# Bleeding During Antithrombotic Therapy in Patients With Atrial Fibrillation

*The Stroke Prevention in Atrial Fibrillation Investigators*

**Background:** The Stroke Prevention in Atrial Fibrillation II study compared warfarin vs aspirin for stroke prevention in atrial fibrillation. Bleeding complications importantly detracted from warfarin's net effectiveness, particularly among older patients.

**Objectives:** To analyze bleeding complications according to assigned therapy. To identify risk factors for bleeding during anticoagulation.

**Methods:** Eleven hundred patients (mean age, 70 years) were randomized to 325 mg of aspirin daily (enteric coated) vs warfarin (target prothrombin time ratio, 1.3 to 1.8; approximate international normalized ratio, 2.0 to 4.5). Major hemorrhages were defined prospectively.

**Results:** The rate of major bleeding while receiving warfarin was 2.3% per year (95% confidence interval [CI], 1.7 to 3.2) vs 1.1% per year (95% CI, 0.7 to 1.8) while receiving aspirin (relative risk, 2.1; 95% CI, 1.1 to 3.1; *P*=.02). Intracranial hemorrhage occurred at 0.9% per year (95% CI, 0.5 to 1.5) with warfarin and 0.3% per year (95% CI, 0.1 to 0.8) with aspirin (relative risk, 2.4; *P*=.08). Age (*P*=.006), increasing number of prescribed medications (*P*=.007), and intensity of anticoagulation (*P*=.02) were independent risks for bleeding at any site during anticoagulation. The rate of major hemorrhage was 1.7% per year in patients aged 75 years or younger who received anticoagulation vs 4.2% per year in older patients (relative risk, 2.6, *P*=.009); rates by age for intracranial bleeding were 0.6% per year and 1.8% per year, respectively (*P*=.05).

**Conclusion:** Advancing age and more intense anticoagulation increase the risk of major hemorrhage in patients given warfarin for stroke prevention.

*(Arch Intern Med. 1996;156:409-416)*

WARFARIN and aspirin are both effective for the prevention of ischemic stroke in patients with atrial fibrillation.[1,2] Warfarin is substantially more effective than aspirin for reducing the rate of ischemic stroke in these patients[2-4]; but in the Stroke Prevention in Atrial Fibrillation II (SPAF II) trial, hemorrhages in elderly patients negated the benefit.[3] The main results of the SPAF II Study have been reported[3]; herein we analyze bleeding complications in detail and identify risk factors for major hemorrhage during anticoagulation.

## RESULTS

### TREATMENTS AND COMPLIANCE

Among warfarin-assigned patients, the mean dose of warfarin was 4.5 mg/d in patients aged 75 years or younger (mean age, 64 years) and 3.7 mg/d in those older than 75 years (mean age, 80 years) to achieve similar intensities of anticoagulation (mean PTR, 1.45 vs 1.46 and mean INR, 2.6 vs 2.7, respectively). The average warfarin dose did not change after converting from PTRs to INRs. Of 16 453 measurements, anticoagulation intensity exceeded the upper limit of the trial's therapeutic range in 5% of the measurements in the younger patients and in 6% of those in the older patients; it was below the lower limit in 20% and 22%, respectively. Among aspirin-assigned patients, compliance estimated by pill count was satisfactory (80% to 105% of expected consumption) in 90% of all follow-up visits in both age groups.

*See Methods on next page*

*The participating investigators are listed on page 411.*

## METHODS

The design and main results of the SPAF II Study have been described.[3,5] In brief, the efficacy and safety of warfarin vs aspirin were compared for prevention of arterial thromboembolism in patients with nonvalvular atrial fibrillation. Patients were stratified by age so that the antithrombotic agents were compared in two populations: patients aged 75 years or younger and those 76 years or older (**Figure 1**). In total, 1100 patients were entered in the study: 715 in the younger age group and 385 in the older.

As a requisite for enrollment, all patients were considered candidates for warfarin anticoagulation. The following were explicit exclusions: dementia; chronic renal failure with a serum creatinine level of greater than 265 μmol/L (3.0 mg/dL); thrombocytopenia ($<100\times10^9$ platelets per liter); anemia (hemoglobin concentration, <100 g/L); baseline prothrombin time more than 2 seconds longer than control on two occasions; systolic blood pressure more than 180 mm Hg and/or diastolic blood pressure more than 100 mm Hg despite treatment; severe chronic alcohol habituation with transaminase values more than three times the normal upper limits; stool guaiac test positive for occult blood; inability to obtain adequate follow-up for monitoring prothrombin times; previous intracranial hemorrhage; gastrointestinal (GI) or genitourinary bleeding within the preceding 6 months; previous severe hemorrhage with a therapeutic prothrombin time while receiving warfarin; conditions predisposing to head trauma; and the requirement for treatment with nonsteroidal anti-inflammatory drugs.

Anticoagulation monitoring was performed in more than 50 clinical laboratories.[6] Initially, the warfarin dose was adjusted to achieve a target prothrombin time ratio (PTR) of 1.3 to 1.8 times control. During the trial, international sensitivity indices (ISIs) were established at the laboratories serving 68% of the warfarin-assigned subjects, and thereafter for these patients the warfarin dosage was regulated within the international normalized ratio (INR) range of 2.0 to 4.5.[6] Thirty-four percent of all determinations used the INR. The anticoagulation effect was monitored at least monthly, and the patients were contacted when a determination was missed. Dose adjustments were made by experienced study nurses supervised by physicians and using a standard algorithm. Patients who developed an indication for a nonsteroidal anti-inflammatory drug that could not be adequately managed with nonacetylated salicylates were withdrawn from warfarin therapy. Aspirin (325 mg daily) was enteric coated (Ecotrin), and compliance was assessed at follow-up every 3 months by pill count.

Bleeding complications were detected locally and submitted for central adjudication. A bleeding event was called major when it involved the central nervous system; required hospitalization, blood transfusion, and/or surgical intervention; or resulted in permanent functional impairment to any degree. All intracranial hemorrhages were confirmed by neuroimaging. Major bleeding episodes were verified independently by two central adjudicators, unblinded to treatment assignment, and reanalyzed using the severity scale of Landefeld et al.[7] The two adjudicators agreed on the classification of hemorrhages as major by study criteria in 100% of cases. Eighty-nine percent (50/56) were also classified as major hemorrhages using the Landefeld severity index. Of six bleeding episodes meeting the former criteria but not the Landefeld criteria, five involved chronic, non–life-threatening blood loss in warfarin-assigned patients. Analyses reported herein considered the 50 bleeding episodes qualifying as major by both criteria based on intention to treat. A secondary on-therapy analysis considered bleeding episodes occurring within 7 days of receiving assigned medication. Outcome was categorized as full recovery, incomplete recovery, or fatality. Incomplete recovery implied a functionally significant adverse health consequence at hospital discharge.

