Improving Antithrombotic Management in Patients With Atrial Fibrillation: Current Status and Perspectives

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ABSTRACT

Despite overwhelming evidence of the benefits of risk-adjusted oral anticoagulation on stroke reduction in patients with atrial fibrillation (AF), there is still considerable undertreatment. A multidisciplinary expert group was formed to discuss issues surrounding anticoagulant treatment of patients with AF to try and achieve consensus on various aspects of the implementation of guidelines on oral anticoagulation therapy in AF. Panel members were cardiologists, hematologists, and laboratory and primary care physicians with specific expertise from Europe and the United States. One of the most important conclusions of the meeting was to enhance guideline adherence by better communication of the data showing that the benefits of stroke reduction outweigh the risk of bleeding associated with treatment with vitamin K antagonists. Management of oral anticoagulation therapy by dedicated centers, such as anticoagulation clinics, or by patient self-management may improve the quality of anticoagulation and facilitate the management of these patients and thereby further facilitate optimal antithrombotic management in patients with AF.

KEYWORDS: Atrial fibrillation, anticoagulation, warfarin, Coumadin, cerebrovascular thrombosis, thromboembolism, bleeding

Most patients with atrial fibrillation (AF) at a stage of their disease need to be treated with vitamin K antagonists (VKAs). Although current guidelines clearly define the indications for treatment, there are barriers among physicians and patients to the implementation of oral anticoagulation. The consensus meeting intended to

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delineate current international standards and to discuss strategies of how to implement and manage adequate VKA treatment.

The main reason for implementing anticoagulation is the higher risk of stroke and the associated higher mortality in AF patients who are not treated. Adjusted-dose oral anticoagulation therapy reduces the risk for stroke efficiently, and this effect outweighs the risk for bleeding, particularly intracranial hemorrhage (ICH).[1,2] AF prevalence is on the rise worldwide due to the increased elderly population. Therefore the number of elderly patients with AF who need VKA treatment will increase. When applying international guidelines such as the joint guidelines of the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC), ~60 to 70% of AF patients should receive VKAs.[1] However, most studies show underutilization of this effective treatment, irrespective of how patients are cared for.

EPIDEMIOLOGY OF ATRIAL FIBRILLATION

AF represents the most common arrhythmia in clinical practice. An estimated 2.5 million people in the United States and >6 million European Union citizens have paroxysmal or persistent AF.[1,3–5] Incidence and prevalence of AF is age dependent. Due to the demographic change and an increasing proportion of the aged population with and without underlying heart disease, prevalence of AF is increasing worldwide with a growth rate of ~2% per year. In the United States, the number of patients with AF has been projected to be ~3.0 million by 2020, increasing to 5.6 million by 2050.[3,4] Following an analysis from the Mayo Clinic in the Midwest, an increase of the number of adults with AF to 12.1 million has been projected and to as many as 15.9 million assuming a continued increase in the incidence of AF.[6]

The prevalence of AF correlates with age, affecting 0.4 to 1% of the entire population and increasing to 8% of the population >80 years of age.[1] AF prevalence varies considerably between countries, although this may partly be a function of the methods of collecting the data and the demographics of the population investigated. In some countries, no specific epidemiological data have been reported. Prevalence of AF is ~1% in Denmark, increasing with age up to ~6% in those patients ≥80 years of age. In Germany, the estimated number of patients with AF is 900,000 (diagnosed in 680,000).[7,8] Based on the Echocardiographic Heart of England Screening study cohort, point prevalence in the UK general population is 1.7% in persons >45 years of age, with a maximum of 12% in subjects >84 years of age.[9] In the United States, overall prevalence of diagnosed AF was estimated as 1.0% in the Anticoagulation and Risk Factors in Atrial Fibrillation study.[3] It increases with older age, ranging from 0.1% among persons <55 years to 3.8% among persons ≥60 years and 9.0% among persons ≥80 years. In the Netherlands, overall prevalence of AF is 5.5%, increasing from 0.7% at 55 to 59 years of age up to 17.8% at ≥85 years of age.[10] According to unpublished data from the Italian Longitudinal Study of Aging study, the prevalence ranges from 2.2% (65 to 69 years of age) to 5.4% (80 to 84 years of age).[11] In a survey of 51 general practitioners in Northern Italy, a prevalence of 1.75% in 41,050 subjects >40 years of age has been found.[12] According to an Italian survey on 9712 subjects 34 to 74 years of age, AF prevalence in men is 0.8% and 0.7% in women.[13]

Like prevalence, incidences of AF increase continually with age at the rate of 0.1% per year for those <40 years of age and >1.5% per year for those >80 years of age.[1] Overall incidence in Germany is reported ~0.2%, and overall incidence in the Netherlands is 1%, increasing with age up to 2.1% in patients ≥85 years of age.[10]

Consensus statement:

- AF is a highly prevalent rhythm disturbance of the heart mainly affecting older people. Due to an aging population, the personal and economic burden of the disease is expected to increase in Europe and the United States.

EFFICACY AND SAFETY OF ORAL ANTICOAGULATION THERAPY IN ATRIAL FIBRILLATION

AF is a major contributor to stroke risk in the elderly. Ischemic stroke rate in patients with nonvalvular AF is up to 7 times that of people without AF, and the risk increases with age.[14,15] AF increases risk of stroke approximately fivefold, 15 to 20.3% of all acute stroke patients have AF, and 36% of acute stroke patients >80 years of age have AF.[16] In many stroke patients, AF is first diagnosed at the time of the event. Although 18 to 21% of patients with AF are asymptomatic,[17,18] they have an increased risk of stroke. Stroke is a leading cause of serious long-term disability in the United States with 15 to 30% being permanently disabled and 20% requiring institutional care at 3 months after onset .[19] Furthermore, AF increases mortality of stroke by 70%, it doubles severity of stroke and increases stroke morbidity as evidenced by more stroke patients with AF in a bedridden state than stroke patients without AF, and it is associated with a higher recurrence rate and with an increase of silent cerebral infarcts.[16,20,21] Taken together, untreated AF is associated with an increased mortality.[21–23]

