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Atrial fibrillation and dementia: an unresolved 'Folie à Deux'

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In Volume 6, Issue 1 of this journal, Saglietto *et al*[1] have made another important contribution to the field of systematic reviews and meta-analyses on atrial fibrillation (AF) and its association with dementia. They have to be congratulated for this effort. In their meta-analysis entitled 'Stroke-independent contribution of atrial fibrillation to dementia: a meta-analysis' the authors systematically reviewed the existing evidence on the association between AF and dementia adjusted for the presence of cerebrovascular accidents (CVA) and transient ischaemic attacks (TIA). For this endeavour, they included five prospective observational studies in their meta-analysis. The authors found an almost 30% (HR 1.28 (1.17 to 1.41)) increased risk of dementia as compared with the general population, which was independent from the presence of CVA/TIA. Based on this meta-analysis and previous data from other groups, Saglietto *et al* suggest that early screening for AF and subsequent AF management may help to prevent dementia.

It is worth mentioning that the relationship between AF and dementia has already been investigated by three previous comprehensive meta-analyses, in whom patients with AF had a 1.38-to-2-fold increased risk of dementia (table 1).[2–4] The novelty of the current meta-analysis is conferred by its statistical adjustment for strokes/TIA, which were rare in the studied population (median 0%, IQR 0%–2%). Therefore, this study adds to the literature by suggesting a stroke/TIA-independent contribution of AF to dementia. The authors also suggest a stronger impact of AF to dementia by other mechanisms than a stroke/TIA-dependent effect, although this latter hypothesis is only derived from an indirect comparison with previous pooled meta-analyses showing an increased risk of dementia of around 40% in patients with AF not completely adjusted for the presence of stroke/TIA.

Several aspects deserve a closer look into the five studies included in this meta-analysis. The association of AF to CVA/TIA depending on the thromboembolic risk profile (CHA_2DS_2-VASc score) is well known and anticoagulation accordingly has its place in current guidelines.[5 6] The association of not only clinical, but subclinical CVA/TIA to the development of dementia has also been established.[7 8] The lack of cerebral imaging in most of the included studies renders it difficult to exclude subclinical CVA as a cause of dementia development. Therefore, care should be taken when assuming an association between AF and dementia independent of repetitive cerebral thromboemboli due to AF leading to both clinical and silent CVA. Although current data suggest an association between AF and an increased risk of dementia independently from stroke/TIA, the same was not true for patients with coronary artery disease.[9] Overall, further mechanisms like diffuse atherosclerosis, systemic inflammation and repetitive episodes of cerebral hypoperfusion and hypertension due to AF on a microvascular level, as recently suggested by an Italian research group, should be further investigated and taken into account as possible elements involved in the complex pathogenesis of AF-related dementia. To further elucidate a causal relationship, prospective randomised trials with early AF screening and treatment, and its impact on the development and course of dementia supported by cerebral imaging are eagerly warranted. Until then, it will remain hypothetical whether AF screening and management can reduce the burden of AF-associated dementia independent from CVA, and whether it is causally involved in its pathogenesis. The lack of systematic reporting of validated thromboembolic risk assessment tools (such as the CHA_2DS_2-VASc and Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA), scores) and anticoagulation in this meta-analysis is a limitation. The authors suggest that guideline-conform oral anticoagulation can be assumed in the included studies. Based on the large European

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Table 1 Meta-analyses investigating an association between atrial fibrillation (AF) and dementia

Meta-analysis	Studies included	Total population and follow-up	Mean age (years)	Association between AF and dementia	Heterogeneity of included studies	Cerebral vascular events
Saglietto *et al*, *Open Heart*, 2019	5 prospective observational studies (2011–2018) including patients with AF and dementia	61 008 median follow-up of 12.5 years	67	HR 1.28 (95% CI 1.17 to 1.41)	I^2 0%	Median value 0% (0–2)
Kwok *et al*, *Neurology*, 2011[3]	14 studies (13 prospective and 1 randomised controlled trial, 1990–2010) including elderly or subjects with ischaemic stroke, with and without dementia at baseline	46 275 Mean follow-up 4.5 years	71.7	OR 2.0 (95% CI 1.4 to 2.7), p<0.001	I^2 75%	Stroke as inclusion criterion in 7 studies (n=2425) and exclusion criterion in 3 studies (n=2058)
Kalantarian and Ruskin, *Ann Intern Med*, 2013[2]	14 studies (9 prospective, 5 cross sectional, 1997–2012) including patients with AF and dementia both with and without stroke	90 338 Mean follow-up: NA	72.5	RR 1.4 (95% CI 1.19 to 1.64)	I^2 69.4%	Stroke as exclusion criterion in 5 studies (n=8130)
Kalantarian and Ruskin, *Ann Intern Med*, 2013[2]	7 studies (5 prospective, 2 cross-sectional) including post-stroke AF patients from 1998 to 2012	2410 Mean follow-up: NA	70.5	RR 2.7 (95% CI 1.82 to 4.00)	NA	100%
Santangeli *et al*, *Heart Rhythm*, 2012[4]	8 prospective observational studies including elderly with normal cognitive function at baseline from 2004 to 2012	77 668 Mean follow-up 7.7±9.1 years (range 1.8–30 years)	range 61–84	HR 1.42 (95% CI 1.17 to 1.72), p<0.001	I^2 50%	0%

NA, not available; RR, relative risk.

PREvention oF thromboemolic events—European Registry in Atrial Fibrillation study with 85% of patients with AF and an elevated thrombembolic risk profile receiving adequate oral anticoagulation, this assumption indeed may be valid.[10]

Some methodological limitations have to be considered. Due to the stringent inclusion criteria, the number of studies included in this meta-analysis was low, which increases the CI of the point estimate. No apparent statistical heterogeneity and asymmetry has been reported among the selected studies, although there was a trend towards asymmetry considering the funnel plot in online supplemental figure 1 and given a p value of 0.06. This asymmetry might have been underestimated by the low number of studies analysed. Moreover, diagnostic criteria for dementia and AF were different among the included studies, so that qualitative heterogeneity is possible.

AF is emerging as a systemic disease of the ageing population. As such, confounding factors like therapies, health behaviours and comorbidities should be considered in pooled analyses, which is very difficult to fully adjust for in these kinds of meta-analyses including non-randomised studies. In this context, it is interesting to note that more than three quarters of the population had AF diagnosed after study inclusion, and incident versus previous AF had no impact on the presence of dementia.

Of note, previous data support the notion that the length of follow-up is crucial for the strength of the association between AF and dementia. However, Saglietto *et al* did not correct for this parameter in their metaregression analysis.[4]

In conclusion, this study provides important hints for further exploring the association between AF and dementia. Current progress in medicine should not only seek to prolong life expectancy, but also guarantee a decorous quality of life, and prevention of AF-associated dementia is certainly such an important goal. Second, the mechanisms underlying this association should be better understood considering AF as a systemic disease. Finally, the role played by new anticoagulant therapies should be better investigated with respect to subclinical CVA.

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