

Anticoagulation Control and Prediction of Adverse Events in Patients With Atrial Fibrillation

A Systematic Review

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Background—To date, there has been no systematic examination of the relationship between international normalized ratio (INR) control measurements and the prediction of adverse events in patients with atrial fibrillation on oral anticoagulation.

Methods and Results—We searched MEDLINE, EMBASE, and Cochrane through January 2008 for studies of atrial fibrillation patients receiving vitamin-K antagonists that reported INR control measures (percentage of time in therapeutic range [TTR] and percentage of INRs in range) and major hemorrhage and thromboembolic events. In total, 47 studies were included from 38 published articles. TTR ranged from 29% to 75%; percentage of INRs ranged from 34% to 84%. From studies reporting both measures, TTR significantly correlated with percentage of INRs in range ($P<0.001$). Randomized controlled trials had better INR control than retrospective studies (64.9% versus 56.4%; $P=0.01$). TTR negatively correlated with major hemorrhage ($r=-0.59$; $P=0.002$) and thromboembolic rates ($r=-0.59$; $P=0.01$). This effect was significant in retrospective studies (major hemorrhage, $r=-0.78$; $P=0.006$ and thromboembolic rate, $r=-0.88$; $P=0.03$) but not in randomized controlled trials (major hemorrhage, $r=0.18$; $P=0.33$ and thromboembolic rate, $r=-0.61$; $P=0.07$). For retrospective studies, a 6.9% improvement in the TTR significantly reduced major hemorrhage by 1 event per 100 patient-years of treatment (95% CI, 0.29 to 1.71 events).

Conclusions—In atrial fibrillation patients receiving orally administered anticoagulation treatment, TTR and percentage of INRs in range effectively predict INR control. Data from retrospective studies support the use of TTR to accurately predict reductions in adverse events. (*Circ Cardiovasc Qual Outcomes*. 2008;1:84-91.)

Key Words: anticoagulants ■ atrial fibrillation ■ hemorrhage ■ thrombosis ■ international normalized ratio

Atrial fibrillation (AF) is a common condition affecting 1 in 10 adults aged >75 years¹ and is a strong independent risk factor for thromboembolism and ischemic stroke.² Adjusted-dose oral anticoagulation is highly efficacious for prevention of all stroke (both ischemic and hemorrhagic), with a risk reduction of 62% (95% CI, 48% to 72%) when compared with placebo.³ Moreover, anticoagulation has recently been shown to be effective in elderly patients aged >75 years.⁴ However, the incidence of bleeding events increases with the intensity of anticoagulation, especially in the elderly population.⁵

range is normally 2.0 to 3.0 for AF,⁶ and an INR <2.0 increases the risk of thromboembolism,⁷ whereas an INR >4.0 increases the risk of major bleeding.^{8,9} Maintaining the INR in the reference range requires regular monitoring and appropriate modification of treatment. Therefore, interest has focused on appropriate measures to determine the therapeutic effectiveness of oral anticoagulation.

A systematic review recommended that ≥ 2 outcome measures should be reported and measures should be selected so that INR determinations and quality of dosing advice can be monitored.¹⁰ These measures include clinical event rates, proportion of INR values in therapeutic range, time in therapeutic range (TTR), and proportion of patients in range. Each of these measures has limitations¹¹ and to date, no study has determined whether either of these correlates with measures of clinical effectiveness or adverse clinical outcome.

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The therapeutic range of anticoagulation is narrow and is measured via the international normalized ratio (INR). The

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And yet, important differences in the observed level of INR control depend on the chosen measure. This difference can be as high as 10% in terms of INR control.¹²

Therefore, this study aims to systematically examine the relationship between outcome measures and adverse clinical events (major hemorrhage and thromboembolic events) in patients with AF receiving oral anticoagulation.

