

Effective Anticoagulation Therapy: Defining the Gap Between Clinical Studies and Clinical Practice

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Abstract

Atrial fibrillation (AF) greatly increases the risk of stroke. Long-term oral therapy with warfarin reduces the risk of AF-related stroke by 62%, and national guidelines now call for warfarin therapy in most patients without specific contraindications to anticoagulation. However, the drug's narrow therapeutic index means that warfarin therapy must be guided by coagulation monitoring. This requirement and other inherent limitations of warfarin have led to widespread underutilization and underanticoagulation in AF patients who require antithrombotic therapy for stroke prevention. Recent studies indicate that in many health systems less than half of warfarin-eligible patients take the drug and even fewer are adequately maintained within a protective therapeutic range. Similarly, despite the documented efficacy of anticoagulation in patients at risk for deep vein thrombosis (DVT) and related pulmonary embolism, prophylaxis for DVT, even in high-risk situations such as following orthopedic surgery, is suboptimal. This article explores the scope of warfarin underutilization and underanticoagulation that exists in current clinical practice. The clinical consequences of warfarin underuse are also described. Discussion in the roundtable after this review explores the causes for the wide treatment gap between anticoagulation clinical trial results and clinical practice outcomes. The economic implications of such a gap and strategies for closing the gap are also discussed by the panelists.

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Atrial fibrillation (AF) and venous thromboembolism (VTE) are disease states that affect an increasingly large proportion of the population. Effective anticoagulation therapy can prevent the serious and costly comorbidities related to these conditions, such as stroke, deep vein thrombosis (DVT), and pulmonary embolism (PE). But this therapy is frequently underused and underdosed. As a prelude to the roundtable discussion focusing on the causes and the economic consequences of this less-than-

ideal use of anticoagulation in clinical practice, this article reviews the evidence base supporting the safety and efficacy of anticoagulation in AF and VTE and summarizes recent studies detailing actual utilization of anticoagulation in diverse health system settings.

The Scope of AF and Stroke

AF is the most common heart rhythm disturbance, accounting for one third of all hospital admissions for arrhythmia.¹ The prevalence of AF in the United States is estimated to be 2.2 million.² Overall, about 0.4% of the general population has AF, with the rate increasing from about 0.1% among persons younger than 55 to 60 years of age to about 9% to 10% among those aged 80 years and older.^{2,3} During the next 20 years, the prevalence is projected to increase to 5.6 million, with more than half of the affected individuals aged 80 years or older.³

AF is responsible for about 15% to 20% of the 700 000 new and recurrent strokes that occur every year in the United States.² Several large longitudinal studies have established that AF increases the risk of stroke by 5- to 7-fold (Table 1).^{4,7} This risk for stroke attributable to AF increases with age. Thus, although the overall annualized risk of stroke is approximately 3% in patients with AF, the yearly risk of stroke in AF patients ≥ 80 years of age is nearly 7%.⁴

These stroke events in patients with AF are often fatal or severely disabling. When considered separately from other cardiovascular diseases, stroke is the third leading cause of death after diseases of the heart and cancer, accounting for more than 1 of 15 deaths.² More than 1 million individuals are living with functional limitations or disabilities resulting from stroke,⁸ and the added burden on family caregivers is widely

Table 1. Atrial Fibrillation (AF) and the Risk of Stroke

Study	Mean Age (Years)	Stroke (% Per Year)		Relative Risk
		AF	No AF	
Framingham, USA	70	4.1	0.74	5.6x
Shibata, Japan	65	5.0	0.90	5.6x
Reykjavik, Iceland	52	1.6	0.23	7.1x
Whitehall, UK	60	1.8	0.26	6.9x

Sources: References 4-6.

acknowledged though not often calculated. The mean per-patient lifetime cost of an ischemic stroke has been estimated at \$140 038 (1999).^{2,9} Overall, the economic cost of stroke in the United States has been set at \$53.6 billion, including \$33 billion for direct medical costs and \$20.6 billion for lost productivity.²

Warfarin: The Current Standard of Stroke Prevention in AF

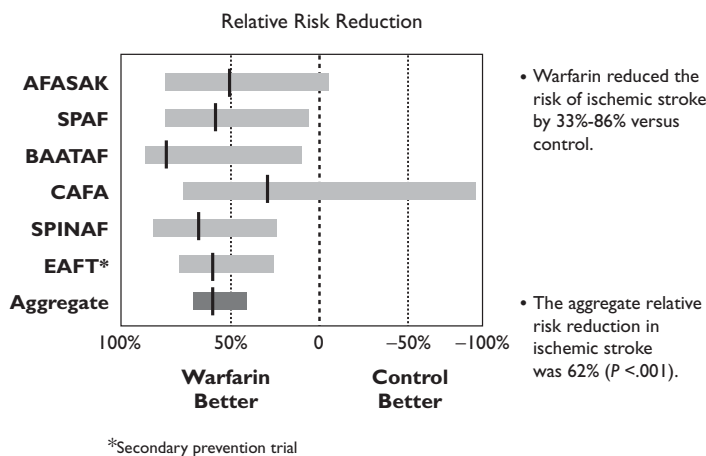
The initial steps in managing AF include identifying any underlying reversible causes,

