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### Non-valvular atrial fibrillation and cognitive function—baseline results of a longitudinal cohort study

SIR—Risk factors for cerebrovascular disease increase the risk of dementia and cognitive decline [1]. Non-valvular atrial fibrillation (NVAf) is an established risk factor for thromboembolism and stroke [2], which is significantly reduced by antithrombotic therapy [3]. Small cross-sectional studies report associations between NVAf, silent cerebral infarction and cognitive impairment [4–10], but there has been no longitudinal work in this area except for one small, highly selective comparison of cognition before and after coronary artery bypass grafting [11]. Given the high prevalence of NVAf in older people [12], we wished to determine whether NVAf is a preventable cause for cognitive decline in a prospective, longitudinal, community-based cohort study. Here we report baseline data comparing detailed neuropsychological testing of NVAf patients and controls, and assessing the effect of antithrombotic therapy.

### Methods

Participants in NVAf and controls in sinus rhythm, recruited from general practice and aged over 60 years, underwent a home visit composed of a validated battery of neuropsychological tests [13]: a health questionnaire; a health status questionnaire (the SF-36 [14]); a physical examination; an ECG and blood tests. Cases and controls were analysed as subgroups according to antithrombotic therapy (aspirin/warfarin/neither).

### Neuropsychological tests

The neuropsychological test battery included measures of selective/divided/sustained attention, short- and long-term verbal and non-verbal memory, information processing and premorbid intelligence.

### Confounding factors

We incorporated all key confounders (age, duration of atrial fibrillation, coronary heart disease, diabetes, hypertension, cholesterol, health status (SF-36), congestive heart failure and education) into a multivariate model (Analysis of Covariance, ANCOVA) as covariates and found almost no

effect of confounders on the neuropsychological tests, with only age showing borderline significance. Extensive additional analysis demonstrated no effect of confounders on the relationship between NVAf and cognitive function, regardless of use of antithrombotic therapy. Therefore we adjusted for age only.

Please see Appendices 1, 2 and 3 in the supplementary data on the journal website ([www.ageing.oupjournals.org](http://www.ageing.oupjournals.org)) for more details of methods, analyses, confounders and neuropsychological tests.

### Results

After baseline interview, 362 participants were included (Table 1). There was no evidence of significant response bias, and cases and controls were comparable in most respects. Please see Appendix 4 in the supplementary data for full details of recruitment, response bias and characteristics of the cohort.

### Baseline cognitive function tests (Table 2)

There were no significant differences ( $P > 0.05$ ) in the means of the neuropsychological tests between cases and controls for the majority of sub-tests after adjustment for age, except for one item, 'time taken to perform the telephone task', where cases performed less well ( $P = 0.003$  adjusted for age).

### Subgroup analysis

Cases and controls were analysed as subgroups and the means of the test scores compared (cases on aspirin ( $n = 62$ ), warfarin ( $n = 80$ ) or neither ( $n = 32$ ), and controls on aspirin ( $n = 52$ ) or neither ( $n = 136$ )). The small sample size in cases who were in the 'neither warfarin nor aspirin' subgroup limits the interpretation of the results for this subgroup.

Initially significant differences between subgroups for the variables logical memory delayed, Rey figure copy, PASAT-4 seconds, telephone task number and digit span, were no longer significant when age was used as a covariate, with the exception of 'telephone task time taken' with aspirin cases performing significantly worse (118.43 seconds) than aspirin controls (90.25 seconds,  $P = 0.004$ ).

### Discussion

This is the largest cross-sectional study comparing cognitive function in older people with NVAf to those in sinus rhythm and adds considerably to previous cross-sectional data.

### Context of existing research

The results presented here contrast with the findings of previous research addressing the association between NVAf and cognitive decline, including our pilot study in the North of England [13], as we found no difference at baseline between patients with NVAf and controls. Furthermore, there was no clear difference between patients on different forms of antithrombotic therapy.

**Table 1.** Characteristics of the cohort

Characteristic	Cases ( <i>n</i> = 174)	Controls ( <i>n</i> = 188)	95% confidence interval for difference between cases and controls
Mean age (years)	75.0	75.4	-2.1-1.25
Current smokers (%)	13.1	15.1	-9.1-5.3
Current daily drinkers (%)	17.7	22.6	-13.1-3.4
Record of coronary heart disease (%)	44.4	31.9	2.4-22.6
Record of diabetes (%)	16.0	4.4	5.3-17.8
Record of hypertension (%)	42.6	35.2	-2.7-17.6
Record of peripheral vascular disease (%)	7.1	6.0	-4.1-6.2
Record of symptomatic heart failure (%)	11.8	1.1	5.6-15.8

**Table 2.** Means for the difference in test score between cases and controls (potential confounders included in the model)