Methods

Eligibility and Search Strategy

We searched the Ovid version of MEDLINE and EMBASE as well as the Cochrane Library through Wiley InterScience for the period from January 1990 to January 2008 using a maximally sensitive strategy. Medical subject headings and synonyms were used for these terms: atrial fibrillation, international normalized ratio, warfarin, anticoagulants, and vitamin-K antagonists (VKAs). No language restriction was applied. We also searched the reference lists of identified articles and reviews.

Studies were included if they satisfied the following criteria:

- The study group was a broadly unselected group of adult patients (≥ 18 years of age) receiving outpatient VKA therapy with the specific indication for treatment being AF
- Retrospective study design, prospective cohort study design, or randomized controlled trials (RCTs)
- INR control reported as percentage of TTR, percentage of INRs in range, or similar measures
- At least 25 patients enrolled in study
- Duration of study or mean follow-up period of ≥ 3 months

Data Abstraction and Analysis

We reviewed the titles and abstracts of all identified articles and selected full-text articles containing data on INR. Only articles clearly not meeting the criteria were excluded at this stage. The remaining articles were then reviewed in detail for inclusion. We extracted data on reported control measures and outcomes, including TTR, percentage of INRs in range, and clinical outcomes of major hemorrhage and thromboembolic events. Reasons for study exclusion were different indication (eg, patients with deep-vein thrombosis), use of prophylactic agents other than VKAs, studies with <25 patients, duration of study <3 months, selected INR range (eg, patients with reference range INR >5 only), and no data on INR. Studies that included participants with postoperative AF or valvular disease were also excluded.

We reported subgroup analyses from the relevant studies that provided adequate data on target INR range (range, 2.0 to 3.0) and study type. Two reviewers extracted data independently, and disagreements were resolved by discussion. The reviewers were not masked to any aspects of the studies (eg, journal types, author names, or institutions).

Major hemorrhage and thromboembolic events were converted to rates (percent per patient-year) to allow for comparison across studies. Overall, major hemorrhage was defined as bleeding requiring hospitalization, transfusion required, or hemorrhage involving critical anatomic sites. Thromboembolic events were defined as the occurrence of a new stroke, myocardial infarction, peripheral embolism, or systemic emboli.

We used SPSS 15.0 for Windows (SPSS, Inc, Chicago, Ill) for the statistical analysis and calculated mean \pm SD and median with interquartile (or range) as summary statistics. Descriptive analysis was performed using ANOVA or Kruskal-Wallis H test. Correlation and regression analysis was performed between INR control measures (TTR or percentage of INRs in range) and adverse outcomes (major hemorrhage or thromboembolic events) with or without weighting by sample size. We excluded studies with missing data from the analysis (19 studies for major bleeding rate, 27 studies for thromboembolic rate, and 19 studies for both). There was no statistical difference between the eliminated and retained studies for

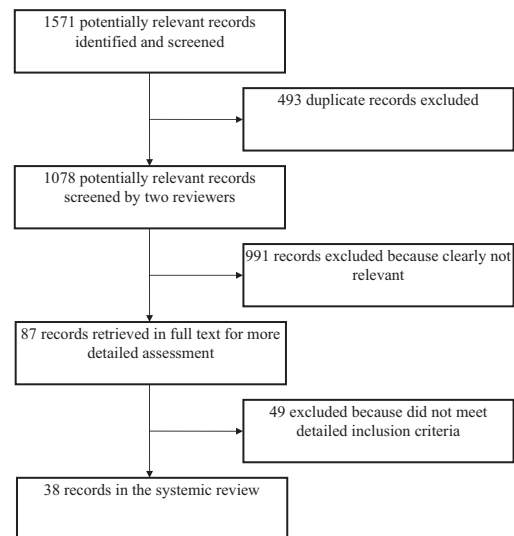


Figure 1. Flowchart of search results.

TTR, mean age, sample size, duration of study, and mean INR tests per patient-year. However, for percentage of INRs in range, the studies with missing data reported significantly lower values (51.5% versus 66.7% [$P=0.01$] for major bleeding rate and 52.8% versus 66.5% [$P=0.02$] for thromboembolic rate).

