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## Recent Vitamin K Literature in the Context of a non-Monotonic Response Curve : Local vs Global Optima and other Speculation

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This note reviews recent vitamin K literature in terms of a previously proposed conceptual non-monotonic relation between vitamin K activity and coagulability. The curve illustrates one sensitive optimum at "moderate" vitamin K activity but a much more tolerant optimum at very high activities. It then considers miscellaneous biochemical topics related to vitamin K and a concise relationship to clinical situation. While vitamin K is used for the addition of Gla domains to mutually moderating proteins, there may be a tendency to assume the vitamin K - coagulability relationship is monotonic preventing recognition of observations to the contrary. Moderation becomes even more significant when considering factors such as trigger density not strictly part of the coagulation "system." No overall curve relating vitamin K status to coagulability prior to my earlier work appears to exist and such a curve may be useful for understanding existing limitations and paradoxes with vitamin K control. Well known reasons for non-monotonicity include proteins C and S but others may exist over a broad range of genetics and conditions. Attempts to add only or of these proteins to correct hypercoagulability have had limited successes and a more complete solution may just involve more vitamin K. "Coagulability" and clots themselves are characterised by many parameters and a single curve will miss details but such a curve may inform vitamin K dosing concerns related to bleeding or occlusion. By non-fibrin effects such as controlling mineralization, vitamin K may also control nuclei or trigger density. The hemostatic response to a trigger may be most effective when it is "explosive" and can quickly shut itself off after isolating the trigger from circulation. In effect, this work suggests that an explosive response creates a more favorable quality-quantity tradeoff enabling the creation of more compact and effective clots at high vitamin K activity ( which could be limited by the supply of reducing equivalents or other factors besides concentration of vitamin K ). The complex regulatory network makes in vitro assessments of only indirect relevance to in vivo situation. This interpretation is considered in terms of selected literature and larger functions in calcium control. These results suggest that problems with anti-coagulation control and such issues as warfarin necrosis are more easily resolved with arbitrarily high levels of vitamin K supported with sufficient reducing equivalents and other forms of calcium control such as moderated vitamin D intake. Several other observations from the literature led to additional speculation that may be interesting for further investigation.

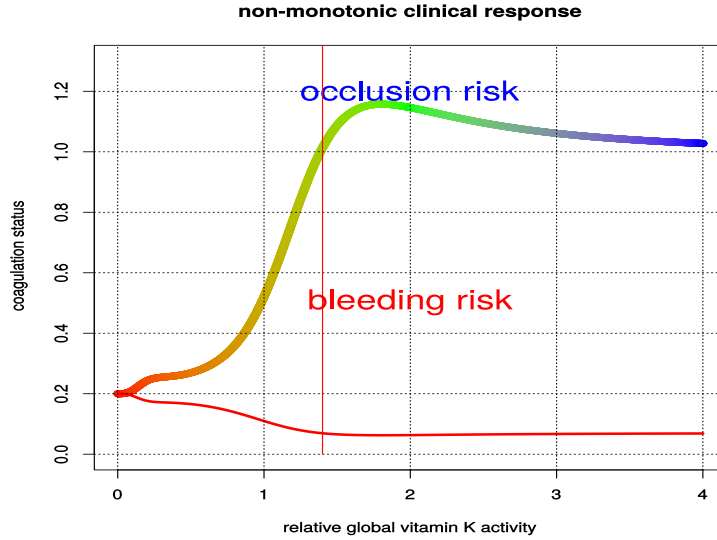


FIG. 1: Conceptual curve suggesting that pathological clotting occurs at intermediate vitamin K activity levels. In this case, triggers can not be effectively isolated by clots composed of cells and poorly organized non-fibrin. At very low activities solids may still form due to non-enzymatic or other poorly controlled processes involving fibrinogen etc. At high enough activity, fibrin clots quickly isolate offensive or damages nuclei and only a very thin impermeable clot is required. Vitamin K mediocrity does not need to precipitate thrombotic disease but it may if the nuclei are present. Red vertical line is the "warfarin optimum" which may be hard to control compared to the wider plateau at very high levels. Dynamic and static effects may be somewhat mingled but this may be useful to pick a vitamin K strategy. The rainbow color simply highlights the possibility that a lot of qualitative factors change along the path pointing to limitations of this graphic. Red curve suggests contribution of non-thrombin derived solids.

## 1. THE CURVE

In previous work [118], a curve similar to Fig. 1 was described illustrating a non-monotonic relationship between coagulability state and vitamin K activity. This was based on a selection of the literature discovered at the time and some personal experience with giving vitamin K to heartworm positive dogs [119] [111] [115]. Consideration of additional literature tends to support the notion but the curve has been modified in Fig. 1 to include non-fibrin clotting by modified fibrinogen, NET's, and cellular components such as platelets and red blood cells. Central to vitamin K dependent coagulation is fibrinogen which is the precursor to fibrin clots although itself is not vitamin K dependent. It had unusual interfacial [157] and adhesion promoting [202] properties that can effect spontaneous chemistry. Fibrinogen has been observed to form solids near injured liver likely due to reactive species and FXIIIa crosslinking can still occur [147]. In cirrhosis, a known tendency for venous thromboembolism and portal vein thrombosis is made worse by vitamin K deficiency [77]. In other work, I described concerns about similar solid formation due to non-enzymatic FGN reactions that accumulate during its circulation lifetime when ROS sources are not well isolated [116] with high-quality fibrin and cellular clots.