Rates of stroke and hemorrhagic events are of primary interest in patients receiving oral anticoagulation therapy. Once the targeted intensity of oral

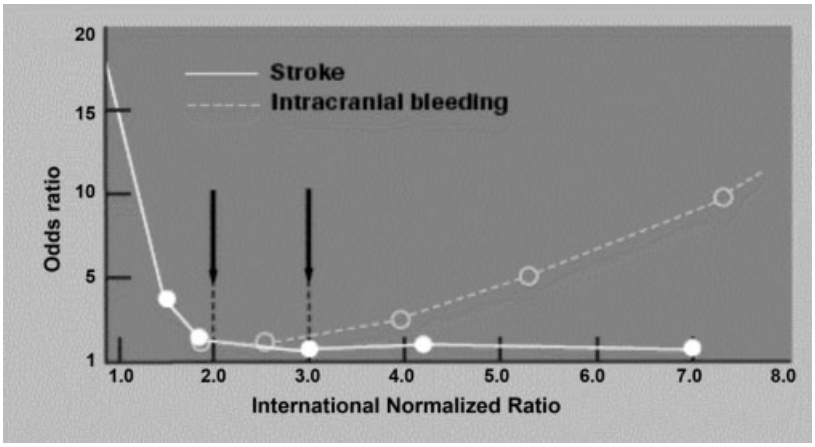

Figure 1 Significant increase in stroke risk with international normalized ratio (INR) values <2.0 and in intracranial bleeding risk with INR values over the range of 3.5 to 4.0.[2]

anticoagulation is achieved, it must be maintained because this protocol is directly related to its derived benefit.[1,24] The most recognized way to measure the therapeutic effectiveness of oral anticoagulation therapy is to measure international normalized ratio (INR) values. Time in therapeutic range, that is, the percentage of values in the targeted therapeutic range once a therapeutic INR has been established, correlates with the main clinical outcomes of bleeding or thrombosis but also represents a research tool for the evaluation of quality of overall care in these patients.[24,25]

Maintaining the intensity of anticoagulation is crucial to achieve effective stroke prevention as well as to avoid bleeding complications, particularly in elderly patients[2] (Fig. 1). For optimal outcomes it is essential to treat underlying heart disease such as coronary artery disease in addition to anticoagulation control in AF patients.[1]

REDUCTION OF STROKE RISK

The superiority of a risk-adjusted oral anticoagulation with VKAs compared with placebo or an aspirin-based therapy on stroke reduction has been clearly demonstrated by many prospective trials (Fig. 2). Oral anticoagulation reduces stroke events of any cause, not only embolic stroke, and it is also associated with a decrease of peripheral embolism.[26] Most trials of anticoagulation in AF were terminated earlier due to overwhelming results in favor of anticoagulation. A meta-analysis of six major trials has demonstrated a risk reduction of stroke (both ischemic and hemorrhagic) by 62% and of all-cause mortality by 26%.[27] Benefits of oral anticoagulation therapy may even have been underestimated because between 25% and 93% of patients were excluded in landmark trials on oral anticoagulation therapy in AF patients (e.g., patients with previous stroke).

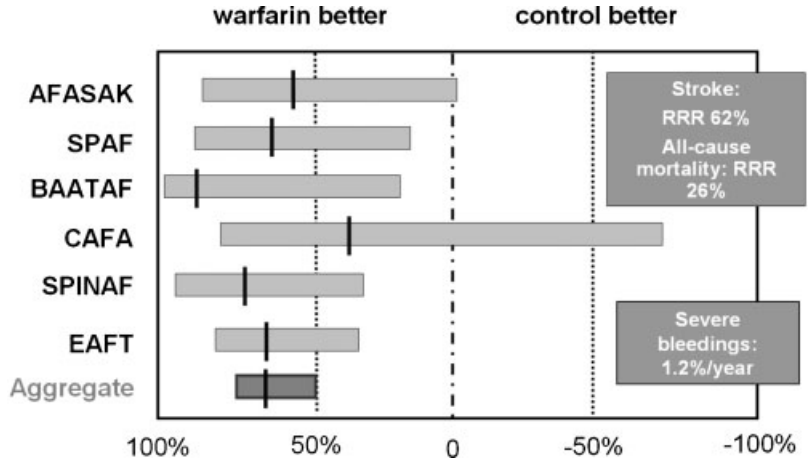

Figure 2 Reduction of stroke risk by oral anticoagulation therapy in prospective atrial fibrillation trials. Adapted from Hart et al.[27] AFASAK, Atrial Fibrillation, Aspirin, and Anticoagulation study; BAATAF, The Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation study; EAFT, European Atrial Fibrillation Trial; RRR, relative risk reduction; SPAF, Stroke Prevention in Atrial Fibrillation study; SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation study.

In a pooled analysis of five large randomized controlled trials, oral anticoagulation with warfarin decreased the risk of stroke by 68% in patients with AF, from 4.5% in the control group (placebo) to 1.4% in the warfarin group.[28] Stroke reduction was more pronounced in women compared with men. In a more recent meta-analysis by Hart et al[29] that included 29 randomized, controlled studies with a total of ~28,000 patients, oral anticoagulation with a coumarin derivative was shown to reduce the risk of a stroke by 64% compared with the control group in patients with nonvalvular AF.[29] Warfarin efficacy is consistent across AF trials with 32 patients needed to treat for 1 year to prevent one stroke in primary prevention and 12 patients in secondary prevention. Oral anticoagulation may be most beneficial for AF patients at higher intrinsic thromboembolic risk.[1]

