

## Case Report

# Clinical decision-making for vitamin K-1 and K-2 deficiency and coronary artery calcification with warfarin therapy: are diet, factor Xa inhibitors or both the answer?

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Coronary artery calcification is a recognised risk factor for ischaemic heart disease and mortality. Evidence is now strong that Mönckeberg's arteriosclerosis, a form of vascular calcification, can be attributable to vitamin K deficiency, but that vitamin K-2, especially the MK-4 form from foods like cheese can be protective. Warfarin blocks the recycling of hepatic and peripheral vitamin K leading to secondary vitamin K deficiency with adverse effects on vasculature, bone, kidneys, brain and other tissues and systems (inflammatory, immune function and neoplasia at least). There is individual susceptibility to vitamin K deficiency and warfarin sensitivity, partly explainable in terms of genetic polymorphisms, epigenetics, diet and pharmacotherapy. The emergence of extensive coronary calcification in a man with atrial fibrillation treated for a decade with warfarin is described by way of illustration and to raise the present clinical management conundrums. Finally, a putative set of recommendations is provided.

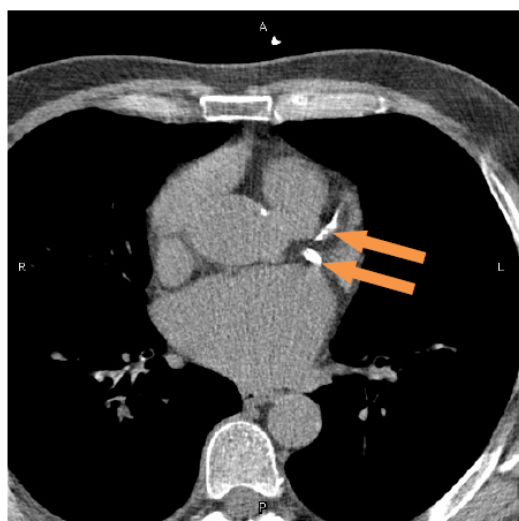
**Key Words:** vitamin K deficiency syndromes, coronary artery calcification, warfarin therapy, cheese and natto, apixaban

### INDEX CASE STUDY

At 61 years a Caucasian man developed atrial fibrillation (AF) and went on warfarin as an anticoagulant and verapamil for rate control. Despite 3 attempts at cardioversion the arrhythmia became persistent. There were no apparent risk factors for the AF – no ischaemic or rheumatic heart disease, no thyroid disease, minimal social use of alcohol, no diabetes and no evidence of cardiomyopathy. His diet was varied and of a plant-food orientation, with fish and beans 2-3 times per week, daily whole grains and green leafy vegetables, with low fat dairy and little cheese, and low in salt (<5 g/day). He was variably on an H-2 receptor antagonist or a proton pump inhibitor (PPI) for gastro-oesophageal reflux, which has been considered a risk factor for AF. There were no cardiovascular risk factors apart from a BMI of 26.8 kg/m<sup>2</sup>, with blood pressure (BP) generally about 135/85, fasting cholesterol 5.3, HDL cholesterol 1.3, triglyceride 1.8 and glucose 4.8 mmol/L. He was a non-smoker. Non-invasive monitoring of neck and peripheral arteries was unremarkable. A year later, he developed angina in stressful circumstances and on sustained effort, but not on formal exercise ECG and echocardiogram testing. Coronary angiography revealed a single lesion which was stented. Calcification was not in evidence in any radiographic investigation. Post-stent he had triple anti-hemostatic with warfarin, clopidogrel and aspirin for 6 months; he has remained on aspirin. For 8 years after commencement of warfarin, angina-on-effort

was occasional, but never during weekly yoga-aerobic and strength training sessions or rarely on recreational hiking. A cardiac thallium scan at this time, because of increased angina frequency revealed a reversible ischaemic region in the infero-lateral myocardium. A second stent was placed at a left coronary-diagonal artery bifurcation and when increased luminal irregularity was noted; triple anti-hemostatic therapy was again implemented, but for 12 months. A post-stent thallium perfusion study showed little benefit from the stent. On warfarin for 10 years and aged 71 years, a cardiac CT showed extensive calcification of the coronary circulation, but quantification was limited by the presence of AF. Imaging also showed peripheral medium distributing arteries (ilio-femoral) to be patchily calcified (Figures 1 and 2). Throughout the decade of warfarin therapy, INR (International Normalised Ratio) has been maintained well into the therapeutic range, almost always between 2.0 and 2.5, on doses of about 7 mg daily. There have been 2 episodes of major soft tissue bruising as a result of moderate trauma.

