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# Is there a connection among atrial fibrillation, anticoagulant treatment, and dementia?

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It is well-known that atrial fibrillation carries an increased risk of stroke and dementia. The connecting pathogenic common mechanism is the thromboembolic state provided by atrial fibrillation, which is responsible for the acute cerebral events, as well as more saddle anatomic lesions, which accumulating over time, could lead to a progressive cognitive decline. It is plausible, instinctively, that oral anticoagulation could decrease this risk, although the possibility of micro-haemorrhages, which cannot be ignored, could make anticoagulation in this contest even dangerous. In this regard, whether there are firm, well established, evidences documenting a significant reduction in stroke occurrence with anticoagulant treatment in atrial fibrillation, the same level of evidences are not supporting the treatment in preventing dementia. Bringing some more clarity to this issue could have some considerable advantages, also in term of healthcare cost containment, considering the high prevalence of atrial fibrillation and dementia in the elderly.

Atrial fibrillation is known to be associated with an increased risk of stroke and dementia.[1–3] The common pathogenetic hypothesis lies in the possibility that the thromboembolic state associated with atrial fibrillation is equally responsible for acute neurological events, as well as for brain anatomical lesions that, over time, result in a progressive cognitive decline.[4] However, while multi-year evidence indicates that anticoagulant therapy significantly reduces the risk of stroke,[5] the arguments in support of a role of the same therapy in the prevention of dementia are not equally univocal.[6–10]

A recent systematic review of 19 studies, for a total of 15 876 patients, did not in fact, suggest any conclusive evidence that oral anticoagulant treatment could bring a greater benefit on the risk of dementia.[9] In particular, where the studies examined offered a prospective follow-up (two studies, one randomized controlled clinical trial), the change in the Mini-Mental Score Examination score from zero time to the end of the follow-up (5.9 years) suggested a difference in the incidence of dementia in favour of oral anticoagulation vs. antiplatelet therapy. However, in the studies that compared the use of oral anticoagulation or antiplatelet therapy with placebo or no treatment, there was no difference between the groups in terms of the incidence of dementia; similarly, the qualitative data offered no evidence.[9] However, this analysis suffered from methodological bias, not least the inclusion of only one randomized controlled clinical trial.

Another retrospective study on the topic was carried out on a total of 10 537 patients treated with warfarin at a target INR of 2–3. The indication for warfarin was represented by atrial fibrillation ($n = 4460$), thromboembolism ($n = 5868$), and mechanical heart valve ($n = 209$). Patients in the last two categories were included only if with a negative history of atrial fibrillation. The primary outcome was dementia. The results of the study showed that patients with atrial fibrillation had higher rates of total dementia (5.8% vs. 1.6%, $P < 0.0001$), Alzheimer's disease (2.8% vs. 0.9%, $P < 0.0001$), and vascular dementia (1.0% vs. 0.2%, $P < 0.0001$) compared to the others.[11] The mean follow-up time was 5.5 years in patients with atrial fibrillation, 8.2 years in valvulopathics, and 7.2 for the thromboembolism group.[11] The authors pointed out, however, how

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patients with atrial fibrillation presented more baseline risk factors for dementia (e.g. hypertension, diabetes, previous stroke) compared to non-fibrillating patients.