In addition to superiority over placebo, there is clear evidence of the efficacy of adjusted-dose oral anticoagulants to reduce stroke, disabling stroke, and other major vascular events for those with nonvalvular AF when compared with antiplatelet therapy.[2,27,30–41] Finally, we now also have data on the superiority of warfarin in the elderly in a primary care setting. In the Birmingham Atrial Fibrillation in the Aged (BAFTA) trial, patients ≥ 75 ($n = 973$) were either treated with 75 mg/day aspirin or warfarin targeting an INR of 2.5 (range, 2.0 to 3.0).[42] There was a significant benefit of warfarin over aspirin treatment in terms of stroke prevention (1.8% versus 3.8% annually). This benefit was maintained in all subgroups of AF patients. Adherence to warfarin was less than adherence to aspirin in the BAFTA trial. Warfarin's relative superiority over aspirin for prevention of ischemic stroke is maintained in paroxysmal AF, prior stroke or transient ischemic attack (TIA), hypertension, heart failure, and diabetes. It possibly is more effective in women and people <75 years of age.[31]

SAFETY OF ORAL ANTICOAGULATION

Overall bleeding risk is increased with warfarin when compared with placebo, and hemorrhage is the major complication of VKA treatment. The rates of major bleeding, however, defined as bleeding severe enough to require hospitalization, blood transfusion, or surgery, were not significantly worsened in AF trials when comparing adjusted-dose warfarin with placebo.[27,28,43] ICH, the most feared and devastating bleeding complication,[44] is uncommon. In a meta-analysis of six trials conducted by Hart et al,[27] the rate of ICH in adjusted-dose warfarin was moderately higher among those taking warfarin (0.3% per year) versus those not taking warfarin (0.1% per year) without reaching statistical difference (Fig. 3). The relative risk for major extracranial hemorrhage was 2.4 (95% confidence interval [CI], 1.2 to 4.6), an absolute increase of 0.3%/year for warfarin patients.[27]

However, there were concerns that the bleeding risk with warfarin was understated because many of the main trials excluded large numbers of patients from randomization, including those perceived to have higher bleed risk.[45] Exclusion from studies would therefore result in a different risk-benefit ratio for these patients than in a real-world setting.[45] Furthermore, observational data from the major warfarin versus aspirin trials suggested that the bleeding risks with warfarin were higher in the elderly, eliciting cautionary notes for warfarin use in those >75 years of age in clinical guidelines.[31] Importantly, the BAFTA trial was designed to test these concerns by randomizing patients >75 years of age with minimal ineligibility criteria and demonstrated the bleeding risk with warfarin was the same as for

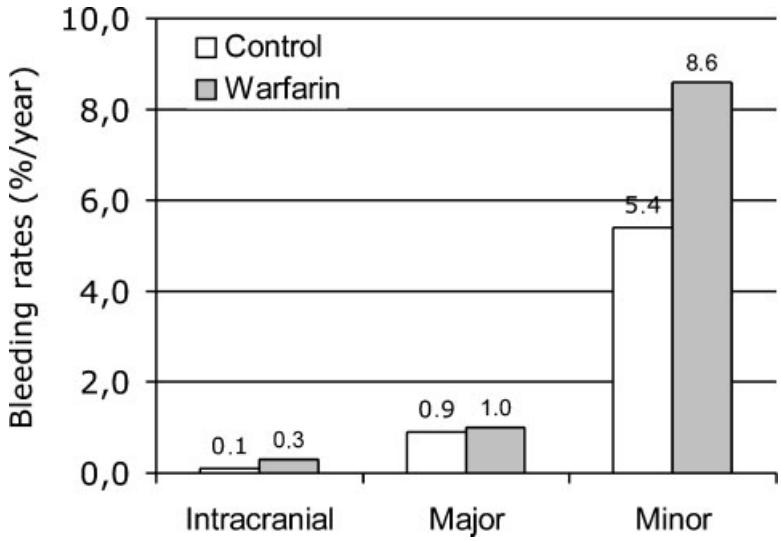

Figure 3 Bleeding rates in atrial fibrillation trials.[28,43]

aspirin.[42] These analogous bleeding findings are confirmed in the meta-analysis update.[46]

The risk of major hemorrhage and ICH in AF patients is mainly related to inadequate oral anticoagulation therapy. Overtreatment with persistent INR values $\geq$4 is associated with an increased risk of major hemorrhage, especially among older patients.[2,47] Therefore, dedicated monitoring of INR values helps to prevent ICH among patients with AF receiving oral anticoagulation therapy.

Consensus position:

- Risk-adjusted oral anticoagulation therapy in AF significantly reduces stroke rates, whereas major bleeding rates are not increased compared with placebo or aspirin within the therapeutic range of INR 2.0 to 3.0.
- In high-risk patients the benefit of stroke reduction outweighs the risk of bleeding associated with treatment with VKAs.
- Avoiding excessive INR values $\geq$4 by way of dedicated monitoring helps to prevent ICH among AF patients.

GUIDELINES ON THE IMPLEMENTATION OF ANTITHROMBOTIC THERAPY IN ATRIAL FIBRILLATION

Practice guidelines such as the 2006 ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation[1] or the Seventh American College of Chest Physicians (ACCP) 2004 guidelines[24] provide detailed recommendations relating to antithrombotic therapy in patients with AF. National guidelines such as those from the United Kingdom,[48] Italy,[49] or Switzerland[50] are mainly based on the ACC/AHA/ESC or ACCP guidelines.