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**Figure 1.** Arrows indicate extensive calcification of the left coronary artery on the cardiac computer tomography (CT).



**Figure 2.** Arrows indicate multiple patchily calcified sites on the distal descending aorta and bilateral ilio-femoral arteries on the limb vascular CT.

Intercurrent illnesses during this decade have included herpes zoster (C2) and temporal arteritis (2 courses of high dose prednisolone with the need for an angiotensin receptor inhibitor, irbesartan for BP control).

The questions now are 1) is the arterial calcification attributable to vitamin K deficiency, both primary (diet) and secondary (warfarin), and is it medial rather than intimal? 2) what, if any, dietary changes might be helpful should vitamin K deficiency be a problem? 3) is the reduced risk of thromboembolic phenomena with warfarin outweighed by the risks of arterial calcification – and the risks of other vitamin K deficiency disorders affecting bone, brain, kidney small vessels and more? 4) is there individual susceptibility to vitamin deficiency which this patient might have exhibited? 5) does this patient's pharmacotherapy represent interactions or synergies which might have exacerbated the risk to vascular biology of warfarin eg aspi-

rin, PPIs, antiarrhythmic agents (verapamil); 6) could an increased intake of vitamin K-2 from foods rich in it reduce the risk of coronary calcification, even in the presence of warfarin therapy? 7) should warfarin use in AF be avoided or used for limited periods only and factor Xa inhibitors like apixaban used instead?

### THE ESSENTIALITY OF VITAMINS K-1 AND K-2 IS PLEIOTROPIC WITH STRUCTURAL AND FUNCTIONAL DIFFERENCES

Vitamin K carboxylates, post-translationally, the amino acid glutamate (Glu) in proteins, which then become gamma-carboxy-glutamate (Gla) residues. These residues in turn chelate calcium.<sup>1</sup>

There are 2 naturally-occurring forms of vitamin K, K-1 or phyloquinone (also known as phytomenadione) and K-2 or menaquinone which itself has several forms designated MK-n, where n is the number of side chain isoprenoid residues.<sup>1,2</sup>

Vitamin K-1 is recycled between the reduced hydroquinone and the oxidized epoxide, with epoxide reductase (VKOR) responsible for the formation of the hydroquinone and which can be blocked by warfarin. In this way, warfarin can create an effective vitamin K deficiency in liver and in peripheral tissues. It is the hepatic coagulant proteins II, VII, IX and X which are therapeutically compromised by warfarin in anticoagulation. But so are Gla proteins in other tissues, like osteocalcin in bone and the vascular wall calcification –inhibiting matrix Gla protein MGP and the growth arrest specific gene 6 protein Gas6, among others. In some way, vitamin K deficiency in the CNS, perhaps because of less good transport in apo-E4 lipoproteins, may exacerbate cognitive impairment. Interestingly, whereas vitamin K-1 is transported in VLDL, K-2 is transported in LDL and HDL<sup>3,4</sup> which may make vitamin K-2 of particular relevance for brain. Gas6 plays a role in inflammation, renal function and cell differentiation.<sup>5</sup> There is preferential accumulation of vitamin K-2 in peripheral tissues like the vasculature.<sup>6</sup> But it appears that it is the MK-4 type which can prevent arterial calcification.<sup>7</sup> Thus, the pleiotropic functions of vitamin K are evident and, as yet, not fully recognised.<sup>8</sup>

There is evidence that the clinical manifestations of vitamin K deficiency may be more evident in some tissues, like bone<sup>9,10,11</sup> and the vasculature,<sup>12</sup> than others like liver. Some of this difference may reflect the tissue specificities of the different forms of vitamin K and the local food culture to deliver the forms required.

