Should Patient Characteristics Influence Target Anticoagulation Intensity for Stroke Prevention in Nonvalvular Atrial Fibrillation? The ATRIA Study

Daniel E. Singer, MD; Yuchiao Chang, PhD; Margaret C. Fang, MD, MPH; Leila H. Borowsky, MPH; Niela K. Pomernacki, RD; Natalia Udaltsova, PhD; Alan S. Go, MD

Background—Randomized trials and observational studies support using an international normalized ratio (INR) target of 2.0 to 3.0 for preventing ischemic stroke in atrial fibrillation. We assessed whether the INR target should be adjusted based on selected patient characteristics.

Methods and Results—We conducted a case–control study nested within the ATRIA cohort’s 9217 atrial fibrillation patients taking warfarin to define the relationship between INR level and the odds of thromboembolism (TE; mainly stroke) and of intracranial hemorrhage (ICH) relative to INR 2.0 to 2.5. We identified 396 TE cases and 164 ICH cases during follow-up. Each case was compared with 4 randomly selected controls matched on calendar date and stroke risk factors using matched univariable analyses and conditional logistic regression. We explored modification of the INR–outcome relationships by the following stroke risk factors: prior stroke, age, and CHADS2 risk score. Overall, the odds of TE were low and stable above INR 1.8. Compared with INR 2.0 to 2.5, the relative odds of TE increased strikingly at INR <1.8 (eg, odds ratio, 3.72; 95% CI, 2.67 to 5.19, at INR 1.4 to 1.7). The odds of ICH increased markedly at INR values >3.5 (eg, odds ratio, 3.56; 95% CI: 1.70 to 7.46, at INR 3.6 to 4.5). The relative odds of ICH were consistently low at INR <3.6. There was no evidence of lower ICH risk at INR levels <2.0. These patterns of risk did not differ substantially by history of stroke, age, or CHADS2 risk score.

Conclusions—Our results confirm that the current standard of INR 2.0 to 3.0 for atrial fibrillation falls in the optimal INR range. Our findings do not support adjustment of INR targets according to previously defined stroke risk factors. (Circ Cardiovasc Qual Outcomes. 2009;2:297-304.)

Key Words: atrial fibrillation ■ anticoagulation ■ prevention and control ■ stroke

Atrial fibrillation (AF) is the most common significant cardiac arrhythmia and a potent cause of ischemic stroke.1 The occurrence of AF is strongly age-dependent with its prevalence rising to approximately 10% among those 80 years of age or older.2 AF accounts for roughly 15% of all strokes in the United States and more than 30% of strokes among those ≥80 years old.1 Long-term warfarin anticoagulation can reverse the risk of ischemic stroke in patients with AF but it raises the risk of major hemorrhage, most importantly, intracranial hemorrhage (ICH).3,4,6 Both the efficacy and safety of warfarin therapy are tightly linked to anticoagulation intensity.5,7–10 The optimal international normalized ratio (INR) target for AF should minimize both the risk of ischemic stroke and ICH. Previous studies have demonstrated that risk of ischemic stroke is minimized at INR levels above 2.0 and risk of ICH is minimized at INR levels below 3.5.5,8,11–14 Such results provide a firm empirical foundation for the standard INR target of 2.0 to 3.0 for patients with AF.13,15

With the marked projected increase in the prevalence of AF in coming decades and the current emphasis on personalized medicine, we considered whether the INR target should be adjusted according to individual patient characteristics.2,16,17 For example, should the target INR range be higher for patients with a prior ischemic stroke, the subgroup at highest risk for future stroke?18 Similarly, should the INR...
target be lower for older patients at high risk of hemorrhage, as one leading guideline suggests.\textsuperscript{19}

In the current analysis, we conducted a nested case–control study among patients with AF taking warfarin in the Anticoagulation and Risk Factors In Atrial Fibrillation (ATRIA) study to assess whether the INR target should be adjusted according to patient history of prior ischemic stroke, age (>75 years versus ≤75 years), and CHADS\textsubscript{2} AF stroke risk score.\textsuperscript{20}

