Benefit of Oral Anticoagulant Over Antiplatelet Therapy in Atrial Fibrillation Depends on the Quality of International Normalized Ratio Control Achieved by Centers and Countries as Measured by Time in Therapeutic Range

Stuart J. Connolly, MA, MD, FRCPC; Janice Pogue, MA, MSc;
John Eikelboom, MBBS, MSc, FRACP, FRCPA; Gregory Flaker, MD;
Patrick Commerford, MB, ChB, FCP(SA); Maria Grazia Franzosi, PhD;
Jeffrey S. Healey, MD, FRCPC; Salim Yusuf, DPhil, FRCPC;
on behalf of the ACTIVE W Investigators

Background—Oral anticoagulation (OAC) therapy is effective in atrial fibrillation but requires vigilance to maintain the international normalized ratio in the therapeutic range. This report examines how differences in time in therapeutic range (TTR) between centers and between countries affect the outcomes of OAC therapy.

Methods and Results—In a posthoc analysis, the TTRs of patients on OAC in a randomized trial of OAC versus clopidogrel plus aspirin (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events [ACTIVE W]) were used to calculate the mean TTR for each of 526 centers and 15 countries. Proportional-hazards analysis, with and without adjustment for baseline variables, was performed, with patients stratified by TTR quartile and country. A wide variation in TTRs was found between centers, with mean TTRs for centers in the 4 quartiles of 44%, 60%, 69%, and 78%. For patients at centers below the median TTR (65%), no treatment benefit was demonstrated as measured by relative risk for vascular events of clopidogrel plus aspirin versus OAC (relative risk, 0.93; 95% confidence interval, 0.70 to 1.24; $P=0.61$). However, for patients at centers with a TTR above the study median, OAC had a marked benefit, reducing vascular events by >2-fold (relative risk, 2.14; 95% confidence interval, 1.61 to 2.85; $P<0.0001$). Mean TTR also varied between countries from 46% to 78%; relative risk (clopidogrel plus aspirin versus OAC) varied from 0.6 to 3.6 (a 5-fold difference). A population-average model predicted that a TTR of 58% would be needed to be confident that patients would benefit from being on OAC.

Conclusions—A wide variation exists in international normalized ratio control, as measured by TTR, between clinical centers and between countries, which has a major impact on the treatment benefit of OAC therapy. For centers and countries, a target threshold TTR exists (estimated between 58% and 65%) below which there appears to be little benefit of OAC over antiplatelet therapy. **(*Circulation*. 2008;118:2029-2037.)**

Key Words: anticoagulants ■ atrial fibrillation ■ arrhythmia ■ prevention ■ stroke

Oral anticoagulation (OAC) is the most effective treatment to prevent stroke and other vascular events in patients with atrial fibrillation (AF).[1] A meta-analysis of randomized trials shows a significant reduction in stroke and vascular events compared with control or aspirin, with somewhat increased risk of major hemorrhage.[2,3] However, because of marked interindividual dose response and day-to-day variation in dose response within individuals, OAC therapy requires ongoing dose adjustment with measurement of the biological effect with the international normalized ratio (INR).

Clinical Perspective p 2037

An INR range of 2.0 to 3.0 has been established as therapeutic by stroke prevention trials in AF[4–6] and through cohort studies.[7,8] It is common sense, therefore, that one should attempt to maximize the time each patient spends within that range of the INR.[4,5,9] Several studies[10,11] also have reported the time in therapeutic range (TTR) achieved in a variety of clinical settings such as in anticoagulation clinics or by community physicians. A meta-regression analysis of recently published studies reported a mean TTR in all studies

Received November 6, 2007; accepted August 27, 2008.

From the Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada (S.J.C., J.P., J.E., J.S.H., S.Y.); University of Missouri, Columbia (G.F.); Cardiac Clinic, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa (P.C.); and Department of Cardiovascular Research, Istituto Mario Negri, Milano, Italy (M.G.F.).

Clinical trial registration information—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00243178.

Correspondence to Dr Stuart Connolly, 237 Barton St E, Suite 504, Hamilton, Ontario, L8L 2X2 Canada. E-mail connostu@phri.ca

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.107.750000**

of 64%.[12] However, recent reports[13,14] from large administrative databases indicate that the TTR of AF patients can be as low as 29% in some areas. Wide variation in TTR also was reported in a recent clinical trial of OAC in AF. Although the mean trial TTR was 65%, one third of patients had a TTR <60%.[15]

Several reports indicate an association between low TTR and increased rates of both vascular events and major hemorrhage in patients on OAC.[15,16] Although it is likely that patients who are rarely in the therapeutic range receive little or no net benefit from OAC, it is not possible from current studies to estimate the minimum TTR needed to achieve a benefit for OAC therapy.

The purpose of this study is to explore the variation in INR control between centers and countries and to observe how this variation affects the effectiveness of OAC therapy compared with dual antiplatelet therapy in patients with AF. A further goal is to determine whether a minimum TTR is needed to achieve a benefit from OAC in AF. This has important implications for health policy because, without a clear benchmark for TTR, it is difficult in implement policy to make improvements. The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) W trial,[9] performed at 526 clinical centers, provides a unique opportunity to study the variation between hospitals and countries and to answer these questions.