The rates of bleeding were based on the number of events per patient-year of exposure. The 95% confidence interval (CI) was estimated using Poisson regression. A limited number of factors designated a priori were examined for a relationship to all major hemorrhage, GI hemorrhage, and parenchymal intracranial hemorrhage when assigned to warfarin therapy. Some factors were available before initiating therapy (ie, baseline factors), others were manifested during follow-up. Factors were selected because of a published association with hemorrhage or because of biological plausibility and included the following: age[8-18]; female gender[12,13]; cerebrovascular disease (in our data represented by a history of stroke, transient ischemic attack, or systemic embolism[10,18-23]); congestive heart failure[12,13]; diabetes[24,25]; history of GI bleeding[10]; hypertension*; number of concurrent medications[9,11,15,21,33,34]; intensity of anticoagulation†; and variability of anticoagulation control.[11,35-37] Univariate relative risk (RR) associated with each factor was estimated using the Cox proportional hazards model and the log rank statistic. For all major hemorrhages, a multivariate model was constructed using variables with univariate significance ($P<.05$) entered sequentially. Because of the small numbers, multivariate models were not computed separately for bleeding complications in the GI tract and brain parenchyma.

Several measures of intensity were used in examining the effect of degree of anticoagulation on risk of bleeding. One measure was the overall mean PTR for each patient.[46] The bleeding rate of patients having a mean PTR above the midpoint of our target range (1.5) was compared with that of patients with a lower mean PTR. Also calculated were the time-dependent risks associated with (1) an average quarterly PTR above 1.5 and (2) any PTR value over 1.8 during a quarter. In each of these across-patient, time-dependent analyses, the bleeding events/quarter were calculated for all quarters with intensity exceeding the threshold compared with all quarters with intensity below the threshold. The variability of PTR measurements was estimated using the method of Fihn et al[35] with a target PTR of 1.5. In all of these analyses, the initial 6 weeks while anticoagulation treatment was stabilized were omitted from consideration. Only PTRs obtained during routine monitoring were included, ie, PTRs obtained at the time of bleeding were excluded.

*References 11, 12, 14, 15, 19, 20, 22, 25-32.*

†*References 8, 9, 11, 12, 16, 18, 21, 27, 32, 34-45.*

The Stroke Prevention in Atrial Fibrillation Investigators are the following (centers are listed in order of the number of patients enrolled):

**Clinical Centers**

**Mayo Clinic and Mayo Foundation, Rochester, Minn:** James H. Chesebro, MD; David O. Wiebers, MD; Anne E. Holland, RN; William T. Bardsley, MD; Scott C. Litin, MD; Irene Meissner, MD; Douglas M. Zerbe, MD.

**The University of Missouri, Columbia:** Greg C. Flaker, MD; Richard Webel, MD; Barbie Nolte, RN; Pat Stevenson, LPN; John Byer, MD; William Wright, MD.

**Hennepin County Medical Center, Abbott Northwestern Hospital, and Park Nicollet Medical Center, Minneapolis, Minn:** David C. Anderson, MD; Richard W. Asinger, MD; Susan M. Newburg, RN; Scott R. Bundlie, MD; Cheryl C. Farmer, RN, MA; Richard L. Koller, MD; John M. Haugland, MD; Martha A. Nance, MD; Ronald M. Tarrel, DO; David N. Dunbar, MD; Charles R. Jorgensen, MD; Scott W. Sharkey, MD.

**University of Texas Health Science Center at San Antonio, and Audie L. Murphy Veterans Hospital:** Anne D. Leonard, RN; Merrill C. Kanter, MD; Diane H. Solomon, MD; Miguel Zabalgoitia, MD.

**Oregon Health Sciences University, Portland:** John H. McAnulty, MD; Christy Marchant, RN, MBA; Bruce M. Coull, MD.

**University of Miami School of Medicine, Miami, Fla:** Roger E. Kelley, MD; Robert Chahine, MD; Malte Palermo, RN; Pura Teixeiro, RN.

**Kaiser Permanente, Portland:** George Feldman, MD; Arthur Hayward, MD; Kate MacMillan, RN; Elizabeth Gandara, RN; Warren Anderson, MD; Nathan Blank, MD; Richard Strauss, MD.

**The University of Arizona College of Medicine, Tucson:** William M. Feinberg, MD; Brenda K. Vold, RN; Karl B. Kern, MD; Christopher Appleton, MD; Denise Bruck; S. Dorr.

**University of California, San Diego Medical Center:** Howard C. Dittrich, MD; John F. Rothrock, MD; Carol Hagenhoff, RN, MPH.

**St John's Mercy Medical Center, St Louis, Mo:** William R. Logan, MD; William P. Hamilton, MD; Barbara J. Green, MD; Rebecca S. Bacon, RN.

**University of Illinois College of Medicine at Chicago and Peoria:** Cathy M. Helgason, MD; George T. Kondos, MD; Julie Hoff, RN, MPH.

**Mount Sinai Medical Center, New York, NY:** Jonathan L. Halperin, MD; Elizabeth B. Rothlauf, RN; Jesse M. Weinberger, MD; Martin E. Goldman, MD.

**Northwestern University Medical School, Chicago:** Vincent T. Miller, MD; Connie J. Hockersmith, RN; Bruce A. Cohen, MD.

**St Louis University Medical Center, St Louis:** Denise L. Janosik, MD; Dorothy J. Cadell, RN; Leanna Kellerman, RN; Camilo R. Gomez, MD; Arthur J. Labovitz, MD.

**University of Colorado School of Medicine, Denver:** Robert M. Rothbart, MD; Gretchen H. Bailey, RN; Caralyn Burkhardt, MD; Lawrence Horwitz, MD.

**Mayo Clinic, Jacksonville, Fla:** J. L. Blackshear; L. Weaver; V. Baker; G. Lee; G. Lane; F. Rubino; R. Safford.

**Statistical Coordinating Center**

**University of Washington, Seattle:** Richard A. Kronmal, PhD.

**Statistics and Epidemiology Research Corp, Seattle:** Ruth McBride; Lesly Pearce, MS; Kristin A. Fletcher, MS; Elaine Nasco.

**Clinical Coordinating Center**

**University of Texas Health Science Center at San Antonio:** Robert G. Hart, MD; David G. Sherman, MD; Robert L. Talbert, PharmD; Patricia A. Heberling.

