Adequacy of Anticoagulation in Patients with Atrial Fibrillation: Effect of Various Parameters

NATAN COHEN, M.D., DORIT ALMOZNINO-SARAFIAN, M.D., IRENA ALON, M.D., OLEG GORELIK, M.D., MARGARITA KOOPFER, M.D., SHULAMIT CHACHASHVILY, M.D., MIRIAM SHTEINSHNAIDER, M.D., VLADIMIR LITVINJUK, M.D., DAVID MODAI, M.D.

Department of Internal Medicine "F," Assaf Harofeh Medical Center (affiliated to Sackler School of Medicine, Tel Aviv University), Zerifin, Israel

Summary

Background: Despite reported evidence of the vital importance of appropriate anticoagulation in patients with chronic atrial fibrillation for stroke prevention, this treatment modality still lags behind optimal requirements.

Hypothesis: Our objectives were to evaluate various doctor- or patient-related factors that influence quality of control and to assess the adequacy of anticoagulation provided by physicians in the community.

Methods: In a retrospective study, International Normalized Ratio (INR) values obtained immediately on admission to hospital were considered representative of previous long-term control.

Results: Only 42% of the relevant 385 patient population fell within the protective anticoagulation range of INR 1.91–4.1. The respective figures for patients with poor (INR < 1.5) or suboptimal (INR 1.51–1.9) control, as well as those whose INR values risked bleeding (INR > 4.1), were 28.3, 14.1, and 15.6%. Patient involvement in treatment positively influenced quality of control. By contrast, age 70–80 years or absence of congestive heart failure negatively affected quality of anticoagulation [$p = 0.07$, odds ratio (OR), 1.7 (95% confidence interval, 0.94–3.08), $p = 0.014$, OR, 2.06 (95% confidence interval, 1.15–3.7) respectively]. The percentage of patients admitted with stroke who had been adequately anticoagulated was significantly lower than that of patients who had no stroke (21 vs. 44.4%). Adequacy of anticoagulation in patients with cardiac prosthetic valves was superior compared with the rest

of the patient population (56.7 vs. 42% with optimal, and only 14.5 vs. 28.3% with poor anticoagulation, respectively), indicating that under the same conditions a better quality of treatment could be achieved.

A related editorial appears on page 355.

Conclusions: Adequacy of anticoagulation in patients with atrial fibrillation lags behind actual recommendations. Better control is required and achievable.

Key words: atrial fibrillation, stroke, anticoagulation, International Normalized Ratio control, follow-up

Introduction

The significant effect of anticoagulation in the prevention of cardioembolic complications in patients with chronic atrial fibrillation has been firmly established in recent years. The rate of stroke has been reduced by two-thirds in patients treated with warfarin.^{1–4}

In a recent publication, recommended guidelines for anticoagulation have been defined (The ACCP Consensus Conference 1998).¹ Despite consensus in the recent literature, a considerable percentage of patients eligible for anticoagulation do not get this treatment.^{5–10} Moreover, the quality of anticoagulation in some of those treated is inadequate;^{11–18} thus, one could anticipate that appropriate anticoagulation would result in a greater reduction of stroke incidence in this patient population.¹¹

The present study was undertaken to evaluate the eventual effects of various factors that could influence adequacy of long-term anticoagulation in such patients in an ambulatory setting. Special attention was paid to factors that produced deviations from protective ranges of anticoagulation. All patients reside in one region of Israel and are served, when required, by the same regional medical center. The factors evaluated included demographic and clinical data as well as the impact of patient cooperation.

Address for reprints:

Natan Cohen, M.D.
Department of Internal Medicine "F"
Assaf Harofeh Medical Center
Zerifin 70300, Israel

Received: March 10, 2000

Accepted with revision: July 19, 2000

Patients and Methods

Background

This study was conducted at Assaf Harofeh Medical Center. This 600-bed regional university hospital entirely serves a population that increased from 320,000 in 1989 to 380,000 in 1997, mainly by absorption of new immigrants from the previous Soviet Union. Patients were treated by family physicians who were general practitioners and by specialists in family medicine or internal medicine, with heterogeneous professional backgrounds and experience.

