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EDITORIAL

Does ablation of atrial fibrillation reduce the likelihood of dementia? A step closer but not yet there

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This editorial refers to 'Less dementia after catheter ablation for atrial fibrillation: a nationwide cohort study'†, by D. Kim *et al.*, on page 4483.

In this issue of the *European Heart Journal*, Daehoon Kim and colleagues report that the development of dementia after catheter ablation for atrial fibrillation (AF) is significantly less when compared with patients who failed ablation or who did not receive ablation and were treated medically.[1] Their data are derived from The Korean National Health Insurance Service database, and the investigators used ICD codes to assess ablation outcomes, underlying comorbidities, and the onset of dementia and its subtypes. Of 9119 patients undergoing ablation and 17 978 patients undergoing medical treatment for rate or rhythm control, propensity matching allowed a comparison between 5863 matched pairs. During a median follow-up of 52 months, overall dementia occurred in 5.6 and 8.1 per 100 person-years, respectively. A significant difference persisted even in patients who had not had an overt stroke.

It has been known for some years that cognitive impairment and dementia are more common in people with AF than in similar people who do not have AF. Both the Rotterdam study[2] and the Cardiovascular Health Study[3] demonstrated this relationship. A large meta-analysis of studies demonstrated a 51% increase in the rate of dementia in association with AF in cross-sectional studies and a 40% increase in prospective cohorts.[4]

Potential mechanisms include systemic embolism, cerebral microinfarcts, variability in beat to beat RR intervals leading to cerebral hypoperfusion, a common series of underlying risk factors such as inflammation, hypertension, diabetes, and heart failure, and subtle changes affecting the autonomic nervous system, which in turn lead to AF (*Figure 1A*). Although anticoagulation with vitamin K antagonists does not eliminate dementia in AF patients, those who are maintained in the therapeutic range for a greater proportion of the time have less likelihood of developing dementia.[5] The Swedish National Database containing >161 000 patients with AF and no previous diagnosis of dementia demonstrated an increased rate of development of dementia in those who were not anticoagulated compared with those who were (*Figure 1B*). This relationship was stronger in the elderly and in those on treatment than in those who were recommended treatment.[1] Several studies have now demonstrated that anticoagulation with direct oral anticoagulants seemed more effective in stifling the development of dementia than treatment with a vitamin K antagonist.[7,8]

The possibility that dementia might be effectively reduced by ablation (*Figure 1B*) of the AF was first raised by Bunch and colleagues in 2011.[9] They were able to compare >4000 patients who underwent left atrial ablation with >1600 age- and gender-matched control patients without AF and with a similar number of AF patients who were not ablated. The study demonstrated that Alzheimer's dementia, senile dementia, and vascular dementia were all significantly increased in the AF patients and that those who underwent ablation developed dementia at a similar rate to control patients who had never suffered from AF and far less often than did AF patients who were not treated with left atrial ablation.

Dongmin Kim and colleagues have previously reported in this journal[10] from the Korean National Health Insurance Service that after propensity matching, incident dementia was more common in patients with incident AF. Both Alzheimer's and vascular dementia were more common than in patients without AF. Those who were treated with an oral anticoagulant had less dementia. A higher

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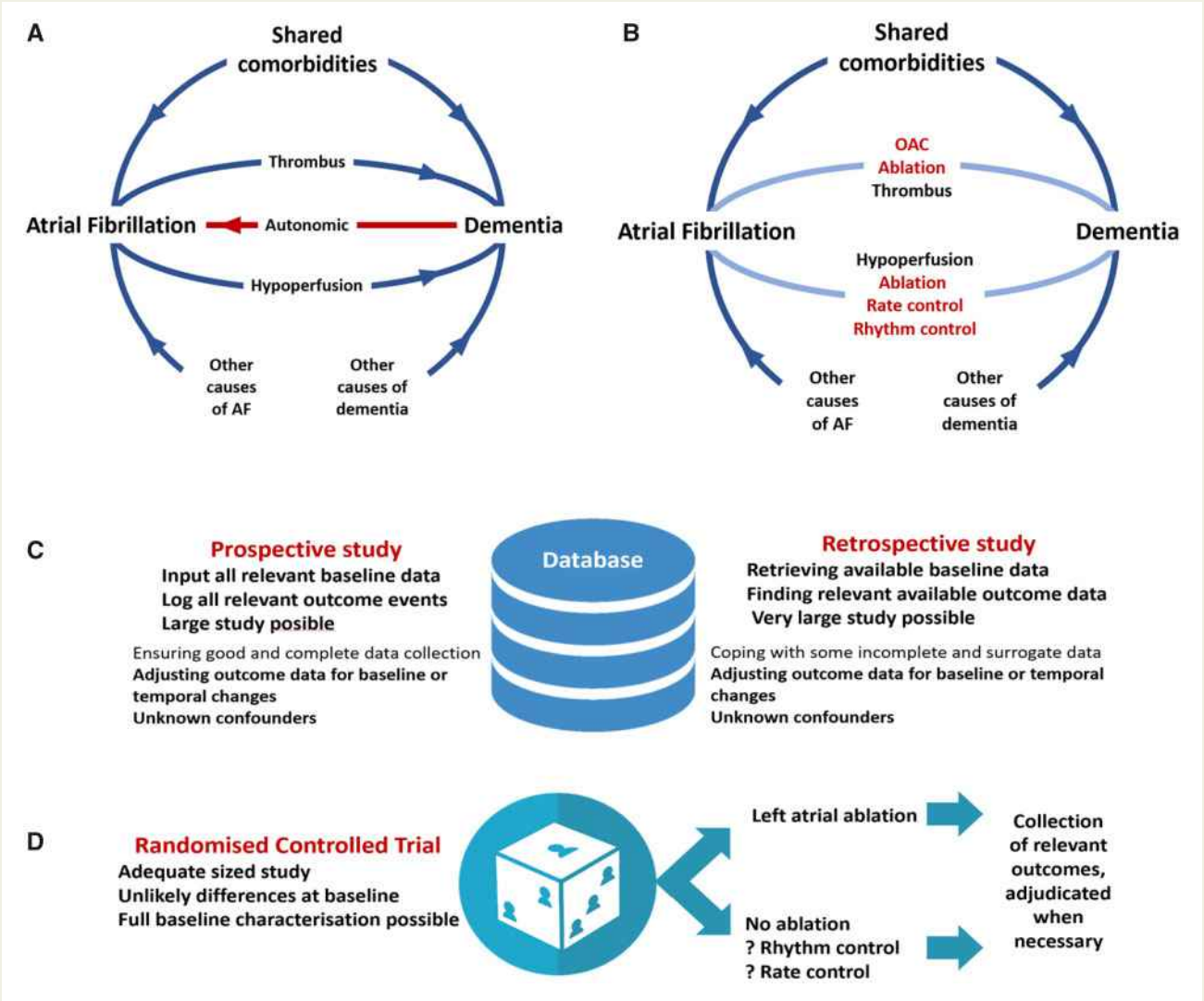

