Meta-Analysis to Assess the Quality of Warfarin Control in Atrial Fibrillation Patients in the United States

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ABSTRACT

BACKGROUND: Atrial fibrillation (AF) affects a significant proportion of the American population and increases ischemic stroke risk by 4- to 5-fold. Oral vitamin K antagonists, such as warfarin, can significantly reduce this stroke risk but can be difficult to dose and monitor. Previous research on the effects of setting (e.g., randomized controlled trials, anticoagulation management by specialty clinics, usual care by community physicians) on the proportion of time spent within therapeutic range for the international normalized ratio (INR) has not specifically examined anticoagulation in AF patients.

OBJECTIVES: Use traditional meta-analytic and meta-regressive techniques to evaluate the effect of specialty clinic versus usual care by community physicians on anticoagulation control, measured as the proportion of time spent in therapeutic INR range, for AF patients that received warfarin anticoagulation in the United States.

METHODS: Studies included in a previously published meta-analysis (van Walraven et al., 2006), which systematically searched reports between 1987 and 2005, were also screened for inclusion in our analysis. A subsequent systematic literature search of MEDLINE, EMBASE, and the Cochrane Central Register of Clinical Trials from January 2005 through February 2008 was conducted. Studies were included if they (a) contained at least 1 warfarin-treated group including more than 25 patients for whom INR control was monitored for at least 3 weeks; (b) included patients treated for AF in the United States; (c) used a patient-time approach (patient-year) to report outcomes; and (d) reported data on the proportion of time spent in traditional therapeutic INR ranges (i.e., a lower limit INR between 1.8 and 2.0 and an upper limit INR between 3.0 and 3.5. Studies with INR goals outside this range were excluded). The proportion of time spent within the therapeutic INR range for each study group was expressed as an incidence density using a person-time approach (in years). All studies were pooled using a random effects model and were weighted by the inverse of the variance of proportion of time spent in the therapeutic range. In order to determine how study setting influenced the proportion of time spent within a therapeutic INR range, both subgroup and meta-regression analyses were conducted.

RESULTS: This analysis included 8 studies and a total of 14 unique warfarin-treated groups; 3 of the 8 studies and 4 of the warfarin groups were not included in the previous meta-analysis (van Walraven et al., 2006). Overall, patients spent a mean 55% (95% CI=51%-58%) of their time in the therapeutic INR range. Meta-regression suggested that AF patients treated in a community usual care setting compared with an anticoagulation clinic spent 11% (95% CI=2%-20%, n=6 studies with 9 study groups) less time in range.

CONCLUSIONS: In the United States, AF patients spend only about one-half the time within therapeutic INR. Anticoagulation clinic services are associated with somewhat better INR control compared with standard community care.

J Manag Care Pharm. 2009;15(3):244-52

What is already known about this subject

- The 2008 practice guidelines from the American College of Chest Physicians include a recommendation to use long-term oral anticoagulation in patients with atrial fibrillation (AF) and a recent stroke or transient ischemic attack, to a target INR of 2.5 (range 2.0 to 3.0; Grade 1A quality of evidence).
- Van Walraven et al. (2006) evaluated 67 studies involving 50,208 patients with 57,155 patient-years of follow-up. Overall, patients taking vitamin K antagonists for a wide range of indications that included atrial fibrillation, venous thromboembolism, cardiovascular disease other than atrial fibrillation, peripheral vascular disease, valvular heart disease, and other indications were within therapeutic INR range 63.6% of the time (95% CI=61.6%-65.6%). For the patients managed in usual care (i.e., by community physicians), time in therapeutic INR was 12.2% lower (95% CI=−19.5 to −4.8%, P<0.001) compared with patients managed in anticoagulation clinics.
- Study setting is a significant predictor of the time spent in therapeutic INR range, with about 66% of the time in therapeutic range for anticoagulation therapy in both randomized controlled trials and anticoagulation clinics versus 57% for community-based care provided by physicians.

What this study adds

- Our meta-analysis assessed 8 studies including a total of 14 groups involving 22,237 warfarin-treated AF patients with 41,199 years of follow-up. Atrial fibrillation patients in the 14 groups spent 55% (95% CI=51%-58%) of their time within the therapeutic INR range.
- Of the 8 studies, 13 groups could be evaluated by setting: warfarin dosing was managed by anticoagulation clinics for 4 (31%) groups and by community (physician) practice, defined as usual care, for 9 (69%). Patients in anticoagulation clinics spent on average 63% (95% CI=58%-68%) of their time in the therapeutic range versus 51% (95% CI=47%-55%) for patients in community practice. Compared with an anticoagulation clinic, patients treated in the usual care (community) setting spent 11% (95% CI=2%-20%, n=6 studies) less time in therapeutic INR range.
- 5 studies (including 8 groups) reported data on the proportion of eligible patients receiving warfarin. Overall, 48% (95% CI=43%-54%) of eligible AF patients received warfarin, including 53% of AF patients managed by anticoagulation clinics, revealing another gap in protection from ischemic stroke.

