

Are the Results of Randomized Controlled Trials on Anticoagulation in Patients With Atrial Fibrillation Generalizable to Clinical Practice?

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Background: Randomized trials demonstrate a clear benefit of anticoagulation in patients with atrial fibrillation at risk of stroke, but the proportion of eligible patients who are treated with anticoagulants remains low. The reluctance to treat all eligible patients with anticoagulants may be due to studies in clinical practice showing variable risk-benefit, raising concerns about application to general medical practice.

Methods: A systematic review of published medical literature was performed to identify studies of patients with atrial fibrillation who were treated with warfarin in actual clinical practice. Data from these studies were compared with pooled data from randomized controlled trials.

Results: Three studies met the predefined criteria, each in a different health care setting, totaling 410 patients with 842 patient-years of follow-up. Patients in clinical prac-

tice were older and had more comorbid conditions compared with trial participants. However, the ischemic stroke rate was similar between clinical practice and randomized studies (1.8% [95% confidence interval {CI}, 0.9%-2.7%] vs 1.4% [95% CI, 0.9%-2.0%]). Intracranial hemorrhage (0.1% [95% CI, 0%-0.3%] vs 0.3% [95% CI, 0.06%-0.5%]) and major bleeding (1.1% [95% CI, 0.4%-1.8%] vs 1.3% [95% CI, 0.8%-1.8%]) rates were also similar. There was a higher rate of minor bleeding in clinical practice than in trials (12.0% [95% CI, 9.7%-14.3%] vs 7.9% [95% CI, 6.6%-9.2%]).

Conclusions: Patients who undergo anticoagulation for atrial fibrillation in actual clinical practice differ from those in randomized trials, but have similar rates of stroke and major bleeding. The risk of minor bleeding is higher and may require more intensive monitoring in practice.

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STROKE IS THE third most common cause of death and the most common cause of severe adult disability.¹ Atrial fibrillation increases the risk of stroke 6-fold, and 20% to 30% of acute ischemic strokes are cardioembolic in origin.^{2,3} These strokes tend to be more severe and are associated with poorer outcomes.⁴

Randomized trials⁵⁻¹¹ have clearly demonstrated the effectiveness of anticoagulation in preventing stroke in patients with atrial fibrillation, and expert panels¹² recommend that all patients with atrial fibrillation at high stroke risk should be considered for anticoagulation. Clinical guidelines, which will identify those at high risk, have also been developed.^{13,14} However, studies¹⁴⁻¹⁶ of clinical practice consistently report that only a quarter to half of eligible patients with atrial fibrillation undergo anticoagulation.

One of the major reasons for this underprescribing is the concern that the benefits of warfarin therapy were demon-

strated in highly selected patients with optimal anticoagulation control and will not be reproduced in actual practice.¹⁷ This was supported by an early report¹⁸ that showed that the quality of anticoagulation, the therapeutic efficacy of warfarin, and the low complication rates seen in randomized trials were not matched in clinical practice. This conflicts with a more recent study¹⁹ that showed that the stroke rate and the risk of major hemorrhage in clinical practice was comparable to that seen in randomized trials for patients with atrial fibrillation undergoing anticoagulation for stroke prevention, despite these patients being older than those included in randomized studies. The limitations of both of these studies were that they were undertaken in single district cohorts with uniform anticoagulation practices and within a single health care system. It is not known whether their findings will be generalizable to other settings with different patient groups, different anticoagulation practices, or different health care systems.

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MATERIALS AND METHODS

A systematic review of the medical literature was performed using Ovid MEDLINE, PubMed, and the Cochrane database searching for keywords (“atrial fibrillation,” “anticoagulation,” and “warfarin”), text words (“clinical,” “actual,” or “mainstream practice”), or a combination of these words. Titles and abstracts were screened for studies of anticoagulation in patients with atrial fibrillation for primary stroke prevention in actual or clinical practice (outside of a controlled trial). The criteria for inclusion were as follows:

1. A prospective cohort or retrospective case note review in which all dropouts had been identified and measures undertaken to minimize nonreport bias. These included enumeration of all eligible patients (and not only those undergoing anticoagulation), changes in treatment, and reasons for failure to reach specified end points.
2. Patients recruited from mainstream clinical practice settings based on stroke risk and the risk of hemorrhage, unrestricted by age, sex, location, or other nonclinical considerations.
3. Anticoagulation undertaken within routine settings using local guidelines and delivered by nonresearch staff.
4. Longitudinal data on stroke rate and hemorrhagic complications.

