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RESEARCH ARTICLE

A REVIEW OF WARFARIN WOES AND NON VITAMIN K DEPENDENT ANTICOAGULANTS BENEFITS

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ABSTRACT

The objective of this review is to raise awareness among medical practitioners and patients. Warfarin is still the most frequently used anticoagulant worldwide in the treatment regimen of mechanical heart valves and any condition that could lead to the formation of blood clots in the blood vessels. This drug is particularly used as a prophylaxis regimen for atrial fibrillation and another use of warfarin to prevent thromboembolism that will lead to Stroke is post artificial heart valve replacement. Furthermore, the mechanism of warfarin helps us see clearly how it inhibits further coagulation of blood. The active direct thrombin and Xa inhibitor drugs have been introduced for the treatment and prevention of venous and arterial thrombosis and such drugs have a much broader therapeutic window than warfarin. Warfarin is seen to cause many side effects such as bleeding. Previous studies indicated that the risk a bleeding in warfarin use is higher than any other anticoagulant use such as heparin and other non-vitamin k dependent drugs. More research is needed to stop promoting the use of warfarin in the society.

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INTRODUCTION

Warfarin, also commonly known by the name Coumadin , is an anticoagulant frequently used in the prevention of thrombosis and thromboembolism, that is the formation of blood clots in the blood vessels and their migration to other parts of the body, respectively. Initially it was introduced in 1948 as a pesticide against rats and mice, and is still used for this purpose till date, although more poisons like brodifacoum have been developed. In the early 1950s, warfarin was seen to be potent and relatively safe treatment to prevent thrombosis and thromboembolism in many disorders. It was approved as a medication in 1954, and has remained the most popular anticoagulant ever since (http://dx.doi.org/10.1371/journal. pone.0071505). Warfarin was and is still the most frequently used anticoagulant worldwide in the treatment regimen of atrial fibrillation, deep vein thrombosis, mechanical heart valves, pulmonary embolism and any condition that could lead to formation of blood clots in the blood vessels (Kim *et al*., 2009). Warfarin is seen to interfere with clotting factor synthesis through inhibition of the C1 subunit of the vitamin K epoxide reductase (VKORC1) enzyme complex, thereby resulting in the decrease of the reinforcement of vitamin K1 epoxide. The degree of depression is dependent on the dosage administered and partly by the patient's VKORC1 genotype. Therapeutic doses of warfarin reduces the total amount of the active form of each vitamin K dependent clotting factor formed by the liver by approximately 30% to 50% (Product Information Coumadin (PDF) 2013). However, when the discovery that vitamin K-dependentmatrix Gla-protein (MGP) is a modifiable and strong factor in the prevention of calcification the arteries, vitamin K was revealed as novel treatment of choice in cardiovascular diseases. The vasculoprotective properties of vitamin K are in part based on the ability to increasegamma-glutamylcarboxylation of MGP, which is an important prerequisite for MGP to inhibit calcification of both blood vessels and heart valves. Records obtained from animal model experiments show that increased intake of vitamin K can prevent and even reverse vascularcalcifications (Brandenburga *et al*., 2015). Despite the

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emergence of new oral antithrombotic agents such as apixaban, dabigatran and rivaroxaban, which have proven to be productive compared with warfarin in some clinical conditions (Fareed *et al*., 2012; Miller *et al*., 2012), warfarin remains the foundation treatment for patients with mechanical heart valves and patients noncompliant to new therapies because in these populations their productivity have not been explored enough (http://dx.doi.org/10.1371/journal. pone.0071505; Ansell, 2010). The objective of this review is to raise awareness among medical practitioners and patients; encourage more in-depth study on vitamin k oral anticoagulants and replace them with non-vitamin k oral anticoagulants to prevent future complications in the patients that use them.