Atrial fibrillation (AF), the most common cardiac rhythm disorder, increases the risk for ischemic stroke 4- to 5-fold.[1,2] Studies have demonstrated that use of oral vitamin K antagonists such as warfarin significantly reduces the risk of stroke by up to 68% compared with no therapy, from a range of 4.5% without warfarin to 1.4% with warfarin.[3] For patients receiving therapy with warfarin, the proportion of time spent in the therapeutic international normalized ratio (INR) range is strongly associated with reduced risk of both bleeding and thromboembolism.[4-6] However, achieving high-quality anticoagulation control can often be difficult and labor intensive with warfarin due to its indirect mode of action and a large number of factors that influence its pharmacokinetics and pharmacodynamics, including patient age, concurrent medications and diet, comorbidities, and genetics.[7]

Understanding the overall quality of anticoagulation management in AF patients in the United States can be challenging because there is variation in the proportion of time spent within the therapeutic INR range among studies. Study-specific factors, such as study setting (randomized trial vs. observational anticoagulation clinic-based trial vs. observational community physician office-based trial) may explain at least some of the variance in reported quality of anticoagulation. A meta-analysis reported by van Walraven et al. in 2006 included studies from around the world and included warfarin as well as 4 vitamin K antagonists that are not available in the United States (acenocoumarol, dicumarol, ethyl biscoumacetate, and phenprocoumon).[8] Van Walraven et al. evaluated 67 studies involving 50,208 patients with 57,155 patient-years of follow-up. Overall, patients taking vitamin K antagonists for a wide range of indications that included atrial fibrillation, venous thromboembolism, cardiovascular disease other than atrial fibrillation, peripheral vascular disease, valvular heart disease, and other indications were within therapeutic INR range 63.6% of the time (95% CI = 61.6%-65.6%).

Outside the United States, self-management of anticoagulation therapy has been a subject of research designed to find methods that might be more effective and efficient than usual care or anticoagulation clinics. Gadisseur et al. (2003) in a randomized trial found that patient self-management using a hand-held prothrombin time monitoring device was at least as effective as specialized physician management in anticoagulation clinics, as measured by the proportion of time spent in INR range.[9] In the systematic review and meta-regression reported by van Walraven et al., 24.4% of the patients were managed in usual care (community physicians); 68.3% of patients were in anticoagulation clinics; and 7.3% of the patients were involved in clinical trials.[8] Meta-regression showed that setting had a significant effect on anticoagulation control, with studies in community practices having significantly lower control than either anticoagulation clinics or clinical trials (–12.2%; 95% CI = –19.5 to –4.8; $P < 0.001$), and self-management was associated with a significant improvement of time spent in the therapeutic range (+ 7.0%; 95% CI = 0.7-13.3;

$P = 0.03$). Study setting was a significant predictor of the time spent in therapeutic INR range, with about 66% of the time in therapeutic range for anticoagulation therapy in both randomized controlled trials and anticoagulation clinics as compared with 57% for community-based care provided by physician.[8]

The findings reported by van Walraven et al.[8] are informative but not specific to AF patients and perhaps not generalizable to the United States for warfarin therapy. Health system infrastructures and practice patterns vary greatly between nations, which can lead to differences in degrees of management. Pengo et al. (2006) highlighted differences in anticoagulation care between countries in a recently published International Study of Anticoagulation Management (ISAM) study.[10] They found superior INR control in Spain and Italy versus the other countries; however, hematologists ran all the clinics in Spain and primarily cardiologists and hematologists ran those in Italy. The studies conducted in the United States, Canada, and Italy used predominantly warfarin, while studies in Spain and France, respectively, used acenocoumarol and fluinione.

The purpose of our analysis was to identify and assess (using traditional meta-analytic and meta-regressive techniques) data from all published randomized trials or cohort studies evaluating the quality of management of warfarin use by AF patients in the United States.

■ Methods

In order to ensure comparability between our results and those of the previous meta-analysis by van Walraven et al.,[8] we utilized similar study selection and statistical analytic methodologies.

Study Selection

We first examined the full-text versions of all 67 studies included in the meta-analysis by van Walraven et al.,[8] which searched reports between 1987 and 2005, for inclusion in our analysis using the entry criteria described below. A subsequent systematic literature search was conducted in MEDLINE, EMBASE, and the Cochrane Central Register of Clinical Trials from January 1, 2005, through the end of February 2008 to identify additional studies (either prospective randomized or observational in design) evaluating warfarin as an anticoagulant in patients with AF. The search used the following Medical Subject Headings (MeSH) and text keywords: *warfarin, vitamin k antagonist, VKA, anticoagulant and international normalized ratio, INR, prothrombin time, PT, PTR.* The resulting citations were then limited to human subjects, clinical trials, and English language publications. Furthermore, a manual search of references from reports of clinical trials or review articles was performed to identify additional relevant trials.

