or clots.<sup>2</sup> To capture the optimal benefits of therapy, the patient's INR must be maintained within a therapeutic range, usually 2-3. When the INR is below range, this indicates that the warfarin dose is too low, putting the patient at risk for blood clots. But when the INR is above range, the warfarin dose is too high, which could predispose the patient to bruising and bleeding.<sup>3,4</sup> Please note that the INR reference range is different for healthy people compared to those undergoing anticoagulant therapy using warfarin.

In a subsequent double-blind, controlled study by the same British group, 70 warfarin-treated patients with unstable anticoagulant control were randomly assigned to receive 150 mcg of oral vitamin K or placebo daily for six months. Of the 35 patients receiving vitamin K supplementation, anticoagulation control improved in 33 patients, including 19 in whom vitamin K supplementation resulted in stable control of anticoagulation. By contrast, only 24 of 33 patients receiving placebo improved to some extent in their degree of anticoagulation control, and only 7 achieved stable control. "*Concomitant supplementation of vitamin K, perhaps through reducing the relative day-to-day variability in dietary vitamin K intake, can significantly improve anticoagulation control in patients with unexplained instability of response to warfarin,*" the investigators wrote.<sup>7</sup>

Patients who have already achieved stable control over anticoagulation with warfarin should be aware that vitamin K supplementation may reduce INR, necessitating an increased warfarin dose for optimal anticoagulation.<sup>8,9</sup> Patients taking warfarin should report the use of multivitamin supplements to their doctor. When changes in INR are unexplained, physicians should also inquire about vitamin K use.<sup>10</sup>

Vitamin K can also correct dangerously high INR levels,<sup>11</sup> and possibly allow anticoagulated patients to safely undergo surgery much sooner than they could without vitamin K.<sup>12</sup> For reducing excessively high INRs in patients taking warfarin, oral and intravenous methods of vitamin K administration are similarly effective.<sup>13</sup>

## VITAMIN K HELPS PREVENT ATHEROSCLEROSIS

New studies have found that vitamin K plays a crucial role in cardiovascular health.<sup>14</sup> Physicians face a difficult challenge in prescribing warfarin to prevent strokes. While offering protection from clots, warfarin can also create a functional vitamin K deficiency, which has been associated with calcification of the arteries.

Patients taking warfarin may be especially susceptible to atherosclerosis resulting from calcium buildup in arterial walls. In a study of patients undergoing surgery for aortic valve replacement, calcium buildup in the valves of warfarin-treated patients before surgery was twice that of patients who did not receive such treatment preoperatively.<sup>15</sup> Warfarin users may thus need to be particularly vigilant about safeguarding their cardiovascular health.

A study utilizing warfarin-treated rats suggested that supplemental vitamin K2 prevents arterial calcification. Compared with vitamin K1, vitamin K2 displayed a particular affinity for protecting crucial artery walls.<sup>16</sup>

Vitamin K2 is crucial for activating matrix Gla-protein (MGP)—a strong inhibitor of vascular calcification. When adequate K2 is available, matrix GLA-protein helps prevent the calcium buildup in blood vessel walls that contributes to vascular disease.<sup>17-19</sup>

In a study of rabbits fed a high-cholesterol diet, supplemental vitamin K2 provided several measures of cardiovascular protection, including decreasing circulating cholesterol, reducing the tendency of blood to clot abnormally, and preventing the development of atherosclerotic plaque and arterial wall thickening.<sup>20</sup>

The impressive Dutch Rotterdam Study assessed the effects of dietary intake of vitamin K2 on heart disease and atherosclerosis

in nearly 5,000 adults. When they entered the study, the 4,807 participants had no history of heart attack. Compared with participants in the lowest third of dietary vitamin K2 intake, those in the highest third had a **57% lower** risk of dying from heart disease, after adjustment for other factors associated with heart disease. They also had a **26% reduction** in risk of dying from any cause, and a 52% lower risk of severe aortic calcification. “These findings suggest that an adequate intake of [vitamin K2] could be important for coronary heart disease prevention,” the investigators determined.<sup>21</sup>

## VITAMIN K AND WARFARIN: *WHAT YOU NEED TO KNOW*

- Vitamin K has long been known to regulate control of blood clotting.
- In patients taking Coumadin® (warfarin) as a blood thinner or anticoagulant, modest doses of vitamin K supplements may improve the stability of anticoagulation therapy—leading to less frequent changes in warfarin dose, and more consistent benefits of therapy.
- If you use warfarin, discuss the possible benefits of low-dose vitamin K supplementation with your physician.
- Over the past decade, vitamin K has also been shown to promote calcium incorporation into bone, increasing bone mineral density and reducing fracture risk.
- Vitamin K may also help reduce calcification of arterial walls, thus helping to reduce the risk of atherosclerosis.
- Current research indicates that vitamin K2 has a greater effect on bone and cardiovascular health than vitamin K1.
- Vitamin K is more easily absorbed and utilized in supplement form than from dietary sources. Studies suggest that the RDA for vitamin K may be too low for optimal effects on bone and cardiovascular health.



## VITAMIN K BOOSTS BONE HEALTH

Vitamin K is now considered one of the missing ingredients in bone health as it enhances the modification of osteocalcin, a protein manufactured by bone cells. Once activated via a vitamin K-dependent process, osteocalcin binds calcium ions and incorporates them in the bone matrix—thereby increasing bone mineralization.<sup>22</sup>

As mentioned earlier, warfarin works by preventing the recycling of vitamin K, diminishing levels of the vitamin available to the body, and contributing to weaker bones and increased fractures.<sup>23</sup> This problem is compounded by the fact that many of the people using warfarin are elderly and already have osteoporosis and compromised bone integrity.

