Atrial fibrillation and mortality: the impact of antithrombotic therapy

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This editorial refers to ‘Mortality predictors and effects of antithrombotic therapies in atrial fibrillation: insights from ACTIVE-W’†, by R. De Caterina et al., on page 2133

All of the current guidelines on antithrombotic therapy for atrial fibrillation (AF) emphasize the prevention of stroke and thromboembolism as the primary goal of such treatment, and existing recommendations for antithrombotic therapy are based on an individual patient’s risk of stroke. These guidelines have been formulated from the numerous clinical trials of antithrombotic therapy in patients with AF conducted over the last 20 years, where the primary endpoint has been stroke or a composite endpoint of stroke/thromboembolism, vascular events, and death. More recently, clinical trials of antithrombotic therapy in patients with AF have rightly included bleeding events as part of the composite primary endpoint, as treatment decisions should be based upon net clinical benefit.

A meta-analysis † of the 12 trials comparing dose-adjusted warfarin with antiplatelet therapy alone, including the largest trial to date, the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W) trial,‡ revealed a 37% reduction [95% confidence interval (CI) 23–48%] in all strokes associated with dose-adjusted warfarin, but did not demonstrate a significant mortality benefit of warfarin over aspirin [relative risk reduction (RRR) 9%; 95% CI –19 to 30%]; equating to a 0.5% absolute mortality risk reduction per year associated with warfarin. However, it has been argued that all strokes should not be grouped together in such analyses as the impact of antithrombotic therapy may have a differential effect on various types of strokes and that not all strokes convey the same mortality risk.

De Caterina and colleagues † have examined the subsequent mortality after the first occurrence of a non-fatal bleed or vascular event among patients enrolled in the ACTIVE-W study. In this secondary analysis of the ACTIVE-W cohort, non-fatal events were defined as those not causing death within 7 days. Non-fatal stroke increased the risk of death 5-fold [hazard ratio (HR) 5.58; 95% CI 3.84–8.10; P < 0.0001], and this risk was significant for both ischaemic and haemorrhagic stroke. Transient ischaemic attacks were not associated with a greater risk of death. However, when strokes were further defined into disabling or non-disabling, based on the Rankin score (≥3 and 1–2, respectively), only disabling strokes were associated with an increased risk of death (HR 9.54; 95% CI 6.42–14.2; P < 0.0001). This may be associated with haemorrhagic strokes, which tend to be more devastating and ultimately fatal compared with ischaemic strokes.

In addition, this analysis † also examined the effect of bleeding on risk of death. Any non-fatal bleeding event increased the risk of death (HR 1.61; 95% 1.18–2.20; P = 0.003), although when analysed further in terms of non-fatal major bleeding vs. minor bleeding, only non-fatal major bleeding increased mortality. De Caterina and colleagues also distinguished between non-severe major bleeds (bleeding requiring transfusion of at least two units of red blood cells or equivalent whole blood) and (more serious) severe major bleeds, and demonstrated that only severe major bleeds were associated with a significant increase in mortality (HR 3.35; 95% CI 2.12–5.27; P < 0.0001). ‡ Unsurprisingly, the risk of haemorrhagic stroke and a poor prognosis may be exacerbated by antithrombotic therapy.

Caution is therefore warranted in the overinterpretation of these results, † given that the study is a secondary analysis of data, with few occurrences of non-disabling strokes resulting in death, only four deaths following haemorrhagic stroke, and only four (6.9%) non-severe major bleeds resulting in death.

The main results of the ACTIVE-W trial demonstrated that vitamin K antagonists (VKAs) were superior to combination clopidogrel and aspirin in the prevention of all strokes [relative risk (RR) 1.72; 95% CI 1.24–2.37; P = 0.001]. † However, a closer examination of the ACTIVE-W results suggests that the benefit of VKAs over combination antiplatelet therapy diminishes as the severity of the stroke increases (non-disabling, disabling, and fatal). Indeed, VKAs did not significantly reduce the risk of a disabling or fatal stroke (RR 1.47; 95% CI 0.98–2.20; P = 0.06, and RR 0.93; 95% CI 0.45–1.94; P = 0.85, respectively), suggesting that...
VKAs were more likely to prevent a minor stroke compared with a more serious stroke. If we turn our attention to look at the effect of antithrombotic therapy on other endpoints, VKAs did not confer a reduction in all-cause mortality (RR 1.01; 95% CI 0.81–1.26; P = 0.91), vascular death (RR 1.14; 95% CI 0.88–1.48; P = 0.34), or non-vascular death (RR 0.76; 95% CI 0.50–1.15; P = 0.20), although VKAs were associated with significantly fewer bleeding events in total (RR 1.21; 95% CI 1.08–1.35; P = 0.001) and a significant net clinical benefit (primary outcome, major bleed, and death) associated with warfarin (RR 1.31; 95% CI 1.12–1.54; P = 0.0008).\footnote{2}

Of note, the ACTIVE-W trial\footnote{2} reported a lower overall incidence of stroke and vascular events compared with other trials of antithrombotic therapy in patients with AF conducted in the 1990s,\footnote{4} but rates similar to those of patients receiving VKAs in the SPORTIF III and V trials.\footnote{5,6} Lower blood pressure targets and tighter blood pressure and international normalized ratio (INR) control evident in clinical trials, in addition to better cardiovascular risk factor management (i.e. widespread use of statins for primary prevention), may help to explain the lower stroke and vascular event rate. The lack of a mortality benefit in favour of warfarin in ACTIVE-W may be partly dependent upon the lack of statistical power, due to the early termination of the trial and the low mortality rate, rather than there being no true effect of the superiority of warfarin over clopidogrel and aspirin combined.

Although mortality is a key outcome, and the prevention of death is important, the emphasis for antithrombotic therapy in patients with AF should remain on the prevention of stroke, particularly disabling strokes and their sequelae, given that not all strokes convey the same mortality risk\footnote{3} and anticoagulation therapy may be less effective at preventing such strokes.\footnote{2} For patients, avoidance of a stroke is their over-riding concern,\footnote{7} and often patients are willing to accept the higher risk of bleeding associated with oral anticoagulant therapy to avoid a disabling stroke, which many view as worse than death.\footnote{7} Individual assessment of the net clinical benefit of antithrombotic treatment for the patient based on stroke and bleeding risk stratification is essential.

**Conflict of interest:** none declared.

**References**