Note that "coagulability" is not really a state that can be quantified by a single variable. Response to nuclei density, initiation, propagation, and termination as well as cellular contributions may all vary. This text attempts to describe the state of affairs as a decrease in quality with loss of vitamin K that can be compensated with larger quantity of solid deposition. If vitamin K activity improves endothelial quality then it may also help reduce trigger density independent of the response modulation. Also lacking is detail of the dynamics and those may be somewhat mingled to make this effective illustrative curve. Briefly, as elaborated later, the peak is largely due to reduced protein C or S availability as vitamin K activity is reduced. From an evolutionary standpoint, this makes some sense as a compensatory response and the dynamics may allow safe restoration as vitamin K is replenished.

Vitamin K is not purely coagulation producing and its important to appreciate the larger evolutionary and regulatory contexts. The importance of coagulation is difficult to overestimate for survival in the "wild" prior to

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modern lifestyles. The textbook process involves conversion of fibrinogen to fibrin and subsequent crosslinking. Fibrinogen deficient mice can survive except for pregnancy [172] while prothrombin KO in mice is uniformly fatal , largely due to brain and heart bleeding, aside from decreased resistance to bacterial infection [138] in the short time before death. When interpreting results like this however its important to question broader applicability due to species differences and experimental conditions such as overall diet. Still, the difference in outcomes may be considered for possible implications of thrombin inhibitors. A response to injury or pathogens ideally is fast but self-regulating. The fast response can be aided by maintaining a high concentration of circulating inactive coagulation proteins such as zymogens of fibrinogen and then rapid cleavage in a self-amplifying cascade as is observed. Indeed, the required response has been described as an "explosive" thrombin burst [109] which is facilitated by the membrane interactions made possible by the vitamin K dependent Gla domains.

#### Thinking outloud

This arrangement itself is quite unusual as the Gla plus calcium allows sequestering of themselves to force exposure of hydrophobic residues Phe, Leu, and Val [174] with dynamics on unusual time scales [137].

The Gla domains also influence interactions such as prothrombin with Factor Va [18],

Positive feedback is great, an important part of an "explosive" response, as long as it is well regulated and self-limiting or exhausting. Earlier, no control loops were considered although an idling current due to constitutive tissue factor expression was known as was the thrombin activation of platelets [76]. Consumption of clotting factors is often assumed to be pathological leading to the term "consumptive coagulopathy" but that need not be the case if they are depleted with the right dynamics. If coagulation is ever going to work well, it has to shut off once the threat has been contained but that may not show up in incomplete simulations. One work found a self-propagating thrombin wave could form that would terminate with protein C [38]. Other simulations produced a propagating coagulation wave that is contrary to an exponentially decaying experimental result [87],

The currently elucidated schemes do not appear to explain observations and additional details need to be considered or hypothesized. This work advances the quality-quantity idea without elaborating details of its implementation. Many signals to nucleate a clot would be better covered up than left exposed if they can not be immediately removed. However, if a high quality clot can not be created, the source continues to signal that it needs to be covered by emitting noxious compounds. Quantity can compensate for quality but any barrier may remain permeable to both clotting factors and noxious substances. Thin cell based barriers like platelets may not stop even "large" molecules from diffusing if they result in gaps. Ironically, it may turn out that anti-platelet therapies simply improve the cell to fibrin ratio in a clot reducing its permeability. A similar result may be obtained with more fibrin. This notion is, however, contrary to one work on clot permeability in vitro. A 2013 study compared the hydraulic permeability of platelet rich and poor clots formed with only thrombin, calcium chloride, and fibrinogen finding that under pressure the permeability decreased with increasing platelet fraction with pore sizes from 4 to 250 nm [192]. However, losses include fluid parameters like viscosity which may not similarly effect diffusion at zero pressure differential across clots between circulation and damaged but intact vessel walls. Lack of any process to densify or crosslink the fibrin ,such as FXIIIa, makes results overestimate fibrin permeability in in vivo real physiological clots. Indeed, loss of FXIIIa crosslinking increased embolic events, decreased time to event, and more erratic but similar clot size in a ferric chloride model in mice [45] suggesting quality matters and low quality creates more overall solid deposition and occlusive disease. Although another work with ferric chloride induced stroke in mice suggested that FXIIIa inhibition could be protective [74] In the clinic, stroke patients showed increased mortality after thrombolytic therapy if they had low FXIII levels [175]. In thinner inhomogeneous physiological clots the distribution of the fibers holding the platelets together may vary substantially as the platelet fraction and thrombin distribution change. Differential pressure may push platelets together making a better seal than would occur at low pressure. In the case of very thin clots, it is unlikely a few layers of thin plates ( platelets ) could be as impermeable as well crosslinked continuous fibrin. Pressure pulses transiently compressing layers of platelets may even act as pumps.

Consumption of protein C may contribute to consumptive coagulopathy [36]. which presumably could be mitigated with faster protein C production and activation. Even platelets express a protein C receptor [53].

#### Thinking outloud

none of what?

None of this matters though if failure to make a high quality "wall" allows nuclei and clotting factors to inter diffuse. This allows the process to make a larger lower quality wall. If coagulation does not work, the organism faces a dilemma of uncontained pathogen spread, blood loss, or a larger pathological occlusion formation. The strategy may not always make sense with modern lifestyles however. It also did not evolve to make laboratory analysis particularly easy as assays have many artifacts including from the new DOAC's even when these are known prior to analysis.