Methods

ACTIVE W design and main results have been reported.[9] Briefly, patients were eligible for participation in ACTIVE W if they had AF and at least one of the following risk factors: age ≥75 years; treatment for systemic hypertension; previous stroke, transient ischemic attack, or non–central nervous system systemic embolism; left ventricular dysfunction; peripheral arterial disease; or (if 55 to 74 years of age) diabetes mellitus or coronary artery disease. Patients were randomized to receive clopidogrel 75 mg/d plus aspirin (75 to 100 mg/d recommended) or OAC. Centers used the vitamin K antagonist in use locally. Patients randomized to OAC were managed by study investigators or by local anticoagulation clinics with a minimum of monthly INR monitoring to maintain the INR between 2.0 and 3.0. Patients randomized to clopidogrel plus aspirin received no INR monitoring. Periodic feedback was received from the coordinating center and from the national coordinators to clinical investigators on their local INR control quality with advice and encouragement to achieve TTR of >60% at their center.

The primary study outcome was the first occurrence of stroke, non–central nervous system systemic embolism, myocardial infarction, or vascular death. Major bleeding was defined as any bleeding requiring transfusion of at least 2 units of red blood cells or the equivalent of whole blood or any bleed associated with death, hypotension requiring inotropic agents, intraocular bleeding leading to substantial loss of vision, bleeding requiring surgical intervention, or symptomatic intracranial hemorrhage. Net benefit was a prespecified outcome defined as the composite of the primary outcome and major bleeding. Stroke included ischemic and hemorrhagic stroke.

The TTR was calculated with the method first described by Rosendaal et al,[17] which uses linear interpolation of INR values in each patient receiving OAC to calculate the percentage of days when the INR is in the therapeutic range (2.0 to 3.0). The first 7 days after treatment is started or restarted, time after permanent discontinuation of OAC and time >5 days from temporary discontinuation were not included in the calculation of TTR. The individual TTRs of all patients randomized to OAC within a center or country were averaged to yield the mean TTR for that center or country. Clinical centers were categorized into quartiles according to mean TTR achieved for their OAC patients. A proportional-hazards analysis was done to estimate event rates on OAC and on clopidogrel plus aspirin and the relative risk (clopidogrel plus aspirin versus OAC), first with center TTR quartile and again with country as the stratification variable. The primary analysis was based on intention to treat (which included all clinical events regardless of whether the patient had discontinued therapy). As a sensitivity analysis, the proportional-hazards analysis by quartiles was repeated with censoring of events after permanent discontinuation of either therapy. Another analysis was done with adjustment for all of the baseline clinical variables that were potentially imbalanced among the TTR quartiles, including age, gender, weight, heart rate, hypertension, heart failure, transient ischemic attack or stroke, peripheral vascular disease, paroxysmal AF, pacemaker, previous bleed, left ventricular hypertrophy, CHADS2 score, history of fall, history of fracture, baseline use of acetylsalicylic acid, baseline use of oral anticoagulant, baseline use of angiotensin receptor blocker, and baseline use of angiotensin-converting enzyme inhibitor. We also performed similar analyses categorizing centers according to percentage of time above an INR of 3, above an INR of 4, and below an INR of 2. An analysis stratified by CHADS2 score was done.

The following events were evaluated: the ACTIVE primary outcome (stroke, myocardial infarction, systemic embolism, or vascular death), major hemorrhage, and net benefit (the composite of the ACTIVE primary outcome plus major hemorrhage).

The relationship between TTR and outcomes was examined first using time-to-event analysis in Cox regression. In addition, to account for the effect of TTR estimated at the site level, we used a population-average model incorporating general estimating equations for binary outcomes using an exchangeable correlational structure.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Variation in TTR

Of the 6706 patients in ACTIVE W, 3371 were randomized to OAC and 3335 to clopidogrel plus aspirin. The risk of the primary outcome (stroke, myocardial infarction, systemic embolism, or vascular death) was increased with clopidogrel plus aspirin compared with OAC (relative risk, 1.44; 95% confidence interval [CI], 1.18 to 1.76; $P=0.0003$). The mean TTR of each patient randomized to and receiving OAC was calculated, and each clinical center was characterized by the mean TTR of all its patients on OAC. The mean TTR for all patients in ACTIVE W was 63.4% (median, 65%). The centers were arranged in quartiles according to their mean TTR with the following ranges: <53.8%, 53.8% to 65.0%, 65.1% to 73.3%, and >73.3%. The mean TTRs of the quartiles were 44%, 60%, 69%, and 78%. The time that was not in range was more often low (<2.0) than high (>3.0) for all quartiles. The percentages of time out of range that was low (rather than high) for the 4 quartiles were 64%, 52%, 53%, and 58%, respectively. Twenty-nine different countries participated in ACTIVE W, and the country mean TTR varied from 46% to 78%. Table 1 shows data on 15 countries with sufficient primary outcome events or major bleeds (at least 10) to calculate the relative risk (clopidogrel plus aspirin versus OAC) for that country. Centers within many countries had consistent TTRs. In the 3 countries with the highest mean TTRs, 92% of patients had TTRs above the study median;

Table 1. TTR And Time to Risk of Stroke, Myocardial Infarction, Systemic Embolism, Vascular Death, or Major Hemorrhage for 15 Countries Participating in ACTIVE W