Despite substantial differences among published schemes,[51] scoring systems for stratifying stroke risk in patients with nonvalvular AF provide some guidance for implementation of oral anticoagulation therapy. The 2006 ACC/AHA/ESC guidelines apply a risk-based approach using the clinical $CHADS_2$ (cardiac failure, hypertension, age, diabetes, and stroke [doubled]) scoring system.[52] In $CHADS_2$, prior stroke or TIA is the strongest independent predictor of stroke followed by diabetes mellitus, history of hypertension, current or history of heart failure, and advanced age.[1,28,53]

Studies have identified INR >4,[54] age >80 years,[55] elevated blood pressure,[56] prior ischemic stroke,[54] and short-term tolerability of oral anticoagulants[47] as major risk factors for intracranial bleeding (Table 1). Especially the latter two risk factors underline the need for adequate initiation of oral anticoagulation in high-risk AF patients. Anticoagulation of elderly patients with AF should be accompanied by tight control of hypertension because modest reductions in blood pressure considerably reduce the risk of ICH.[57]

Table 1 Clinical Risk Factors for Major Hemorrhage during Oral Anticoagulation Therapy*

Firmly linked
Advanced age $\geq$80 yr
Intensity of oral anticoagulation (INR $\geq$4)
Prior ischemic cerebrovascular disease
Hypertension (especially systolic)
Occasionally reported
Atrial fibrillation
Diabetes mellitus
Proximity to initiation of anticoagulation (<90 d)
Concomitant use of antiplatelet agents
Prior hemorrhage
Dementia
Liver disease
History of falling
Renal dysfunction (creatinine concentration >130 μmol/L or 1.5 mg/dL)
Active malignancy
Potential precipitating events
Minor head trauma
Acute alcohol intoxication
Acutely elevated blood pressure
Severe migraine attack

*Adapted from [47,54–56,58,59]
INR, international normalized ratio.

CURRENT RECOMMENDATIONS

According to the ACC/AHA/ESC guidelines, patients with prior stroke, TIA, other thromboembolism, or with rheumatic heart disease are at highest risk for stroke and clearly need oral anticoagulation. The guidelines specify when risk factors indicate that aspirin is sufficient for antithrombotic treatment and when risk factors suggest a patient is a candidate for oral anticoagulation therapy (Table 2). VKAs are indicated if a patient has one high-risk factor or more than one moderate risk factor. Aspirin is sufficient in a patient with no other risk factors for stroke. If there is one moderate stroke risk factor, either aspirin or VKAs can be used, according to patient and physician preference.

Oral anticoagulation is considered monotherapy for AF patients. The concomitant use of an antiplatelet agent and oral anticoagulation has proven not to be beneficial over oral anticoagulation monotherapy but rather seems to increase ICH risk in the elderly.[61] Awaiting the results of the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events-A trial, recent data from a post hoc subgroup analysis of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and

Table 2 Summary of Recommendations for Antithrombotic Therapy in Patients with Atrial Fibrillation Dependent on Risk Group and Definition of the Risk Groups

Risk Groups	Recommended Therapy	
No risk factors	Aspirin 81–325 mg/d	
One moderate risk factor	Aspirin 81–325 mg/d or	
	Oral anticoagulation (INR 2.0–3.0; target value: 2.5)	
A high-risk factor or >1 moderate risk factor	Oral anticoagulation (INR 2.0–3.0; target value: 2.5)	
Less Validated or Less Important Risk Factors	**Moderate Risk Factors**	**High Risk Factors**
Female gender	Age ≥75 yr	Previous stroke
Age 65–74 yr	Hypertension	TIA or thromboembolism
Thyroid hyperfunction (thyreotoxicosis)	Heart failure	Mitral stenosis
	Left ventricular function ≤35%	Mechanical valve replacement*
	Diabetes mellitus	

*For mechanical valve replacement, target INR >2.5.
INR, international normalized ratio; TIA, transient ischemia attack.
Adapted from 60.

Avoidance trial indicate the same holds true for dual antiplatelet therapy in low-risk patients.[62] In anticoagulated patients with concomitant stents, antiplatelet therapy is managed according to stent guidelines and intensity of oral anticoagulation remains unchanged (INR, 2.0 to 3.0; target value, 2.5). In these patients, anticoagulation monitoring needs to be performed at an increased frequency.

Little data are available on the thromboembolic risk of the patient with atrial flutter. However, based on evidence that the thromboembolic risk is elevated compared with sinus rhythm patients but slightly lower than that of AF patients,[63] the antithrombotic regimen is the same for both arrhythmias, atrial flutter and AF.

Except in AF patients with mechanical valves, the target INR should be 2.5 (range, 2.0 to 3.0). This is based on data demonstrating an INR <2 is not associated with a lower ICH risk in elderly AF patients compared with INR values between 2.0 and 3.0,[64] but both the risk for[65] and mortality of ischemic stroke[2] do increase when the INR drops below 2.0. In the Euro-Heart Survey on AF, guideline-adherent antithrombotic treatment of high-risk patients was associated with improved outcomes compared with a higher chance of thromboembolism in undertreated patients.[66] In this survey, overtreatment was not associated with a higher chance of major bleeding (Fig. 4).

Referral of AF patients to a specialist one time is strongly recommended when initiating antithrombotic therapy. For implementation and management of oral anticoagulation, therapy determination of INR is preferable over expressing the results as prothrombin time (PT) or Quick %.

Consensus position:

- International practice guidelines such as the 2006 ACC/AHA/ESC guidelines provide helpful guidance on how to manage oral anticoagulation therapy in patients with AF.

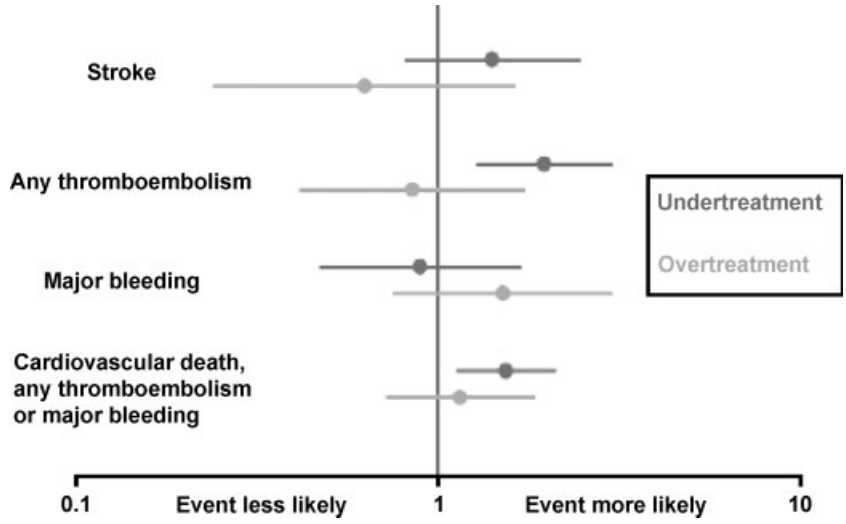

Figure 4 Multivariable effect of antithrombotic guideline deviance on 1-year outcome. Results are reported as odds ratio (OR) with 95% confidence interval compared with the reference group ''guideline adherence'' (OR, 1).[66]

