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We have no real evidence related to anticoagulation plus aspirin for stroke prevention in atrial fibrillation

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ABSTRACT A critical appraisal and clinical application of Flaker GC, Gruber M, Connolly SJ, et al. Risks and benefits of combining aspirin with anticoagulant therapy in patients with atrial fibrillation: an exploratory analysis of stroke prevention using an oral thrombin inhibitor in atrial fibrillation (SPORTIF) trials. *Am Heart J*. 2006;152:967-973. doi: 10.1016/j.ahj.2006.06.024

Keywords: *atrial fibrillation, warfarin, aspirin, stroke*

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 activity. We interrogated his automatic implantable cardioverter-defibrillator device (AICD) and diagnosed ventricular tachycardia and ventricular fibrillation episodes that we believe triggered his syncopal episodes. During the course of his hospital stay he was also diagnosed with LV thrombus on ultrasound. Past medical history includes 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. This regimen had been started during the course of his prior care. Our rounding team needed to decide what preventative measures against future strokes were appropriate. His risks for future stroke included not only atrial fibrillation, but also documented left ventricular thrombus in the setting of low left ventricular ejection fraction. We had to decide whether to continue the 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

Flaker GC, Gruber M, Connolly SJ, et al. Risks and benefits of combining aspirin with anticoagulant therapy in patients with atrial fibrillation: an exploratory analysis of stroke prevention using an oral thrombin inhibitor in atrial fibrillation (SPORTIF) trials. *Am Heart J*. 2006;152:967-973. doi: 10.1016/j.ahj.2006.06.024

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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. The literature search began with a review of pertinent articles on management of stroke risk for patients with atrial fibrillation, using keywords "atrial fibrillation" and "stroke prevention." Further search for "anticoagulation plus aspirin for atrial fibrillation" yields articles and trials related to combination therapy including the appraised article. Current thinking and discussion of this topic is influenced by post-hoc analyses from 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[6].

This post-hoc analysis was chosen as the paper for this appraisal over the previous Stroke Prevention in Atrial Fibrillation (SPAF) III and Second Copenhagen Atrial Fibrillation, Aspirin and Anticoagulant Therapy Study (AFASAK 2) studies because 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[7-8]. SPORTIF III and V are the largest clinical trials to date involving anti-thrombotic therapy in atrial fibrillation, contain more recent data, and were randomized in nature. A combined 17 systematic reviews and 1260 journal articles, representative of their impact on the field, have referenced SPORTIF III and V trials. 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 hypothesis of the SPORTIF trials was to show non-inferiority of Ximelagatran compared to warfarin for the prevention of stroke in atrial fibrillation (AF). Ximelagatran is a thrombin inhibitor similar to dabigatran[9] and required extrapolation to the current standard of care using Xa inhibitors[2-3]. As the SPORTIF III and V trials were prospective multi-center, randomized, double-blinded trials with good follow up, the level of evidence for those studies is 1b based on the Oxford CEBM levels of evidence. The post-hoc analysis by Flaker et al. pooled participant data from both trials containing 7304 patients (25 patients had unavailable medication logs).

Critical Appraisal

The research article chosen 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." Thus the level of evidence for the paper reviewed is Level 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 being 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 to be 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. The post-hoc analysis baseline differences between groups is reflective of real clinical settings where patients receive low dose aspirin. The differences at baseline make any real comparative efficacy difficult. In fact, these differences are large enough to conclude that the subgroups considered are actually sampling from two distinct and different populations of patients. If that is actually true, it is improper to compare these subgroups or draw any conclusion from such a comparison. Because 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

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must be taken into consideration when evaluating the primary endpoints between the two groups. The authors attempted to control for these variables using multivariable regression, but this can only account for confounding and variables already existing in the dataset. This draws attention to the lack of randomization (and its equalization of bias) for the hypothesis expressed in the clinical question. Although not well described in the paper, it is odd that the unadjusted data and the multivariable analysis showed similar results given that the baseline data differed so much. Overall, this post-hoc analysis provides little solid evidence to answer our clinical question. Yet, it is sometimes used when making clinical decisions.