	Patients per TTR Quartile (Low to High), n					Clopidogrel+Aspirin		OAC		Clopidogrel+ASA vs OAC		
Country	1	2	3	4	Mean TTR	Events	%/y	Events	%/y	RR	95% CI	*P*
South Africa	55	43	0	0	46.3	5	8.42	8	14.94	0.57	0.19–1.75	0.33
Brazil	188	25	25	8	47.1	13	9.38	14	9.43	1.01	0.47–2.15	0.98
Russia	188	28	0	41	53.4	13	7.92	7	4.16	1.88	0.75–4.70	0.18
Poland	313	224	86	18	55.3	18	4.71	19	4.94	0.95	0.50–1.81	0.87
Belgium	4	128	9	0	58.7	11	11.91	6	6.72	1.81	0.67–4.90	0.24
United States	135	460	363	116	62.9	59	8.02	48	6.6	1.25	0.85–1.83	0.26
Netherlands	65	98	163	49	64.0	15	6.65	7	3.17	2.12	0.86–5.20	0.10
Argentina	40	79	76	106	64.5	10	6.02	10	5.9	1.03	0.43–2.48	0.94
Czech Republic	11	110	64	48	66.8	7	4.67	5	3.32	1.45	0.46–4.56	0.53
Italy	23	15	107	21	67.2	8	7.46	4	3.83	1.94	0.59–6.46	0.28
Canada	45	259	480	316	68.5	61	8.94	34	4.89	1.88	1.23–2.86	0.003
Germany	0	149	261	171	69.3	22	5.82	15	3.95	1.51	0.78–2.90	0.22
Australia	5	12	54	145	74.5	18	12.92	5	3.76	3.60	1.34–9.71	0.01
United Kingdom	2	34	59	199	74.8	12	7.03	7	3.97	1.79	0.71–4.55	0.22
Sweden	0	0	28	96	77.8	11	14.42	4	5.33	2.86	0.91–8.97	0.07

ASA indicates acetylsalicylic acid; RR, relative risk. Rows are ordered by mean TTR.

and in the 3 countries with the lowest mean TTRs, 86% of patients had TTRs below the median. However, large variation was also found within other countries. For example, in the United States, 135 patients (12.6%) were treated in the lowest-quartile centers; 460 (42.8%), 363 (33.8%), and 116 (10.8%) were treated at centers in the next 3 ascending quartiles. Rates of study medication discontinuation at 18 months were 7.8% for OAC and 13.8% for clopidogrel plus aspirin.

Baseline Characteristics

Table 2 shows baseline clinical characteristics of study patients treated at centers with TTRs above and below the study median TTR according to randomized treatment. Few major differences were found between the groups; however, patients at centers with better TTRs were more likely to have been on OAC at the time of randomization and were less likely to have a history of heart failure.

Effect of TTR on Treatment Effect of OAC

In Table 3, all patients are stratified according to the TTR quartile of their center. For example, 668 patients were randomized to clopidogrel plus aspirin and 674 patients were randomized to OAC at centers achieving the lowest quartile of TTR for their OAC patients. The relative risk (clopidogrel plus aspirin versus OAC) is a measure of the treatment benefit of OAC over clopidogrel plus aspirin. Values of 1.0 indicate that treatments are equivalent; values >1.0 indicate a greater risk of events on clopidogrel plus aspirin compared with OAC. For the ACTIVE primary outcome (stroke, myocardial infarction, systemic embolism, or vascular death), the relative risk of an event increases from the lowest quartile to the highest ($P=0.0008$ for interaction). In the lowest 2 quartiles, the relative risks are 0.91 and 0.95, respectively, In the upper 2 quartiles, the relative risks are 2.29 and 1.95. Similar patterns are seen for major hemorrhage, for the composite of the primary outcome plus major hemorrhage, and for stroke. Figure 1 shows 2 time-to-event curves for the primary outcome (stroke, myocardial infarction, systemic embolism, or vascular death) for patients at centers below the study median TTR on the left and above the study median TTR on the right. For patients at centers with mean TTRs below the median, no reduction in events occurs with OAC (relative risk, 0.93; 95% CI, 0.70 to 1.24; $P=0.61$), but for patients at centers with TTRs above the median, OAC reduced vascular events >2-fold (relative risk, 2.14; 95% CI, 1.61 to 2.85; $P<0.0001$). Figure 2 uses a similar format for the outcome of stroke. A similar pattern is observed.

Differences in patient characteristics in the 4 quartiles could account for some of the observed effect of TTR quartile on the OAC treatment effect. To examine this possibility, a proportional-hazards analysis was done with adjustment for differences in baseline variables (19 variables included in the model). After adjustment for baseline patient characteristics, the interaction between INR quartile and relative risk was essentially unchanged (the statistical significance of the interaction changed from $P=0.008$ to $P=0.004$), indicating that the observed effect of TTR quartile on OAC treatment benefit is robust and largely independent of differences in patient characteristics between quartiles. Another sensitivity analysis with censoring of events occurring after study drug discontinuation showed that the effect of TTR quartile on relative risk was virtually unchanged (the statistical significance for the interaction for the primary outcome

Table 2. Patient Baseline Characteristics and INR Control According to the TTR of Their Center

	Patients at Centers With a Mean TTR <65%		Patients at Centers With a Mean TTR ≥65%	
	Clopidogrel+ASA	OAC	Clopidogrel+ASA	OAC
Time at an INR <2.0, %	...	26.9±13.6	...	15.0±5.1
Time at an INR>3.0, %	...	19.6±10.4	...	12.2±5.2
Time at an INR 2–3, %	...	53.4±10.0	...	72.8±5.7
Age, y	69.6±9.6	69.7±9.8	70.8±9.1	70.7±9.3
Body mass index, kg/m^2	29.0±5.0	28.9±5.0	28.8±4.9	28.6±5.0
CHADS2 risk score	2.0±1.1	2.0±1.2	2.0±1.1	2.0±1.1
Systolic BP, mm Hg	132.3±18.6	132.5±18.7	133.2±19.5	133.5±18.8
Male, n (%)	1058 (66.2)	1025 (64.1)	1161 (66.8)	1186 (67.0)
AF history >2 y, n (%)	930 (58.2)	932 (58.3)	1056 (60.8)	1055 (59.6)
Prior hypertension, n (%)	1325 (82.9)	1333 (83.3)	1430 (82.3)	1434 (81.0)
Prior stroke/TIA, n (%)	232 (14.5)	245 (15.3)	278 (16.0)	265 (15.0)
Prior myocardial infarction, n (%)	291 (18.2)	294 (18.4)	282 (16.2)	297 (16.8)
Prior peripheral arterial disease, n (%)	59 (3.7)	68 (4.3)	58 (3.3)	50 (2.8)
Prior heart failure, n (%)	538 (33.7)	572 (35.8)	453 (26.1)	468 (26.4)
Prior diabetes mellitus, n (%)	341 (21.3)	338 (21.1)	371 (21.4)	379 (21.4)
OAC at baseline, n (%)	1168 (73.1)	1193 (74.6)	1358 (78.2)	1434 (81.0)
Aspirin at baseline, n (%)	540 (33.8)	455 (28.4)	465 (26.8)	429 (24.2)
ACE inhibitor at baseline, n (%)	884 (55.3)	915 (57.2)	888 (51.1)	942 (53.2)
ARB agent at baseline, n (%)	208 (13.0)	193 (12.1)	300 (17.3)	295 (16.7)
β-Blockers at baseline, n (%)	925 (57.9)	902 (56.4)	1019 (58.7)	995 (56.2)

