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Outpatient management of oral vitamin K antagonist therapy: defining and measuring high-quality management

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Oral anticoagulation therapy with warfarin is the mainstay of prevention and treatment of thromboembolic disease. However, it remains one of the leading causes of harmful medication errors and medication-related adverse events. The beneficial outcomes of oral anticoagulation therapy are directly dependent upon the quality of dose and anticoagulation management, but the literature is not robust with regards to what constitutes such management. This review focuses on, and attempts to define, the parameters of high-quality anticoagulation management and identifies the appropriate outcome measures constituting high-quality management. Elements discussed include the most fundamental measure, time in therapeutic range, along with other parameters including therapy initiation, time to therapeutic range, dosing management when patients are not in therapeutic range, perioperative dosing management, patient education, and other important outcome measures. Healthcare providers who manage oral anticoagulation therapy should utilize these parameters as a measure of their performance in an effort to achieve high-quality anticoagulation management.

KEYWORDS: anticoagulation • quality • vitamin K antagonist • warfarin

Oral anticoagulation therapy with the vitamin K antagonists (VKA), particularly warfarin, which is the most commonly used VKA, continues to increase worldwide due to the aging population and its efficacy in preventing stroke in patients with atrial fibrillation or recurrent thromboembolism in patients with deep vein thrombosis (DVT) and pulmonary embolism (PE) [1]. Despite improved awareness of warfarin's efficacy and safety, the management of warfarin remains complex due to its intricate pharmacokinetic and pharmacodynamic properties and narrow therapeutic range. It is among one of the top five medications associated with drug errors that cause harm and has been shown to be one of the most common causes of emergency room visits due to an adverse event [2,3,101]. National healthcare regulatory agencies have recently targeted anticoagulants, including warfarin, as high-risk medications and are focused on ensuring the safe use

of these agents. One such agency, the Joint Commission, has proposed new 2008 National Patient Safety Goals aimed at minimizing the risks associated with warfarin use and reducing adverse events [102].

The beneficial outcomes of oral anticoagulation therapy are directly dependent upon achieving and maintaining an optimal international normalized ratio (INR) therapeutic range which requires high-quality anticoagulation management (HQACM) [1]. What constitutes HQACM of warfarin is poorly defined, as are the outcome measures of HQACM. The aim of this review is to identify and discuss the elements of HQACM of warfarin and to define, when possible, the appropriate measures to assess HQACM. This review specifically does not address the 'how to' of HQACM. For detailed information on managing the VKAs, the reader is referred to a number of excellent reviews [1,4,5].

What constitutes high-quality anticoagulation management?

The ultimate goals of warfarin management are to obtain the highest efficacy (preventing thromboembolism), while minimizing risk (preventing bleeding). This can be achieved by promptly reaching and maintaining a therapeutic level of anticoagulation as measured by the INR. Various management components, however, are required to be in place to achieve HQACM goals. Such components include a knowledgeable healthcare provider, an organized system of follow-up, reliable monitoring and good patient communication and education [1,6].

Achieving & measuring efficacy

Initiation of anticoagulation

The initiation of warfarin therapy requires an appropriate starting dose, frequent INR monitoring and proper overlap with intravenous heparin or subcutaneous low-molecular-weight heparin (LMWH) if an immediate anticoagulant effect is required. Despite the early effect on the INR that occurs usually within the first 2–3 days of initial warfarin therapy, an anti-thrombotic effect typically requires several more days based on the time required for complete reduction of the vitamin K-dependent coagulation factors (II, VII, IX, X) [7,8]. To achieve a rapid antithrombotic effect, heparin or LMWH is administered concurrently and overlapped with warfarin for at least 5 days until the INR has been in the therapeutic range for at least 2 days to allow for further reduction of Factors X and II [1].

An appropriate warfarin starting dose should generally be 5 mg, although as little as 1–2 mg and up to 10 mg has been shown to be as effective in certain populations depending on the patients' sensitivity to warfarin. Large loading doses (>10 mg) are not recommended [7,9,10]. Loading doses have been associated with a high risk of early hemorrhage and a false sense of complete anticoagulation in early treatment [1]. A starting dose of less than 5 mg might be appropriate in the elderly, in patients with impaired nutrition, liver disease, congestive heart failure, following major surgery, and in patients who are at high risk of bleeding or have had a recent heart valve replacement [1,11,12]. Many institutions have adopted the use of validated warfarin dosing algorithms and nomograms (TABLE 1) as guides to dosing patients based on INR response [7,9,10].

Prompt achievement of a therapeutic INR results in improved clinical outcomes. [1,13] The SPORTIF studies demonstrated that good INR control at 6 months when compared with patients who had poor INR control at 6 months, was associated with optimal INR control for the remainder of the study period [15]. Earlier studies showed that INR control in the first 30 days of warfarin therapy is predictive of subsequent INR control [16]. Thus, achieving the target INR and maintaining therapeutic anticoagulation control in patients within the first 6 months of therapy is imperative.

Recent studies suggest that pharmacogenetic-based dosing may improve time to reach therapeutic range, predict the appropriate maintenance dose more accurately, reduce early over-anticoagulation and, therefore, result in fewer hemorrhagic adverse events [15,16].

Table 1. Example of a warfarin initiation nomogram.