Two investigators (Cios and Coleman) reviewed all potentially relevant articles independently, with disagreement resolved by a third investigator (Baker). To be included in this meta-analysis, studies had to (a) contain at least 1 warfarin-treated group including at least 25 patients for whom INR control was monitored for

| TABLE 1 | Characteristics of U.S. Atrial Fibrillation Warfarin Studies and Groups |

Study	Design	Warfarin Indication	Number of Warfarin-Treated Patients	Follow-Up	Study Group	Interpolation Method	Patient Years of Follow-Up[a]	Proportion (95% CI)[b]
Samsa et al., 2000[17]	RD	AF—identified by new ECG, chart documentation of AF, diagnostic code for AF+warfarin	43 61 125	NR	AC Clinic Community Community	Linear Linear Linear	32.3[a] 45.8[a] 93.8[a]	0.60 (0.43-0.75) 0.47 (0.33-0.61) 0.36 (0.27-0.46)
McCormick et al., 2001[18]	RD	AF—identified by ECG or physician documentation of AF	174	1 year	Community	Linear	174[a]	0.51 (0.44-0.58)
Matchar, 2003[20]	PD	AF	363 363 317 317	9 months	Clinic/Comm Community Community Community	Other Other Other Other	272.3[a] 272.3[a] 237.8[a] 237.8[a]	0.56 (0.50-0.61) 0.49 (0.43-0.55) 0.48 (0.42-0.54) 0.52 (0.46-0.59)
Go et al., 2003[21]	RD	Nonvalvular AF	7,445	2.35 years (1.83-2.81)[c]	Community	Linear	12,958	0.63 (0.62-0.63)
Menzin et al., 2005[26]	RD	Nonvalvular AF	600	10.5 ± 3.2 months[d]	AC Clinic	Linear	525[a]	0.62 (0.58-0.66)
Shen et al., 2007[31]	RD	Hospitalization for AF or atrial flutter	11,016	3.3 years (1.0-5.1)[b]	Community	Linear	24,179	0.55 (0.54-0.55)
Hylek et al., 2007[35]	PD	AF—verified by ECG	306	1 year	AC Clinic	Linear	360	0.58 (0.53-0.63)
Nichol et al., 2008[38]	RD	Nonvalvular AF	756 351	NR	Community AC Clinic	Halving Halving	1,164.2[a] 919.6[a]	0.42 (0.39-0.45) 0.68 (0.65-0.71)

[a]For the indicated studies, patient-years of follow-up were estimated using number of patients in each group and the length of follow-up reported in the study.
[b]Mean (95% confidence interval) proportion of time spent within the therapeutic INR range; none of these patients self-managed their own warfarin regimens.
[c]Data reported as median (interquartile range).
[d]Data reported as mean ± standard deviation.
AC = anticoagulation; AF = atrial fibrillation; CI = confidence interval; Comm = community; ECG = electrocardiogram; Method = International Normalized Ratio interpolation method used in the study; NR = not reported; PD = prospective design; RD = retrospective design.

at least 3 weeks; (b) include only patients treated for AF within the United States; (c) use a patient-time approach that requires the measurement of serial INRs in each study subject and an interpolation (any interpolation method was accepted, but linear was used preferentially when available) of the values between actual measures so that anticoagulation status could be estimated for each day of observation; and (d) report data on the proportion of time spent in traditional therapeutic INR ranges (i.e., a lower limit INR between 1.8 and 2.0 and an upper limit INR between 3.0 and 3.5. Studies with INR goals outside this range were excluded).[2] Finally, if studies reported INR control on the same patient group at different time periods, only the time period of the longest duration was included. Studies were excluded if serial INRs were measured after the systemic administration of vitamin K, as these measurements may not be a true marker of anticoagulation status.

Data Abstraction

Two investigators (Cios, Coleman) used a common data abstraction tool but independently abstracted all data. If a disagreement arose it was resolved by a third investigator (Baker). The following information was obtained from each study: author identification, year of publication, geographic location of the study, type of anticoagulant used, and the study setting (designated as anticoagula-

tion clinic, randomized trial, or community practice). The setting was designated using the following definitions: (a) an anticoagulation clinic if the study took place in an anticoagulation clinic or if the stated role of the study clinicians in patient care was limited to managing anticoagulation; (b) a randomized trial if random allocation was employed to assign subjects to receive warfarin or another non-warfarin therapy; and (c) all others were classified as community practice. All of the preceding definitions were similar to those used by van Walraven et al.[8]

Statistical Analysis

The proportion of time spent within the therapeutic INR range for each study group was expressed as an incidence density using a person-time approach (in years). The numerator was calculated as the proportion of time that the group spent within the INR range multiplied by the observation time. The denominator was the total observation time for each study group (or the total study observation time multiplied by the proportion of patients in each study group, if the observation time for the individual study group was not reported in a given study). Ninety-five percent confidence intervals (CI) were calculated for each incidence density using the Wilson score method without continuity correction.[11] For the purposes of this meta-analysis, all studies were pooled using a random effects model and were

weighted by the inverse of the variance of proportion of time spent in the therapeutic range.[8,12]