controlling the heart rate, and using pharmacologic or electric cardioversion to control heart rhythm.^{1,10} Long-term management of the patient at risk for recurrent AF requires either ongoing rate or rhythm control and, unless contraindicated, anticoagulation to prevent thromboembolic events. To prevent initial or recurring strokes in these AF patients, long-term anticoagulant therapy with the oral vitamin K antagonist sodium warfarin is the therapy most often employed.

Randomized trials from the 1980s and early 1990s have documented the benefits of oral anticoagulation with warfarin in preventing stroke associated with AF. A meta-analysis of 5 major primary prevention trials¹¹⁻¹⁵ and 1 secondary prevention study¹⁶ involving an aggregate of more than 4600 patients with AF showed that warfarin reduced the relative risk of stroke by 62% compared with placebo or control (Figure 1).¹⁷ Although there are clear benefits to aspirin administration in these patients, the benefits do not approach those attributable to warfarin.¹⁸ Compared with placebo or control, aspirin reduced the relative risk of stroke by 22% in the major trials that included this comparison. However, compared with aspirin, warfarin reduced the relative risk of stroke by 36%. A number of observational studies, although limited by their small size and selective patient populations, generally support the findings of randomized trials that warfarin is significantly more effective than placebo or aspirin in preventing stroke in AF patients.¹⁹⁻²³

Based on this large body of convincing evidence, clinical guidelines for stroke pre-

Figure 1. Randomized Trials of Stroke Prevention in Atrial Fibrillation: Risk Reduction with Anticoagulation



AFASAK indicates Atrial Fibrillation, Aspirin, and Anticoagulation [Peterson 1989]; SPAF, Stroke Prevention in Atrial Fibrillation [SPAF 1991]; BAATAF: Boston Area Anticoagulation Trial for Atrial Fibrillation [BATAAF 1990]; CAFA, Canadian Atrial Fibrillation Anticoagulation [Connolly 1991]; SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation [Ezekowitz 1992]; EAFT, European Atrial Fibrillation Trial [EAFT 1993].

Source: Reference 17.

Table 2. ACCP Recommendations for Stroke Prevention in Atrial Fibrillation

Risk Category	Goal INR	Duration	Comment
No risk factors	None	Chronic	Aspirin 325 mg qd
1 moderate-risk factor	2.0-3.0	Chronic	Or aspirin 325 mg qd
>1 moderate-risk factor or any high-risk factor	2.0-3.0	Chronic	
Moderate-risk factors:	Age 65-75 years	CAD	Diabetes
High-risk factors:	Age >75 ↓ LV function	HTN mV dz	hx TIA/stroke/TE valve replacement

ACCP indicates American College of Chest Physicians; INR, international normalized ratio; CAD, coronary artery disease; HTN, hypertension; LV, left ventricular; mV dz, millivolt; TIA, transient ischemic attack; TE, thromboembolism. Source: Reference 23.

vention in AF have been developed. Consensus guidelines from the American College of Chest Physicians (ACCP) are based on stratification of patients into high-, moderate-, and low-risk groups for stroke (Table 2).²⁴ In fact, most patients with AF have more than 1 moderate-risk factor or at least 1 high-risk factor, which means that patients with AF require long-term oral anticoagulation with warfarin. The widely accepted goal for the international normalized ratio (INR) in these patients is 2.0 to 3.0, a range intended to preserve the efficacy of stroke prevention while minimizing the risk of major hemorrhage. Updated ACCP guidelines are expected later this year.