Thirty-two articles were retrieved for more detailed analysis. The references of these articles were scanned to identify other articles with similar characteristics, which may have been missed in database searches. Articles were

assessed independently by each of us for various variables, including type of study, patient numbers, demographics, warfarin exposure, mortality, stroke incidence, bleeding complications, and anticoagulation control. We agreed on the inclusion of 6 articles,¹⁸⁻²³ which gave information on at least 7 of the variables previously mentioned for further joint review. Following the review, 2 studies^{21,22} were excluded because they reported results from all patients undergoing anticoagulation (those with deep vein thromboses, pulmonary embolism, and prosthetic valves) and it was not possible to obtain data on the subgroup with atrial fibrillation alone. One study²³ (a retrospective study of elderly nursing home residents) was not included in the analyses, because all patients were in institutional care and were not representative of mainstream practice. Only 3 studies¹⁸⁻²⁰ met all the predefined criteria for inclusion in the review.

Comparisons were made between individual studies and pooled data from these studies with combined data from randomized controlled trials.¹¹ Two-sample confidence intervals (CIs) for the difference of means and proportions were used to compare important prognostic variables between randomized trials and the present sample. The event rate per 100 patient-years was calculated, and the exact Poisson CIs were used for comparisons of clinical outcomes. A Cox proportional hazards analysis was used to adjust for differences in patient characteristics. Despite the study on institutionalized patients not meeting predefined criteria, a second analysis of pooled data that included the results of this study was undertaken to evaluate if such inclusion significantly affected the results of the main analysis.

The ultimate objective of anticoagulation for atrial fibrillation is to reduce the incidence of stroke in “real-life” conditions. Routine clinical settings have a high proportion of patients who would not meet strict inclusion criteria and may not be as compliant with interventions as those included in randomized studies. The interventions are delivered by staff or services that may not perform as well as those in trials. Widespread implementation of anticoagulation will have greater support in actual practice if experience in a range of clinical settings continues to show a benefit with anticoagulation. In view of this, a literature review was undertaken to identify non-randomized clinical studies on anticoagulation in patients with atrial fibrillation, which were analyzed in the context of randomized trials to determine if trial efficacy translated into clinical effectiveness.

RESULTS

Three studies¹⁸⁻²⁰ (one each from the United States, Canada, and England) met the predefined criteria for inclusion. These studies had similar definitions for atrial fibrillation, risk stratification, and criteria for anticoagulation. The definitions of end points (ischemic stroke) and of major and minor hemorrhages were similar among the 3 studies. Tests of homogeneity were applied and did not show significant ($P > .05$ for all) differences in outcome variables.

In the US study,¹⁸ anticoagulation was undertaken in 156 (66%) of 238 patients with atrial fibrillation in a health maintenance organization. Of the 82 patients (34%) not undergoing anticoagulation, 40 had contraindications to warfarin use, 12 refused treatment, and 30 were not offered anticoagulation for unspecified reasons. The English study¹⁹ was undertaken in a district hospital and included 167 (49%) of the 344 patients with atrial fibrillation from outpatient settings. Of the 177 patients excluded, 76 were taking warfarin before the study, 38 had contraindications to anticoagulation, 5 refused treatment, and 58 were not offered anticoagulation because of a low stroke risk. In the Canadian study,²⁰ undertaken in a teaching and a community hospital, 87 (39%) of 221 patients took warfarin for the duration of the study. Reasons for exclusion from anticoagulation were not available.

Patients in the English study were significantly older than those included in the US (age difference, 8 years; $P = .01$) and the Canadian (age difference, 6 years; $P = .02$) studies (**Table 1**). There was also a significantly ($P = .001$) higher proportion of women included in the English study compared with the other 2 studies. Patients included in all 3 studies had high levels of comorbidity. Pooled data from clinical studies showed that patients in actual practice were, on average, 6 years older and consisted of a higher proportion of women compared with patients included in randomized trials (Table 1). A significantly

Table 1. Patient Characteristics of Studies in Clinical Practice and Pooled Clinical and Trial Data*