**Writing Committee (Given Alphabetically)**

David C. Anderson, MD, Minneapolis (chair); George Feldman, MD, Portland; Robert G. Hart, MD, San Antonio; Karl B. Kern, MD, Tucson; Scott C. Litin, MD, Rochester; Ruth McBride, Seattle; and Robert L. Talbert, PharmD, San Antonio.

**Safety/Monitoring Committee**

**Boston University, Boston, Mass:** Theodore Colton, ScD.

**Knoll Pharmaceuticals, Whippany, NJ:** David E. Levy, MD.

**Harvard University, Boston:** James D. Marsh, MD.

**Henry Ford Hospital, Detroit, Mich:** K. M. A. Welch, MD.

**National Institute of Neurological Disorders and Stroke, Bethesda, Md:** John R. Marler, MD; Michael D. Walker, MD.

## MAJOR BLEEDING BY TREATMENT ASSIGNMENT

Considering both age strata together (mean age, 70 years), 50 major hemorrhages occurred: 16 (2.9%) in 545 aspirin-assigned patients and 34 (6.1%) in 555 warfarin-assigned patients during a mean follow-up of 2.6 years. The rates of all major bleeding were significantly higher in those assigned to warfarin (2.3% per year; 95% CI, 1.7 to 3.2) compared with the aspirin group (1.1% per year; 95% CI, 0.7 to 1.8) (RR, 2.1; 95% CI, 1.1 to 3.1; $P$=.02). Intracranial hemorrhage occurred at a rate of 0.9% per year (95% CI, 0.5 to 1.5) in warfarin-assigned patients and at 0.3% per year (95% CI, 0.1 to 0.8) in aspirin-assigned patients (RR, 2.4; $P$=.08). Among patients who received anticoagulation, the risks of all major hemorrhage (RR, 2.6; $P$=.009) and intracranial hemorrhage (RR, 3.2; $P$=.05) were greater in those older than 75 years vs younger patients. There was no relationship between rate of hemorrhage and duration of study participation (**Figure 2**); specifically, the rate was not measurably higher in the early period of warfarin use.

## LOCATION OF BLEEDING AND CLINICAL ASPECTS

The anatomic distribution of hemorrhages was similar for the two antithrombotic agents, the most common site being the GI tract (**Table 1**). The bleeding source was above the ligament of Treitz in six of eight aspirin-related bleeding episodes and in nine of 14 GI bleeding episodes in those patients receiving warfarin. An underlying lesion was documented in seven patients receiving aspirin and in 10 receiving warfarin. In one aspirin-assigned patient a neoplastic lesion was demonstrated in the workup. The lesions in the other cases were as follows: aspirin: gastric ulcer (n=2), esophageal varices (n=2), gastritis (n=1), diverticulitis (n=1); warfarin: gastric ulcer (n=3), gastritis (n=3), duodenal ulcer (n=2), and diverticulitis (n=2).

Other major non–nervous system hemorrhages occurred in three and seven patients assigned to the aspirin and warfarin groups, respectively. All three bleeding episodes from aspirin involved excessive surgical blood loss (two at coronary bypass grafting, one after prostate surgery). Of the bleeding episodes from warfarin, two were traumatic soft-tissue hemorrhages, and two were excessive blood loss during surgery (dental, cardiac). The three remaining episodes were spontaneous bleeding into the genitourinary tract, the pericardium, and the retroperitoneal space, with the last following coronary lytic therapy.

More than a third (18 of 50) of the major hemorrhages were intracranial. A history of recent head trauma was elicited in the two subdural hemorrhages in aspirin-assigned patients and in three of the four subdural hemorrhages in warfarin-assigned patients. Prothrombin time ratios on admission in the four warfarin-related subdural cases were 1.2, 1.3, 1.8, and 2.0. A berry aneurysm was the source of subarachnoid hemorrhage in a single aspirin-assigned patient.

The largest share of intracranial hemorrhages were parenchymal (11 of 18), and these accounted for the majority of fatal bleeding episodes in both aspirin- (two of three) and warfarin-treated patients (six of 10) (Table 1). Both parenchymal hemorrhages in aspirin-assigned patients were hemispheric ganglionic in location and fatal.

The location of parenchymal intracranial bleeding in warfarin-assigned patients was lobar in three, cerebellar in two, and hemispheric ganglionic in four. The evolution of the neurologic deficit was progressive over 6 to 12 hours in three patients, apparently abrupt in two, and indeterminable in four (three patients were found unconscious). No specific precipitating factors (eg, acutely elevated blood pressure, aspirin ingestion, minor trauma) could be identified in these cases. The outcome was poor: six cases (67%) were fatal, and no patient reached full functional recovery.

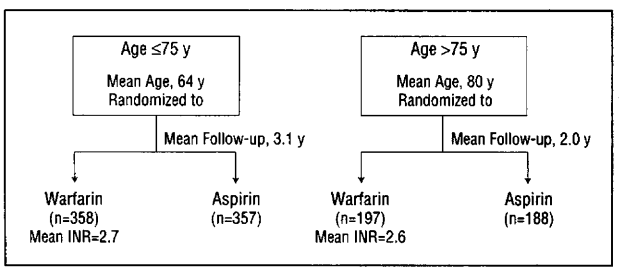


**Figure 1.** *Design of the Stroke Prevention in Atrial Fibrillation II Study.*[5] *Anticoagulation of eligible patients with atrial fibrillation. INR indicates international normalized ratio.*

## ANALYSIS AND EFFECT OF ANTICOAGULATION INTENSITY WHILE RECEIVING THERAPY

Using the 7-day rule, 12 of 16 major hemorrhages in aspirin-assigned patients and 33 of 34 major hemorrhages in warfarin-assigned patients occurred while receiving therapy. When bleeding was detected, the PTRs of 16 warfarin-assigned patients were within the trial's therapeutic range; 13 were above and four were below the range. The mean PTR was 1.42 at the last routine determination before major bleeding and 2.11 at admission for major hemorrhage (**Figure 3**).

