



## reviews

# Warfarin Anticoagulation and Outcomes in Patients With Atrial Fibrillation\*

## A Systematic Review and Metaanalysis

Matthew W. Reynolds, PhD; Kyle Fahrbach, PhD; Ole Hauch, MD; Gail Wygant, RN, MS; Rhonda Estok, RN, BSN; Catherine Cella; and Luba Nalysnyk, MD, MPH

**Objective:** To examine the relationship between international normalized ratio (INR) and outcomes (major bleeding events and strokes) in patients with atrial fibrillation (AF) receiving anticoagulation with warfarin.

**Methods:** A systematic review and metaanalysis of studies published in the English language between January 1, 1985, and October 30, 2002, was performed. MEDLINE (PubMed), Current Contents, and relevant reference lists were searched. Studies enrolling patients with nonvalvular AF receiving warfarin anticoagulation were eligible for inclusion if they reported stroke and/or major bleeding events in relation to INR, or time spent in therapeutic range. The risk of bleeds in overanticoagulated patients (INR > 3) and the risk of strokes in underanticoagulated patients (INR < 2) were assessed.

**Results:** Twenty-one studies (6,248 patients) met all inclusion criteria. Of the 21 studies, a target conventional INR of 2 to 3 was used in 9 studies. An INR < 2, compared with an INR ≥ 2, was associated with an odds ratio (OR) for ischemic events of 5.07 (95% confidence interval [CI], 2.92 to 8.80). An INR > 3, compared with an INR ≤ 3, was associated with an OR for bleeding events of 3.21 (95% CI, 1.24 to 8.28). On average, in the four studies with a target INR range of 2 to 3, patients with AF receiving warfarin spent 61% of time within, 13% of time above, and 26% below the therapeutic range.

**Conclusion:** Available evidence indicates that in patients with nonvalvular AF, the risk of ischemic stroke with insufficient warfarin anticoagulation (INR < 2), and the risk of bleeding events with overanticoagulation (INR > 3) are significantly higher relative to patients with AF maintained within the recommended INR of 2 to 3. However, the published data are sparse, heterogeneous, and primarily reported from clinical trials. More studies evaluating clinical outcomes in relation to INR are needed, especially in a real-world setting. (CHEST 2004; 126:1938–1945)

**Key words:** anticoagulation; atrial fibrillation; warfarin

**Abbreviations:** AF = atrial fibrillation; CI = confidence interval; INR = international normalized ratio; OR = odds ratio; RCT = randomized clinical trial; TIA = transient ischemic attack; UCS = uncontrolled case series

**Learning Objectives:** 1. To recognize that the INR below 2.0 was associated with a 5-fold increase in the risk of stroke in patients with nonvalvular atrial fibrillation. 2. To understand that an INR over 3 increased the risk of major bleeding 3-fold.

Atrial fibrillation (AF) occurs in 2% of adults aged 65 to 75 years, 5% of adults > 75 years old, and 14% of adults > 84 years old.<sup>1</sup> The presence of AF has been found to more than quadruple the risk of stroke.<sup>2</sup> Since AF is such a strong risk factor for stroke and is so common in older, stroke-prone individuals, it accounts for approximately 14% of all

strokes in patients > 60 years old, or 75,000 strokes per year.<sup>3</sup> A series of clinical trials<sup>4–9</sup> that began in the mid-1980s provided substantial evidence for the effectiveness of warfarin in the prevention of stroke in patients with AF. However, anticoagulation with warfarin is not without risk, and therapeutic ranges are narrow. Underanticoagulation may result in

thrombotic events, and overanticoagulation carries an increased risk of hemorrhage. Efficacy and safety of anticoagulation in AF are dependent on the maintenance of the international normalized ratio (INR) between 2 to 3 as recommended by current practice guidelines.<sup>10</sup>

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The aim of this systematic review and meta-analysis was to examine the relationship between INR and selected outcomes (bleeds and strokes) in patients with nonvalvular AF receiving anticoagulation. It will quantify the risk of bleeding in association with overanticoagulation (INR > 3) and the risk of stroke and/or other ischemic events associated with underanticoagulation (INR < 2). Further, in studies that report information regarding the time spent in therapeutic range, this review will summarize and analyze the level of INR control in patients with AF.