Day	International normalized ratio	Warfarin dose (mg)
1	-	5
2	-	5
3	<1.5	10
	1.5–1.9	5
	2.0–3.0	2.5
	>3	0
4	<1.5	10
	1.5–1.9	7.5
	2.0–3.0	5
	>3	0
5	<2.0	10
	2.0–3.0	5
	>3	0
6	<1.5	12.5
	1.5–1.9	10
	2.0–3.0	7.5
	>3	0

Data from [10].

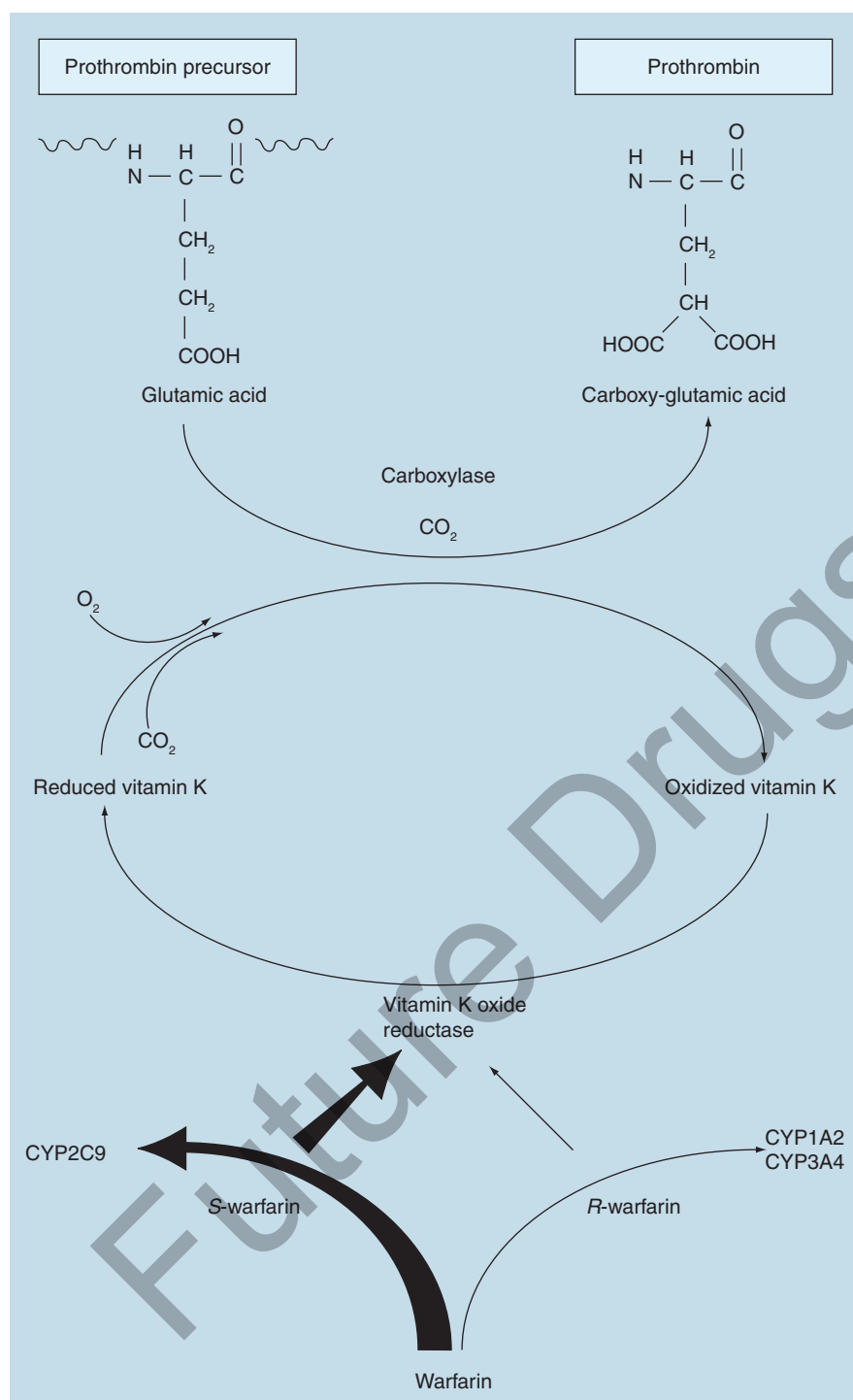


Figure 1. Vitamin K1 is reduced to vitamin KH2. The major warfarin-sensitive enzyme in this reaction is the vitamin K oxide reductase mainly inhibited by the S-enantiomer of warfarin. S-warfarin is metabolized by the p450 cytochrome enzyme, CYP2C9.

Warfarin exists as a racemic mixture to two stereo isomers. The S-enantiomer is approximately three times more potent than the R-enantiomer and is metabolized by different cytochrome enzymes (FIGURE 1).