## PREDICTORS OF BLEEDING IN PATIENTS WHO RECEIVED ANTICOAGULATION

Univariate analysis of potential risks for bleeding in warfarin-assigned patients are displayed in **Table 2**. By multivariate analysis, the only baseline characteristics that significantly and independently correlated with warfarin-related major

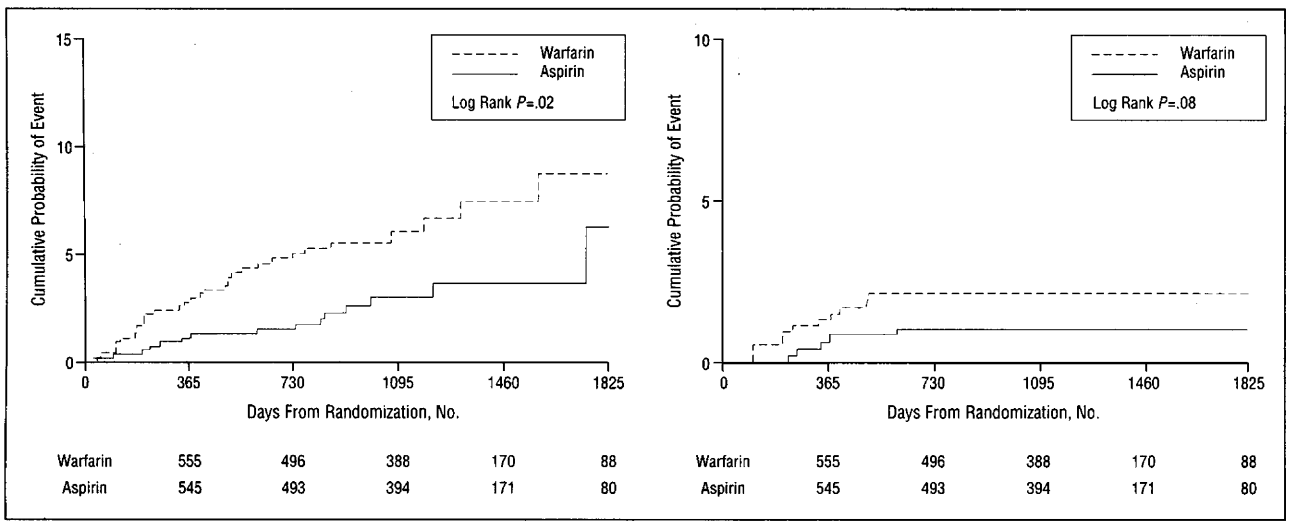


**Figure 2.** *Kaplan-Meier plots of all major bleeding events (left) and intracranial bleeding (right) in warfarin- and aspirin-assigned patients of all ages.*

**Table 1. Major Hemorrhages According to Treatment Assignment***

| | Age ≤75 y | | Age >75 y | |
|---|---|---|---|---|
| | Aspirin (n=357) | Warfarin (n=358) | Aspirin (n=188) | Warfarin (n=197) |
| Patient-years | 1072 | 1079 | 373 | 385 |
| Major hemorrhages | 10 | 18 | 6 | 16 |
| Rate, % per year | 0.9 | 1.7 | 1.6 | 4.2 |
| 95% CI | 0.5-2.6 | 1.1-2.6 | 0.7-3.6 | 2.5-6.8 |
| Fatal† | 2 | 4 | 1 | 6 |
| Incomplete recovery | 1 | 2 | 2 | 3 |
| Location | | | | |
| GI tract | 6 | 7 | 2 | 7 |
| Other | 2 | 5 | 1 | 2 |
| Intracranial | 2 | 6 | 3 | 7 |
| Rate, % per year | 0.2 | 0.6 | 0.8 | 1.8 |
| 95% CI | 0.05-0.7 | 0.2-1.2 | 0.3-2.5 | 0.9-3.8 |
| Parenchymal | 1 | 3 | 1 | 6 |
| Subdural | 0 | 3 | 2 | 1 |
| Subarachnoid | 1 | 0 | 0 | 0 |
| Therapy stopped because of minor bleeding | 1 | 12 | 1 | 5 |

**Data are based on intention-to-treat analysis and the bleeding criteria of Landefeld et al.[7] Of 50 major hemorrhages, four aspirin-assigned patients and one warfarin-assigned patient had not received the study drug within 7 days of the bleeding event. CI indicates confidence interval; GI, gastrointestinal.*

*†There were 13 fatal bleeding sites: aspirin, central nervous system (two) and GI tract (one); warfarin, central nervous system (seven) and GI tract (three).*

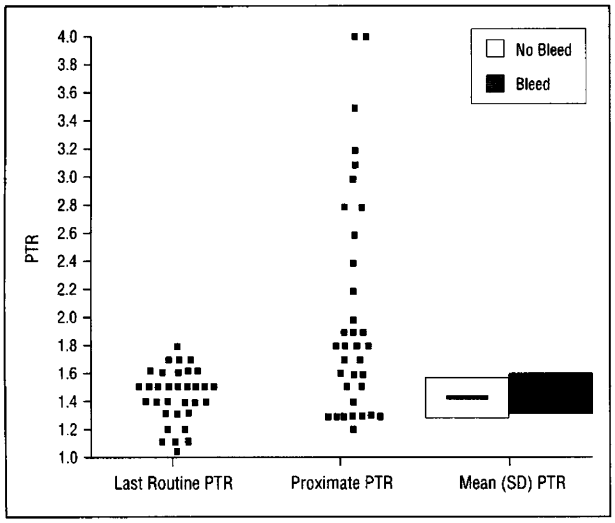


**Figure 3.** *Individual prothrombin time ratios (PTRs [solid squares]) at last routine measurement before hemorrhage (column 1) and proximate to discovery of bleeding (column 2). Proximate PTRs plotted at 4.0 are actually 4.8 and 6.2. Routine PTR means±SDs of patients with bleeding episodes vs all other patients (column 3).*

hemorrhage were advanced age (P=.006) and increasing number of prescription drugs (P=.007). Patients aged 75 years or younger who were taking three prescription drugs or less had a yearly rate of 1.2% per year (95% CI, 0.6 to 2.4); those who were either older or taking more than three drugs had a rate of 2.9% per year (95% CI, 1.8 to 4.6); and those with both features had a rate of 5.2% per year (95% CI, 2.6 to 10.3) (P=.01 for neither vs both; other comparisons, not significant). There was no difference

