The role of anticoagulation plus aspirin in atrial fibrillation is unknown

Clinical Context
Mr. FB is a 62 year old male presenting to the emergency room with multiple syncopal episodes over the past three days. The last episode was witnessed by family members who saw him suddenly lose consciousness and muscle tone only to regain consciousness about 10-20 seconds later with confusion. Per family there were no associated convulsions, incontinence, or other signs of seizure behaviour. On the inpatient service he was diagnosed with VT/VF episodes that triggered his syncopal episodes followed by AICD activation and defibrillation through AICD interrogation. During the course of his hospital stay he was diagnosed with LV thrombus on ultrasound. Past medical history include congestive heart failure with EF <20% s/p biventricular AICD placement, atrial fibrillation, chronic obstructive pulmonary disease, hypertension, and left ventricular thrombus. Among his home medications, he was taking aspirin 81mg and warfarin for the prevention of stroke due to atrial fibrillation, a common combination found in patients with atrial fibrillation to prevent stroke and treat other comorbid conditions but may also increase risk of bleeding. Preventative measures against future strokes in this patient necessitated deciding whether to continue patient on warfarin and aspirin combination therapy or use warfarin alone.

Clinical Question
Does the addition of aspirin to warfarin therapy reduce the risk of future stroke in patients with atrial fibrillation?

Research Article

Literature Review
It is well established that secondary prevention for coronary artery disease includes aspirin\(^1\) and that anticoagulation reduces the risk of recurrent stroke for patients with atrial fibrillation\(^2-3\). However, there is no research evidence for the role of aspirin plus anticoagulation to prevent recurrent stroke. While many studies and meta-analyses were found through these sources, the most substantial and prominent study upon which most contemporary papers derived hypotheses and post-hoc analyses from was the Stroke Prevention Using an ORal Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) trials III and V\(^4-5\). These trials were originally designed to determine the non-inferiority of a new oral direct thrombin inhibitor Ximelagatran compared to warfarin in the prevention of stroke and embolism in patients with high risk atrial fibrillation.
While not directly examining the use of aspirin in combination with warfarin, a much-cited post-hoc analysis of these two SPORTIF trials looked at exactly this combination based on the data from the trials.

This post-hoc analysis was chosen over the previous Stroke Prevention in Atrial Fibrillation (SPAF) III and Second Copenhagen Atrial Fibrillation, Aspirin and Anticoagulant Therapy Study (AFASAK 2) studies as the topic for this appraisal due to the fact that these prior trials of anticoagulation plus aspirin tested the hypothesis that low dose anticoagulation plus aspirin might be safer, but that hypothesis was proven wrong. SPORTIF III and V are the largest clinical trials to date involving anti-thrombotic therapy in atrial fibrillation, contains more recent data, and was randomized in nature. SPORTIF III and V trials have been referenced by a combined 17 systematic reviews and 1260 journal articles, representative of their impact on the field. The SPORTIF III and V trials had identical protocols except SPORTIF III involved open-label design with 3407 patients randomized at 259 sites across 23 countries in Europe, Asia, Australia, while SPORTIF V was double-blinded with 3922 patients in the US and Canada, for a grand total of 7329 patients. The post-hoc analysis by Flaker et al. pooled participant data from both trials containing 7304 patients (25 patients had unavailable medication logs). The hypothesis of the SPORTIF trials was to show non-inferiority of Ximelagatran compared to warfarin. Ximelagatran is a thrombin inhibitor similar to dabigatran and required extrapolation to the current standard of care using Xa inhibitors.

As the SPORTIF III and V trials were prospective multi-center, randomized, double-blinded trials with good follow up, the level of evidence for the studies is level 1b based on the Oxford CEBM levels of evidence.

Critical Appraisal

The research article is a post-hoc analysis of the SPORTIF III and V and the authors correctly state that, 'as such, the results of this post hoc analysis must be considered hypothesis generating rather than conclusive. CEBM level of evidence V (expert opinion). SPORTIF III and V are prospective studies with two parallel treatment groups receiving randomized treatment with either dose-adjusted warfarin (to an INR of 2-3) or Ximelagatran 36mg BID. Inclusion criteria for both studies included: Age >18, persistent or paroxysmal atrial fibrillation verified by at least 2 ECGs, one or more stroke risk factors in addition to AF defined as concomitant hypertension, age > 75, previous stroke or TIA or systemic embolism, left ventricular dysfunction, age >65 with coronary artery disease, and age >65 with diabetes mellitus. The exclusion criteria were many, the most important ones relevant to our patient is that only patients taking aspirin <100mg/day were allowed to participate, and they must not be on any other antithrombotic drugs. Our patient satisfied this and all other exclusion criteria of the study.