## MATERIALS AND METHODS

In general, procedures for this review followed established best methods for the evolving science of systematic review research.<sup>11,12</sup> A protocol was written prospectively, which stated the objectives, search criteria, study selection criteria, data elements of interest, and plans for analysis.

### Literature Search

We conducted a systematic literature review using MEDLINE and Current Contents to identify relevant articles published in the English language between January 1, 1985, and October 30, 2002. We also manually searched references of retrieved articles to identify additional relevant published studies. Search criteria included MEDLINE medical subject heading terms for AF, anticoagulants, and warfarin.

We accepted studies of any design with patients with nonvalvular AF receiving warfarin as long as they reported the outcomes of interest (stroke and/or bleeding events) in relation to INR

and/or time spent in, above, or below the INR therapeutic range. Studies in which all or a vast majority ( $\geq 85\%$ ) of patients enrolled had nonvalvular AF, either chronic or paroxysmal, were eligible for inclusion. Only groups receiving anticoagulation with warfarin alone were analyzed; groups receiving combination therapy were not analyzed.

### Database Development

Data from all accepted studies were extracted to a data form by one investigator, and all elements were reviewed and agreed on by a second investigator before data entry. Data elements sought from each accepted study were protocol-specified study, patient and treatment characteristics, INR information (*ie*, time in range), and number of patients with adverse events of interest by INR strata.

### Statistical Analysis

Descriptive data were summarized across studies using simple counts and means. The incidences of outcomes of interest (bleeds: major and minor and strokes and transient ischemic attacks [TIAs]) were pooled across treatment groups. Odds ratios (ORs) for outcomes of interest were computed for individual studies and then pooled across studies using random-effects modeling.<sup>13</sup> All studies for which an OR was calculated reported the number of patients with events in range and out of range; most studies did not report the in-range and out-of-range number of patients without events. In these studies, the  $2 \times 2$  table used to calculate a study OR required estimation of total event and nonevent counts using percentage of patients/measurements/time-in-range data. For instance, if 100 patients were evaluated for events, and 30% of INR measurements were INR < 2, it was assumed that 30 patients had INRs < 2. These total counts, combined with the reported event counts (*eg*, a study might report that five of the patients who had strokes had an INR < 2) were used to estimate the number of patients without events in and out of range.

Events per person-year rates were calculated for all studies reporting both events below/above the key INR ranges (< 2 and  $\geq 2$  for stroke,  $\leq 3$  and > 3 for major bleeds) and a percentage of time/measurements/patients for each of those ranges. The numerator was the number of events within that INR range; the denominator was the estimated number of patient-years spent within that INR range in the study. For instance, a 2-year study of 200 patients would have a total of 400 observed patient-years. If 30% of observations were with an INR < 2, the denominator for the INR < 2 calculation would be  $0.30 \times 400 = 120$  patient-years. Statistical analyses were conducted using SAS version 8.1 (SAS Institute; Cary, NC).

## RESULTS

### Studies

Seven hundred forty-one abstracts were screened, and 211 full articles were retrieved. Of these, 21 primary (and 9 linked) studies<sup>5-9,14-38</sup> met our inclusion criteria and were accepted for this review. Most of the remaining articles were rejected either because INR was not reported, or the study included a mixed population, in which outcomes for patients with AF were not separable.

Table 1 presents a summary of study characteristics

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\*From MetaWorks Inc. (Drs. Reynolds, Fahrbach, and Nalysnyk, Ms. Estok, and Ms. Cella), Medford, MA; and AstraZeneca LP (Dr. Hauch and Ms. Wygant), Wilmington, DE. Sponsored by AstraZeneca LP, Wilmington, DE.

