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Research Article

Vitamin K Antagonists and Cognitive Function in Older Adults: The Three-City Cohort Study

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Abstract

Background: A growing body of evidence supports a beneficial role for vitamin K in brain and cognition, notably in studies where animals are rendered vitamin K deficient by warfarin, a potent vitamin K antagonist (VKA). Given VKAs are commonly used oral anticoagulants in older persons, we investigated the relationship between VKA therapy and cognitive performances over 10 years in participants of the Three-City study.

Methods: The Three-City cohort included 7,133 nondemented community dwellers, aged 65 years or older at baseline. Exposures to VKAs and platelet aggregation inhibitors, another antithrombotic agent, were determined at baseline. Participants underwent cognitive assessment at baseline and every 2 years over 10 years. Associations were analyzed with mixed linear models adjusting for many covariates including VKA and platelet aggregation inhibitor indications.

Results: About 239 (3.4%) and 1,192 (16.7%) of the participants were treated with VKAs and platelet aggregation inhibitors at baseline, respectively. VKA treatment was significantly associated with worse performances on Benton Visual Retention Test assessing visual memory (adjusted mean difference −0.29; $p = .02$ in multivariate models) and Isaacs Set Test assessing verbal fluency (adjusted mean difference −1.37; $p = .0009$) at baseline. Treatment with VKAs was not associated with global cognitive functioning on the Mini Mental State Examination, neither with rate of subsequent decline in scores on all three cognitive tests. No associations were found between platelet aggregation inhibitors and cognitive performances or rate of decline.

Conclusion: These findings do not indicate a long-term detrimental effect of VKAs on cognition, but the risk–benefit balance of VKA treatment still deserves further research.

Keywords: Vitamin K antagonist—Cognitive decline—Aging—Cohort

Discovered for its implication in hemostasis, evidence is growing for a role of vitamin K in brain function and cognition (1). Concentrations of vitamin K are high in rat and human brains (2,3) and were shown to respond to vitamin K intakes in rodents (4–6). Vitamin K is involved in brain sphingolipid metabolism and in the activation of proteins required for neuronal and glial cell functions (1). High vitamin K status has also been associated with better cognitive performance in rats (5) and healthy older adults (7). Furthermore, rodents treated with warfarin, a potent vitamin K antagonist (VKA), show decreased brain vitamin K concentrations (4,8), altered sphingolipid profile (8,9), and worse cognitive performance (8).

VKAs, notably warfarin, are commonly prescribed oral anticoagulants for the prevention of thromboembolic diseases, a frequent condition in older adults. However, data on the relationship between VKA and cognition in humans are scarce. In men at cardiovascular risk, cognitive performance appeared poorer following low-dose warfarin treatment compared to aspirin or placebo (10). In a cross-sectional study conducted among geriatric patients, taking VKA was significantly associated with a higher risk of having cognitive impairment (11). Although VKAs could potentially alter brain function, they can also benefit cognition through their antithrombotic effects, the primary result of VKAs being to suppress the coagulation cascade. Indeed, risk of dementia over 3 years was lower in participants with atrial fibrillation prescribed warfarin compared to those not prescribed, with borderline significance when adjusting for comorbidity (12). However, treatment with warfarin was not associated with the risk of cognitive impairment after stroke in another study (13).

This study aimed to investigate the relationships between VKA therapy and cognitive performance and decline over 10 years in a large cohort of community-dwelling older adults. In order to better control for residual confounding by cardiovascular diseases leading to the prescription of antithrombotic agents, we also investigated the associations between platelet aggregation inhibitors (PAIs) and cognition in an attempt to compare the specific effects of VKAs to those of another frequently prescribed antithrombotic agent.

Methods

Participants

This longitudinal study was conducted among participants from the Three-City study, a prospective cohort study of vascular risk factors for dementia, which included 9,294 community dwellers living in Bordeaux, Dijon, or Montpellier (France), aged 65 years and older at baseline in 1999–2000. The general methods of the Three-City study have been described elsewhere (14) and are available at http://www.three-city-study.com/the-three-city-study.php. The protocol of the Three-City study has been approved by the Consultative Committee for the Protection of Persons participating in Biomedical Research of the Kremlin-Bicêtre University Hospital (Paris, France). This research adheres to the principles of the Declaration of Helsinki. All participants gave their written informed consent.

For the present analyses, we excluded 214 participants who were diagnosed as demented at baseline based on a three-step diagnostic procedure including neuropsychological testing, examination by a neurologist, and final validation and classification by an expert committee. We further excluded 1,124 participants with missing data for any covariate at baseline and 823 others who had no cognitive assessment at follow-up. Thus, the study sample was composed of 7,133 individuals with at least one neuropsychological reexamination on each of the three following neuropsychological tests over 10 years.