Methods

Source Cohort Population and Follow-Up

The ATRIA cohort consists of 13,559 adults with diagnosed nonvalvular atrial fibrillation who received care within Kaiser Permanente of Northern California, a large integrated healthcare delivery system. Cohort assembly has been described in detail previously.\textsuperscript{3} Briefly, we identified patients with a diagnosis of atrial fibrillation between July 1, 1996 and December 31, 1997 by searching outpatient databases where an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) diagnosis of atrial fibrillation (427.31) was assigned, and by searching electrocardiographic databases for a diagnosis of atrial fibrillation. Patients with at least 1 outpatient diagnosis of atrial fibrillation and an electrocardiographic diagnosis of atrial fibrillation were included in the cohort. Patients with a diagnosis of atrial fibrillation assigned at more than 1 outpatient visit and who did not have electrocardiographic database confirmation were also included in the cohort because medical record review of a sample of such patients revealed that the great majority had ECG documentation of atrial fibrillation, most of which occurred before the start date of the ECG database. The date of the first diagnosis of atrial fibrillation during the period of cohort assembly was considered the patient’s index date. The cohort was followed through September 30, 2003. Median follow-up was 6 years (interquartile range, 3.1 to 6.7). Patient follow-up was censored at death or disenrollment from the health plan. To include only patients with nonvalvular atrial fibrillation that was presumably not transient, we excluded patients with diagnoses of mitral stenosis, valvular repair or replacement, transient postoperative atrial fibrillation, or concurrent hyperthyroidism.

Patient Characteristics

We searched clinical inpatient and ambulatory visit databases during the 5 years before each patient’s index date to identify previously diagnosed ischemic stroke, heart failure, coronary heart disease, and hypertension using relevant ICD-9 codes.\textsuperscript{3} We used a validated, comprehensive health plan diabetes registry to identify patients with diabetes mellitus. Ascertainment of these stroke risk factors was validated against review of samples of outpatient medical records; crude agreement was high (78\% to 96\%), and corresponding kappa statistics ranged from 0.51 to 0.89. Importantly, stroke risk prediction based on risk factors ascertained in the ATRIA study was in good agreement with risk schemes generated by pooled randomized trial and chart-based cohort study data.\textsuperscript{3,20–22} Concomitant use of aspirin was available from medical charts for 97\% of cases of TE and cases of ICH. Use of aspirin at the time of the controls’ selected INR test was not known.

Warfarin Status

The current analyses focus exclusively on patients taking warfarin. Warfarin status was based on dispensed warfarin prescriptions and INR values in automated pharmacy and laboratory databases using methods previously described.\textsuperscript{3} We validated this computerized approach versus the warfarin status documented in the medical record at the time of an outcome event for 1,207 patients in the ATRIA cohort with a resulting kappa statistic of 0.84. Nearly all discrepancies were attributable to patients’ transiently discontinuing warfarin.\textsuperscript{3,23}

Cases of Thromboembolism and Intracranial Hemorrhage

Thromboembolism

We searched hospitalization and billing claims databases through September 30, 2003, for primary ICD-9 discharge diagnoses indicating potential thromboembolism (TE), including both stroke and systemic embolism (ICD-9 codes available on request).\textsuperscript{3} For both potential TE events and hemorrhagic events (see below), medical record analysts obtained the relevant medical records using a structured protocol. These records were then reviewed by an outcomes review committee composed of physicians. A validated ischemic stroke was defined as a neurological deficit of sudden onset that persisted for more than 24 hours, corresponded to a vascular territory in the absence of primary hemorrhage, and was not explained by other causes (eg, trauma, infection, or vasculitis). A valid peripheral embolism was defined as an embolus identified by radiographic imaging, intraoperative examination, or pathological findings in the absence of underlying atherosclerotic disease in the affected artery. All events were independently verified by 2 outcomes review committee members. Disagreements were resolved by a third committee member. If further clarification was needed, the final decision was made by a consulting neurologist. All TE events were first events occurring during study follow-up. Patients sustaining such events were censored from follow-up for an ICH event. For 3\% of cases of TE, an eligible INR level at the time of event was not available.

Intracranial Hemorrhage

We searched hospital and billing claims databases through September 30, 2003, for primary and secondary discharge diagnoses of ICH, including intraparenchymal, subdural, and subarachnoid hemorrhage (codes available on request). ICH associated with a concomitant discharge diagnosis of major trauma (ICD-9 codes 852.1, 852.3, 852.5, and 853.1) was excluded. Hemorrhagic events not leading to hospitalization or death were excluded. We adjudicated potential hemorrhagic events using the protocol described above for TE events. All ICH events were first events occurring during study follow-up. Patients sustaining such events were censored from follow-up for a TE event. For 15\% of cases of ICH an eligible INR level at the time of the event was not available.

Outcome events occurring outside health plan facilities are also recorded in health plan databases and discharge summaries from such outside facilities were available for review.

Controls

Eligible controls had to be taking warfarin and not have had a TE or ICH during study follow-up up to 90 days after the calendar date of a matched case’s event. Patients sustaining 1 type of outcome event could not later serve as a control for the other type of outcome event. Controls had to have an outpatient INR value recorded within 90 days of the matched case’s event. Controls were matched to individual cases on age within 5 years, sex, prior ischemic stroke, and diagnosis of diabetes, hypertension, and heart failure, based on their status at the time of the matched INR test. From among eligible controls, 4 were randomly selected for each case, with replacement. Sixteen percent of controls served as controls for more than 1 case. Eleven percent of controls became cases at a later calendar date.