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Correspondence to: Matthew W. Reynolds, PhD, 10 President's Landing, Third Floor, Medford, MA 02155; e-mail: [Mreynolds@metaworksinc.com](mailto:Mreynolds@metaworksinc.com)

**Table 1—Study Characteristics**

Characteristics	Studies, No.	Treatment groups, No.	Patients, No.
Total	21	27	6,248
Publication year			
1989–1995	5	5	1,571
1996–2002	16	22	4,677
Study location			
North America	7	8	2,548
Europe	8	12	2,835
Other	6	7	865
Study design			
Interventional			
RCT	11	17	4,405
UCS	1	1	35
Observational			
Prospective cohort	4	4	844
Retrospective cohort	5	5	964
Nonvalvular AF			
Chronic only	7	10	2,002
Mixed/not reported	14	17	4,246
Anticoagulation*			
INR 2–3†	9	9	2,046
Variable conventional intensity‡	11	11	2,819
Low intensity§	5	5	691
Warfarin plus aspirin	2	2	692
Prevention type			
Primary prevention	17	22	5,366
Secondary prevention	4	5	882
Sponsorship			
Industry	9	13	3,461
Not reported	12	14	2,787

\*Anticoagulation total exceeds the total number of studies, as some studies included more than one group with different target INR ranges.

†Includes target INR 2.0–3.5 in some patients on one study.<sup>31</sup>

‡Target INRs of 1.4–2.8, 1.5–3.5, 1.91–4.1, 2.0–3.5, 2.5–4.0, 2.5–3.5, 2.0–4.5, 2.2–3.5, and two studies with variable intensity.

§Target INRs of 1.1–1.6, 1.5–2.0, 1.5–2.1, one group of mini-dose warfarin, and one group of fixed-dose warfarin without INR target.

for the accepted studies. Included studies consisted of 11 randomized clinical trials (RCTs)<sup>5,7–9,23,24,29,32,34,35,37</sup> enrolling the majority of patients (n = 4,405), 9 observational studies<sup>14,15,17,18,25,26,30,31,38</sup> (n = 1,808), and 1 uncontrolled case series (UCS)<sup>27</sup> (n = 35). The small UCS was grouped with the observational studies for analysis purposes. Of the 21 studies, 17 studies<sup>5,7,8,14,15,17,18,23–27,30–32,34,35</sup> (n = 5,366) were primary prevention, and 4 studies<sup>9,29,37,38</sup> (n = 882) were secondary prevention studies enrolling only patients with AF with a previous stroke or TIA.

Included in the 21 studies were 9 studies<sup>7,14,15,23,25,26,31,21,34</sup> of patients with AF (n = 2,046) receiving anticoagulation with a target INR of 2 to 3. This was the primary population of interest in the main statistical analysis. In 11 other groups of patients with AF (n = 2,819), conventional anticoagulation intensity was variable, with INR targets rang-

ing from 1.4 to 4.5.<sup>5,8,9,17,18,24,29,30,35,37,38</sup> There were also five groups (n = 691) receiving low-intensity anticoagulation (INR range, 1.1 to 2.1),<sup>23,24,27,32,37</sup> and two groups (n = 692) were receiving a combination treatment of warfarin and aspirin.<sup>23,34</sup> The latter two combination groups were not analyzed.

### Ischemic Events Incidence (Pooled Results)

The pooled incidence of ischemic events was calculated for reference purposes. Table 2 displays the pooled incidence of stroke and TIA in patients with AF by INR target ranges. The results are presented for all studies, and also stratified by study design (RCT vs observational studies). For groups with a target INR of 2 to 3,<sup>7,15,23,26,31,32,34</sup> the incidence of stroke was 2.1%. The incidence of stroke was higher in groups with other INR ranges, especially the low-intensity category (1.1 to 2.1),<sup>23,24,27,32,37</sup> where stroke occurred in 5.8% of patients. The frequency of TIAs did not vary as widely across these different INR ranges.

### Bleeding Events Incidence (Pooled Results)

Incidences of bleeding events by INR target category are also presented in Table 2. The incidence of major bleeds (predominantly cerebral bleeds) in groups with an INR target of 2 to 3,<sup>7,15,23,26,31,32,34</sup> was lower (2.6%), compared with those with much wider therapeutic ranges for anticoagulation (3.6%).<sup>5,8,9,18,24,29,30,35,37,38</sup> Minor bleeds were, as expected, more frequent than major bleeds in both INR target categories. All of the pooled incidences should be interpreted with caution, however, because of the small number of studies contributing to each stratum.