- The antithrombotic treatment of patients with atrial flutter is the same as that for AF patients.
- Physicians should first evaluate stroke risk and bleeding risk in a given patient. Then risks and benefits of oral anticoagulation therapy should be discussed.
- If appropriate, oral anticoagulation should be initiated when one high-risk factor or more than one moderate risk factor are present.
- Oral anticoagulation therapy should be used as monotherapy in AF patients. The only exceptions are AF patients requiring concomitant clopidogrel treatment during the first 9 to 12 months after coronary stenting.
- Determination of INR is preferable over expressing the results as prothrombin time (PT) or Quick %. The target INR value should be 2.5 (range, 2.0 to 3.0).

IMPLEMENTATION OF ANTICOAGULATION GUIDELINES IN CLINICAL PRACTICE

Although AF is highly prevalent in general practice and guidelines are in place, many patients are still undertreated or not treated at all. It has been estimated that worldwide an average of only 30% of patients with AF are treated with oral anticoagulation,[67] whereas an estimated 60 to 70% should be.[1]

In Germany and the Netherlands, ~60% of patients are treated according to guidelines; in Denmark, ~75%.[7,14,60] Guideline adherence in Italy is not clearly known but may be 10% in a series of AF patients admitted to hospital with a first-ever stroke[68] to <50%.[69] In a single-center study from Italy among 255 patients with nonvalvular AF admitted to an internal medicine ward from 2001 to 2005, 85% of them high-risk patients, 62% received VKAs, but a fourth of these patients were undercoagulated. Among the high-risk patients, only 47.2% were adequately anticoagulated, 17.9% were undercoagulated, 23.4% received aspirin, and 11.5%, no antithrombotic treatment.[69] But patients not only are undertreated: In the Netherlands, overtreatment has been reported in as many as 18% of anticoagulated AF patients,[14,66] exposing them to an increased risk of bleeding.

Whereas many high-risk AF patients are not anticoagulated adequately, it has been clearly demonstrated that guideline-adherent treatment is associated with improved outcomes.[66,70] Several barriers to implementation of oral anticoagulation therapy exist.

AWARENESS AND ESTIMATE OF TRUE RISK

Strong evidence indicates that physicians underestimate the risk of stroke in their patients with AF and overestimate the risk of severe bleeding, particularly in the elderly.[70–73] Unfortunately, stroke prevention as a positive result of oral anticoagulation cannot be perceived by physicians directly. In contrast, major bleeding as a side effect of anticoagulation therapy can be experienced by physicians. Positive reinforcement pointing out the effectiveness of oral anticoagulation therapy is absent. As a consequence, physicians tend to ascribe stroke events to the disease itself and bleeding to treatment, and they fear iatrogenic complications but not stroke as the more frequent complication of AF. Accordingly, it has been shown that a physician's experience with bleeding events associated with oral anticoagulation therapy reduced warfarin prescribing, whereas the experience of stroke in a patient while not on warfarin did not affect subsequent prescribing.[74]

In another study, 15.8% of 596 general practitioners reported having a patient with AF experience an ICH with anticoagulation, and 45.8% had a patient with known AF experience a stroke without anticoagulation.[75] However, only 45.6% of the physicians selected an anticoagulant in the presence of a minor falls risk when presented with a patient at "very high risk" of stroke, and 17.1% would anticoagulate if the patient had a treated peptic ulcer.[75] Family physicians with less decisional conflict and those who were more experienced were more likely to endorse anticoagulation.

Among very elderly AF patients, the decision to prescribe oral anticoagulants is strongly influenced by contraindications. Hemorrhage, falls, and patient refusal or history of nonadherence to treatment constituted nearly 80% of the physician-cited reasons for not prescribing warfarin in AF patients who had been considered for anticoagulation therapy in one study.[59]

For many patients with AF, physicians' fears of the risk of bleeding related to anticoagulant therapy are often exaggerated and unfounded. Physicians should be aware of the impact of AF and the devastating consequences of not treating it adequately. They should also be able to discern absolute from relative contraindications. Strategies to optimize the management of AF should address psychological barriers to using anticoagulation as well. The key issue in selecting patients with AF for oral anticoagulation therapy is accurately estimating their stroke risk, with risk of hemorrhage during anticoagulation a lesser issue, relevant to only a few patients.

ACCESS TO GUIDELINES

Better access to the evidence base should enable clinicians to advise their patients appropriately. Often guidelines are too large and complex and, as a result, even specialists may not have consensus on treatment decisions (e.g., in patients presenting with high INR levels). Moreover, international guidelines are available only in English and not in local languages. What is more, few guidelines on oral anticoagulation therapy

aim at the needs of general practitioners, which may include topics such as bleeding risk stratification, bridging therapy, or dual treatment with anticoagulants and antiplatelets. Because AF only represents a small part of a general practitioner's job, these physicians need simple guidance and suggestions for clear-cut decisions. This is critical to counter the concerns over treatment risk and perceived complications of oral anticoagulation therapy for some physicians. In some countries, the average general physician may not be well trained in treating AF but should be confident, as a minimum, about screening patients for AF and identifying those patients who need treatment. Special referral guidelines would also be of particular interest for general practitioners. They should help the physician to decide on when to refer the patient to specialist evaluation and treatment and to identify the "red flags" of oral anticoagulation therapy monitoring. Factors to consider include prevalence and costs; definition and symptoms; impact on patients, such as the risk of death and disability in stroke; diagnosis and assessment; and treatment options.