Statistical Analysis

This case–control analysis nested within the ATRIA cohort is limited to patients contributing person-time on warfarin. For cases, we used the patient’s first INR on admission for the event as recorded in the medical chart, before any intervention to alter the INR. For controls, we used the outpatient INR closest to the calendar date of the matched case’s event. In the analysis of the overall set of cases and controls, we used 8 INR categories (≤1.3, 1.4 to 1.7, 1.8 to 1.9, 2.0 to 2.5, 2.6 to 3.0, 3.1 to 3.5, 3.6 to 4.5, and >4.5) to explore effects of low and high INR values in greater detail. To increase precision in assessing subgroup effects we used only 6 INR categories: <1.5, 1.5 to 1.9, 2.0 to 2.5, 2.6 to 3.0, 3.1 to 3.5, and ≥3.6. Odds ratios (ORs) for TE or ICH are reported with INR 2.0 to
2.5 as the referent category. We focus on modification of the ORs for different INR categories by patient characteristics. We report analyses for all cases and controls and for subgroups dichotomized by history of prior ischemic stroke, age 75 years, and by aggregated CHADS2 stroke risk score categories. The CHADS2 risk scheme assigns 1 point for congestive heart failure (“C”), 1 point for a diagnosis of hypertension (“H”), 1 point for age greater than 75 years (“A”), 1 point for diagnosed diabetes mellitus (“D”), and 2 points for a history of prior stroke (“S2”). We compared those with a diagnosis of hypertension (“H”), 1 point for age greater than 75 years (“A”), 1 point for congestive heart failure (“C”), 1 point for a history of prior stroke (“S2”). We compared those with a diagnosis of hypertension (“H”), 1 point for age greater than 75 years (“A”), 1 point for congestive heart failure (“C”), 1 point for a history of prior stroke (“S2”). We compared those with a diagnosis of hypertension (“H”), 1 point for age greater than 75 years (“A”), 1 point for congestive heart failure (“C”), 1 point for a history of prior stroke (“S2”). We compared those with a diagnosis of hypertension (“H”), 1 point for age greater than 75 years (“A”), 1 point for congestive heart failure (“C”), 1 point for a history of prior stroke (“S2”). We compared those with a diagnosis of hypertension (“H”), 1 point for age greater than 75 years (“A”), 1 point for congestive heart failure (“C”), 1 point for a history of prior stroke (“S2”). We compared those with a diagnosis of hypertension (“H”), 1 point for age greater than 75 years (“A”), 1 point for congestive heart failure (“C”), 1 point for a history of prior stroke (“S2”). We compared those with a diagnosis of hypertension (“H”), 1 point for age greater than 75 years (“A”), 1 point for congestive heart failure (“C”), 1 point for a history of prior stroke (“S2”). We compared those with a diagnosis of hypertension (“H”), 1 point for age greater than 75 years (“A”), 1 point for congestive heart failure (“C”), 1 point for a history of prior stroke (“S2”). We compared those with a diagnosis of hypertension (“H”), 1 point for age greater than 75 years (“A”), 1 point for congestive heart failure (“C”), 1 point for a history of prior stroke (“S2”). We compared those with a diagnosis of hypertension (“H”), 1 point for age greater than 75 years (“A”), 1 point for congestive heart failure (“C”), 1 point for a history of prior stroke (“S2”). We compared those with a diagnosis of hypertension (“H”), 1 point for age greater than 75 years (“A”), 1 point for congestive heart failure (“C”), 1 point for a history of prior stroke (“S2”). We compared those with a diagnosis of hypertension (“H”), 1 point for age greater than 75 years (we include only INR 1.8 to 2.5 as the referent category. We tested for interaction of INR effects with categories of prior stroke, age, and CHADS2 risk score, as described above. All analyses were performed using SAS software, version 9.1.3 (SAS Institute, Inc.).

The research was approved by the Institutional Review Boards at Massachusetts General Hospital and at Kaiser Foundation Research Institute. Waiver of informed consent was obtained because of the nature of the study. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

**Results**

Among 9217 patients with nonvalvular atrial fibrillation contributing 33 497 person-years on warfarin, we identified 397 eligible thromboembolic events (including 364 ischemic strokes and 33 systemic emboli) and 164 eligible ICHs (including 83 intracerebral hemorrhages, 55 subdural hemorrhages, and 26 “other” intracranial bleeding events) with an index INR level available. We identified 4 matched controls for 559 of the 561 total events (395 TE and 164 ICH), and 1 control for 1 TE case. We excluded the 1 remaining TE event because there were no matched controls.