### Target Anticoagulation Achieved

Only six studies<sup>5,7,8,23,26,32</sup> reported the percentage of time patients with AF receiving anticoagulation spent in INR therapeutic range. Other studies reported achievement of target anticoagulation as number (percentage) of patients in range (four treatment groups),<sup>15,18,37</sup> or number (percentage) of measurements in range (five treatment groups).<sup>9,24,29,34</sup> The exact methods for obtaining these estimates were not always reported, so it is possible that in some studies a percentage of measures in range, for instance, was used to estimate a percentage of patients or percentage of time in therapeutic range. Nevertheless, these categories may not be similar and therefore were summarized separately. Table 3 displays these results by INR target range.

In groups with an INR target of 2 to 3,<sup>7,23,26,32</sup> patients with AF on average spent 61.3% of time in

**Table 2—Incidence of Ischemic and Bleeding Events (Pooled Results)\***

Events	INR (2–3)†	Variable (1.4–4.5)‡	Low Intensity (1.1–2.1)
Overall			
Ischemic events			
Stroke	36/1,719 (2.1)	123/2,633 (4.7)	38/656 (5.8)
TIA	25/1,133 (2.2)	14/815 (1.7)	4/167 (2.4)
RCT			
Ischemic events			
Stroke	27/1,033 (2.60)	76/2,004 (3.8)	38/656 (5.80)
TIA	18/880 (2.00)	14/815 (1.7)	4/167 (2.40)
Observational studies§			
Ischemic events			
Stroke	9/686 (1.30)	47/629 (7.50)	Not reported
TIA	7/253 (2.80)	Not reported	Not reported
Overall			
Bleeding events			
Major bleeding	45/1,719 (2.6)	69/1,913 (3.6)	14/656 (2.1)
Minor bleeding	123/1,043 (11.8)	148/1,071 (13.8)	21/227 (9.3)
RCT			
Bleeding events			
Major bleeding	26/1,033 (2.5)	65/1,669 (3.9)	14/656 (2.1)
Minor bleeding	72/357 (20.2)	132/983 (13.4)	21/227 (9.3)
Observational studies§			
Bleeding events			
Major bleeding	19/686 (2.8)	4/244 (1.6)	Not reported
Minor bleeding	51/686 (7.4)	16/88 (18.2)	Not reported

\*Data are presented as No. of patients with event/total No. of patients assessed for event (%).

†Includes one group with target INR 2–3 or 2–3.5.

‡Target INR 2–3 groups excluded.

§Includes one UCS.

range, 12.7% above range, and 26.0% below range. The outcomes were similar in RCTs and observational studies. When presented as percentage of patients in range (one study), only 34.8% of patients were reported as being in range, with 56.5% of patients reported as being below target INR range. One study<sup>34</sup> reported results as a percentage of measurements in range for patients with a target INR range of 2 to 3; this study found 61.0% of measurements within target range with

14.0% of measurements above range and 25.0% of measurements below range.

Groups with more variable INR ranges<sup>5,8,9,18,24,37</sup> spent slightly less time in range (48.1%), had fewer measurements in range (70.3%), but reported slightly higher percentage of patients in range (45.2%). It should be noted that these results are based on only two studies in each reporting stratum and that studies are exclusive from each other.