Single nucleotide polymorphisms (SNPs) in the gene coding for CYP2C9, the principal enzyme responsible for metabolizing the S-enantiomer of warfarin, will alter the metabolism rate of warfarin significantly. This polymorphism can influence how quickly the initial anticoagulant effects are seen, as well as the dose required to maintain a therapeutic INR [15,17]. The target enzyme inhibited by warfarin is termed the vitamin K oxide reductase complex (VKORC) 1 (FIGURE 1). Similarly, various mutations in the gene coding for VKORC1 enzyme will lead to a protein that is either sensitive or resistant to warfarin inhibition and, therefore, will also affect the initial dose required to achieve and maintain a therapeutic INR. Retrospective analyses demonstrate that CYP2C9 and VKORC1 genotype along with other patient specific clinical factors, such as age, BMI, race or concomitant medications, will account for over 50% of the variability of dose requirement [15–21]. To date, two small prospective pilot trials have been conducted and, although not powered to do so, neither were able to show a significant decrease in adverse events nor improved time in therapeutic range (TTR) [22,23]. Properly designed, randomized trials are needed to determine whether pharmacogenetic-based dosing proves to be beneficial compared with high quality dose and INR management. Thus, pharmacogenetic-based dosing is not, at this time, considered to be essential for HQACM.

Measures and benchmarks of HQACM:

- Proportion of patients with use of appropriate initial dose
 - Initial dose of warfarin with 5–10 mg, with a dose of no more than 5 mg in patients who are elderly, malnourished, have congestive heart failure, liver impairment or have had recent major surgery
- Proportion of patients with appropriate overlap of therapy with heparin
 - Overlap for at least 4–5 days and until two consecutive INRs are in therapeutic range approximately 24 h apart
- Proportion of patients with prompt achievement of therapeutic INR and maintenance in therapeutic range in first month

- Rapid achievement and maintenance of therapeutic anticoagulation, but quantitative benchmarks have not been defined

Maintaining therapeutic anticoagulation

Once the targeted intensity of oral anticoagulation is achieved, it must be maintained, as this is directly related to its derived benefit [1]. The most recognized way to measure the therapeutic effectiveness of warfarin over time is to measure TTR. TTR has been shown to strongly correlate with the principal clinical outcomes of hemorrhage or thrombosis and, thus, TTR is a reliable measure of HQACM [1,24]. Increased TTR has also been associated with decreased mortality, myocardial infarction and stroke rates [25].

TTR can be measured by a number of methods and no standardized consensus exists as to which is the best measure [26–28]. The three primary methods utilized are Rosendaal's linear interpolation, the percent (fraction) of INRs in range, and the point-in-time or cross-section of records methodology. All three methods have specific advantages and disadvantages (TABLE 2). The majority of recent studies utilize Rosendaal's linear interpolation methodology [25]. This method assumes that a linear relationship exists between two INR values, given that not more than 8 weeks has elapsed between the two. It allocates a specific INR value to each day between tests for each patient, allowing one to calculate INR specific incidence rates of adverse events, such as bleeding complications. Linear interpolation is the only method that incorporates time.

The percent of INRs in range method utilizes the number of INRs within target range for all patients divided by the overall number of INRs during that selected time interval. It is simple to calculate and requires a minimum of one INR value per patient. The percentage in range method is affected by the frequency of INR measurements. If an INR is out of range, which frequently occurs when therapy is interrupted for procedures, more INR measurements will be required and would increase the out of range percentage. In addition, this method does not consider individual patients nor take actual days within target range into account.

The cross-section of records method examines the number of INRs in range at one point in time divided by the total number of INR values on all patients at that point in time. This method does not reflect how patients are managed over time and it assumes that the time-point selected is representative of the remainder of the time.

The methods employed to measure TTR differ throughout clinical trials, making direct comparison often difficult and emphasizing the need to standardize INR reporting. The few studies that have compared one method with another have not correlated outcomes with adverse events and none are robust enough to recommend one method over another [26–28]. One argument for the use of TTR is that a minority of patients account for a majority of the out of range INRs and events. Therefore, if poor control is improved in the minority, it should reduce most complications. A recent retrospective study was conducted in patients treated with warfarin for DVT or PE, to assess

Table 2. Characteristics of common methodology to calculate time in therapeutic range.

	Definition	Advantages	Disadvantages
Rosendaal's linear interpolation method	Assumes linear relationship exists between two INR values and allocates a specific INR value to each day between tests for each patient	Incorporates time Allows one to calculate INR specific incidence rates of adverse events	Exclude period of time of more than 8 weeks between INR draws Calculation is more difficult Does not consider individual patients Extreme out of range INR values may bias overall results
Percent of INR's in range	Percent of the number of INRs within target range for all patients divided by total number of INRs during that selected time interval	Simple to calculate Requires only one INR value per patient Not influenced by extent of INR out of range	Affected by frequency of INR draws Does not take into account actual days within target range Does not consider individual patients
Cross section of records	Looks at number of INRs in range at one point in time divided by total number of INRs done on all patients at that point in time	Simple to calculate Considers individual patients Not influenced by extent of INR out of range	Assumes that the point in time selective is representative of rest of the time Does not take into account actual days within target range Does not reflect how patients are managed over time

INR: International normalized ratio.
Data from [29].

the impact of the achieved intensity of anticoagulation and individual time in therapeutic range (ITTR) on clinical outcome [29]. ITTR utilizes Rosendaal's linear interpolation method for TTR, however, it looks at individual time spent in range for each individual patient. Results of ITTR were very similar to numbers reported in other trials utilizing TTR linear methods or other methods [1]. Lower ITTR percentages correlated with higher percentages of recurrent thromboembolism and major bleeding.