Matching created a group of controls very similar to the cases in their matched characteristics for both the TE and ICH events (Table). The mean age for TE cases was 77.4 years, and the mean age for TE controls was 77.2 years. The mean age for ICH cases was 77.7 years versus 77.6 years for ICH controls. Likewise, the percent of cases and controls with the matched features of sex, diagnosis of prior stroke, diabetes, hypertension, heart failure, and consequent CHADS2 scores were the same. The median INR for TE cases was 1.7 (interquartile range, 1.3 to 2.2), and the median INR for TE controls was 2.2 (interquartile range, 1.8 to 2.7). Sixty-three percent of the TE cases occurred when INR values were below the standard range of 2.0 to 3.0, whereas only 33% of the TE controls’ INRs were below 2.0. Median INR for ICH cases was 2.6 (interquartile range, 2.0 to 3.4), and median INR for ICH controls was 2.3 (interquartile range, 1.9 to 2.8). Twenty-two percent of ICH cases and 5% of ICH controls had an INR ≥3.6. Whereas most TE events on warfarin occurred at clearly subtherapeutic levels, most ICH events did not occur during periods of excessive anticoagulation intensity.

In Figure 1A we plot the OR, relative to INR 2.0 to 2.5, of TE and of ICH versus 8 ordered INR categories for the entire set of cases and controls. For TE the point estimate of the OR remains close to 1.0 for all INR values of ≤1.8, although we note the CI for INR 1.8 to 1.9 is broad and skewed to values above 1.0 (OR, 1.25; 95% CI, 0.80 to 1.96). The OR increases strikingly at INR 1.4 to 1.7 (OR, 3.72; 95% CI, 2.67 to 5.19) and increases further at INR ≤1.3 (OR, 7.52; 95% CI, 5.20 to 10.86). For ICH, the ORs increase strikingly at INR values above 3.5. For INR 3.6 to 4.5 the OR is 3.56 (95% CI, 1.70 to 7.46), and for INR >4.5, the OR rises remarkably to 12.27 (95% CI, 5.45 to 27.61). There was a small, nonsignificant increase in the odds of ICH at INR 2.6 to 3.0 (OR, 1.60; 95% CI, 0.97 to 2.62) but the odds actually decreased in the next higher INR interval. Of note, there was no decrease in the odds of ICH relative to INR 2.0 to 2.5 at INR values below 2.0. The “U-shaped” curve resulting from the overlap of the TE and ICH curves in Figure 1A shows a pattern of markedly higher TE risk at INR <1.8 and markedly higher ICH risk at INR values greater than 3.5. The relative odds for both types of outcome are lowest in the INR range of 1.8 to 3.5.

To preserve power in the analysis of subgroup effects we reduced the number of INR categories from 8 to 6, using 2 broader categories less than INR 2.0 (ie, 1.5 to 1.9 and <1.5) and INR 2.5 to 3.5. However, the pattern of relative odds is robust to this approach, and the results remained similar using the broader INR categories.

Table. Case and Control Characteristics by Event Type

<table>
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<tr>
<th>CHADS2 Score</th>
<th>Controls (n=1581)</th>
<th>TE Cases (n=396)</th>
<th>Controls (n=656)</th>
<th>ICH Cases (n=164)</th>
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<tr>
<td>0 to 2</td>
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<td>CHADS2 =0 to 2</td>
<td>n</td>
<td>788</td>
<td>197</td>
<td>388</td>
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<td>%</td>
<td>49.8</td>
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<td>59.2</td>
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<tr>
<td>CHADS2 =3 to 6</td>
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<td>268</td>
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<td>%</td>
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<td>40.8</td>
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<tr>
<td>INR</td>
<td>(tests)</td>
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<td>656</td>
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<td>2.7</td>
<td>2.2</td>
<td>2.8</td>
<td>3.4</td>
</tr>
</tbody>
</table>
and only 1 category for INR values above 3.5 (ie, INR ≥3.6). Figure 1B plots the odds ratios of TE and of ICH relative to INR 2.0 to 2.5 as a function of this set of 6 INR categories for the entire set of cases and controls. As is evident, the main features of the INR/outcomes relationships are preserved.