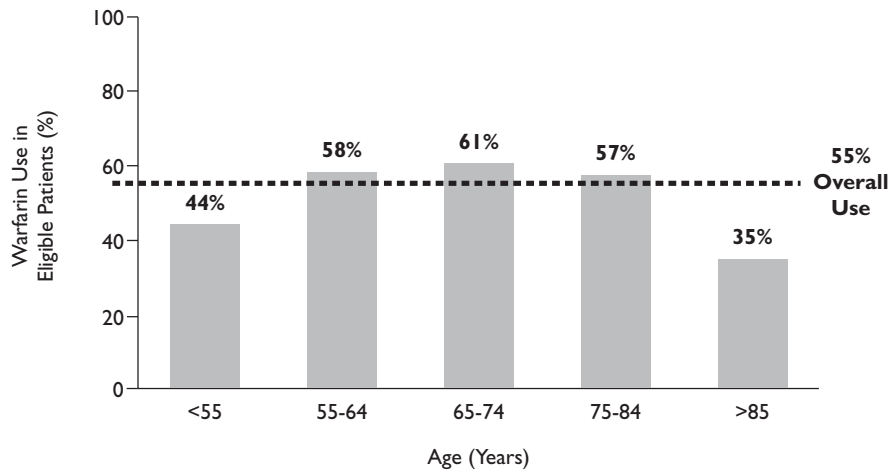
Although the evidence supporting warfarin efficacy in stroke prevention leaves little room for interpretation, the practical limitations associated with this oral anticoagulant are equally clear. The array of warfarin limitations include delayed onset of action (3-5 days to achieve an antithrombotic effect), highly variable dose-response effect, a narrow therapeutic index, drug-drug interactions, drug-food interactions (eg, dietary vitamin K and excessive alcohol), and disease state interactions. These inherent limitations of warfarin create the need for routine coagulation monitoring, a need that has been addressed in many healthcare settings by the implementation of anticoagulation clinics. But even within the supportive environment of the anticoagula-

tion clinic, patients and physicians have problems initiating and adhering to warfarin therapy. In most clinical practice settings outside of the artificial clinical study setting, warfarin is underutilized. And even when the drug is initiated, the intensity of anticoagulation is often too low.

Underutilization of Warfarin

A growing body of evidence indicates that warfarin is routinely underutilized for stroke prevention in patients with AF. For example, in a quality-of-care report recently published by the Centers for Medicare & Medicaid Services, only 57% of inpatients were found to receive warfarin for AF.² One of the earliest summaries documenting the extent of warfarin underutilization came from the Clinical Quality Improvement Network in Canada, a group that evaluated 3575 patients diagnosed with AF as they were leaving 1 of 12 study hospitals.²⁵ Although 24% of patients were released with a prescription for warfarin, 30% for aspirin, and 8% for both antithrombotics, 33% of patients left the hospital without any kind of stroke prevention medication.

Similar levels of warfarin underutilization have been demonstrated in ambulatory patients, a population that is generally younger and with less comorbid disease. A large health maintenance organization (HMO) reviewed warfarin use in the 3 months before or after AF diagnosis in 11 082

Figure 2. Warfarin Use in 11082 Ambulatory Patients with Atrial Fibrillation

Source: Reference 18.

patients with nonvalvular AF and no known contraindications to the antithrombotic agent.²⁰ Overall, 55% of these warfarin-eligible patients were actually using the drug, with the lowest rates seen in the oldest patients—the group that is at highest risk of stroke (Figure 2). Although the overall level of utilization in this HMO was actually higher than that reported in previous analyses of outpatients, the authors still conclude that interventions are needed to increase the use of warfarin among appropriate candidates.

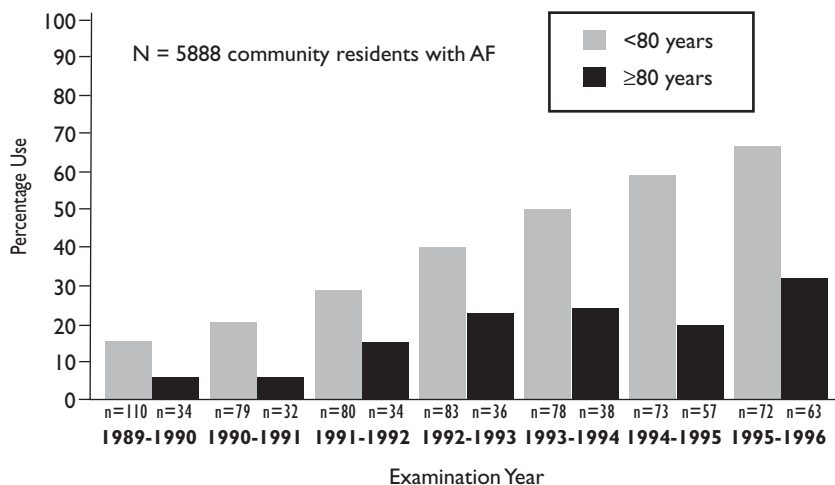
More recently, warfarin use was evaluated in 429 residents of a Connecticut long-term care facility who had AF.²⁶ Overall, only 42% of these individuals (mean age, 87 years) were receiving warfarin; more than 30% of at-risk residents received neither aspirin nor warfarin. Even among the 83 patients identified as ideal candidates for warfarin (ie, no risk factor for hemorrhage), only 44 (53%) received warfarin. The extreme level of physician caution in warfarin prescribing in the elderly is also reflected in this study's finding that INR values were within the therapeutic range only 51% of the time.

