To the editor:

Vitamin K supplementation during oral anticoagulation: cautions

In response to the paper by Sconce et al,[1] we would like to point out that we have previously suggested the possibility of using vitamin K as a buffer to increase the stability of oral anticoagulation therapy.[2] However, we suggested the use of vitamin K_2 instead of vitamin K_1. The potential danger of giving K_1 with warfarin is that it may increase the arterial calcification risk. There are several indications that the use of K_2 may have at least the same ability to stabilize oral anticoagulation and appears to prevent arterial calcification. The drawbacks of using K_1 as a buffer to stabilize the anticoagulation response include the following: (1) K_1 has a relatively short half-life (1-2 hours), so that a single daily dose may result in substantial fluctuations of circulating and tissue K_1 concentrations. Therefore, the stability of anticoagulation may be further improved by using a vitamin K species with a longer half-life. (2) K_1 is taken up preferentially by the liver[3] so that extrahepatic tissues are more susceptible to vitamin K deficiency than the liver. This effect is exacerbated when K_1 and warfarin are combined; indeed, this combination has been used by Price et al to induce rapid arterial calcification.[4] Although the amount of warfarin used by Price et al to induce calcification in rats is higher than would normally be used in oral anticoagulation therapy, there are reports that patients on long-time normal warfarin therapy have increased calcification of aortic valves.[5,6] Therefore, though increasing both K_1 intake and warfarin dosage may improve oral anticoagulation stability, it probably also increases vascular calcification risk.[5,6]

A major advantage of K_2 is that it is not preferentially targeted to the liver. A number of tissues—including the vessel wall—accumulate K_2 at high levels.[6] This results in protection by K_2 but not by K_1 against warfarin-induced calcification.[7] Also, K_2 can be used in the liver equally as well as K_1. Of the commercially available forms, we recommend MK-7 (NattoPharma, Oslo, Norway; or E. T. Horn, La Mirada, CA). MK-7 is transported to extrahepatic tissues via low-density lipoprotein (LDL).[8] A further advantage of MK-7 is that it has a relatively long half-life (3 days). This longer half-life will probably result in more stable anticoagulation.

Although vitamin K_2 may have signaling functions independent from its role in gamma glutamyl carboxylation, supplementation with vitamin K_2 (MK-7) in doses as high as 45 mg/day seems to have no adverse effects.[9] Indeed, it seems to impede the growth of certain tumors and also to promote vascular health,[9] and reduces fractures in postmenopausal women.[10]

Based on these considerations, we propose that a new trial be designed in which patients on anticoagulation therapy receive MK-7 rather than K_1. At first it will be necessary to adjust the International Normalized Ratio (INR) based upon the dose of MK-7 and warfarin. These patients should also be followed to determine the extent to which this protocol prevents arterial calcification. In this regard, it is noteworthy that the risk of cardiovascular calcification by oral anticoagulation therapy (even without additional K_1) is receiving increasing attention.[5,6]

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Conflict-of-interest disclosure: D.W.S. has applied for patents on VKOR and its use in predicting warfarin dosage. C.V. is a consultant for E. T. Horn and does contract research for NattoPharma.

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Response:

Vitamin K supplementation during oral anticoagulation: no real cause for concern

We are familiar with the concept that oral anticoagulants, by inhibiting the recycling of vitamin K epoxide into its quinone form, might interfere with the functioning of glutamate-containing proteins not associated with hemostasis, in particular matrix Gla-protein, the potent inhibitor of soft tissue calcification, and osteocalcin, promoter of bone formation. The use of coumarins has increased rapidly in the last 15 years following the first publication that anticoagulation therapy is beneficial for thromboembolic prophylaxis in patients with atrial fibrillation.[1]Long-term use of coumarins, in what are now large patient populations, has not firmly established a clinically significant association between therapy and risk of arterial calcification. Work in young rats has established that menaquinone (vitamin K_2), but not phylloquinone (vitamin K_1), has a protective effect against warfarin-induced