Evaluation of Warfarin versus Aspirin on the Incidence of Thromboembolic Complications in Patients with Nonvalvular Atrial Fibrillation
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Introduction

Atrial fibrillation (AF) is an arrhythmia characterized by an electrical and mechanical abnormality that predisposes to blood stasis and subsequent thrombi formation. Approximately 2 million people in the United States have AF. [1] Its incidence increases with age and is seen in < 1% of people aged 40-65 years, 2-5% of people aged 65-74 years, and > 5% of people aged greater than 75 years. [2] Embolic stroke is the most devastating complication arising from atrial fibrillation. The use of warfarin or aspirin as antithrombotic agents are recommended for the prevention of thromboembolism. [1]

Warfarin is an anticoagulant which inhibits enzymes responsible for synthesis of factors II, VII, IX and X. Thereby preventing clot formation. Warfarin requires routine monitoring and is associated with bleeding. Aspirin is an antiplatelet agent which blocks prostaglandin synthetase action, resulting in decreased formation of the platelet-aggregating substance thromboxane A2. Aspirin is associated with bleeding, however does not require routine monitoring.

According to 2004 Chest guidelines [8] on antithrombotic therapy in atrial fibrillation, the following is recommended: All vitamin K antagonist recommendations have a target international normalized ratio [INR] of 2.5; range, 2.0 to 3.0, in patients with persistent or paroxysmal AF at high risk of stroke (i.e., those with prior ischemic stroke, transient ischemic attack, or systemic embolism, age >75 years, moderately or severely impaired left ventricular systolic function and/or congestive heart failure, history of hypertension, or diabetes mellitus), anticoagulation with an oral vitamin K antagonist is recommended. In patients with persistent AF, age 65 to 75 years, in the absence of other risk factors, antithrombotic therapy with either an oral vitamin K antagonist or aspirin, 325mg/d is recommended. In patients with persistent AF < 65 years and with no other risk factors, aspirin 325mg/d is recommended.

The purpose of this paper is to review five studies (Table 1) which compare the effects of warfarin versus aspirin on the incidence of thromboembolic complications in patients with nonvalvular atrial fibrillation.

Evaluation of the studies

The AFASAK study was a randomized, placebo-controlled study. A total of 1007 patients with chronic atrial fibrillation were to be treated for duration of 2 years. Patients were recruited from two outpatient electrocardiography laboratories to which they had been referred by their general practitioners. After diagnosis of atrial fibrillation was made, the general practitioner was informed about the study and if he or she agreed, the patient was invited to take part in the study. The mean age was 74 years. Patients were

randomized to either warfarin (INR 2.8-4.2) open label, aspirin 75mg once daily or placebo in a double-blind fashion. The incidences of thromboembolic complications were estimated by Kaplan-Meier life-table methods. Treatment comparisons of both primary and secondary endpoints were based on log-rank test. Comparability between groups at randomization was assessed by chi-square and Kruskal-Wallis test. The goal of this study was to compare the efficacy of warfarin versus low dose aspirin therapy.

The SPAF I study was a randomized, double-blind, placebo-controlled, multicenter study. A total of 1330 patients with constant or intermittent atrial fibrillation were treated for duration 1.3years. Patients were identified as inpatients or outpatients from public, private, and Veterans Administration health-care facilities by review of electrocardiographic logs, by direct referral from participating and nonparticipating physicians and by self-referral. During most of the enrollment period, age greater than 75 years was ineligible to receive warfarin because fear of hemorrhage. The mean age was 67 years. Patients in group 1 (anticoagulation candidates) were randomized to receive either open –label warfarin (INR 2.0-4.5), aspirin (325mg) in double- blind fashion, or matched placebo in a double blind fashion. Patients in group 2 (non-anticoagulation candidates) were randomized to either aspirin (325mg) or placebo. In this study warfarin would be compared with placebo in warfarin-eligible patients only, and all patients receiving aspirin would be compared with all patients receiving placebo. Primary and secondary events were reported by neurologist. Verification was done by the Events Committee which was unaware of treatment allocation. Analyses were based on intention to treat. Baseline comparisons performed by chi-square and t test, Comparisons of treatments for both primary and secondary events used the log-rank test. Event rates computed using Kaplan-Meier. Ninety-five percent confidence intervals calculated on the basis of relative risk. The goal of this study was to determine whether aspirin was of benefit in all eligible patients and whether warfarin was of benefit in the subset of patients who could and would take warfarin.

