REVIEW ARTICLE

Current Trial-Associated Outcomes With Warfarin in Prevention of Stroke in Patients With Nonvalvular Atrial Fibrillation

A Meta-analysis

Shikhar Agarwal, MD, MPH, CPH; Rory Hachamovitch, MD, MS; Venu Menon, MD

Background: Although several new antithrombotic agents have been developed for stroke prevention in patients with nonvalvular atrial fibrillation (AF), many patients will continue to be treated with warfarin worldwide. We performed a meta-analysis of safety and efficacy outcomes in patients with AF treated with warfarin for stroke prevention in large contemporary randomized controlled trials (RCTs).

Methods: We searched the MEDLINE, EMBASE, and Cochrane databases for relevant studies; RCTs comparing warfarin with an alternative thromboprophylaxis strategy with at least 400 patients in the warfarin arm and reporting stroke as an efficacy outcome were included.

Results: Eight RCTs with 55 789 patient-years of warfarin therapy follow-up were included. Overall time spent in the therapeutic range was 55% to 68%. The annual incidence of stroke or systemic embolism in patients with AF taking warfarin was estimated to be 1.66% (95% CI, 1.41%-1.91%). Major bleeding rates varied from 1.40% to 3.40% per year across the studies. The risk of stroke per year was significantly higher in elderly patients (2.27%), female patients (2.12%), patients with a history of stroke (2.64%), and patients reporting no previous exposure to vitamin K antagonists (1.96%). There was a significant increase in the annual incidence of stroke with progressively increasing $CHADS_2$ (congestive heart failure, hypertension, age, diabetes, and prior stroke) scores.

Conclusions: Current use of warfarin as a stroke prevention agent in patients with AF is associated with a low rate of residual stroke or systemic embolism estimated to be 1.66% per year. Compared with a previous meta-analysis, there has been significant improvement in the proportion of time spent in therapeutic anticoagulation, with a resultant decline in observed stroke rates.

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NONVALVULAR ATRIAL FIbrillation (AF) is associated with a 5-fold increase in the risk of ischemic stroke and has been implicated as a causal factor in as many as 15% to 20% of all ischemic strokes.[1] A meta-analysis[2] of 6 randomized controlled trials (RCTs) comparing the efficacy of warfarin with that of placebo in stroke prevention in AF demonstrated a significant reduction in stroke and all-cause mortality in patients treated with warfarin compared with no antithrombotic treatment. Patients with AF at the highest risk of stroke, particularly those with previous stroke or transient ischemic attack (TIA), derived the greatest absolute risk reduction with warfarin compared with aspirin or no antithrombotic treatment.[2] Although a more recent meta-analysis[3] evaluating the efficacy of available antithrombotic therapies for patients with AF included 29 RCTs, no new trials comparing warfarin with placebo were available for inclusion.

See Invited Commentary at end of article

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Novel antithrombotic agents have been developed as alternatives to warfarin (eg, direct thrombin inhibitors[4-6] and selective factor Xa inhibitors[7-9]), several of which have been demonstrated to be superior to warfarin in clinical trials.[6,8,9] In addition to therapeutic efficacy, these newer agents are easy to administer, are consistent in effect, and lack interaction with other medications and

Author Affiliations: Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio.

dietary agents. Initial utilization of these agents may, however, be hampered by cost. Consequently, despite its proven inadequacies and the need for close laboratory supervision, we expect treatment with warfarin to continue as the dominant therapy for patients with AF, especially in the setting of limited financial resources. Physicians may also delay using these promising newer agents in their patients as they await safety data in the "real world." Furthermore, there have been significant advances in warfarin utilization for primary and secondary stroke prevention in patients with AF, including the use of target international normalized ratio (INR), INR monitoring routines, increased physician emphasis on compliance, and a better understanding of genetic and environmental interactions.[10,11]

Faced with these newer choices, it is imperative that physicians precisely estimate the inherent bleeding risk accompanying warfarin treatment in eligible candidates with nonvalvular AF using current data over historical rates obtained in the previous decade. To this end, we conducted a contemporary meta-analysis of recent RCTs comparing warfarin with an alternative antithrombotic therapy for stroke prevention in patients with AF with the goal of determining the absolute safety and efficacy of warfarin treatment in AF. This analysis will potentially provide physicians with the best current estimate of the risks and benefits of this treatment in their individual patients. These results could potentially aid the decision process for warfarin therapy for individual physicians and allow health systems to evaluate the cost efficacy of adopting newer agents universally or in specific high-risk clinical subsets.

METHODS

STUDY CHARACTERISTICS

We evaluated all RCTs reporting the safety and efficacy of warfarin therapy in patients with nonvalvular AF published in the English language during the past 10 years (2001-2011). Trials were included if they compared warfarin with an alternative antithrombotic regimen for primary or secondary stroke prevention in patients with nonvalvular AF. The studies included for meta-analysis were restricted to high-quality trials (Jadad score ≥3) including at least 400 patients with AF in the warfarin arm.[12] This cutoff point of 400 patients was established a priori to restrict the meta-analysis to robust and large clinical trials only, enabling accurate assessment of event rates. The Jadad score is a validated method for assessing the methodological quality of RCTs based on randomization strategy, blinding, and withdrawals and dropouts.[12]

SEARCH STRATEGY

A computerized literature search of the MEDLINE, EMBASE, and Cochrane databases was conducted using Medical Subject Headings and keywords such as *warfarin, vitamin K antagonists, atrial fibrillation,* and *atrial arrhythmias* coupled with outcomes searched using terms such as *stroke, cerebrovascular accident, transient ischemic attack,* and *TIA*.

