

Cognitive Impairment as Determinant for Sub-Optimal Control of Oral Anticoagulation Treatment in Elderly Patients with Atrial Fibrillation

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Abstract

Background and objective: Atrial fibrillation is an indication for oral anticoagulation treatment. Maintaining the International Normalized Ratio (INR) within the therapeutic range minimises thromboembolic and bleeding complications. We have investigated whether cognitive capacity affects control of anticoagulation in elderly patients with atrial fibrillation.

Patients and methods: A retrospective study was conducted to investigate the association between cognitive impairment and control of anticoagulation. Patients ≥ 70 years of age with atrial fibrillation using acenocoumarol (nicoumalone) as anticoagulant were included. All patients were monitored by the Anticoagulation Clinic in the Midden-Brabant region in the Netherlands. The cognitive function of all patients was assessed using the Mini-Mental State Examination (MMSE) on the index date. INR values were obtained from the year preceding the index date. Patients with an MMSE score < 23 were defined as cognitively impaired. The primary outcome of the study was the incidence of an INR value within the therapeutic range of 2.0–3.4 during $\leq 70\%$ of treatment time in the year prior to the cognitive function assessment. The secondary endpoint was the number of patients with an INR < 2.0 or ≥ 6.0 at least once during this year. Logistic regression analysis was used to evaluate the association between cognitive function and control of anticoagulation.

Results: A total of 152 patients were included in the study. An MMSE score < 23 was associated with an inadequate INR control (odds ratio [OR] 2.77; 95% CI 1.13, 6.74). After correction for hospital admission and change of possibly

interacting medication (both also associated with inadequate INR control), this association remained statistically significant. Significantly more patients with an MMSE score <23 had one or more INR values of six or higher (OR 3.06; 95% CI 1.14, 8.18).

Conclusion: In elderly people with atrial fibrillation using oral anticoagulation, an MMSE score <23 is independently associated with an inadequate INR control, mainly because of an increased number of suprathreshold INR values. This finding should be taken into account when making decisions about use of oral anticoagulants in the elderly.

Atrial fibrillation is an important indication for use of oral anticoagulants to prevent thromboembolism.^[1-3] Several clinical trials have shown that oral anticoagulants prevent ischaemic stroke in patients with atrial fibrillation.^[4-7] The prevalence of atrial fibrillation increases with age.^[8] Obviously, cognitive disorders also occur increasingly with aging. In addition, a disproportionately high number of patients with atrial fibrillation show cognitive disturbances.^[9-11] These cognitive disorders may impair adequate control of oral anticoagulant therapy, because good adherence and a thorough understanding of the correct use of this class of drugs with a small therapeutic index is necessary. By regularly determining the International Normalized Ratio (INR) and adjusting dosage on the basis of this INR when necessary, it is possible to attain a therapeutic effect and minimise complications.^[4-7]

In the Netherlands, monitoring of oral anticoagulant therapy is conducted by a network of specialised anticoagulant services.^[12] Nurses instruct patients at the start of anticoagulation treatment. Doctors who specialise in anticoagulation therapy dose patients with coumarin derivatives with the help of a computerised dosing program. Patients inform the anticoagulation service about changes in co-medication, illness and any complications of anticoagulation therapy (acenocoumarol [nicoumalone] or phenprocoumon in The Netherlands). This system of specialised anticoagulant services provides optimum care for the patient taking oral anticoagulants.

However, even with this system, there remains a subgroup of patients for whom stabilisation of the INR within the therapeutic range is difficult.

Studies to date have largely focused on the contributions of co-morbidities and co-medications to poor control of anticoagulation.^[13-15] The influence of cognitive disorders on control of anticoagulant treatment has been investigated previously in only one small study.^[16] Therefore, we examined whether cognitive impairment is a determinant of inadequate control of anticoagulant therapy in a larger group of elderly patients with atrial fibrillation.

Methods

Study Design and Population

This study was a retrospective study of patients monitored by an anticoagulation service. All patients ≥ 70 years of age who were treated with acenocoumarol for atrial fibrillation during the year before the cognitive assessment were included in the study. Exclusion criteria included co-existence of another indication for use of acenocoumarol that required another therapeutic range, severe liver insufficiency, living in a nursing home or not living on one's own, dependence on intensive nursing, use of acenocoumarol for <1 year, and lack of informed consent. Patients were monitored by the Anticoagulant Service Midden-Brabant, such that the INR was measured at least once every 6 weeks and subse-

quent anticoagulant advice was given on the basis of the measured INR value.

The principal investigator (BvD) visited study patients once at home on the index date. These house visits took place between March and May 2003. At the time of the house visit, the principal investigator was not aware of the INR values of the patients.

The study was approved by the Medical Ethics Committee of the TweeSteden Hospital.