#### Thinking outloud

failure to distinguish FGN from fibrin may make a good central point

Analysis of vitamin K impact even on clotting is complicated by the limited laboratory approaches to measuring

the state of the coagulation system in a patient relevant way. Positive feedback and large gradients create a lot of opportunities for modelling difficulties. This work recognizes lab values as being ambiguous and tries to consider ways in which a robust coagulation system may be able to work and then consider if in vitro work is generally consistent with these ideas. Even the DOAC's, introduced in a controlled intentional way, may not always be considered in clinical sample interpretation. With many triggers, steep spatial gradients, and positive feedback loops, definition and measurement of useful parameters is itself a challenge. In fact, not until about 2015 were fibrinogen and fibrin even distinguished but making that distinction points to an important role for fibrin in clotting and infection [99] [152]. Further, fibrinogen is sufficient for aggregation of human platelets although not mouse unless transfected with human glycoprotein VI [107]. Clearer understanding likely will show the limited utility of thrombin inhibition and important species differences. By 2013 the regulatory and moderating role of protein C was well known [21]. Protein S binds to phosphatidylserine on apoptotic cells and regulates C4BP and consequently C4b regulating complement response [189] and it inhibits prothrombinase in a coordinated way [96]. But still the original functions of vitamin K were largely associated with increasing clotting in nebulous terms.

The introduction of DOAC's directly inhibiting thrombin or factor Xa, further demonstrated the problems with lab characterisation of the coagulation system. Even when the DOAC's were dosed in known amounts, the interferences with lab tests, in particular functional tests, were not appreciated. While this can be corrected, it does illustrate the problems interpreting functional assays, specifically an in vitro clotting time, to measure concentration of fibrinogen. Several interferences and work -arounds are now known [52] [135] but the larger problem is interpreting one or two functional tests as the concentration of some specific component, such as fibrinogen or protein C, remains. As fibrinogen may "age" or become modified, a functional assay would be more useful than a total concentration but the right function needs to be measured and a detailed subtype concentration may be more useful. Alternatively, all possible variants could be quantified individually but the practicality is questionable and then open to functional interpretation.

Vitamin K dependent calcium binding sites provide a variety of functions. Vitamin K is often introduced in popular press or other superficial coverage as an important part of pathological coagulation and occlusive disease. However, it is important to note that the actual coagulant precursor, fibrinogen, is not even vitamin K dependent. Recent reviews [16] [131] [130] list currently known vitamin K dependent proteins, the functions of vitamin K, and consequences of incomplete vitamin K activity. More precisely, then, instead of just promoting coagulation an important function of vitamin K is producing calcium binding sites known as Gla domains.

The human coagulation system mostly descended from other proteins [43]. Vitamin K dependent calcium binding Gla domain is more evolutionarily diverse than earlier thought, appearing even in marine organisms [67] with  $\gamma$ -carboxylation occurring in molluscs [11] and chordates [86] with functions including modulation of ion channels [10]. Interaction with calcium (and other calcium modulators like citrate and vitamin D) then is important context for understanding the clinical impact of vitamin K. The Gla domains are important for interaction with phosphatidylserine and activity enhancement of several coagulation related proteins [17]. Mutations effecting the protein S Gla domain may cause thrombotic disease [158] highlighting the control aspect of vitamin K dependent modifications.

For these and likely other reasons, vitamin K, among others [57], is associated with diverse outcomes such as optimal brain health [31]. [149] and menaquinone-7 may even reduce natural age related cognitive impairment in rats [50]. As if vitamin K was not counterintuitive enough, thrombin or mutant thrombins has also been proposed as an anti-coagulant if its only action is to activate protein C [26]. Although prothrombin cleaved to meizothrombin which is anti-coagulant [108] but labelled as "paradoxical." Apparently it is much better at activating protein C than alpha thrombin [65].

One damage associated signal that may illustrate the "covering up" issue is Von Willebrand Factor(vWF). vWF is released from and then binds to endothelial cells or platelets [62]. High serum levels may be associated with increased risk of venous thromboembolism [48] and major adverse cardiac events [56]. A 2022 result suggests that vWF reacts only with fibrin rather than fibrinogen to make clots quickly [153]. A thin impermeable barrier could keep vWF out of circulation and hopefully become passive. A study of mice with diet induced obesity (high fat diet) developed enhanced secretion and impaired clearance of vWF along with less fibrin in clots [126]. Its difficult to rule out fibrin deficiency due to vitamin K deficiency related to the high fat diet. In fact lipophilic vitamins are a likely issue with high-fat diets [46] and in mice vitamin K supplementation can correct some bone [83] and mitochondria or muscle [171] problems. However, there is no obvious indication that vitamin K supplementation reduces red thrombus although red thrombus may be NET dependent [23] and therefore indirectly controlled by vitamin K.

Personal experience giving vitamin K to dogs in cases often considered for anti-thrombotics has been good. In one case, a pregnant pit bull with heartworm and later diagnosed fibroids (unpublished personal communication from vet who removed them) did well with vitamin K among other things [119]. An earlier heartworm positive dog did well too [111] [115]. Note that all dogs received a broad range of nutrients rotated in a way to avoid some competitions. All that can really be said about the vitamin K is that it did not appear unsafe under these conditions. Note that significant citrate was typically included.

Hopefully this introduction explained the origin of the proposed curve, explained some of the problems with prior art, but created several more questions. The rest of this work covers some topics that should further support the curve but organized as plausibility considerations. At issue is interpretation of specific observations and the validity of various conclusions that need to be re-examined. Miscellaneous observations that could be a basis for further resolution are listed in the conclusion.

#### Thinking aloud

part of the organization issue is it is mostly a collection of stuff I thought was interesting, the proverbial "darlings".