In patients with AF and a recent history of stroke, warfarin utilization is also disturbingly low. In a study tracking 278 Medicare patients with AF discharged following ischemic stroke, the rate of warfarin use was 78% in patients 65 to 74 years of age,

58% in those 75 to 84 years of age, and only 31% in patients 85 years of age or older.²⁷

Finally, clinicians should be aware that warfarin use might be even less prevalent among patients of lower socioeconomic status. A recent evaluation of 11 699 Ohio Medicaid patients with new-onset nonvalvular AF showed that only 12% of these individuals who had no apparent contraindications (and only 10% of all patients) filled a prescription for warfarin in the week before or the month after development of AF.²⁸ Factors that predicted decreased use of warfarin included age younger than 55 years or 85 years and older, past intracranial or gastrointestinal hemorrhage, and alcohol or drug abuse. Homelessness, psychiatric disease, and a lack of a caregiver were also noted by the authors as possible causes of low warfarin prescribing.

This discouraging snapshot of current warfarin use patterns should be viewed in historical perspective. During the past decade, there have been encouraging trends in the proper utilization of warfarin in stroke prevention. In particular, following the publication of the major randomized trials with warfarin and the treatment guidelines based on these trials, the overall outpatient use of oral anticoagulation steadily increased from below 10% in the early 1980s to as high as 50% in the mid-1990s.^{29,30} As shown in

Figure 3. Slow Gains in Warfarin Utilization

AF indicates atrial fibrillation.

Source: Reference 29.

Figure 3, a community-based study of anticoagulation use in nearly 6000 patients with AF identified on electrocardiograms showed that overall use of warfarin increased 4-fold from 13% in 1990 to about 50% in 1996 ($P < .001$).²⁹ Such steady improvement in appropriate anticoagulation over the years has been attributed in some settings to the emergence of anticoagulation clinics to help manage the complex monitoring of warfarin therapy. These clinics typically provide a structured environment for patient education and counseling, order and review of INR test results, make dosing adjustments, and provide consultations related to issues such as whether to provide bridge therapy during temporary discontinuation of warfarin before invasive procedures. However, even while viewing the generally positive temporal trend of anticoagulant use in AF depicted in Figure 3, it should be noted that patients older than 80 years of age are still significantly less likely to receive warfarin ($P < .001$).²⁹

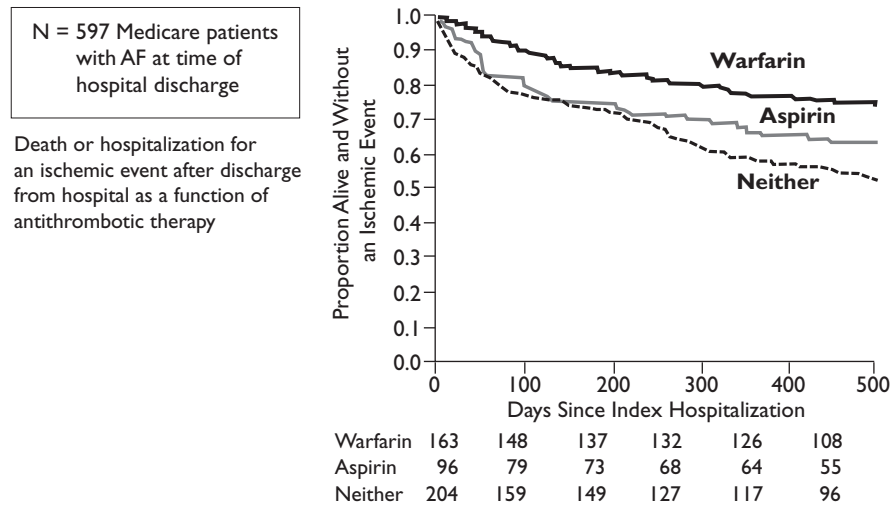
The consequences of underuse of appropriate antithrombotic therapy were recently made clear in a study of nearly 600 Medicare patients with long-term AF.²¹ Similar to the utilization studies, only 328 (55%) of the 597 patients received some form of antithrombotic therapy at discharge—34% warfarin and 21% aspirin. The rates of thrombotic

events were measured in these elderly frail patients (a group typically excluded from randomized clinical trials) during a 2-year period. As shown in **Figure 4**, the proportion of patients having no ischemic events or deaths from any cause was lower in patients receiving warfarin versus those not receiving therapy or aspirin. Warfarin was associated with a relative risk reduction of 24% ($P = .003$). The risk reduction associated with aspirin was only 5% ($P = .56$).

