INR Stability, Clinical Importance, and Predictors in Patients With Atrial Fibrillation and Venous Thromboembolism Receiving Vitamin K Antagonists

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Abstract

Objective: Compare and contrast systematic reviews/meta-analyses assessing the time in the therapeutic range (TTR) for vitamin K antagonists (VKAs), clinical impact, and predictors. **Data Sources:** OVID MEDLINE search (1980–June 1, 2016) using the terms “vitamin K antagonist or warfarin” and “systematic review or meta-analysis” with backwards citation tracking from procured articles. **Study Selection and Data Extraction:** Search results were limited to systematic reviews assessing TTR with VKAs in patients with atrial fibrillation (AF) or venous thromboembolism (VTE). **Data Synthesis:** Six systematic reviews assessed TTR (4 in AF, 2 in VTE), and 3 of those assessed control at the time of a thrombotic or bleeding event (2 in AF, 1 in VTE). In patients on VKAs, greater TTR is correlated with fewer thromboembolic events and bleeding complications. VKA naïve patients have a harder time maintaining TTR than those with a previous knowledge of the likely therapeutic dose. Patients in the United States spend less TTR than those in other countries. Randomized clinical trials and anticoagulation clinics achieve greater TTR than those treated outside of these settings. The overall TTR has not improved from the first systematic reviews to the newest ones even though they were conducted 10 years apart and contained many new studies. Also, TTR in AF and VTE is similar. **Conclusions:** TTR is an important metric of VKA efficacy and safety and needs to be optimized. Many factors such as being VKA naïve can compromise TTR, and the use of anticoagulation clinics to optimize therapy is an important approach.

Keywords

vitamin K antagonists, warfarin, INR, control, therapeutic range

Introduction

The impact of vitamin K antagonists (VKAs) on clotting is indirectly assessed via the international normalized ratio (INR). It is a calculated variable using the prothrombin time (PT) raised to a thromboplastin-specific international sensitivity index (ISI) via the formula: $INR = (PT)^{ISI}$.¹ The VKA INR range for a disease is supposed to reflect the intersection between what is needed to substantively reduce the risk of clotting with an acceptable risk of bleeding.¹ VKAs can prevent stroke or systemic embolization among patients with atrial fibrillation (AF) and can treat and prevent venous thromboembolism (VTE). While the randomized clinical trial (RCT) evidence showing VKA efficacy in both AF and VTE is strong, these trials do not elucidate the impact of tightly maintaining a therapeutic INR over time versus less rigorous control or predictors of INR stability.¹

Time in the therapeutic range (TTR) is a marker of INR stability within the therapeutic range over time and is most commonly determined using the linear interpolation method.² The linear interpolation method compares a previous INR

reading to a current reading to determine the likely INR for each day in between the 2 actual readings assuming a linear increase or decrease in the INR between the 2 points. This is done for every actual INR measurement over a specified period of time and then the percentage of real or interpolated days the INR is within range is the TTR over that time.² One limitation of the linear interpolation method is that the INR could change much more radically between visits than a linear change between the 2 known points. The more frequently the INR is measured the less interpolation is needed and the more accurate the results. A free online calculator is available to calculate a patient's TTR and provide an example of how the data are input into the calculator.³

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There have been several systematic reviews with meta-analyses assessing the ability to achieve and maintain therapeutic INRs with VKAs and the implications of INR instability, which also provide insight into predictors of control. We seek to provide general information on anticoagulation in AF and VTE, assess how well TTR is achieved in patients receiving VKAs, identify the implications of poor INR control, and identify predictors of poor TTR.

Data Sources

An OVID MEDLINE search from 1980 to June 1, 2016, using the terms “vitamin K antagonist or warfarin” and “systematic review or meta-analysis” with backwards citation tracking from procured articles was conducted.

Study Selection and Data Extraction

After providing some general information on AF and VTE, this review focuses on systematic reviews/meta-analyses of RCT and/or non-RCT studies assessing the ability to achieve and maintain therapeutic INRs in patients with AF and VTE and the implications of INR control. Systematic reviews assessing TTR with VKAs in patients with AF or VTE or assessing the link between INR control and outcomes were selected and summarized in this umbrella review. Predictors of poorer control from these sources are also presented and compared with that of a large observational study.