For patients with and without a history of prior ischemic stroke, we again observed a significant increase in odds of TE at INR levels below 2.0 (Figure 2). Compared with INR 2.0 to 2.5, the odds of TE were more than doubled in the INR 1.5 to 1.9 range for those with (OR, 2.34; 95% CI, 1.17 to 4.66)

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Figure 1. A, ORs for TE (396 cases, 1581 controls) and ICH (164 cases, 656 controls) by INR level in adults with nonvalvular AF, with 8 INR categories using INR 2.0 to 2.5 as the referent. Vertical bars indicate 95% CIs. The numbers of cases and controls for each INR category are given below the figure. B, ORs for TE (396 cases, 1581 controls) and ICH (164 cases, 656 controls) by INR level in adults with nonvalvular AF, with 6 INR categories using INR 2.0 to 2.5 as the referent. Vertical bars indicate 95% CIs. The numbers of cases and controls for each INR category are given below the figure.
and without prior stroke (OR, 2.31; 95% CI, 1.62 to 3.31). This effect was even more pronounced at INR levels <1.5 (OR, 6.87; 95% CI, 3.37 to 14.00, for those with a history of prior stroke; OR, 7.40; 95% CI, 4.98 to 10.99, for those without a history of prior stroke). ORs for ICH at INR ≥3.6 were 3.83 (95% CI, 1.26 to 11.66) and 7.45 (95% CI, 3.82 to 14.53), for those with and without stroke, respectively. For those with and without a prior stroke, the odds of TE did not decrease significantly at INR levels above 2.0. As reflected in our overall analyses, there was a small increase in odds of ICH at INR 2.6 to 3.0 among those without a prior stroke that was of borderline significance (OR, 1.76; \(P=0.050\)). This effect was not preserved in the INR 3.1 to 3.5 range. The odds of ICH were not increased at INR 2.6 to 3.0 for those with a prior stroke.

Analyses with age dichotomized as <75 and ≥75 (Figure 3) show that risk of TE was significantly elevated in both age groups at INR <2.0. At INR levels above 2.5, risk of TE was low in both age groups and not significantly different from the risk at INR 2.0 to 2.5. For both age groups the odds of ICH rose strikingly at INR levels ≥3.6 (OR, 5.26; 95% CI, 2.17 to 12.76, for those age <75 years; OR, 6.83; 95% CI, 3.23 to 14.47, for those age ≥75 years). Among those age 75 or older, the relative odds of ICH were modestly elevated at INR levels of 2.6 to 3.0 (OR, 2.06; \(P=0.016\)) but were not significantly elevated at INR 3.1 to 3.5 (OR, 1.74; \(P=0.14\)).

Figure 4 displays the ORs for TE and ICH according to CHADS\(_2\) stroke risk score dichotomized as CHADS\(_2\) 0 to 2 (lower stroke risk) and CHADS\(_2\) 3 to 6 (higher stroke risk). Consistent with our previous analyses, for both CHADS\(_2\) categories there was a significant increase in the odds of TE at INR levels <2.0. Odds of TE for both CHADS\(_2\) groups remained essentially flat above INR 2.5 relative to INR 2.0 to 2.5. The relative odds for ICH increased significantly in both groups at INR ≥3.6, but this increase was more striking in the lower risk CHADS\(_2\) category (OR, 11.01; 95% CI, 5.07 to 23.88 versus OR, 2.90; 95% CI, 1.20 to 7.03). For INR below 2.0, the odds of ICH were largely the same as those for the referent category of INR 2.0 to 2.5. Once again, we observed a modest increase in relative odds for ICH at INR 2.6 to 3.0 in a subgroup, here CHADS\(_2\) 0 to 2 (OR, 1.90; 95% CI, 0.98 to 3.68), but the relative odds decreased to 1.0 (95% CI, 0.38 to 2.61) at INR 3.1 to 3.5.

Concomitant use of aspirin was noted in 4.5% of TE cases and 6.7% of ICH cases and was not related to INR level at the time of the event (\(P=0.39\) for cases of TE; \(P=0.83\) for cases of ICH, both by Fisher exact test).

In separate logistic models of TE and ICH, we explored interactions between INR categories and the subgroup variables of prior stroke, age (dichotomized at age 75 years), and CHADS\(_2\) categories (categorized as 0 to 2 versus 3 to 6). Of the 30 interaction terms tested in the 6 separate models, the only statistically significant interaction detected was between CHADS\(_2\) categories and INR ≥3.6 (\(P=0.026\)) in the logistic model of ICH.