Underanticoagulation with Warfarin

In improving the quality of anticoagulation therapy for stroke prevention, clinicians and health systems must not only strive to place more of their appropriately screened AF patients on warfarin regimens, but also to ensure that these patients are maintained within the proper therapeutic range. An INR range of 2.0 to 3.0 is the widely accepted goal for most patients with nonvalvular AF.^{1,24} Insufficient dosing of warfarin (with INR below 2.0) can lead to ischemic stroke and death, whereas excessive dosing (INR above 4.0) increases the risk of intracranial bleeding.³¹⁻³³ Although this numerical INR range is widely understood by clinicians, what is less appreciated is that the slope of increased bleeding risk associated with INR over 3.0 is not as steep as the slope of increased stroke risk for INRs

Figure 4. Adverse Outcomes Associated with Underuse of Warfarin



AF indicates atrial fibrillation.
 Source: Reference 21.

below 2.0 (**Figure 5**).^{31,32} In other words, underanticoagulation may be riskier than overcoagulation. And so, notwithstanding the natural clinician tendency to “first do no harm,” it is absolutely critical to maintain the INR above the lower limit of the therapeutic range. An INR of 1.5 or 1.7 is dramatically less effective in preventing stroke in most patients with AF, but is unfortunately all too common in everyday clinical practice.

One retrospective study evaluated the proportion of time that 660 patients with AF managed by internists or family practitioners were maintained within their INR goal. In the one third of the group (34.7%) that was actually receiving warfarin therapy, the INR values were out of range more than half of the time; 38.2% were below 2.0 and 18.2% were above 3.0.³⁴ Practices with access to anticoagulation clinics had slightly higher rates of within-goal INRs, but even such relatively intensive management will likely achieve anticoagulation goals only 65% or 70% of the time. Overall, this evaluation points out the current magnitude of ineffectiveness with oral anticoagulation. If this study reflects the facts in most clinical practices today, which it likely does, then about 65% of AF patients seen in primary care are not receiving any warfarin, 6% are above INR range, 13% are below range, and only 15% of

these eligible patients are being treated and are within INR range.³⁴

The clinical impact of subtherapeutic anticoagulation with warfarin has been explored in a recent study by Hylek and colleagues.³³ In almost 600 patients with AF presenting to a hospital with ischemic stroke, 32% were receiving warfarin therapy. Warfarin-treated patients with an INR of less than 2.0 at the time of admission were much more likely to have a fatal or severe stroke event. In patients with INRs below or above 2.0, the rates of fatal stroke were 9% and 1%, respectively, and the rates of major stroke (ie, patients not independent in their day-to-day functioning) were 44% and 38%, respectively. Overall, 59% of warfarin-treated patients with INRs below 2.0 had a severe stroke as defined across 3 categories compared with 43% of patients with INRs above 2.0 (odds ratio, 1.9; 95% confidence interval [CI]; INR, 1.1-3.4). In addition, those patients maintained above the 2.0 INR had a lower 30-day mortality rate compared with those below their INR target (hazard ratio, 3.4; 95% CI; INR, 1.1-10.1). In fact, the 30-day mortality rate among warfarin-treated patients below INR 2.0 was similar to that seen in AF patients taking only aspirin (**Figure 6**).³³ Thus, INRs above 2.0 not only reduce the frequency of stroke in patients

with AF but also stroke severity and stroke-related mortality.

Prophylaxis of VTE

The rate of VTE is estimated to occur in 48 of 100 000 persons, and the rate of those with DVT and PE is estimated to occur in 69 of 100 000 persons.³⁵ The average death rate from PE is about 8%, which usually occurs during the first 30 days of onset.³⁶

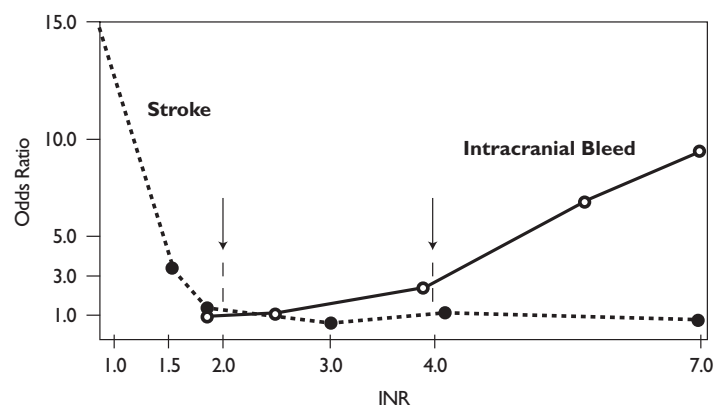
The ACCP has determined that the risk of VTE without prophylaxis is substantial (Table 3); in the group of patients at highest risk for VTE, such as those undergoing orthopedic surgery, the risk of fatal PE approaches 5%.³⁷

However, the risk of VTE can be greatly reduced with timely anticoagulation (Table 4).^{37,38} Despite the ongoing controversies about the selection of individual drugs for VTE prophylaxis (eg, unfractionated heparin vs low-molecular-weight heparin in the medically ill patient) and timing of the initiation of prophylaxis (eg, pre- or postoperative administration), there is clearly a large number of surgical and medical patients who stand to benefit from VTE prophylaxis.