Cognitive Assessment

At baseline, the same standardized clinical protocol was used to assess cognitive function in the three study centers. Neuropsychological examination carried out by trained investigators included the Mini Mental Status Examination (MMSE) for global cognitive functioning (15), the Isaacs Set Test (IST) for verbal fluency (total number of items produced within 15 seconds in each of the four categories) (16) and the Benton Visual Retention Test (BVRT; multichoice format [forms F and G]) for visual working memory (17). These three cognitive tests were the only tests available at each follow-up and administered uniformly in all study centers.

Antithrombotic Exposure

A comprehensive inventory of all drugs used during the preceding month was performed at baseline by trained interviewers during a standardized face-to-face interview. Medical prescriptions and medications themselves were checked. Drug names were coded using the Anatomical Therapeutic Chemical (ATC) classification system (18). In this study, we considered either all antithrombotic agents (ATC code B01A), VKA only (ATC code B01AA), or PAI only (ATC code B01AC).

Covariates

History of cardiovascular disease (self-reported heart arrhythmias, stroke, angina pectoris, myocardial infarction, lower-limb arteritis, cardiovascular, and arterial surgery) was established according to standardized questions during the face-to-face interview. In addition, 6,343 participants (88.9%) accepted to have electrocardiography at baseline: this examination was used to confirm a diagnosis of atrial fibrillation. These cardiovascular diseases were used as adjustment variables and were considered for the estimation of the propensity scores, as detailed in the statistical methods.

Other covariates included age, gender, education, marital status, body mass index computed as weight (kilogram) divided by the square of height (meter), smoking (in pack-years), high blood cholesterol (≥7.25 mmol/L or treated by lipid-lowering drug), high blood pressure (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg), fasting glycemia (normal, elevated between ≥6.1 and <7 mmol/L, diabetes if ≥7 mmol/L or under antidiabetic treatment), high depressive symptoms according to the Center-for-Epidemiologic Studies Depression Scale (19) (>16 for men and >22 for women), *APOE* genotype (at least one epsilon 4 allele, *APOE4*), and daily consumption of fruits and vegetables; vegetables being the primary dietary sources of vitamin K.

Statistical Analyses

Participants included in the study sample were compared to those excluded because of missing data at baseline or follow-up. Participants were classified according to their consumption of any antithrombotic agent, VKA or PAI, and compared for their baseline characteristics and cognitive performances. Three separate mixed linear models were used to estimate the association of type of antithrombotic treatment at baseline (VKA and PAI as explanatory variables in the same model) with cognitive scores at baseline and over time on each of the three neuropsychological tests as dependent variables, respectively. For MMSE (score range 0–30), the square

root of number of errors calculated as $(30\text{-MMSE})^{1/2}$ was used instead of the total score for reasons of normality (20) thus that variable decreased with better cognitive performance. For IST and BVRT, the total score was used as independent variable; it increased with increasing cognitive performance.

Time was centered at zero to have the fixed effect of the exposure (VKA or PAI) be interpreted as its effect on cognitive performance at baseline. Annual rate of cognitive decline was estimated and the interaction between exposure and time was interpreted as the effect of that exposure on the annual rate of change. The β coefficient of treatment with VKAs or PAIs represents their respective association with baseline mean cognitive scores, whereas the β coefficient for the treatment × time terms represents their association with cognitive change.

In addition to the two main explanatory variables (taking VKA or PAI at baseline), these models were adjusted for potential confounding factors measured at baseline, including age, gender, education, study center (model 1), and additionally vascular diseases grouped in five categories (cardiac arrhythmia, including atrial fibrillation, coronary heart disease, previous cardiac surgery other than for coronary heart disease, arteritis of the lower limb, previous stroke), marital status, high depressive symptoms, *APOE4*, body mass index, smoking, hypercholesterolemia, high blood pressure, glycemia (in three classes), fruit and vegetable intake (model 2), the interaction of each covariate with time, and a correction term for practice effect induced by repetition of a test (binary variable coded 1 for the first cognitive examination at baseline vs zero else, ie, at each follow-up) (21). Conditions for using linear models were verified.

In sensitivity analyses, we first replicated our analyses (i) on a subsample of participants without history of stroke at baseline and (ii) by adjusting for antidementia drugs (ie, memantine and anticholinesterases) and (iii) by focusing on the recall items of the MMSE, due to the low metrological properties of this test. Second, we estimated propensity scores to adjust for potential indication biases (22,23). To estimate the respective conditional probability of receiving VKAs or PAIs, two propensity scores were constructed using logistic regression with the following baseline characteristics as explanatory variables: vascular diseases (same as above), age, gender, education, smoking, hypercholesterolemia, and glycemia levels. Mixed linear models on each cognitive outcome were adjusted for these two propensity scores used as continuous variables, in addition to all previous covariates.