ASA indicates acetylsalicylic acid: BP, blood pressure; TIA, transient ischemic attack; ACE, angiotensin-converting enzyme; and ARB, angiotensin receptor blocking. Values are mean±SD when appropriate.

changed minimally from 0.0008 to 0.001). Analyses of the effect of TTR quartile on the treatment effects of OAC versus clopidogrel plus aspirin for the primary outcome and for major hemorrhage were repeated with stratification by the patient's CHADS2 score (≥2 versus <2). In both high- and low-CHADS2 patients, the relationship between TTR quartile and the treatments effects of OAC was the same as that observed in the whole study population.

We also explored the specific effect of time below an INR of 2 on the risk of the primary outcome and the effect of time above an INR of 3 on the risk of major hemorrhage to separate out these 2 different aspects of time out of range. The median percentage of time below an INR of 2 of all study patients was 18%. For centers with less than the median time below an INR of 2 (better INR control), the relative risk (clopidogrel plus aspirin versus OAC) for the primary outcome was 1.59 (fewer outcomes on OAC), and for sites with more time below an INR of 2 (worse INR control), the relative risk was 1.31 (P for interaction=0.36). The median percentage of time above an INR of 3 for all patients was 14%. For centers with less than the median time above an INR of 3 (better INR control), the relative risk for major bleeding was 1.44 (less bleeding on OAC), and for sites with more time above an INR of 3 (worse INR control), the relative risk was 0.81 (more bleeding on OAC; P for interaction=0.049). This analysis indicates that time above target range is associated with significantly increased bleeding and that time below range is associated with a trend to fewer embolic events. It supports the validity of the main analysis, which combines the 2 in the concept of TTR.

Population-Average Model and Analysis of Countries

To better understand the relationship between the treatment benefit of OAC (versus clopidogrel plus aspirin) and TTR, 2 additional analyses were performed. A population-average model was used to account for the clustering of TTR at sites. The outcome of stroke, myocardial infarction, non–central nervous system embolism, vascular death, or major hemorrhage was used to have sufficient numbers of events to perform the analysis. As illustrated in Figure 3, this model shows that the relationship between relative risk and TTR is positive with increasing benefit from OAC with increasing TTR and that the relationship is nonlinear. It also is possible to estimate the minimum TTR needed to have at least some benefit from OAC. When the lower bound of the 95% CI for the odds ratio is 1.0, the TTR is 58%. At TTR values >58%, it is reasonable to expect that a patient benefits significantly from being on OAC. At TTR values <58%, one cannot confidently expect any net benefit from being on OAC.

We also analyzed the relationship between relative risk and TTR according to country. Table 1 shows details about the TTR for each country, as well as annual event rates for the composite outcome of stroke, myocardial infarction, systemic embolus, vascular death, or major hemorrhage. The relative

Table 3. Treatment Effects According to Center TTR Quartile: Risk Estimated by Time-to-Event Analysis