Outcomes

The primary outcome was the incidence of an INR value within the therapeutic range of 2.0–3.4 during $\leq 70\%$ of treatment time over the 1-year period preceding cognitive function assessment (on the index date).^[17] The INR values measured in the year prior to the index date were converted with the help of the computer program INRDAY^[18] to a percentage of time during which the INR had a value of between 2.0 and 3.4. The Federation of Dutch Anticoagulant Services considers this INR range as optimal for the indication of atrial fibrillation.^[14,19]

The secondary outcome of the study was the number of patients who had an INR value < 2.0 or ≥ 6.0 measured at least once during the year preceding the cognitive function assessment. Such patients are at greatest risk of thromboembolism or haemorrhage.^[5,13,20-22]

Study Determinant

At the home visit on the index date, patients were evaluated on the Mini-Mental State Examination (MMSE).^[23] This test includes 19 questions which concentrate on cognitive aspects of mental functions and requires 5–10 minutes to complete. A maximum score of 30 points is possible; patients in this study with an MMSE score < 23 were defined as having a diminished cognitive capacity.

Potential Confounding Factors

At the home visit the following patient characteristics were recorded: age, sex, extent of supervision of taking of medications (full, partial or no supervision, in which full supervision was defined as supervision over the actual drug intake and partial supervision was defined as having the patient's drugs dispensed in a 'week box' by the pharmacy [a week box contains all the drugs the patient has to take the next week, sorted by day and by administration time]), any hospital admission in the year preceding the index date (where hospitalisation was defined as any admission for > 2 consecutive days), life events (e.g. death of spouse, moving house) in a period of 2–50 weeks preceding the index date, social status (living alone or living together), living status (living at one's own home or in an elderly home), current medications, and the patient's pharmacy. When the social or living status altered during the year preceding the index date, the status which lasted longest was used.

The medication history was obtained from the patient's pharmacy. Any concomitant medication used during the year preceding the index date that had the potential for a drug-drug interaction with acenocoumarol was noted. Examples included antibacterials, allopurinol, amiodarone, antiepileptics, bile acid-binding resins, fibrates, oral imidazoles/triazoles, tamoxifen and thyromimetics/thyrostatics.^[13-15] Initiation or discontinuation of these drugs in the 2–50 week period preceding the index date was defined as a change in potentially interacting medication.

Data Analysis

Data were processed with the help of MS Excel 2000 and were analysed with SPSS (Statistical Package for the Social Sciences) version 11.0. We estimated that 20% of patients with a well controlled INR ($> 70\%$ of treatment time within the therapeutic

Table I. General patient characteristics (n = 152)

	INR 2.0–3.4 >70% of treatment time (n = 106)	INR 2.0–3.4 ≤70% of treatment time (n = 46)
Age (mean [SD])	78.8 (5.3)	79.5 (5.3)
Sex (number of males [%])	62 (58.5)	23 (50.0)
MMSE <23 (%)	12 (11.3)	12 (26.1)
Extent of supervision of medication taking (number of patients [%])		
full supervision	9 (8.5)	6 (13.0)
partial supervision	11 (10.4)	5 (10.9)
no supervision	86 (81.1)	35 (76.1)
Hospital admission (number of patients admitted to hospital in the preceding year [%])	14 (13.2)	14 (30.4)
Life event (number of patients with a life event in preceding year [%])	9 (8.5)	7 (15.2)
Social status (number of patients living alone [%])	45 (42.5)	26 (56.5)
Living status (number of patients living in a rest home [%])	11 (10.4)	7 (15.2)
Changes in medication (number of patients with at least one change in medication possibly interacting with coumarins [%])	39 (36.8)	26 (56.5)

INR = International Normalized Ratio; **MMSE** = Mini-Mental State Examination.

range of 2.0–3.4) would have an MMSE score <23. A relative risk of 2 was considered clinically relevant. Given a power of 0.80 and a two-sided significance level of 0.05, 160 patients needed to be included in the study.

The associations between individual variables and inadequate INR control were assessed by univariate logistic regression analysis and expressed as odds ratios (OR) with 95% confidence intervals (95% CI). Subsequently, a multivariate analysis was conducted that included the factors significantly associated with inadequate INR control in the univariate analysis. Univariate and multivariate logistic regression analysis was also used to analyse the number of patients with at least one INR value <2.0 or ≥6.0 (for the determinant). Again, multivariate analysis included factors significantly associated with the outcome parameter, i.e. at least one INR value <2.0 or ≥6.0.

