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Editorial

Atrial fibrillation and cognitive impairment: some answers but many questions

Fibrilación auricular y deterioro cognitivo: algunas respuestas, pero muchas preguntas

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Atrial fibrillation (AF) is the most common arrhythmia in Spain. Its prevalence increases with age, reaching rates of 18% to 20% in people older than 80 years. AF affects a third of elderly patients admitted for any cause to internal medicine or geriatric units.[1] Within the elderly population, cognitive disorders are highly prevalent clinical syndromes,[2] and AF patients therefore very often have some degree of cognitive impairment.[3]

The relationship between AF and dementia is complex. Cognitive impairment is not simply one among several comorbidities occurring with AF. Rather, AF is itself a risk factor that contributes to the cognitive decline.[3] A recent study of AF patients found that microbleeds linked to embolic events increase the risk of vascular dementia even when they do not manifest as clinical stroke.[4] In the study cohort of 1737 AF patients (mean age 73 years; 90% on anticoagulant therapy), brain magnetic resonance imaging (MRI) detected a high burden of cerebrovascular lesions. Almost none of these lesions had been diagnosed previously; however, they are now believed to have triggered the progressive decline in cognitive function, as has already been documented for lesions manifesting as stroke. These clinically silent infarcts thus go some way to explaining the elevated risk of cognitive alterations in these patients.[4] Possible connections have also been reported between AF and Alzheimer dementia, with chronic hypoperfusion secondary to abnormal heart rate and the proinflammatory state in AF both promoting white matter abnormalities and cerebral amyloid deposits.[5] The risk that AF will lead to cognitive impairment is increased by the co-occurrence of other cardiovascular risk factors such as hypertension, diabetes, obesity, hypercholesterolemia, and smoking.

Longitudinal studies of AF patients with no cognitive impairment at the time of diagnosis suggest that careful use of appropriate anticoagulant therapy can significantly reduce the incidence of cognitive disorders.[3] A recent study assessed dementia risk in male and female AF patients with a very low embolic risk (CHA_2DS_2-VASc 0 or 1); even for this risk profile, patients treated with oral anticoagulants had a lower dementia risk than those from whom treatment was withheld (probably because their physicians followed guideline recommendations contraindicating anticoagulant therapy for patients at very low risk).[6]

For patients with confirmed dementia at the time of AF diagnosis, there is greater uncertainty about the suitability of anticoagulant therapy and which type of treatment is appropriate. Against this background, the recent article by Cobas Paz et al. in *Revista Española de Cardiología* is especially relevant.[7] This study reports data from a single-center retrospective registry of 3549 AF patients ≥ 85 years and analyzes the 221 patients (6.1%) who at the time of AF diagnosis had moderate to severe dementia (between stages 5 and 7 on the Reisberg global deterioration scale [GDS]). Of these patients, 88 (60.2%) were anticoagulated, mostly with vitamin K antagonists (VKAs). Assessment at 2.8 years of follow-up revealed an association between anticoagulation and a lower risk of embolism, although the bleeding risk was higher (hazard ratio [HR] for embolic events = 0.36; 95% confidence interval [95%CI], 0.15-0.84; HR for bleeding events = 2.44; 95%CI, 1.04-5.71). Anticoagulation therapy was not associated with lower mortality in dementia patients (adjusted HR = 1.04; 95%CI, 0.63-1.72; $P = .541$; HR after propensity score matching = 0.91; 95%CI, 0.45-1.83; $P = .785$).

The results of the study by Cobas Paz et al. are a first step toward evidence-based guidelines for this group of patients, who are underrepresented in clinical trials and other intervention studies but are very frequent in real-world clinical practice.[8] The authors recognize a number of study limitations, many of them related to the retrospective nature of the study. Important limitations in this category include the likely underestimation of the percentage of AF patients with dementia, the nonrecording of the reason for not anticoagulating some patients, and the small sample size (133 nonanticoagulated vs 88 coagulated patients). Another limitation is that the authors were unable to analyze anticoagulant dose adjustment in patients receiving this treatment; this is an especially important issue in this population group, in which the underdosing risk is significant. The authors also do not mention if the patients received a specific treatment for dementia, which might have influenced health outcomes.