Further difficulties when interpreting TTR may occur depending on what is included in the TTR measurement. Some investigators measure their performance using an expanded INR range (1.8–3.2) which will result in a much greater TTR compared with the recommended range of 2.0–3.0. Additionally, INR results from new patients in the first few months of anticoagulation, prior to establishing a steady dose, will reduce the TTR compared with measuring only established patients. TTR could be further decreased if INR values during episodes when invasive procedures are performed are included.

A recent metaregression analysis of 67 studies with mixed models of anticoagulation management found that patients spend more than a third of their time outside of therapeutic range and are therapeutic 63.6% of the time [30]. Although the goal of therapy should be to have 100% of INRs in range, a realistic and achievable aim of the rate, which reflects HQACM, is 65–70% [1,31]. Thus, as described, there are many factors that may lead to inadequate TTR, including how it is measured, what is included and the quality of dose management. Despite the heterogeneity, healthcare providers should assess their performance by monitoring TTR on a regular basis utilizing a consistent methodology.

Measures and benchmarks of HQACM:

- Proportion of patient INRs or time in TTR measured using consistent methodology
 - 60–70% TTR using an exact therapeutic range of 2–3 or 2.5–3.5 in patients on anticoagulation therapy for at least 1 month

Monitoring anticoagulation at the appropriate frequency

Timely INR monitoring is required for HQACM. Since many environmental factors, such as medications, diet and concomitant disease states can alter the pharmacokinetics of warfarin, frequent INR monitoring is necessary to ensure that a patient is continually therapeutic. The optimal frequency of long-term INR monitoring is influenced by patient compliance, transient fluctuations of comorbid conditions, the addition or discontinuation of medications, the quality of dose-adjustment decisions and whether the patient has demonstrated a stable dose response. In one study, patients with prosthetic mechanical heart valves who were on stable therapy for at least 6 months were randomized to INR monitoring at 6- or 4-week intervals [32]. There was no apparent difference in the time in, above, or below range between the groups; however, the actual interval of monitoring was 24.9 days in the 6-week group and 22.5 days in

the 4-week group. Horstkotte *et al.* found that the percentage of INRs within target range for patients with mechanical cardiac valves increased from 48% when monitoring was performed at an average interval of 24 days to 89% when monitoring was performed at an average of every 4 days by home self-testing using a point-of-care (POC) monitor [33]. Additionally, a recent large study of patients with chronic atrial fibrillation looked at over 250,000 INRs and found a greater time-in-range as the testing interval decreased from every 5 weeks to every 3 weeks [34]. It is suggested that patients on chronic warfarin therapy should be monitored no less than every 4 weeks [1]. More frequent monitoring is advisable in patients who exhibit an unstable dose response.

After a patient has had a recent dose adjustment, INR monitoring should remain frequent in order to see the effects of the dose change which typically takes about 3–5 days; therefore, follow-up should be every 4–6 days. [37] Once a patient's INR is stabilized, INR monitoring intervals can be extended to every 2 weeks and eventually to every 4 weeks [1].

Measures and benchmarks of HQACM:

- Frequency of monitoring
 - At least once every 4 weeks for stable patients
 - At least once every 2 weeks for unstable patients
- Proportion of patients with an INR within 1 week of an out of range INR
 - INR measured no more than 1 week after a dose change

Managing perioperative dosing

Patients on long-term warfarin therapy often require invasive procedures necessitating interruption of therapy. Management requires a careful risk versus benefit assessment (the risk of thromboembolism if therapy is interrupted; the risk of bleeding if therapy is continued or if alternative therapy is used). There are no randomized trials comparing the various options, but there are a growing number of prospective cohort studies and large observational studies providing some guidance. TABLE 3 summarizes the results of these studies, most of which have used LMWH as an alternative anticoagulant. The traditional approach of stopping warfarin and bringing patients into the hospital for intravenous heparin as an agent that can be rapidly discontinued and restarted pre- and post-operatively is diminishing. Today, most patients are treated with LMWH on an outpatient basis if an alternative, rapidly-acting anticoagulant is needed peri-operatively. Full doses of LMWH are generally recommended, especially for individuals with a high risk of thromboembolism (Box 1). For those with a low-to-moderate risk of thromboembolism once warfarin is discontinued, none or prophylactic doses of LMWH may be considered while the warfarin is being reloaded, especially if the risk of thromboembolism is low. Knowing the daily risk of thromboembolism when anticoagulation is discontinued over short intervals of time is difficult since specific risk information is not available and one must extrapolate

from other literature. Once the invasive procedure has been completed, one must consider the post-operative risk of thromboembolism engendered by the procedure as well as the risk of post-operative bleeding. If there is a question about the safety of reinstating anticoagulation soon after surgery, one can start with a prophylactic lower dose of LMWH or hold therapy for an additional 24–48 h. Restarting anticoagulation too soon after surgery may lead to bleeding, which then leads to a further and prolonged delay of reinstatement of therapy, and a further risk of thromboembolism [36]. TABLE 4 summarizes the most recent guidelines from the American College of Chest Physicians Consensus Guidelines on the recommended interventions [1].

Additional consensus guidelines recommend that a systematic process be in place to follow patients and identify particular needs for each patient, including the anticoagulation plan prior to an invasive procedure. The healthcare provider must provide continuity of care, which includes communication with all of the patient's concomitant healthcare practitioners, especially the individual performing the procedure. A lack of communication can result in poor patient outcomes.