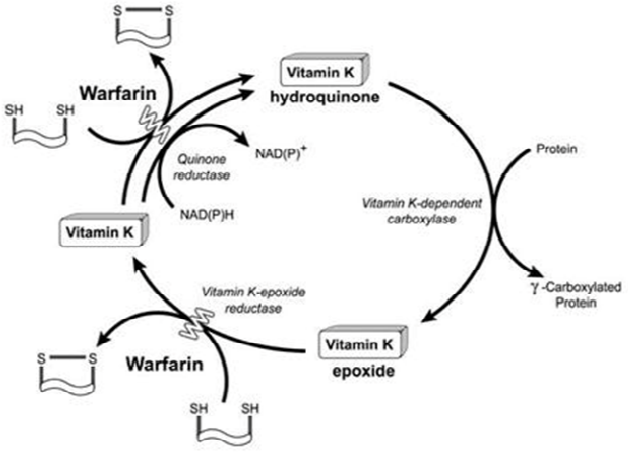
Use of Warfarin

The clinical use of Warfarin and coumarin anticoagulants started with the discovery of an anticoagulant substance from spoiled sweet clover silage that resulted in hemorrhagic disease in cattle when fed by it. The same substance was shown to be a toxic agent called bis-hydroxycoumarin, effective rodenticides were then developed from synthetic derivatives of the agent. Only thereafter were substances derived from coumarin shown to be useful as anticoagulants in humans, with very careful monitoring (Bertram G. Katzung *et al*., 2009). However when a patient is at risk of thromboembolism, warfarin is the go to medication. Thromboembolism is a common problem in post-surgical patients, immobile persons are at high risk of thromboembolism such as the elderly, crippled, those with malignant diseases, patients confined to a bed, long distance travelers and patients with history of thrombosis (Parveen Kumar and Michael Clark, 2012). Warfarin is particularly used as a prophylaxis regimen for atrial fibrillation. A reason why atrial fibrillation causes such an agitation in clinical practice that prompts medical doctors to use warfarin is because atrial fibrillation is a significant risk factor accounting for about 15% of all strokes in mostly older patients (Goldstein *et al*., 2011). Worldwide approximately 15 million people experience a stroke each year (World Health Organization, 2004).

Another use of warfarin to prevent thromboembolism that will lead to stroke is post artificial heart valve replacement. After a heart valve replacement, patients are typically put on warfarin to fight and prevent clotting so that heart attack or stroke would be prevented. Warfarin has been seen to be very effective when a patient is diagnosed with pulmonary embolism. Pulmonary embolism (PE) is a blockage of an artery in the lungs by a substance that has traveled from elsewhere in the body through the bloodstream (embolism) (What Is Pulmonary Embolism?, 2011). Warfarin is also used in antiphospholipid syndrome which is an autoimmune, hypercoagulable condition caused by antiphospholipid antibodies. APS causes blood clots (thrombosis) in both veins and arteries and also in pregnancy-related complications like stillbirth, miscarriage, premature delivery and severe preeclampsia (Aps | Action, 2013) It is also been used occasionally after heart attacks as a result of myocardial infarctions, but is way less effective at preventing new thromboses in coronary arteries. Preventing cloths in arteries is usually undertaken with antiplatelet drugs, which have a different mechanism from warfarin (which normally has no effect on platelet function) (Hirsh *et al*., 2003).

Mechanism of interaction between Warfarin and Vitamin K

The mechanism of warfarin helps us see clearly how it inhibits further coagulation of blood but it also shows its interference in the mechanism of vitamin K. Vitamin K antagonists, also known as oralanticoagulants (OACs), are widely used for the treatment and prophylaxis of thromboebolic diseases. Short-term OAC treatment is applied often after deep venous thrombosis, while atrialfibrillation or after prosthetic heart valve implantation require long term treatment (Block, 2001). The below Figure 1 indicated; Vitamin K is decarboxylated in the process and needs to be recycled. The enzyme Vitamin K-epoxide reductase (VKORC) is essential in this cycle. It is this re-carboxylation by VKORC that is inhibited by Warfarin. Carboxylation of glutamate residues to γ-carboxyglutamates (Gla) on the N-terminal regions of vitamin K–dependent proteins requires vitamin K as a cofactor (Whitlon *et al*., 1978). Formation of coagulation factors II, VII, IX, and X is hence blocked by blocking this process. When the vitamin K conversion cycle is inhibited, warfarin will influence hepatic production of partially decarboxylated proteins with greatly decreased coagulant activity (Friedman *et al*., 1977; Malhotra *et al*., 1985). Carboxylation promotes the binding of phospholipid surfaces to the vitamin K–dependent coagulation factors, thereby accelerating blood coagulation (Nelsestuen, 1976).