It is unrealistic to aim for a significant mortality reduction among AF patients older than 85 years with moderate to severe dementia, and therefore the main goal in this patient group should be to reduce morbidity. It is also important to note that the authors included patients with very severe or even end-stage dementia (GDS 7). Anticoagulant therapy is not normally indicated for this dementia stage, and reducing mortality due to dementia is likely

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unachievable for these patients. There are currently no evidence-based guidelines defining which dementia stages are suitable for the initiation of anticoagulant therapy in AF patients; equally, there are no guidelines on when it is advisable to withdraw anticoagulant therapy during dementia progression. Experts in the field concur in recommending the maintenance of oral anticoagulation even in patients in GDS stage 6; however, there is also agreement that cognition should not be the sole criterion for initiating or maintaining anticoagulation, and this decision should always be based on a comprehensive geriatric assessment to determine an appropriate level of autonomous function and moderate comorbidity.[9,10] In the Swedish dementia registry (2007-2014; mean age 82 years), anticoagulation (26% of patients, all with VKAs) reduced mortality risk in patients with any degree of cognitive impairment, albeit at the cost of a slightly increased bleeding risk.[11] A new dementia diagnosis sometimes gives rise to the misperception that anticoagulant therapy is no longer necessary. However, maintaining therapy can reduce mortality, as demonstrated by registry data from patients with a mean age of 79.5 years at diagnosis and monitored over a mid- to long-term follow-up (4 years).[12] Future studies should analyze patients in GDS stages 4 to 6 to provide comprehensive knowledge of the risks and benefits of initiating or maintaining anticoagulation in elderly patients with dementia.

Another area requiring attention is the potential benefit of brain MRI in these patients. There is currently no consensus on the need for systematic brain MRI to identify patients with dementia and a high risk of intracranial hemorrhage. Amyloid angiopathy is a very common finding in elderly dementia patients, and its presence can increase the risk of lobar cerebral microbleeds. These microbleeds are a risk factor for intraparenchymal hemorrhage, especially in patients with a history of stroke or concomitant antiplatelet therapy. We would therefore recommend brain MRI scans of all elderly dementia patients with a high bleeding risk in order to detect the burden of amyloid angiopathy and microbleeds. Significant parenchymal involvement should prompt physicians to consider withdrawing oral anticoagulants or at least switching to direct acting oral anticoagulants (DAOCs), which appear to have a better safety profile in these patients.[13]

Worsening cognitive function in patients treated with VKAs has also been linked to insufficient time in therapeutic range, another setting in which DAOCs appear to produce better outcomes.[9] Clinical trials, meta-analyses, and observational registries show that the efficacy and safety of DAOCs are similar or superior to those of VKAs.[14]

Despite this evidence, there is little information available on the possible benefits of DAOCs vs VKAs in elderly patients. In observational studies of very elderly patients with or without cognitive impairment, the interpretation of results is problematic because of the high frequency of confounding and selection factors, such as the higher frequency of VKA therapy in the frailest patients.[15]