The primary endpoint of the post hoc analysis 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 pool of 481 individuals taking warfarin plus 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 plus systemic embolism endpoint, the warfarin-only group had 1.55% incidence while the warfarin plus aspirin group had 1.7% incidence (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 plus loss of hemoglobin of 20g/L, or requiring transfusion of at least 2 units of blood). This combination endpoint doesn't allow for analysis of intracranial bleeds, which presumably had severe complications, compared to significant blood loss in the gastrointestinal or genitourinary systems, which could be managed with transfusion and no lasting functional deficits. The results are not reported in significant enough detail for the reader to make these calculations independently. One must imagine that these data exist in the original data sets, but the lack of meaningful reporting hinders the clinical utility of assessing evidence. The warfarin-only group had significantly less incidence of major bleeding (2.3%) versus the warfarin plus aspirin group (3.9%) with p=0.01, which mostly occurred in the GI tract (38.2%) versus central nervous system (CNS) bleed (7.1%). These results translate to the NNH for combination of warfarin plus aspirin group being 62.5. Showing a similar trend, incidence of major plus minor bleed (confirmed bleeds not fitting criteria for major bleed) was also significantly less in the warfarin-only group as compared to the warfarin plus aspirin group (36.8% vs 62.8%, p=<0.01), translating to a NNH of 3.8 when using the warfarin plus aspirin combination.

The authors suggest that the addition of aspirin to anticoagulation therapy did not reduce incidence of stroke or stroke plus systemic embolism while increasing the risk of major and minor bleeding. These conclusions are consistent with the findings of the ORBIT-AF national registry[10].

Clinical Application

This pooled analysis of data from the SPORTIF III and V trials does little to assist clinical decision-making for patients requiring warfarin therapy for AF who have previously been put on low dose aspirin, as was the case with our patient Mr. FB. The findings showed that the addition of aspirin provided no additional benefit with respect to stroke or systemic embolism reduction but conversely increased the risk of both major and minor bleeding. While this analysis argues against the practice of continuing patients on dual aspirin anti-platelet and vitamin K antagonist anti-coagulation, the methodological flaws preclude any definitive guidance for clinical care. Patients like Mr. FB whose home medications included with low-dose aspirin (81mg) without strong indication for continued use (i.e., previous coronary event) could be considered for discontinuation of the aspirin, but this remains a clinical judgement because of the lack of quality evidence. Clinicians must make this decision on an individual basis, considering the risk of harm and the risk of benefit to their particular patient.

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 harms 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 deserve 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.

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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.

It is hoped that practicing and aspiring clinicians use this appraisal and its precautions about the quality of evidence to help them make appropriate management decisions and counseling to patients. It is particularly important to be able to engage in clinical discussions with colleagues who espouse to know the answer to this dilemma. We must always avoid becoming overly dependent upon the conclusions of the authors.

References

1. Guirguis-Blake JM, Evans CV, Senger CA, et al. Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the U.S. Preventive Services Task Force: A Systematic Evidence Review for the U.S. Preventive Services Task Force. *Annals of Internal Medicine* 2016;164(12);804. doi: 10.7326/m15-2113
2. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Eng J Med* 2011; doi: 10.1056/NEJMoa1107039.
3. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; doi: 10.1056/NEJMoa1009638.
4. Executive Steering Committee, on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct inhibitor ximelagatran compared with warfarin patients with non-valvular atrial fibrillation (SPORTIF III): randomized controlled trial. *Lancet* 2003;362:1691 -8. doi: 10.1016/S0140-6736(03)14841-6.
5. SPORTIF Executive Committee, for the SPORTIF V Investigators. Ximelagatran vs. warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA* 2005;293:690 -8. doi: 10.1001/jama.293.6.690.
6. Flaker GC, Gruber M, Connolly SJ, et al. Risks and benefits of combining aspirin with anticoagulant therapy in patients with atrial fibrillation: an exploratory analysis of stroke prevention using an oral thrombin inhibitor in atrial fibrillation (SPORTIF) trials. *Am Heart J*. 2006;152:967-973. doi: 10.1016/j.ahj.2006.06.024
7. Stroke Prevention Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: the Stroke Prevention in Atrial Fibrillation III randomized clinical trial. *Lancet* 1996;348:633-8. doi:10.1016/S0140-6736(96)03487-3.
8. Koefoed BG, Gullov AL, Petersen P. Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulant Therapy Study (AFASAK 2): Methods and Design. *J Thromb Thrombolysis* 1995:2:125-130. doi: 10.1007/BF01064380.
9. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Eng J Med* 2009. 361(12):1139-51. doi: 10.1056/NEJMoa0905561.
10. Steinberg BA, Kim S, Piccini JP, et al. Use and associated risks of concomitant aspirin therapy with oral anticoagulation in patients with atrial fibrillation: insights from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Registry. *Circulation* 2013;128(7):721-728. doi: 10.1161/CIRCULATIONAHA.113.002927.

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