Neuropsychological test	Mean score (SD) case ( <i>n</i> = 174)	Mean score (SD) control ( <i>n</i> = 188)	Mean difference in score case-control	95% confidence interval after adjustment for covariates	<i>P</i> value	Scoring range	High is good
MMSE	28.4 (1.6)	28.5 (1.6)	-0.01	-0.31 0.43	0.906	0-30	Yes
Logical memory immediate (raw)	14.3 (5.9)	15.0 (6.0)	-0.70	-2.49 0.19	0.440	0-50	Yes
Logical memory delayed (raw)	10.8 (6.8)	10.9 (6.4)	-0.10	-1.66 1.14	0.804	0-50	Yes
Rey complex figure copy	31.9 (4.5)	31.9 (4.8)	0.00	-1.01 1.06	0.789	0-36	Yes
Rey complex figure delayed	12.5 (6.5)	13.6 (7.0)	-1.10	-2.23 0.80	0.078	0-36	Yes
Map search (1 minute left)	15.9 (8.4)	17.5 (9.4)	-1.60	-3.25 0.87	0.061	0-20	Yes
Map search (1 minute right)	5.0 (7.1)	5.5 (7.6)	-0.50	-2.27 1.23	0.482	0-20	Yes
Map search (2 minutes left)	9.2 (7.2)	10.0 (7.9)	-0.80	-2.33 1.17	0.206	0-20	Yes
Map search (2 minutes right)	8.8 (8.1)	9.7 (8.9)	-0.90	-3.45 0.56	0.318	0-20	Yes
Telephone task: no. of targets	17.4 (3.3)	17.7 (2.7)	-0.30	-0.86 0.48	0.437	1-20	Yes
Telephone task: time taken (minutes)	104.2 (43.9)	92.9 (35.0)	11.30	5.4 22.34	0.003*	0-4	No
Telephone task: dual task decrement	5.5 (20.5)	2.9 (3.8)	2.60	-0.87 6.00	0.098	Variable	No
NART, no. of errors	22.0 (10.2)	21.4 (9.9)	0.60	-0.95 3.75	0.933	0-50	No
NART, predicted IQ	103.5 (12.8)	103.5 (13.8)	0.00	-4.13 2.15	0.475	69-131	Yes
PASAT (4-seconds)	29.6 (16.1)	30.1 (18.1)	-0.50	-3.75 3.91	0.720	0-60	Yes
PASAT (2-seconds)	12.0 (12.3)	12.7 (13.3)	-0.70	-3.97 2.06	0.654	0-60	Yes
Digit span	13.5 (3.6)	13.8 (3.7)	-0.30	-1.19 0.51	0.456	0-28	Yes

MMSE = Mini-mental State Examination; NART = National Adult Reading Test; PASAT = Paced Auditory Serial Test.

\**P* < 0.05.

Previous research had demonstrated an association between NVAf and poor performance on neuropsychological assessment [7-10], but has to date been restricted to small cross-sectional studies of selective populations without careful consideration of potential confounders or of the effect of antithrombotic therapy.

There are several possible reasons for this disparity. First, the CAFÉ (Cognition and Atrial Fibrillation Evaluation) cohort was larger than most previous studies (e.g. 44 [7] and 42 [8] cases used compared with 174 in this study), except for the Rotterdam study, which included 195 cases [9]. Secondly, our cohort was maximally representative, whilst in three of the previous studies, sampling was of inpatients/secondary care registers [8, 10, 11]. Please see Appendix 5 in the supplementary data for details of differences in characteristics between studies.

Thirdly, our cohort was restricted to those with a known duration of NVAf of 5 years or less, whilst others included longstanding cases with potentially more progressive cognitive decline. Whilst it is unlikely that this is the sole explanation in what is the largest cross-sectional comparison of its type, our follow-up assessment will explore this further.

Fourthly, we used neuropsychological tests measuring a wide range of cognitive domains, in contrast to the more limited neuropsychological assessment employed by some of the previous studies [7-9].

Finally, our cases had higher levels of treatment with antithrombotic therapy (81.6%) than those of earlier studies (26% [9], 50% [7]), probably due to greater awareness of appropriate management of NVAf. This treatment may reduce cognitive decline, although our subgroup analysis provides no evidence for this.

### Potential confounders

Whilst we found differences between cases and controls for diabetes, cholesterol, coronary heart disease, congestive heart failure and SF-36 score, these did not confound our findings. Although we measured mental health status using the SF-36, a more specific measure of depression may be preferable; therefore we have incorporated the Geriatric Depression Scale [15] into follow-up visits.

### Selection and response bias

Please see Appendix 6 in the supplementary data for a full exploration of the possibility of selection and response bias.

## Research letters

In summary, the design of our prospective cohort study made the use of certain exclusion criteria, such as previous stroke and dementia, unavoidable and may therefore have led to underestimation of the extent of cognitive decline in our population. However, it is unlikely that this alone is sufficient to explain our negative findings. In addition, comparison of characteristics of responders and non-responders suggested selection bias is unlikely, despite the relatively small number of potential subjects included.

### Survival effects

It is possible that our findings may have been affected by the healthy survivor effect, since those with cognitive impairment and dementia have higher mortality than those without [16–19]. Therefore, attrition due to mortality in any study of cognitive function, including the existing cross-sectional work on this topic, may lead to bias and underestimation of the extent of cognitive impairment in both cases and controls. However, this survival effect is likely to be stronger in more advanced dementia [9]. In this study, we tried to include patients with recent onset atrial fibrillation. Nonetheless it is possible that some healthy survivor effect may have contributed to our negative findings, but is unlikely to fully explain them.