**Table 2. Univariate Risk of Bleeding During Warfarin Anticoagulation According to Patient Characteristics at Entry and During Follow-up***

| Baseline Features | Warfarin-Treated Patients, % | Rate, Percent per Year | RR | P |
|---|---|---|---|---|
| Age >75 y | 36 | 4.2 | 2.6 | .009 |
| Female gender | 31 | 2.6 | 1.1 | ... |
| History of | | | | |
| Thromboembolism | 8 | 4.0 | 1.9 | ... |
| Congestive heart failure | 21 | 4.0 | 2.0 | .05 |
| Diabetes | 14 | 4.1 | 1.9 | .09 |
| GI bleeding | 9 | 3.5 | 1.6 | ... |
| Documented ulcer | 9 | 0.8 | 0.3 | ... |
| Abdominal pain | 5 | 1.5 | 0.6 | ... |
| Hypertension | 52 | 2.5 | 1.1 | ... |
| Systolic BP ≥160 mm Hg | 15 | 3.8 | 1.8 | ... |
| Diastolic BP ≥90 mm Hg | 18 | 2.5 | 1.1 | ... |
| Use at entry of | | | | |
| Tobacco | 12 | 4.0 | 1.9 | .1 |
| NSAIDs | 43 | 2.7 | 1.3 | ... |
| Histamine$_2$ blocker | 4 | 3.3 | 1.5 | ... |
| Alcohol | 32 | 2.0 | 1.0 | ... |
| Other prescriptions | ... | ... | 1.2/drug | .003 |
| During follow-up | | | | |
| PTR (A)† | ... | ... | ... | .02 |
| PTR (B)‡ | ... | ... | 3.3 | .03 |
| PTR (C)§ | ... | ... | 3.2 | .03 |
| PTR fluctuation‖ | ... | ... | ... | .05 |
| Systolic BP ≥160 mm Hg | ... | ... | 1.4 | ... |
| Diastolic BP ≥90 mm Hg | ... | ... | 0.7 | ... |
| Use of alcohol | ... | ... | 0.9 | ... |
| Smoking | ... | ... | 1.1 | ... |
| Pulse pressure | ... | ... | 1.0 | ... |

**RR indicates relative risk; GI, gastrointestinal; BP, blood pressure; NSAIDs, nonsteroidal anti-inflammatory drugs; and PTR, prothrombin time ratio.*

*†Intensity was measured by within-patient mean PTR during follow-up—PTR (A).[46]*

*‡Intensity was measured by within-patient mean PTR at each quarterly follow-up, and the estimated RR is that associated with a mean PTR of more than 1.5 in a 3-month period—PTR (B).*

*§Intensity was measured by any PTR of more than 1.8 during a quarterly follow-up, and the estimated RR is that associated with observation of one or more PTRs of more than 1.8 in a 3-month period—PTR (C).*

*‖Variability or fluctuation of PTR was estimated using the method of Fihn et al.[35]*

between the mean PTR in those taking three drugs or less (1.44) vs more than three drugs (1.45), and there was no difference in variability of anticoagulant effect in these groups. Of specific individual medications and medication groups, only nonacetylated salicylates were specifically associated with major hemorrhage, whether used at entry (RR, 4.0; P=.001) or during follow-up in a time-dependent analysis (RR, 3.2; P=.003).

Intensity of anticoagulant effect was an independent contributor to risk of major bleeding measured by the mean PTR (P=.02) (Figure 3) as well as by whether the upper therapeutic limit of 1.8 was exceeded during each quarter of the follow-up (P=.07). The relationship of increasing intensity to bleeding was apparent only in the patients older than 75 years. In those with a mean PTR of 1.5 or less (n=141), the rate of major bleeding was 2.7% per year (95% CI, 1.4 to 5.5); while in those with a mean PTR of more than 1.5 (n=40),

**Table 3. Parenchymal Intracranial Hemorrhages During Anticoagulation***

| Age, y/Sex | Duration of Warfarin Therapy, mo | Mean BP at Entry and at 1 mo | Mean During Follow-up | | At Last Visit | | At Bleeding Episode |
|---|---|---|---|---|---|---|---|
| | | | BP | PTR | BP | PTR | PTR |
| 80/M | 4 | 144/75 | 142/82 | 1.6 | 134/74 | 1.5 | 1.5 |
| 79/M | 4 | 121/70 | 115/66 | 1.4 | 120/70 | 1.5 | 1.3 |
| 79/F | 12 | 128/72 | 133/79 | 1.6 | 138/80 | 1.2 | 1.3 |
| 81/F | 16 | 168/96 | 148/82 | 1.5 | 140/70 | 1.3 | 2.0 |
| 65/M | 17 | 163/98 | 135/86 | 1.4 | 130/80 | 1.6 | 1.6 |
| 81/F | 7 | 168/77 | 164/77 | 1.6 | 138/66 | 1.7 | 1.5 |
| 80/F | 3 | 128/56 | 110/70 | 1.2 | 110/70 | 1.1 | 1.7 |
| 72/M | 7 | 196/115 | 173/100 | 1.2 | 166/90 | 1.5 | 1.3 |
| 65/F | 8 | 136/90 | 139/90 | 1.4 | 140/78 | 1.4 | 1.6 |
| Average age, y 76 | 9 | 150/83 | 140/81 | 1.43 | 135/75 | 1.42 | 1.54 |
| SPAF† 70 | ‡ | 136/79 | 134/78 | 1.45 | ... | ... | ... |

*BP indicates blood pressure; PTR, prothrombin time ratio.
†All other Stroke Prevention in Atrial Fibrillation (SPAF) patients (excluding those with parenchymal intracranial bleeding).
‡Expected mean time to hemorrhage if random, 16 months.

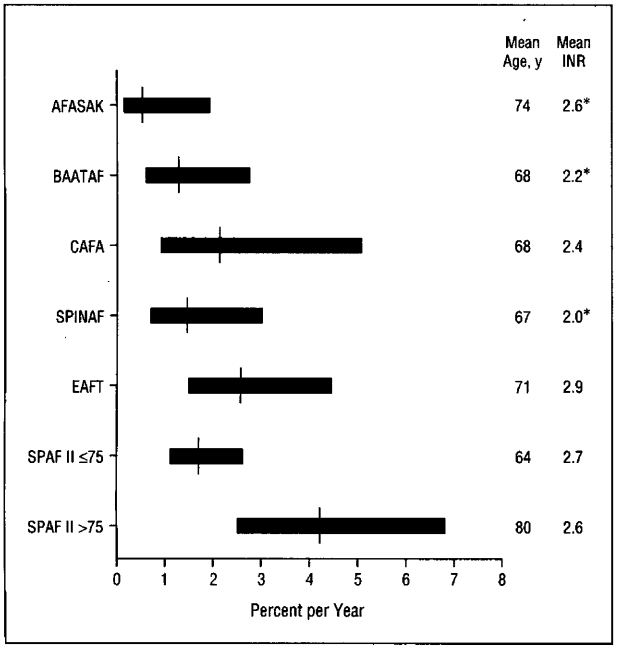


**Figure 4.** *Anticoagulation and major hemorrhage in six clinical trials involving patients with atrial fibrillation. Vertical lines indicate the rates of major hemorrhage (percentage per year); horizontal bars, 95% confidence intervals; INR, international normalized ratio; asterisks, mean INRs were estimated for trials reporting prothrombin time ratios; AFASAK, Atrial Fibrillation, Aspirin, Anticoagulation Trial[59]; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation[57]; CAFA, Canadian Atrial Fibrillation Anticoagulation Study[60]; SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation Trial; EAFT, European Atrial Fibrillation Trial[4]; and SPAF II, Stroke Prevention in Atrial Fibrillation. Protocols for these studies are described elsewhere.[2,4]*

the rate was 9.0% per year (95% CI, 4.5 to 18.0) (*P*=.16). Anticoagulation intensity was not a significant risk factor in patients aged 75 years or younger; the bleeding rate was 1.7% per year for those with a mean PTR more or less than 1.5. Major bleeding was more frequent in patients with the greatest variation of anticoagulation effect (*P*=.05).