**Table 3—Anticoagulation Intensity Outcomes\***

Variables	INR (2–3)†		Variable (1.4–4.5)‡		Low Intensity (1.1–2.1)	
	%	n (t)	%	n (t)	%	n (t)
Time in range	61.3	415 (4)	48.1	286 (2)	NR	NR
Time above range	12.7	86 (4)	6.9	41 (2)	NR	NR
Time below range	26.0	176 (4)	45.0	268 (2)	NR	NR
Patients in range	34.8	16 (1)	45.2	199 (2)	91.7	55 (1)
Patients above range	10.9	5 (1)	13.9	61 (2)	5.0	3 (1)
Patients below range	56.5	26 (1)	40.9	180 (2)	3.3	2 (1)
Measurements in range	61.0	319 (1)	70.3	562 (3)	74.9	209 (1)
Measurements above range	14.0	73 (1)	6.6	53 (3)	11.8	33 (1)
Measurements below range	25.0	131 (1)	15.8	126 (3)	12.9	36 (1)

\*All pooled data were weighted by sample size of the treatment group using the No. of patients evaluated for INR efficacy.

†Includes one group with target INR 2–3 or 2–3.5.

‡Target INR 2–3 groups excluded.

*Stroke and Bleeding Events Outside the Target INR Range*

Table 4 presents the incidence of ischemic stroke, in all studies with available data and by study design, occurring in underanticoagulated patients (INR < 2) and those with normal anticoagulation (INR ≥ 2). The stroke incidence is much higher in underanticoagulated patients with AF (7.4 events vs 1.3 events per 100 patient-years). Higher stroke incidence was observed in observational studies as compared with RCTs. The incidence of stroke in underanticoagulated patients in observational studies compared with normal anticoagulation was 9.8 events vs 1.6 events per 100 patient-years, as compared with RCTs that reported 3.1 events vs 0.5 events per 100 patient-years.

Table 4 also presents the incidence of major bleeding events occurring in overanticoagulated patients (INR > 3) and those with normal anticoagulation (INR ≤ 3). Major bleeds were much more common in overanticoagulated patients with AF (3.7 events per 100 patient-years) than in normally anticoagulated patients (1.4 events per 100 patient-years). Patients with AF in observational studies had an incidence of major bleeds of 4.7 events vs 1.0 events per 100 patient-years in overanticoagulated vs appropriately anticoagulated patients, respectively. Similarly, randomized trials reported rates of 3.3 events vs 1.5 events per 100 patient-years.

**Table 4—Ischemic Stroke and Major Bleeding Incidence by INR (Patient-Years Analysis)**

Variables	Events (Treatment Groups), No.	Patient-Years, No.	Events per 100 Patient-Years, No.
<b>Ischemic stroke</b>			
All studies			
INR < 2	34 (7)	457.11	7.4
INR ≥ 2	15 (7)	1,178.88	1.3
Study design			
RCT			
INR < 2	5 (3)	161.07	3.1
INR ≥ 2	2 (3)	370.67	0.5
Observational studies			
INR < 2	29 (4)	296.04	9.8
INR ≥ 2	13 (4)	808.21	1.6
<b>Major bleeding</b>			
All studies			
INR > 3	30 (7)	2,159.15	14
INR ≤ 3	13 (7)	349.59	3.7
Study design			
RCT			
INR > 3	24 (5)	1,570.55	1.5
INR ≤ 3	8 (5)	243.19	3.3
Observational studies			
INR > 3	6 (2)	588.60	1.0
INR ≤ 3	5 (2)	106.40	4.7

The meta-analysis confirms these pooled results. Meta-analytic results of ORs for stroke and major bleeds are presented in Table 5. For strokes, only studies<sup>7,15,17,18,25,26,31,37</sup> with extractable information for the lower INR target boundary of ≥ 2 were included in the meta-analyses; for major bleeds, only studies<sup>7,8,15,23,31,32,34</sup> with extractable information for an upper INR target boundary of ≤ 3 were included in these analyses. The overall OR for ischemic stroke for patients with INR < 2 vs INR ≥ 2 is 5.07 (95% confidence interval [CI], 2.92 to 8.80), which means that underanticoagulated patients with AF are significantly more likely to have stroke than those maintained within normal anticoagulation range. Also, the ORs for stroke in underanticoagulated vs normal anticoagulated patients are higher in primary prevention studies than secondary prevention studies (5.28 vs 1.09), and in studies enrolling both patients with chronic and paroxysmal AF compared to patients with entirely chronic AF (7.28 vs 3.42).<sup>7,15,18,25,26,31,32,37</sup>