STUDY OUTCOMES

The primary efficacy outcome was defined as the occurrence of ischemic or hemorrhagic stroke or non–central nervous system (non-CNS) embolism. Secondary efficacy end points were studied using pooled analysis and included myocardial infarction (MI), all-cause mortality, and composite adverse vascular events (including stroke, non-CNS embolism, MI, and death). Safety outcomes included major bleeding, intracranial hemorrhage, clinically relevant nonmajor bleeding, and minor bleeding. The definition of major bleeding varied considerably across included studies; hence, a valid pooled estimate could not be calculated. In addition to the safety and efficacy outcomes noted previously herein, we also studied the net clinical benefit, which was mentioned in 5 of the included trials.[5,6,9,13,14] The net clinical benefit outcome has been defined as major adverse vascular events (including stroke, systemic embolism, and MI), death, or major bleeding episodes. In the context of the present meta-analysis aiming to calculate absolute event rates without a comparison group, the term *net clinical benefit* seems to be a misnomer. We, therefore, refer to it as the *cumulative adverse event rate* to estimate the additive thromboembolic event rate, which was not prevented by warfarin therapy, and the major bleeding rate, which occurred as a result of warfarin therapy.

DATA EXTRACTION

One of us (S.A.) reviewed all the titles and their abstracts selected using the search strategy and retrieved full-text articles for all potentially relevant studies. The full-text articles were subsequently reviewed with a primary focus on inclusion criteria, study outcomes, and methodological quality. If the clinical trial met the inclusion criteria based on these 3 characteristics, it was included in the analysis. The data from the study were then extracted using predesigned structured forms. Completed forms were reviewed by one of us (V.M.) for accuracy and validity. Disagreements, if any, were resolved by the mutual consensus of all 3 of us. After the data elements were verified for accuracy, they were subsequently entered into statistical software for further analysis.

STATISTICAL ANALYSIS

Statistical analysis was conducted using the metan function in STATA, version 10.0 (StataCorp LP). The meta-analysis has been reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[15] Due to a relatively small proportion of primary events in each study, the data were assumed to follow a Poisson distribution. For each study, a 95% CI estimate for the respective outcome was computed using standard Poisson tables. Pooled event rates (expressed as percentage per year) for the safety and efficacy outcomes in the warfarin arm were calculated using standard methods. Fixed-effects modeling was primarily used to conduct outcomes meta-analysis from included studies. Random-effects modeling was used in the case of statistically significant heterogeneity.

Assessment of heterogeneity was achieved by comparing the inclusion and exclusion criteria and the minor differences in the design and conduct of the clinical trials. We assessed for heterogeneity using the I^2 test ($I^2 > 50\%$ with $P < .05$ implies significant heterogeneity). In cases of significant heterogeneity, the heterogeneity was first explored in the studies, and subsequently a random-effects meta-analysis was performed to statistically account for the heterogeneity. Publication bias was assessed using the funnel plot method and Begg and Mazumdar rank correlation testing.[16]

Subgroup analyses were performed to determine event rates in different strata of the study population. All the subgroup analyses were prespecified. All the P values were 2-tailed, with statistical significance specified at $P < .05$ and CIs computed at the 95% level.

Table 1. Characteristics of the 8 Included Trials[a]

Source[b]	Inclusion Criteria	Primary End Point	Definition of Major Bleeding
ACTIVE W,[14] 2006	AF with age ≥75 y or treatment for hypertension or previous stroke/TIA/non-CNS embolism or LVEF <45% or PAD AF with age 55-74 y with DM or previous CAD	Composite of stroke, non-CNS embolism, MI, or vascular death	Bleeding associated with death, drop in hemoglobin ≥5.0 g/dL, hypotension requiring inotropes, ≥2-U RBC transfusion, intraocular bleeding, intracranial bleeding, or need for surgical intervention other than vascular repair
SPORTIF V,[4] 2005	AF with age ≥75 y or hypertension or LV dysfunction (LVEF <40% or symptomatic systolic or diastolic heart failure) or previous stroke/TIA/non-CNS embolism AF with age >65 y with CAD or DM	Composite of stroke or non-CNS embolism	Bleeding associated with death, drop in hemoglobin ≥2.0 g/dL, ≥2-U RBC transfusion, or bleeding that was intracranial (excluding intracerebral), retroperitoneal, spinal, ocular, pericardial, or atraumatic articular
BAFTA,[13] 2007	AF or atrial flutter with age ≥75 y with no contraindications to warfarin use	Composite of stroke, intracranial hemorrhage, or non-CNS embolism	Extracranial bleeding that was fatal or required transfusion or surgery or intracranial hemorrhage including hemorrhagic stroke
Amadeus,[7] 2008	AF with age ≥75 y or treatment for hypertension, LV dysfunction, previous ischemic stroke/TIA/ non-CNS embolism AF with age >65 y with DM or CAD	Composite of stroke or non-CNS embolism	Bleeding associated with death, drop in hemoglobin ≥2.0 g/dL, ≥2-U RBC transfusion, intracranial bleeding, or bleeding affecting a "critical anatomical site"
SPORTIF III,[5] 2003	AF with age ≥75 y or hypertension (BP <180/100 mm Hg) needing treatment or LV dysfunction (LVEF <40% or symptomatic CHF) or previous stroke/TIA/non-CNS embolism AF with age >65 y with DM or CAD	Composite of stroke or non-CNS embolism	Bleeding associated with death, drop in hemoglobin ≥2.0 g/dL, ≥2-U RBC transfusion, or bleeding affecting a critical anatomical site (intracranial, spinal, intraocular, retroperitoneal, pericardial, or atraumatic intra-articular)
RE-LY,[6] 2009	AF with age ≥75 y or LVEF <40% or NYHA class II or higher symptoms or previous stroke/TIA/non-CNS embolism AF with age >65 y with DM or hypertension or CAD	Composite of stroke or non-CNS embolism	Bleeding causing a reduction in hemoglobin ≥2.0 g/dL, ≥2-U RBC transfusion, or "symptomatic bleeding in a critical area or organ"
ROCKET-AF,[8] 2011	AF with previous stroke/TIA/ non-CNS embolism AF with a $CHADS_2$ score ≥2	Composite of stroke or non-CNS embolism	Bleeding associated with death, drop in hemoglobin ≥2.0 g/dL, ≥2-U RBC transfusion, permanent disability, or bleeding affecting a critical anatomical site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome)
ARISTOTLE,[9] 2011	AF or atrial flutter with age ≥75 y or hypertension requiring treatment, DM, symptomatic heart failure, LVEF <40%, previous stroke/TIA/ non-CNS embolism	Composite of stroke or non-CNS embolism	Bleeding associated with death, drop in hemoglobin ≥2.0 g/dL, ≥2-U RBC transfusion, or bleeding affecting a critical anatomical site (intracranial, spinal, intraocular, retroperitoneal, pericardial, intra-articular, or intramuscular with compartment syndrome)

Abbreviations: AF, atrial fibrillation; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CNS, central nervous system; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral artery disease; RBC, red blood cell; TIA, transient ischemic attack.

SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.

[a] The target international normalized ratio in the warfarin arm was 2.0 to 3.0 in all 8 studies.

[b] See the "Results" section for expansions of the study names.

RESULTS

Eight RCTs including 32 053 patients were included in the meta-analysis. The pooled analysis yielded 55 789 patient-years of follow-up. The characteristics of the included trials are given in **Table 1**. There were minor differences in the inclusion criteria, primary safety end point, and efficacy outcomes across the trials. The flow diagram for study selection is depicted in **Figure 1**.

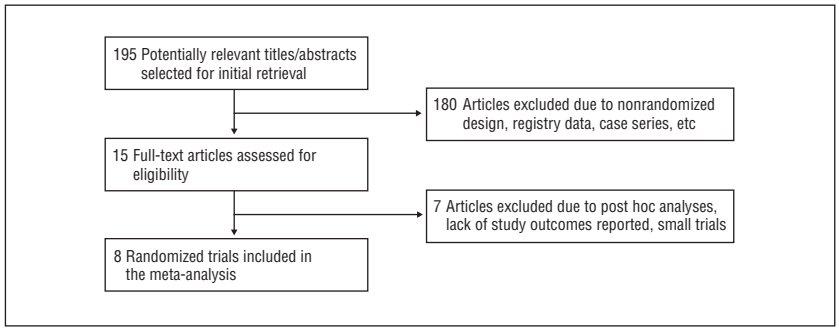

Figure 1. Flow diagram showing selection of the studies for the meta-analysis.

The comparison group for the warfarin arm consisted of ximelagatran in 2 trials (Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation [SPORTIF] III[5] and SPORTIF V][4]) and the following drugs in 1 trial each idraparinux (Amadeus[7]), aspirin (Birmingham Atrial Fibrillation Treatment of the Aged [BAFTA][13]), aspirin along with clopidogrel (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events [ACTIVE W][14]), dabigatran (Randomized Evaluation of Long-term Anticoagulant Therapy [RE-LY][6]), rivoraxa-

Table 2. Baseline Characteristics of Included Patients Across Clinical Trials in the Warfarin Arm[a]

Characteristic	ACTIVE W,[14] 2006	SPORTIF V,[4] 2005	Amadeus,[7] 2008	SPORTIF III,[5] 2003	BAFTA,[13] 2007	RE-LY,[6] 2009	ROCKET-AF,[8] 2011	ARISTOTLE,[9] 2011
Comparison group	Aspirin + clopidogrel	Ximelagatran	Idraparinux	Ximelagatran	Aspirin	Dabigatran	Rivaroxaban	Apixaban
Patients, No.	3371	1962	2293	1703	488	6022	7133	9081
Age, mean (SD), y	70.2 (9.5)	71.6 (9.0)	70.2 (9.1)	70.1 (8.6)	81.5 (4.3)	71.6 (8.6)	73 (65-78)[b]	70 (63-76)[b]
Age >75 y, No. (%)	NA	820 (42)	727 (32)	565 (33)	488 (100)	NA	3082 (43.2)	2828 (31.1)
Male sex, No. (%)	2211 (66)	1353 (69)	1501 (65)	1196 (70)	267 (54.7)	3809 (63.3)	4301 (60.3)	5899 (65.0)
Hypertension, No. (%)	2767 (82)	1582 (81)	1764 (77)	1230 (72)	259 (53.1)	4750 (78.9)	6474 (90.8)	7954 (87.6)
Systolic BP, mean (SD)	133 (18.8)	132 (18)	135.9 (18.5)	139 (18)	139.9 (19.2)	131.2 (17.4)	130 (120-140)[b]	130 (120-140)[b]
Diabetes mellitus, No. (%)	717 (21)	373 (19)	NA	290 (17)	68 (13.9)	1410 (23.4)	2817 (39.5)	2263 (24.9)
Weight, mean (SD), kg	NA	89.1 (21.3)	83 (42.3-181)[b]	81.7 (16.9)	NA	82.7 (19.7)	NA	82 (70-95)
BMI, mean (SD)	28.7 (5.0)	29.6 (6.2)	NA	NA	NA	NA	28.1 (25.1-31.8)[b]	NA
Coronary artery disease, No. (%)	1259 (37)	803 (41)	NA	558 (33)	NA	NA	NA	NA
Myocardial infarction, No. (%)	591 (18)	NA	NA	NA	47 (9.6)	968 (16.1)	1286 (18.0)	1266 (13.9)
Previous stroke/TIA, No. (%)	510 (15)	348 (18)	575 (25)	405 (24)	64 (13.1)	1195 (19.8)	3895 (54.6)	1790 (19.7)
Systemic embolism, No. (%)	NA	85 (4.3)	NA	77 (5)	NA	NA	NA	NA
Atrial fibrillation type, No. (%)								
Paroxysmal	594 (18)	270 (14)	813 (36)	124 (7)	NA	2036 (33.8)	1269 (17.8)	1412 (15.5)
Persistent	468 (14)	NA	214 (9)	NA	NA	1930 (32.0)	5762 (80.8)	NA
Permanent	2305 (68)	NA	1258 (55)	NA	NA	2055 (34.1)	NA	NA
Heart failure, No. (%)	1040 (31)	788 (40)	543 (24)[c]	584 (34)[c]	96 (19.7)	1922 (31.9)	4441 (62.3)	3216 (35.4)
$CHADS_2$ score, mean (SD)	2.0 (1.1)	NA	NA	NA	NA	2.1 (1.1)	3.46 (0.95)	2.1 (1.1)
$CHADS_2$ score, No. (%)								
0-1	NA	NA	909 (40)	NA	349 (71.5)	1859 (30.9)	0	3083 (34.0)
2	NA	NA	739 (32)	NA	NA	2230 (37.0)	934 (13.1)	3254 (35.8)
>2	NA	NA	645 (28)	NA	139 (28.5)	1933 (32.1)	6199 (86.9)	2744 (30.2)
Previous medications, No. (%)								
Oral anticoagulant	2627 (78)	1661 (85)	1741 (76)	1235 (73)	194 (39.8)	2929 (48.6)	4461 (62.5)	5193 (57.2)
Aspirin	884 (26)	367 (19)	NA	359 (21)	203 (41.6)	2442 (40.6)	2619 (36.7)	2773 (30.5)
Statin	1254 (37)	NA	NA	NA	NA	2673 (44.4)	3077 (43.2)	4095 (45.1)
Follow-up								
Median, mo	15.4	20	NA	NA	32.4	NA	23.6	21.6
Mean, mo	NA	20 (5.1)	11.3 (5.5)	16.3 (4.8)	NA	24	NA	NA
Patient-years	4242	3212	2159	2440	1318	12 044	14 028	16 346
Quality of the trial, Jadad score	3	4	3	3	3	3	4	4