## 2. VITAMIN K STEREOTYPE

Concerns about vitamin K may derive from its association with pathological coagulation and over-generalization of theoretical or ex vivo works. Vitamin K antagonists such as warfarin are well known and produce measurable benefits which may make it seem counterintuitive to find a better solution in the opposite direction

#### Thinking aloud

x avoid rat poison comment as if a hitler analogy lol

. There may be a presumption that if vitamin K antagonism fixes some problems, then more must be bad. Indeed, some limited work suggests that more circulating vitamin K is associated with higher stroke risk [89] but that is exactly what is predicted of the low vitamin K part of the proposed curve. Confusing results of vitamin K intake and outcomes may be considered in terms of the non-monotonic curve presented here. The expectations may be so great, that when supplementation fails to create a hypercoagulable state it seems to be a noteworthy result [69] but this too makes sense if the supplementation is great enough to get to the plateau of Fig. 1. An inverse association was found between blood phyloquinone and risk of ischemic stroke among Chinese with hypertension and high BMI [190].

Due to the complex nature of the coagulation system, "hypercoagulability" takes on many forms. In 2000, several forms were recognized including defects in protein C and S with treatment consisting of warfarin sometimes leading to "warfarin necrosis" [177]. The existence of "warfarin necrosis", likely due to faster decay of protein C than procoagulant proteins [84], points to the consideration of "safe passage" from the narrow warfarin optimum to the more tolerant high-vitamin K region. While unfavorable dynamics in one direction do not assure a safer route in the other direction, there is some indication that exists [118]. One case report illustrates some issues with managing an INR about 10 and necrotic lesions [151] that finally led to consideration of vitamin K before returning to anticoagulants leading to amputation and eventually hospice care. While not intuitive, its worth speculating on which genetic conditions may even be better treated with vitamin K supplements instead of antagonists. Note too that a fast fall in vitamin K cycling activity, which may occur from limited reducing equivalents, could presumably produce effects similar to warfarin necrosis or paradoxical "hypercoagulability" either locally or systemically.

Ironically, as opposed to vitamin D [120] ( see historical controversies on fortification limits [60] [187] ), I was unable to locate a single case report of vitamin K overdose other than concerns about INR in warfarin patients. This excludes, of course, the non-natural vitamin K3 [130].

In healthy people anyway the consensus seems to be that supplementation, particularly of MK-7, does not create a coagulation or any other problem [156]. Currently there is even consideration of recommending more vitamin K intake for stroke patients [191] although this is based on food association studies.

A 2021 review suggested K2 supplementation for improved cardiovascular outcomes and suggested it failed to create a hypercoagulable state [69].

It is recognized that anticoagulation in the elderly is difficult due to narrow window [34]. However, supplementation or increased vitamin K status correlates with various favorable clinical results [167] including cognitive function [19] and cardiovascular health [69].

#### Thinking aloud

why no bone health here? lead with CVD as that was the point

Proteins C and S are well known vitamin K dependent coagulation moderators but their relative response to vitamin K supplementation may be unclear. Prothrombin and protein C carboxylation status in response to warfarin were explored as early as 1989 [32]. Neonatal vitamin K deficiency is a well known problem and some literature exists although it may not be applicable to mature people. A 1993 investigation into vitamin K deficiency and replenishment of neonates suggested proteins C and S gamma-carboxylate in parallel with coagulant proteins minimizes chance of vitamin K related coagulopathies [121]. A study comparing des-carboxy prothrombin and protein C in term and premature babies found correlations between the two and suggested hepatic cycling rates may be limited while cautioning that lab results were sensitive to methods [22] but no scatter plots to look for various trends. It is also worth noting though that they quote 4-60 hour half life for protein C. This may make it effected by short term loss



of reducing equivalents that can occur under "stress." Indeed, cytosolic NADPH limitation may be a big driver of pathology [9].

Another study of protein C in mice suggested that extra-hepatic mRNA could be reduced in response to LPS exposure [195] suggesting that more vitamin K may not help. However, while some relative reduction in protein C may be adaptive it is not clear how this relates to other factors like prothrombin.

### 3. WORD GAMES : BLOOD THICKNESS

Anti-coagulants may be colloquially described as "blood thinners" and indeed blood viscosity does appear to correlate with cardiovascular disease [35] [181] [100] [25] [20] . The association was described at least since the 1980's [29] [41] and recently recognized with covid-19 mortality [30]. While the details remain to be worked out [42] , protein content and notably fibrinogen content as well as RBC physical properties are thought to dominate viscosity measures [15]. RBC flexibility or deformability is thought to be an important component of blood function [47].

Vitamin K antagonists do reduce blood viscosity in many studies [92] but that is not always the case [98]. By eliminating on sink for fibrinogen, fibrinogen and blood viscosity would be expected to increase after warfarin dosing. When reductions in blood viscosity in response to warfarin do occur, it may not have anything to do with the coagulation cascade directly. As early as 1985, A small rat study suggested that RBC deformability and low hematocrit were more important than fibrinogen levels [63]. Accidental modification can occur when attempting to achieve some other goal. Blood rheology can be modified by calcium channel blockers [85] and blood calcium also may correlate with viscosity [185]. Warfarin usage is also associated with calcium deposition in arteries which may suggest important calcium redistribution.

Early on, erythrocyte flexibility was observed in ponies along with a blood viscosity fall in response to warfarin treatment [5]. It is entirely possible that clinical benefits for warfarin relate to RBC rheology as much as vitamin K antagonism or reduced coagulation. Literature on other thrombin inhibitors or DOAC's may be interesting for comparison in a later work. Similarly, heparin may have clinical impact due to effects other than anti-coagulation which are preparation specific [102]. Accidental or unappreciated effects of details or formulation are likely to be a common issue. Literature fragmentation may be common and has been seen before in related topics with vitamin D [112] and may occur in benzoate for brain disease effects other than d-amino acid oxidase activity do not appear to be considered [110].