Results

Participants in the study sample (n = 7,133) included fewer men, were younger, more educated, more often married or smokers, had a lower burden of cardiovascular disease and depressive symptoms, and took fewer antithrombotic agents, including VKAs and PAIs, than those excluded at baseline because of missing data (n = 1,124; Supplementary e-Table 1). Median duration of follow-up was 6.94 years, interquartile range was 3.96–8.88. Participants excluded at follow-up for lack of cognitive assessment (n = 823) were slightly older, less educated, more depressed, more likely to smoke, to suffer from diabetes, and to eat fewer fruits and vegetables than the 7,133 participants (Supplementary e-Table 1). They also had more vascular diseases but did not differ significantly for gender, marital status, *APOE4*, body mass index, hypercholesterolemia, high blood pressure, and use of any antithrombotic drug.

At baseline, 1,436 participants (20.1%) were treated with antithrombotic drugs, including 239 (3.4%) with VKAs and 1,192 (16.7%) with PAIs (three individuals took both medications), whereas eight took another antithrombotic treatment (ATC code B01AB heparin group). Among individuals treated with VKAs at baseline, 88.3% were still reporting treatment with VKA on at least one follow-up. This proportion was 88.7% among those treated with PAIs. Those treated with antithrombotic agents were older, more educated, had higher body mass index, more depressive symptoms, and included a higher proportion of men and *APOE4* carriers than nontreated individuals (Table 1). As expected, they were more likely to report cardiovascular diseases as well as cardiovascular risk factors (Table 2). Of note, about two thirds of VKA-treated participants and 27.5% of those treated with PAI had heart arrhythmia. These cardiac arrhythmias included 141 cases of atrial fibrillation diagnosed by electrocardiography in the 6,343 participants who underwent this examination at baseline: 24.3% of the participants taking VKA, 3.4% of those receiving PAI, and only 1.1% of those without any antithrombotic treatment had atrial fibrillation on the electrocardiography.

In unadjusted cross-sectional analyses at baseline, participants taking VKAs or PAIs scored significantly lower on each of the three cognitive tests (Table 2). When not considering major confounders (Model 1), cognitive performances are associated with both VKA and PAI use. In contrast, in fully adjusted mixed models, only treatment with VKA remained significantly associated with worse performances on the BVRT (adjusted mean difference –0.29 [*SE* 0.12]) and IST (adjusted mean difference –1.37 [*SE* 0.41]) at baseline (Table 3, model 2). There was no significant association between VKA intake at baseline and cognitive decline over 10 years on any of the three cognitive tests, as shown by the nonsignificant interaction terms with time. Treatment with PAIs was not more associated with cognitive performance at baseline or cognitive decline in these multivariate models.

In sensitivity analyses, the exclusion of participants with history of stroke did not change the previously observed associations (Supplementary e-Table 3), nor did adjustment for antidementia drugs or the restriction to the recall items of the MMSE (data not shown). Moreover, multivariate models adjusted for propensity scores in addition to the same covariates as in the models presented above yielded very similar results, with virtually unchanged β coefficients (Supplementary e-Table 2). Treatment with VKAs remained significantly associated with lower score on BVRT and IST at baseline.

Discussion

In cross-sectional analyses at baseline, older adults treated with VKAs, but not those treated with PAIs, had significantly, although clinically modest, lower performance in visual working memory and verbal fluency compared to individuals receiving neither antithrombotic treatment. However, there was no association between antithrombotic treatment (VKAs or PAIs) and subsequent cognitive decline over 10 years, as shown by nonsignificant interactions between treatment and time, meaning that slopes of decline were parallel whatever treatment status at baseline. To our knowledge, the present study is the first to specifically examine associations between VKA therapy and cognitive performance over time in a large population-based sample.

Four small studies have examined the impact of VKAs on cognition, providing inconsistent results. In 1997, Richards and coworkers explored the possible protective effect of antithrombotic agents (low-dose aspirin and/or warfarin) on cognitive function in an ancillary study of a randomized placebo-controlled factorial trial in men (10). Although any active treatment for at least five years

Table 1. Characteristics of the Participants at Baseline According to Antithrombotic Drug Use. The Three-City Study, *N* = 7,133 (1999–2000)