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; NA, not available; TIA, transient ischemic attack.

[a] See the "Results" section for expansions of the study names.

[b] Median (interquartile range).

[c] Left ventricular dysfunction.

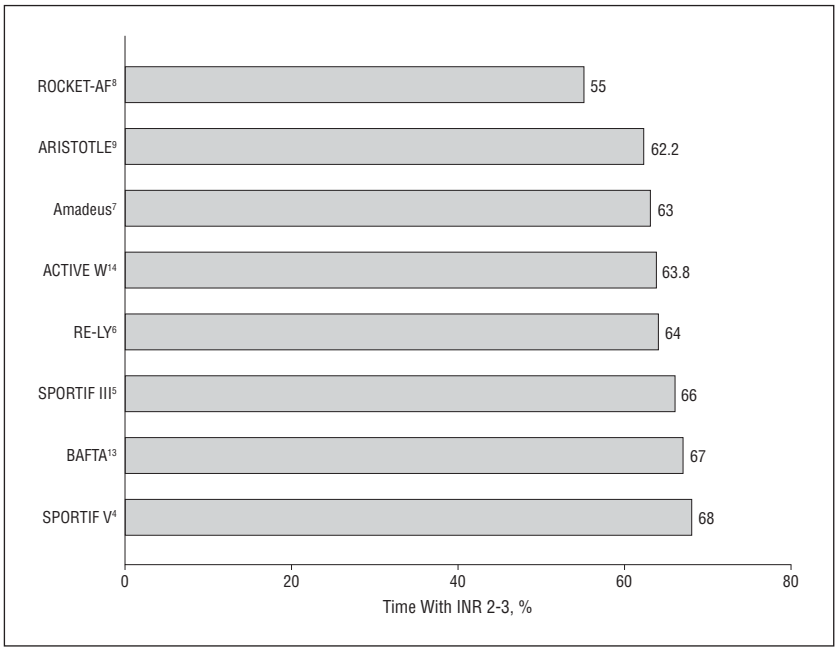

Figure 2. Bar graph demonstrating the proportion of time spent in therapeutic anticoagulation across the included studies. INR indicates international normalized ratio. See the "Results" section for expansions of the study names.

ban (ROCKET-AF [Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation][8]), and apixaban (ARISTOTLE [Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation][9]). The characteristics of included patients in the warfarin arm of each trial are given in **Table 2**. We observed significant heterogeneity in the baseline characteristics of included individuals across various trials. The proportion of patients with $CHADS_2$ scores greater than 2, implying a significantly higher risk of stroke, varied from 28% in the Amadeus trial[7] to 87% in the ROCKET-AF trial.[8] Similarly, the proportion of patients with exposure to vitamin K antagonists before enrollment in the trial varied from 39.8% in the BAFTA trial[13] to 85% in the SPORTIF V trial.[4] **Figure 2** demon-

Table 3. Summary of Efficacy and Safety Outcomes Derived From the Warfarin Arm of Included Trials[a]