	Clopidogrel+ASA			OAC			Clopidogrel+ASA vs OAC			
	n	Events, n	%/y	n	Events, n	%/y	RR	95% CI	*P*	*P* for Interaction
Stroke, myocardial infarction, vascular death, or systemic embolism										
Quartile 1 (TTR <53.8%)	668	41	4.95	674	45	5.48	0.91	0.60–1.39	0.66	
Quartile 2 (TTR 53.8%–65.0%)	930	49	4.20	926	51	4.46	0.95	0.64–1.40	0.79	
Quartile 3 (TTR 65.1%–73.2%)	974	85	6.85	1004	39	3.04	2.29	1.57–3.35	<0.0001	
Quartile 4 (TTR >73.3%)	763	59	6.24	767	31	3.25	1.95	1.26–3.02	0.003	0.0008
Major hemorrhage										
Quartile 1 (TTR <53.8%)	668	12	1.45	674	24	2.92	0.49	0.25–0.99	0.046	
Quartile 2 (TTR 53.8%–65.0%)	930	22	1.89	926	27	2.36	0.79	0.45–1.40	0.42	
Quartile 3 (TTR 65.1%–73.2%)	974	42	3.38	1004	25	1.95	1.75	1.07–2.87	0.027	
Quartile 4 (TTR >73.3%)	763	25	2.64	767	17	1.78	1.48	0.80–2.75	0.21	0.013
Stroke, myocardial infarction, systemic embolism vascular death, or major hemorrhage										
Quartile 1 (TTR <53.8%)	668	53	6.40	674	59	7.18	0.89	0.62–1.29	0.55	
Quartile 2 (TTR 53.8%–65.0%)	930	70	6.00	926	70	6.13	0.98	0.71–1.37	0.92	
Quartile 3 (TTR 65.1%–73.2%)	974	113	9.10	1004	57	4.44	2.10	1.53–2.89	<0.0001	
Quartile 4 (TTR >73.3%)	763	80	8.46	767	44	4.62	1.87	1.30–2.71	0.0008	0.0003
Stroke										
Quartile 1 (TTR <53.8%)	668	18	2.17	674	16	1.95	1.12	0.57–2.20	0.74	
Quartile 2 (TTR 53.8%–65.0%)	930	19	1.63	926	14	1.23	1.33	0.67–2.66	0.41	
Quartile 3 (TTR 65.1%–73.2%)	974	38	3.06	1004	16	1.25	2.49	1.39–4.47	0.002	
Quartile 4 (TTR >73.3%)	763	25	2.64	767	13	1.36	1.95	1.00–3.82	0.05	0.2887
Stroke+Non-CNS systemic embolism										
Quartile 1 (TTR <53.8%)	668	20	2.42	674	16	1.95	1.25	0.65–2.41	0.51	
Quartile 2 (TTR 53.8%–65.0%)	930	25	2.14	926	14	1.23	1.76	0.91–3.39	0.09	
Quartile 3 (TTR 65.1%–73.2%)	974	44	3.54	1004	18	1.40	2.57	1.48–4.44	0.0008	
Quartile 4 (TTR >73.3%)	763	29	3.07	767	14	1.47	2.11	1.12–4.00	0.02	0.4034

ASA indicates acetylsalicylic acid; RR, relative risk; and CNS, central nervous system. TTR was measured only in patients randomized to OAC. The interaction measured is between RR (clopidogrel plus ASA vs OAC) and quartile.

risk varies between countries studied from 0.6 to 3.6 (a 5-fold variation). This difference is explained in part by the TTR achieved, which varied from 46% to 78% between countries. Each of these 15 countries has been plotted in Figure 3 to show that data from individual countries closely follow the relationship between relative risk and TTR that was derived from the population-average model.

Discussion

Main Study Findings

A wide variation exists between centers and between countries in the success of maintaining the INR of patients with AF in the therapeutic range of 2.0 to 3.0, even within the relatively controlled setting of this clinical trial. The success of INR control, as measured by TTR, is an important determinant of the benefit of OAC over antiplatelet therapy. A marked benefit was found against stroke and against total vascular events for OAC patients treated at centers that had mean TTRs above the study median of 65%; no apparent benefit was found for the other half of OAC patients who were treated at centers achieving mean TTRs below 65%. This strong relationship between TTR and benefit of OAC was confirmed by the population-average analysis and by analysis of individual countries. These findings indicate that a threshold TTR exists below which the benefit of OAC over clopidogrel plus aspirin is questionable. The analysis based on quartiles of INR achieved by centers indicates a critical value for TTR of 65%. The population-average model suggests a minimum TTR threshold of ≈58%.

Health Policy Implications

These findings have implications for health policy. This study shows that a wide variation exists among physician practices, hospitals, and healthcare systems in quality of anticoagulation control. This variation needs to be addressed if the full potential of OAC therapy is to be realized. In ACTIVE W, about half of the centers were not delivering OAC therapy in a way that achieved the expected benefit and that may even be associated with an increased risk of hemorrhage. The finding of a threshold below which OAC benefits are diminished, or

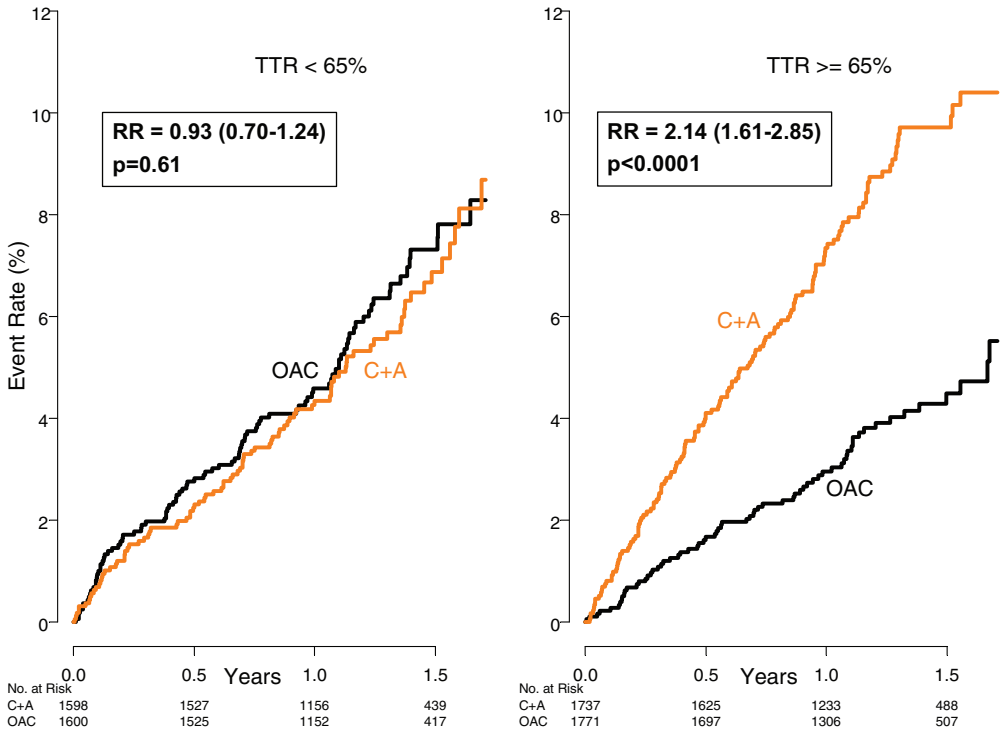

Figure 1. Cumulative risk of stroke, myocardial infarction, systemic embolism, or vascular death for patients treated at centers with a TTR below or above the study median (65%). RR indicates relative risk: C+A, clopidogrel plus aspirin.

do not occur, points to a potentially useful program for improved quality of anticoagulation: routine measurement of the center TTR for patients with AF and then corrective action if the TTR is <65%. Some countries achieved a TTR of close to 75%, and greater benefits of OAC were observed.