Data Synthesis

Atrial Fibrillation

AF is the most common sustained arrhythmia in the United States and can be initiated by reentry circuits or ectopic foci in the pulmonary veins or atria.⁴ The left atrial appendage is a pouch on the left atria that in the absence of atrial contraction is prone to coagulation. Clots in the left atrial appendage can be dislodged and travel into the arteries, especially the carotid arteries where it can increase the risk of cerebrovascular accidents. The 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines for AF recommend that the risk of thromboembolism be calculated for all patients using the CHA2DS2-Vasc scoring algorithm with all patients achieving a score of 2 or more receiving anticoagulation with either VKA therapy or a newer oral anticoagulant. In the CHA2DS2-Vasc scoring system, patients are given a single point for chronic heart failure, hypertension, age 65 to 74 years (2 points for age >75 years), diabetes, vascular disease (myocardial infarction, peripheral artery disease, aortic atherosclerosis), and female gender, and 2 points for a history of stroke, transient ischemic attack, or prior thromboembolic event.

If a VKA is selected, an INR range of 2 to 3 is recommended unless patients have mechanical heart valves where the INR could be 2 to 3 or 2.5 to 3.5 depending of the type and location of the prosthesis. While the level of evidence is stronger for VKAs than for newer oral anticoagulants (Level A versus B) in the guidelines, if patients with non-valvular AF are unable to maintain a therapeutic INR, the guidelines state that newer oral anticoagulants should be used. The use of warfarin dosed to achieve an INR of 2 to 3 was found to reduce the risk of stroke and systematic embolization better than no therapy, aspirin, aspirin plus clopidogrel, and warfarin therapy dosed to a lower intensity INR.⁵

Four systematic reviews with meta-analyses in AF patients provide useful data in this umbrella review (Table 1).⁶⁻⁹ The main differences between the systematic reviews are related to the number of studies available for inclusion, the cutoff period for included studies, countries where the studies were conducted, and whether they were limited to warfarin or open to other VKAs. The first worldwide systematic review by Reynolds (2004)⁶ included 21 studies with 6248 patients and was limited to warfarin only, while the most recent systematic review by Mearns AF (2014)⁹ included 95 studies and 117329 patients and included various VKAs. Even with all of these differences, the results of both systematic reviews show that TTR is 61% and that people on VKAs are more apt to be below than above the therapeutic range. From 2002 when Reynolds et al completed their literature search until 2013 when Mearns et al completed theirs, there has been no improvement in INR maintenance.⁶⁻⁹ This suggests that even with years of additional experience in managing patients on VKAs and other measures such as pharmacogenomics, we have not been able to enhance INR control.

An important observation by Mearns AF 2014 is that patients newly initiating VKA therapy spend significantly less TTR than VKA-experienced patients.⁹ This suggests that it is riskier to initiate VKA therapy in naïve patients than to continue VKA therapy once patients are stabilized. This makes sense given the multitude of factors affecting initial INR control with VKAs such as polymorphisms in CYP2C9 or vitamin K reductase genes (and whether people are heterozygous or homozygous for the polymorphisms), liver function, smoking status, ethnicity, age, and body surface area.^{10,11} Since these factors do not readily change in an individual, it is the initial dosing period where instability is more likely to manifest. Other factors such as alterations in dietary intake of vitamin K and adding or subtracting drugs that affect CYP2C9 or 1A2 isoenzymes can affect stability periodically during long-term therapy.^{5,10}

The Baker 2009 systematic review focused on the United States and only included warfarin AF trials.⁸ They found that the TTR was only 55%, which is consistent with the Mearns 2014 systematic review where patients in Europe/United Kingdom had a higher TTR than those in the United States.^{8,9} This may be a result of North America's near