**Discussion**

Crucial to the success of any anticoagulant medication is defining an intensity that effectively prevents the formation of pathological thrombi without excessively increasing the risk of major hemorrhage.\(^5,7-10,14,24\) Prior observational studies have found that INR levels between 2.0 and 4.0 define such an optimal range for oral vitamin K antagonists, notably warfarin, for stroke prevention for individuals with AF.\(^5,8,11-14\) The remarkable success of vitamin K antagonist therapy in randomized trials to prevent stroke in AF is strong evidence...
of the value of the now standard target INR range of 2.0 to 3.0.\textsuperscript{4,25–27} However, with so many AF patients receiving anticoagulants, it is reasonable to consider whether INR targets should be adjusted according to patient features.\textsuperscript{3,28,29} At least 1 leading set of guidelines has recommended considering lower INR targets in elderly patients with AF who are believed to be at high risk for bleeding.\textsuperscript{19} Similarly, one might consider targeting higher INR levels for individuals with AF who have had a prior stroke, a feature which puts them at highest risk for a recurrent event. This has been suggested for AF patients with mitral stenosis.\textsuperscript{18} We have addressed these types of questions using nested case–control analyses from our large ATRIA cohort study. We believe our results provide the most powerful assessment to date of the relative odds of both TE and of ICH as a function of INR level in a common population of patients with AF and in important subgroups of AF patients. We find that the odds of TE increase sharply at INR levels below 1.8 and that the odds of ICH increase sharply at INR levels above 3.5. Although INR 1.8 is slightly lower than the threshold value of 2.0 that we reported in previous studies,\textsuperscript{8} the CI for this OR primarily includes values above 1.0, with an upper bound close to an OR of 2.0, and is consistent with our previous analysis. The trough of the “U-shaped” curve described by the relationships between INR level and odds of TE and of ICH includes the standard INR target range for AF of 2.0 to 3.0. The tails of the curves demonstrate 2 other important features. First, the odds of TE do not decrease further at INR levels above 2.0 to 2.5 and, second, the odds of ICH do not decrease further at INR levels below 2.0 to 2.5. These findings confirm that there is little gain in safety by targeting INR levels below 2.0 and no apparent gain in efficacy by targeting INR levels above 3.0.

We did observe a small increase in the odds of ICH at INR 2.6 to 3.0 compared with INR 2.0 to 2.5. This increase was of borderline statistical significance. Further, for the adjacent higher interval, INR 3.1 to 3.5, the relative odds of ICH was actually lower. The dominant finding on the higher end of the INR range is the striking increase in odds of ICH at INR levels above 3.5.

The general pattern of INR value versus odds of TE or ICH was seen in all subgroups that we tested. The one discordant finding worth noting was the differential impact of INR \(\geq 3.6\) on the odds of ICH for our 2 CHADS\(_2\) subgroups. The lower risk subgroup had a much greater increase in odds of ICH than the CHADS\(_2\) 3 to 6 subgroup. However, the odds of ICH clearly increased markedly in both CHADS\(_2\) subgroups. Considering all our results, we think the best interpretation is that no substantial subgroup effect was demonstrated and that the overall pattern (Figure 1) should be considered to apply to all patients.

Multiple prior investigations of warfarin-related hemorrhages have combined both intra- and extracranial hemorrhages and have demonstrated that risk of hemorrhage is sensitive to the intensity of anticoagulation.\textsuperscript{30–36} We focus exclusively on ICH because the impact of such events is commensurate with the impact of the ischemic strokes we are attempting to prevent with warfarin. This approach has been incorporated into leading guidelines for AF and parallels prior analyses of optimizing choice of INR target levels in patients with mechanical heart valves.\textsuperscript{7,19} We have previously shown that ICHs account for nearly 90% of all the fatalities resulting from warfarin-associated hemorrhage and nearly all the resulting disability among survivors.\textsuperscript{37} To a first approximation, the decision to use warfarin in patients with AF and the choice of INR target hinges on the trade-off between ischemic strokes prevented and ICHs induced.

Establishing the relationship between INR level and occurrence of adverse events demands large numbers of infrequent events among patients taking anticoagulants. We chose an observational approach, using a nested case–control design. It would be very difficult to study this relationship in detail via randomized trials. The size of the trial would have to be quite large, reflecting the multiple INR target intervals tested. Individuals randomized to adjacent small INR intervals would achieve highly overlapping actual INR levels. Analysis of such trials by INR achieved would sacrifice the benefit of randomization.\textsuperscript{14,25} Importantly, no single randomized trial has accumulated nearly enough ICH events to precisely describe these INR versus outcome relationships. Although trials can powerfully assess the comparative efficacy of broadly different INR targets (eg, INR 1.2 to 1.5 versus 2.0 to 3.0 in the SPAF III trial), they are not easily adapted to study the efficacy of the entire range of INR levels.\textsuperscript{25} Our case–control approach is similar to previous person-years analyses addressing optimal INR targets.\textsuperscript{5,8,24}

As an observational design, our study is subject to confounding. In our univariable graphical analyses, we matched cases and controls on known risk factors for stroke which include the 2 dominant non-MRI risk factors for ICH, ie, age and prior stroke.\textsuperscript{23,38,39} These risk factors were also controlled for in our multivariable analyses, and the results of the graphical and multivariable analyses are in agreement. Because our case–control design was nested within a carefully followed cohort study, all cases were incident events and selection biases were minimized. We did not have information on concomitant aspirin use in our control patients. However, chart review of case events revealed that concomitant use of aspirin with warfarin was uncommon and unrelated to the INR level at the time of the event. It is unlikely that additional use of aspirin affected the relationships we describe.