Much evidence has been found that medical practice is an important determinant of TTR. Although clearly patient-specific factors exist such as genetic polymorphisms, age, and compliance with medications, physician- and medical system–related factors also contribute, particularly because the dosing of OAC is variable between patients and often requires ongoing adjustment. The use of anticoagulation clinics[12] and computer-assisted decision support tools[18] has been shown to improve TTR.

The Therapeutic Range for INR

The relationship between INR and stroke in patients with AF has been carefully documented for the outcome of stroke. Hylek and coworkers[7] studied 74 consecutive patients with AF who had an ischemic stroke while taking warfarin. Using the INR on admission and a case-control method, they reported that the risks of stroke were sharply higher at INRs <2.0. At an INR of 1.7, the adjusted odds ratio for stroke was 2-fold higher than for an INR of 2.0. At an INR of 1.5, it was 3.3-fold higher. In a systematic review and meta-analysis, Reynolds et al[19] summarized 21 studies reporting stroke and major bleeding events in relationship to INR. Of 9 studies using an INR target range of 2.0 to 3.0, an INR <2.0 was associated with an odds ratio for ischemic events of 5.07, and an INR of >3 was associated with an odds ratio for bleeding events of 3.2. The present findings support these observations using a different method and for both the outcome of stroke and total vascular events.

Previous Studies of TTR

Previous studies have reported a relationship between TTR and outcomes in both venous thromboembolic disease and AF. Veeger et al[20] reported increased rates of recurrent venous thromboembolism and major bleeding when patients with a TTR <45% were compared with those having a TTR >65%. Jones et al[16] reported that in AF patients a 10% increase in time out of therapeutic range was associated with an increased risk of ischemic stroke (odds ratio, 1.10; $P=0.006$). In an analysis of patients on warfarin in the Stroke Prevention Using an Oral Direct Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) trials,[15] a lower TTR was predictive of death, stroke, systemic embolism, and myocardial infarction. Although these studies make the link between TTR and patient outcomes, they do not address whether a critical level of TTR exists below which OAC therapy is ineffective. By characterizing the TTR, not just of patients but also of centers and countries, we can evaluate the effect that TTR has on the relative effectiveness of OAC versus antiplatelet therapy and show the minimum TTR required to achieve a benefit of OAC. Many patients in ACTIVE W were treated at centers with TTRs below this threshold; for them, OAC therapy provided little or no benefit.

Population-Average Model and Analysis by Country

The population-average model indicates that a clear relationship exists between TTR and effect of OAC versus clopi-

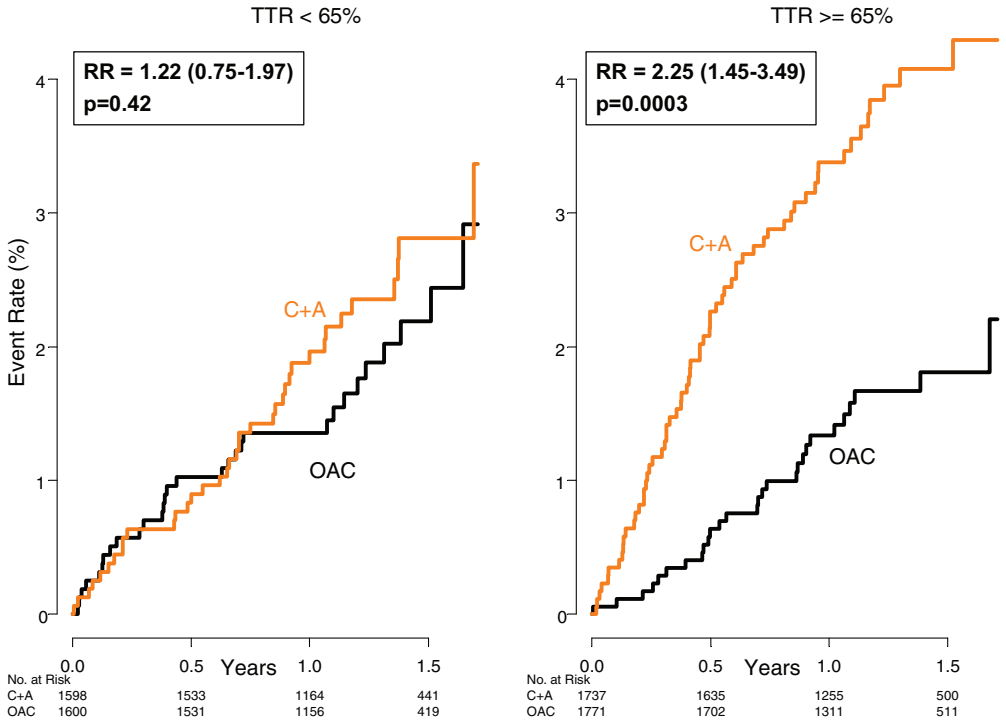

Figure 2. Cumulative risk of stroke for patients treated at centers with a TTR below or above the study median (65%). RR indicates relative risk: C+A, clopidogrel plus aspirin.

dogrel plus aspirin that is nonlinear, with more rapidly increasing benefit as the TTR increases above the study median value of 65%. Analysis of individual countries shows that there also is a relationship between the TTR achieved within a country and the observed benefit from OAC (as expressed by the relative risk).