Considering only GI hemorrhages, univariate analysis incriminated age (RR, 1.1 per year; *P*=.008) and number of medications taken at baseline (RR, 1.2 per drug; *P*=.03) as risk factors for major hemorrhage. A history of congestive heart failure (RR, 2.7; *P*=.03) also emerged as a significant predictor for GI hemorrhage. Multivariate analysis was not performed because of an insufficient number of events.

Advanced age was a predictor of parenchymal intracranial hemorrhage. The rate of parenchymal intracranial hemorrhage was 0.3% per year (95% CI, 0.09 to 0.9) in warfarin-assigned patients aged 75 years or younger and 1.5% per year (95% CI, 0.7 to 3.5) in those older than 75 years (RR, 3.7; *P*=.05). Univariate analysis demonstrated an increased risk of parenchymal intracranial hemorrhage in patients with a history of thromboembolism who received anticoagulation (RR, 6.3; *P*=.003) and those with either systolic hypertension (≥160 mm Hg) (RR, 4.4; *P*=.02) or diastolic hypertension (≥90 mm Hg) (RR, 3.6; *P*=.04) at entry. Blood pressure and anticoagulation intensity measured at the last routine occasion before bleeding (the last potential opportunity to intervene to prevent bleeding) were not alarmingly elevated (**Table 3**).

## COMMENT

Major bleeding influenced the benefit-risk ratios of the antithrombotic agents tested in the SPAF II study.[3] We detected a substantial rate of bleeding among warfarin-assigned patients at advanced age, and many of these hemorrhages were intracranial. The intracranial bleeding rate of 1.8% per year among those older than 75 years canceled the benefit of warfarin over aspirin for the prevention of ischemic strokes in these elderly patients.

The effect of age on anticoagulation-related bleeding has been disputed (positive association,[8-18] no association[33,35,36,41,47,48]); although, with one exception,[48] studies finding no association between age and bleeding involved patient groups with a mean age of less than 60 years. A trend for the bleeding rate to rise with age was also found in the aspirin-treated patients in the SPAF II Study (*P*=.11), suggesting that increased bleeding may be age related regardless of the antithrombotic agent. Wintzen et al[32] found that warfarin increased intracranial hemorrhage 10-fold com-

pared with untreated patients in a population-based, retrospective study. The very high rate in the elderly, they reasoned, may reflect the increasing spontaneous hemorrhage rate multiplied by the effect of anticoagulation.

In addition to advanced age, the use of multiple drugs was an independent risk factor for bleeding during anticoagulation, as reported by others.[9,11,15,21,33,34] Multiple drug use was not associated with differences in anticoagulation control in our study, but it was a marker for medical comorbidity, which itself has been reported to be associated with bleeding.[10,35] A relationship between bleeding and nonacetylated salicylate use during anticoagulation was found in an exploratory analysis. This relationship has not been previously reported, and it may be a chance correlation.

There was an association between intensity of anticoagulation and major hemorrhage. As a group, patients who bled were anticoagulated at a slightly greater intensity than those who did not. Importantly, our analyses suggest that elderly patients, who may be at intrinsically higher risk, bleed at a lower rate if anticoagulated less intensely (ie, PTR below 1.5, approximate INR of 3.0).

Both intensity and variability of anticoagulation effect were associated with bleeding complications. These relationships may have been even more apparent if INRs rather than less reliable PTRs had been used to regulate anticoagulation throughout the trial. It is possible that the use of PTRs contributed to the substantial bleeding rate.[6,49] It is reasonable to expect that targeting a lower range will reduce bleeding risk. It is not as straightforward to translate the measures of variability into a recommendation for general clinical practice, where variability may be even greater than in clinical trials.[50,51] Avoidance of dietary factors and drugs that affect warfarin's anticoagulant activity would appear to be sensible.[52] Guideline-based consultation services,[53] anticoagulation clinics,[54] home-monitoring devices,[55] and computer modeling to determine optimal monitoring intervals[56] are other measures that have been reported to reduce variability of anticoagulation control.

Other clinical trials using PTR to regulate anticoagulation in patients with atrial fibrillation targeted a lower intensity range (eg, the Boston Area Anticoagulation Trial for Atrial Fibrillation, 1.2 to 1.5[57]; Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Trial, 1.2 to 1.5[58]). We adopted INR measurements during the course of the trial whenever local laboratory ISIs could be obtained. An INR target of 2.0 to 4.5 was established with the goal of continuing the same intensity of anticoagulation, considering the original PTR target and the range of international sensitivity indices of thromboplastins employed by the individual laboratories used by our patients.[6] Three major clinical trials of patients with atrial fibrillation regulated the intensity of anticoagulation using INRs throughout, and the SPAF II Study's upper limit of the target intensity range (4.5) was higher than all three (Atrial Fibrillation, Aspirin, Anticoagulation Trial, 2.8 to 4.2[59]; Canadian Atrial Fibrillation Anticoagulation Study, 2.0 to 3.0[60]; and European Atrial Fibrillation Trial, 2.5 to 4.0[4]).

The rate of major bleeding (2.3% per year) among all warfarin-assigned patients exceeded that of the other trials of anticoagulation therapy for primary stroke prevention in patients with atrial fibrillation (**Figure 4**). This may have been owing to play of chance, the higher upper limit of anticoagulation intensity targeted in the SPAF II Study, or the specific inclusion of a cohort of elderly people (mean age, 80 years) who had a 4.2% per year rate of bleeding. The rate of bleeding in the younger subtrial (1.7% per year) was similar to those in the other primary prevention trials (Figure 4). The high rate of intracranial hemorrhage in our elderly patients (1.8% per year) was the decisive factor in canceling warfarin's effectiveness in that group. In contrast, a recent analysis of pooled data from 223 patients older than 75 years in the other trials found a substantially lower rate of intracranial hemorrhage (0.3% per year; 95% CI, 0.04 to 2.1) during anticoagulation.[61]

As increasing numbers of elderly patients with atrial fibrillation receive long-term anticoagulation to prevent stroke,[62] anticoagulation-related parenchymal intracranial hemorrhage is becoming a more frequent problem. Confirming previous reports, we found that the risk for this complication increases with age,[10,16,18] with a history of thromboembolism,[10,18,22,29,63] and with elevated blood pressure at the time of initiation of warfarin therapy.[15,19,20,22,25-32] The relationship of parenchymal intracranial hemorrhage to the intensity of anticoagulation has been controversial.[27,64] A recent case-control study[18] found a doubling of risk with each 0.5 increase in PTR. On average, these strokes are much more severe and more often fatal than ischemic strokes in patients with atrial fibrillation. In the SPAF II Study, 36% (9/25) of the strokes that occurred while receiving warfarin therapy were parenchymal hemorrhages. Early diagnosis and urgent reversal of anticoagulation may be of benefit,[65] as progression of hematoma over many hours is common. Optimal treatment of this complication has not been defined, and further studies are urgently needed.