While all patients in the study met the above criteria and were randomized into groups, because the studies did not set out to study aspirin directly, there were some important baseline differences between the groups of patients receiving aspirin with warfarin and those taking
warfarin or ximelagatran alone. Patients taking low dose aspirin were more likely men (76 vs 68%), Asian (9.5 vs 5%), have smoking history (62% vs 57%), less frequent alcohol users (41% vs 46%), have higher incidence of previous stroke or TIA (26 vs 20%), LV dysfunction (41 vs 36%), diabetes mellitus (27.5 vs 23%) and CAD (69 vs 41%). These differences only appear in the post-hoc analysis and presumably reflect the standard of care that dual therapy is more common in patients with both atrial fibrillation and coronary artery disease or coronary artery disease equivalents. Despite these baseline differences, the post-hoc analysis is reflective of real clinical settings receiving low dose aspirin will have many baseline characteristics as the patient population receiving both aspirin and warfarin in the study, thus the extrapolated findings will likely also apply to the greater patient population taking low-dose aspirin. However, as gender, previous stroke/TIA, LV dysfunction, and diabetes mellitus are all major risk factors considered in the CHAD2DS2-VASc scoring system for estimating risk of stroke with AF, the baseline differences must be taken into consideration when evaluating the primary endpoints between the two groups.

The primary endpoint of the study was stroke (ischemic or hemorrhagic) and/or systemic embolism according to intention-to-treat analysis. For stroke, analysis of 3172 individuals taking warfarin alone showed 1.5% incidence over 17.4 month follow up versus the 481 pool of individuals taking warfarin + aspirin showing a 1.7% incidence over the same period (p=0.71). Therefore, no difference in stroke incidence was seen in the group receiving additional low-dose aspirin in combination with warfarin anti-coagulation. For combined stroke + systemic embolism endpoint, warfarin-only group had 1.55% incidence while warfarin + aspirin group had 1.7% incidence with p=0.78, again showing no difference between these two groups. Of note, the trials contained multiple levels of blinded endpoint assessment, such as review of all detected cerebrovascular events by an independent, blinded central adjudication committee, which reduces the chance of bias from study-affiliated neurologists.

The study also contained many secondary events analysed in the same manner including major bleed (defined as fatal, at critical site, overt + loss of hemoglobin of 20g/L, or requiring transfusion of at least 2 units of blood), for which the warfarin-only group had significantly less incidence of bleeding (2.3%) versus the warfarin + aspirin group (3.9%) with p=0.01, which mostly occurred in the GI tract (38.2%) versus CNS bleed (7.1%). These results translate to the NNH for combination of warfarin + aspirin group being 62.5. Showing a similar trend, incidence of major + minor bleed (confirmed bleeds not fitting criteria for major bleed) was also significantly less in the warfarin-only group as compared to the warfarin + aspirin group (36.8% vs 62.8%, p=<0.01), translating to a NNH of 3.8 when using the warfarin + aspirin combination.

In all, these results suggest that the addition of aspirin to anticoagulation therapy did not reduce incidence of stroke or stroke + systemic embolism while increasing the risk of major and minor bleeding. These conclusions are consistent with the findings of the ORBIT-AF national registry.
that enrolled 10126 AF patients from 176 US practices and compared rates of bleeding, hospitalization, ischemic events, and mortality between anticoagulation only and anticoagulation + Aspirin therapy after 6 months. They found that the combination was independently associated with significantly increased risk for bleeding compared to anticoagulation alone with hazard ratio 1.52, 95% confidence interval, 1.20-1.96. This registry's findings are strengthened by their care in adjusting for baseline characteristics between the two groups and performed appropriate risk stratification\textsuperscript{10}.

Clinical Application

This pooled analysis of data from the SPORTIF III and V trials was of great benefit in terms of clinical decision-making for patients requiring warfarin therapy for AF who are already put on low dose aspirin previously, as was the case in our patient Mr. FB. The findings showed that the addition of aspirin not only provided no additional benefit with respect to stroke or systemic embolism reduction but conversely increased the risk of both major and minor bleeding. This strongly argues against the practice of continuing patients on dual aspirin anti-platelet and vitamin K antagonist anti-coagulation. Patients like Mr. FB whose home medications included with low-dose aspirin (81mg) without strong indication for continued use (ie. s/p STEMI) should have it discontinued when initiating warfarin prophylaxis of stroke due to non-valvular AF, and patients who were not already on aspirin should not start unless other indications demand it (ie. s/p STEMI) and the benefits clearly outweigh the risks.

Our patient did not meet any criteria that necessitated the continuation of aspirin and was agreeable to being taken off aspirin after consideration of the risks and benefits. He was maintained on warfarin monotherapy for the duration of the hospitalization and continued to do well until discharge.

A few take-home points emerge from this appraisal that deserves special emphasis:

1) The combination of anti-platelet and anti-coagulation therapy for the prevention of stroke in patients with non-valvular AF has not been shown to confer added benefit compared to anti-coagulation alone

2) The benefit of aspirin may outweigh the risks of increased chances of bleeding in certain individuals and must be evaluated on a case-to-case basis

This appraisal aims to help patients make informed decisions about risk and benefit of taking combination treatment for stroke prevention in AF, and properly weigh the trade-off between cardiac and neurological protection from thrombosis and that of major and minor bleeding. It is hoped that practicing and aspiring clinicians can use this appraisal as a guide to current available evidence and its interpretation that would help them provide appropriate management decisions and counseling to patients and apply similar research methodology to discover, evaluate, and
synthesize best possible information in an evidence-based manner to find answers to similar clinical questions in the future.

References