The differences in TTR occurring between centers and regions do not appear to be due to differences in patient characteristics. Table 2 shows differences between patients according to whether they were at a center with above-average TTR. However, the analysis, which adjusted for the baseline differences between patients, still showed a very strong relationship between TTR and OAC treatment effect. Medical system differences may explain regional differences but account less well for differences between hospitals within countries, which were often quite large. All differences between centers and countries should have been minimized in the context of a clinical trial in which virtually all participating centers were led by cardiology specialists expert in the management of AF. All centers were expected to aim to achieve the protocol-mandated target INR range of 2.0 to 3.0, and no evidence has been found that they did not attempt to do so. A minimum monthly measurement of INR was mandated by the protocol; and there was ongoing feedback to centers about INR control, as well as encouragement from national coordinators and the coordinating center. Some centers used a shorter-acting vitamin K antagonist (acenocoumarol), which is associated with more variability in INR

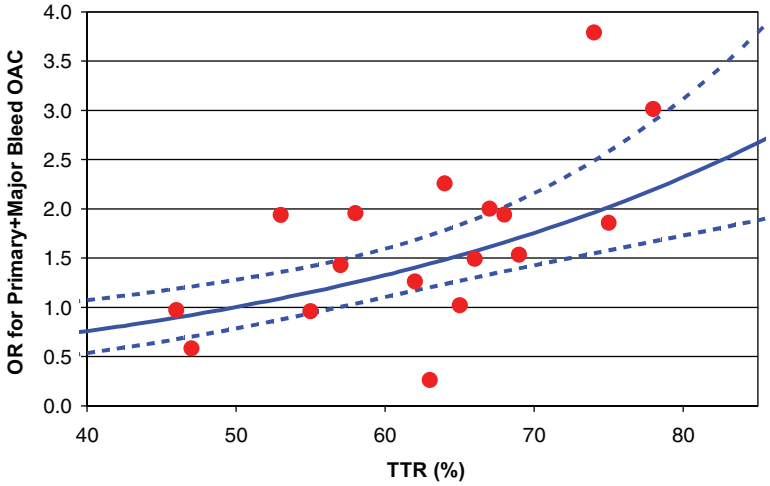

Figure 3. Relationship between the odds ratio (OR) of stroke, myocardial infarction, systemic embolism, vascular death, or major hemorrhage and TTR using population-average logistic regression. The hatched lines show the 95% CI of the OR. The relationship is described by the following equation: log (OR)=−1.4+0.028×TTR. Each dot represents 1 country participating in ACTIVE, showing the relationship between the OR and TTR for that country (for all countries with ≥10 events). OR is for clopidogrel plus aspirin vs OAC.

levels and possibly worse INR control; this fact could explain some of the variation between centers and countries in TTRs.[21]

Potential Study Limitations

The analysis by quartiles is based on a postrandomization stratification variable, the TTR achieved by centers. To reduce potential bias, the analysis was based on intention to treat. Both the sensitivity analysis based on the on-treatment principle and the analysis adjusted for differences in patient baseline characteristics yielded similar results. The study was unblinded, and bias could be introduced in terms of concomitant medical management and/or assessment of events. This study excluded the first 7 days after initiation of OAC therapy from the calculation of TTR. It is possible that this time was not long enough to achieve a stable INR, especially in OAC-naïve patients. Variation exists in the event rates between quartiles for patients randomized to clopidogrel plus aspirin that is not explained by the data but is likely due to differences in patient characteristics between groups. Unlike many AF trials in which stroke plus systemic embolism was the primary outcome, the primary outcome in ACTIVE was a composite of vascular events. However, the association between TTR and outcomes is consistent for the outcomes of both stroke and vascular events. The analysis by country is limited by the fact that some countries had too few events to be included in the analysis.

The observation of a relationship between TTR and treatment benefit of OAC does not prove causality. However, causality is strongly suggested by the strength and consistency of the relationship observed. It is also biologically plausible that at some lower level of INR control, there would cease to be a benefit from OAC therapy over antiplatelet therapy, which is generally less effective but does not need monitoring. This analysis is based on grouping patients by center or country, and it does not answer whether any benefit of OAC is found in the individual hard-to-control patient with low TTR.

Implications

All centers should attempt to achieve the highest possible TTR, but this is challenging. Although patient differences undoubtedly play a role in the variation in TTRs that we observed, the present data suggest that medical system factors specific to center and region are very important. Practices, centers, and regions need to assess the TTR achieved in their own patients and to set a minimum target TTR of 60% to 65%. Medical systems that cannot achieve this goal for biological, systematic, economic, or social reasons should consider not preferring OAC in AF patients.

Sources of Funding

The ACTIVE study was funded by Sanofi-Aventis and Bristol Myers-Squibb.

Disclosures

Drs Connolly and Yusuf received a grant from the sponsors to lead and coordinate the ACTIVE study. The other authors report no conflicts.