We examined publication bias by constructing a funnel plot of precision (SE of log TTR or SE of log percentage of INRs in range) against log TTR (or log percentage of INRs in range). In addition, we used Begg rank correlation and Egger linear regression tests to assess funnel plot asymmetry with Stata 10 for Windows (Stata Corp, College Station, Tex).¹³

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

We identified 1571 citations (Figure 1). Of these, 2 authors screened 1078 abstracts (493 duplicate records were excluded) and independently reviewed 87 full-text articles for inclusion and data extraction. A total of 38 articles met the eligibility criteria, reporting 47 study groups (we use “studies” to refer to different groups if reported in the same article). Only 3 articles reported on cohorts including subjects receiving different VKAs (including warfarin),^{14–16} and the VKA used was not reported in 1 article.¹⁷ Thirty-two articles used a target range of 2.0 to 3.0, and 6 articles^{18–23} reported slight variations on this range (ie, 2.0 to 3.5).

Of the identified studies, 27 were retrospective, 5 were prospective cohorts, and 15 were RCTs, with a total of 33 976 participants (Table 1). Data were from the United States (18 studies, including 1 from the United States and Canada), the United Kingdom (10 studies), Italy (4 studies), Canada (3 studies), Spain (3 studies), France (1 study), Germany (1 study), Denmark (1 study), Belgium (1 study), Norway (1 study), The Netherlands (1 study) and Israel (1 study); 2 studies were multinational, from 13 and 23 countries, respectively. The mean age in studies ranged from 64 to 87 years (median, 72 years); duration of studies ranged from 4 to 42 months (median, 15 months); and mean INR tests number per patient-year ranged from 11 to 37 (median, 18). No statistically significant differences were found between different

Table 1. Characteristics of 47 Studies (38 Articles) Reporting INR Control and Outcomes

