Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

ScriptSwitch™ Rapid Update 1 – February 2018

Oral anticoagulants: do they reduce the risk of dementia in people with atrial fibrillation?

A Swedish retrospective cohort study found a lower risk of dementia in people with atrial fibrillation (AF) who took oral anticoagulants (OAC) compared with those with AF who were not taking them. Although further research is required to confirm the findings of this observational study, this may provide another reason for a person with AF to choose to take an OAC.

Reference: Friberg L and Rosenqvist M. Less dementia with oral anticoagulation in atrial fibrillation. European Heart Journal. 2017. ehx579, https://doi.org/10.1093/eurheartj/ehx579

What do we know already?

- AF is the most common sustained cardiac arrhythmia and affects around one million people in the UK. While AF can occur in adults of any age, it becomes more common with increasing age. People with AF have a five-fold greater risk of stroke and thromboembolism than people without AF, and stroke severity is usually greater when stroke is associated with AF than with other causes. People with AF are also nearly twice as likely to die prematurely than people in sinus rhythm.
- The association between AF and dementia is well-documented. While age alone may account for this apparent association, recent research has provided evidence that AF is associated with an increased risk of incident dementia, independent of clinical stroke, and a meta-analysis of observational studies has yielded a hazard ratio (HR) of 1.4.
- OACs form the cornerstone of therapy of AF, protecting against the large emboli which cause stroke and reducing the risk of stroke by about two-thirds. However, while OACs also protect against small emboli that cause microinfarctions that eventually lead to cognitive deterioration, it is unknown whether this effect of OACs can prevent AF-related dementia.

What does this evidence add?

- This Swedish retrospective cohort study looked at the incidence of new dementia in over 444,000 adults with AF and no previous diagnosis of dementia. After propensity score matching, people treated with OACs at baseline were found to have a 29% lower relative risk of dementia than people not treated with OACs (HR 0.71, 95% confidence interval [CI] 0.68 to 0.74).
- The benefit of OAC treatment was observed to be greater if the OAC was initiated soon after diagnosis of AF rather than later, suggesting a dose-response relationship between unprotected time in AF and development of dementia. Moreover, there was a trend towards more benefit from treatment in people at higher risk of stroke i.e. those with higher CHA_2DS_2-VASc scores.
- The study authors discuss the limitations of their study including the potential for unadjusted confounding and the lack of complete medical histories for the patients. They note that ideally prospective randomised controlled trials are needed to prove that OACs protect against dementia in AF. However, such trials would be unethical, as it is not possible to give placebo to patients with AF and then wait for either a stroke or dementia to occur. A study randomising patients with AF to either dabigatran or warfarin with incident dementia as a primary endpoint is underway and is expected to be completed by 2021.

Study details

Study design:

- 456,960 individuals in Sweden with a diagnosis of AF during 2006 and 2014 were identified from the Swedish Patient Register (a source of good quality data according to previously published validation studies). 12,854 individuals with a previous diagnosis of dementia were excluded and no other exclusions were made, leaving 444,106 patients in the study.
- At baseline, 241,160 patients (54.3%) were not receiving an OAC, 190,570 (42.9%) used warfarin, 199 (0.04%) used phenprocoumon (a vitamin K antagonist [VKA] that is not available in the UK), and 12,916 patients (2.9%) used a non-vitamin K oral anticoagulant (NOAC).
- To account for confounding by indication, (i.e. elderly patients with AF with cognitive impairment at baseline not being offered an OAC as often as non-cognitively impaired patients), the authors analysed four "falsification endpoints": influenza, hospitalisation for fall, new diagnosis of diabetes and new diagnosis of chronic obstructive airways disease. All falsification endpoints were considered unlikely to be affected by OAC therapy. The rational was that if an association was found with one or more of the falsification endpoints and OAC, it may then be postulated that the OAC is not the cause of the outcome and that other unknown factor(s) may be the cause which could not be accounted for in the subsequent analysis.

Results:

- During over 1.5 million years of follow-up, 26,210 patients received a new diagnosis of dementia (1.73 per 100 years at risk).
- Patients who developed dementia were older and had more co-morbidities. The strongest predictors for dementia were age (HR per decade 2.19, 95% CI 2.16 to 2.22), Parkinson's disease (HR 2.46, 95% CI 2.25 to 2.69), absence of OAC treatment (HR 2.08, 95% CI 1.73 to 2.53) and alcohol abuse (HR 1.53, 95% CI 1.41 to 1.66).
- The incidence of dementia among OAC users was lower than among patients not treated with an OAC (1.14 *vs.* 1.78 per 100 patient years at risk, $p < 0.001$).
- There was considerable crossover between treatment groups, defined by treatment at baseline, which may attenuate the associations between treatment and outcome. Furthermore, patients taking an OAC at baseline were younger and healthier. However, after propensity score matching, OAC treatment was associated with a 29% lower risk of dementia than non-treatment in the intention-to-treat analysis (HR 0.71, 95% CI 0.68 to 0.74) and a 48% lower dementia risk in the on-treatment analysis (HR 0.52, 95% CI 0.50 to 0.55).
- There was an interaction between OAC treatment and the time since AF diagnosis suggesting that the benefit of treatment may be greater if initiated early rather than late. Moreover, the authors reported that there was a trend towards more benefit from treatment in patients with higher CHA_2DS_2-VASc scores, suggesting that microembolisation might be the cause of dementia people with AF.
- OAC treatment showed no association with two of the falsification endpoints (influenza and falls) and a weak association with incident diabetes and chronic obstructive airways disease, but in the opposite direction to that of dementia. This suggests that there may be unknown factors affecting the results, but that these factors may attenuate rather than accentuate the benefits of OAC treatment.
- When NOACs and VKAs (mainly warfarin) were compared to no treatment, the risk of dementia appeared to be lower with NOAC (HR 0.48, 95% CI 0.40 to 0.58) than with VKAs (HR 0.62, 95% CI 0.60 to 0.64). This was also true in the on-treatment analysis (NOAC HR 0.30, 95% CI 0.22 to 0.42 *vs.* VKA HR 0.53, 95% CI 0.50 to 0.56). However, the NOAC and VKA groups differed in several baseline characteristics that were considered to account for the differences shown, and a further analysis taking account of these factors showed no differences regarding dementia risk.

Level of evidence:
Level 2 according to SORT criteria.

Study funding:
No conflicts of interest declared by the authors in relation to this specific study. Consultancy fees and grants from a number of pharmaceutical companies are declared.