Measures and benchmarks of HQACM:

- Proportion of patients for whom appropriate perioperative bridging has been utilized
 - Multiple options depending on indication for anticoagulation and procedure (TABLE 4)
- Frequency of peri-operative hemorrhage or thrombosis in patients requiring peri-operative warfarin management
 - Variable based on indication for anticoagulation and procedure

Managing nontherapeutic INRs

Fluctuations in INR occur for many reasons, including changes in diet and/or vitamin K intake, medication effects or noncompliance. The management of a nontherapeutic INR is not well standardized and alternative interventions have not been thoroughly compared. INRs slightly outside the therapeutic range can be managed by adjusting the cumulative weekly warfarin dose up or down in increments of 5 to 20% or by more frequent monitoring with the expectation that the INR will return to therapeutic levels without a dosage change. For higher INR values between 4.0 and 10.0, warfarin may be held for a day or more followed by a reduction in the weekly dose and more frequent monitoring [1].

In treating patients with an elevated INR, one must evaluate the utility of vitamin K. When vitamin K is used, small doses are recommended in order to avoid over-correction and creating a state of warfarin resistance. Many studies show that with small doses of vitamin K (in the range of 1–2.5 mg orally), the INR returns to therapeutic range more quickly than without vitamin K, although a small percent of patient INRs will fall into the subtherapeutic range [38,39]. The use of a fixed small dose of vitamin K may not be

appropriate for all elevations of the INR. Sconce *et al.* recently suggested that the vitamin K dose used to correct an elevated INR should be titrated based on the degree of INR elevation as well as other factors, including patient age, body weight, other comorbidities, and even *CYP2C9* and *VKORC1* genotype [40]. However, the exact titration formula is not known, and the current recommendation is still to use small doses with a particular goal of avoiding over-correction and a state of warfarin resistance. This is particularly cogent for patients who are not actively bleeding [1,41]. The response to subcutaneous vitamin K is less predictable than to oral vitamin K, as well as sometimes delayed and, therefore, is not recommended. [42–44]. The oral administration of vitamin K is preferred as it is predictably effective and has the advantages of safety and convenience over parenteral routes [44–46]. Vitamin K by slow intravenous infusion should only be used when there is a greater urgency to reverse anticoagulation, such as in the presence of major bleeding, or if there is impaired vitamin K absorption, but intravenous injection may be associated with anaphylactic reactions [42,47,48]. A dose range of 1.0–2.5 mg is effective when the INR is between 5.0 and 9.0, but larger doses (ie, 2.5–5 mg), are required to correct INRs of more than 9.0 [1]. TABLE 5 summarizes guidelines from an expert consensus group on the management of nontherapeutic INRs and bleeding.

Measures and benchmarks of HQACM:

- Proportion of patients whose INR is out of range and have appropriate dose management
 - Compliance with recognized guidelines, such as the CHEST Consensus Guidelines (TABLE 5) [1]
- Rate of hemorrhage or thromboembolism in patients with a nontherapeutic INR
 - No established standard
- Use of vitamin K for supertherapeutic INR
 - Compliance with recognized guidelines, such as the CHEST Consensus Guidelines (TABLE 5) [1]

Achieving & measuring safety

Overall hemorrhagic/thromboembolic rates

Hemorrhage or thromboembolism are often the consequences of inadequate anticoagulation management with resulting over or under-anticoagulation. Early identification of potential risk factors that may lead to such complications may result in avoidance or minimizing of grave consequences [6]. Hemorrhagic adverse events with warfarin therapy are associated with factors such as indication for anticoagulation, concomitant illnesses or medications, whether patients are new to therapy or on established long-term therapy, the quality of anticoagulation management, and the management setting [1]. Due to the number of variables that affect the rate of complications, it is difficult to estimate an anticipated expected rate of hemorrhagic events. It is also difficult to determine a standard rate because clinical studies utilize different bleeding definitions.

Table 3. Prospective cohort studies of perioperative management of warfarin therapy.

Study	Patients (n)	Indication	Treatment	Arterial thromboembolism (%)	Venous thromboembolism (%)	Major bleeds (%)	Ref.
Katholi (1978)	235	MHV	UFH	0	NA	2	[72]
Spandorfer (1999)	20	MHV, AF, VTE	Enox 1mg/kg b.i.d.	0	NA	1	[73]
Galla (2000)	88	MHV	Enox 30 mg b.i.d.	0	NA	3	[74]
Nutescu (2001)	23	CVA; hypercoagulation	Dalt 100 IU/kg b.i.d.	0	NA	0	[75]
Tinmouth (2001)	24	MHV, AF, VTE	Dalt 200 IU/kg q.d.	1	0	0	[76]
Wilson (2001)	47	MHV, AF, VTE	Dalt 200 IU/kg q.d. 120 IU/kg b.i.d.	1	0	0	[77]
Ferreira (2003)	82	MHV	Enox 1 mg/kg b.i.d.	0	NA	1	[78]
Baudo (2004)	411	MHV, AF, VTE	Variable dosing	2	0	7	[79]
Douketis (2004)	650	MHV, AF	Dalt 100 IU/kg b.i.d.	4	0	6	[80]
Kovacs (2004)	224	MHV, AF	Dalt 200 IU/kg q.d.	2	NA	15	[81]
Constans (2007)	98	MHV, AF, VTE	Bemi 3500 IU q.d.	0	0	0	[82]
Turpie (2004)	220	MHV	Enox 1mg/kg b.i.d.	0	NA	8	[83]
Omran (2005)	362	MHV, AF	Enox 1 mg/kg q.d. or b.i.d.	0	NA	1	[84]
Jaffer (2005)	69	MHV, AF, VTE	Enox 1 mg/kg b.i.d.	0	0	0	[85]
Spyropoulos (2006)	901	MHV, AF, VTE	UFH or LMWH prophylactic & therapy dose	8	2	31	[86]
Dunn (2006)	260	AF, VTE	Enox 1.5 mg/kg q.d.	4	1	8	[87]
Malato (2006)	228	MHV, AF, VTE	LMWH, prophylactic & therapy dose	3	1	6	[88]
Halbritter (2007)	311	MHV, AF, VTE, CHF	UFH & LMWH therapy	1	3	7	[89]

