

# Combination Anticoagulant and Antiplatelet Therapy in Atrial Fibrillation Patients

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The question of whether or not combination antithrombotic therapy is beneficial in terms of a reduction in fatal and non-fatal vascular events in atrial fibrillation (AF) is an important question which essentially remains unanswered. Original randomised controlled trials in AF patients examining the efficacy of combination oral anticoagulant (OAC) and antiplatelet therapy for stroke prevention in AF, by comparing either fixed dose (or low intensity international normalized ratio, INR, <1.5) anticoagulation plus aspirin with dose-adjusted warfarin (INR, 2.0-3.0), or dose-adjusted warfarin  $\pm$  aspirin, have not reported any additional benefit of fixed dose (or low intensity) anticoagulation plus aspirin over dose-adjusted warfarin alone.<sup>1</sup> The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE)-W trial also showed that anticoagulation with dose-adjusted warfarin (INR, 2.0-3.0) was superior to the combination of clopidogrel plus aspirin for the prevention of vascular events in patients with AF at high risk of stroke, particularly in those already taking OAC (RR, 1.50; 95% CI, 1.19-1.80) with a non-significant difference in major bleeding (RR, 1.30; 95% CI, 0.94-1.79).<sup>2</sup> The subsequent results of the ACTIVE-A trial demonstrated that clopidogrel plus aspirin was superior to aspirin monotherapy for stroke prevention (RR, 0.72; 95% CI, 0.6-0.83;  $P<.001$ ), but combination antiplatelet therapy was associated with a greater

risk of major haemorrhage (RR, 1.57; 95% CI, 1.29-1.92;  $P<.001$ ).<sup>3</sup>

More recently, 3 randomized controlled trials<sup>4-6</sup> and 1 post-hoc analysis of the combined datasets from the Stroke Prevention using an Oral Thrombin Inhibitor in atrial Fibrillation (SPORTIF) III and IV trials<sup>7</sup> have examined the effect of combination antithrombotic therapy (that is, OAC plus antiplatelet therapy) versus anticoagulation alone on vascular events and bleeding, in AF patients. The Fluindione, Fibrillation Auriculaire, Aspirin et Contraste Spontané (FFAACs) study, which compared fluindione plus placebo (anticoagulation alone) with fluindione plus aspirin (combination therapy; INR target, 2.0-2.6), was stopped prematurely due to poor recruitment ( $n=157$ ), and hence was underpowered to examine the primary outcome, but demonstrated a higher bleeding event rate in the combination arm.<sup>4</sup>

In addition, a subgroup analysis of patients on antiplatelet therapy plus either idraparinux (an injectable indirect factor Xa inhibitor) or adjusted-dose vitamin K antagonists (INR target, 2.0-3.0) enrolled in the Atrial Fibrillation Trial of Monitored Adjusted Dose Vitamin-K Antagonist, Comparing Efficacy and Safety With Unadjusted SanOrg34006/idraparinux (AMADEUS) trial,<sup>6</sup> revealed that clinically relevant bleeding was more frequent in the 971 (21%) patients who took aspirin in combination with the anticoagulant (30.5 per 100 patient-years with idraparinux vs 17.7 per 100 patient-years with vitamin K antagonists) and in the 126 (3%) patients who took clopidogrel or ticlopidine (42.7 per 100 patient-years with idraparinux and 23.4 per 100 patient-years with vitamin K antagonists), than in those not taking concomitant antiplatelet therapy (16.4 per 100 patient-years with idraparinux and 9.3 per 100 patient-years with vitamin K antagonists).<sup>6</sup> The effect of combination anticoagulant and antiplatelet therapy on vascular events in this subset of AMADEUS trial participants has not yet been fully reported.

A retrospective post-hoc analysis of the combined datasets of the SPORTIF III and IV<sup>7</sup>

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trials, compared ximelagatran (an oral direct thrombin inhibitor) with warfarin in AF patients at moderate to high risk of thromboembolism, and examined those on concomitant aspirin therapy with those not on aspirin. There was no reduction in stroke or vascular events (death or myocardial infarction [MI]) with combination therapy. However, combination therapy was associated with higher bleeding rates (major and minor) compared to patients receiving either alone; aspirin use in patients on warfarin significantly increased the risk of bleeding (HR, 1.58; 95% CI, 1.01-2.49) compared to warfarin alone (3.9% vs 2.3%; per year, respectively;  $P=.01$ ). The data from these 3 studies of combination antithrombotic therapy versus anticoagulation alone in AF patients is therefore equivocal, given that one study was underpowered to examine the effect of such treatment on thromboembolic risk,<sup>4</sup> 1 has not yet reported the full data for vascular events,<sup>6</sup> and 1 was a retrospective post-hoc analysis of 2 combined randomized controlled trials.<sup>7</sup>

Perhaps the most promising randomized controlled trial of combination antithrombotic therapy in AF patients to date was the National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF),<sup>5</sup> which compared the antiplatelet agent triflusal 600 mg/d alone, acenocoumarol (INR, 2.0-3.0) alone, with combination acenocoumarol (INR, 2.0-3.0) and triflusal in 1209 patients at intermediate (>60 years or with stroke risk factors) or high risk (mitral stenosis  $\pm$  previous embolism) of thromboembolism. Results from the original analysis<sup>5</sup> demonstrated that combination therapy significantly reduced the primary endpoint (vascular death/transient ischaemic attack [TIA]/non-fatal stroke/systemic embolism) compared to anticoagulant therapy alone in both groups (HR, 0.33; 95% CI, 0.12-0.91;  $P=.02$  and HR, 0.51; 95% CI, 0.27-0.96;  $P=.03$ ). There was approximately a 60% relative risk reduction in vascular events and severe bleeding combined in the dual therapy arm compared to OAC-alone (HR, 0.38; 95% CI, 0.17-0.87;  $P=.02$ ) or antiplatelet-therapy alone (HR, 0.39; 95% CI, 0.17-0.87;  $P=.02$ ).<sup>5</sup> Surprisingly, no further trials have been conducted using triflusal despite these promising preliminary results.