### Study design

The ideal study design to assess the effect of antithrombotic therapy on cognitive status would be a randomised controlled trial. However, this would be unethical since the protective effect of warfarin and aspirin against stroke is well proven [3]. This therefore suggests that a more appropriate study design would be a prospective longitudinal cohort study, with repeated assessment of cognitive function.

### Neuropsychological test battery

Literature suggests that vascular cognitive impairment is related to speed, attention, information processing and executive function more than other domains [20], although the Framingham study has demonstrated lower cognitive performance across multiple cognitive domains, including visual-spatial memory, in those with cerebrovascular risk factors [21]. The CAFÉ neuropsychological test battery contained valid measures of attention, speed and information processing. However, although the MMSE contains a crude estimate of executive function, ideally we would have measured this more extensively, and in a future study such assessments would be added. Such measures may be more sensitive in detecting small changes in cognitive function due to NVAF. Some previous cross-sectional studies have included specific tests of executive function, although two studies relied only on the Mini-mental State Examination for all assessment of cognitive decline [8, 9]. Therefore, it is unlikely that the absence of a specific measure of executive function in our study is responsible for the difference between our results and those of previous studies.

In conclusion, our study finds no convincing difference in cognitive function between cases with recent onset NVAF and controls, nor between patients on anticoagulant/antiplatelet therapy and those left untreated. These

findings are likely to be more reliable and valid than those of the preceding studies since they derive from a larger, representative community-based population. Subsequent measurement of cognitive decline over time, which is the best way to assess this relationship, will explore our original hypothesis, that older people with NVAF have increased risk of cognitive decline. Furthermore, stratification of our cohort may clarify the potential role of antithrombotic therapy in the prevention of cognitive impairment in patients with NVAF.

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### Conflicts of Interest

There were no conflicts of interest.

### Informed consent

Ethical approval was provided by the appropriate NHS Local Research Ethics Committees. Written, informed consent was obtained from all participants.

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## Tolerability of spironolactone as adjunctive treatment for heart failure in patients over 75 years of age

SIR—Following the RALES (Randomised Aldactone Evaluation) study of 1999 [1, 2], guidelines recommend adjunctive treatment of moderate to severe heart failure with spironolactone, in addition to angiotensin-converting enzyme (ACE) inhibitors [3].

The RALES study, a randomised placebo-controlled trial of spironolactone in 1,663 heart failure patients already taking

ACE inhibitors, found that spironolactone reduced heart failure symptoms, hospitalisations and mortality, and there was no major increase in renal failure or life-threatening hyperkalaemia. However, the mean age of patients enrolled in RALES was only  $66 \pm 12$  years, whereas heart failure is predominantly a syndrome of older people, the average age at diagnosis being 76 years. Adverse drug events are often more common in older populations. Since the publication of RALES, several case reports have raised concerns about the risks of hyperkalaemia and renal failure with adjunctive spironolactone treatment for heart failure in clinical practice, especially in older patients [4–7]. A time-series analysis of hospitalisation and prescription data in Ontario reported an increase in hyperkalaemia-associated morbidity and mortality, following the publication of RALES [8].

We audited the prescribing of spironolactone to patients aged  $\geq 75$  years, to see whether patients prescribed spironolactone are being monitored in accordance with RALES study guidelines, and to determine the incidence of renal failure and life-threatening hyperkalaemia in a district general hospital setting. We also hoped to identify predictors of spironolactone adverse events.

## Methods

This was a retrospective case note review for which local research ethics committee approval was granted. All those over 75 years of age, with a clinical diagnosis of heart failure, who had been prescribed spironolactone in conjunction with an ACE inhibitor between September 1999 (the date of publication of the RALES study) and the end of July 2003 were studied.

Patients were identified from the hospital's inpatient and outpatient databases. Demographic and clinical data were recorded as well as adverse events.

Baseline serum potassium and creatinine concentrations at spironolactone initiation, as well as follow-up values on treatment were recorded from case notes and the hospital laboratory database. Given that serum creatinine concentration is a relatively poor marker of renal function in older people, baseline creatinine clearances were also calculated using the Cockcroft–Gault equation [9].

The definitions for severe hyperkalaemia and renal failure were taken as potassium  $\geq 6.0$  mmol/l and creatinine  $\geq 354$   $\mu$ mol/l, since these were the cut-off levels at which spironolactone treatment was withdrawn in RALES [1, 2]. Potassium concentrations above 5.5 mmol/l and the absolute and percentage rises in creatinine for all patients were also recorded. Intercurrent illnesses consisting of sepsis, vomiting or diarrhoea were noted. Adverse events were expressed as proportions of the total number of patients on treatment.

## Results

### Subjects

Sixty-six patients aged 75 years or over (age range 75–94 years), with heart failure, taking ACE inhibitor and spironolactone were identified. Altogether 3,703 patients