In order to determine how study setting influenced the proportion of time spent within a therapeutic INR range, both subgroup and meta-regression analyses were conducted. Meta-regression analysis allows evaluating the effect of study setting independent of other influencing study design aspects (i.e., year, etc.). A multiple linear mixed method model using both random- and fixed-effects was utilized for meta-regression, which was weighted by the inverse of the variance of proportion of time spent in the therapeutic range.[13,14] By conducting a mixed linear model, we accounted for the potential lack of independence of INR control within studies. Thus, study groups were treated as dependent within studies, but as independent across studies. The use of mixed linear models helps to avoid the biased estimation of variable deviation (i.e., standard error) that can arise due to the potential lack of independence among multiple groups within the same study.[8] Random effects were assumed for study-level factors, including the covariates listed below, and fixed effects for patient-level factors. Study level covariates incorporated into the model include study design (community vs. anticoagulation clinic), study year (from 1998-2002 and 2003-2008), use of self-management or not,[9] and interpolation method (linear or other). No hierarchy was used in the model for these covariates. Statistical analysis was performed using StatsDirect version 2.4.6 (StatsDirect Ltd., Cheshire, England) and SPSS, version 15.0 (SPSS Inc., Chicago, IL).

■ Results

Our review of studies included in the van Walraven et al. study[8] yielded 14 studies meeting our preliminary inclusion criteria (conducted in the United States, evaluating warfarin, and limited to patients with AF).[15-28] Our updated systematic search from January 2005 through February 2008 (as depicted in Figure 1) identified an additional 536 studies for full text review, of which 526 were excluded. Of the studies excluded, most were excluded because they were not conducted in the United States, or they were not a primary study. Our preliminary screening process resulted in a total of 24 studies, including a total of 43 separate groups.[15-38] Of these, 16 studies were excluded because patients were included for indications other than AF.[14,15,19,22-25,27-30,32-34,36,37] Thus, 8 studies, including a total of 14 study groups, met all of the inclusion criteria and were included in the final analysis (Table 1).[17,18,20,21,26,31,35,38]

The study groups enrolled a median of 317 patients (interquartile range, 150 to 482 patients; total = 22,237 warfarin-treated patients),[31] who were followed for a median of 272.3 patient-years (range, 123.9 to 980.8 patient-years; total = 41,471.9 patient-years). Patients spent a median of 146.6 patient-years (range, 74.9 to 524 patient-years; total = 23,752.1 patient-years) within the therapeutic INR range. Patient-years data were cal-

culated in 5 of the included studies,[17,18,20,26,38] whereas the other 3 studies reported the required data.[21,31,35] Four groups (31%) were treated in anticoagulation clinics,[17,26,35,38] while 9 (69%) were treated in community practice.[17,18,20,21,31,38] One group in the study by Matchar (2003)[20] could not be classified as either an anticoagulation clinic or community practice because warfarin control was reported in this group of patients prior to their use or nonuse of an anticoagulation clinic. No randomized controlled trials (RCTs) met our inclusion criteria; thus, no RCTs were available for evaluation in our study.