For major bleeds, for patients with INR > 3 vs ≤ 3, the OR is 3.21 (95% CI, 1.24 to 8.28), meaning that overanticoagulated patients are significantly more likely to experience major bleeds than those normally anticoagulated. The ORs for major bleeding in overanticoagulated vs normal anticoagulated patients were higher in observational studies compared with RCTs (5.67 vs 2.37), and in studies enrolling only patients with chronic AF compared with mixed AF populations (4.06 vs 2.72).<sup>7,8,15,23,31,32,39</sup>

There were also several studies<sup>9,17,25,30,31,32</sup> providing information on stroke and bleeds by multiple INR strata, which allowed some exploration of the spectrum of the risk of events along a more continuous INR range. The ORs for stroke and bleeds were calculated for each stratum within each such study that also had a normal reference INR range available (INR 2 to 3). Table 6 shows the meta-analyzed OR results. Although there appears to be significant heterogeneity in the study results for the extreme stratum of INR for the ischemic events, there is a significantly elevated OR of 2.11 (95% CI, 1.06 to 4.19) for the INR 1.5 to 2.0 stratum compared with the INR 2 to 3 reference group. The OR point estimate for the INR < 1.5 stratum is 3.25 for ischemic events, but the 95% CI (0.45 to 23.46) is wide and includes 1, and is therefore not statistically significant. The OR for major bleeds for INR 3 to 4 compared with INR 2 to 3 is 2.34 (95% CI, 0.54 to 10.10), and does not reach statistical significance. The OR for INR > 4 compared with the INR 2 to 3 reference group is highly significant at 33.23 (95% CI, 9.12 to 121.07).

**Table 5—OR for Ischemic and Bleeding Events\***

Variables	Ischemic Stroke INR < 2 vs INR ≥ 2			Major Bleeding INR > 3 vs INR ≤ 3				
	Treatment Groups, No.	Patients, No.	OR (95% CI)	Q p Value	Treatment Groups, No.	Patients, No.	OR (95% CI)	Q p Value
Overall results	8	1,754	5.07 (2.92–8.80)	0.66	7	1,812	3.21 (1.24–8.28)	0.15
Prevention type								
Primary prevention	7	1,699	5.28 (3.03–9.20)	0.66	7	1,812	3.21 (1.24–8.28)	0.15
Secondary prevention	1	55	1.09 (0.03–34.04)	Not reported	Not reported	Not reported	Not reported	Not reported
Study design								
RCT	3	395	4.53 (0.84–24.42)	0.63	5	1,293	2.37 (0.63–8.96)	0.12
Observational studies†	5	1,359	5.09 (2.74–9.45)	0.41	2	519	5.67 (1.63–19.77)	0.46
Type of AF								
Chronic	3	705	3.42 (1.70–6.88)	0.98	3	583	4.06 (0.39–42.54)	0.06
Mixed	5	1,049	7.28 (3.93–13.49)	0.70	4	1,229	2.72 (1.07–6.92)	0.34

\*Q p value = result of test of homogeneity (p < 0.05 indicates heterogeneity).

†Includes on UCS.

**Table 6—Metaanalysis of ORs for Multiple INR Strata**

Variables	Treatment Groups, No.	Patients, No.	OR (95% CI)*
Ischemic events			
INR < 1.5	5	761	3.25 (0.45–23.46)†
INR 1.5–2.0	5	703	2.11 (1.06–4.19)
INR 3.0–4.0	3	349	1.19 (0.49–2.91)
INR > 4.0	3	291	1.49 (0.12–12.30)†
Major bleeding			
INR < 2.0	2	493	2.19 (0.40–11.87)
INR 3.0–4.0	2	507	2.34 (0.54–10.10)
INR > 4.0	2	409	33.23 (9.12–121.07)

\*Relative to INR 2–3 reference range.

†Indicates significant heterogeneity.