### 4. PARTIAL CARBOXYLATION AND REDUCED PH

Probably the oldest indication of a relationship between vitamin K and pH is a study on the response of phytoplankton *Emiliania huxleyi* to acidification. The authors found increased synthesis of proteins likely to be involved in vitamin K synthesis [81] merging ancient issues with mineralization, pH, and energy usage.

Today, one enigma that may offer important context and perspective on vitamin K is osteocalcin which oddly seems most effective in an undercarboxylated state. It is secreted mostly from osteoblasts and is evolutionarily ancient appearing first with "bony structures" apparently derived from the MGP ( and also called BGP ) that appeared coincident with "cartilaginous structures" but today interacts with insulin, fertility, and cognition [201]. Essentially sufficient for a stress response, serum levels increase after exercise and decline after midlife ( reversible by osteocalcin injection ) with known functions relating too pancreas, memory and exercise capacity Undercarboxylation occurs due to removal in the low pH lacunae but it may also occur during PTM by glutamate signalling [14] . It is interesting to speculate that OCN may also decarboxylate in the lactate rich low pH environments around oxygen deficits. Further, excess glutamate may be suspected of depressing gamma carboxylation more generally leading to undercarboxylated vitamin K dependent proteins. Interestingly, some decreases were observed at lower chronic doses although MSG is known to provoke clotting acutely [144] presumably through other mechanisms ( although maybe including protein C inhibition ) and is not a clean test. Interestingly, Gas6 was found to reduce apoptosis during CO2 induced acidification [37] although its carboxylation state was not examined.

It may be expected then that levels of partially carboxylated proteins could mediate mood by various means. Indeed, there is some evidence relating vitamin K status and presumably then carboxylation rate to various mental states. A small rat study suggested improvement in anxiety and depression in rats fed a high fat/fructose diet [59] . And indeed "perceived stress" appeared to correlate with the intake of many nutrients including vitamins A,C,B-X, and K as well as essential amino acids [90].

pH or acidosis related coagulopathy may be interesting to investigate. Currently there do seem to be acidosis related coagulopathies that remain incompletely understood [61] even in specific settings such as trauma [129] or transplantation [39].

## 5. CLINICAL IMPACT IN VARIOUS CONDITIONS

For children and young adults without specific conditions, vitamin K appears to be recognized as safe in unlimited amounts but there is generally not a compelling need for supplements. Vitamin K usage for neonates is well known and is quickly evolving for older populations. Neonatal supplementation has been cited here in passing as results were relevant to dynamics of vitamin K dependent proteins in response to vitamin K activity changes. More recent indications for the elderly will be the main focus here however as these illustrate some functions that are not explicitly coagulation related and thoughts on cryptic deficiencies in other populations. Less familiar targets include brain and bone and endothelial cells in general with wide ranging implications for health. Explicit consideration of vitamin K supplements would likely impact larger overall treatment plans that may include other coagulation modifiers such as aspirin. Therefore, recent results related to these entities are also shown

Vitamin K is increasingly recognized as a mediator of conditions of old age [167]. [123]. As of 2019 its general role in aging was recognized and a consensus developing that increased intake reduced CVD incidence [166]. Its important to remember though that no single vitamin is likely to be deficient in isolation. Dietary or digestive defects may impact many vitamins even with a "single point of failure." In general, digestive incompetence may be a correlate of old age [114].

A variety of observations link vitamin K cycling to calcium fate. However, consistent results with either vitamin K or vitamin K antagonists are not always obtained. Clinical trials for osteoporosis in post menopausal women have been conducted with some successes [58]. *MGP*<sup>-/-</sup> or MGP-KO mice exhibit osteopenia and MGP depletion increases bone resorption and osteoclast production [200] apparently contrary to other functions. Besides being vitamin K dependent, MGP expression is regulated by vitamin D, retinoic acid, calcium, and various growth factors [88]. It is thought to improve osteoporosis/osteopenia and muscle mass while being susceptible to pancreatic insufficiency [2] making it an ideal candidate for diseases of old age and requiring care for absorption if GI problems are present. While being chemically much different, it may share uptake issues with other suspects like tryptophan or vitamin D. A trial on osteopenic postmenopausal women with 5mg/day of K1 demonstrated possible protection against fracture and cancer without changing bone mineral density [103]. A 2022 review of the trials suggests significant fracture risk reduction but only questionable BMD improvement [162] motivating the importance of clinical endpoints. Mineral density may not be as important as architecture- bone is not chalk.

However, other vitamins may have to be considered or even limited to get an effective overall nutrient profile. 500 micrograms of K1 added to 600mg of Ca and 400IU cholecalciferol could not improve coronary artery calcification (CAC) although it did decrease ucMGP (uncarboxylated matrix Gla Protein) in 60-80 year olds in generally good health [165]. However, mineralization may be regulated locally rather than by serum levels [139] and coronary artery calcification may depend on general malnutrition as determined from serum albumin and BMI [7] or some combination of several nutrients. At least one report suggested MK-4 in a high phosphate environment could lead to calcification via PXR [198].

Most recently, a role in brain sulfatide production was elucidated. In 2007, sulfatide depletion was identified as a very early sign of Alzheimer's disease and modulated by apoE [66]. Vitamin K has been linked to sulfatides in the brain in several settings including remyelination [150] and in young mice and rats since 1996 [173]. Low intake from a 2015 observational study associated with worse MMSE scores in people 65 years or older [31]. At least as early as 2001, vitamin K deficiency was suspected of contributing to Alzheimer's and CVD. Reduced blood levels associated with AD risk factor APOE4 [1] in one study although the opposite genotype-phenotype association was found in a study of Chinese and British people [196]. Interestingly, the opposite association appears to hold for vitamin D [105] although this may be non-monotonic. Inconsistent results may point to a genotype modulating the vitamin D dose-response curve as I had earlier suggested with possible concerns about lifestyle factors [113]. A very recent study suggested brain and plasma vitamin K associated with less cognitive decline [19].