Overall, patients within the 14 included groups spent 55% (95% CI = 51%-58%) of their time within the therapeutic INR range (Figure 2). Differences by study setting were observed, with patients in an anticoagulation clinic spending a mean 63% (95% CI = 58%-68%) of their time in the therapeutic range versus 51% (95% CI = 47%-55%) for patients in community practice. As no RCTs met our inclusion criteria, we could not evaluate this subgroup. After controlling for covariates, meta-regression analyses showed similar results to that of the subgroup analyses. Compared with an anticoagulation clinic, patients treated in a community setting spent 11% (95% CI = 2%-20%, n = 6 studies, with 9 study groups) less time in range. Although the differences were not statistically significant, recently reported studies showed more improved INR control than older ones (difference of 9% [95% CI = −4% to 21%]); prospective studies showed more improved control than retrospective ones (2% [95% CI = −10% to 14%]); and studies using linear interpolation methods showed more improved control than studies using other methods (2% [95% CI = −10% to 15%]).
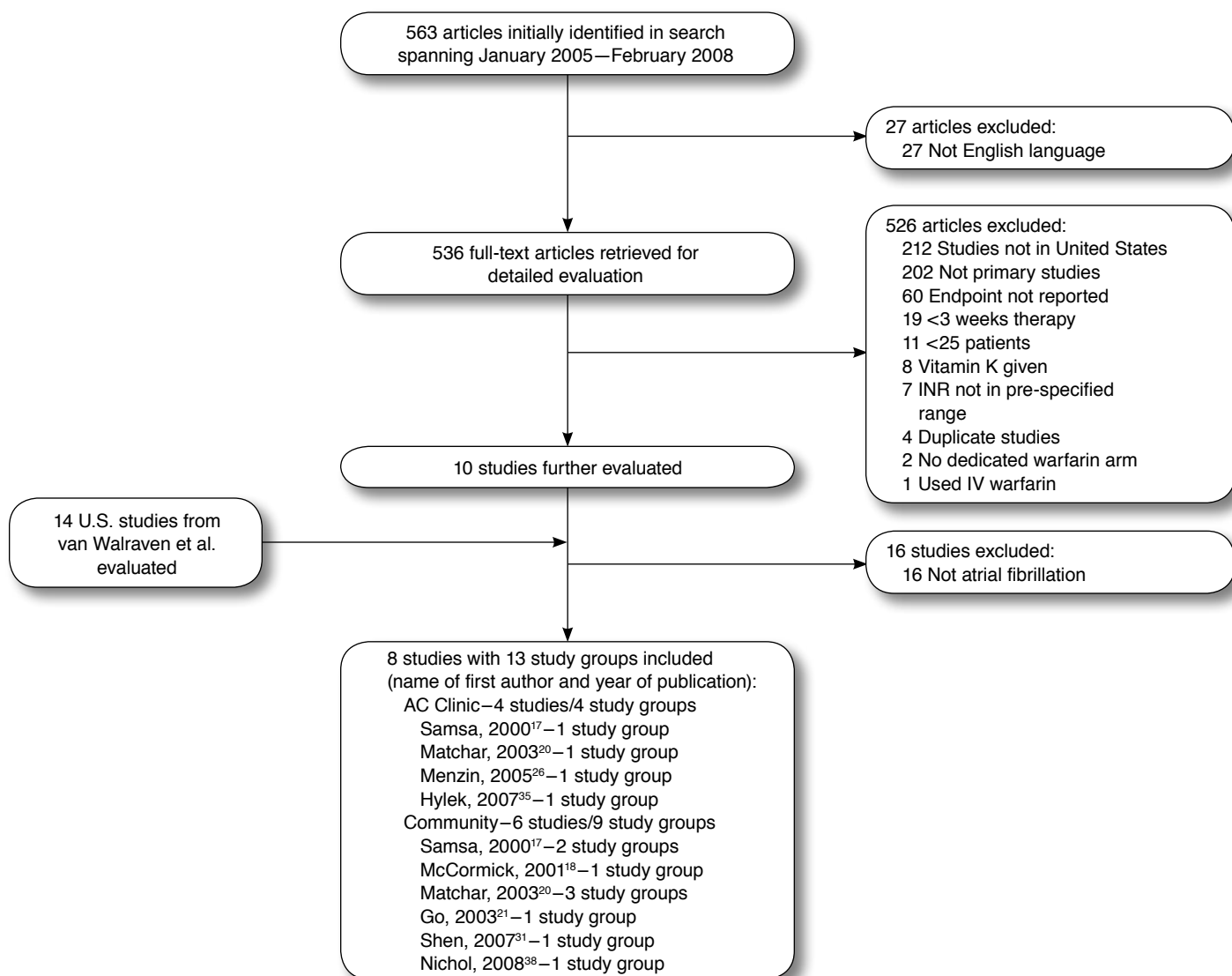
We also evaluated the proportion of warfarin-eligible patients who received warfarin in studies that measured that outcome. A total of 5 trials (including 8 study groups) reported data on the proportion of eligible patients receiving warfarin (Figure 3).[17,18,20,21,31] Overall, 48% (95% CI = 43%-54%) of eligible AF patients received warfarin.

■ Discussion

Warfarin has been shown in clinical trials to significantly reduce the risk of stroke in AF patients by 64% (absolute risk reduction 2.7% for primary prevention, 8.4% for secondary prevention) versus control (placebo or no treatment).[39] Based on these findings, evidence-based practice guidelines consistently recommend vitamin K antagonists for all patients with AF and at least 1 other risk factor.[2] Rates of efficacy, unfortunately, have not translated into the real world. A recent analysis of Medicare beneficiaries with AF showed a disappointing 35% reduction in ischemic strokes among patients exposed to warfarin versus those that did not receive warfarin, revealing a discrepancy between effectiveness in clinical trials and actual clinical practice.[40] The results of our analysis help provide insight into reasons for this discrepancy.

In our meta-analysis of studies evaluating anticoagulation

FIGURE 1 Flow Diagram of Study Identification, Inclusion and Exclusion

563 articles initially identified in search spanning January 2005—February 2008

27 articles excluded:
27 Not English language

536 full-text articles retrieved for detailed evaluation

526 articles excluded:
212 Studies not in United States
202 Not primary studies
60 Endpoint not reported
19 <3 weeks therapy
11 <25 patients
8 Vitamin K given
7 INR not in pre-specified range
4 Duplicate studies
2 No dedicated warfarin arm
1 Used IV warfarin