Patients

The charts of all patients admitted between 1990 and 1998 to this medical center with chronic atrial fibrillation as one of the diagnoses (ICD-9-CM, diagnostic code 427.3.1) were reviewed by physicians who were members of this medical department. In this review, the code of atrial fibrillation was verified by comparison with the same diagnosis as registered by the summarizing physician in the chart. Thus, any registration error using the diagnostic code only was avoided. For those on warfarin, International Normalized Ratio (INR) values were determined on admission. Patients who were referred for inappropriate or risky anticoagulation were excluded.

All patients had been maintained on warfarin for at least 3 months prior to admission, INR being monitored by the family physician and executed in a general medical laboratory. The INR assessed on admission was considered representative of all values of the preceding period.

Methods

In order to evaluate eventual effects of various factors on adequacy of anticoagulation, a wide spectrum of parameters was statistically analyzed and grouped under the following headings.

Demographic factors: Gender, age, duration of residence in Israel, and command of the Hebrew language.

Clinical parameters: Known risk factors for cardioembolic stroke, including previous stroke or transient ischemic attack (TIA), congestive heart failure (CHF), hypertension, diabetes mellitus (DM), or ischemic heart disease (IHD).

Patient involvement: Three months or more following discharge, patients were contacted by phone and asked a number of questions by which their degree of involvement in their warfarin treatment could be defined. Accordingly, they were classified into the following groups: (1) mere awareness of the last and previous sequential INR values; (2) active patient involvement in warfarin treatment including awareness of the risks and advantages involved, and active participation in warfarin management. To avoid interrogator-related variability of replies, all patients were questioned by the same investigator (D.A.).

All of these data were compared with the respective INR values of the same patient obtained on previous admission, to which the patient was blinded.

Diagnosis on admission: Adequacy of anticoagulation was assessed in patients in whom the last admission was due to ischemic stroke, hemorrhage, or a different diagnosis.

Comparison with a group of patients with cardiac prosthetic valves: A group of patients with atrial fibrillation carrying mechanical or biological prosthetic valves served as a yardstick for optimal anticoagulation. As such, they were compared with the rest of the patients.

Assessment of Treatment Adequacy

All INR results were classified into the following four ranges, ranked according to adequacy of anticoagulation: (1) INR < 1.5, inadequate; (2) INR 1.51–1.9, borderline (these ranges have been so defined in accordance with references in the literature indicating that they confer partial protection from stroke^{19, 20}); (3) INR 1.91–4.1, protective anticoagulation,²¹ providing protection from stroke for patients with²² and without prosthetic valves while the risk of bleeding is minimal;^{1, 21} (4) INR > 4.11, associated with an increased bleeding risk.¹

Statistical Analysis

The comparison with respect to the adequacy of treatment at four anticoagulation categories was done using the chi-square test. For patients with more than one hospitalization, only the most recent one was included in the analysis. Statistical significance was set at $p \leq 0.05$. In another statistical analysis, the patient group without prosthetic valves was analyzed, this time using only two anticoagulation categories, namely, INR 1.91–4.1, defined protective, versus all the rest of the patients who were inadequately anticoagulated (INR < 1.5, 1.51–1.9, > 4.11). The chi-square test was used again and significance level was set at $p \leq 0.05$. In a second stage, logistic regression analysis was used to identify independent variables associated with poor anticoagulation. Variables found to be significant at $p < 0.2$ were introduced into the logistic model.

Results

Quality of Anticoagulation According to Demographic and Clinical Parameters

The study group included 74 patients with and 385 patients without prosthetic valves. Four patients of the former subgroup had caged ball valves. Table I depicts INR values of the 385 patients, divided into the four classical ranges. None of the demographic or clinical data emerged as significant on statistical analysis.

Subsequently, after classification of the spectrum of INR values into two ranges, that is, those conferring protection (1.91–4.1) versus inadequate anticoagulation (namely, all the rest), only the group of patients aged 70–80 years emerged as inadequately anticoagulated compared with the rest of the patients ($p = 0.01$).