Endothelial function's relationship to vitamin K is most directly described by Gas6 although that may incidentally impact coagulation too. For example, Gas6 is thought to help uptake of pro-coagulant platelet secreted microparticles [68]. The literature is somewhat mixed and some results suggest it could be pathological. It has been reported to increase inflammation [178] and induce tissue factor expression [91] as well as promote venous thrombosis [155]. However, it appears to protect the brain from inflammation after hemorrhage [176], improve pulmonary arterial hypertension along with a role for BMPR2 [142] [180] and it may also preserve barrier function and reduce permeability during sepsis [141]. One small study found associations between low levels of Gas6 and type 2 diabetes and carotid atherosclerosis [55]. It has a well known anti-apoptotic effect on endothelial cells [71] and vascular smooth muscle cells [125] as well as reducing inflammation in response to silicosis [194]. Its difficult to immediately dismiss the conflicting results but overall it is likely that deficiency may contribute to disease.

Unfortunately, a of clinical experience with vitamin K function has been gained by antagonism or inhibition of vitamin K dependent proteins or coagulation and is relevant to understanding overall cause and effect. Significant clinical experience has been gained with new "DOAC's" that typically are selective for reducing thrombin activity

either by inhibiting thrombin directly or factor Xa [164] of prothrombinase. In theory then these are cleaner ways to slow down fibrin generation. As they have much wider therapeutic windows than warfarin, presumably the fibrin reduction level is not critical but off target effects would have to be considered such as RBC rheology as described earlier. Comparisons to antiplatelet and aspirin protocols appear to be a learning experience as bleeding can offset any benefits in occlusive disease [161]. Some successes were with combination therapy versus aspirin alone as in COMPASS [145]. With other anti-platelets only being superior to aspirin by a small but statistically significant amount in some trials although at that time in 2019 aspirin had a "strong track record" [64],

Many possible concerns exist with clotting inhibition ranging from purely hypothetical to having been realized in various ways. The risks largely depend on the pathological entity which is no longer covered up. Certainly blood loss is one class but another important one is pathogens. Failure to clear infection can occur. This was recently shown in zebrafish for warfarin, aspirin, or ticagrelor [179] and the organism is accepted as a decent model for human coagulation [163]. Frequent infections may motivate an interest in vitamin K [12]. One recent work observed a well known relation between thrombosis and bacterial infection and found an affinity for fibrinogen and ability to modify clot properties by *Staphylococcus epidermidis* [184]. An overwhelming fast response may be needed to avoid a proliferation of pathological clots and stop spread. A review of the protein C pathway suggested benefits in *e coli* challenge [51].

Various specific indications have produced unsatisfactory results. For example, "More specifically, the REALIGN (Dabigatran Versus Warfarin in Patients With Mechanical Heart Valves) trial established the use of DOACs as contraindicated in patients with mechanical heart valves.26 The study was terminated early, as patients with mechanical prosthetic heart valves experienced excess thromboembolic and bleeding events." [28] The same article suggested bleeding offset some of the benefits in COMPASS adding DOAC to aspirin. Trials stopped early for excess mortality include AFIRE when adding antiplatelet to rivaroxaban. Use against VTE in cancer seems robust however.

The ASPREE and ANTISEPSIS results were interesting too. With ASPREE showing excess mortality with low dose aspirin in those older than 65 or 70 largely due to cancer and some bleeding but thought to be less than post hoc general population controls even though stopped early for futility [80]. Analysis for ANTISEPSIS did not find a benefit for sepsis although interaction with cancer may be one limitation [49]. A cohort study including the US "stroke belt" showed sepsis more common in aspirin users but that evaporated on correction and there were differences among the user and non-user groups [79]. Additional concerns exist when used to delay antibiotic usage in UTI's and increase infection persistence despite aspirin having some anti-biotic properties as well as anti-inflammatory [143]. A mortality-delay relation has also been explored in relation to coagulation factors in mouse sepsis [72]. Reduced platelet function may allow infection to spread easier but use of aspirin may also delay prescription of effective antibiotics [93].

Response to damage and invaders is often more effective if it is fast but regulated. If sufficient resources do not exist, a long battle may play out. Clotting employs positive feedback using many zymogens to achieve fast and decisive response but that strategy will be a problem if it does not achieve a victory and shut itself off. A trigger needs to be quickly buried with a barrier impermeable to diffusion by clot forming reactants. If that does not happen, a long futile clotting process may continue creating clots that may only be effective in stopping red blood cells.

## 6. GREATER RESILIENCY

The coagulation pathways certainly make organisms more resilient to injuries in the "real world" but that improved fitness extends beyond coagulation. Some forms of improved fitness do indeed relate to coagulation. For example, vitamin K appears to facilitate better responses to hypoxia as may occur with ischemia due to coagulation errors among other causes. In general, vitamin K coagulation pathways are largely self moderating over many states and genetics. Another level of moderation may come from greater resilience to transient occlusive disease. Although it is also interesting to note that "ischemic preconditioning" is protective against future ischemia [199], Vitamin K appears to be neuroprotective to rats when given after experimental ischemia [132]. Menaquinone improved rat astrocyte response to hypoxia likely through Gas6 [197]. Vitamin K is a robust protector against ferroptosis and in this role can use warfarin insensitive FSP1 and NAD(P)H for reduction to VKH2 [128]. Gas6 is a locally produced vitamin K dependent protein [154]. Rather than solely being produced in the liver, it is now thought that, "Virtually every tissue expresses at least 1 of the 16 known VKD proteins, which have functions that include hemostasis, calcium homeostasis, signal transduction, growth control, and apoptosis.1" [159].