10 studies further evaluated

14 U.S. studies from van Walraven et al. evaluated

16 studies excluded:
16 Not atrial fibrillation

8 studies with 13 study groups included
(name of first author and year of publication):
AC Clinic−4 studies/4 study groups
Samsa, 2000[17]−1 study group
Matchar, 2003[20]−1 study group
Menzin, 2005[26]−1 study group
Hylek, 2007[35]−1 study group
Community−6 studies/9 study groups
Samsa, 2000[17]−2 study groups
McCormick, 2001[18]−1 study group
Matchar, 2003[20]−3 study groups
Go, 2003[21]−1 study group
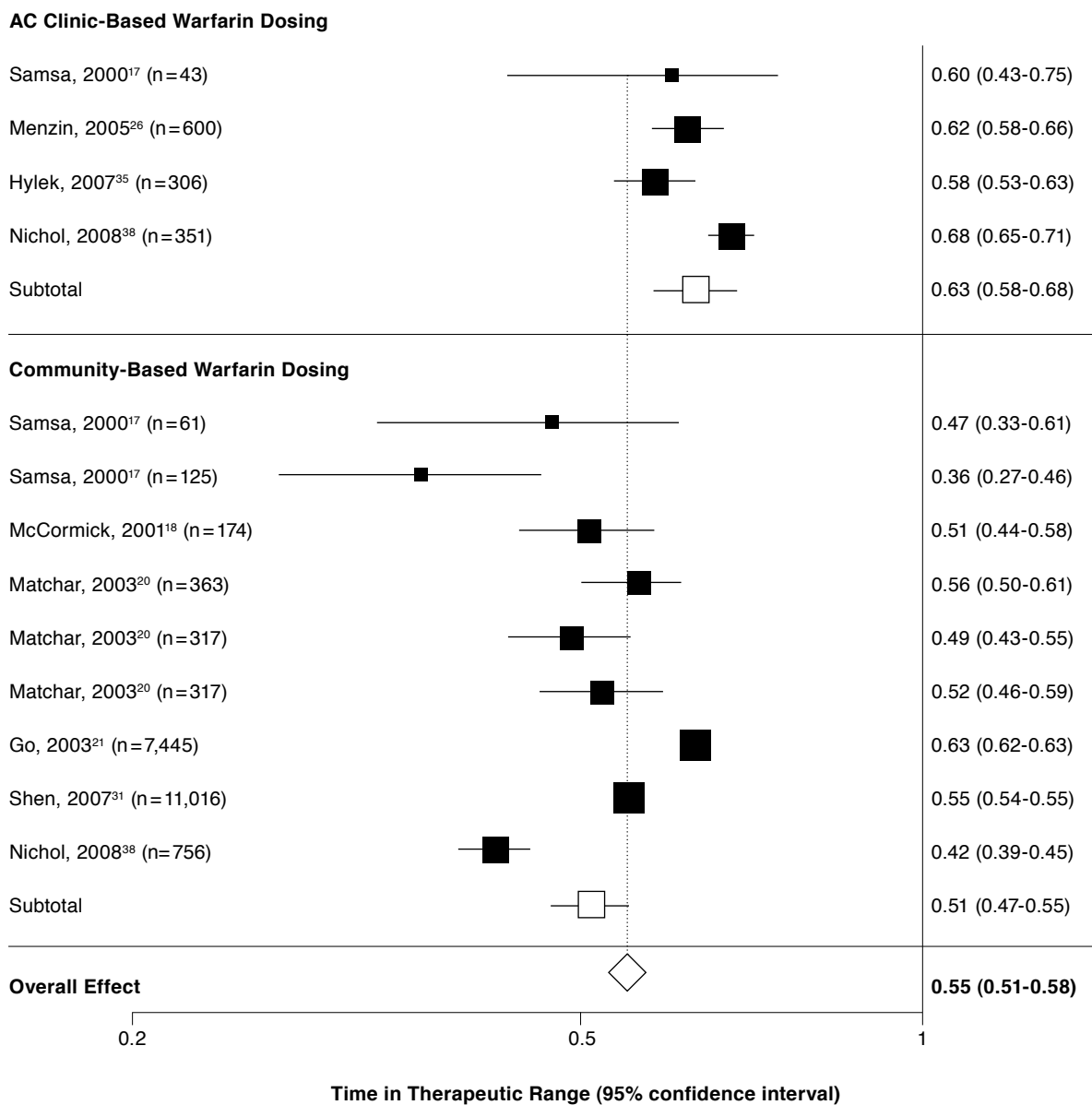Shen, 2007[31]−1 study group
Nichol, 2008[38]−1 study group

One group in the study by Matchar (2003)[20] could not be classified as either an AC clinic or community practice; warfarin control was reported in this group of patients prior to their use of either an AC clinic or not, and thus their classification could not be determined as either community practice or AC clinic.
AC = anticoagulation; INR = international normalized ratio; IV = intravenous; SM = self management.

control in AF patients in the United States, we found that patients spent a relatively low percentage of their time within the therapeutic INR range while on warfarin (55%, 95% CI = 51%-58%). In addition, meta-regression showed that studies of usual care in the community found poorer control as measured by time within INR therapeutic range than did studies of anticoagulation clinics.

Our meta-analytic methods differed from those of van Walraven et al.[8] and Dolan et al. (2008)[41] in notable ways. By including only studies evaluating anticoagulation control in AF patients in the

United States and limiting the evaluation exclusively to warfarin, the information is more readily applicable to the U.S. population (greater external validity). The 2 prior meta-analyses conducted by van Walraven et al. and Dolan et al. included studies evaluating a variety of warfarin indications (e.g., atrial fibrillation, venous thromboembolism, stroke), thus limiting the ability to apply their results to a particular population. We also included published U.S. trials to ensure that our observations apply to U.S. practice patterns. Since we found better INR control with anticoagulation clinics compared with community-based care, our findings help

FIGURE 2 Cumulative Effect of Warfarin Management on the Proportion of Time Spent Within Therapeutic INR Range[a]