Clues regarding the importance of vitamin K to bone health were first revealed in 1984, with the observation that patients who had fractures because of osteoporosis also had vitamin K levels 70% lower than those of age-matched controls.<sup>24</sup> Subsequent research confirmed that low bone mineral density and osteoporotic fractures were linked to low serum levels of vitamin K.<sup>25,26</sup>

In the large and prestigious Framingham Heart Study, a dietary questionnaire given to 335 men and 553 women (average age 75 years) showed that those with the lowest vitamin K intake had a **65% greater** risk of suffering a hip fracture, compared to those who had the highest vitamin K intake.<sup>27</sup>

## VITAMIN K BASICS

Dietary vitamin K1 (phylloquinone) is mainly found in lettuce, spinach, broccoli, dark green leafy vegetables, and certain dietary oils, but may be difficult to absorb from food sources.<sup>30</sup> One study found that blood levels of vitamin K1 were five times higher after consuming a 500-mcg phylloquinone (vitamin K) tablet than after eating 150 grams of raw spinach or equivalent amounts of fresh broccoli or romaine lettuce.<sup>31</sup> Commercially prepared vitamin K1 (phytonadione) is chemically identical to naturally occurring vitamin K1. Approximately 60-70% of the daily dietary intake of phylloquinone is lost to the body by excretion, which emphasizes the need for a continuous dietary supply to maintain tissue reserves.<sup>18</sup>

Bacteria that normally colonize the large intestine synthesize an active form of vitamin K. Until recently it was thought that up to 50% of the human vitamin K requirement might be met by bacterial synthesis. Recent research indicates that the contribution of bacterial synthesis is much less than previously thought.<sup>32</sup>

Vitamin K2 (menaquinone)—which current scientific data point to as being more critical to cardiovascular health than vitamin K1—occurs in much smaller quantities in the diet, mostly in butter, eggs, cow liver, fermented products, and cheese.<sup>18</sup> The best source of dietary K2 is fermented soybeans—known to the Japanese as natto. Vitamin K2 derived from natto is commercially available as menaquinone, or MK-7.

The popularity of natto consumption in Japan could help explain why the Japanese eating their traditional diet have lower rates of heart disease and osteoporosis than do those in Western countries, where fermented soybeans are rarely eaten. For example, a study of nearly 1,000 postmenopausal Japanese women showed that increased consumption of natto was linked to increased bone mineral density at the hip and wrist, which scientists attributed to the effects of vitamin K and/or bioavailable isoflavones.<sup>33</sup>

In human studies, amounts of vitamin K2 that can be absorbed after taking a supplement given by mouth are up to 10 times greater than for K1, and it has a longer-lasting effect.<sup>18</sup> The liver breaks down K1 within eight hours after it is consumed, whereas K2 lasts in the bloodstream for up to 72 hours, where it is available to assist calcium transport into bone, to protect the arterial wall from calcium deposits, and to stabilize INR in patients taking warfarin.<sup>34</sup>

Although many older women in the United States take calcium supplements in the hope of lowering their risk for osteoporosis and fractures, these efforts may be ineffective if they are deficient in vitamin K. In a double-blind, controlled trial, healthy older women who took vitamin K (200 mcg K1), vitamin D (400 IU), and calcium (1000 mg) daily for two years had a modest but significant increase in bone mineral content at some bone sites, as compared with women who took placebo.<sup>28</sup>

In a review of all randomized controlled trials in which human adults received vitamin K1 or K2 supplements by mouth for six months or more, scientists identified 13 studies with data on bone loss and 7 studies that reported fracture rates. Overwhelmingly, the data showed that supplemental vitamin K1 or K2 reduced loss of bone mass. Vitamin K2 in particular was associated with increased bone mineral density, as well as lower fracture rates—by 60% at the spine, 77% at the hip, and an amazing 81% at all non-spinal sites.<sup>29</sup>

For those taking warfarin, it is important to discuss incorporating low-dose vitamin K into your regimen in order to prevent further deterioration of precious bone mass.

# REPORT

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#### DOSAGE AND SAFETY

Currently, the recommended daily allowance (RDA) of vitamin K is 70-80 mcg/day for men and 60-65 mcg/day for women.<sup>23</sup> Recent studies of vitamins K1 and K2 suggest that the present RDA is too low to fully protect against atherosclerosis and heart disease.<sup>17,35</sup> Some experts now suggest that low-dose vitamin K supplementation (50-150 mcg/day) may help stabilize fluctuations in INR in individuals who use warfarin.<sup>5</sup> If you use warfarin, discuss the possible benefits of vitamin K supplementation with your physician. Certain medications, including cholestyramine, colestipol, mineral oil, and orlistat may decrease the absorption of vitamin K. Large doses of salicylates such as aspirin may result in vitamin K deficiency. Cephalosporin antibiotics can cause vitamin K deficiency.<sup>23</sup>

#### CONCLUSION

Recent evidence clearly indicates that vitamin K is crucial not only for proper regulation of blood clotting, but also for optimal bone and cardiovascular health. In patients on long-term treatment with the anticoagulant warfarin, vitamin K may also facilitate control of anticoagulation therapy, so that the INR remains in ideal range, without frequent changes in the warfarin dose. The result may be more consistent benefits of therapy—such as decreased risk for heart attack and stroke, and fewer risks—such as hemorrhaging. If you use warfarin, discuss the benefits of modest vitamin K supplementation with your physician.

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