International and national guidelines should be harmonized and also be published and diffused in local languages and adapted to local practice patterns. Short and simple guideline versions should be prepared for use in primary care medicine. In addition to the complete paper version, an updated backup guideline Web site could be implemented. Guideline versions in electronic formats such as for personal digital assistants and personal computers as well as easy-to-use calculator tools should assist in balancing the benefits and risks of oral anticoagulation therapy for the individual patient.

EDUCATIONAL ISSUES

Physician specialty is an important determinant for VKA use. In a Dutch study, cardiologists showed best guideline adherence, whereas general practitioners were less adherent to guidelines.[76] Similarly, in the Stroke and Atrial Fibrillation Ensemble II study, factors independently associated with prescription of oral anticoagulation were mainly related to the characteristics of the practitioner.[77] Being followed up by a cardiologist or a younger general practitioner were the strongest predictors of VKA treatment. Underutilization of oral anticoagulation therapy as well as differences between treatment by general practitioners and specialists may therefore not only result from inappropriate perceptions of stroke and bleeding risks and consequences. Other reasons may be insufficient education, resulting in a lack of knowledge about oral anticoagulation therapy, and avoidance of responsibility for the patient.

Living with anticoagulants has become more demanding for patients than just taking the medication prescribed by the doctor. Patients therefore need to take responsibility by getting involved. The reward is control of the therapy in contrast to letting the therapy control the patients' lives.[78] According to studies such as the West Birmingham Atrial Fibrillation Project,[79] however, many patients with AF possess limited knowledge of AF, its consequences, and therapies. Most patients (61%) believed AF was "not serious," and many patients were not aware that AF predisposed to stroke. Only 52% were aware of the reason for anticoagulation treatment, whereas the rest of the patients started therapy just because their "doctor told them to." A minority felt that their physician provided adequate information regarding warfarin therapy.[79] Poor patient adherence to treatment is potentially a major source for poor anticoagulation control even among patients being treated in dedicated management systems where the importance of adherence is continually emphasized.[80] The key to success is to communicate with patients to meet their requirements and improve their quality of life. Care of anticoagulated patients means to diagnose, educate, and treat them. Adherence rates are also related to access to INR testing and the burden of monitoring.[81,82] In this regard point-of-care testing may offer advantages to physicians because rapidly available results enable them to communicate their treatment decision immediately to the patient.

Educational intervention programs improve knowledge about and/or control of oral anticoagulation therapy for AF.[83–85] Such programs may include regular teaching sessions, information booklets, workbooks, or slide presentations and can be addressed to individuals or groups of patients. However, education of the anticoagulated patient is time consuming for physicians and stuffed with learning content for patients, and therefore often neglected. Thus educational programs should attempt to maximize office efficiency by delegating this task to physician extenders, nurses, pharmacists, or perhaps an office-based computer.[84] When written information is applied, the patient's reading skills have to be considered because the patient's reading abilities may be lower than the readability of the written information. It is important to have information that is understandable and culturally relevant to prevent the outcome of internal bleeding.[86] Despite the practical value of making the patient as knowledgeable as possible, the best strategy for educating patients about anticoagulation is yet to be determined.[84]

Consensus position:

- International and national guidelines should be harmonized and be published and diffused in local languages and adapted to local practice patterns. Short and simple guideline versions should be prepared for use in primary care medicine.

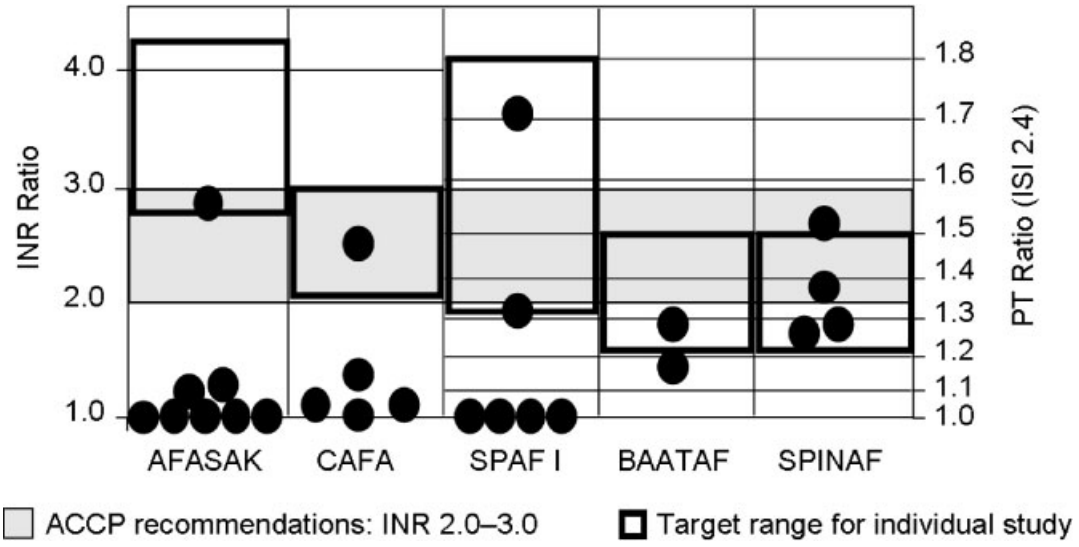

Figure 5 Intensity of anticoagulation when stroke occurred in patients assigned to warfarin in atrial fibrillation trials.[32,88–92] Undercoagulated patients are more prone to have stroke (black balls). ACCP, American College of Chest Physicians; AFASAK, Atrial Fibrillation, Aspirin, and Anticoagulation Study; BAATAF, The Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation study; INR, international normalized ratio; ISI, international sensitivity index; PT, prothrombin time; SPAF, Stroke Prevention in Atrial Fibrillation study; SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation.