Outcome	ACTIVE W,[14] 2006	SPORTIF V,[4] 2005	BAFTA,[13] 2007	Amadeus,[7] 2008	SPORTIF III,[5] 2003	RE-LY,[6] 2009	ROCKET-AF,[8] 2011	ARISTOTLE,[9] 2011
Efficacy Outcomes								
Patients, No.	3371	1962	488	2107	1703	6022	7082[b]	9081
Person-years	4242	3212	1318	1984	2440	12 044	13 928	16 346
Stroke or non-CNS embolism	59 (1.40)	37 (1.2)	22 (1.68)	27 (1.3)	56 (2.3)	199 (1.69)	243 (2.2)[b]	265 (1.60)
Ischemic/unknown	42 (1.00)	36 (1.1)	15 (1.14)	20 (0.9)	46 (1.9)	142 (1.20)	161 (1.42)[b]	175 (1.05)
Hemorrhagic	15 (0.36)	2 (0.1)	6 (0.50)	5 (0.2)	9 (0.4)	45 (0.38)	50 (0.44)[b]	78 (0.47)
Non-CNS embolism	4 (0.10)	1 (0.03)	1 (0.10)	2 (0.1)	2 (0.1)	NA	22 (0.19)[b]	17 (0.10)
Myocardial infarction	23 (0.55)	37 (1.4)[b]	15 (1.10)	13 (0.6)	13 (0.6)	63 (0.53)	126 (1.12)[b]	102 (0.61)
Stroke severity								
Fatal	15 (0.36)	3 (0.1)	13 (1.00)	2 (0.1)	9 (0.4)	118 (1.00)	67 (0.59)[b]	67 (0.41)
Disabling	40 (0.95)	7 (0.2)	8 (0.60)	NA	8 (0.3)		57 (0.50)[b]	50 (0.31)
Nondisabling	17 (0.40)	27 (0.84)	0 (0)	NA	39 (1.6)	69 (0.58)	87 (0.77)[b]	133 (0.81)
All-cause mortality	158 (3.76)	123 (3.8)	107 (8.00)	61 (2.9)[c]	79 (3.2)	487 (4.13)	250 (2.21)[b]	669 (3.94)
Vascular deaths	106 (2.52)	NA	56 (4.24)	35 (1.7)[c]	33 (1.4)	317 (2.69)	193 (1.71)[b]	343 (2.02)
Composite outcome[d]	165 (3.93)	119 (4.30)[b]	76 (5.90)	NA	116 (4.94)[b]	NA	519 (4.62)[b]	906 (5.49)
Safety Outcomes								
Patients, No.	3371	1953	488	2108	1703	6022	7125	9052
Person-years	4208	2709	1318	1984	2250	12 044	14 013	14 952
Bleeding								
Major[e]	93 (2.21)	84 (3.10)[b]	25 (1.89)	29 (1.40)	41 (1.80)[b]	397 (3.36)	386 (3.40)[b]	462 (3.09)
Fatal	11 (0.26)	1 (0.04)[b]	NA	2 (0.10)	7 (0.31)[b]	NA	55 (0.50)[b]	NA
Clinically relevant nonmajor	NA	NA	NA	206 (10.30)	NA	NA	1151 (11.40)[b]	415 (2.78)
Minor	481 (11.45)	854 (44.00)[b]	NA	NA	506 (22.49)[b]	1931 (16.37)	NA	2598 (21.90)
Intracranial hemorrhage	21 (0.50)	9 (0.33)[b]	8 (0.61)	9 (0.40)	13 (0.58)[b]	87 (0.74)	84 (0.70)[b]	122 (0.80)
Cumulative adverse event rate[f]	271 (6.45)	NA	39 (3.00)	NA	143 (6.12)[b]	904 (7.64)	NA	1168 (7.20)

Abbreviations: CNS, central nervous system; NA, not available.
[a] See the "Results" section for expansions of the study names. Values in parentheses represent the event rate expressed as percentage per year.
[b] Value from the on-treatment model.
[c] Data for death are available from 2131 patients in the Amadeus trial.
[d] Composite outcome includes stroke, non-CNS embolism, myocardial infarction, and all-cause death. Composite outcome in the ROCKET-AF and ACTIVE W trials included stroke, non-CNS embolism, myocardial infarction, and vascular deaths. Composite outcome in the BAFTA trial included stroke, myocardial infarction, pulmonary embolus, and vascular death.
[e] Major bleeding includes severe bleeding and fatal bleeding.
[f] Cumulative adverse event rate is defined as the incidence rate of major vascular events reported or death or major bleeding episodes.

strates that the percentage of the trial spent in therapeutic INR varied from 55% in the ROCKET-AF trial[8] to 68% in the SPORTIF V trial.[4]

Table 3 demonstrates the event rates of efficacy outcomes in the warfarin arm across the included trials. The rate of stroke or non-CNS embolism varied from 1.2% to 2.3% per year. Similarly, the rates of MI, all-cause mortality, and composite outcomes varied from 0.53% to 1.4% per year, 2.21% to 8.00% per year, and 3.93% to 5.90% per year, respectively. The pooled analysis of safety outcomes is demonstrated in **Figure 3**. The pooled event rate (95% CI) for stroke or non-CNS embolism was calculated to be 1.66% (1.41%-1.91%) per year. Similarly, the pooled event rates (95% CIs) for MI, all-cause mortality, and composite outcomes were calculated to be 0.76% (0.57%-0.96%) per year, 3.83% (3.07%-4.58%) per year, and 4.80% (4.22%-5.38%) per year, respectively. Analysis of publication bias using the funnel plot method and the Begg and Mazumdar rank correlation method did not reveal any significant publication bias in the reporting of efficacy outcomes examined in the meta-analysis.[16]

The definition of major and minor bleeding varied considerably across the included studies; hence, a valid pooled estimate for these outcomes could not be calculated. The incidence of major bleeding episodes ranged from 1.40% to 3.40% per year. The safety outcomes in the warfarin arm across the included trials are summarized in Table 3. The annual rate of intracranial hemorrhage in patients with AF taking warfarin ranged from 0.33% to 0.80% per year. Meta-analysis of intracranial hemorrhage yielded a pooled event rate of 0.61% (95% CI, 0.48%-0.73%) per year. The cumulative adverse event rate, defined as major vascular events reported or death or major bleeding episodes, was observed to range from 3.00% per year in the BAFTA trial[13] to 7.64% per year in the RE-LY trial.[6] Significant variation in the definition of the cumulative adverse event rate across the studies precluded a valid pooled meta-analysis.

Table 4 demonstrates the event rates for stroke and non-CNS embolism in patients treated with warfarin across the included trials, stratified by prespecified subgroups. There was a significantly higher incidence of stroke or non-CNS embolism in patients 75 years and older (n = 6398; 2.27% per year) compared with those younger than 75 years (n = 10 252; 1.62% per year; $P < .001$). In addition, we observed a significantly higher pooled incidence of stroke or non-CNS embolism in females (n = 8419) compared with in males (n = 14 262; $P < .001$) and in patients with a history of stroke or TIA compared with