The presence of dementia should not be viewed as sufficient justification for not prescribing oral anticoagulants to AF patients. In our opinion, anticoagulant therapy in dementia patients is justified to significantly reduce embolic events, which can have devastating clinical and functional effects in patients $\geq$ 85 years with mild to moderate dementia. That said, it is very important to carry out a comprehensive geriatric assessment that includes data on quality of life and assessments of bleeding risk and the risk of poor treatment adherence. Nevertheless, these recommendations are unlikely to apply to patients with more advanced dementia (GDS 7). For these patients, the decision on whether to withhold or withdraw anticoagulation should be agreed with family or caregivers after informing them of the risks and benefits. On a final note, we propose that cognitive assessment and perhaps systematic MRI should be included in the routine assessment of elderly patients with AF, since these measures would improve patient stratification and decision-making.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. López Soto A, Formiga F, Bosch X, García Alegría J. Prevalencia de la fibrilación auricular y factores relacionados en pacientes ancianos hospitalizados: estudio ESFINGE. *Med Clin (Barc).* 2012;138:231–237.
2. Martínez-Lage P, Martín-Carrasco M, Arrieta E, Rodrigo J, Formiga F. Map of Alzheimer's disease and other dementias in Spain. MapEA Project. *Rev Esp Geriatr Gerontol.* 2018;53:26–37.
3. Diener HC, Hart RG, Koudstaal PJ, Lane DA, Lip GYH. Atrial fibrillation and cognitive function: JACC review topic of the week. *J Am Coll Cardiol.* 2019;73:612–619.
4. Conen D, Rodondi N, Müller A, et al. Relationships of overt and silent brain lesions with cognitive function in patients with atrial fibrillation. *J Am Coll Cardiol.* 2019;73:989–999.
5. Ihara M, Washida K. Linking atrial fibrillation with Alzheimer's disease: epidemiological, pathological, and mechanistic evidence. *J Alzheimers Dis.* 2018;62:61–72.
6. Friberg L, Andersson T, Rosenqvist M. Less dementia and stroke in low-risk patients with atrial fibrillation taking oral anticoagulation. *Eur Heart J.* 2019;40:2327–2335.
7. Cobas Paz R, Raposeiras Roubín S, Abu Assi E, et al. Impact of anticoagulation in patients with dementia and atrial fibrillation Results of the CardioCHUVI-FA registry. *Rev Esp Cardiol.* 2020;73:877–884.
8. Requena Calleja MA, Arenas Miquélez A, Díez-Manglano J, et al. Sarcopenia, frailty, cognitive impairment and mortality in elderly patients with non-valvular atrial fibrillation. *Rev Clin Esp.* 2019;219:424–432.
9. Suárez Fernández C, Formiga F, Camafort M, et al. Antithrombotic treatment in elderly patients with atrial fibrillation: a practical approach. *BMC Cardiovasc Disord.* 2015;15:143.
10. Petidier Torregrossa R, Abizanda Soler P, Noguerón García A, et al. Anticoagulación en población anciana con fibrilación auricular no valvular. *Rev Esp Geriatr Gerontol.* 2018;53:344–355.
11. Subic A, Cermakova P, Religa D, et al. Treatment of atrial fibrillation in patients with dementia: a cohort study from the Swedish Dementia Registry. *J Alzheimers Dis.* 2018;61:1119–1128.
12. Orkaby AR, Ozonoff A, Reisman JI, Miller DR, Zhao S, Rose AJ. Continued use of warfarin in veterans with atrial fibrillation after dementia diagnosis. *J Am Geriatr Soc.* 2017;65:249–256.
13. DeSimone CV, Graff-Radford J, El-Harasis MA, Rabinstein AA, Asirvatham SJ, Holmes Jr DR. Cerebral amyloid angiopathy: diagnosis, clinical implications, and management strategies in atrial fibrillation. *J Am Coll Cardiol.* 2017;70:1173–1182.
14. Fanning L, Lau WCY, Mongkhon P, et al. Safety and effectiveness of direct oral anticoagulants vs warfarin in people with atrial fibrillation and dementia. *J Am Med Dir Assoc.* 2020. http://dx.doi.org/10.1016/j.jamda 2019 11.022.
15. Anguita Sánchez M, Bertomeu Martínez V, Ruiz Ortiz M, et al. FANTASIIA study investigators Direct oral anticoagulants versus vitamin K antagonists in real-world patients with nonvalvular atrial fibrillation. The FANTASIIA study. *Rev Esp Cardiol.* 2020;73:14–20.