### FOOD AND MICROBIOMIC SOURCES OF VITAMIN K

Vitamin K-1 comes mainly from green leafy vegetables because of its role in photosynthesis. It can be converted to vitamin K-2 of the MK-4 type in animal tissues including the pancreas, testes and vasculature. Other forms of MK-n are produced by bacteria in fermented foods like natto (from soy), cheese and fermented vegetables (eg kimchi and sauerkraut), but are also found in eggs and chicken liver.

Broad spectrum antibiotics can markedly reduce vitamin K status which presumably indicates a major gut microbial source of vitamin K, but the conversion of K-1 to

K-2 may take place in the gut wall.<sup>11</sup> With the present surge in gut microbiomic research, its role in vitamin K nutrition should become clearer.

### VITAMIN K DEFICIENCY SYNDROMES

Vitamin K deficiency is widespread among some populations, especially the elderly, even where the food supply would be thought to be adequate as in Japan.<sup>13</sup>

It will be clear from the pleiotropic effects of vitamin K through vitamin K dependent proteins (VKDPs) that its deficiency, whether primary as dietary inadequacy or secondary through the use of the coumarin warfarin, could produce a spectrum of clinical sequelae. But the recognition of vitamin K syndromes is unusual in practice. This probably results from a lack of awareness of food sources of vitamin K-2 as well as the better known K-1, and their differential tissue specificities.

VKDP osteocalcin status is compromised by poor vitamin K intakes as well as warfarin therapy which need to be taken into account in osteoporosis management. For the prevention of vascular calcification, it may be the MK-4 form of K-2 which is most important, with cheese a particularly useful source. Foods like natto and cheese provide other MK-n as well both MK-4 and MK-7 are favourable for osteocalcin and bone health. This may be indirectly relevant to arterial health. Bone is increasingly recognised as an endocrine organ in its own right with osteocalcin being involved in energy regulation, insulin resistance and cardiovascular risk.<sup>14,15</sup>

Vascular calcification may be an important feature of vitamin K deficiency<sup>5</sup> and of warfarin therapy.<sup>16</sup> Nevertheless, anecdotally, not all patients on warfarin develop arterial calcification, although the incidence and risk are not quantified in any available study. But, presumptively, there would seem to be predisposing factors which might include genetic and epigenetic mechanisms, background diet and use of medications which themselves alter vitamin K status or sensitivity.<sup>1,5</sup> Renal impairment is itself associated with vascular calcification and sufferers will constitute one of the more susceptible groups to vitamin K deficiency.<sup>5</sup> Abdominal obesity and diabetes also increase the likelihood of vascular calcification.<sup>12,17</sup>

For drug interactions, broad spectrum antibiotics (altering the vitamin K producing and transforming gut microbiome), PPIs (which alter divalent cation metabolism, especially of magnesium, and increases risk of fracture), salicylates (which inhibit K-2 less than K-1), steroids (with their osteopenic effects), antihypertensives (which may be associated with vascular calcification although circumstantially) statins (which may protect against vascular calcification and osteoporosis,<sup>12,18</sup> and vitamin D supplements (through hyperphosphatemia). Thus, it is difficult to isolate warfarin effects alone in the pathogenesis of vascular calcification, although the mechanisms are highly plausible.

### CORONARY ARTERY CALCIFICATION: IS MEDIAL ARTERIAL (MÖNCKEBERG'S) CALCIFICATION ACCEPTABLE?

In the longitudinal Rotterdam study, increased intake of vitamin K-2, but not K-1, was inversely related to all-cause mortality and aortic calcification.<sup>19</sup> This has been

supported by the Beulens cross-sectional study of postmenopausal women.<sup>20</sup>

The pathology is that of medial calcification, known as Mönckeberg's arteriosclerosis, which is not that of atherosclerosis.<sup>12,19,21</sup>

Coronary artery calcification is a significant predictor of risk for ischaemic heart disease and mortality. It would appear that this applies to Mönckeberg's arteriosclerosis as well as to intimal or intimo-medial calcification, although the relative risks of these types of calcification has not been evaluated.