AF: Atrial fibrillation; b.i.d.: Twice daily; bemi: Bemicarlin; CHF: Congestive heart failure; dalt: Dalteparin; enox: Enoxaparin; LMWH: Low-molecular-weight heparin; MHV: Mechanical heart valve; NA: Not applicable; q.i.d.: Once daily; UFH: Unfractionated heparin; VTE: Venous thromboembolism.

Box 1. Estimated risk for thromboembolism with anticoagulation for various treatment indications.

High risk:

- Mitral valve prosthesis
- Older, caged-ball or tilting disc aortic valve prosthesis
- Recent (6 months) stroke or transient ischemic attack
- High-risk atrial fibrillation
- Recent (3 months) venous thromboembolism

Low risk:

- Bileaflet aortic valve prosthesis (without atrial fibrillation)
- Low-risk atrial fibrillation
- Single venous thromboembolism (> 6 months)

Clinical studies show that bleeding rates vary by indication for long-term anticoagulation therapy. Cannegeiter *et al.* reported a major bleeding rate of 1.4% per patient year (95% confidence interval [CI] 1.2–1.5) for mechanical heart valve patients, pooled from 46 clinical studies [49]. A meta-analysis of various cohort and clinical studies in patients with atrial fibrillation showed a major bleeding rate of 1.1–1.3% per patient year [50]. However, bleeding rates are higher in the first 3 months of warfarin therapy in comparison with rates of patients on established treatment. In a systematic review of patients on warfarin for venous thromboembolism (VTE), Linkins *et al.* found that major bleeding rates in the first 3 months were 8.9% per patient year, whereas after 3 months, the rates dropped to 2.5% [51]. Based on varying indication, it is suggested that hemorrhagic events can be expected in 1–3% per patient year.

Hemorrhagic rates reported in clinical studies may also not reflect the rates experienced in real world practice because high-risk or elderly patients are often excluded from studies, and the quality of dose management is often better in clinical trials and may be difficult to duplicate in real world patient care. The comparison of anticoagulation management through a coordinated anticoagulation management service (AMS) versus usual care (UC) has demonstrated that bleeding rates occur less in those managed through an AMS [1]. Retrospective studies of patients managed through usual care, have a reported average of 4.4% per patient year major bleed [1,52–54] compared with patients managed through AMS with an average of 2.2% per patient year [29,55–57]. Cortelazzo *et al.* compared UC with an AMS in patients with mechanical heart valves and found a statistically significant increase in major bleeding in UC patients 4.7 versus 1% per patient year in patients managed by an AMS ($p < 0.01$) [58]. Similarly, Chiquette *et al.* studied 224 patients and showed a statistically significant decrease in major bleeding in patients managed by an AMS versus UC (2.0 vs 3.9% per patient year; $p < 0.05$) [59].

Similar to hemorrhagic event rates, the rates of thromboembolic complications vary depending on the warfarin indication and patient-specific factors listed above. A pooled

analysis by Cannegeiter *et al.* found that mechanical heart valve patients reported a thromboembolic rate ranging from 0.5–4% per patient year, with the majority of studies, however, reporting a rate of 1–2% per patient year [49]. Thromboembolic rates of 1.4–1.8% per patient year have been reported in pooled data of five clinical trials in patients with atrial fibrillation [60]. Other studies have, in fact, shown slightly increased ranges. Based on such trials, the expected thromboembolic rates for patients on warfarin therapy should be no higher than 1–2% per patient year. In addition, thromboembolic rates vary depending on the type of anticoagulation management utilized, UC or AMS. The effect of UC on thromboembolic rates mimic those rates of hemorrhage, in that a high incidence of these complications exist with UC than in those patients managed by AMS [1,29,52,56–59].

Measures and benchmarks of HQACM:

- Overall rate of major hemorrhagic adverse event rates (established patients)
 - No higher than 1–2% per patient year
- Overall rate of thromboembolic adverse event rates (established patients)
 - No higher than 1–2% per patient year

Managing bleeding

Patients who are actively bleeding or at a high risk of bleeding should be managed by rapid lowering of the INR. Interventions for the prompt reduction of the INR include infusions of fresh-frozen plasma (FFP), prothrombin concentrates, or recombinant factor VIIa, along with vitamin K to stimulate endogenous factor production. The severity and location of the bleeding and the level of the INR will influence the approach and choice of agent.