Study	Duration of Study, Months	Mean Age, Years	Sample Size	Mean INR Tests per Patient-Year	TTR, %			INRs, %			Events Rate (% per Patient-Year)	
					In Range	Below	Above	In Range	Below	Above	Major Bleeding	Thromboembolic
Anderson (2004) US ^{24*}	12	—	87	13	—	—	—	60	25	14	—	—
Menzin et al (2005) US ^{25*}	11	72	600	19	62	25	13	—	—	—	3.6	1.0
Nichol et al (anticoagulation clinic) (2008) US ^{26*}	31	—	351	25	68	21	11	—	—	—	2.3	—
Nichol et al (routine care) (2008) US ^{26*}	19	—	756	19	42	49	9	—	—	—	6.3	—
Gaughan et al (2000) US ^{18*}	8	—	—	—	—	—	—	54	—	—	—	—
Sarawate et al (2006) US ^{27*}	—	74	614	—	29	49	22	—	—	—	—	—
Bratland (2006) Norwegian ^{28*}	16	72	427	—	57	18	25	—	—	—	2.4	—
Currie et al (stable) (2005) UK ^{29*}	35	72	784	11	75	—	—	—	—	—	0.4	0.8
Currie et al (unstable) (2005) UK ^{29*}	35	74	729	26	56	—	—	—	—	—	1.2	2.3
Jones et al (2005) UK ^{30*}	—	73	2223	23	68	17	15	—	—	—	—	—
Neree (2006) Belgium ^{14*}	4	74	395	32	53	9	39	—	—	—	4.4	2.9
Malik and Taylor (2000) US ^{31*}	24	68	247	—	59	27	14	—	—	—	—	—
Yousef et al (2004) UK ^{32*}	12	73	739	37	62	23	14	—	—	—	3.8	1.8
Samsa et al (triangle practices) (2000) US ^{33*}	9	69	—	—	36	52	12	34	51	15	—	—
Samsa et al (no anticoagulation clinic) (2000) US ^{33*}	9	69	—	—	47	34	19	44	34	23	—	—
McCormick et al (2001) US ^{34*}	12	87	174	35†	51	36	13	—	—	—	—	—
Espuny et al (primary care) (2004) Spain ^{35*}	38	76	25	15	—	—	—	44	—	—	—	—
Espuny et al (hospital) (2004) Spain ^{35*}	42	75	87	12	—	—	—	51	—	—	—	—
Copland et al (2001) UK ^{19*}	17	70	328	—	—	—	—	68	10	22	2.8	—
Ansell et al (2007) Italy ^{15*}	12	72	177	17†	70	20	10	60	26	14	—	—
Ansell et al (2007) Spain ^{15*}	12	72	218	11†	65	18	17	59	23	18	—	—
Ansell et al (2007) US ^{15*}	12	75	686	17†	58	28	14	51	32	17	—	—
Ansell et al (2007) Canada ^{15*}	12	74	152	18†	63	25	12	58	28	14	—	—
Ansell et al (2007) France ^{15*}	12	73	278	17†	59	14	27	51	20	29	—	—
Burton et al (2006) UK ^{16*}	37	77	601	—	68	—	—	—	—	—	2.6	—
Boulanger et al (2006) US ^{36*}	12	69	6454	—	48	38	14	—	—	—	—	—
Shalev et al (2007) Israel ^{37*}	—	—	4408	19†	48	35	17	—	—	—	—	—
Abdelhafiz and Wheeldon (2004) UK ^{38†}	19	72	402	16	66	20	14	—	—	—	1.7	—
Hylek et al (2007) US ^{5†}	9	77	472	28	58	29	13	—	—	—	7.2	—
McBride et al (2007) Germany ^{17†}	6	71	324	—	56	14	30	—	—	—	—	—
Kalra et al (2000) UK ^{39†}	17	77	167	—	61	26	13	—	—	—	1.7	3.8
Pengo et al (2001) Italy ^{40†}	17	68	433	18	63	21	16	—	—	—	1.8	1.6
Matchar et al (2002) US ^{41§}	9	76	680	—	54	32	15	—	—	—	2.0	5.0
CAFA (1991) Canada ^{42§}	15	68	187	—	44	40	17	—	—	—	2.1	3.4
EAFT (1993) 13 countries ^{20§}	28	71	225	—	—	—	—	59	32	9	2.6	3.7
SPAF II (<75) (1994) US ^{22§}	37	64	358	—	—	—	—	75	20	5	1.7	2.8
SPAF II (>75) (1994) US ^{22§}	24	80	197	—	—	—	—	72	22	6	4.2	5.6
SPAF III (1996) US ^{7§}	13	71	523	—	—	—	—	61	25	14	2.1	5.3
SIFA (1997) Italian ^{21§}	12	72	454	—	—	—	—	84	14	2	1.3	2.2
Pengo et al (1998) Italy ^{43§}	14	74	153	14	70	18	12	—	—	—	2.7	1.1
AFASAK II (1998) Denmark ^{44§}	25	73	170	—	73	18	9	—	—	—	1.1	2.8
PATAF (stratum 1) (1999) Netherlands ^{23§}	37	70	131	—	—	—	—	48	28	24	0.5	1.3

(Continued)

Table 1. Continued

Study	Duration of Study, Months	Mean Age, Years	Sample Size	Mean INR Tests per Patient-Year	TTR, %			INRs, %			Events Rate (% per Patient-Year)	
					In Range	Below	Above	In Range	Below	Above	Major Bleeding	Thromboembolic
ACTIVE W (2006) Canada ^{45§}	15†	70	3371	—	64	21	15	—	—	—	2.2	1.6
WASPO (2007) UK ^{46§}	12	84†	36	—	70	—	—	—	—	—	—	—
BAFTA (2007) UK ^{4§}	32	82	488	—	67	19	14	—	—	—	1.9	—
SPORTIF III (2003) 23 countries ^{47§}	16	70	1703	—	66	—	—	—	—	—	1.7	2.9
SPORTIF V (2005) US and Canada ^{48§}	20	72	1962	—	68	20	12	—	—	—	2.8	1.9

— indicates data not reported.