### IS INCREASED VITAMIN K-2 INTAKE A WAY TO REDUCE CORONARY CALCIFICATION WITH WARFARIN?

The available experimental and population studies would suggest that higher intakes of vitamin K-2 would reduce the risk of vascular calcification and that they may even allow some reversal.<sup>21</sup> Since foods like cheese might provide a way to this, present ideas about such fatty foods and cardiovascular disease (CVD) might need review, especially since there is no evidence that these foods in their own right present a CVD risk. It is conceivable that they might achieve this in the face of effective warfarin anticoagulation through its hepatic effects, while minimising its adverse vascular effects.

### CAN FACTOR XA INHIBITORS (LIKE APIXABAN) REDUCE THE RISKS OF VITAMIN K DEFICIENCY?

If anticoagulation can be confined to factor X, it should allow the other non-coagulant functions of vitamin K to be met by diet and the avoidance of vitamin K deficiency-related vascular calcification, along with other functions as with bone health. At present apixaban looks the most promising agent in this category insofar as reversibility of its action and side effects are concerned, at least insofar as AF is concerned (especially in the presence of ischaemic heart disease). But time will tell whether there are long term, as yet unrecognised complications and whether all-cause and disease-specific mortalities are favourable.

### SHOULD WARFARIN BE USED FOR MORE THAN SHORT-TERM THERAPY?

It may be that warfarin could be used for limited time periods with little consequence through vitamin K deficiency, or that its safety might be improved by judicious simultaneous use of vitamin K-2. But, at present, we have little information as to time to effect.

### CONCLUSIONS AND RECOMMENDATIONS

1. There is substantial evidence that warfarin-induced vitamin K deficiency can lead to a spectrum of vitamin K deficiency disorders, including vascular calcification.
2. The risk for vitamin K deficiency-related vascular calcification may be minimised by higher intakes of vitamin K-2 which may be sourced from cheese, eggs and fermented foods like natto, although the different MK-n forms of vitamin K-2 may have benefit differentials; cheese with MK-4 has the most evidence at present, challenging the conventional wisdom that cardio-

vascular-protective foods need to be invariably low fat (as has been recognized for fatty fish, nuts and other seed-foods).

3. The clinical identification of individuals susceptible to vascular calcification, by diet, disease or associated pharmacotherapy, may allow better risk-benefit evaluation of warfarin therapy especially in AF.
4. Individuals susceptible to vascular calcification should have a baseline coronary artery calcification assessment and review.
5. Individuals susceptible to vascular calcification with AF are candidates for factor X antagonists instead of warfarin.

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## 維生素 K 拮抗劑治療而致維生素 K-1 和 K-2 缺乏及冠狀動脈鈣化的臨床決策：飲食、第十凝血因子抑制劑或者兩者解答嗎？

冠狀動脈鈣化被認為是缺血性心臟病及死亡的危險因子。Mönckeberg 型動脈粥狀硬化是一種血管鈣化，現在有力的證據顯示這可能是維生素 K 缺乏所導致；維生素 K-2，特別是來自於食物，像是乳酪的 MK-4 型式則具保護作用。維生素 K 拮抗劑-warfarin 阻斷肝及周邊的維生素 K 循環，造成次發性維生素 K 缺乏，而引發脈管結構、骨頭、腎臟、腦及其它組織系統的副作用(例如發炎、免疫功能及腫瘤)。個體對維生素 K 缺乏的易感性及 warfarin 敏感性，部分可以基因多型性、表觀遺傳學、飲食及藥物治療所解釋。本文描述一位有心房顫動的男性病患，在過去十年一直以 warfarin 治療，被發現有廣泛性的冠狀動脈鈣化，因而帶出這個目前臨床管理的難題。最後提出一套推斷的建議。

**關鍵字：**維生素 K 缺乏症狀、冠狀動脈鈣化、維生素 K 拮抗劑治療、乳酪及納豆、apixaban