In sum, we analyzed the relationships between INR level achieved and odds of TE and of ICH using the nearly 400 validated cases of TE, mainly ischemic stroke, and 164 validated cases of ICH sustained by individuals with AF taking warfarin in the ATRIA cohort. These most precise assessments of such relationships to date within a common population largely replicate earlier findings that the odds of both TE and ICH are lowest at INR levels from 1.8 through mid-3s. In addition, these analyses indicate that risk of TE is not further reduced at INR levels above 3.0, nor is risk of ICH further reduced at INR levels below 2.0. Our subgroup analyses argue against adjusting INR targets according to the patient characteristics we tested. In particular, we found no evidence to support reducing the target INR range for older patients with AF or increasing the target INR range in patients with prior ischemic stroke. The optimal approach to minimizing both TE and ICH events across all AF subgroups...
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Disclosures
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References
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Daniel E. Singer, Yuchiao Chang, Margaret C. Fang, Leila H. Borowsky, Niela K. Pomernacki, Natalia Udaltsova and Alan S. Go

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Appendix A: 95% Confidence Intervals for Figures 2-4

1. Ninety-five % confidence intervals for the odds ratios shown in Figure 2 for TE and ICH stratified by history of ischemic stroke are as follows: At INR<1.5: TE without a prior stroke, OR=7.40 (95% CI: 4.98-10.99); TE with a prior stroke, OR=6.87 (95% CI: 3.37-14.00); ICH without a prior stroke, OR=1.51 (95% CI: 0.67-3.43); ICH with a prior stroke, OR=0.81 (95% CI: 0.09-7.29). At INR=1.5-1.9: TE without a prior stroke, OR=2.31 (95% CI: 1.62-3.31); TE with a prior stroke, OR=2.34 (95% CI: 1.17-4.66); ICH without a prior stroke, OR=1.01 (95% CI: 0.56-1.85); ICH with a prior stroke, OR=0.69 (95% CI: 0.21-2.33). At INR=2.6-3.0: TE without a prior stroke, OR=0.95 (95% CI: 0.59-1.53); TE with a prior stroke, OR=1.67 (95% CI: 0.73-3.78); ICH without a prior stroke, OR=1.76 (95% CI: 1.00-3.10); ICH with a prior stroke, OR=1.17 (95% CI: 0.42-3.27). At INR=3.1-3.5: TE without a prior stroke, OR=0.81 (95% CI: 0.40-1.64); TE with a prior stroke, OR=1.37 (95% CI: 0.42-4.47); ICH without a prior stroke, OR=1.15 (95% CI: 0.53-2.49); ICH with a prior stroke, OR=1.42 (95% CI: 0.44-4.58). At INR≥3.6: TE without a prior stroke, OR=1.26 (95% CI: 0.69-2.29); TE with a prior stroke, OR=0.82 (95% CI: 0.22-3.01); ICH without a prior stroke, OR=7.45 (95% CI: 3.82-14.53); ICH with a prior stroke, OR=3.83 (95% CI: 1.26-11.66).

2. Ninety-five % confidence intervals for the odds ratios shown in Figure 3 for TE and ICH stratified by age group are as follows: At INR<1.5: TE, age <75, OR=8.48 (95% CI: 4.56-15.77); TE, age ≥75, OR=6.67 (95% CI: 4.40-10.10); ICH, age <75, OR=1.07 (95% CI: 0.28-4.17); ICH, age ≥75, OR=1.54 (95% CI: 0.62-3.87). At INR=1.5-1.9: TE, age <75, OR=2.68 (95% CI: 1.52-4.73); TE, age ≥75, OR=2.15 (95% CI: 1.46-3.16);
ICH, age <75, OR=0.88 (95% CI: 0.37-2.06); ICH, age ≥75, OR=0.95 (95% CI: 0.48-1.89). **At INR=2.6-3.0:** TE, age <75, OR=0.90 (95% CI: 0.42-1.94); TE, age ≥75, OR=1.19 (95% CI: 0.73-1.92); ICH, age <75, OR=0.80 (95% CI: 0.29-2.19); ICH, age ≥75, OR=2.06 (95% CI: 1.15-3.69). **At INR=3.1-3.5:** TE, age <75, OR=0.46 (95% CI: 0.10-2.04); TE, age ≥75, OR=1.10 (95% CI: 0.56-2.15); ICH, age <75, OR=0.42 (95% CI: 0.09-1.97); ICH, age ≥75, OR=1.74 (95% CI: 0.84-3.63). **At INR≥3.6:** TE, age <75, OR=0.38 (95% CI: 0.09-1.68); TE, age ≥75, OR=1.54 (95% CI: 0.85-2.79); ICH, age <75, OR=5.26 (95% CI: 2.17-12.76); ICH, age ≥75, OR=6.83 (95% CI: 3.23-14.47).