Source: Vita Kbv (www.vitak.com/carbox.htm) (Figure 1)

Vitamin KH2 which is the reduced form of vitamin K is greatly important for γ-Carboxylation. Warfarin and other forms of coumarins block the formation of vitamin KH2 by inhibiting vitamin K epoxide reductase, thereby limiting the γ-carboxylation of the vitamin K–dependent coagulant proteins. Furthermore, vitamin k dependent anticoagulants suppress carboxylation of the regulatory anticoagulant proteins C and S. The anticoagulant effect of warfarin and the likes of it can be overcome by low doses of vitamin K1 (phytonadione) due to the ability of vitamin K1 to bypass vitamin K epoxide reductase. Patients treated with large doses of vitamin K1 can become resistant to warfarin because vitamin K1 accumulating in the liver is available to bypass vitamin K epoxide reductase. Whereas nutritional deficiency of vitamin K1 affects hepatic carboxylation, vitamin K2 deficiency primarily affects

peripheral carboxylation. Warfarin affects both path- ways. By blocking hepatic carboxylation, anticoagulation results, and by obstructing peripheral carboxylation, most likely will lead to vascular injury. About the peripheral pathway of VKDP carboxylation, more research is highly necessary because on this, there is more to be discovered (JohnDanziger Renal Division *et al*., 2008). Although warfarin has been widely investigated in the cardiovascularliterature, particularly in its relationship to arterial bypass graft patency, most trials have depended on using angiography in evaluation of lumenpatency. Since vascularcalcification is frequently limited to the media of blood vessel, not affecting the lumen, it remains difficult to make an absolute conclusions. However, a small computed tomography study discovered that the use of warfarin was associated with both coronary and valvularcalcification (Koos *et al*., 1996). Histopathologic examination of aorticvalves replaced in the case of aortic stenosis found that the patients treated with warfarin had a two-fold increase in valvular calcification (Leon *et al*., 2004). Warfarin also interferes with the carboxylation of Gla proteins synthesized in bone (Hauschka *et al*., 1989; Price, 1988; Maillard *et al*., 1992). Although these effects contribute to abnormal fetal bone formation when mothers are treated with warfarin during pregnancy (Pettifor and Benson, 1975), there is no evidence that warfarin directly affects bone metabolism when administered to children or adults.Osteocalcin, a VKDP important in skeletal health is inhibited by warfarin, and animals placed on warfarin therapy develop osteopenia within months (JohnDanziger Renal Division, 2008; John Danziger, 2008). In vitro experiments have shown that warfarin inhibits both Gas-6 (Pearson, 2007) and MGP (Nakano *et al*., 1997) carboxylation. Looking at the mechanism of warfarin and other coumarins and how it interferes with vitamin K in both hepatic and peripheral carboxylation to achieve it anticoagulation effect it is clear that use warfarin is causing more harm than good. More research is highly recommended to bring a solution to this problem.

Non Vitamin K dependent Anticoagualnts

A large number of orally active direct thrombin and Xa inhibitor drugs have been introduced for the treatment and prevention of venous and arterial thrombosis. Such drugs have a much broader therapeutic window than warfarin and offer the project of fixed drug dosing without the need to monitor coagulation. They do not however have specific antidotes.

Apixaban is a novel oral direct factor Xa inhibitor that has been shown to reduce the risk of stroke in a similar population in comparison with aspirin. In patients with atrial fibrillation and at least one additional risk factor for stroke the prescription of Apixaban, in comparison to warfarin, significantly reduced the risk of stroke or systemic embolism by 21%, major bleeding by 31%, and death by 11% (Christopher, 2011).

Manesh R. Patel *et al* in a randomized trial, compared **Rivaroxaban** a Xa inhibitor with warfarin for the prevention of stroke or systemic embolism among patients with non-valvular atrial fibrillation who were highly at risk for stroke. In both the primary analysis, which included patients in the per-protocol population, and in the intention-to-treat analysis, found that rivaroxaban was non-inferior to warfarin. In the primary safety analysis, difference between rivaroxaban and warfarin with respect to rates of major or non-major clinically relevant bleeding was not significant (Manesh and Patel, 2011).