For long-term prevention of recurrent VTE, warfarin is increasingly being administered beyond the acute phase, and in some cases the outpatient oral anticoagulation is continued indefinitely.³⁹⁻⁴³ Current guidelines call for individualization of therapy based on the patient's underlying risk for recurrence as well as the risk of bleeding; for example, patients with a first DVT and reversible risk factors such as surgery, immobilization, or trauma should receive 3 to 6 months of warfarin.^{37,43,44,45}

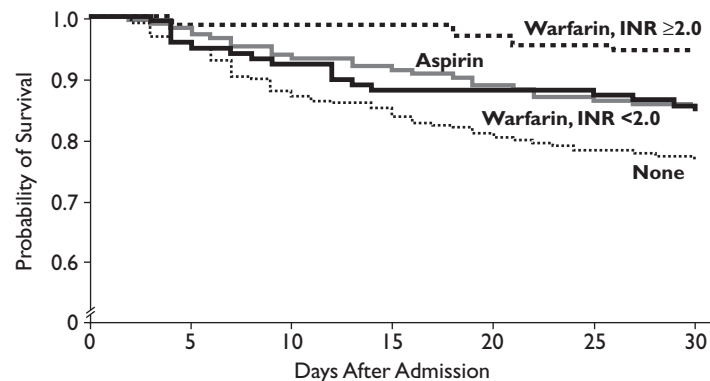
Unfortunately, as with AF, a large body of literature now documents the underutilization in high-risk patients, such as those undergoing surgery or who are medically ill. One of the largest and most recent studies gauging the level of adequate anticoagulation for VTE was the DVT FREE Registry, a coordinated effort that prospectively evaluated 5451 patients with DVT from 183 different clinical sites around the United States.⁴⁶ Of the 2726 patients who had DVT diagnosed while in the hospital, only 1147 (42%) had received prophylaxis in the past 30 days.

Figure 5. Balancing Risks in AF Patients on Warfarin: INR at Time of Event



AF indicates atrial fibrillation; INR, international normalized ratio. The 2 lines represent 2 separate studies. The solid line indicates the risk of hemorrhage associated which increases with overanticoagulation. The dashed line indicates the risk of stroke, which increases with underanticoagulation. Sources: References 31, 32.

Figure 6. Effect of Intensity of Oral Anticoagulation on Stroke-related 30-day Mortality (n = 596 Patients with Atrial Fibrillation and Ischemic Strokes)



INR indicates international normalized ratio. Source: Reference 33.

Another registry-based study evaluating prophylaxis of DVT/PE is the National Anticoagulation Benchmark and Outcomes Report (NABOR) Project.⁴⁷ This large ongoing study has already found that 14.4% of orthopedic surgery patients—who are at extremely high risk for VTE—had received either inadequate prophylaxis (ie, aspirin) or none at all. Also, although current evidence supports continuing anticoagulation

Table 3. Risk of Venous Thromboembolism Without Prophylaxis

	Low Risk, %	Moderate Risk, %	High Risk, %	Highest Risk, %
Calf DVT	2	10-20	20-40	40-80
Proximal DVT	0.4	2-4	4-8	10-20
Clinical PE	0.2	1-2	2-4	4-10
Fatal PE	0.002	0.1-0.4	0.5-1	0.2-5

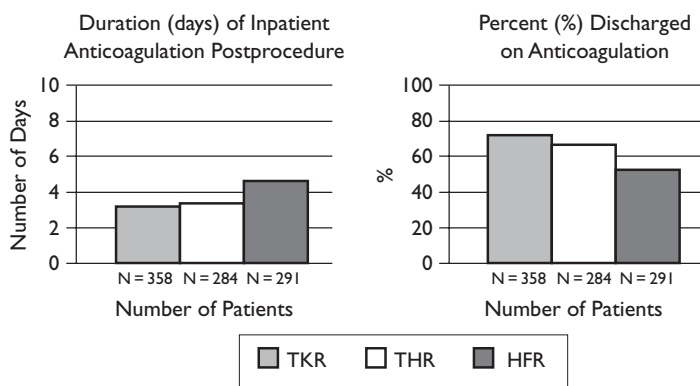
DVT indicates deep vein thromboembolism; PE, pulmonary embolism.
 Source: Reference 34.