For life-threatening bleeding, including intracranial hemorrhage, the INR must be corrected immediately. FFP may be administered, however, it often requires large volumes and may take hours to infuse [61]. By comparison, factor concentrates will achieve INR correction and the cessation of bleeding more efficiently than FFP [62]. Yasaka *et al.* found that a dose of 500 IU of prothrombin complex concentrate (PCC) (contains the vitamin K-dependent factors II, VII, IX, and X) was optimal for rapid reversal for an INR of less than 5.0, but that higher doses might be needed for more elevated INRs [63]. Recombinant factor VIIa has also been shown to effectively lower the INR and control bleeding, despite lacking US FDA approval for this indication [64,65]. Recombinant factor VIIa has an extremely short half-life and should be administered with intravenous vitamin K to stimulate endogenous factor production. It has also been associated with a small incidence of thromboembolic complications, as have some PCCs. Doses of 15–90 µg/kg have been used, although doses at the lower end may be just as effective, as demonstrated in a prospective observational study of 16 patients with major warfarin-related bleeding

Table 4. Guidelines on the perioperative management of warfarin therapy.

Condition	Description
Low risk of thromboembolism	Stop warfarin therapy approximately 4 days before surgery, allow the INR to return to near normal, briefly use postoperative prophylaxis (if the intervention itself creates a higher risk of thrombosis) with a low dose of UFH (5000 units SQ) or a prophylactic dose of LMWH and simultaneously begin warfarin therapy; alternatively, a low dose of UFH or a prophylaxis dose of LMWH can also be used preoperatively
Intermediate risk of thromboembolism	Stop warfarin approximately 4 days before surgery, allow the INR to fall, cover the patient beginning 2 days preoperatively with a low dose of UFH (5000 units SQ) or a prophylactic dose of LMWH and then commence therapy with low-dose UFH or LMWH and warfarin postoperatively; some individuals would recommend a higher dose of UFH or a full dose LMWH in this setting
High risk of thromboembolism	Stop warfarin approximately 4 days before surgery, allow the INR to return to normal; begin therapy with a full dose of UFH or a full dose of LMWH as the INR falls (approximately 2 days preoperatively); UFH can be given as an SQ injection as an outpatient and can then be given as a continuous intravenous infusion after hospital admission in preparation for surgery and discontinued approximately 5 h before surgery with the expectation that the anticoagulant effect will have worn off at the time of surgery; it is also possible to continue with SQ UFH or LMWH and to stop therapy 12–24 h before surgery with the expectation that the anticoagulant effect will be very low or have worn off at the time of surgery
Low risk of bleeding	Continue warfarin therapy at a lower dose and operate at an INR of 1.3–1.5, an intensity that has been shown to be safe in randomized trials of gynecologic and orthopedic surgical patients; the dose of warfarin can be lowered 4 or 5 days before surgery; warfarin therapy can then be restarted postoperatively, supplemented with a low dose of UFH (5000 u SQ) or a prophylactic dose of LMWH if necessary

Data from [1].

where a dose of approximately 16 ug/kg was adequate for rapid reversal of the INR and a desirable hemostatic effect in 14 of the 16 patients [66].

Additional guideline statements recommend that anticoagulation providers have a policy in place for managing major and minor bleeding episodes, signs of thromboembolism or other warfarin-related adverse effects [6]. See TABLE 5 for a summary of guidelines formulated by an expert consensus group.

Measures and benchmarks of HQACM:

- Management of acute bleeding events; use of vitamin K, fresh frozen plasma, prothrombin complex concentrates, recombinant Factor VIIa
 - Compliance with recognized guidelines, such as the CHEST Consensus Guidelines (TABLE 5) [1]

Patient education

A key component to successful HQACM is patient education. The relationship between increased patient knowledge and improved anticoagulation therapeutic control is well documented, as is the correlation between increased bleeding events with insufficient anticoagulant knowledge [9,67,68]. As a result, well designed patient educational programs are shown to increase adherence to therapy, thereby, improving overall outcomes [6].

A cross-sectional survey conducted by Davis *et al.* found that in an urban, indigent, minority community, inadequate

adherence was significantly associated with poor anticoagulation control ($p = 0.01$) [69]. Numerous studies demonstrate the significant association between non-adherence and suboptimal anticoagulation management. IN-RANGE, a recent prospective cohort study of patient adherence on anticoagulation control confirmed the significant association between under-adherence and subtherapeutic INRs (<1.5) through multivariate analysis ($p = 0.001$) [70].

Patients who are nonadherent to their anticoagulation regimen are more likely to be younger patients, males and those patients who do not know why warfarin has been prescribed [71,72]. Orensky *et al.* reported that noncompliant patients felt more burdened by taking warfarin and perceived fewer health benefits than those who were compliant [71]. As perceived benefits of taking warfarin increased and perceived barriers, such as living arrangements and drug regimen decreased, the reported noncompliance decreased as well. Frequent and thorough education emphasizing benefits of warfarin therapy and decreasing perceived barriers could increase adherence to therapy, thereby achieving HQACM.

Measures and benchmarks of HQACM:

- The proportion of patients receiving education regarding warfarin therapy
 - Documented education at initiation of anticoagulation
 - Periodic education review

Table 5. Guidelines to manage nontherapeutic INRs or bleeding.