In summary, our results demonstrate that the risk of bleeding, particularly intracranial hemorrhage, must be carefully weighed when considering anticoagulation for elderly patients. The intensity and variability of anticoagulation were independently related to occurrence of all major bleeding events; however, characteristics at entry (particularly patients' age) were at least as important as anticoagulation management. Less intensive anticoagulation may reduce the rate of bleeding in patients with high intrinsic risk. Ironically, advanced age, hypertension, and previous thromboembolism are predictors of both ischemic stroke[66] and anticoagulation-associated intraparenchymal hemorrhage. Alternative antithrombotic regimens to prevent stroke in patients with atrial fibrillation are now being tested in the SPAF III Study and other ongoing clinical trials[67] to find safer treatment strategies.

*Accepted for publication June 28, 1995.*

*This study was supported by Public Health Service grant R01-NS-24224, National Institute of Neurological Disorders and Stroke, Bethesda, Md.*

*We gratefully acknowledge the encouragement and helpful suggestions of C. Seth Landefeld, MD.*

*Correspondence to the Department of Neurology, Hennepin County Medical Center, 701 Park Ave S, Minneapolis, MN 55415 (Dr Anderson).*

*Reprint requests to the Statistics and Epidemiology Research Corp, 1107 NE 45th St, Suite 520, Seattle, WA 98105 (Ms McBride).*