Table 4. Recommendations on Prophylaxis of Venous Thromboembolism

Low Risk, %	Moderate Risk	High Risk	Highest Risk
Early ambulation	LDUH (q12h) LMWH IPC ES	LDUH (q8-12h) LMWH IPC	LMWH Oral anticoagulants IPC/ES + LMWH/LDUH Adjusted-dose UFH

LDUH indicates low-dose unfractionated heparin; LMWH, low-molecular-weight heparin; IPC, intermittent pneumatic compression; ES, electrical stimulation; UFH, unfractionated heparin.
 Source: Reference 34.

Figure 7. Inadequate Duration of Anticoagulation Prophylaxis for Orthopedic Surgery



TKR indicates total knee replacement; THR, total hip replacement; HFR, hip fracture repair.

for a minimum of 7 to 10 days, and possibly as long as 30 days, in this surgical setting, the NABOR data indicate that most patients having major orthopedic surgery are receiving only 3 to 5 days of anticoagu-

lation (Figure 7). This inadequate average duration of prophylaxis can undoubtedly be attributed in some measure to the trend toward shorter hospital stays after surgery. But even as the postsurgical inpatient recovery time is truncated, only about 70% of patients having total knee or hip replacement are discharged with anticoagulation.

Summary

Anticoagulation offers a clear benefit in patients with AF, and clinical guidelines have been developed to support anticoagulation with warfarin for stroke prevention. However, the inherent properties of warfarin related to bleeding risk and the requirement for therapeutic monitoring have contributed to a vast underutilization of this oral therapy to prevent stroke in patients with AF. Furthermore, in those patients who are maintained on warfarin, physician and patient reluctance to pursue the goal INR between 2.0 and 3.0 contributes to widespread underanticoagulation. Thus, although

it remains the most widely used oral anticoagulant in North America,⁴⁷ this vitamin K antagonist has never achieved in everyday clinical practice the levels of stroke reduction proved in formal clinical trials. In the area of VTE prophylaxis, anticoagulants are similarly underutilized.⁴⁸ Again, although the benefits of extended anticoagulation in settings such as orthopedic surgery are clear, the actual initiation and intensity of anticoagulation falls well short of the standard set by national guidelines. In the roundtable discussion, which appears in this supplement, the potential causes of suboptimal anticoagulation are explored along with the economic implications of such a gap between clinical studies and clinical reality. In the concluding article, the potential of novel antithrombotic therapies to close this treatment gap is briefly reviewed.

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REFERENCES

1. Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients with Atrial Fibrillation): developed in collaboration with the North American Society of Pacing and Electrophysiology. *J Am Coll Cardiol.* 2001;38:1231-1266.
2. American Heart Association. *Heart Disease and Stroke Statistics—2004 Update.* Dallas, Tex: American Heart Association; 2003.
3. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *JAMA.* 2001;285:2370-2375.
4. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke.* 1991;22:983-988.
5. Nakayama T, Date C, Yokoyama T, Yoshiike N, Yamaguchi M, Tanaka H. A 15.5-year follow-up study of stroke in a Japanese provincial city. The Shibata study. *Stroke.* 1997;28:45-52.
6. Onundarson PT, Thorgeirsson G, Jonmundsson E, Sigfusson N, Hardarson T. Chronic atrial fibrillation—epidemiologic features and 14 year follow-up: a case control study. *Eur Heart J.* 1987;8:521-527.
7. Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ. Epidemiology and natural history of atrial fibrillation: clinical implications. *J Am Coll Cardiol.* 2001;37:371-378.
8. Prevalence of disabilities and associated health conditions among adults—United States, 1999. *MMWR Morb Mortal Wkly Rep.* 2001;50:120-125.
9. Taylor TN, Davis PH, Torner JC, Holmes J, Meyer JW, Jacobson MF. Lifetime cost of stroke in the United States. *Stroke.* 1996;27:1459-1466.
10. McNamara RL, Tamariz LJ, Segal JB, Bass EB. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. *Ann Intern Med.* 2003;139:1018-1033.
11. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet.* 1989;1:175-179.
12. Cairns JA. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation.* 1991;84:527-539.
13. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. *N Engl J Med.* 1990;323:1505-1511.
14. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) study. *J Am Coll Cardiol.* 1991;18:349-355.
15. Ezekowitz MD, Bridgers SL, James KE, et al. Warfarin in the prevention of stroke associated with non-rheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *N Engl J Med.* 1992;327:1406-1412.
16. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet.* 1993;342:1255-1262.
17. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med.* 1994;154:1449-1457.
18. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med.* 1999;131:492-501.
19. Go AS. Efficacy of anticoagulation for stroke prevention and risk stratification in atrial fibrillation: translating trials into clinical practice. *Am J Manag Care.* 2004;10: S58-S65.
20. Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *Ann Intern Med.* 1999;131:927-934.
21. Gage BF, Boechler M, Doggette AL, et al. Adverse outcomes and predictors of underuse of antithrombotic therapy in Medicare beneficiaries with chronic atrial fibrillation. *Stroke.* 2000;31:822-827.
22. Evans A, Perez I, Yu G, Kalra L. Should stroke subtype influence anticoagulation decisions to prevent recurrence in stroke patients with atrial fibrillation? *Stroke.* 2001;32:2828-2832.
23. Frost L, Johnsen SP, Pedersen L, Toft E, Husted S, Sorensen HT. Atrial fibrillation or flutter and stroke: a Danish population-based study of the effectiveness of oral anticoagulation in clinical practice. *J Intern Med.* 2002;252:64-69.
24. Albers GW, Dalen JE, Laupacis A, Manning WJ, Petersen P, Singer DE. Antithrombotic therapy in atrial fibrillation. *Chest.* 2001;119:194S-206S.
25. Thromboembolic prophylaxis in 3575 hospitalized patients with atrial fibrillation. The Clinical Quality