- In addition to the complete paper version of guidelines, an updated backup Web site may be prepared. It would be helpful to provide an easy-to-use calculator for balancing and checking benefits and risks of oral anticoagulation therapy in the individual patient in electronic formats.
- General physicians need better education on the management of oral anticoagulation and to be aware of the importance of AF and the consequences of not treating it adequately. Special referral guidelines may help them decide when to refer the patient to specialist evaluation and treatment and to identify the "red flags" of oral anticoagulation therapy monitoring.

IMPACT OF UNDERUTILIZATION OF ANTICOAGULATION IN PATIENTS WITH ATRIAL FIBRILLATION

When patients with AF do not receive any or no adequate oral anticoagulation therapy, the risk of stroke and death is increased.[2] In a Swiss study, ~16% of stroke patients who had a history of AF were not on oral anticoagulation, providing evidence that for many of the stroke patients AF is diagnosed first at the time of stroke. In another study, 31% of unselected AF patients without contraindications were not treated with oral anticoagulants.[70] If these patients had been treated according to guidelines, an estimated event rate of 4.9% per year could have been prevented. A meta-analysis of nine studies using a target conventional INR of 2.0 to 3.0, the overall odds ratio for ischemic stroke for patients with INR <2 as compared with INR ≥2 was 5.07 (95% CI, 2.92 to 8.80).[87] This means that undercoagulated patients with AF are significantly more likely to have stroke than those maintained within the recommended INR range (Fig. 5).

ECONOMIC ASPECTS

AF represents a considerable cost burden on health-care systems due to therapeutic interventions associated with increased AF morbidity and mortality.[93] In the United States, the number of hospitalizations related to AF almost increased threefold in 2000 compared with 20 years ago.[94] Fig. 6 shows the annual estimated costs of care and health resource utilization for the management of AF according to data from the United Kingdom,[95] France,[96] and the United States.[97] In the UK-based survey, an increase of the National Health Service budget, from 0.6 to 1.2% in 1995 to 0.9 to 2.4% by 2000, has been observed.[95]

Costs attributable to AF have to be considered in the context of different management strategies. In a pharmacoeconomic review, Szucs and Bramkamp showed that treatment with warfarin is highly cost effective both compared with aspirin or no therapy in patients with AF at moderate-to-high risk of stroke.[98] The cost effectiveness of anticoagulation therapy is driven by the achieved risk reduction rather than the potential benefits estimated from clinical trials. Failure to maintain optimal anticoagulation places patients at risk of complications such as stroke, the management of which is a significant cost driver.[98] Undertreatment with INR values outside the target range increases

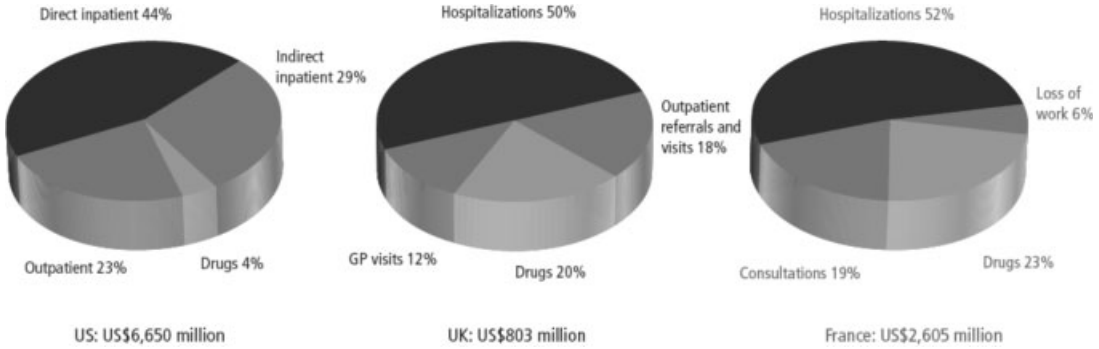

Figure 6 Estimated annual costs of atrial fibrillation in the United States,[97] United Kingdom,[95] and France.[96] GP, general practitioner.

hospitalization rates.[19,99] A Canadian and a U.S. study showed that INR monitoring led to fewer complications as well as to lower costs for health-care professionals.[100,101] However, only a small amount of the potential anticoagulation cost-saving benefit is currently attained due to undertreatment with VKAs. The U.S. study presented that if half of the AF patients in routine medical care currently receiving oral anticoagulation were optimally anticoagulated, $1.3 billion would have been saved in 2004. Oral anticoagulation for stroke prevention, in addition to an optimized anticoagulation care, could even have saved up to $2.4 billion.

ANTICOAGULATION MANAGEMENT

Anticoagulation management should consider various aspects of anticoagulation therapy that are addressed differently by different methods of anticoagulation management (Table 3). Not all management strategies work the same for all patients, and the physician should evaluate what works best for the individual patient for major convenience. A major problem for oral anticoagulation control independent from the strategy used is the instability of lifestyle of a patient as well as the loss of patients or lack of adherence[80] during treatment. Anticoagulation management may also be complicated (e.g., by interacting drugs, diet, or traveling). Another major influence on INR variation results from the time point of testing, particularly when treating a patient with a substance having a short half-life such as acenocoumarol.[102]

ELEMENTS OF ANTICOAGULATION MANAGEMENT

Basically there are two styles of anticoagulation management: In the informal style, oral anticoagulation is managed by the individual practitioner who cares for the patient. In this essentially unstructured "usual care" option, patients may show up once per month. In contrast, a formal approach to anticoagulation management promotes systematic, structured care of the patients. The persons involved in structured care adopt an active attitude. The formal approach meets the requirements of "high quality anticoagulation monitoring" and is the preferred management style where available.[103]

INR testing can be performed in different ways. Blood may be sampled by venipuncture or by simple fingerstick, and INR values can be measured in a central laboratory or by point-of-care coagulometers. INR testing may be performed either by health-care professionals or by the patient or a surrogate at home (e.g., a nurse visiting older patients who are not able to manage self-testing on their own). All methods of INR testing are accurate and capable of providing reliable results. Anticoagulant dose may be adjusted by health-care professionals, as in the usual care or patient self-testing (PST) options, or by the patient or a surrogate, as in patient self-management (PSM). In any of these options, competency is needed to ensure correct dose adjustments.