However, the current issue of the journal reports the long-term follow-up (mean, 4.92 years) of a proportion (66%) of the original NASPEAF cohort.<sup>8</sup> The authors compared the number of ischaemic, haemorrhagic, systemic or coronary ischaemic events or cardiovascular deaths occurring after 2001 in patients receiving acenocoumarol alone ( $n=265$ ; INR, 2.0-3.0), combination acenocoumarol (INR, 1.9-2.5) plus

either triflusal 600 mg/d ( $n=155$ ) or 300 mg/d ( $n=120$ ), or aspirin 100 mg/d ( $n=34$ ).<sup>8</sup> These analyses revealed that combination therapy of OAC with triflusal 600 mg/d significantly reduced the occurrence of the primary endpoint compared to OAC alone (HR, 0.33, 95% CI, 0.14-0.80;  $P=.014$ ]; an identical reduction to that seen in the intermediate risk group in the original NASPEAF cohort.<sup>5</sup> In addition, when considering only the randomized patients from the original NASPEAF cohort, patients receiving combination therapy of OAC with triflusal 600 mg/d experienced fewer primary outcomes than patients receiving OAC alone (1.48 vs 3.37;  $P=0.04$ ). There was no significant within-in group differences in number of primary endpoints between the 2 study periods (1995-2001 and >2001) for patients receiving OAC alone or combination therapy.<sup>8</sup> Combination therapy was associated with an increased risk of ischaemic events ( $P=.031$ ) in patients receiving triflusal 300 mg/d and a greater incidence of severe bleeding among patients on aspirin ( $P=.008$ ).

However, caution is warranted in the interpretation of the results from this long-term follow-up of the NASPEAF cohort. First, this is a secondary analysis and not all the patients were randomized to their treatment unlike the original NASPEAF cohort. However, the results from this analysis<sup>8</sup> mirror those reported originally,<sup>5</sup> and hold true even when current analyses were restricted to include only randomized patients.<sup>8</sup> Second, the present analyses examined primary events occurring after 2001 and the event rate may have been influenced by the time period examined. However, there were no within group differences in primary endpoints when comparing the original follow-up period (1995-2001) and those occurring after 2001. Finally, the analyses conducted on patients receiving acenocoumarol and aspirin are probably not adequately powered, given the small number of patients in this group ( $n=34$ ) and the greater prevalence of men, the elderly ( $\geq 75$  years), and those with a previous embolism (ie, greater risk of stroke and bleeding) in this group.

Despite the original<sup>5</sup> and long-term follow-up<sup>8</sup> results from the NASPEAF, which demonstrate a reduction in vascular events with combination antithrombotic therapy over anticoagulation alone, combination therapy is still not recommended in the current guidelines for AF alone. The main problem with antithrombotic therapy is the increased risk of bleeding, and the concomitant use of antiplatelets with anticoagulants significantly increases this risk. A recent systematic review and meta-analysis of randomised controlled trials comparing oral

anticoagulation plus aspirin to oral anticoagulation alone (at the same dose or target INR), with  $\geq 3$  months follow-up, in patients at risk for vascular outcomes, including 2 studies in AF patients, demonstrated that combination therapy did not reduce the rate of arterial thromboembolism in patients with AF (OR, 0.99; 95% CI, 0.47-2.07) and there was no overall difference in all-cause mortality with either treatment (OR, 0.98; 95% CI, 0.77-1.25).<sup>9</sup> However, the risk of major bleeding was much higher for patients receiving combination therapy versus OAC therapy alone (3.8% vs 2.8%; OR, 1.43; 95% CI, 1.00-2.02).<sup>9</sup> Further, a recent retrospective analysis of 1848 new users of OAC (acenocoumarol or phenprocoumon) on concomitant antiplatelet therapy (aspirin, clopidogrel, and dipyridamole), demonstrated that all antiplatelet drugs increased the risk of major bleeding when used in combination with OAC, with the greatest bleeding risk evident with clopidogrel (OR, 2.9; 95% CI, 1.2-6.9;  $P=.018$ ) followed by aspirin (OR, 1.6; 95% CI, 1.3-1.9;  $P<.001$ ) and

dipyridamole (OR, 1.5; 95% CI, 1.0-2.3;  $P=.078$ ), even after adjustment for use of nonsteroidal anti-inflammatory drugs, antibiotics usage, steroids and gastroprotective agents.<sup>10</sup>

It must also be recognized that bleeding is multifactorial and careful consideration of associated comorbidities and concomitant therapies ought to be taken into account prior to initiation of OAC or combining potent antithrombotic drugs in any patient. Clearly, a balance between the prevention of thromboembolism and safety (ie, bleeding risk) is paramount when combination therapy is being considered. Whilst more data for triflusal are required, we know that adding aspirin or clopidogrel to OAC does not reduce thromboembolism in stable vascular disease, but does increase bleeding risk.<sup>11</sup> The difficult management scenario arises when we have to deal with anticoagulated patients who present with an acute coronary syndrome or have to undergo percutaneous coronary intervention and/or stenting.<sup>12</sup>

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