- Improvement Network (CQIN) Investigators. *Can J Cardiol*. 1998;14:695-702.
26. **McCormick D, Gurwitz JH, Goldberg RJ, et al.** Prevalence and quality of warfarin use for patients with atrial fibrillation in the long-term care setting. *Arch Intern Med*. 2001;161:2458-2463.
27. **Brass LM, Krumholz HM, Scinto JD, Mathur D, Radford M.** Warfarin use following ischemic stroke among Medicare patients with atrial fibrillation. *Arch Intern Med*. 1998;158:2093-2100.
28. **Johnston JA, Cluxton RJ Jr, Heaton PC, Guo JJ, Moomaw CJ, Eckman MH.** Predictors of warfarin use among Ohio Medicaid patients with new-onset non-valvular atrial fibrillation. *Arch Intern Med*. 2003;163:1705-1710.
29. **Smith NL, Psaty BM, Furberg CD, et al.** Temporal trends in the use of anticoagulants among older adults with atrial fibrillation. *Arch Intern Med*. 1999;159:1574-1578.
30. **Stafford RS, Singer DE.** Recent national patterns of warfarin use in atrial fibrillation. *Circulation*. 1998;97:1231-1233.
31. **Hylek EM, Singer DE.** Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med*. 1994;120:897-902.
32. **Hylek EM, Skates SJ, Sheehan MA, Singer DE.** An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *N Engl J Med*. 1996;335:540-546.
33. **Hylek EM, Go AS, Chang Y, et al.** Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med*. 2003;349:1019-1026.
34. **Samsa GP, Matchar DB, Goldstein LB, et al.** Quality of anticoagulation management among patients with atrial fibrillation: results of a review of medical records from 2 communities. *Arch Intern Med*. 2000;160:967-973.
35. **Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melto LJ 3rd.** Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med*. 1998;158:585-593.
36. **Stein PD, Kayali F, Olson RE.** Estimated case fatality rate of pulmonary embolism, 1979 to 1998. *Am J Cardiol*. 2004;93:1197-1199.
37. **Geerts WH, Heit JA, Clagett GP, et al.** Prevention of venous thromboembolism. *Chest*. 2001;119(1 suppl):132S-175S.
38. **Mismetti P, Laporte-Simitsidis S, Tardy B, et al.** Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. *Thromb Haemost*. 2000;83:14-19.
39. **Kearon C, Gent M, Hirsh J, et al.** A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med*. 1999;340:901-907.
40. **Schulman S, Granqvist S, Holmstrom M, et al.** The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. The Duration of Anticoagulation Trial Study Group. *N Engl J Med*. 1997;336:393-398.
41. **Agnelli G, Prandoni P, Santamaria MG, et al.** Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. *N Engl J Med*. 2001;345:165-169.
42. **Ridker PM, Goldhaber SZ, Danielson E, et al.** Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med*. 2003;348:1425-1434.
43. **Kearon C, Ginsberg JS, Kovacs MJ, et al.** Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med*. 2003;349:631-639.
44. **Hirsh J, Fuster V, Ansell J, et al.** American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *J Am Coll Cardiol*. 2003;41:1633-1652.
45. **Hyers TM, Agnelli G, Hull RD, et al.** Antithrombotic therapy for venous thromboembolic disease. *Chest*. 2001;119:176S-193S.
46. **Goldhaber SZ, Tapson VF; DVT FREE Steering Committee.** A prospective registry of 5,451 patients with ultrasound-confirmed deep vein thrombosis. *Am J Cardiol*. 2004;93:259-262.
47. **Caprini JA, Ballard DJ, Becker RC, et al.** Disparities in antithrombotic management. *Circulation*. 2004;109(20):e231-84 (abstract P148).
48. **Nutescu EA.** Antithrombotic therapy for the treatment of venous thromboembolism. *Am J Manag Care*. 2003;9:S103-S114.