*Retrospective study.

†Median value.

‡Prospective cohort study.

§Randomized controlled trial.

study designs for mean age ($F=0.003$; $P=0.99$), duration of studies ($F=0.88$; $P=0.42$), and mean INRs test interval ($F=0.33$; $P=0.73$).

No funnel plot asymmetry was noted for TTR (Begg, $P=0.13$; Egger, $P=0.15$) or percentage of INRs in range (Begg, $P=0.60$; Egger, $P=0.22$).

TTR was used in 36 of 47 (77%) studies and percentage of INRs in range in 18 of 47 (38%), with 7 (15%) studies reporting both measures (Table 2). In these 7 studies, TTR ($56.9 \pm 11.7\%$) significantly correlated with percentage of INRs in range ($51.0 \pm 9.4\%$; $r=0.99$; $P<0.001$). A composite measure of INR control was calculated using TTR when provided or percentage of INRs in range.

Compared with RCTs, retrospective studies had a significantly lower percentage of INRs in range ($52.8 \pm 9.1\%$ versus $66.5 \pm 12.9\%$; $P=0.02$), and a significantly lower composite of TTR and percentage of INRs in range ($56.4 \pm 10.9\%$ versus $64.9 \pm 10.5\%$; $P=0.01$). No significant difference was found between prospective cohort and RCTs ($P=0.44$) or retrospective studies ($P=0.38$; Figure 2).

Major hemorrhage was reported in 28 (60%) studies and thromboembolic events in 20 (43%) studies (Table 1). In all studies, the median rate of major hemorrhage was 2.2 (interquartile, 1.7 to 2.8) per 100 patient-years, and the median rate of thromboembolic was 2.5 (interquartile, 1.6 to 3.6) per 100 patient-years. There was no significant relationship between percentage of time above range and major hemorrhage ($r=-0.05$; $P=0.42$) or between percentage of time below range and thromboembolic rates ($r=0.48$; $P=0.07$). As for percentage of INRs in range, no significant relationship with adverse outcome rates was found in all study designs or in different study designs ($P>0.05$).

TTR negatively correlated with major hemorrhage and thromboembolic rates ($r=-0.59$; $P=0.002$ and $r=-0.59$; $P=0.01$). A linear regression occurred after weighting by sample size between TTR and major hemorrhage (Y [major hemorrhage rate] = $10.104 - 0.120X[\text{TTR}]$, $R^2=0.35$; $P=0.004$) and between TTR and thromboembolic rate (Y [thromboembolic rate] = $8.313 - 0.098X[\text{TTR}]$, $R^2=0.35$; $P=0.03$). Thus, an 8.3% increase in TTR significantly reduced major hemorrhage by 1 event per 100 patient-years (95% CI, 0.35 to 1.64 events), and a 10.2% increase in TTR reduced thromboembolic events by 1 event per 100 patient-years (95% CI, 0.14 to 1.85 events; Figure 3). The unweighted regression analysis produced similar results for major hemorrhage rate (Y [major hemorrhage rate] = $8.367 - 0.092X[\text{TTR}]$, $R^2=0.23$; $P=0.028$) and thromboembolic rate (Y [thromboembolic rate] = $7.323 - 0.080X[\text{TTR}]$, $R^2=0.32$; $P=0.034$).