Table 1. Systematic Reviews Assessing INR Stability With VKAs in AF⁶⁻⁹

Name, Year, Trials Included	Countries Assessed	VKAs Assessed	Main Results			Other
Measures of INR Control			Overall TTR and PINRR Results (95% CI)	Predictors of TTR (95% CI)	(95% CI)	
Reynolds 2004 Trials: 4 N = 677	North America, Europe, multinational	Warfarin	TTR: 61% <TTR: 24% >TTR: 13%	No data		
Wan 2008 Trials: 47 N = 33976	North America, United Kingdom, Europe, Israel, multinational	Various VKAs	Retro studies TTR: 59% (29% to 75%) Pros studies TTR: 61% (56% to 66%) RCTs TTR: 67% (44% to 73%)	TTR negatively correlated with: Major hemorrhage ($r = -.59$, $P = .002$) Thromboembolism ($r = -.59$, $P = .01$)	8% ↑TTR will ↓ major hemorrhage by 1 event per 100 pt years (0.35-1.64 events) 10% ↑ TTR will ↓ major hemorrhage by 1 event per 100 pt years (0.14-1.85 events)	
Baker 2009 Trials: 8 N = 22237	United States	Warfarin	Retro studies PINRR: 53% (34% to 68%) Pros studies PINRR: No data RCT PINRR: 67% (48% to 84%) TTR: 55% (51% to 58%)	Community TTR: 51% (47% to 55%) AC clinic TTR: 63% (58% to 68%) Community vs AC clinic TTR ↓ 11% (2% to 20%) Community VKA = ↓ TTR than AC clinic or RCTs	Eligible patients receiving warfarin: 48% (0.43% to 0.54%)	
Mearns 2014 Trials: 68 N = 117329	North America, Europe, United Kingdom, Asia, Middle East, multinational	Various VKAs	TTR: 61% (59% to 62%) <TTR: 25% (23% to 27%) >TTR 14% (13% to 15%) PINRR: 56% (53% to 59%) <PINRR: 26% (23% to 29%) >PINRR 13% (11% to 17%)	VKA naïve = ↓ TTR than those with prior VKA use Europe/United Kingdom = ↑ TTR than North America		
INR Control Around Time of Event			INR <2.0 (95% CI)	INR >3 (95% CI)		
Reynolds 2004 Trials: 9 N = 6248	North America, Europe, multinational	Warfarin	OR for ischemic events: 5.1 (2.9-8.8)	OR for bleeding events: 3.2 (1.2-8.3)		
Mearns 2014 Trials: 43 N = 65361	North America, Europe, United Kingdom, Asia, Middle East, multinational	Various VKAs	57% (50% to 64%) of thromboembolic events 56% (48% to 64%) of ischemic strokes	43% (35% to 51%) of bleeding events 45% (29% to 63%) of ICH		

Abbreviations: CI, confidence interval; INR, international normalized ratio; OR, odds ratio; PINRR, proportion of INRs in range; Pros, prospective; Pt, patient; retro, retrospective; TTR, time in therapeutic range; various VKAs (warfarin, acenocoumarol, tecarfarin, phenprocoumon, fenprocoumon); VKA, vitamin K antagonists.

exclusive use of warfarin, which has been shown in previous analyses to result in as much as a 9% lower TTR compared to other VKAs as well as North America's less widespread use of proven strategies to increase TTR such as anticoagulation clinics and patient self-monitoring.¹²⁻¹⁴ The more homogenous ethnic make-up of individual European countries versus the United States might also be a factor in helping clinicians understand how to dose VKAs in their populations.

In the Baker 2009 and Mearns AF 2014 systematic reviews, there was better INR control in RCTs and anticoagulation clinics versus regular management of anticoagulation in the physician's office.^{8,9} This may be the result of increasing the frequency of monitoring, providing more organized care, and focusing more on improving poor VKA-drug compliance (as low as 68% at 6 months) in RCTs and anticoagulation clinics versus the physician's office.¹⁴ Only about one third of patients receiving VKAs in the United States have access to an anticoagulation clinic due to time, distance, economic, or other access-to-care issues.¹⁴

With the relatively low TTR that patients experience, an important consideration is whether lesser or greater TTR affects clinical events (Table 1). The major systematic reviews assessing this area defined their endpoints a bit differently. The Reynolds 2004 systematic review defined their major endpoints as stroke or bleeding; Mearns AF 2014 defined major hemorrhages as intracranial hemorrhage or bleeding requiring hospitalization, blood transfusion or surgical treatment, or bleeding at a critical anatomic location while thromboembolic events were defined as ischemic stroke, systemic emboli, VTE, and myocardial infarction; and Wan 2008 defined major hemorrhage as bleeding requiring hospitalization, transfusion, or bleeding in critical anatomic sites and thromboembolic events as a new stroke, myocardial infarction, pulmonary embolism, or systemic emboli. While thromboembolic and hemorrhagic events can occur in patients with a therapeutic INR; the odds of experiencing ischemic events or bleeding events in the Reynolds 2004 systematic review were 5.1 and 3.2 times higher if the INR was <2 or >3, respectively.⁶ Similarly, a sizeable percentage of thromboembolic and hemorrhagic events happened in the Mearns AF 2014 systematic review when the INR was <2 or >3, respectively.⁹ However, perhaps the strongest evaluation of the value of achieving greater TTR comes from the Wan 2008 systematic review where they significantly correlated greater TTR with lower rates of major hemorrhage and thromboembolism.⁷ As such, the efficacy and safety of VKAs appear strongly tethered to the quality of INR control achieved.