Because factors such as medications, diet, and concurrent diseases can alter the pharmacokinetics of

Table 3 Elements of Anticoagulation Management

Elements	Options
Management style	Formal, structured anticoagulation management
	Informal, unstructured anticoagulation management
Method of INR testing	Venipuncture, laboratory
	Professional point-of-care testing
	Point-of-care testing by patient or surrogate
Supervision of adjustments and decision making	Health-care professional
	Patient or surrogate
Frequency of testing	Historically once a month (4–6 wk)
	More frequent in selected situations
	Individually determined for each patient

INR, international normalized ratio.

VKAs, frequent INR monitoring is necessary to ensure that a patient remains within therapeutic range.[104] Health-care providers should assess their performance by monitoring INR regularly using a consistent methodology. Historically, oral anticoagulation therapy has been monitored once a month. Testing not only allows for dose adjustments but is also important for reassurance of the patients in terms of avoidance of bleeding. INR testing should be performed at least every 4 to 6 weeks, and more frequent testing of no longer than 2 weeks is required in selected situations such as unstable patients.[24] Special considerations that may warrant more frequent testing are a huge bleeding risk or periods of instability. The International Self-Monitoring Association for Oral Anticoagulation 2005 guidelines recommend a testing interval of no longer than 4 weeks for stable patients and weekly testing for PST and PSM.[105] Computerized decision support algorithms, which calculate monitoring intervals based on prior results, provide the optimum method for achieving good anticoagulation control,[106–109] but they are not available everywhere.

ANTICOAGULATION MANAGEMENT MODALITIES

Traditionally four strategies of oral anticoagulation therapy management have been established: "usual" care by general practitioners or specialists, anticoagulation clinics, PST, and PSM. In the usual care option, patients are cared for, along with all other patients, by their personal physician. Table 4 presents an overview of the advantages and disadvantages of different anticoagulation management modalities.

When compared with usual care, coagulation monitoring in dedicated anticoagulation clinics shows a 59% reduction in major hemorrhagic events and 68% reduction in thrombotic events when compared with usual care[110] due to improvements in INR time in a range[111] leading to reduced bleeding events.[112] Several studies have shown that PSM of oral anticoagulation using point-of-care coagulometers improves the quality of anticoagulation, thus reducing complication rates and mortality compared with usual care and that it is at least as good as or even slightly better than management in anticoagulation clinics.[113–115] Accordingly, the current

Table 4 Synopsis of Advantages and Disadvantages of Anticoagulation Management Modalities

Management Modality	Advantages	Disadvantages
Usual medical care (venipuncture and laboratory testing)	Reliable INR results; external quality control system	Time consuming
	Results part of an integrated medical record	Delayed results and decision making
	Dose adjustments and decision making by a health-care professional	Allows management of all anticoagulated patients
		Venipuncture necessary
		Transportation effects
PST/PSM (fingerstick and point-of-care testing)	Reliable INR results; internal quality control system	Lacks external quality control system
	Convenient to patients and physicians; easy to use	Testing needs education and training
	Results within minutes allow for rapid decision making	Some patients may not be able to carry out self-testing or self-management
	Use of small specimen volumes; venipuncture and needlestick injuries can be avoided	
	Allows patients to take on more responsibility for their own health	
Dedicated management systems (venipuncture and laboratory testing or fingerstick and point-of-care testing)	Reliable INR results; external and/or internal quality systems	Disadvantages depend on the testing method used (see above)
	Advantages depend on the testing method used (see above)	
	Management by trained anticoagulation specialists	
	Efficient use of resources	

INR, international normalized ratio; PST, patient self-testing; PSM, patient self-management.

ACCP guidelines advocate PSM and PST for the management of patients with AF.[1] Better INR control by PSM than by usual care translates into better outcomes of the patients.[116]

Currently, the Department of Veterans Affairs Cooperative Study 481, "The Home INR Study" (THINRS), is underway to compare anticoagulation management with frequent PST using a point-of-care device to high-quality anticoagulation management implemented by an anticoagulation service with conventional monitoring of prothrombin time by INR on major health outcomes.[117] To assess the effect of PST frequency on oral anticoagulation outcomes, patients randomized to PST are assigned in a substudy of THINRS to weekly, twice-weekly, or once-every-4-weeks testing. The results will help to determine the exact place of self-testing versus dedicated care in oral anticoagulation monitoring.

There are regional differences in oral anticoagulation management strategies. In the Netherlands, formal anticoagulation management predominates. Blood is in general drawn by venipuncture, and anticoagulation is managed by anticoagulation clinics. Moreover, pharmacists are integrated in the management of the patients. In Italy, 75% of the patients are formally managed by their general practitioners but often are self-managed without any formal education. In the United States, health-care environments are extremely diverse, so PSM currently is not applicable. Usually patients are referred to venipuncture, but caring of the patients is informal. In Germany, a sophisticated PSM training system exists. Furthermore, there are important regional differences concerning reimbursement by health insurances: In Germany, where self-management is reimbursed for patients with mechanical heart valves and on a single-case basis also for patients with atrial fibrillation, <100,000 patients perform PSM, whereas point-of-care testing by physicians is not adequately reimbursed. In the United Kingdom, test strips needed for point-of-care testing are reimbursed, but not the devices; in Switzerland, a sophisticated PSM training system exists comparable to Germany and ~50 to 90% of PSM costs are reimbursed by health insurance companies; in Denmark, ~4% of patients perform PSM with full reimbursement and 50 to 60% of INR measurements at general practitioners are performed with point-of-care devices and reimbursed.

Consensus position:

- Reliable access to accurate INR monitoring is important for optimal management of oral anticoagulation therapy. A formal, structured management style is preferable when available. The frequency of testing has to be determined for each individual patient.
- All methods of INR testing are capable of providing reliable results.
- Dose adjustments of anticoagulants require competency (i.e., trained professionals or educated patients/surrogates).

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