In retrospective studies alone, a significant correlation occurred between TTR and major hemorrhage ($r=-0.78$; $P=0.006$) and thromboembolic rate ($r=-0.88$; $P=0.03$). A linear relationship occurred between TTR and major hemorrhage (Y [major hemorrhage rate] = $11.716 - 0.145X[\text{TTR}]$, $R^2=0.61$; $P=0.01$) and between TTR and thromboembolic rate (Y [thromboembolic rate] = $6.943 - 0.084X[\text{TTR}]$, $R^2=0.77$; $P=0.05$). Studies were not affected by selection of a weighted or unweighted model. Thus, in retrospective studies, a 6.9% increase in TTR significantly reduced major hemorrhage by 1 event per 100 patient-years (95% CI, 0.29 to 1.71 events), and an 11.9% increase in TTR reduced thromboembolic events by 1 event per 100 patient-years (95% CI, -0.01 to 2.02 events; Figure 4). However, this linear relationship does not exist in RCTs ($r=0.18$; $P=0.33$ for major hemorrhage and $r=-0.61$; $P=0.07$ for thromboembolic event; Figure 5).

Table 2. Median (Range) INR Control in Different Study Designs

Study Design	Time, %					INRs, %				
	No.	In Range	No.	Below Range	Above Range	No.	In Range	No.	Below Range	Above Range
Retrospective studies	22	59 (29–75)	19	25 (9–52)	14 (9–39)	12	53 (34–68)	9	26 (10–51)	17 (14–29)
Prospective cohort studies	5	61 (56–66)	5	21 (14–29)	14 (13–30)	0	—	—	—	—
Randomized control trials	9	67 (44–73)	7	20 (18–40)	14 (9–17)	6	67 (48–84)	6	24 (14–32)	8 (2–24)

INR indicates international normalized ratio.

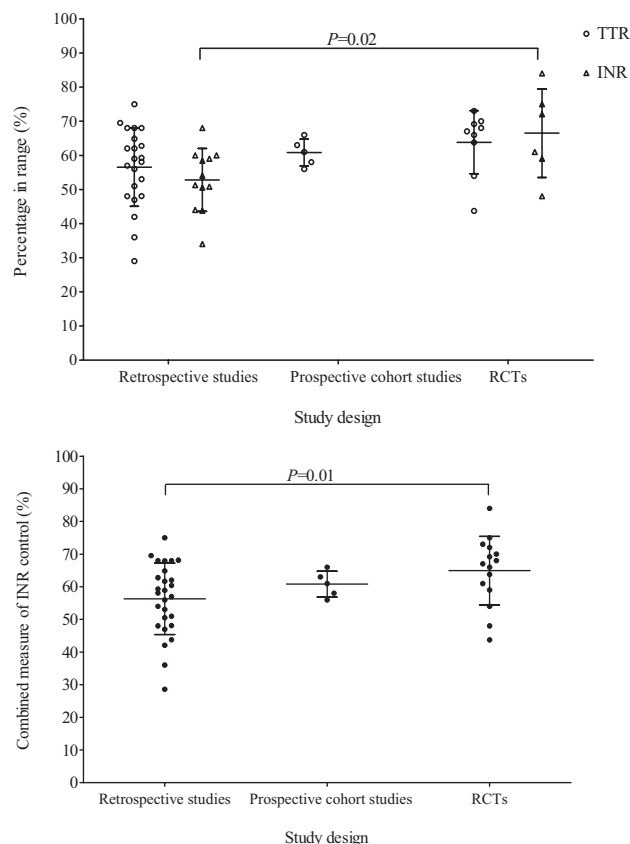


Figure 2. Distribution of TTR and INRs in range in different study designs. Probability values are reported for significant interactions between study designs. Error bar indicates mean \pm SD.

Discussion

We determined that TTR and percentage of INRs in range were the most reported measures in studies of patients with AF who were receiving orally administered anticoagulation