AC Clinic-Based Warfarin Dosing

Samsa, 2000[17] (n=43)	0.60 (0.43-0.75)
Menzin, 2005[26] (n=600)	0.62 (0.58-0.66)
Hylek, 2007[35] (n=306)	0.58 (0.53-0.63)
Nichol, 2008[38] (n=351)	0.68 (0.65-0.71)
Subtotal	0.63 (0.58-0.68)

Community-Based Warfarin Dosing

Samsa, 2000[17] (n=61)	0.47 (0.33-0.61)
Samsa, 2000[17] (n=125)	0.36 (0.27-0.46)
McCormick, 2001[18] (n=174)	0.51 (0.44-0.58)
Matchar, 2003[20] (n=363)	0.56 (0.50-0.61)
Matchar, 2003[20] (n=317)	0.49 (0.43-0.55)
Matchar, 2003[20] (n=317)	0.52 (0.46-0.59)
Go, 2003[21] (n=7,445)	0.63 (0.62-0.63)
Shen, 2007[31] (n=11,016)	0.55 (0.54-0.55)
Nichol, 2008[38] (n=756)	0.42 (0.39-0.45)
Subtotal	0.51 (0.47-0.55)
Overall Effect	**0.55 (0.51-0.58)**

0.2   0.5   1

Time in Therapeutic Range (95% confidence interval)

[a]*The squares represent individual studies, and the size of the square represents the weight given to each study in the meta-analysis. Error bars represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending upwards from 1 is the null value. None of these studies were randomized controlled trials. List of studies shows name of first author and year of publication.*
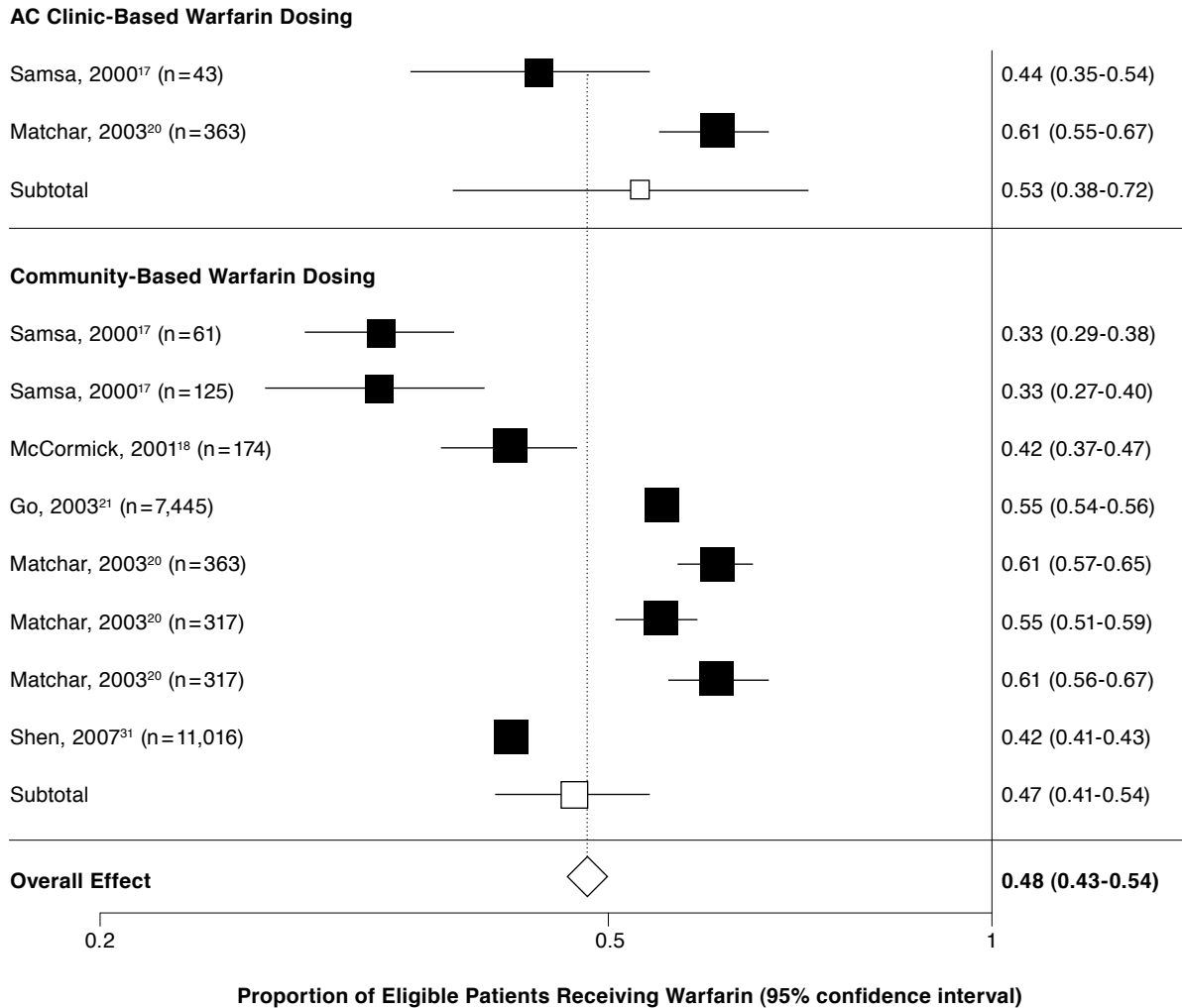*AC = anticoagulation.*

