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COMISSIONED EDITORIAL

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Clearing the cognitive cloud – DOACs or VKAs for reducing dementia risk in patients with AF?

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It is now widely acknowledged that cognitive decline and dementia present a challenge in the treatment and management of patients with atrial fibrillation (AF). Cognitive difficulties in patients with AF directly impacts their care(1). In particular, it reduces understanding of treatment options which are increasingly requiring patient input in joint clinical decision making. It also has a negative impact on adherence to treatment as medications such as oral anticoagulants (OACs) need to be taken consistently in a timely manner over a long period of time to maintain their efficacy for stroke prevention. It is also clear that cognitive decline and dementia impacts independent living, progressively interfering with tasks in daily life and the ability to sustain healthy living choices such as exercise which are important in AF management. Over time, these challenges lead to an overall reduction in quality of life.

The exact mechanisms linking AF and dementia are likely to be complex and multifactorial, presenting a demanding challenge for researchers to tackle. Nevertheless, it is apparent that one of the most plausible risk factors for brain dysfunction is the presence of chronic and recurrent micro emboli. Within this framework, cognitive decline and dementia manifest on a disease spectrum which include transient ischemic attacks and stroke. Therefore, intuitively, the use, timing, and efficacies of OACs play a role in modifying this risk. It is now clear from many large observational studies that patients with AF who use OACs are more protected from cerebrovascular diseases, even if their stroke risk is low(2-4). Direct oral anticoagulants (DOACs), which were first introduced in 2010, provide all the benefits of vitamin K antagonists (VKAs) without the downsides of close INR monitoring and drug-drug interactions. With the extensive comparative safety and efficacy trials of DOACs vs VKAs, coupled with more than a decade of experience with widespread use of these medications, and having antidotes for all of the DOACs, it is now widely accepted that DOACs are the recommended stroke prevention therapy of choice for patients with AF.

As DOACs steadily replace VKAs in clinical practice, the selection of OAC type for prevention of cognitive decline and dementia has emerged as a significant question. In their timely study, Cadogan et al. conducted the first study using representative data from a real-world UK population to investigate the association between OAC type and incident dementia or mild cognitive impairment (MCI)(5). The authors identified patients with newly diagnosed AF and compared the incidence of diagnosed dementia and MCI between patients who were prescribed VKAs and DOACs. Since they were licensed in the UK from 2013, the use of DOACs have been steadily increasing. In this contemporary study, there was a similar proportion of patients on VKAs and DOACs. In 39, 200 patients, 3.2% of patients received a diagnosis of dementia and 4.0%, MCI. Cadogan et al. observed that patients who were on DOACs were 16% less likely to be diagnosed with dementia (hazard ratio, HR 0.84, 95% confidence intervals, CI 0.73, 0.98) and there was a 24% reduced risk for MCI (HR 0.74, 95% CI 0.65, 0.84), after adjusting for 27 demographic and lifestyle factors, clinical conditions, and well as medications. These patterns persisted even after only including dementia occurring at least one year after first OAC prescription (HR 0.81, 95% CI 0.67, 0.98). This is an important contribution to the emerging literature comparing DOACs and VKAs.

Retrospective studies such as Cadogan et al. provide valuable insight into existing trends which warrant confirmation in prospective studies. The CAF trial (NCT03061006) compares warfarin's and dabigatran's impact on cognitive decline and incident dementia for 24 months(6). Though the number of patients in CAF trial is modest (CAF, N=120), with a relatively short follow-up period, it will provide the first prospective insights into use of different OACs and its impact on dementia. The ARTESIA (NCT01938248) neurocognitive sub-study (N=1000) will reveal the minimal burden of AF burden associated with cognitive decline or dementia in patients on apixaban or aspirin, while BRAIN-AF (NCT02387229) will investigate if low stroke risk patients on rivaroxaban or aspirin experience cognitive benefits from OACs. In parallel, it is of importance for basic scientists investigating the coagulation cascade to help us understand how the mechanisms of action of DOACs and VKAs are differentially impacting the risk of dementia.

Adherence and persistence have been and are still tough challenges in the use of OACs. A recent investigation into time trends amongst patients receiving their first OAC prescription following a diagnosis of AF revealed that adherence to VKAs was 51% while the 3 NOACs studied were at 67%, 63%, and 65% for dabigatran, rivaroxaban, and apixaban respectively. Persistence at one year was slightly higher, 63% for VKAs and 61%, 72%, and 79% for dabigatran, rivaroxaban, and apixaban(7). These suboptimal rates are a cause for concern, even more so if the OACs also play a role in preventing cognitive decline and dementia. The conventional approaches to increase adherence are to increase patient education and have more frequent monitoring, however, this can create a strain on healthcare personnel and resources. It is time to create a greater role for health psychologists and implementation scientists to uncover behavioural drivers and motivators of adherence, as well as to shape and co-create more effective messaging of the importance of OACs with the patients themselves.

While we take away the positive message that there is now further evidence for the use of OACs, particularly DOACs, to prevent dementia and MCI in patients with AF, let us also remember that there remains a proportion of patients who will still progress to experience these neurological conditions despite optimal therapy, and those who are contraindicated for DOACs. For them, we need to accelerate efforts for early detection by identifying appropriate and sensitive cognitive test batteries or biomarkers to incorporate into clinical routines for management of AF. There is also an urgency to identify early intervention methods and create a structure of care for patients who receive a diagnosis of MCI or dementia while being treated for AF. The field of cognitive rehabilitation offers opportunities for exploration of techniques and interventions which could be valuable in maintaining or improving the quality of life for these patients. While Cadogan et al. considered a significant number of potential confounders in their study, cognitive function in older age can also be affected by education level, family history, exposure to stress and trauma, exposure to air pollution, social connection or isolation, dietary choices and nutrition, sense of purpose, etc. Therefore, there is scope for collecting more and better data which could reveal novel intervention targets.

In conclusion, it is clear that the administration of DOACs is not only associated with decline in AF-related stroke but also leads to efficient use of resources and cost savings for healthcare systems(8). Now, it can add another feather to its cap with its likely ability to positively impact dementia diagnoses in patients with AF. These indications of additional cognitive protection should ease the decision-making process for initiation of oral anticoagulation with DOACs, and we eagerly await outcomes of prospective studies in this area. As there is no cure for dementia, our best bet lies in early identification and early intervention to prevent non-reversible changes.

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Footnotes

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