The SPAF II study was a direct extension of the SPAF I study. The SPAF II a cohort study was a randomized, multicenter study which consisted of two parallel clinical trials involving 1100 patients. The study participants included all of the anticoagulation-eligible patients randomized to aspirin or warfarin in the SPAF-1 study. Additionally, 265 SPAF I study participants (most previously assigned to placebo) were rerandomized in the SPAF II study. The study duration was 5 years. Patients were assigned to aspirin (325mg) or warfarin (INR 2.0 – 4.5) in two groups < 75 years or > 75 years. Both patients and investigators were aware of therapy. All suspected neurologic events were evaluated by an on-site study neurologist and verified by an events committee, which had no knowledge of therapy assignment. The 95% confidence interval for the absolute difference in primary event rates was calculated on the basis of observed rates, the log-rank statistic was used for analyses of primary and secondary events comparing time to event with warfarin versus aspirin. The goal of this study was to see whether warfarin would reduce the risk of primary events compared with aspirin by an absolute rate of 2% or more per year in younger patients (< 75years) and by 4% or more in older patients (>75years).

The PATAF trial was a randomized control trial. A total of 729 patients were assigned to treatment. The study duration was 2.7 years. The mean age was 75 years. Patients eligible for standard anticoagulation (stratum 1) were randomly assigned to aspirin (150mg/d), low anticoagulation (warfarin INR 1.1-1.6) or standard anticoagulation (warfarin INR 2.5-3.5). Patients ineligible for standard anticoagulation (stratum 2) were randomized to between aspirin (150mg) and low anticoagulation (warfarin INR 1.1-1.6). Patients were single blinded for the two intensities of anticoagulant, but end point ascertainments were blinded for treatment. Analysis was based on intention to treat approach with a log rank test and Cox regression analysis. The goal of this study was to compare the effectiveness of aspirin and warfarin in preventing thromboembolsm in atrial fibrillation.

The EAFT study was a randomized, placebo-controlled, multicenter study. A total Of 1007 patients with non-rheumatic atrial fibrillation and a recent TIA or minor ischemic stroke. This study focused on secondary prevention. The study duration was 2.3 years. Patients were assigned to two groups. Group 1 (eligible for anticoagulants) randomized to receive either open-label warfarin (INR 2.5- 4.0) or double-blind treatment with aspirin (300mg) or placebo). Patients ineligible were entered in group 2 and randomized to double-blind treatment with aspirin (300mg) or matching placebo. All outcome events were independently classified by at least 3 members of the auditing Committee for Outcome Events, reviewers were unaware of the allocated treatment. Differences of opinion were discussed within the Executive committee, which was also blinded. An independent Data Monitoring Committee monitored the study results. Baseline comparisons between groups were done by chi-square and t-test, the occurrence of primary outcome events was compared in terms of the hazard ratio. All analyses were based on an intention to treat premise. The goal of this study was to compare the effectiveness of aspirin and warfarin in the secondary prevention of thromboembolic events in patients with a recent transient ischemic attack or minor ischemic stroke.

Critique/Analysis

In each of the five studies patients were given warfarin treatment in an openly fashion. This was done for safety reasons. However, giving warfarin open-label can increase the likelihood of bias. In two of the five studies, both the AFASAK and SPAF II studies, warfarin was given openly and both patients and investigators were aware of therapy assignment. This could increase chance of both patient and investigator biases. This problem was addressed by using outside evaluators unaware of the treatments to analyze the data. According to the SPAF I study randomized patients had a mean age 67 years. This trial had an age limit and did not enroll patients older than 75 years because of fear of excess risk of hemorrhage. The mean age in the SPAF I study was lower than the other four studies. This could cause concern knowing that the incidence of stroke increases with age.[1] The PATAF study enrolled patients with less severe disease than the other studies which could cause concern. Looking at statistical analyses all studies were based on intention-to treat premise except when specified. This analysis incorporates all enrolled patients regardless of whether they completed the study or had a complete data file.

The INR target goal for each study was higher than that which is recommended by Chest guidelines (INR of 2-3, target of 2.5).[8] Four of the five studies, the AFASAK, SPAF I, SPAF II and EAFT are all older studies which used prothrombin time ratios which was converted to current usage of INR. The INR target goal for each study was not appropriate for this patient group.