Achieving a TTR of 68% (with 20% below range and 12% above range) versus a TTR of 48% (with 38% below range and 14% above) was assessed for cost-effectiveness in a Markov transition state model.¹⁵ The implications of

achieving a TTR of 68% versus 48% was modeled at 832 versus 984 ischemic strokes, 6.92 versus 6.72 quality adjusted life years (QALYs), and costs of \$77 764 versus \$84 248. As such TTR is an important determinant of efficacy and costs, so the costs associated with anticoagulation clinic care needs to be assessed in light of the total costs of therapy.

Venous Thromboembolism

VTEs can arise from a host of genetic and hereditary factors or secondary to cancer, surgery, obesity, heart failure, hormonal therapy, or pregnancy and manifest as either a deep vein thrombosis or pulmonary embolism.¹⁶ Approximately 12 million patients in the United States are at risk of developing VTE annually.¹⁷ In the 2016 CHEST guidelines, the American College of Chest Physicians (ACCP) recommends dabigatran, rivaroxaban, apixaban, or edoxaban over VKAs as long-term (first 3 months) anticoagulant therapy in patients with leg DVT or pulmonary embolism and no cancer but VKAs are recommended over low-molecular-weight heparins.¹⁸ In cancer patients, low-molecular-weight heparins are recommended over the orally available anticoagulants including VKAs. The recommended target INR range for VKAs in VTE is between 2.0 and 3.0.¹⁸

The first 6 months after experiencing a VTE event comprise the time period during which a patient is most at risk for a recurrent event. During the first 6 months after experiencing VTE, the cumulative proportion of patients with recurrent VTE is 2%, 6%, and 8% to 10% at 2 weeks, 3 months, and 6 months, respectively.^{19,20} The estimated rate of VTE recurrence over 2 years after stopping anticoagulation therapy was 3.3% or 7.4% per patient-year depending on whether the initial VTE was provoked by transient risk factors or not.²¹

There have been 2 systematic reviews with meta-analyses assessing the quality of VKA anticoagulation control in VTE patients with one of these systematic reviews assessing the impact of quality anticoagulation control on thromboembolic or bleeding outcomes (Table 2).^{22,23} The main difference between the 2 VTE systematic reviews is the cutoff period for included studies and the way they analyzed their data. The first worldwide systematic review by Erkens 2012 included 40 studies with 26 064 patients, while the most recent systematic review by Mearns VTE 2014 included 53 studies and 48 790 patients and they both allowed studies evaluating various VKAs.^{22,23} In Erkens 2012 there was an improvement in the TTR over time ranging from 54% at 1 month to 75% at 1 year if the first 3 months of VKA therapy are excluded.²² However, those who withdrew from the trials were not factored into longer term TTR control data. As such, whether this truly reflects improved TTR for previously unstable patients or only the continuation of

Table 2. Systematic Reviews Assessing INR Stability With VKAs in VTE^{22,23}.

Name, Year, Trials Included	Countries Assessed	VKAs Assessed	Main Results	
Measures of INR Control			Overall TTR and PINRR Results (95%CI)	Predictors of TTR (95%CI)
Erkens 2012 Trials: 40 N = 26,064	Multinational	Various VKAs	Month 1—TTR: 54%; <TTR: 42%; >TTR: 12% Months 1-3—TTR: 56%; <TTR: 35%; >TTR: 19% Months 1-6+—TTR: 60%; <TTR: 24%; >TTR: 17% Months 4 to 12+—TTR: 75%; <TTR: 21%; >TTR: 12%	No data
Mearns 2014 Trials: 53 N = 48 790	Multinational	Various VKAs	TTR: 61% (59% to 63%) <TTR: 25% (23% to 26%) >TTR: 15% (14% to 17%) PINRR: 59% (54% to 64%) <PINRR: 26% (23% to 29%) >PINRR: 13% (9% to 19%)	TTR negatively correlated with: Major hemorrhage ($r = -.30$, $P = .02$) Recurrent VTE ($r = -.46$, $P = .01$)
INR Control Around Time of Event			INR <2.0 (95% CI)	INR >3 (95% CI)
Mearns 2014 Trials: 16 N = 35 236	Multinational	Various VKAs	58% (39% to 77%) of recurrent VTE events	48% (34% to 61%) of hemorrhage events