It functions through non-gamma carboxylation means to reduce inflammation and oxidative stress [166] although these words tend to be a bit general.

At very high doses in rats, it had varying effects on coagulation similar to phytol and geranylgeraniol suggesting an effect of the side chain rather than gamma carboxylation [160]. This suggests however that at these doses K1 may encourage clotting as opposed to K2.

Many of these benefits may be due to interactions within the mitochondria although direct evidence for this in



humans is lacking. For example, it appears important for muscle and nerve health via mitochondria [124] and it is thought to improve mitochondrial function in mice fed a high-fat diet [171].

The overall structure of a quinone and side chain makes it attractive to consider as a part of electron transport. This may be the case in *Drosophila* [186] but despite entering the mitochondria, no evidence has been found to support the idea that, in human cells, it can replace ubiquinone [27]. In any case, the range of benefits appear to coincide well with many concerns.

## 7. SUPPLEMENT INSTEAD OF ANTAGONIZE

Generally vitamin K is considered in terms of coagulation and there is a tendency to antagonize it even as regulatory proteins like C and S may be the first victims of insufficient reduced vitamin K. While this response may be adaptive, making clotting easier if there is less vitamin K, it does not always have a beneficial result. It is becoming apparent that vitamin K antagonism may not be the optimal solution or may even be counter productive and consideration of supplementation occurs. Many attempts have been made to supplement only with specific vitamin K dependent proteins such as activated protein C. Generally these run into control and bleeding problems again motivating vitamin K as a better controlled solution over a range of genetics and conditions. . For example, this was considered in 2019 with idiopathic pulmonary fibrosis [24] and it now appears that vitamin K dependent periostin is involved in other remodelling activities including cardiac fibrosis [193] Given the link between cardiac fibrosis and atrial fibrillation [95], you have to suspect that vitamin K supplements rather than antagonists may be beneficial in this case too. That is, additional vitamin K would actually improve clot quality and be disease modifying.

At least one case report involving covid-19 replaced aspirin and clopidogrel on presentation with vitamin K on discharge [8] even as anticoagulant strategies continue to get a lot of attention.

Even in sepsis, the errors in models have been recognized and the futility of blanket anti-coagulation has yielded to the need for compartmentalization of pathogens [168] although strategies tend to continue to focus on particular anti-coagulant components such as activated protein C.

Protein C comes up in cancers [146] as they are often considered hypercoagulable states and vitamin K itself has been explored too. Some literature has suggests other concerns with breast [188] and liver cancer [182]. Yet, vitamin K may inhibit some cancer [101]. While a trial in hepatocellular carcinoma did not show a benefit [78], it may synergize significantly with sorafenib [70]. The test of vitamin K were done in spite of coagulation issues, notably portal vein thrombosis, associated with HCC [106],

Even in occlusive disease such as ischemic stroke, activated protein C is being explored due to failure of thrombolytics [3]. While not vitamin K per se, the fast response of protein C and S to supplementation point to possible utility and "safe passage" from the narrow warfarin optimum to the wider latitude high-K state. Prior use of activated protein C appears to have mixed results and the warfarin necrosis associated with inhibition points to additional vitamin K dependent factors in resolving the circulatory issues.

Figures 2 for K1 and to a lesser extent Figure 3 for K2 intake in [13] demonstrate increasing various CVD risks at lower vitamin K intakes mostly reproducing the higher dose part of the curve in [118]. The intakes were estimated from self reported food frequency questionnaires. These data limit the quality of the result and the intake levels covered are quite moderate around 30-100 $\mu$ grams/day .

## 8. OF COURSE, COVID-19

covid-19 is a good example of the evolution of treatment approaches to new conditions that may respond to vitamin K. Coagulopathy has been a persistent component of covid-19 with a lot of attention to anti-coagulants [33] although a correlation between vitamin K deficiency and severe disease has been recognized too [104] [75]. In another work, uncarboxylated MGP (dp-ucMGP) correlated with IL-6 which correlated with poor outcomes compared to marginal significance for vitamin D [183]. Previously, I had suggested vitamin K, along with other ideas such as citrate, as an covid-19 intervention [114]. The 2022 review of covid-19 coagulopathy cites NET's and protein C [33] as important factors recognized early on issues that may be addressed with vitamin K [114] [117]. Vitamin K correlated with covid-19 severity as measured by dephosphorylated uncarboxylated matrix Gla protein (dp-ucMGP) after correcting for other factors [40]. In another small study, it was also found to be higher in controls than covid-19 patients [133]. While not much has been done with high-dose vitamin K supplementation, attempts have been made to consider just one vitamin K protein at a time such as C and S. Low protein C has been observed in patients and considered [122] while Protein S depletion [54] blamed for the cytokine storm and other covid-19 complications [94] perhaps related to complement. Neither may work well alone due to being an incomplete solution without the other vitamin K dependent proteins.

Other work more generally considers vitamin K for older people ( $> 50$ ) while pointing to a reduced activation of protein S and consequent thrombogenicity in covid-19 patients due to vitamin K depletion as well as Gas6 in brain function [148]. One small study from early 2021 found clear patterns in MGP carboxylation among healthy and covid-19 survivors or non survivors [97]. A small study from 2021 found about a factor of 2 reduced blood levels of vitamin K in covid-19 patients compared to healthy controls and an insignificant increase with severity with an opposite situation of vWF [133].