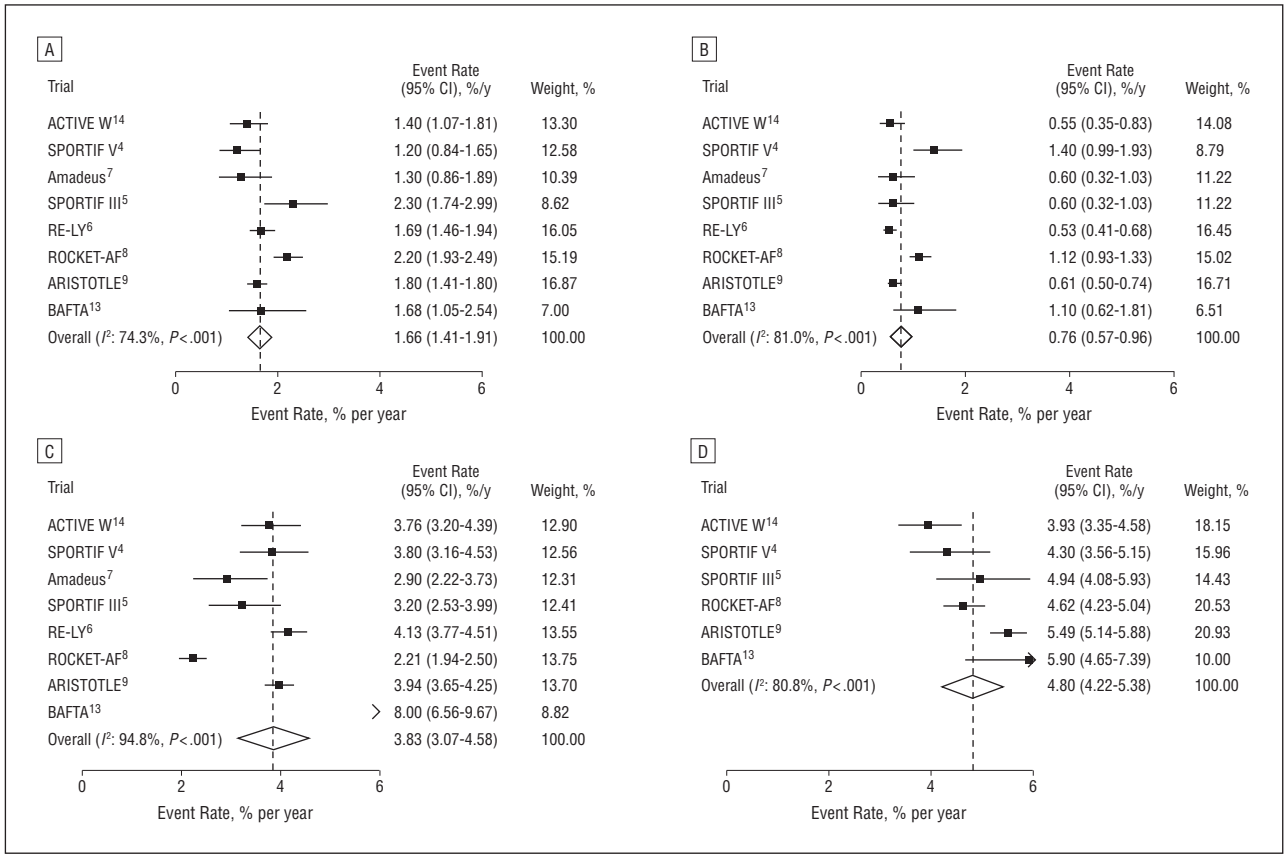

Figure 3. Forest plots demonstrating pooled estimates of safety outcomes. All the estimates were derived from random-effects modeling. A, Stroke or non–central nervous system embolism. B, Myocardial infarction. C, All-cause mortality. D, Composite outcome. See the "Results" section for expansions of the study names. Diamonds indicate the overall summary estimate for the analysis (width of the diamond represents the 95% CI).

Table 4. Event Rates (95% CIs) of Stroke and Non-CNS Embolism in the Warfarin Arm Across Trials Stratified by Prespecified Subgroups[a]

Subgroup	Amadeus,[7] 2008	BAFTA,[13] 2007	RE-LY,[6] 2009	ROCKET-AF,[8] 2011	ARISTOTLE,[9] 2011	Pooled Estimate (95% CI)		
						Event Rate (%/y)	Relative Risk[b]	*P* Value
Age, y								
<75	NA	NA	NA	1.90 (1.61-2.23)	1.36 (1.16-1.59)	1.62 (1.09-2.15)	1 [Reference]	
≥75	NA	1.68 (1.05-2.53)	NA	2.50 (2.12-2.93)	2.20 (1.81-2.65)	2.27 (1.99-2.54)	1.44 (1.18-1.76)	<.001
Sex								
Male	NA	1.40 (0.67-2.58)	1.49 (1.23-1.79)	1.92 (1.64-2.24)	1.50 (1.28-1.75)	1.60 (1.45-1.76)	1 [Reference]	
Female	NA	2.30 (1.26-3.86)	2.03 (1.63-2.50)	2.54 (2.14-2.99)	1.80 (1.47-2.18)	2.12 (1.74-2.51)	1.29 (1.13-1.49)	<.001
Previous stroke/TIA/ non-CNS embolism								
No	NA	1.60 (0.96-24.99)	1.43 (1.20-1.69)	1.81 (1.50-2.17)	1.20 (1.03-1.40)	1.45 (1.14-1.76)	1 [Reference]	
Yes	NA	3.10 (1.01-7.23)	2.74 (2.12-3.49)	2.45 (2.11-2.82)	3.20 (2.60-3.90)	2.64 (2.36-2.93)	1.88 (1.31-2.71)	.001
Previous oral vitamin K antagonist exposure								
Yes	NA	1.40 (0.51-3.05)	1.70 (1.38-2.07)	1.97 (1.69-2.28)	1.50 (1.26-1.77)	1.70 (1.53-1.86)	1 [Reference]	
No	NA	2.00 (1.19-3.16)	1.67 (1.36-2.03)	2.47 (2.07-2.93)	1.80 (1.50-2.14)	1.96 (1.58-2.34)	1.16 (1.01-1.33)	.04
$CHADS_2$ score								
0-1	0.50 (0.14-1.28)	NA	1.05 (0.75-1.44)	NA	0.90 (0.67-1.18)	0.89 (0.66-1.13)	1 [Reference]	
2	1.00 (0.40-2.06)	NA	1.38 (1.06-1.77)	1.93 (1.35-2.67)	1.40 (1.11-1.74)	1.43 (1.19-1.66)	1.46 (1.13-1.89)	.004
3-6	2.70 (1.54-4.39)	2.50 (1.14-4.75)	2.68 (2.19-3.25)	2.19 (1.94-2.47)	2.80 (2.34-3.32)	2.50 (2.17-2.82)	2.89 (2.28-3.66)	<.001

Abbreviations: CNS, central nervous system; NA, not available; TIA, transient ischemic attack.