A direct thrombin inhibitor **Dabigatran** administered twice daily was compared with open- label warfarin. The 150-mg dose of dabigatran administered twice daily, as compared with warfarin, was shown to reduce the rate of stroke which includes ischemic or unspecified stroke, with a similar overall rate of bleeding, although the rate of gastrointestinal hemorrhage was increased. The 110-mg dose administered two times daily was associated with similar rate of stroke with warfarin but with a lower rate of hemorrhage. Both doses emerge as better than warfarin with lower rates of intracranial hemorrhage (Bates *et al*., 2008). There was also no evidence of liver toxicity making dabigatran a safe and effective treatment for venous thromboembolism as warfarin is. Therefore the favorable results of the NOAC indicate that the use of warfarin will soon fade and so will its many side effects (Schulman *et al*., 2009).

DISCUSSION

Warfarin a vitamin K dependent anticoagulant is seen to cause many side effects related to vitamin k deficiency apart from bleeding. The side effects of the drug clearly outweighs the use of it. Used widely in atrialfibrillation, stroke, and hypercoagulable disorders, warfarin has gained widespread popularity for its anticoagulant effects. By blocking VKDP (Vitamin K Dependent Proteins) carboxylation within the liver, it prevents the hepatic formation of clotting the factors. However, warfarin affects peripheral carboxylation as well, by interfering with the peripheralproduction of VKDPs. Like other anticoagulants the major side effect of warfarin is bleeding. At least half of bleeding complications with the warfarin occur when the INR exceeds the therapeutic range (Robert *et al*., 2013).

Bleeding can be as mild as epistaxis and severe as intracranial hemorrhage (Schulman *et al*., 2008)

The risk of bleeding gets more severe in patients with a history of stroke, high blood pressure, malignancies, kidney problems, alcohol abuse and liver disease (http://www.mayoclinic. org/diseases-conditions/deep-vein-thrombosis/in-depth/ warfarin-side-effects/art-20047592). Thorough reviews state that the risk a bleeding in warfarin use is higher than any other anticoagulant use such as heparin. The risk of anticoagulant-related bleeding is more severe at the beginning of therapy (Landefeld and Beyth, 1993). Some risk scores exists to predict bleeding in people using warfarin and similar anticoagulants. A generally used score (HAS-BLED) includes known predictors of warfarin-related bleeding: uncontrolled high blood pressure (H), abnormal kidney function (A), previous stroke (S), history of previous bleeding condition (B), previous labile INR when on anticoagulation (L), elderly as defined by age over 65 (E), and drugs associated with bleeding (e.g. aspirin) or alcohol abuse (D). While their use is recommended in clinical practice guidelines (Camm *et al*., 2012) they are only moderately effective in predicting bleeding risk and do not perform well in predicting hemorrhagic stroke (Shoeb and Fang, 2013).

Bleeding risk is likely to be increased in patients on hemodialysis (Elliott *et al*., 2007). Another score used to evaluate bleeding risk on anticoagulation therapy, specifically Warfarin or Coumadin, is the ATRIA score, which uses a weighted additive scale of clinical findings to determine bleeding risk stratification (Fang *et al*., 2011). The risks of bleeding become more severe when warfarin is combined with antiplateletdrugssuch as aspirin, clopidogrel or nonsteroidal anti-inflammatory drugs (NSAIDs) (Delaney *et al*., 2007).

