Stroke prevention in atrial fibrillation: antiplatelet therapy revisited

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This editorial refers to ‘Antithrombotic therapy in elderly patients with atrial fibrillation: effects and bleeding complications: a stratified analysis of the NASPEAF randomized trial’† by F. Pérez-Gómez et al., on page 996

Stroke and thrombo-embolism can be catastrophic complications of atrial fibrillation (AF), and this link is so compelling that up to 15% of all ischaemic stroke can be directly attributable to AF. Nevertheless, therapeutic decisions for stroke prevention have long been guided by many good clinical trials of thromboprophylaxis in AF, which show that adjusted-dose warfarin significantly reduces the risk of ischaemic stroke or systemic embolism compared with placebo [relative risk (RR): 0.33; 95% confidence interval (CI): 0.24–0.45]. Warfarin is also superior to aspirin (RR: 0.59; 95% CI: 0.40–0.86) or fixed low-dose (low intensity) warfarin therapy for stroke prevention. The evidence in favour of warfarin as thromboprophylaxis for AF is therefore irrefutable, especially for ‘high-risk’ patients with AF.

In contrast, the use of aspirin only reduces the risk of stroke in AF by 22% (95% CI: 2–38) compared with control. More worryingly, there appears to be a general misconception over the efficacy of aspirin in AF among the medical community. The reduction in stroke risk by 22% with aspirin, as mentioned above, is largely driven by data from the Stroke Prevention in Atrial Fibrillation (SPAF)-I clinical trial, where participants in an ‘anticoagulation-eligible’ arm were randomized to warfarin, aspirin, or placebo (group 1), whereas in the ‘anticoagulation-ineligible’ arm (group 2, defined by physician/patient preference or the presence of contraindications), patients were randomized to either aspirin or placebo. Initial analyses give a 94% risk reduction of aspirin vs. placebo ($P < 0.001$) in group 1, whereas in group 2, aspirin only conferred an RR of 8% ($P = 0.75$)—the net result by combining the aspirin vs. placebo data from groups 1 and 2 was an overall stroke risk reduction of 42% with aspirin against placebo ($P = 0.002$).

This internal inconsistency from the SPAF-I trial continues to be much debated, but it is noteworthy that the 22% stroke risk reduction with aspirin in AF is broadly similar to the stroke reduction seen by antiplatelet therapy use in high-risk vascular disease patients. Since AF frequently co-exists with vascular disease, it is likely that we are seeing an effect of aspirin on vascular disease, rather than on stroke associated with AF per se. Also, thrombogenesis in AF is largely coagulation-related and the platelet abnormalities in AF, where present, are not much more than that seen with the associated vascular disease alone. Assuming the efficacy of aspirin is simply due to its effect on comorbid vascular risk factors, there should (theoretically) be little difference in aspirin effect in relation to its dose—whether 75, 160, or 325 mg daily—except that more adverse effects occur with higher aspirin doses. However, the one trial in AF per se that has tested aspirin 75 mg daily vs. placebo did not demonstrate a significant beneficial reduction in stroke, and only the clinical trials testing 325 mg daily showed some (debatable) benefit. Many guidelines still recommend aspirin for ‘low-risk’ patients with AF, but the recent Japanese Atrial Fibrillation stroke trial even questions this approach, showing that aspirin was no better (or perhaps worse) than placebo in low-risk AF patients. Indeed, the use of aspirin may be to treat (or reassure) the prescriber, rather than the patient.

Others have investigated whether dual anti-platelet therapy may provide a safer, and more efficacious, alternative. The ACTIVE-W (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events) trial, for example, directly compared anticoagulation against aspirin–clopidogrel combination therapy and was discontinued early because of overwhelming evidence for the superiority of anticoagulation over antiplatelet therapy. This again should come as little surprise given the pathophysiology of thrombogenesis in AF and that atrial thrombus tends to be fibrin-rich rather than platelet-rich. Although major bleeding rates were similar between the two treatment arms in ACTIVE-W, patients taking the aspirin–clopidogrel combination did report more frequent minor bleeds.

Perhaps the combination of aspirin and low-dose anticoagulation may allow for stroke risk reduction, while avoiding excess bleeding risk. This issue has been addressed in several trials, all of which failed to show the superiority of aspirin plus Vitamin K antagonist (VKA) combination therapy over anticoagulation therapy alone. In the FFAACS (Fluindione, Fibrillation Auriculaire, Aspirin et Contraste...
Spontane) trial, for example, adjusted-dose fluindione (a VKA) plus aspirin was compared against VKA alone, with no difference in thrombo-embolism, but showed a particularly high bleeding rate in the combination treatment arm (13.1%) compared with the VKA only group (1.2%) \(P = 0.003\).\(^7\)

For stroke thromboprophylaxis per se, the evidence so far suggests that aspirin is an inferior choice for stroke prevention in high-risk patients and does not appear to be additive to warfarin. The efficacy of aspirin in low-risk AF patients is also debated. One ongoing clinical trial of warfarin vs. aspirin 75 mg daily, the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study, will inform us of the ideal strategy for stroke prevention in an elderly (age \(\geq 75\)) primary care population with AF. For now, perhaps, the only setting where warfarin can be combined with antiplatelet therapy (that includes aspirin and/or clopidogrel) in the setting of non-valvular AF is in relation to percutaneous coronary intervention and stenting, given this is increasingly the norm in managing acute coronary syndromes and the increasing use of drug-eluting stents (and the concerns of late stent thrombosis) necessitate the prolonged use of antiplatelet therapy.\(^8\)

However, other non-aspirin antiplatelet drugs may be another option. The SIFA (Studio Italiano Fibrillazione Atriale) secondary prevention trial\(^9\) compared the effects of indobufen (100 or 200 mg bid, a reversible inhibitor of platelet cyclo-oxygenase) against warfarin in 916 AF patients with a recent cerebral ischaemic episode. The primary outcome was 10.6% in the indobufen group vs. 9.0% in the warfarin group \(P = \text{NS}\), with only four cases (0.9%) of gastrointestinal bleeding, all in the warfarin group. Unfortunately, further trials of indobufen in AF have not been published.