Abbreviations: CI, confidence interval; INR, international normalized ratio; PINRR, proportion of INRs in range; TTR, time in therapeutic range; Various VKAs (warfarin, acenocoumarol, tecarfarin, phenprocoumon, fenprocoumon); VKA, vitamin K antagonists.

therapy in patients with previously high TTR is not known but possible. However, regardless of the timeframe, people were approximately twice as likely to be under-anticoagulated than over-anticoagulated.²² The Mearns VTE 2014 systematic review was conducted similarly to the Mearns AF 2014 systematic review and is therefore a strong way to assess INR control across these 2 major disease states.^{9,23} Patients being treated for VTE spent 61% of their TTR, 25% of their time under-anticoagulated, and 15% of their time over-anticoagulated, which is almost superimposable to the results in the Mearns AF 2014.^{9,23} This suggests that the indication for VKAs is not a big factor in INR control if the target INR range is the same.

The predictors of TTR with VKAs in VTE patients are congruent with AF patients as well.^{9,23} Mearns VTE 2014 found that VKA-naïve patients have on average a 14% decrease in TTR (−14.2% [−19.9% to 8.5%]) compared to those receiving a VKA in the past.²³ Taken in light of the findings from Erkens 2012, this suggests that there is poorer INR control early on in treatment in the absence of previous insight on the required patient-specific dose.^{22,23} Mearns VTE 2014 found that TTR is 11% longer (10.7% [4.2% to 17.2%]) in patients receiving VKAs in Europe/United Kingdom compared to North America.²³ Finally, patients being cared for in anticoagulation clinics or in randomized

controlled trials spend 7% more TTR (7.1% [0.1% to 13.8%]) than those treated in their physician's offices.²³

Similarly to AF data, achieving a greater TTR is an important driver of final health outcomes. In the Mearns VTE 2014 systematic review, 58% of VTE events occurred while the INR was <2 and 48% of hemorrhages occurred with an INR >3.²³ Using meta-regression analysis, TTR was negatively correlated with both recurrent VTE and major hemorrhage so both efficacy and safety are improved with greater TTR. There are many factors that can induce thromboembolism or bleeding in VKA-treated patients, and even with improvements in TTR, some patients will still experience untoward events. In this systematic review, 42% and 52% of VTE and bleeding events occurred when the INRs suggested a lower risk of occurrence.²³

Predictors of Control

While not limited solely to either AF or VTE patients, one large (N = 124 619) retrospective assessment determined patient factors that can affect VKA TTR.²⁴ They found that TTR was 48% during initial therapy and 61% for chronic management, similar to the aforementioned systematic reviews. Important predictors of poor TTR during therapy initiation in this observational study included

hospitalizations, larger number of baseline medications, alcohol abuse, cancer, and bipolar disease, while predictors of poorer TTR during chronic management included all of these factors except for bipolar disease and additionally included female gender, dementia, nonalcohol substance abuse, and chronic liver disease.²⁴

Conclusions

In this umbrella review of systematic reviews with meta-analyses assessing VKA therapy in either AF or VTE, we found that maximizing TTR is a critical determinant of efficacy and safety but is difficult to achieve, especially in VKA-naïve patients where there is an absence of previous knowledge of the likely therapeutic dose. TTR in AF and VTE is similar and factors affecting TTR in AF also seem to affect VTE similarly. While VKAs have been available for decades, there have not been improvements in the TTR in contemporary practice. Patients in anticoagulation clinics and RCTs achieve greater TTR than patients receiving care in their physician's office, offering a modality to enhance the safety and efficacy of VKA therapy. There are real costs associated with failure to achieve high TTR, which can be used to support broader participation in anticoagulation clinics. VKAs are well-studied and effective drugs but one cannot anticipate achieving the balance of benefit to harms seen in RCTs unless one's patient is being seen in an anticoagulation clinic. Finally, even with optimized TTR, a number of patients will continue to experience thromboembolism and bleeding due to intractable factors such as underlying diseases. However, enhancing TTR is an incredibly important determinant of both efficacy and safety and it is modifiable.

Declaration of Conflicting Interests

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