Results

The anticoagulation service identified 179 patients who met the inclusion criteria. Of these, 27 patients were subsequently excluded: ten because of lack of interest, five lived in remote areas, three

lived in a nursing home, three were absent at the time of the appointment, two were not available on one of the arranged dates, two lived in a specialised home with intensive nursing and two were terminally ill. Thus, 152 patients were included in the study, of whom 55% were men. Table I shows the general characteristics of the study population, divided into those with an INR within the therapeutic range >70% of treatment time versus those with an INR within the therapeutic range ≤70% of treatment time.

Patients with an MMSE score <23 had an INR within the therapeutic range for 68% of the treatment period, whereas patients with an MMSE score ≥23 had an INR within the therapeutic range for 76% of the treatment time. On univariate analysis, an MMSE score <23 was associated with inadequate INR control (OR 2.77; 95% CI 1.13, 6.74). In addition, both hospital admission (OR 2.88; 95% CI 1.24, 6.68) and a change in potentially interacting medication (OR 2.23; 95% CI 1.11, 4.52) were associated with inadequate INR control. No other variables were statistically significantly associated with INR control (table II).

On multivariate analysis, after adjustment for the variables admission to hospital and change of potentially interacting medication, an MMSE score <23 was still associated with inadequate INR control (OR 2.57; 95% CI 1.02, 6.48).

Table III shows the results for the secondary outcome parameter in relation to cognitive function. On univariate analysis, a significantly higher number of patients having an MMSE score <23 had one or more INR values of ≥ 6.0 (OR 3.06; 95% CI 1.14, 8.18) [table III]. After adjustment for supervision of coumarin intake (the only potential confounder that was found to be statistically significantly associated with the outcome parameter in univariate analysis), this association was no longer statistically significant (table III). The number of patients with one or more INR values <2.0 was not significantly higher in patients with an MMSE score <23 (OR 1.03; 95% CI 0.39, 2.67) [table IV]. After adjustment for potential confounders, these findings remained the same (table IV).

Discussion

Our data demonstrate a significant, independent association between cognitive impairment and inadequate INR control in elderly patients taking acenocoumarol for atrial fibrillation. In addition, patients with an MMSE score <23 had a significantly higher chance of INR values ≥ 6.0 , which could lead to a higher rate of bleeding complications, although this association was not independent of other variables.

Until now, only one small study has evaluated the association between cognitive impairment and inadequate INR control. This study in 18 patients showed a significant association between cognitive impairment (MMSE score ≤ 26) and supratherapeutic INR response.^[16]

One of the strengths of our study is the fact that we used pharmacy records to obtain the patient's drug history. Thus, recall bias did not influence our data relating to concomitantly used drugs. However, we did not check which 'over-the-counter' drugs the patient used. Therefore, we may have missed some

Table II. Associations between individual variables and outcome values (INR 2.0–3.4 $\leq 70\%$ of treatment time versus INR 2.0–3.4 $>70\%$ of treatment time)

Determinant	Univariate		Multivariate ^a	
	OR	(95% CI)	OR	(95% CI)
Cognitive impairment (reference = MMSE score ≥ 23)	2.77	(1.13–6.74)	2.57	(1.02–6.48)
Change in one or more possibly interacting drugs (reference = no change)	2.23	(1.11–4.52)	2.19	(1.05–4.54)
Life event (reference = no life event)	1.93	(0.67–5.56)	1.52	(0.50–4.58)
Hospital admission (reference = no hospital admission)	2.88	(1.24–6.68)	2.79	(1.16–6.67)
Supervision of coumarin intake (categorised)				
no supervision	reference	-	reference	-
partial supervision	1.12	(0.36–3.45)	0.69	(0.19–2.57)
complete supervision	1.64	(0.54–4.95)	0.62	(0.15–2.61)
Social status (reference = living with spouse)	1.76	(0.88–3.54)	1.82	(0.87–3.81)
Living status (reference = rest home)	0.65	(0.23–1.79)	0.79	(0.25–2.47)
Gender (reference = female)	0.71	(0.35–1.42)	0.76	(0.36–1.58)
Age	1.03	(0.96–1.10)	1.01	(0.94–1.09)

a Adjusted for co-variables significantly associated with outcome value ($\leq 70\%$ of INR values within range 2.0–3.4) in univariate analysis.

CI = confidence interval; MMSE = Mini-Mental State Examination; OR = odds ratio.

relevant drug-drug interactions, such as those with NSAIDs.

A further limitation of our study is the fact that we did not assess all potential characteristics known to interfere with anticoagulant therapy. Congestive heart failure, diarrhoea, malabsorption of fat, hypermetabolic status, fever, low body mass index, nonsmoking, low physical activity, recent decrease in alcohol consumption, loss of weight and going on vacation are risk factors for overanticoagulation.^[22,24] We did not assess patients for the presence of co-morbid conditions, other than severe liver insufficiency, known to influence INR values. Older patients with cognitive disorders may have co-morbid conditions that present asymptotically or that might not be remembered. Co-morbid conditions may influence the pharmacokinetics of acenocoumarol. Thus, the association we found may have been confounded by factors we did not study.