Figure 1 (*A*) The multiple potential causative or aggravating mechanisms for the established association between AF and dementia. (*B*) Therapy with oral anticoagulants or left atrial ablation, rhythm or rate control of AF may reduce or prevent the contribution of AF to dementia. (*C*) Some similarities and differences between prospective and retrospective database analysis approaches for clarifying the relationship of the arrhythmia and dementia, and the potential value of therapy. (*D*) The design of a randomized controlled trial to determine with more certainty the effect of ablation of AF on possible outcomes such as dementia.

CHA_2DS_2-VASc score was associated with more dementia, perhaps implying that underlying cardiovascular disease was in part responsible for the dementia risk.

Now Daehoon Kim *et al.* have reported the results in patients who underwent ablation compared with those who did not. They report that left atrial ablation which did not seem to have been fully successful was not associated with less dementia. They inferred that the restoration and maintenance of sinus rhythm was the important mechanism, rather than the procedure itself, which has been associated with at least transient worsening of cognitive function, possibly due to embolism of air, plaque, or thrombus during the ablation procedure. Although this is a good speculation it is far from certain, given that there was no direct evidence of AF burden post-procedure available to the investigators. Post-procedure repeat ablation, cardioversion, and antiarrhythmic drug use were the only indices of AF recurrence and that recurrence might have been a single episode, or a very low burden of AF. Also, since much AF post-ablation is entirely asymptomatic, the assignment of AF recurrence implying and the extent of sinus rhythm using these parameters is far from certain (*Figure 1C*).

Fibrillation is an increasingly common condition which is present in ~1–2% of the general population but in >10% of those over the age of 80 years. Dementia is also common in the elderly. Many of these patients will also have a range of significant cardiovascular and neurodegenerative conditions irrespective of the presence of AF. There will inevitably be an association between AF and dementia. Any degree of adjustment may not fully eliminate bias and the presence of these two comorbidities may be by chance rather than due to the causation of one by the other. It is not possible to randomize the presence or absence of AF and so we are left with trying to treat the

AF, for example with oral anticoagulants, or better still using a technique such as left atrial ablation which might eliminate the arrhythmia. It is not surprising that retrospective evaluations of database information should be analysed for this purpose. However, such interrogation is also bedevilled by unknown or uncorrectable residual confounders. This is certainly possible in this case. For example, (i) the type of AF was not known, but paroxysmal AF responds more readily to ablation; (ii) the success of antiarrhythmic drug treatment was not assessable, but may have suppressed much of the AF; and (iii) in Korea those suffering dementia have free medical care, which may distort the diagnosis of dementia.

The evidence that we so far have suggests that AF, predominantly the arrhythmia itself rather than any shared comorbidities, is largely responsible for the increase in dementia. However, we have only observational studies or retrospective analyses with potential important residual confounders, imperfect assessment of the success of ablation, and inadequate cognitive function outcomes to infer that the elimination or reduction of the burden of AF reduces incident dementia. It is essential that, as for anticoagulation, ablation of the left atrium to reduce or eliminate AF be evaluated with a randomized and controlled trial with accurate determination of the residual burden of AF and specific measures of cognitive function (*Figure 1D*). Without such studies, the potential benefit of treatments for the arrhythmia and its complications remains speculative. Several relatively small randomized studies are underway, such as Cognitive Impairment in AF (DIAL-F; NCT01816308 980), but have not yet reported.

The study reported by Daehoon Kim and colleagues does provide more evidence leading us a step closer to discovering whether AF provokes dementia, and that it is not a chance association. However, it provides only limited circumstantial evidence that the rhythm itself is responsible for the cognitive impairment and that eliminating the arrhythmia by left atrial ablation will delay or reduce the likelihood of dementia. We may be closer to the answer, but we are not at the finishing post yet.

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