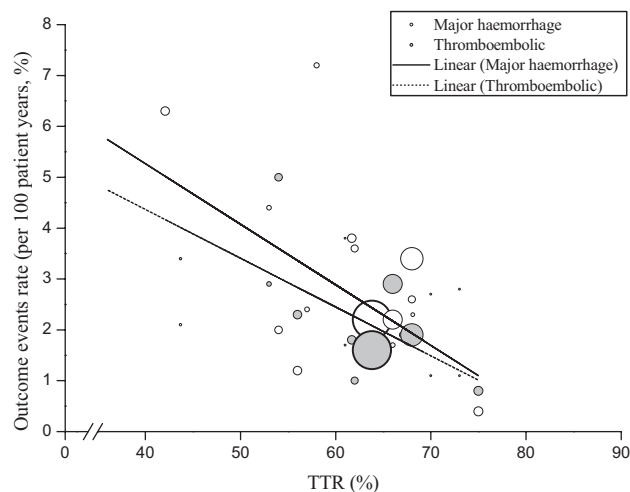


Figure 3. TTR versus adverse events (weighted by sample size) for all studies. TTR versus major hemorrhage rate ($n=21$), correlation: $r=-0.59$; $P=0.002$; linear regression: Y (major hemorrhage rate) $=10.104-0.120X(\text{TTR})$, $R^2=0.35$; $P=0.004$. TTR versus thromboembolic rate ($n=14$), correlation: $r=-0.59$; $P=0.01$; linear regression: Y (thromboembolic rate) $=8.313-0.098X(\text{TTR})$, $R^2=0.35$; $P=0.03$.

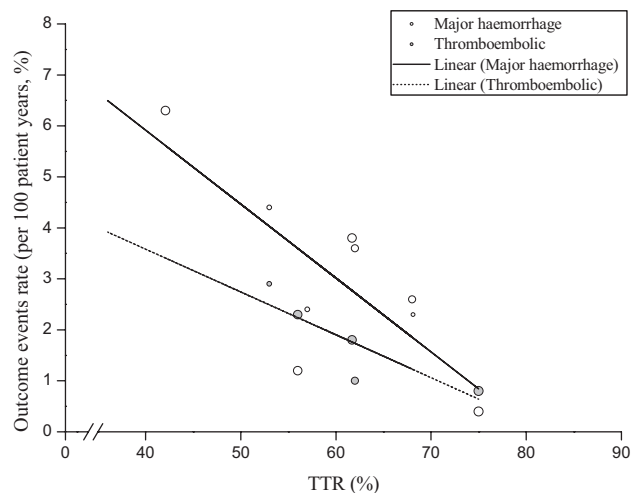


Figure 4. TTR versus adverse events (weighted by sample size) for retrospective studies. TTR versus major hemorrhage rate ($n=9$), correlation: $r=-0.78$; $P=0.006$; linear regression: Y (major hemorrhage rate) $=11.716-0.145X(\text{TTR})$, $R^2=0.61$; $P=0.01$. TTR versus thromboembolic rate ($n=5$), correlation: $r=-0.88$; $P=0.026$; linear regression: Y (thromboembolic rate) $=6.943-0.084X(\text{TTR})$, $R^2=0.77$; $P=0.05$.

treatment. Most of those also reported percentage of INRs above and below target values. However, only a small proportion of studies (15%) reported both TTR and percentage of INRs in range.

We found that TTR had a significant relationship with adverse outcomes in all studies, including major hemorrhage and thromboembolic rates, supporting the reporting of TTR as the optimal measure of INR control. In retrospective studies, a strong negative correlation existed between TTR and adverse clinical outcomes. As a consequence, a 7% improvement in TTR would lead to a reduction of 1 major hemorrhage per 100 patient-years, and a 12% improvement in TTR would lead to a reduction of 1 thromboembolic event per 100 patient-years. The reason for the lack of relationship in RCTs is likely to be the relatively tight control of INR in