INR range	Guidelines
INR more than therapeutic range but less than 5.0; no significant bleeding	Lower dose or omit dose; monitor more frequently, and resume at lower dose when INR therapeutic; if only minimally above therapeutic range, no dose reduction may be required.
INR more than 5.0, but less than 9.0; no significant bleeding	Omit next one or two doses, monitor more frequently and resume at lower dose when INR in therapeutic range. Alternatively, omit dose and give VK (1–2.5 mg orally), particularly if at increased risk of bleeding. If more rapid reversal is required because the patient requires urgent surgery, VK (5 mg orally, maximum) can be given with the expectation that a reduction of the INR will occur in 24 h. If the INR is still high, additional VK ₁ (1–2 mg orally) can be administered.
INR of 9.0 or more; no significant bleeding	Hold warfarin therapy and give higher dose of VK ₁ (2.5–5 mg orally) with the expectation that the INR will be reduced substantially in 24–48 h. Monitor more frequently and use additional VK if necessary. Resume therapy at lower dose when INR therapeutic.
Serious bleeding at any elevation of INR	Hold warfarin therapy and give VK (10 mg by slow intravenous infusion), supplemented with fresh frozen plasma, prothrombin complex concentrate, or recombinant VIIa depending on the urgency of the situation; VK can be repeated every 12 h.
Life-threatening bleeding	Hold warfarin therapy and give prothrombin complex concentrate or recombinant VIIa supplemented with VK (10 mg by slow intravenous infusion); repeat if necessary depending on INR.
Administration of VK	In patients with mild to moderately elevated INRs without major bleeding, we recommend that when VK is to be given, it be administered orally rather than subcutaneously.
INR: International normalized ratio; VK: Vitamin K. Data from [1].	

Measuring one's own performance

HQACM requires a qualified professional managing therapy in a systematic or coordinated manner [6]. In a dedicated anticoagulation clinic, this often involves the development of evidence-based policies and procedures to guide personnel and management decisions. Competent and qualified staff must be in place. Certification is not mandated, however, opportunities for certification exist [103] and professional staff should be encouraged to attain certification.

Awareness of performance can only be obtained by periodic assessments using the measures and benchmarks discussed in this article. Knowledge of one's performance can lead to quality improvement initiatives in under-performing areas such that the ultimate goal of HQACM can be realized.

Measures and benchmarks of HQACM:

- Assessment of performance using the elements of HQACM
 - Benchmarks as defined for each performance element
 - Proportion of staff having completed a certification program

Conclusion

Oral anticoagulation therapy with the vitamin K antagonist, warfarin, remains the mainstay for the prevention and treatment of thromboembolic disease. The beneficial outcomes of oral anticoagulation therapy are directly dependent upon attaining HQACM. HQACM involves achieving and measuring efficacy through appropriate therapy initiation, maintenance of therapeutic

anticoagulation measured through TTR, monitoring anticoagulation at the appropriate frequency, managing peri-operative dosing and managing nontherapeutic INRs. HQACM also involves achieving and measuring safety through bleeding management, patient education and extensive communication. Most HQACM outcome measures can be met through attaining defined benchmarks and should be assessed on a regular basis.

Expert commentary

Warfarin has one of the highest risk profiles of almost any medication and HQACM is essential to reduce adverse events. Defined outcome measures and benchmarks that constitute HQACM for warfarin utilization do not exist. Furthermore, recent initiatives from regulatory and quality improvement agencies nationwide have been promulgated to ensure the safe use of anticoagulant medications. Such organizations are setting mandates to attain optimal oral anticoagulant care and by meeting the benchmarks for HQACM defined in this article, those mandates would be fulfilled.

The development of new anticoagulants to replace warfarin is on the horizon. The optimal anticoagulant to replace warfarin would be an oral agent with predictable dosing, minimal drug and food interactions, and one that does not require monitoring. Nevertheless, once such an agent comes to market, it will take time to transition patients from warfarin to the new agent, and in the long term, perhaps only patients with mechanical heart valves will remain on warfarin since such patients are not currently in

trials of these new agents. Warfarin use will not become extinct upon the introduction of new agents, however, its use can be expected to decrease significantly.

Five-year view

In 5 years time, based on increased recommendations from national quality and regulatory agencies, more anticoagulation programs will need to meet such HQACM outcomes measures and benchmarks as defined in this article. In 5 years, warfarin quality measures will remain the same as defined in this article, however the number of programs attaining the defined benchmarks will be increased. In addition, there will be a gradual increase in patient self testing, but not to the extent seen some European countries. Novel, oral anticoagulant agents will be introduced within the next 5 years, however, warfarin use will remain standard of care.

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Key issues

- Warfarin's beneficial outcomes are directly dependent upon attaining high-quality anticoagulation management (HQACM).
- HQACM involves achieving and measuring efficacy and safety of warfarin therapy, patient education and communication.
- Achieving and measuring efficacy of warfarin therapy includes:
 - Appropriate initiation of therapy, including initial dose, appropriate heparin or low molecular weight heparin overlap and prompt achievement of therapeutic international normalized ratio (INR)
 - Maintaining a therapeutic INR, measured through time in therapeutic range
 - Monitoring anticoagulation effects at appropriate frequencies, no longer than every 4 weeks
 - Managing perioperative dosing
 - Managing nontherapeutic INRs
- Achieving and measuring safety of warfarin therapy includes:
 - Managing bleeding events
- Additional factors for attaining HQACM include patient education and communication.
- Anticoagulation providers should assess their performance of meeting benchmarks on a regular basis.

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