## REFERENCES


1. Stroke Prevention in Atrial Fibrillation Investigators. Stroke prevention in atrial fibrillation study: final results. *Circulation.* 1991;84:527-539.
2. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. *Arch Intern Med.* 1994;154:1449-1457.
3. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet.* 1994;343:687-691.
4. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet.* 1993;342:1255-1262.
5. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin compared to aspirin for prevention of arterial thromboembolism in atrial fibrillation: design and patient characteristics of the Stroke Prevention in Atrial Fibrillation II Study. *Cerebrovasc Dis.* 1992;2:332-341.
6. Bussey HI, Force RW, Bianco TM, Leonard AD. Reliance on prothrombin time ratios causes significant errors in anticoagulation therapy. *Arch Intern Med.* 1992;152:278-282.
7. Landefeld CS, Anderson PA, Goodnough LT, et al. The bleeding severity index: validation and comparison to other methods for classifying bleeding complications of medical therapy. *J Clin Epidemiol.* 1989;42:711-718.
8. Coon WW, Willis PW III. Hemorrhagic complications of anticoagulant therapy. *Arch Intern Med.* 1974;133:386-392.
9. Husted S, Andreasen F. The influence of age on the response to anticoagulants. *Br J Clin Pharmacol.* 1977;4:559-565.
10. Landefeld CS, Goldman L. Major bleeding in oupatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. *Am J Med.* 1989;87:144-152.
11. Launbjerg J, Egeblad H, Heaf J, Nielsen NH, Fugleholm AM, Ladefoged K. Bleeding complications to oral anticoagulant therapy: multivariate analysis of 1010 treatment years in 551 outpatients. *J Intern Med.* 1991;229:351-355.
12. Petitti DB, Strom BL, Melmon KL. Prothrombin time ratio and other factors associated with bleeding in patients treated with warfarin. *J Clin Epidemiol.* 1989;42:759-764.
13. Peyman MA. The significance of haemorrhage during the treatment of patients with the coumarin anticoagulants. *Acta Med Scand.* 1958;162(suppl 339):1-62.
14. Pollard JW, Hamilton MJ, Christensen NA, Achor RWP. Problems associated with long-term anticoagulant therapy: observations in 139 cases. *Circulation.* 1962;25:311-317.
15. Roos J, van Joost HE. The cause of bleeding during anticoagulant treatment. *Acta Med Scand.* 1965;178:129-131.
16. Schulman S, Lockner D. Relationship between thromboembolic complications and intensity of treatment during long-term prophylaxis with oral anticoagulants following DVT. *Thromb Haemost.* 1985;53:137-140.
17. Van der Meer FJM, Rosendaal FR, Vandenbroucke JP, Briet E. Bleeding complications in oral anticoagulant therapy. *Arch Intern Med.* 1993;153:1557-1562.
18. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med.* 1994;120:897-902.
19. Askey JM. Hemorrhage during long-term anticoagulant drug therapy, I: intracranial hemorrhage. *Calif Med.* 1966;104:6-10.
20. Levine MN, Raskob G, Hirsh J. Risk of haemorrhage associated with long-term anticoagulant therapy. *Drugs.* 1985;30:444-460.
21. Levine MN, Hirsh J, Landefeld S, Raskob G. Hemorrhagic complications of anticoagulant treatment. *Chest.* 1992;102(suppl):352s-363s.
22. Barron KD, Fergusson G. Intracranial hemorrhage as a complication of anticoagulant therapy. *Neurology.* 1959;9:447-455.
23. Lieberman A, Hass WK, Pinto R, et al. Intracranial hemorrhage and infarction in anticoagulated patients with prosthetic heart valves. *Stroke.* 1978;9:18-24.
24. Dawson I, van Bockel JH, Ferrari MD, van der Meer FJM, Brand R, Terpstra JL. Ischemic and hemorrhagic stroke in patients on oral anticoagulants after reconstruction for chronic lower limb ischemia. *Stroke.* 1993;24:1655-1663.
25. Mattle H, Kohler S, Huber P, Rohner M, Steinsiepe KF. Anticoagulation-related intracranial extracerebral haemorrhage. *J Neurol Neurosurg Psychiatry.* 1989;52:829-837.
26. Hill AB, Marshall J, Shaw DA. A controlled clinical trial of long-term anticoagulant therapy in cerebrovascular disease. *Q J Med.* 1960;29:597-609.
27. Kase CS, Robinson RK, Stein RW, et al. Anticoagulant-related intracerebral hemorrhage. *Neurology.* 1985;35:943-948.
28. Levine M, Hirsh J. Hemorrhagic complications of long-term anticoagulant therapy for ischemic cerebral vascular disease. *Stroke.* 1986;17:111-116.
29. Levine MN, Raskob G, Hirsh J. Hemorrhagic complications of long-term anticoagulant therapy. *Chest.* 1989;95(suppl):27s-36s.
30. Strang RR, Tovi D. Subdural haematomas complicating anticoagulant therapy. *BMJ.* 1962;1:845-846.
31. Wells CE, Urrea D. Cerebrovascular accidents in patients receiving anticoagulant drugs. *Arch Neurol.* 1960;5:553-558.
32. Wintzen AR, de Jonge H, Loeliger EA, Bots GTAM. The risk of intracerebral hemorrhage during oral anticoagulant treatment: a population study. *Ann Neurol.* 1984;16:553-558.
33. Davis FB, Estruch MT, Samson-Corvera EB, Voigt GC, Tobin JD. Management of anticoagulation in outpatients: experience with an anticoagulation service in a municipal hospital setting. *Arch Intern Med.* 1977;137:197-202.
34. Kelton JG, Hirsh J. Bleeding associated with antithrombotic therapy. *Semin Hematol.* 1980;17:259-291.
35. Fihn SD, McDonell M, Martin D, et al. Risk factors for complications of chronic anticoagulation: a multicenter study. *Ann Intern Med.* 1993;118:511-520.
36. Forfar JC. A 7-year analysis of haemorrhage in patients on long-term anticoagulant treatment. *Br Heart J.* 1979;42:128-132.
37. Forfar JC. Prediction of hemorrhage during long-term oral coumarin anticoagulation by excessive prothrombin ratio. *Am Heart J.* 1982;103:445-446.
38. Hull R, Hirsh J, Jay R, et al. Different intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. *N Engl J Med.* 1982;307:1676-1681.
39. Landefeld CS, Rosenblatt MW, Goldman L. Bleeding in outpatients treated with warfarin: relation to the prothrombin time and important remediable lesions. *Am J Med.* 1989;87:153-159.
40. Moshos CB, Wong PCY, Sise HS. Controlled study of the effective level of long-term anticoagulation. *JAMA.* 1964;190:799-805.
41. Petty GW, Lennihan L, Mohr JP, et al. Complications of long-term anticoagulation. *Ann Neurol.* 1988;23:570-574.
42. Saour JN, Sieck JO, Mamo LAR, Gallus AS. Trial of different intensities of anticoagulation in patients with prosthetic heart valves. *N Engl J Med.* 1990;322:428-432.
43. Turpie AGG, Hirsh J, Gunstensen J, Nelson H, Gent M. Randomized comparison of two intensities of oral anticoagulant therapy after tissue heart valve replacement. *Lancet.* 1988;1:1242-1245.
44. Zweifler AJ. Relation of prothrombin concentration to bleeding during oral anticoagulant therapy: its importance in detection of latent organic lesions. *N Engl J Med.* 1962;267:283-285.
45. Wilcox CM, Truss CD. Gastrointestinal bleeding in patients receiving long-term anticoagulant therapy. *Am J Med.* 1988;84:683-690.
46. Blom G. *Statistical Estimates and Transformed Beta Variables.* New York, NY: John Wiley & Sons Inc; 1958.
47. Gurwitz JH, Goldberg RJ, Holden A, Knapie N, Ansell J. Age-related risks of long-term oral anticoagulant therapy. *Arch Intern Med.* 1988;148:1733-1736.
48. Second Report of the Sixty Plus Reinfarction Study Research Group. Risks of long-term oral anticoagulant therapy in elderly patients after myocardial infarction. *Lancet.* 1982;1:64-68.
49. Eckman MH, Levine HJ, Pauker SG. Effect of laboratory variation in the prothrombin-time ratio on the results of oral anticoagulant therapy. *N Engl J Med.* 1993;329:696-702.
50. Gottlieb LK, Salem-Schatz S. Anticoagulation in atrial fibrillation: does efficacy in clinical trials translate into effectiveness in practice? *Arch Intern Med.* 1994;154:1945-1953.
51. Gitter MJ, Jaeger TM, Petterson TM, Gersh BJ, Silverstein MD. Bleeding and thromboembolism during anticoagulant therapy: a population-based study in Rochester, Minnesota. *Mayo Clin Proc.* 1995;70:725-733.
52. Wells PS, Holbrook AM, Crowther NR, Hirsh J. Interactions of warfarin with drugs and food. *Ann Intern Med.* 1994;121:676-683.
53. Landefeld CS, Anderson PA. Guideline-based consultation to prevent anticoagulant-related bleeding: a randomized, controlled trial in a teaching hospital. *Ann Intern Med.* 1992;116:829-837.
54. McInnes GT, Helenglass G. The performance of clinics for outpatient control of anticoagulation. *J R Coll Physicians Lond.* 1987;21:42-45.
55. White RH, McCurdy SA, von Marensdorff H, Woodruff DE Jr, Leftgoff L. Home prothrombin time monitoring after the initiation of warfarin therapy: a randomized, prospective study. *Ann Intern Med.* 1989;111:730-737.
56. Kent DL, Vermes D, McDonell M, Henikoff J, Fihn SD. A model for planning optimal follow-up for outpatients on warfarin anticoagulation. *Med Decis Making.* 1992;12:132-141.
57. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med.* 1990;323:1505-1511.
58. Ezekowitz MD, Bridgers SL, James KE, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. *N Engl J Med.* 1992;327:1406-1412.
59. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. *Lancet.* 1989;1:175-179.
60. Connolly SJ, Laupacis A, Gent M, et al. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol.* 1991;18:349-355.
61. Connolly S for the Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation II Study. *Lancet.* 1994;343:1509.
62. Laupacis A, Albers G, Dunn M, Feinberg W. Antithrombotic therapy in atrial fibrillation. *Chest.* 1992;102(suppl):426s-433s.
63. Staaf G, Norrving B, Nilsson B. Intracerebral hematomas during anticoagulant treatment. *Acta Neurol Scand.* 1987;76:391. Abstract.
64. Franke CL, De Jonge J, van Swieten JC, Op de Coul AAW, van Gijn J. Intracerebral hematomas during anticoagulant treatment. *Stroke.* 1990;21:726-730.
65. Fredriksson K, Norrving B, Stromblad LG. Emergency reversal of anticoagulation after intracerebral hemorrhage. *Stroke.* 1992;23:972-977.
66. The Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation, I: clinical features of patients at risk. *Ann Intern Med.* 1992;116:1-5.
67. Stroke Editorial Office. Major ongoing stroke trials. *Stroke.* 1994;25:541-545.