## DISCUSSION

The results are in line with the current clinical belief<sup>39</sup> that low INR is associated with an increased risk of stroke and high INR is associated with increased risk of bleeding. The available evidence indicates a higher incidence of ischemic stroke in patients with nonvalvular AF with insufficient anticoagulation (INR < 2), and a higher incidence of bleeding events in overanticoagulated patients with nonvalvular AF (INR > 3). Further, the results of well-controlled, published clinical trials<sup>7,23,32</sup> show that patients with nonvalvular AF receiving warfarin anticoagulation spend, on average, only approximately 60% of time in the INR therapeutic range. Approximately 25% of the time, patients with nonvalvular AF are below the minimum target INR of 2, and thus are not adequately protected against stroke. Another 13% of the time, patients spend time above the upper INR limit of 3, and are at increased risk for major bleeding events.

It is clear that the incidence of events is associated not just with time in range, but the target INR range itself. The wider targets (INR 1.4 to 4.5) have higher incidence of both strokes and bleeds, and the low-intensity targets (INR 1.1 to 2.1) have a higher incidence of stroke. It would seem that this would be related to having more patients who are successfully in the target range, but are still treated to an INR < 2 or an INR > 3. Patients with nonvalvular AF who are treated to an INR target of 1.1 to 2.1 may be minimizing their risk of bleeds, but may not be fully protected from the risk of stroke.

There are several previous meta-analyses<sup>40,41</sup> that have addressed the effectiveness of warfarin in patients with AF, but none of them have specifically addressed the risk of stroke and bleed events associated with INR. This meta-analysis was able to address the evidence gap that existed regarding the association between INR and risk of stroke and bleeds.

Recent publications<sup>42,43</sup> from a large integrated

delivery system have reported similar findings both with respect to time in range, which was reported to be 62.5%, and with respect to the relationship between INR and outcomes. Eighty percent of the patients in this study were managed by a coagulation service. Whereas the relationship between INR and outcomes seem to be well documented by the current meta-analyses and the study of the large, integrated health delivery system,<sup>42,43</sup> these reports cannot be taken as an indication of outcomes of warfarin therapy in routine medical care. Time in range has been documented, in a few studies<sup>44,45</sup> addressing the issues, to be much lower in routine medical management than it has been reported in clinical trials and coagulation clinics. Additionally, modeling studies<sup>46,47</sup> have demonstrated that the outcomes of anticoagulation with warfarin are highly dependent of how warfarin is managed and the level of INR control achieved. It is possible that one or more novel fixed-dose antithrombotic agents that do not require anticoagulation monitoring currently in development for stroke prevention in patients with AF may overcome the problems of managing INR associated with warfarin therapy.<sup>48</sup>

The main limitation of this review and meta-analysis is that study variability and incomplete reporting limited the number of studies that could be included in the meta-analysis. Before 1990, there were very few studies that provided information on INR, since most studies used prothrombin time as the marker for warfarin intensity. Additionally, the majority of studies (and patients) included in the INR analyses were based on data from RCTs, which provide detailed information on INR and outcomes, but which may not provide evidence that is generalizable to the non-RCT general population. There was an apparent lack of information on the INR control and INR association with adverse events in particular for non-RCT treatment. Additional information on treatment setting such as general practitioner treatment vs coagulation clinics may provide additional detail on factors that influence time in INR range and the link to adverse events.

An additional limitation is that this was an analysis of study group data rather than individual patient-level data. That distinction must be made, as analyses were unable to control for known risk factors for stroke, such as previous stroke, previous bleeds, and older age. Observational cohort studies may provide a better opportunity to assess real-world effectiveness. Currently, there are few published observational nonclinical trial studies that link INR to outcomes. Over the past few years, it has been increasingly more common for individual patient databases, based on either insurance claims or electronic medical records, to include laboratory results along with a longitudinal patient medical history. These

databases may be an important and useful source of information in understanding the real-life relationship between INR and outcomes like bleeds and strokes.

Conversely, the fact that this was a literature review of studies (as compared with an individual patient-level analysis) is also the biggest strength of this review because these results represent all of the best evidence from the available published literature. The conclusions support the clinical belief that the level of INR is directly related to an increased risk of stroke or bleeds.

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