The SPAF II study predicted to show warfarin superior to aspirin. Three analyses were planned. Primary analysis compared warfarin with aspirin for prevention of ischemic stroke and systemic embolism (primary events) on an intention to treat basis. Secondary analyses, specified in advance, included the effect of therapies on all strokes with residual functional deficit and primary events plus vascular death. A non- inferiority analysis was planned. A safety committee not involved in the conduct of the trial monitored for either of two outcomes an unexpected large benefit of warfarin over aspirin or sufficient evidence that the trial could not show advantage for warfarin. Due to low event rate one of the three planned analyses was conducted. For the primary hypotheses, the 95% confidence interval (the adjusted p-value is 0.0425) for absolute difference in primary event rates. The PATAF study predicted to show a non-inferiority analysis, that both treatments were equivalent, and aspirin would be treatment of choice because it does not require routine monitoring. A one sided test was performed in this study.

Interim analyses was planned after 31,62,and 93 primary events in the low anticoagulation and aspirin groups combined with significance levels of 0.001, 0.008 and 0.017 as boundaries for the one sided P value from the stratified log rank test. The trial would be stopped when there was at least a 90% probability that the final analyses would result in a significant difference if the trial was continued. Values of 0.71, 0.34 and 0.16 were used as boundaries, when there is at least an 80% probability that the final analysis result in non-significant difference.

Summary of findings

The five randomized studies detailed in Table 1 provide valuable information on the use of warfarin and aspirin in patients with nonvalvular atrial fibrillation. The trials demonstrate that both warfarin and aspirin reduce the risk of thromboembolic complications in patients with non- rheumatic atrial fibrillation. Patients in the younger age group (< 75 years) in the SPAF II study had a low risk of stroke on aspirin. Patients in the PATAF study had less severe disease and had low overall event rate for stroke. These two trials demonstrate that younger patients without risk factors would benefit little from warfarin. The AFASAK, SPAF II, and SPAF I (indirectly) demonstrated a greater reduction of primary events in patients receiving warfarin compared to aspirin. The EAFT study evaluated secondary prevention in patients with non-rheumatic atrial fibrillation. This study demonstrated warfarin to be more effective than aspirin in preventing recurrent stroke.

Clinical Recommendations

Data presented from the five studies (Table 1) revealed a difference in favor of warfarin compared to aspirin for the prevention of thromboembolic complications. However, in younger patients with less severe disease, with no risk factors for thromboembolic disease, the outcomes fell within the bounds of noninferiority criteria. There was no significant difference in regard to ischemic stroke, in patients treated with aspirin or warfarin in this group. Therefore, warfarin is superior to aspirin in older patients with more advanced disease. The recommended INR target goal for warfarin is 2.5 with a range of 2 to 3.[8] Aspirin has the advantage of convenience dosing without the need for routine monitoring, and therefore is preferred over warfarin in younger patients without risk factors.

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Table 1. Evaluation of Warfarin versus Aspirin Outcome Trials in Patients with Nonvalvular Atrial Fibrillation.

Author(s) Date/ref#	Study Design	# of Subjects	Inclusion Criteria	Exclusion Criteria	Study Location	Study Duration
Petersen P, et. al 1989 **AFASAK**	**Placebo-controlled Randomized**	**N=1007**	**1)18 years** **2)chronic AF**	**1)Previous anticoagulationtherapy > 6 months** **2)cerebrovascular events past month** **3)Contraindication aspirin or warfarin** **4) Previous side effects aspirin or warfarin** **5)Current treatment aspirin or warfarin** **6) Pregnancy or breastfeeding** **7)BP>160/100** **8)Psychiatric disease** **9)Chronic alcoholism** **10)Heart surgery with valve replacement** **11)Sinus rhythm** **12)Rheumatic heart disease** **13) Refusal to participate**	**Copenhagen, Denmark**	**2 years**
Stroke prevention in Atrial Fibrillation Investigators, 1994 **SPAF-II**	**Parallel, randomized**	**n=1100**	**1)Adults atrial fibrillation in previous 12 months** **2)Patients who had ischemic stroke or transient ischemic attack> 2 years before entry eligible.**	**1)Patients with prosthetic heart valves, mitral stenosis.** **2)Patients with requirements for or contraindicaions to aspirin or warfarin.** **3)Patients <60 without overt cardiovascular disease**	**National, Multicenter (16 centers)**	**5 years**
Hellemons BS, et. al 1999 **PATAF**	**Randomized, controlled**	**n=729**	**1)>60 years with chronic or intermittent atrial fibrillation within past 2 years.**	**1)Treatable causes of atrial fibrillation, previous stroke, rheumatic valvular disease, MI, cardiovascular surgery in past year, cardiomyopathy, CHF, cardiac aneurysm, history systemic embolism, retinal infarction, coumadin in past 3 months, CI aspirin or coumadin, duodenal ulcer, GI bleed, blood pressure >185/105**	**Netherlands**	**2.7 years**
European Atrial Fibrillation Study group 1993 **EAFT**	**Randomized, placebo-controlled, multicenter**	**n=1007**	**1).25 years with TIA or minor ischemic stroke** **2)AF or Paroxysmal AF**	**1)AF secondary to disorder** **2) CI to aspirin** **3) Taking NSAID's or anti-platelets** **4) Prosthetic valves, cardiac aneurysm.**	**IInternational, Multicenter**	**2.3 years**
Stroke Prevention in Atrial Fibrillation Investigators 1992 **SPAF-I**	**Double-blind, placebo-controlled, randomized,**	**n=1330**	**1)Diagnosis AF in preceding 12 months** **2)History stroke or TIA 2 years before entry**	**1)Unable obtain consent or follow-up** **2)Recent stroke, TIA, or systemic embolism.** **3)Prosthetic cardiac valve.** **4) Recent myocardial infarction,** **5)Coronary bypass surgery, or angioplasty** **6)Transient, self-limited AF.**	**National, Multicenter**	**1.3 years**