On multivariate analysis, the age group of 70–80 years emerged again, this time as an independent variable, as being less adequately controlled than the younger or older age

TABLE I Patient characteristics and adequacy of anticoagulation

	Number of patients	Number and percent (%) of patients with				p Value
		Adequate anticoagulation INR 1.91–4.1	Borderline anticoagulation INR 1.51–1.9	Inadequate anticoagulation INR < 1.5	Increased bleeding risk INR > 4.11	
Entire group	385	162 (42.0)	54 (14.0)	109 (28.3)	60 (15.5)	0.103
Males	168	70 (41.6)	29 (17.2)	41 (24.4)	28 (16.9)	
Females	217	90 (41.4)	25 (11.5)	69 (31.7)	33 (15.2)	
Age ≤ 70	168	78 (46.3)	23 (13.6)	42 (25.0)	25 (14.8)	0.227
Age 70–80	164	56 (34.1)	24 (14.6)	53 (32.3)	31 (18.9)	
Age > 80	53	28 (52.8)	7 (13.2)	14 (26.4)	4 (7.5)	
Satisfactory command of Hebrew ^a	280	118 (42.1)	40 (14.2)	83 (29.6)	39 (13.9)	0.666
Poor command of Hebrew	78	35 (44.8)	12 (15.3)	17 (21.7)	14 (17.9)	0.736
Hospitalized before 1994	110	43 (39.0)	14 (12.7)	36 (32.7)	17 (15.4)	
Hospitalized since 1995	275	118 (42.9)	39 (14.1)	75 (27.2)	43 (15.6)	
Years in Israel < 5 ^b	37	16 (43.2)	4 (10.8)	9 (24.3)	8 (21.6)	0.775
Years in Israel > 5	285	125 (43.8)	44 (15.4)	75 (26.3)	41 (14.3)	0.742
Atrial diameter < 4.5 cm ^c	91	41 (45.0)	13 (14.2)	28 (30.7)	9 (9.8)	
Atrial diameter > 4.5 cm	205	83 (40.6)	27 (13.1)	63 (30.7)	32 (15.6)	
Hypertension	221	93 (42.0)	33 (14.9)	62 (28.0)	33 (14.9)	0.963
No hypertension	164	69 (42.0)	21 (12.8)	47 (28.6)	27 (16.4)	0.376
Congestive heart failure	237	107 (45.1)	35 (14.7)	59 (24.8)	36 (15.1)	
No congestive heart failure	148	55 (37.1)	19 (12.8)	50 (33.7)	24 (16.2)	
Past history of stroke	106	42 (39.6)	16 (15.0)	33 (31.1)	15 (14.1)	0.451
No past history of stroke	279	120 (43.0)	38 (13.6)	76 (27.2)	45 (16.1)	0.338
Diabetes mellitus	112	41 (36.6)	17 (15.1)	38 (33.9)	16 (14.2)	
No diabetes mellitus	273	121 (44.3)	37 (13.5)	71 (26.0)	44 (16.1)	
Hypercholesterolemia	88	37 (42.0)	10 (11.3)	28 (31.8)	13 (14.7)	0.759
No hypercholesterolemia	297	125 (42.0)	44 (14.8)	81 (27.2)	47 (15.8)	0.232
Coronary heart disease	222	98 (44.3)	35 (15.7)	53 (23.8)	36 (16.2)	
No coronary heart disease	163	64 (39.2)	19 (11.6)	56 (34.3)	24 (14.7)	

^a Missing data for 27 (7%) of patients.^b Missing data for 63 (16.3%) of patients.^c Echocardiographic data were available for 296 patients.

Abbreviation: INR = International Normalized Ratio.

groups; $p = 0.076$ OR 1.702 [95% confidence interval (CI), 0.94–3.08]. Moreover, absence of CHF emerged as an independently significant risk for worse anticoagulation [$p = 0.014$, OR 2.06 (95% CI, 1.15–3.70)].

The Effect of Patient Involvement on Quality of Anticoagulation

Patient awareness of their exact INR values correlated significantly ($p = 0.021$) with better control (Table II). Thus, 55.9% of this group had an INR range of 1.91–4.1 on admission compared with 31.0% of those blinded to their INR values. Moreover, the respective percentages of patients with an INR < 1.5 were 17.8 versus 33.3%.