In contrast, the combination of VKA with another antiplatelet drug, triflusal (which is a novel cyclo-oxygenase inhibitor structurally related to salicylates), has attracted recent interest. In 2004, the Spanish National Study for Prevention of Atrial Fibrillation (NASPEAF) randomized trial first reported impressive results using a triflusal plus VKA combination (INR 1.4–2.4) compared with VKA therapy alone for stroke prevention in AF, and the stratified analysis from this clinical trial is given in Pérez-Gómez et al.\(^10\) This study was notable for two reasons. First, patients with AF and mitral stenosis (a known potent stroke risk factor) were not excluded. Secondly, this study is the first to demonstrate that the combination of triflusal with moderate intensity VKA anticoagulation can provide both adequate stroke protection and a lower bleeding risk when compared with standard anticoagulation alone. The NASPEAF subanalysis\(^10\) concluded that the triflusal/VKA combination was even safe and effective in an elderly (age \(\geq 75\)) cohort of patients compared with anticoagulation alone, even if this was at the expense of more frequent non-fatal gastric bleeding. These findings held true even for those elderly patients who have had a prior embolic event and therefore are at the greatest risk for stroke.

As mentioned above, these data are all the more exciting given the increasing clinical need for co-prescription of antiplatelet drugs and VKAs. The drive towards aggressive coronary revascularization and the high prevalence of AF among patients with coronary artery disease has introduced further apprehension among cardiologists as to the most appropriate application of antithrombotic therapy, given the requirement for both anticoagulation and antiplatelet strategies in this patient cohort, especially in the setting of coronary stents.\(^8\) However, the co-administration of several drugs that may enhance bleeding tendency is of great concern, particularly given that bleeding rates with even antiplatelet drugs alone can be problematic.

With the recent demise of further development of ximelagatran, the first oral direct thrombin inhibitor and the first new oral anticoagulant class for a long time, on safety grounds, the race to develop efficacious and safe alternatives to the VKAs has been thrown wide-open once more. Although a variety of oral direct thrombin and factor Xa inhibitors are currently undergoing clinical evaluation, perhaps the flexibility of triflusal as an antiplatelet agent in combination with VKAs may provide a viable alternative, particularly in coronary revascularization. More clinical trials with this combination treatment are needed, which include ‘real-world’ patients with AF, who often have multiple comorbidities and concomitant therapies. We also need to understand the underlying pathophysiological reasons to explain why triflusal–VKA combination therapy works (and is safe) in AF, but aspirin–VKA combination therapy or aspirin–clopidogrel does not. We therefore await further developments with triflusal in AF, with some interest.

Until then, the role of antiplatelet therapy for stroke prevention in AF needs to be revisited, for a pragmatic and critical re-appraisal on its usefulness for stroke prevention, with particular reference to aspirin.

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References
Clinical vignette

Coronary Buerger’s disease with a peripheral arterial aneurysm

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This male patient was diagnosed as Buerger’s disease at 25 years of age. He developed ulcers on the first and fifth toes of right foot at 38 years of age, and was admitted to our hospital due to ischaemic leg pain at rest. Physical examination revealed an absence of dorsalis pedis pulses bilaterally. Digital subtraction angiography of right lower leg showed complete occlusion of both anterior and posterior tibial arteries with typical corkscrew-like collateralizations (Panel A). Subsequent coronary angiogram revealed complete occlusion of the middle segment of left anterior descending artery. Corkscrew collaterals (Panel B) and intact right coronary artery supplied blood stream distally. He has no history of angina pectoris, and a thallium scan demonstrated normal myocardial perfusion (Panel C). An aneurysm was incidentally found in the distal segment of right femoral artery (Panel D) by systemic examination of arteries using computed tomography. Three-dimensional reconstruction of the image of computed tomography gave precise image of this aneurysm (Panel E). Only a few cases of coronary involvement and one case of thoracoabdominal aneurysm complicated with Buerger’s disease have been reported. To the best of our knowledge, this is the first case of Buerger’s disease with both coronary artery occlusion and an aneurysm in peripheral artery.

Panel A. Digital subtraction angiography of right lower leg, demonstrating complete occlusion of both anterior (arrows) and posterior (arrow head) tibial arteries with typical corkscrew-like collateralizations.

Panel B. Coronary angiogram revealing complete occlusion (arrows) of left anterior descending artery, filled distally (dotted-lined arrows) via corkscrew collaterals (arrow heads).

Panel C. Thallium myocardial perfusion imaging in the short axis (left) and the vertical long axis (right).

Panels D and E. Axial view (Panel D) and three-dimensional reconstruction (Panel E) of the computed tomographic scan, demonstrating an aneurysm in the distal segment of right femoral artery.