Characteristic	Study			Pooled Data		Difference (95% CI)
	Gottlieb and Salem-Schatz ¹⁸	Kalra et al ¹⁹	Caro et al ²⁰	ACP	RCT ¹¹	
No. of patients	156	167	87	410	1225	...
Follow-up, patient-years	156	313	217	842	1889	...
Age, mean, y	69	77	71	73	67	6 (3 to 11)
Women, %	34	58	36	44	25	19 (14 to 24)
Hypertension, %	53	43	43	47	45	2 (-4 to 8)
Diabetes mellitus, %	26	15	24	21	13	8 (4 to 12)
Previous TIA or CVA, %	17	14	21	17	6	11 (7 to 15)
Congestive cardiac failure, %	42	20	34	31	20	11 (8 to 14)
Ischemic heart disease, %	24	26	30	26	36	-10 (-13 to -7)

*ACP indicates actual clinical practice; RCT, randomized controlled trial; CI, confidence interval; TIA, transient ischemic attack; CVA, cerebrovascular accident; and ellipses, data not applicable.

Table 2. Event Numbers and Rates in Studies and Combined Clinical and Combined Trial Data*

Variable	Study						Pooled Data				Rate Difference (CI)†‡
	Gottlieb and Salem-Schatz ¹⁸		Kalra et al ¹⁹		Caro et al ²⁰		ACP		RCT ¹¹		
	No. of Patients	Rate (CI)†	No. of Patients	Rate (CI)†	No. of Patients	Rate (CI)†	No. of Patients	Rate (CI)†	No. of Patients	Rate (CI)†	
Ischemic stroke	5	1.6 (0.2 to 3.0)	6	2.0 (0.4 to 3.6)	4	1.8 (0 to 4.5)	15	1.8 (0.9 to 2.7)	26	1.4 (0.9 to 2.0)	0.4 (-0.7 to 1.5)
Intracranial hemorrhage	0	0	1	0.3 (0 to 0.9)	0	0	1	0.1 (0 to 0.3)	5	0.3 (0.06 to 0.5)	0.2 (-0.1 to 0.5)
Bleeding											
Major	2	0.6 (0 to 1.5)	4	1.3 (0.04 to 2.6)	4	1.8 (0.2 to 3.4)	10	1.1 (0.4 to 1.8)	24	1.3 (0.8 to 1.8)	0.2 (-0.7 to 1.1)
Minor	42	13.5 (9.4 to 17.6)	16	5.1 (2.6 to 7.6)	45	20.7 (14.7 to 26.8)	103	12 (9.7 to 14.3)	150	7.9 (6.6 to 9.2)	4.1 (1.4 to 6.8)

*CI indicates 95% Poisson confidence interval; ACP, actual clinical practice; and RCT, randomized controlled trial.

†Rates are expressed in events per 100 patient-years' exposure.

‡RCT vs ACP.

($P = .001$) higher proportion of patients in the clinical sample had previous cerebrovascular disease.

Although the target international normalized ratio was similar in all studies,²⁴ anticoagulation was managed differently. In the United States, long-term anticoagulation was managed by the patient's primary care internist, whereas in England, this was undertaken in a general anticoagulation clinic run by the hematology department. Patients in the Canadian study underwent anticoagulation by individual physicians (internists, general practitioners, cardiologists, or hematologists) according to their own practice (J. Caro, MD, written communication, 2000). In clinical trials, patients' international normalized ratios were in the target range on 68% of days, which was significantly more than achieved in clinical practice ($P < .001$). There was also a significant difference in days spent in the target range between the US and the English studies (50% vs 61% of days; $P < .01$). The international normalized ratios were higher than the desired range for 30% of the days in the US ($P < .001$) and 13% of the days in the English studies compared with 8% of the days in clinical trials. There were no differences in the proportion of days spent be-

low the target range among randomized trials and clinical studies.

The annual event rate for ischemic stroke for patients undergoing anticoagulation was similar among the 3 studies and varied between 1.6% and 2.0% (**Table 2**). The annual stroke rate of individual studies and of pooled data from these studies compared favorably with that of patients who underwent anticoagulation in the pooled analysis of randomized trials. Only 1 of 410 patients who underwent anticoagulation in actual practice had an intracranial hemorrhage, and major bleeding was seen in only 10 patients (Table 2). The annual event rate for major bleeding in the clinical studies was also not different from that seen in the combined data from randomized trials. The annual rate of minor bleeding in clinical practice was significantly ($P = .002$) higher than in randomized studies.