Of the patients actively involved in their treatment, 60.1% had an INR of 1.91–4.1 on admission compared with 42.1% of those not involved. The respective percentages of patients admitted with INR values exceeding 4.11 were 3.3 versus 16.8%.

The Effect of Adequacy of Anticoagulation on Admission Diagnosis

The correlation between adequacy of anticoagulation and the diagnosis on the most recent admission was analyzed and found to be highly significant ($p = 0.001$) (Table II). Thus, 48.4% of the stroke patients were poorly anticoagulated (INR < 1.5) and 64.2% of patients with hemorrhage had risky INR (> 4.11). The respective INR values for the noncomplicated group (the rest of the patients) were 25.7 and 14.2%.

Comparison between Patient Groups with or without Prosthetic Valves

A significant statistical difference between the two groups was evident ($p = 0.05$). As can be seen (Table II), the group with prosthetic valves was better anticoagulated, 56.7 versus 42%, with an INR of 1.91–4.1. Moreover, 28.3% of the patients with-

TABLE II Effects on adequacy of anticoagulation of patient cooperation, diagnosis on admission, and a comparison with the group of patients with prosthetic valves

		Number and percent (%) of patients with				
	Number of patients	Adequate anticoagulation INR 1.91–4.1	Borderline anticoagulation INR 1.51–1.9	Inadequate anticoagulation INR < 1.5	Increased bleeding risk INR >4.11	p Value
Degree of patient involvement in treatment						
Patients actively involved in treatment	30	18 (60.1)	3 (10.0)	8 (26.6)	1 (3.3)	0.168
Patients not involved in treatment	83	35 (42.1)	15 (18.0)	19 (22.8)	14 (16.8)	
Patients aware of their INR results	84	47 (55.9)	10 (11.9)	15 (17.8)	12 (14.2)	0.021
Patients not aware of their INR results	87	27 (31.0)	15 (17.2)	29 (33.3)	16 (18.3)	
Quality of anticoagulation against diagnosis on admission						
Patients admitted with stroke	33	7 (21.2)	7 (21.2)	16 (48.4)	3 (9.0)	0.001
Patients admitted with hemorrhage	14	5 (35.7)	0 (0)	0 (0)	9 (64.2)	
Remaining patients	245	109 (44.4)	38 (15.5)	63 (25.7)	35 (14.2)	
Comparison with a group of patients with cardiac prosthetic valve						
Patients with prosthetic valves	74	42 (56.7)	12 (16.2)	11 (14.8)	9 (12.1)	0.05
Patients without prosthetic valves	385	162 (42.0)	54 (14.0)	109 (28.3)	60 (15.5)	

out prosthetic valves were poorly anticoagulated (INR < 1.5) compared with only 14.48% of the prosthetic valve group.

Discussion

The effectiveness of anticoagulation in preventing cardioembolic events in patients with nonrheumatic atrial fibrillation has been proved repeatedly.^{1–4} Implementation of this concept depends on a variety of factors, some doctor related and some patient dependent. Moreover, the quality of anticoagulation is greatly affected by the nature of the setting, that is, specialized anticoagulation clinic,^{13, 15} long-term care facility,¹⁴ health management organization,^{13, 16} or other.¹⁵ In addition, the design of the study, prospective or retrospective, and the frequency of INR determinations exert a significant impact on adequacy of control.

In the majority of studies published in the last 15 years, a wide diversity prevails with respect to the laboratory methods used to estimate anticoagulation, that is, INR versus prothrombin ratio (PTR); the goals for optimal therapeutic range; and methods of presentation of results, namely, percent of within-range sequential results per patient versus percent of patients presenting with adequate anticoagulation at any given time.^{2, 11–16} Accordingly, within the period covered by the present retrospective study, the definition of adequate ranges of anticoagulation has varied with results of ongoing reports. Regardless of the methods and the setting, review of the literature indicates that the quality of anticoagulation has not improved over the years. With few exceptions, the percentage of patients adequately anticoagulated has generally remained in the range of 40–60%,^{11–18} thus exposing a substantial patient population to the risk of stroke.