Other side effects of warfarin use include; warfarin necrosis in patients deficient in protein C (Chan *et al*., 2000), purple toe syndrome (Talmadge and Spyropoulos, 2003), osteoporosis has also been seen to likely be a result of the warfarin side effect. as seen in three studies in 1999 (Caraballo *et al*., 1999), 2002 (Pilon *et al*., 2004) and 2006 (Gage *et al*., 2006). Several studies have implicated warfarin use in vascular and valvularcalcification (Palaniswamy *et al*., 2011). A rarely talked about side effect is calcification of cartilages, blood vessels and even heart valves. Any suggestion that warfarin might be associated with vascularcalcification raises the question as to why so many people, when placed on warfarin, do not develop vascularcalcification. Perhaps the complexity of the vitamin K-dependent carboxylation process might explain why some patients may be at higher risk for the development of associated vascularcalcification. Ultimately, these observations raise questions about whether the risk of vascularcalcification should be added to the risk of bleeding when considering whether to initiate certainpatients on warfarin. Interestingly, patients anticoagulated for peripheralvascular disease had an almost 10 times higher risk of bleeding than those anticoagulated for other reasons (Anand *et al*., 2007). It is intriguing to wonder whether certainpatients have global underactivity of their carboxylation processes, such as those with undetected vitamin K deficiency, and if suchpatients develop premature vascular disease and/or higher rates of bleeding complications when placed on warfarin. Although this is purely speculative at this point, it raises interesting questions about whether there might be certainidentifiablepopulations that are particularly at risk to develop bleeding and vascularcalcification when placed on warfarin. Genetic variation in the carboxylation enzymes has been shown to explain individual sensitivity to the anticoagulant effect of warfarin. Polymorphisms in the VKOR gene, cytochrome P4502C9 (CYP2C9) (Bodin *et al*., 2005), and calumenin (Gonzalez-Conejero *et al*., 2007) all have been showed to modulate warfarin's anticoagulant effect. Recentdata suggest that this genetic variation might be associated with warfarin's vascular effects as well. Certain polymorphisms of VKORC1 have been associated with stroke and aorticdissection (Wang *et al*., 2006). This relationship between certain genetic polymorphisms and vascular disease propose that, the more sensitive certain individuals are to the anticoagulant effect of warfarin, they may be more likely to be at risk for the vascularcalcificationtendencies as well. As a result of how complex the carboxylation process is and the prominent differences between hepatic and peripheral carboxylation, it is possible that warfarin might affect the vitamin K-dependent mechanisms in the liver and blood vessels in various ways. Recent statistics show that low doses of warfarin can inhibit peripheral carboxylation without affecting hepatic carboxylation (Hara *et al*., 2005), indicating that vascular VKDPs may be more sensitive to warfarin than the clotting factors produced by hepatic cells. Evolvingstatistics suggest that the end-stage renal disease (ESRD) population, a group already affected by vascularcalcification, may be onesuchgroup (Hermans *et al*., 2007).

However, when a patient on warfarin needs to go through surgery, he/she is advised to stop warfarin. Once an individual is put on warfarin treatment for whatever reason, there could be risks of stopping abruptly. The side effects of suddenly stopping warfarin varies from one individual to another. However the most common side effect of abruptly stopping the oral anticoagulant is formation of blot clots. A person who abruptly stops taking warfarin is at a higher risk for stroke because the blood regains its ability to clot (American Association of Blood Banks, 2014). This makes the ability to curtail the side effects of warfarin even more inconvenient for both patient and physician. Therefore, alternative oralanticoagulants, the direct thrombin inhibitor Dabigatranand the factor Xa inhibitor Rivaroxaban, have recently been shown in randomized clinical trials to be at least as effective as warfarin in preventing stroke. These agents, like Apixaban**,** has the key advantage of convenience, since anticoagulation monitoring will not be frequently needed. These alternative NOAC therapies still perform the function of preventing thrombolytic embolisms like warfarin at the same time don't interfere with the vitamin K metabolism , that been said this reduces the other side effects of using OAC when the choice of anticoagulation therapy is NOAC.

Conclusion

This article reviews current knowledge on the association between warfarin, vitamin K and cardiovascular health. These studies also address the issues whether vitamin K substitution helps modifying relevantcardiovascularsurrogatessuch as vascularcalcification and whether non-vitamin K oralanticoagulants provide an alternative to support cardiovascular health benefits. More research is needed before endorsing the use of warfarin in the society.

Conflict of interest

The authors declare that there is no conflict of interest.

Author contributions

AF implemented the data collection/ management/analysis tools/wrote the paper. SL, YW, revised and commented on the draft. All authors approved the final version of the paper and submission.

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