[a] See the "Results" section for expansions of the study names. The SPORTIF III and SPORTIF V trials did not report event rates in the specified subgroups in the table. The outcome reported in the subgroup analyses in the ACTIVE W trial is a composite outcome including stroke, non-CNS embolism, vascular death, and myocardial infarction and, hence, was deemed unsuitable for pooled analysis.

[b] Pooled relative risk estimates were derived from studies that provided effect estimates for all strata in a subgroup.

Table 5. Summary Statistics Obtained From the Studies Included in the Previous Meta-analysis[2a]

Statistic	Source						Pooled Estimate (95% CI)
	BAATAF,[17] 1990	SPINAF,[18] 1992	SPAF,[19] 1991	AFASAK,[20] 1989	CAFA[21] 1991	EAFT,[22] 1993	
Patients, No.	212	260	210	335	187	225	NA
Patient-years	487	440	263	413	237	507	NA
Target INR	1.5-2.7	1.4-2.8	2.0-4.5	2.8-4.2	2.0-3.0	2.5-4.0	NA
INR values within therapeutic range, %	83	56	71	42	43.7	59	NA
Stroke/non-CNS embolism, No. (%)	2 (0.41)	5 (1.14)	8 (3.04)	9 (2.18)	8 (3.38)	20 (3.95)	2.09 (0.89-3.30)
Major bleeding events, No. (%)	3 (0.62)	6 (1.36)	4 (1.54)	NA	5 (2.50)	13 (2.56)	NA
All-cause mortality, No. (%)	11 (2.26)	15 (3.30)	6 (2.31)	NA[b]	NA[b]	41 (8.09)	3.82 (1.60-6.05)

Abbreviations: CNS, central nervous system; INR, international normalized ratio; NA, not available.
[a] See the respective references for expansions of the study names.
[b] Only vascular deaths were reported in the CAFA and AFASAK trials.

in patients without previous cerebrovascular events ($P=.001$). Patients with no history of exposure to vitamin K antagonists (n=9925) had a significantly higher incidence of stroke or non-CNS embolism compared with patients who reported use of vitamin K antagonists at the time of enrollment (n=12 756; relative risk, 1.16; 95% CI, 1.01-1.33). Meta-analysis of stroke or non-CNS embolism stratified by $CHADS_2$ score yielded pooled annual event rates (95% CIs) of 0.89% (0.66%-1.13%) per year for scores of 1 or less (n=5851), 1.43% (1.19%-1.66%) per year for scores of 2 (n=7157), and 2.50% (2.17%-2.82%) per year for scores of 3 or greater (n=11 660). Compared with the lowest-risk category ($CHADS_2$ score ≤ 1), the relative risk of stroke or non-CNS embolism was significantly higher in the intermediate-risk category ($CHADS_2$ score of 2) (relative risk, 1.46; 95% CI, 1.13-1.89; $P=.004$) and in the high-risk category ($CHADS_2$ score ≥ 3) (relative risk, 2.89; 95% CI, 2.28-3.66; $P<.001$).

COMPARISON WITH EARLIER DATA

Table 5 provides the summary statistics obtained from the studies included in the previous meta-analysis examining trials from 1989 to 1993 that evaluated the efficacy and safety of warfarin compared with placebo.[2,17-22] Meta-analysis of stroke or systemic embolism events across these earlier studies yielded a pooled event rate of 2.09% per year. This was a considerably higher estimate compared with the incidence rate of stroke observed in the present meta-analysis. There was significant variation in the target INR range observed in the earlier clinical trials. The lower limit of the target INR range was less than 2.0 in the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF)[17] and the Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF)[18] trials. In addition, there was significant variation in the proportion of time in the target INR range. Only 2 clinical trials (BAATAF[17] and Stroke Prevention in Atrial Fibrillation [SPAF][19]) had 60% or greater values in the target INR range. In comparison, the clinical trials included in the present meta-analysis have a uniform target INR range (2.0-3.0), with 7 of 8 trials having greater than 60% of INR values in the target therapeutic range.

COMMENT

The present meta-analysis takes advantage of a large body of contemporary evidence to evaluate the efficacy and safety of warfarin therapy in patients with nonvalvular AF treated with warfarin. Using a database of more than 30 000 patients, the pooled annual incidence rate of stroke or non-CNS embolism was estimated to be 1.66%, considerably lower than the 2.09% in a previous meta-analysis. Due to nonstandardized definitions, rates of major bleeding events ranged from 1.40% to 3.40% per year. Subgroup analyses demonstrated a significantly increased risk of thromboembolic complications in females, in patients 75 years and older, in patients with previous stroke or TIA, and in patients with no previous exposure to vitamin K antagonists. Stratifying the study population by $CHADS_2$ score, event rates for stroke or non-CNS embolism were estimated to be 0.89% per year for the low-risk (score ≤ 1), 1.43% per year for the intermediate-risk (score of 2), and 2.50% per year for the high-risk (score ≥ 3) categories. We observed a significantly higher risk of thromboembolic events in warfarin-treated patients with intermediate risk (1.43% per year) or high risk (2.50% per year) than in patients at low risk for stroke (0.89% per year).