Data from the study on institutionalized patients²³ were combined with the pooled data from the other 3 studies¹⁸⁻²⁰ to evaluate whether this inclusion significantly changed the results. This study²³ showed a stroke rate of 2.1% (95% CI, 0.1%-4.1%), and the major bleeding rate (with a broader definition of major bleeding) was

5.9% (95% CI, 2.0%-7.9%). These rates, combined with the pooled data of the actual clinical practice group, showed a stroke rate of 1.8% (95% CI, 1.0%-2.6%; $P=.4$) and a major hemorrhage rate of 2.1% (95% CI, 1.5%-2.7%; $P=.14$), which also were not significantly different from the pooled randomized controlled trial data.

COMMENT

Despite the diversity of settings and anticoagulation practices, there were no significant differences in the annual ischemic stroke rate or major bleeding rate in patients undergoing anticoagulation between studies in actual clinical practice. Although patients in clinical practice were significantly older and had higher levels of comorbidity, the annual stroke and major hemorrhage rates for individual studies and for combined data from all clinical practice studies were comparable to those seen in randomized studies. These findings show that anticoagulation in patients with atrial fibrillation is effective and safe in general medical practice in different settings.

The present study suggests that anticoagulation control in actual clinical practice is likely to be poorer than achieved in clinical trials. Several risk factors for poor anticoagulation control have been suggested; they can be clinical (eg, intercurrent illness or use of other drugs), psychological (eg, mood or compliance),²⁵ or environmental (access to and differences between anticoagulation services).²⁶ These factors need to be addressed when planning services. The poorer anticoagulation control did not translate into less effective prevention of stroke, probably because there were no significant differences between the time spent below the target range between actual practice and randomized studies. However, there was a significant increase in the number of minor hemorrhages in actual practice, especially in studies in which patients spent a longer time above the target range. This increase may have important implications for patients' perceptions of health and benefit from treatment, which would affect compliance.²⁷ It also has important implications for the costs of care in terms of service use by patients with these complications and the need for increased monitoring to prevent such episodes.

Strictly speaking, the method of meta-analysis can only be applied to randomized controlled studies.^{28,29} Although there are inherent problems in combining observational data from nonidentical sources, the pooling of results from several different sources can be invaluable in overcoming the potential lack of generalizability of small studies in single settings. The pooling of data from several similar observational studies may also increase the power of analysis, ensuring that important differences between actual practice and randomized trials are not obscured by large CIs in small studies. There were no significant differences on homogeneity testing among the studies included in this analysis. The pooling of data resulted in the narrowing of CIs for events to the level at which they were nearly identical to those for pooled data from randomized studies, giving further support to the findings of individual studies.

Although pooled data analyses provide a broad overview of existing evidence, they have their own limita-

tions.²⁹ These analyses are heavily dependent on published data, and a bias due to nonpublication of negative results cannot be prevented.³⁰ Although statistical methods to detect possible publication bias exist,³¹ these would not be meaningful with the few studies available for this analysis. Differences in the method of data collection or analysis may be another source of bias. The case note review undertaken by Gottlieb and Salem-Schatz¹⁸ is likely to lead to an underestimation of fatal events (or complications), as only patients alive at the time of the study were included. The exclusion from analysis of patients who withdrew from warfarin therapy before reaching a study end point²⁰ can result in underestimation of minor adverse events. The use of "intention-to-treat" rather than "on treatment" analysis¹⁹ may underestimate the benefit of anticoagulation. There were differences between groups in age, sex, and comorbidity among studies (Table 1), which reflect differences in the populations in which these studies were undertaken. For example, the US study¹⁸ was undertaken in a health maintenance organization that is likely to include younger patients than the English study,¹⁹ which was undertaken in an area with a higher than average proportion of older people. Despite the variability between the populations and limitations in methods, the comparability of outcomes in clinical settings reinforces the central message that anticoagulation can be safe and effective in a range of mainstream settings.

There is a risk that adoption of practice recommendations based on results of controlled clinical trials may fail to yield optimal results in clinical practice. This is because randomized controlled studies tend to focus on single defined interventions, and other variables are controlled. Clinical practice, on the other hand, is complex and consists of various connected components, which need to be taken into account.³² These include not only the treatment in question or the patients requiring such treatment but the whole spectrum of how the treatment is provided and the environmental constraints of the setting in which it is provided. This overview of studies in actual practice shows that research-based knowledge can be synthesized with real-life factors to provide an effective system for preventing stroke in patients with atrial fibrillation in a wide range of patients treated in diverse clinical settings.

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