As the situation was not deemed essentially different in the framework of our area, we undertook the present investigation

with a twofold purpose: first, to assess accurately adequacy of anticoagulation in this setting, and second, to analyze the effect of various factors producing poor treatment. The retrospective design was selected for both purposes. It allowed an objective review of long-term anticoagulation implemented by a relatively great number of physicians with heterogeneous professional backgrounds, who were free to adopt frequency and target of treatment according to individual judgment. Moreover, it made possible a statistical dissection of the effect of a variety of doctor- or patient-related factors on quality of control. The results of this study indicate that, similar to other reports, only 42% of the patient population free of prosthetic valves fell within the protective INR range of 1.91–4.1. Recent guidelines recommend maintenance of patients with atrial fibrillation free of prosthetic valves within an INR range of 2–3.¹ For those carrying non-ball cage prosthetic valves, the recommended INR was maximally extended to 3.5.²² On the other hand, INR values below 4 have been reported not to be involved with an increased bleeding risk. Such risk rises dramatically with INR exceeding 4.¹ We thus felt justified to define an INR range of 1.91–4.1 as conferring protection without increasing bleeding risk. Moreover, one of the principal aims of this study was to investigate factors that lead or contribute to inadequate anticoagulation involving universally accepted risks of cardioembolic or hemorrhagic events. It was surprising that the age group of 70–80 years was significantly less appropriately anticoagulated than both the younger and the older patients. It is possible that patients < 70 years were considered by their physicians to be at a smaller risk for developing bleeding complications. On the other hand, in the older age group (> 80 years), once a decision to treat was reached by the physician, this same risk constituted a compelling factor for more meticulous supervision. A similar argument probably prevailed regarding the doctors' tendency to invest a greater effort in adequately controlled patients with CHF. Obviously,

these patients inherently present a greater tendency for thromboembolic events as well as difficulty of management because of the variety of comorbid conditions requiring additional medications. In this respect, one should stress the frequency of impairments in liver function among these patients, imposing an additional difficulty in adequately controlling INR.

Patient gender, command of the Hebrew language, or duration of residence in the country did not affect quality of anticoagulation. Likewise, factors known to increase the risk for cardioembolic events, namely, previous stroke, hypertension, DM, or IHD, similarly did not encourage the physician to achieve better anticoagulation.

In this analysis, the importance of patient awareness or active involvement in the treatment has been confirmed, lending support to previous recommendations.²³⁻²⁵

The effects of insufficient or exaggerated anticoagulation have been clearly demonstrated in this report. Patients hospitalized with stroke included a significantly greater percentage of individuals poorly anticoagulated (INR < 1.5) and a smaller percentage of patients within the target INR. A mirror image was evident with respect to patients admitted with hemorrhage. This group presented with a significantly high percentage of patients exhibiting an INR > 4.11.

Similar to previous reports,¹¹⁻¹⁸ it is evident from the present analysis that despite compelling evidence progressively accumulating in the literature, quality of anticoagulation did not improve during the period 1990-1998. This was not due to insurmountable factors, as evidenced by the significantly superior anticoagulation achieved under the same circumstances in the group of patients with prosthetic valves. This better anticoagulation consisted not only of a greater percentage of patients of the latter group who fell into optimal INR range, but of significantly smaller ratios of the same group whose INR values were poor or risky. Moreover, it is obvious that the percentage of patients with prosthetic valves who are adequately anticoagulated (56.7%), and certainly the percentage in the other groups, could be increased substantially and thus serious pathophysiologic consequences, such as stroke or bleeding, could be markedly diminished. To achieve this goal, more effort is required both in persuading the medical community of the vital importance of adequate anticoagulation and in achieving greater patient involvement in management.