Author(s) Date/ref#	Treatment Regimens Evaluated	Outcome Variables Measured & Method of Measurement	Major Findings (Results)
Petersen P, et. al 1989 **AFASAK**	**1)Patients randomized to warfarin openly, or aspirin 75mg or placebo double blinded.** **2)Therapeutic range warfarin INR 2.4-4.2**	**1)Primary endpoint- thromboembolic complication (TIA, minor stroke, nondisabling stroke, disabling stroke, fatal stroke, embolism to viscera or to extremities).** **2)Secondary endpoint –death.** **Patients evaluated by physical exam and ECG, every 3 months for first 6 months, then every 6 months. Thromboembolic episodes classified by neurologist according to clinical signs or medically confirmed history of acute onset of neurological deficit.**	**1)Total of 46 thromboembolic complication occurred; 5,20, and 21; warfarin, aspirn, and placebo groups, respectively.** **2)There were 3 vascular deaths in warfarin group, 12 aspirin group and 15 in placebo group.** **3)23 patients side effects on warfarin (21 nonf-fatal bleeds), 2 in aspirin goup bleeding episodes, no bleeding episodes placebo group**
Stroke prevention in Atrial Fibrillation Investigators, 1994 **SPAF-II**	**1)Patient had equal chance being assigned to aspirin (325mg) or warfarin(INR 2.0-4.5)** **2)Randomization by computer for two groups (<75 and >75years)** **3) Patient and investigators aware of therapy assignment**	**Primary analysis (intent to treat)** **1)Primary event- ischemic stroke and systemic embolism.** **Secondary analysis** **1)All strokes (ischaemic or hemorrhagic)** **2) Primary event plus vascular death.** **Patients evaluated quarterly and events detected during interview and physical exams.Suspected events evaluated by neurologist and verified by events committee;**	Patients <75 years **1)Withdrawal unrelated to primary event or major hemorrhage 4.2% aspirin assigned patients and 6.8% assigned warfarin.** **Primary analysis** **1)Primary events- 21 and 14; aspirin and warfarin, respectively.** **Secondary analysis** **1)All strokes with residual deficit- 20 events in aspirin and 15 events in warfain group** **2)Primary event or vascular death- 40 and 32; aspirin, warfarin, respectively.** Patients>75 years **1)Withdrawal unrelated primary event or major hemorrhage 4.3% and 10.5%, aspirin and warfarin, respectively.** **Secondary analysis** **1)All strokes with residual deficit-18 and 14 events, aspirin and warfarin, respectively.** **2)Primary event or vascular death- 27 and 29 events, aspirin and warfarin, respectively.** **In < 75 years rates major hemorrhage 0.9% per year with aspirin and 1.7% per year with warfarin. For patients >75 data were, respectively 1.6% and 4.2%.** **Combined results of all ages, warfarin group had 0.8% lower rate of primary events than aspirin. Rate per year all strokes with residual defiit 2.2% with warfarin and 2.5% with aspirin. Primary events plus vascular deaths was 0.9% favouring warfarin.**