to confirm the results seen in other previous evaluations.[8,10,41] An additional prior meta-analysis conducted by Reynolds et al. (2004) reported the overall impact of warfarin anticoagulation on clinical outcomes in patients with AF.[42] They showed that, in studies with an INR range of 2-3, patients spent 61% of their time within the therapeutic INR range. These results are similar to ours and demonstrate the lack of adequate anticoagulation control in patients treated with oral vitamin K antagonists for AF.

The low achievement of anticoagulation control seen in our study is of concern. Unfortunately, a significant portion of

FIGURE 3 Proportion of Eligible Atrial Fibrillation Patients Receiving Warfarin[a]

AC Clinic-Based Warfarin Dosing

Samsa, 2000[17] (n=43) 0.44 (0.35-0.54)

Matchar, 2003[20] (n=363) 0.61 (0.55-0.67)

Subtotal 0.53 (0.38-0.72)

Community-Based Warfarin Dosing

Samsa, 2000[17] (n=61) 0.33 (0.29-0.38)

Samsa, 2000[17] (n=125) 0.33 (0.27-0.40)

McCormick, 2001[18] (n=174) 0.42 (0.37-0.47)

Go, 2003[21] (n=7,445) 0.55 (0.54-0.56)

Matchar, 2003[20] (n=363) 0.61 (0.57-0.65)

Matchar, 2003[20] (n=317) 0.55 (0.51-0.59)

Matchar, 2003[20] (n=317) 0.61 (0.56-0.67)

Shen, 2007[31] (n=11,016) 0.42 (0.41-0.43)

Subtotal 0.47 (0.41-0.54)

Overall Effect **0.48 (0.43-0.54)**

0.2   0.5   1

Proportion of Eligible Patients Receiving Warfarin (95% confidence interval)

[a]The squares represent individual studies, and the size of the square represents the weight given to each study in the meta-analysis. Error bars represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending upwards from 1 is the null value. None of these studies were randomized controlled trials. List of studies shows name of first author and year of publication.
AC = anticoagulation.

the time that patients spend on oral anticoagulants is outside of the therapeutic range. Economic modeling studies have projected improved outcomes and cost-savings from increasing the proportion of time spent within range. Chiquette et al. (1998) estimated that with improvements in time spent within the therapeutic range (64.0% vs. 51.0%) patients experienced lower rates of significant bleeding (defined as a decrease in hematocrit greater than 3% or hemoglobin level greater than 1.2 milligrams per deciliter; 8.1% vs. 35.0%) and thromboembolic events (3.3% vs 11.8%), as well as significant cost savings ($162,058 per 100 patient-years), driven mainly by reduced hospitalizations and emergency room visits.[15]

However, as we saw in the present study of 4 groups managed by anticoagulation clinics, patients still spend over one-third of their time out of the therapeutic range.[41,43-45] Even within clinics, newer warfarin dosing strategies—including computer-aided dosing (time within therapeutic INR range = 56% vs. 32% with usual care),[16] specialty-pharmacy clinics (71% of time spent within range),[23] and genotype-guided dosing[32] (30.7% of INRs were out of range with genotype dosing vs. 33.1% with standard dosing)—have been investigated, with only modest improvement in overall time spent within the therapeutic INR range.

Limitations

The results of our study must be taken within the context of its limitations. As with all meta-analyses, publication bias is a potential concern. However, given the systematic nature of our literature search from January 2005 until February 2008, this risk was minimized. A second limitation of our meta-analysis is that the INR control in RCTs could not be evaluated, since none were identified by our search. Since no significant differences were seen in the results between RCTs and anticoagulation clinics in the previous van Walraven. study (2006), it might be concluded that anticoagulation clinics and RCTs provide similar control, both of which are superior to community practice.[8] However, according to Go et al. (2003),[21] clinical trials evaluating warfarin in patients with nonvalvular AF translated well into their clinical practice. In addition, Matchar (2003) found no differences in INR control between patients randomized to either anticoagulation clinics or usual care.[20] An additional limitation to this study is the differing interpolation methods used to report the time in therapeutic range among the studies. Although our model showed that the interpolation method used did not significantly impact the overall study results, caution must be used when interpreting these data. It should also be noted that the included study samples were clinically and methodologically heterogeneous, as can be seen in Table 1. For example, studies included various settings (e.g., community, clinic, and hospital) and types of AF (e.g., nonvalvular atrial fibrillation and atrial flutter).

■ Conclusions

In the United States, patients who receive warfarin anticoagulation spend only about one-half the time within therapeutic INR. The use of anticoagulation clinic services by patients with AF improves INR control to 63% of the time on warfarin therapy versus 51% for usual community care.

Authors

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