References

1. 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.
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. van Walraven C, Hart RG, Singer DE, Laupacis A, Connolly S, Petersen P, Koudstaal PJ, Chang Y, Hellemons B. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA*. 2002;288:2441–2448.
4. Stroke Prevention in Atrial Fibrillation Investigators. 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. *Lancet*. 1996;348:633–638.
5. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C, for the CAFA Study Investigators. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol*. 1991;18:349–355.
6. SPORTIF Executive Steering Committee for the SPORTIF V Investigators. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA*. 2005;293:690–698.
7. 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.
8. Fang MC, Chang Y, Hylek EM, Rosand J, Greenberg SM, Go AS, Singer DE. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. *Ann Intern Med*. 2004;141:745–752.
9. ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Pfeffer M, Hohnloser S, Yusuf S. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE W): a randomized controlled trial. *Lancet*. 2006;367:1903–1912.
10. Menzin J, Boulanger L, Hauch O, Friedman M, Marple CB, Wygant G, Hurley JS, Pezzella S, Kaatz S. Quality of anticoagulation control and costs of monitoring warfarin therapy among patients with atrial fibrillation in clinic settings: a multi-site managed-care study. *Ann Pharmacother*. 2005;39:446–451.
11. Pengo V, Pegoraro C, Cucchini U, Iliceto S. Worldwide management of oral anticoagulant therapy: the ISAM Study. *J Thromb Thrombolysis*. 2006;21:73–77.
12. van Walraven C, Jennings A, Oake N, Fergusson D, Forster AJ. Effect of study setting on anticoagulation control: a systemic review and metaregression. *Chest*. 2006;129:1155–1166.
13. Samsa GP, Matchar DB, Goldstein LB, Bonito AJ, Lux LJ, Witter DM, Bian J. Quality of anticoagulation management among patients with atrial fibrillation. *Arch Intern Med*. 2000;160:967–973.
14. Sarawate C, Sikirica MV, Willey VJ, Bullano MF, Hauch O. Monitoring anticoagulation in atrial fibrillation. *J Thromb Thrombolysis*. 2006;21:191–198.
15. White HD, Gruber M, Feyzi J, Kaatz S, Tse H, Husted S, Albers GW. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. *Arch Intern Med*. 2007;167:239–245.
16. Jones M, McEwan P, Morgan C, Peters JR, Goodfellow J, Currie CJ. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of treatment with warfarin in patients with non-valvular atrial fibrillation: a record linkage study in a large British population. *Heart*. 2005;91:472–477.
17. Rosendaal FR, Cannegieter SC, van der Meer FJ, Brier E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost*. 1993;69:236–239.
18. Garg AX, Adhikari NK, McDonald H, Rosas-Arellano MP, Devereaux PJ, Beyene J, Sam J, Haynes RB. Effects of computerized clinical

decision support systems on practitioner performance and patient outcomes: a systematic review. *JAMA*. 2005;293:1223–1238.
19. Reynolds MW, Fahrbach K, Hauch O, Wygant G, Estok R, Cella C, Nalysnyk L. Warfarin anticoagulation and outcomes in patients with atrial fibrillation: a systemic review and meta-analysis. *Chest*. 2004;126:1938–1945.
20. Veeger N, Piersma-Wichers M, Tijssen JG, Hillege HL, van der Meer J. Individual time within target range in patients treated with vitamin K antagonists: main determinant of quality of anticoagulation and predictor of clinical outcome: a retrospective study of 2300 consecutive patients with venous thromboembolism. *Br J Haematol*. 2005;128:513–519.
21. van Geest-Daalderop JHH, Hutten BA, Pequeriaux NC, Haas FJ, Levi M, Sturk A. The influence on INRs and coagulation factors of the time span between blood sample collection and intake of phenprocoumon or acenocoumarol: Consequences for the assessment of the dose. *Thromb Haemost*. 2007;98:738–746.

CLINICAL PERSPECTIVE

Oral anticoagulation (OAC) has proved to be beneficial for the reduction of stroke and vascular events in atrial fibrillation. Previous studies have clearly shown that OAC therapy needs to be controlled carefully so that the international normalized ratio of the prothrombin time remains in the therapeutic range, between 2 and 3. However, this target is not always achieved. Previous studies have shown that the time in the therapeutic range (TTR) varies between patients and that a high TTR is associated with increased risk of stroke and bleeding. No previous study has indicated the minimum TTR needed to achieve a beneficial response from OAC. The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE W) study data have been used to develop an estimate of the minimal TTR needed to confidently achieve a benefit compared with therapy with clopidogrel and aspirin. This estimate is based on comparing the outcomes of patients in ACTIVE W randomized to either OAC or clopidogrel plus aspirin. The analysis used stratification according to the TTR achieved by each clinical center in its OAC patients. Only patients at centers with TTR above the study median of 65% benefited from OAC compared with clopidogrel plus aspirin. An analysis by country has also been carried out, and a strong relationship has been found between the TTR achieved by a country and the benefit of OAC. The estimate of the minimum TTR needed to achieve a benefit from OAC therapy is between 58% and 65%. Centers that achieve below this level cannot be confident that their patients are benefiting from OAC compared with antiplatelet therapy. An even higher TTR (ie >70%) is associated with even greater benefit from OAC and was achieved in some countries. These data indicate that providers of OAC therapy need to evaluate how well they deliver OAC to patients with atrial fibrillation, with the intent of achieving a minimum TTR of 58% to 65% and an optimal control of >70% TTR.

Benefit of Oral Anticoagulant Over Antiplatelet Therapy in Atrial Fibrillation Depends on the Quality of International Normalized Ratio Control Achieved by Centers and Countries as Measured by Time in Therapeutic Range

Stuart J. Connolly, Janice Pogue, John Eikelboom, Gregory Flaker, Patrick Commerford, Maria Grazia Franzosi, Jeffrey S. Healey and Salim Yusuf
on behalf of the ACTIVE W Investigators

Circulation. 2008;118:2029-2037; originally published online October 27, 2008;
doi: 10.1161/CIRCULATIONAHA.107.750000
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539