References

1. Laupacis A, Albers G, Dalen J, Dunn MI, Jacobson AK, Signer DE: Antithrombotic therapy in atrial fibrillation. *Chest* 1998;114: 579s-589s
2. 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
3. Hart RG, Halperin JL: Atrial fibrillation and thromboembolism: A decade of progress in stroke prevention. *Ann Intern Med* 1999;131: 688-695
4. Atrial Fibrillation Investigators: 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
5. Stafford RS, Singer DE: Recent national patterns of warfarin use in atrial fibrillation. *Circulation* 1998;97:1231-1233
6. Antani MR, Beyth RJ, Covinsky KE, Anderson PA, Miller DG, Cebul RD, Quinn LM, Landefeld CS: Failure to prescribe warfarin to patients with nonrheumatic atrial fibrillation. *J Gen Intern Med* 1996;11:713-720
7. Whittle J, Wickenheiser L, Venditti LN: Is warfarin underused in the treatment of elderly persons with atrial fibrillation? *Arch Intern Med* 1997;157:441-445
8. Albers GW, Yim JM, Belew KM, Bittar N, Hattner CR, Phillips BG, Kemp S, Hall EA, Morton DJ, Vlasses PH: Status of anti-thrombotic therapy for patients with atrial fibrillation in university hospitals. *Arch Intern Med* 1996;156:2311-2316
9. Sudlow M, Rodgers H, Kenny RA, Thomson R: Population based study of use of anticoagulants among patients with atrial fibrillation in the community. *Br Med J* 1997;314:1529-1530
10. Lip GYH, Tean KN, Dunn FG: Treatment of atrial fibrillation in a district general hospital. *Br Heart J* 1994;71:92-95
11. Albers GW, Bittar L, Young RN, Hattner AJ, Gandi PD, Kemp EA, Hall RN, Morton J, Yim J, Vlasses PH: Clinical characteristics and management of acute stroke in patients with atrial fibrillation admitted to US university hospital. *Neurology* 1997;48:1598-1604
12. Lanzarotti CJ, Olshansky B: Thromboembolism in chronic atrial flutter: Is the risk underestimated? *J Am Coll Cardiol* 1997;15: 1506-1511
13. Pell JP, Mciver B, Stuart P, Malone DN, Alcock J: Comparison of anticoagulant control among patients attending general practice and a hospital anticoagulant clinic. *Br J Gen Pract* 1993;43: 152-154
14. Gurwitz JH, Monette J, Rochon PA, Eckler MA, Avorn J: Atrial fibrillation and stroke prevention with warfarin in the long-term care setting. *Arch Intern Med* 1997;157:978-984
15. Chiquette E, Amato MG, Bussey HI: Comparison of an anticoagulation clinic with usual medical care. *Arch Intern Med* 1998;158: 1641-1647
16. Petersen P, Godtfredsen J, Boysen G, Andersen ED, Andersen B: Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. *Lancet* 1989;173-179
17. Doble N, Baron JH: Anticoagulation control with warfarin by junior hospital doctors. *J R Soc Med* 1987;80:627
18. Gottlieb LK, Salem-Schatz S: Anticoagulation in atrial fibrillation: Does efficacy in clinical trials translate into effectiveness in practice? *Arch Intern Med* 1994;154:1945-1953
19. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke prevention in atrial fibrillation III randomized clinical trial. Stroke prevention in atrial fibrillation investigators. *Lancet* 1999;348:633-638
20. 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
21. Sheffield JVL, Larson EB: Update in general internal medicine. Anticoagulation and atrial fibrillation. *Ann Intern Med* 1997;127: 45-46
22. Stein PD, Alpert JS, Dalen JE, Horstkotte D, Turpie AGG: Anti-thrombotic therapy in patients with mechanical and biological prosthetic heart valves. *Chest* 1998;114:602S-610S
23. Kumars S, Haigh JR, Rhodes LE, Peaker S, Davies JA, Roberts BE, Feely MP: Poor compliance is a major factor in unstable outpatient control of anticoagulant therapy. *Thromb Haemost* 1989;62: 729-732
24. Sawicki PT: A structured teaching and self-management program for patients receiving oral anticoagulation: A randomized controlled trial. *J Am Med Assoc* 1999;281:145-150
25. Vanscoy GJ, Coax WC: Oral anticoagulation: Improving the risk-benefit ratio. *J Fam Pract* 1995;41:261-269