The "hypercoagulability" associated with covid-19 includes high d-dimers and higher fibrinogen levels [134]. Elevated FGN could enable faster production ( perhaps unbalanced low quality clots ), reduced hepatic clearance, or actually reduced clot formation rates. D-dimers could reflect clot velocity but also liver damage. Elevated D-dimers with measured hypofibrinolysis could reflect a lung-specific fibrinolysis [73] which points to the limitations of another coagulation related assay. Note also that phagocytic fibrin clearance may be an unappreciated factor [127] [136]. Generally it seems phagocytosis of apoptotic cells is regulated by protein S [82] [6] which may make it important for this pathway suggesting high d-dimers are related to protein S deficiency. Work from the 1990's found some significant attributes of the non-plasmin fibrinolytic pathway involving monocytes not effected by serine protease inhibitors but inhibited by Factor X and thought to be lysosomal [4]. A lytic role for monocytes and Mac-I within their larger clotting role has been described [170]. Cathepsin-D appears to degrade fibrinogen and fibrin [169] while other secreted cathepsins have been considered as causes of disease with signature fragment patterns [44]. It is possible that the real harm related to elevated d-dimers is the increased usage of the promiscuous plasmin instead of alternatives such as lysosomal degradation.

Vitamin K blood levels may not reflect adequacy of internal stores or cycling rate but may correlate somewhat.

## 9. CONCLUSIONS

Vitamin K excess may create a pathological mix of dependent proteins in some limited combinations of genetics and conditions such as with limitations in protein S or C but in most known cases likely does not cause pathological clotting at arbitrarily high activities or concentrations. For coagulation to ever work, it is likely to be "explosive" and self limiting. A high quality clot can isolate the trigger and prevent the diffusion of danger signals allowing for reasonably silent removal. A low quality clot may not be able to sequester clotting signals and a futile coagulation process can occur until some factors are depleted and then continue in a possibly worse state. Laboratory attempts to recreate a subset of this intricate system may produce misleading results. In most cases, vitamin K supplementation with adequate supply of reducing equivalents is probably more beneficial than limitation. Attempts to simply supply activated protein C have not been fully successful probably because other vitamin K dependent products such as protein S are also required for good outcomes.

At least four observations from the literature that may not be appreciated include significance of non-plasmin clot removal, the likely need for reducing equivalents over hour time scales to maintain protein C levels, and the ability of free glutamate to impact gamma carboxylation of vitamin K dependent proteins, and finally the clinical relevance of low pH on gamma carboxylation. The first was incidental to the work but correlations of high d-dimers and clinical outcome along with other observations suggest reconsideration of phagocytosis and monocytes as healthy clot removal approaches. It may be interesting to determine if IDH1 needs support during "hypercoagulable" stress or if chronic high Glu intake causes clinical symptoms by this interference independent of any acute effects of MSG or glutamate. In either case, there is plenty of suggestion that idiopathic coagulopathies may be due to nutrient derangements beyond any single nutrient but vitamin K activity could be a central issue. NADPH may be regenerated from cytosolic citrate [140] and a role in clot control by this mechanism may not have been considered.

## 10. SUPPLEMENTAL INFORMATION

### 10.1. Computer Code

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2. Free software including Linux, R, LaTeX etc.
3. Thanks everyone who contributed incidental support.

## Appendix A: Statement of Conflicts

No specific funding was used in this effort and there are no relationships with others that could create a conflict of interest. I would like to develop these ideas further and have obvious bias towards making them appear successful. Barbara Cade, the dog owner, has worked in the pet food industry but this does not likely create a conflict. We have no interest in the makers of any of the products named in this work.

## Appendix B: About the Authors and Facility

This work was performed at a dog rescue run by Barbara Cade and housed in rural Georgia. The author of this report ,Mike Marchywka, has a background in electrical engineering and has done extensive research using free online literature sources. I hope to find additional people interested in critically examining the results and verify that they can be reproduced effectively to treat other dogs.

## Appendix C: Symbols, Abbreviations and Colloquialisms

TERM definition and meaning

## Appendix D: General caveats and disclaimer

This document was created in the hope it will be interesting to someone including me by providing information about some topic that may include personal experience or a literature review or description of a speculative theory or idea. There is no assurance that the content of this work will be useful for any particular purpose.

All statements in this document were true to the best of my knowledge at the time they were made and every attempt is made to assure they are not misleading or confusing. However, information provided by others and observations that can be manipulated by unknown causes ( "gaslighting" ) may be misleading. Any use of this information should be preceded by validation including replication where feasible. Errors may enter into the final work at every step from conception and research to final editing.

Documents labelled "NOTES" or "not public" contain substantial informal or speculative content that may be terse and poorly edited or even sarcastic or profane. Documents labelled as "public" have generally been edited to be more coherent but probably have not been reviewed or proof read.

Generally non-public documents are labelled as such to avoid confusion and embarrassment and should be read with that understanding.

## Appendix E: Citing this as a tech report or white paper

Note: This is mostly manually entered and not assured to be error free.  
This is tech report MJM-2022-015.

Version	Date	Comments
0.01	2022-11-02	Create from empty.tex template
-	December 28, 2022	version 0.10 MJM-2022-015
0.10	2022-12-28	Note version, stalled
1.0	20xx-xx-xx	First revision for distribution

Released versions,  
build script needs to include empty releases.tex

Version	Date	URL
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Supporting files. Note that some dates,sizes, and md5's will change as this is rebuilt.

This really needs to include the data analysis code but right now it is auto generated picking up things from prior build in many cases

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