

Pro/Contra Article

Pro: “Anti-platelet therapy is an alternative to oral anticoagulation for atrial fibrillation”

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Atrial fibrillation (AF) is present in approximately 1% of the population and is responsible for one of every six strokes (1–3). In patients with AF and additional risk factors, oral anticoagulation (OAC) reduces the risk of stroke by 64% (95% confidence interval [CI]: 49% – 74%) [4]. However, concerns about drug interactions (5), bleeding risks (6) and the challenges of international normalised ratio (INR) monitoring have limited the use of OAC (4, 7, 8). In the European Heart Survey on atrial fibrillation, only 67% of eligible patients were prescribed OAC (9). Even when OAC is used, a therapeutic INR (2.0 – 3.0) is achieved less than 65% of the time, thereby limiting the effectiveness of this therapy (6, 10). Considerable efforts have been made to find alternative methods to prevent stroke in patients with AF.

Several clinical trials in patients with AF evaluated “low-dose” warfarin as an alternative to adjusted-dose warfarin; however, this strategy was not as effective at preventing thrombo-embolic events and did not reduce the risk of bleeding (11). Other trials evaluated anti-platelet therapy with aspirin as a means of stroke prevention in patients with AF (4). Aspirin is easy to administer, is associated with a low risk of major bleeding and does reduce the risk of stroke by 22% (95% CI: 6% – 35%) (4). However; in trials comparing OAC to aspirin, OAC is more effective, reducing stroke by an additional 39% (95% CI: 22% – 52%) (4). Although these data might suggest that adjusted-dose OAC is still the ideal stroke prevention therapy for all patients with AF and additional risk factors, the reality is that for many patients, anti-platelet therapy may still be preferred.

The most appropriate stroke prevention strategy for an individual patient with AF depends on their baseline risk of stroke, which can be determined using one of several risk stratification schemes (12). Current guidelines recommend that for patients with no additional risk factors for stroke, that treatment with aspirin is sufficient prophylaxis (13). For patients with a single moderate risk factor for stroke (hypertension, diabetes mellitus, heart failure or age ≥ 75 years; i.e. CHADS₂ score of 1), the guidelines suggest that either aspirin or OAC is appropriate therapy (13). This recommendation is based in part on the low annual risk of stroke in these pa-

tients, which is approximately 1–1.5% per year in clinical trials (14). Although a secondary analysis of the ACTIVE-W trial suggested that patients with a CHADS₂ score of 1 had a lower rate of stroke when treated with OAC compared to combination therapy with clopidogrel and aspirin (15), it should be noted that the majority patients in ACTIVE-W had been treated with OAC prior to study enrolment and had better INR control and less bleeding than patients who recently started on OAC (14). Even in this selected group of OAC-“responders”, the absolute reduction in stroke risk for patients with a CHADS₂ score of 1 was only 0.8% per year (15). For many patients, this small absolute risk reduction is insufficient compensation for the challenges associated with OAC.

Another important observation from the ACTIVE-W trial was that the benefit of OAC over the combination of clopidogrel plus aspirin was highly dependent on the quality of INR control achieved by individual centres (16). Although the overall result of ACTIVE-W demonstrated that OAC was more effective at preventing strokes and resulted in no excess in major bleeding, at sites with the lowest quartile of INR control ($< 54\%$ of results in the therapeutic range of 2.0 – 3.0), OAC offered no reduction in stroke and doubled the risk of major bleeding (16). Similar observations have been made in a large, community-based cohort study (10). Thus in patients for whom guidelines recommend the use of OAC, but for whom good INR control is elusive, treatment with aspirin or the combination of aspirin and clopidogrel may actually be preferred (14).

Despite the benefits of OAC in clinical trials, many patients do not receive this therapy (8) due to a relative contra-indication or due to patient or physician preference (17). In an attempt to further reduce stroke in these patients, the ACTIVE-A trial evaluated combination anti-platelet therapy in AF patients who would not or could not take OAC, despite an indication (17). In this trial, all patients received aspirin at a dose of 75–100 mg/day and either clopidogrel 75 mg/day or a matching placebo. One quarter of patients had an identified risk factor for bleeding (such as prior bleeding with OAC, predisposition to falls, persistent blood pressure $> 160/100$, severe alcohol abuse, thrombocytopenia, chronic renal insufficiency, chronic use of non-steroidal

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anti-inflammatory agents or documented peptic ulcer disease in the past year) and one quarter simply did not wish to take OAC. The remaining 50% were felt by their physician to be inappropriate for OAC, although a precise reason was not given (17).

ACTIVE-A demonstrated a significant 11% reduction in its primary outcome of stroke, non-CNS embolism, myocardial infarction and vascular death using the combination of aspirin and clopidogrel, which was driven by a 28% reduction in stroke (17). There was a statistically significant, 0.7% per year increase in major bleeding with combination anti-platelet therapy; however, this risk was outweighed in size and severity by the reduction in myocardial infarction and stroke (17). Thus although not as effective as OAC (14), combination anti-platelet therapy is more effective than aspirin alone for stroke prevention in AF and currently has a role in the treatment of high-risk AF patients who are unsuitable for OAC therapy. As well, in patients with AF and another indication for combined aspirin and clopidogrel such as a recent acute coronary syndrome or coronary stent implantation, the results of ACTIVE-A provide some reassurance that OAC can be withheld, at least temporarily, to reduce bleeding risk without too much compromise on stroke prevention.

In selecting the appropriate strategy to prevent stroke in an individual patient with AF, clinicians must consider the patient's risk of stroke, their risk of bleeding, concomitant indications for either anti-platelet medications or OAC, anticipated challenges with INR control and patient preference. Weighing all of these, anti-platelet therapy is the most appropriate strategy for many patients. For the 22% of AF patients with a CHADS₂ score of 0

(2), their low observed risk of stroke makes aspirin the preferred treatment option (13). Given the slightly higher stroke risk among the 32% of AF patients with a CHADS₂ score of 1 (2), aspirin, the combination of aspirin plus clopidogrel (17) and OAC are all appropriate options, with the ultimate choice between therapies hinging on patient preference, bleeding risk and concomitant indications for one of these therapies. For patients who are at higher risk of stroke, but who cannot or will not take OAC; the combination of aspirin plus clopidogrel has now been shown to provide greater protection against stroke than aspirin alone (17). Finally, for OAC-treated patients who cannot achieve good INR control, combination anti-platelet therapy may be a safer and equally effective alternative to OAC (16).

Although OAC is the treatment of choice for patients with AF who are at high risk of stroke, this evidence-based therapy is not used by one third of such patients. Additional treatment choices may soon be available for patients with AF, which would be particularly useful for patients in whom OAC is not used because of poor INR control, inability to comply with INR monitoring or drug-interactions. Both oral direct thrombin inhibitors (18) and factor Xa inhibitors overcome these limitations of warfarin and may find a role in stroke prevention among these groups of patients, who are typically treated with anti-platelet agents. However; even if one or more of these agents is approved in the next few years for the treatment of AF, the sizeable number of low-risk AF patients and patients with concomitant indications for anti-platelet agents will ensure that these drugs still play an important role in the management of AF.

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