Warfarin has been a pharmacotherapeutic standard for stroke prevention in AF; its efficacy for stroke prevention has been demonstrated in patients with AF, particularly those with a high baseline risk of stroke (eg, older age groups).[23-25] In a previous meta-analysis,[2] dose-adjusted warfarin therapy was shown to reduce the risk of stroke by 62% and the risk of death by 25% compared with placebo. Several model-based studies have shown warfarin to be an extremely cost-effective strategy for stroke prevention, especially in patients older than 75 years.[26] Gage et al[23] concluded that the use of warfarin in patients with nonvalvular AF with 1 or more risk factors for stroke was appropriate and cost-effective, with treatment costing approximately $8000 per quality-adjusted life-year saved. Even after consideration of the costs associated with regular INR testing, in most settings, the overall cost of therapeutic strategies using these newer agents

will exceed the costs of comparative strategies incorporating generic warfarin. Thus, despite the development of newer antithrombotic agents with increased ease of administration that are superior or noninferior to warfarin,[6,8,9] most patients with nonvalvular AF will probably continue to be treated with warfarin in the near future owing to cost considerations. Indeed, warfarin will likely continue to be widely used as the drug of choice in several countries around the world.

The clinical and cost-related outcomes associated with warfarin therapy depend on the duration of therapeutic anticoagulation (indicating the quality of anticoagulation) and rates of warfarin discontinuation.[27] We observed a significant overall decline in thromboembolic event rates with warfarin therapy compared with that previously reported in a meta-analysis that compared rates on warfarin with placebo. This decline in event rate is likely due to the increased rates of therapeutic anticoagulation observed in recent studies. Although far from perfect, the proportion of time spent in therapeutic anticoagulation ranged from 55% to 68% across the recent clinical trials, with patients in 7 of 8 trials being therapeutically anticoagulated more than 60% of the time. In addition, the reduction in the stroke rates may be partially attributable to a significant improvement in the management of atherosclerotic risk factors, such as hypertension and dyslipidemia.[28,29]

This meta-analysis attempted to summarize a large body of contemporary evidence derived from RCT data. The large number of patients included in this meta-analysis increases the strength, validity, and generalizability of the results. By limiting the analysis to results from RCTs, we were able to estimate event rates in a subset of the AF population that has no contraindications to newer antithrombotic agents. These estimates are potentially useful because with expansion of the population eligible for the newer agents in the near future, physicians are going to be faced with the issue of conveying absolute safety and efficacy of warfarin to their patients, especially in resource-constrained settings.

Potential limitations stem from the substantial heterogeneity encountered in multiple comparisons. In our opinion, the significant heterogeneity is a reflection of varying event rates in different settings and populations rather than a profound limitation of the study per se. The cumulative event rate reported, therefore, provides a more reliable event rate than that reported in individual trials.

In conclusion, use of warfarin as a stroke prevention strategy in patients with nonvalvular AF is associated with a low risk of stroke or non-CNS embolism, estimated to be 1.66% per year. Besides thromboembolic events, the pooled incidences of MI, death, and composite outcome were estimated to be 0.76%, 3.83%, and 4.80% per year, respectively. Although there was significant heterogeneity in the definition of bleeding outcomes across studies, the rates of major bleeding ranged from 1.40% to 3.40% per year. We noted a progressive increase in the incidence of stroke with increasing $CHADS_2$ score. In addition, age 75 years and older, female sex, previous stroke or TIA, and lack of exposure to oral vitamin K antagonists were associated with higher risk of thromboembolism with warfarin use.

There has been a significant reduction in the stroke event rate with warfarin treatment during the past 2 decades. This reduction may be secondary to a considerable improvement in the quality of anticoagulation as reflected by a greater proportion of time spent in therapeutic anticoagulation.

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Correspondence: Venu Menon, MD, Coronary Intensive Care Unit, Cleveland Clinic, 9500 Euclid Ave, Desk J 1-5, Cleveland, OH 44195 (menonv@ccf.org).
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INVITED COMMENTARY

A New Era in Stroke Prevention for Atrial Fibrillation

The article by Agarwal et al[1] summarizing the performance of warfarin in recent trials of stroke prevention in atrial fibrillation (AF) in this issue of the *Archives* provides an opportunity to review the growing set of novel anticoagulation alternatives for patients with AF and the remaining role for warfarin.

Atrial fibrillation, the most common significant cardiac arrhythmia, raises the risk of ischemic stroke 5-fold. Dose-adjusted warfarin therapy reduces this risk by two-thirds.[2] However, warfarin therapy is burdensome and risky, and its effect varies as a result of food and drug interactions and genetic differences.[3] The safe management of warfarin therapy demands frequent international normalized ratio (INR) testing and dose adjustment as well as ongoing patient education regarding common hazards. The risks of ischemic stroke and intracranial hemorrhage are minimized at INR values of 1.8 to 3.5.[4] Beyond this range, the risks increase steeply.

Linearly interpolated time in the standard therapeutic range (TTR) (INR, 2.0-3.0) for AF is a common metric of warfarin anticoagulation quality. Higher TTRs are associated with lower risks of ischemic stroke and intracranial hemorrhage.[5] Time in therapeutic range varies across individuals and centers. Even in recent clinical trials, patients who were receiving warfarin therapy were out of range approximately one-third of the time. Warfarin treatment at TTRs of 45% or less is probably not providing patients net clinical benefit. Warfarin management appears to have improved in recent years, particularly through the use of anticoagulation management services.[3] A Swedish national registry now reports mean TTR values of 76%.[6] Using an expanded INR target range of 1.8 to 3.2, the mean TTR increases to 88%! Still, warfarin therapy remains problematic. Twenty-five percent of patients who begin taking warfarin quit during their first year of therapy, and approximately 40% of appropriate patients with AF do not receive warfarin.[2] These patients and those with low TTR values represent an important gap in stroke prevention.

Several novel anticoagulant replacements for warfarin have recently been developed. These oral agents are given in fixed doses and are largely free of interactions with drugs and foods. They have rapid onset and offset of action. Initially, warfarin appeared too good to beat in randomized trials. The trials of these novel agents simply sought to establish noninferiority in preventing stroke. It was assumed that if noninferiority could be demonstrated, use of the new drugs would be preferred because of obvious chal-