3. Ninety-five % confidence intervals for the odds ratios shown in Figure 4 stratified by CHADS2 score are as follows: **At INR<1.5:** TE, CHADS2 = 0-2, OR=7.78 (95% CI: 4.78-12.68); TE, CHADS2 = 3-6, OR=6.84 (95% CI: 4.19-11.16); ICH, CHADS2 = 0-2, OR=1.94 (95% CI: 0.75-5.00); ICH, CHADS2 = 3-6, OR=0.79 (95% CI: 0.21-2.94). **At INR=1.5-1.9:** TE, CHADS2 = 0-2, OR=2.57 (95% CI: 1.67-3.97); TE, CHADS2 = 3-6, OR=2.09 (95% CI: 1.31-3.34); ICH, CHADS2 = 0-2, OR=1.24 (95% CI: 0.62-2.47); ICH, CHADS2 = 3-6, OR=0.62 (95% CI: 0.26-1.48). **At INR=2.6-3.0:** TE, CHADS2 = 0-2, OR=0.88 (95% CI: 0.48-1.61); TE, CHADS2 = 3-6, OR=1.32 (95% CI: 0.75-2.31); ICH, CHADS2 = 0-2, OR=1.90 (95% CI: 0.98-3.68); ICH, CHADS2 = 3-6, OR=1.28 (95% CI: 0.61-2.72). **At INR=3.1-3.5:** TE, CHADS2 = 0-2, OR=0.47 (95% CI: 0.16-1.36); TE, CHADS2 = 3-6, OR=1.47 (95% CI: 0.68-3.16); ICH, CHADS2 = 0-2, OR=1.00 (95% CI: 0.38-2.61); ICH, CHADS2 = 3-6, OR=1.44 (95% CI: 0.60-3.48). **At INR≥3.6:** TE, CHADS2 = 0-2, OR=0.94 (95% CI: 0.42-2.11); TE, CHADS2 = 3-6, OR=1.40 (95% CI:
0.67-2.93); ICH, CHADS₂ = 0-2, OR=11.01 (95% CI: 5.07-23.88); ICH, CHADS₂ = 3-6, OR=2.90 (95% CI: 1.20-7.03).
Appendix A: 95% Confidence Intervals for Figures 2-4

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3. Ninety-five % confidence intervals for the odds ratios shown in Figure 4 stratified by CHADS₂ score are as follows: **At INR<1.5:** TE, CHADS₂ = 0-2, OR=7.78 (95% CI: 4.78-12.68); TE, CHADS₂ = 3-6, OR=6.84 (95% CI: 4.19-11.16); ICH, CHADS₂ = 0-2, OR=1.94 (95% CI: 0.75-5.00); ICH, CHADS₂ = 3-6, OR=0.79 (95% CI: 0.21-2.94). **At INR=1.5-1.9:** TE, CHADS₂ = 0-2, OR=2.57 (95% CI: 1.67-3.97); TE, CHADS₂ = 3-6, OR=2.09 (95% CI: 1.31-3.34); ICH, CHADS₂ = 0-2, OR=1.24 (95% CI: 0.62-2.47); ICH, CHADS₂ = 3-6, OR=0.62 (95% CI: 0.26-1.48). **At INR=2.6-3.0:** TE, CHADS₂ = 0-2, OR=0.88 (95% CI: 0.48-1.61); TE, CHADS₂ = 3-6, OR=1.32 (95% CI: 0.75-2.31); ICH, CHADS₂ = 0-2, OR=1.90 (95% CI: 0.98-3.68); ICH, CHADS₂ = 3-6, OR=1.28 (95% CI: 0.61-2.72). **At INR=3.1-3.5:** TE, CHADS₂ = 0-2, OR=0.47 (95% CI: 0.16-1.36); TE, CHADS₂ = 3-6, OR=1.47 (95% CI: 0.68-3.16); ICH, CHADS₂ = 0-2, OR=1.00 (95% CI: 0.38-2.61); ICH, CHADS₂ = 3-6, OR=1.44 (95% CI: 0.60-3.48). **At INR≥3.6:** TE, CHADS₂ = 0-2, OR=0.94 (95% CI: 0.42-2.11); TE, CHADS₂ = 3-6, OR=1.40 (95% CI:
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