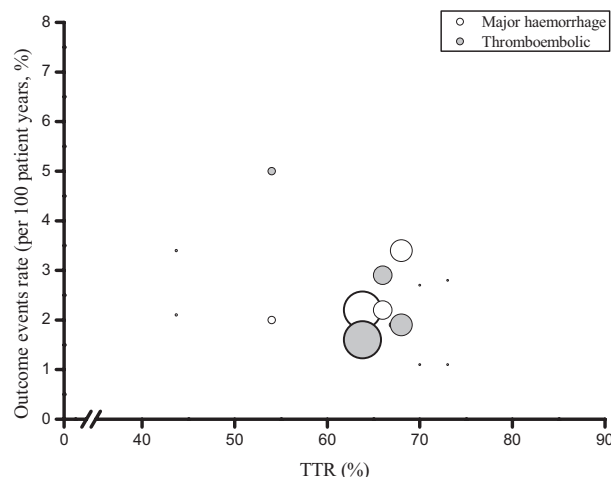


Figure 5. TTR versus adverse events (weighted by sample size) for randomized controlled trials. TTR versus major hemorrhage rate ($n=8$), correlation: $r=0.18$, $P=0.33$. TTR versus thromboembolic rate ($n=7$), correlation: $r=-0.61$, $P=0.07$.

the studies, which reduces the power of the linear relationship.

Our review has some potential limitations. First, although our search was comprehensive, the potential exists for missing both published studies (although this was minimized, because we looked at all references in identified articles) and unpublished studies. Second, variability in the details of studies can affect the results in different study designs. It is clear that a great number of factors can affect patients' risk of clinical events (eg, patient characteristics, indication for anticoagulation, and risk factors).⁴⁹ The level of details provided by studies was not similar, and problems with completeness of information existed. In addition, it is difficult to determine to what extent the reporting of both control measures impinges on study quality. To standardize as far as possible the INR ranges and clinical characteristics of the population, we restricted our review to 1 condition (AF). It was impossible to analyze the effects of extreme values of range and effects on outcomes because of incomplete information. Third, in some studies, the outcome measures were not blindly assessed or independently verified, which could have inflated the apparent results.⁵⁰ However, analysis of blinding revealed there was no difference between studies with or without outcome blinding. Fourth, from our current analysis, the extent to which these results are linear across all ranges of INR control is unknown, particularly at the high and low ends of INR control, because these results were obtained for TTR range between 30% and 75%. Finally, although correlation existed between the 2 measures in the 7 studies reporting both TTR and percentage INRs in range, there was still a mean difference of 6% between them ($P=0.001$). To address this issue, we recommend that all future studies report both measures.

Conclusion

The key findings from our investigation are as follows:

- Most studies of anticoagulation control in AF report TTR or percentage of INRs in range, with low INR control and relatively high adverse events;
- TTR and percentage of INRs in range can be used to predict adverse events in anticoagulated AF patients;
- As little as a 7% improvement in TTR reduced major hemorrhage by 1 event per 100 patient years;
- A reduction in thromboembolic rate by 1 event per 100 patient years can be achieved by a 12% increase in TTR;
- TTR and percentage of INRs in range should both be reported and used as predictors in studies of oral anticoagulation; and
- Anticoagulation services should aim for a TTR between 70% and 80% to optimize benefits and reduce harm for patients.

Clinically, we have set a benchmark by which anticoagulation services can evaluate the impact of improving the percentage of TTR in their patient cohort. A small improvement in percentage of TTR may have a large impact on clinical care. However, when TTR cannot be calculated, percentage of

INRs in range could be used as a proxy, given the strong correlation between the 2 measures.

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Disclosures

None.

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CLINICAL PERSPECTIVE

To obtain optimal benefits of anticoagulation control, patients need to be maintained within their international normalized ratio reference range, which requires regular monitoring and appropriate modification of treatment. This study systematically examined the relationship between international normalized ratio control measurements and the prediction of adverse events in patients with atrial fibrillation on oral anticoagulation. In anticoagulated atrial fibrillation patients, time in therapeutic range and percentage of international normalized ratios in range effectively predict international normalized ratio control, and data from retrospective studies support the use of time in therapeutic range to accurately predict reductions in adverse events across populations. For example, a small increment in time in therapeutic range (7%) can lead to a reduction in major hemorrhage by 1 event per 100 patient-years of treatment. On the basis of our analysis, anticoagulation services should aim for a time in therapeutic range between 70% and 80% to optimize patient benefit and minimize harm.