On the other hand, the effect of cognitive disorders on anticoagulation treatment in everyday practice might be greater than that shown in this study, because our study population consisted of patients who had been treated for at least 1 year. It is plausible that anticoagulation therapy was withdrawn earlier in patients with evidently poor adherence or adverse effects. Furthermore, we dichotomised cognitive functioning by using a cut-off level of 23 points on the MMSE. It is well known that people with MMSE scores >23 points can also have cognitive deficits that affect everyday activities considerably.^[25,26] Indeed, the study of Lackie et al.^[16] demonstrated an association between supratherapeutic INR response and MMSE values ≤ 26 . Po-

tentially, in our study, dichotomising the MMSE score at a cut-off level of 23 points could have weakened the association between cognitive impairment and inadequate INR control.

We measured MMSE at the index date and then analysed INR values documented over the 1 year period before the index date. This strategy implies, of course, that MMSE may have been better 1 year before the index date. Thus, we recommend that prospective studies be conducted to confirm the results of our study.

We chose 'time spent within an INR range of 2.0–3.4' as a measure of INR control. This INR range is used in The Netherlands for the treatment of atrial fibrillation.^[14,19] However, in North America the therapeutic range for this indication is 2–3. Choosing this range of INR as a measure of INR control in our study would probably have resulted in overall less control, but it does not seem likely that the results between both MMSE groups would have differed.

Other outcome measures could also have been defined, such as time spent below or above INR therapeutic range.^[27] However, we were primarily interested in the ability of patients with a low MMSE to maintain their INR within therapeutic range, and we chose the primary outcome of the study accordingly. Safety and lack of efficacy were chosen as secondary outcome measures. As has been the case in several earlier studies,^[5,13,20–22] we expressed those secondary endpoints as the number of INR values ≥ 6 and < 2 , respectively. These cut-off points have a good correlation with bleeding and lack of efficacy.^[28] However, a final limitation of

Table III. Patients with at least one INR value ≥ 6 versus no INR value ≥ 6 by MMSE score < 23 and MMSE score ≥ 23

	At least 1 INR ≥ 6	No INR ≥ 6	Univariate analysis		Multivariate analysis ^a	
			OR	95% CI	OR	95% CI
MMSE < 23	8 (33%)	16 (67%)	3.06	1.14–8.18	2.41	0.71–8.13
MMSE ≥ 23	18 (14%)	110 (86%)	reference		reference	

a Adjusted for co-variables significantly associated with outcome in univariate analysis, i.e. supervision of coumarin intake.

CI = confidence interval; INR = International Normalized Ratio; MMSE = Mini-Mental State Examination; OR = odds ratio.

Table IV. Patients with at least one INR value <2 versus no INR value <2 by MMSE score <23 and MMSE score ≥23

	At least 1 INR <2	No INR <2	Univariate analysis		Multivariate analysis ^a	
			OR	95% CI	OR	95% CI
MMSE <23	17 (71%)	7 (29%)	1.03	0.39–2.67	0.83	0.29–2.32
MMSE ≥23	90 (70%)	38 (30%)	reference		reference	

a Adjusted for co-variables significantly associated with outcome value in univariate analysis, i.e. hospital admission and change in one or more possibly interacting drugs.

CI = confidence interval; INR = International Normalized Ratio; MMSE = Mini-Mental State Examination; OR = odds ratio.

our study was the lack of clinically relevant endpoints, such as bleeding and thromboembolism. Our study population was too small to study these effects. Nevertheless, because INR is closely correlated with these clinical endpoints,^[28] our study does indicate that effects on bleeding and thromboembolism of inadequate INR control as a result of cognitive impairment may be seen in larger populations.

The association between disturbances of cognitive functioning (as measured by MMSE score) and inadequate anticoagulant control can be explained by a higher degree of nonadherence, since correction for degree of supervision did not influence the association between INR control and MMSE.^[29] This assumption could be confirmed by accurately counting administered acenocoumarol tablets, possibly through electronic monitoring.^[30,31] Nonadherence with antihypertensive therapy regimens has been demonstrated in elderly patients with cognitive disorders who are living alone.^[32] Furthermore, one study showed that better understanding of anticoagulation therapy on the patient's part resulted in improved control of INR.^[33]

Several studies have reported the significance of weighing the advantages and disadvantages of anticoagulation treatment in elderly patients with atrial fibrillation.^[34-36] Notwithstanding its limitations, our study shows that an MMSE score <23 is a factor that should be taken into account when prescribing anticoagulant therapy.

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