Another study wanted to test the hypothesis that patients with atrial fibrillation with a low percentage of time in the therapeutic range (TTR) were at greater risk of dementia due to excessive or insufficient anticoagulation.[12] For this purpose, a total of 2605 patients (age 73.7 ± 10.8 years, 54% of men) were studied without a history of dementia or stroke/transient ischaemic attack. The patients were in therapeutic range 63.1 ± 21.3% of the time, while in an insufficient coagulation condition (INR < 2.0) or excessive (INR > 3.0), respectively, 25.6% ± 17.9% and 16.2% ± 13.6%. The diagnosis of dementia (senile: 1.4%; vascular: 0.3%; Alzheimer: 2.5%) involved 109 patients, equal to 4.2% of the total. After adjustment, the lower TTR categories were associated with a significant increase in dementia risk.[12] Additional data come from an analysis of patients undergoing long-term anticoagulation with warfarin or direct oral anticoagulants (DOAC) for the prevention of thromboembolism, with the aim of assessing the risk of death, stroke/transient ischaemic attack, major bleeding, and dementia based on the anticoagulant therapy received.[10] A total of 5254 patients (2627 per group, 59% men) were examined, with a mean age of 72.4 ± 10.9 years. Most patients were taking long-term anticoagulants for the management of atrial fibrillation (warfarin: 96.5%, DOAC: 92.7%; $P < 0.0001$). Rivaroxaban (55.3%) was the most commonly used DOAC, followed by apixaban (22.5%) and dabigatran (22.2%). The results of the multivariate analysis showed that patients receiving DOAC exhibited a lower risk of dementia than those treated with warfarin, with no difference between molecules.[10] To better illuminate this topic, a clinical trial was launched in 2017—and should be completed in 2021—with the incidence of dementia as the primary endpoint in a population of patients with atrial fibrillation randomized to taking dabigatran or warfarin (ClinicalTrials ID.gov NCT03061006). Furthermore, a supratherapeutic INR in patients receiving an antiplatelet agent in addition to warfarin was associated with an increased risk of dementia, suggesting a potential role for microbleeds in the pathogenesis of dementia in atrial fibrillation.[13] A further observational study to examine the association between incident dementia during warfarin therapy and TTR was carried out on a population of 2800 patients without cognitive decline with atrial fibrillation, examined in the decade 2000–10.[14] The average age of the patients was 71.2 years; 53% were men ($n = 1495$) and warfarin was prescribed 50.5% ($n = 1414$) within 90 days of being diagnosed with atrial fibrillation, with adherence to treatment throughout the confirmed follow-up in 43% of patients. It should be reiterated that this cohort exhibited considerable comorbidities, with 63.4% of patients having a $CHA_2DS_2$-VASc score of 2 or more. After a median follow-up of 5.0 ± 3.7 years, the diagnosis of incident dementia was confirmed in 357 individuals (12.8%). After adjustment for confounding factors, compared to non-anticoagulated individuals, the use of warfarin was associated with a 20% lower risk of dementia, especially in individuals with higher INR TTR. An increase in TTR, in terms of reduced time spent in suboptimal or excessive anticoagulation, seemed to be associated with a reduction in the risk of dementia. Rather surprisingly, there was no association between warfarin use and risk of dementia after stratification by $CHA_2DS_2$-VASc score.[14] The delay in the establishment of anticoagulant therapy in atrial fibrillation also appears to be associated with an increased risk of dementia.[15] This is revealed by a study of 76 230 patients with atrial fibrillation without a history of dementia, average age 69.2 ± 12.7 years (56.8% men), with risk factors represented by arterial hypertension, diabetes mellitus, and heart failure. The primary endpoint was incident dementia. Of the total, 10 461 patients were on antiplatelet therapy, while 64 647 took the anticoagulant warfarin. The delay between the diagnosis of atrial fibrillation and the start of antiplatelet or anticoagulant treatment was calculated: latency was ≤30 days in 43.6% of patients, from 31 days to 1 year in 10.6% of patients, between 1 and 3 years in 13.5% of patients, and over 3 years in 32.3% of patients. When antiplatelet (acetylsalicylic acid) or anticoagulant (warfarin) therapy was not undertaken within 30 days of the diagnosis of atrial fibrillation, the risk of dementia was significantly increased [hazard ratio (HR) 1.63; $P = 0.05$].

Very recently, the results of a Swedish retrospective study on patients with hospital diagnosis of atrial fibrillation and no previous diagnosis of dementia, relative to the period 2006–14, have also been published. The study included 444 106 patients, showing that those taking anticoagulants at the beginning of the observation period had a 29% lower risk of dementia compared to patients not on anticoagulant treatment, without differences between new oral anticoagulants and warfarin (HR 0.97, 95% confidence interval 0.67–1.40).[7] In other words, the risk of dementia was about twice that in newly diagnosed patients with non-anticoagulated atrial fibrillation. The importance of this theme is remarkable in the context of the increase in life expectancy, together with that of the load of cardiovascular risk factors—two phenomena that we are witnessing growth in recent decades. Consequently, identifying strategies that allow to stem the phenomenon of dementia as a consequence of atrial fibrillation appears to be of primary importance. The socio-economic burden of dementia, in fact, is significant: data for 2013 estimated at 44.3 million people in the world suffering from a form of dementia, of which over one million people only in Italy.[16] The new cases of illness are over 7.7 million each year, i.e. a new case every 4 s.[16] The prevalence of dementia in industrialized countries is around 8% in the over-65s and rises to over 20% after 80 years, with estimates, according to some projections, tripling over the next 30 years. The economic consideration seems to amount to over 600 billion dollars a year.[16] Atrial fibrillation has been shown to be associated with both reduced brain volume and impaired memory, independent of signs of cerebral infarction.[4] It is, therefore, plausible, given the association between atrial fibrillation and stroke, that microemboli may have a role in the association between atrial fibrillation and dementia and, intuitively, that oral anticoagulation may reduce this risk. However, the role of microbleeds cannot be set aside, affecting the possibility that anticoagulation may even be harmful in this context. It has also been hypothesized that

cerebral hypoperfusion due to changes in the ejection fraction secondary to atrial fibrillation, or even to bradycardia due to remodelling of the sinus node that is often associated with this arrhythmia, may contribute to the associated cognitive deterioration. It is also true that an effective rhythm control appears, in turn, to mitigate the risk of dementia, as observed in a recent clinical study, in which the risk of dementia was similar in subjects in sinus rhythm and in those with atrial fibrillation subjected to catheter ablation.[17] In conclusion, intervening in the modulation of cardiovascular risk associated with atrial fibrillation is mandatory, and studies specifically designed to verify the additional benefit on the incidence of dementia by the application of the appropriate therapeutic strategies are desirable, also with a view to a prudent management of public resources.

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