Author(s) Date/ref#	Treatment Regimens Evaluated	Outcome Variables Measured & Method of Measurement	Major Findings (Results
Hellemons BS, et. al 1999 **PATAF**	**1)Patients eligible for standard intensity warfarin (INR 2.5-3.5) randomly assigned to standard anticoagulation, very low intensity warfarin or aspirin 150mg/day (stratum1).** **2)Patients ineligible for standard anticoagulation were randomly assigned to low anticoagulation or aspirin (stratum 2).**	**1)Primary events-stroke, systemic arterial embolism, major hemorrhage, vascular death** **2)Secondary events-Nonfatal myocardial infarction, retinal infarction, TIA, minor bleeding complication, or non-vascular death.** **General practitioners followed up patients at four month intervals. Events were independently reviewed by two members of the event committees.**	**1)Primary outcome events per year-total of 30 (Stratum-1)10,8,12, standard AC, low AC and aspirin respectively. (Stratum-2) total 78, 37,41, low AC and aspirin respectively.** **2)Outcome events according to treatment** **Total deaths (stratum1) 12,8,17, standard AC, low AC and aspirin respectively. Stratum2-24,25, low AC and aspirin respectively.** **Vascular deaths-Stratum-1 9,4,9 standard AC, low Ac and aspirin respectively. Stratum 2- 24,25, low Ac and aspirin respectively.** **Non-vascular deaths-(stratum-1)3,4,8 standard AC, low AC and aspirin respectively.(Stratum-2) 9,24 low anticoagulation and aspirin respectively.** **All strokes- (stratum 1) 3,4,8, standard AC, low Ac and aspirin respectively. (Stratum2) 14,18 low AC and aspirin respectively** **All embolism-(Stratum1) 3,3,5 standard AC, low AC, and aspirin. (Stratum2) 13,18 low AC and aspirin respectively.** **23 total major bleeds 10,2,11; low AC, standard AC and aspirin respectively.**
European Atrial Fibrillation Study group 1993 **EAFT**	**1)Patients eligible for AC (group1) randomly assigned to either open-label warfarin (INR 2.5-4.0) or double blind with aspirin 300mg or placebo.** **2) Patients ineligible entered group 2 randomised to double-blind with aspirin 300mg or matching placebo.**	**1)Primary event-death from vascular disease, non-fatal stroke, non-fatal myocardial infarction or systemic embolus.** **Ct scan at time of event. All outcome events classified by committee which were blinded.**	**Warfarin vs placebo** **1)Primary events- 43,67; warfarin,placebo respectively.** **2) All strokes-20,50; warfarin,placebo respectively** **3)All deaths – 41(30 vascular and 11 nonvascular) and 44 (35 vascular and 9 non-vascular) warfarin and aspirin, respectively.** **Aspirin vs placebo** **1)Primary events-130,136; aspirin and placebo respectively.** **2)All strokes- 88,90; aspirin and placebo respectively.** **3)All deaths- 102 (78 vascular and 24 nonvascular) aspirin and 99 (78 vascular and 21 nonvascular) aspirin and placebo, respectively.** **Major bleeds- 13 and 3; warfarin and placebo respectively, 6 and 4; aspirin and placebo, respectively.**

Author(s) Date/ref#	Treatment Regimens Evaluated	Outcome Variables Measured & Method of Measurement	Major Findings (Results)
Stroke Prevention in Atrial Fibrillation Investigators 1991 **SPAF I**	**1)Group1 assigned to open-label warfarin (INR 2.0-4.5), aspirin in a double-blind fashion or matched placebo.** **2)Group 2 received wither aspirin or placebo double blind fashion.** **3) In both group 1 and 2 aspirin dose was 325mg/day**	**1)Primary events- ischemic stroke or systemic embolism.** **2)Secondary events- death, myocardial infarction, TIA or unstable agina pectoris requiring hospital admission.** **All patients followed for 3 months to detect complications and events.Events reported by neurologist or cardiologist and verified by Events Committee, which were unaware of treamtment.**	**Total primary events 6(2.3%/yr) and 18 (7.4%/yr) in warfarin and placebo, respectively.** **Reduction in primary events in those assigned warfarin (67%).** **2)Aspirin vs Placebo** **Total primary events 26(3.6%/yr) and 46(6.3%/yr) in aspirin and placebo, respectively.** **Reduction in primary events in those assigned aspirin (42%).** **Major Complications** **Warfarin 4 (1.5%/yr)** **Placebo 4(1.6%/yr)** **Aspirin 10(1.4%/yr)** **Placebo 14(1.9%/yr)**