	No Antithrombotic Drug (*n* = 5,697)		Any Antithrombotic Drug (*n* = 1,436)			Vitamin K Antagonists (*n* = 239)			Platelet Aggregation Inhibitors (*n* = 1,192)		
	n	%	*n*	%	*p* Value*	*n*	%	*p* Value*	*n*	%	*p* Value*
Age (y)†	5,697	73.3 (5.1)	1,436	75.3 (5.3)	<.0001†	239	75.3 (4.8)	<.0001†	1,192	75.3 (5.4)	<.0001†
Men	1,957	34.4	777	54.1	<.0001	129	54.0	<.0001	647	54.3	<.0001
Education					.007			.76			.003
No or primary	1,347	23.6	368	25.6		61	25.5		305	25.6	
Secondary, short	2,123	37.3	481	33.5		81	33.9		399	33.5	
Secondary, long	1,176	20.6	278	19.4		51	21.3		225	18.9	
University	1,051	18.5	309	21.5		46	19.3		263	22.1	
Marital status					.004			.18			.01
Married	3,386	59.4	910	63.4		148	61.9		759	63.7	
Divorced	439	7.7	82	5.7		16	6.7		66	5.5	
Widowed	1,458	25.6	362	25.2		66	27.6		294	24.7	
Single	414	7.3	82	5.7		9	3.8		73	6.1	
High depressive symptoms	693	12.2	213	14.8	.007	43	18.0	.007	169	14.2	.06
APOE4, at least one	1,102	19.3	323	22.5	.008	65	27.2	.003	257	21.6	.08
BMI (kg/m^2)†	5,697	25.6 (4.0)	1,436	26.1 (3.9)	<.0001	239	26.6 (4.2)	<.0001	1,192	25.9 (3.9)	.003
Daily consumption of fruits and vegetables	4,664	81.9	1,150	81.1	.12	191	79.9	.44	955	80.1	.16
Smoking (pack-years)					<.0001			.01			<.0001
Never smoker	3,668	64.4	753	52.4		134	56.1		616	51.7	
(0–10)	789	13.8	200	13.9		34	14.2		163	13.7	
(10–20)	395	6.9	141	9.8		18	7.5		123	10.3	
(20–30)	334	5.9	133	9.3		25	10.5		108	9.0	
≥30	511	9.0	209	14.6		28	11.7		182	15.3	
High blood pressure	3,485	61.2	928	64.6	.02	153	64.0	.38	771	64.7	.02
Hypercholesterolemia	1,957	34.4	704	49.0	<.0001	109	45.6	.0003	596	50.0	<.0001
Glycemia					<.0001			.06			<.0001
Normal (<6.1 mmol/L)	5,049	88.6	1,198	83.4		200	83.7		994	83.4	
High (6.1 ≤ glycemia ≤ 7 mmol/L)	193	3.4	58	4.1		13	5.4		45	3.8	
Diabetes (>7 mmol/L or treated)	455	8.0	180	12.5		26	10.9		153	12.8	

Note: BMI = body mass index.

*Comparison with the group taking no antithrombotic drug, Student's *t* tests for continuous variables and chi-square tests for class variables.

†Results are mean (*SD*).

Table 2. Cognitive Performance and Vascular Diagnoses of the Participants at Baseline According to Treatment With Vitamin K Antagonists or Platelet Aggregation Inhibitors. The Three-City Study, *N* = 7,133 (1999–2000)

	No Antithrombotic Drug (*n* = 5,697)		Vitamin K Antagonists (*n* = 239)			Platelet Aggregation Inhibitors (*n* = 1,192)		
	N	%	*n*	%	*p* Value*	*n*	%	*p* Value*
Cardiac arrhythmia	668	11.7	151	63.2	<.0001	328	27.5	<.0001
Coronary heart disease	286	5.0	75	31.4	<.0001	417	35.0	<.0001
Past cardiac surgery	15	0.3	38	15.9	<.0001	20	1.7	<.0001
Arteritis of the lower limb	114	2.0	14	5.9	<.0001	137	11.5	<.0001
Past stroke	79	1.4	33	13.8	<.0001	157	13.2	<.0001
MMSE score†	5,697	27.5 (1.9)	239	27.2 (2.0)	.04	1,192	27.3 (1.8)	.0002
BVRT score†	5,697	11.6 (2.0)	239	11.2 (2.2)	.002	1,192	11.4 (2.1)	.002
IST score†	5,697	32.4 (6.8)	239	29.8 (6.1)	<.0001	1,192	31.4 (6.8)	<.0001

Note: BVRT = Benton Visual Retention Test; IST = Isaacs Set Test; MMSE = Mini Mental State Examination.
*Comparison with the group taking no antithrombotic drug, Student's t tests for continuous variables and chi-square tests for class variables.
†Results are mean (SD).

was associated with better cognitive performance compared to placebo, several scores tended to be poorer among those taking warfarin compared to those taking aspirin or placebo (10). However, these data are from a subgroup analysis within a trial not designed for this purpose with no measure of cognitive performance at baseline. The second study reported a borderline significant inverse association between warfarin treatment and the presence of dementia 3 years later, suggesting a potential protective effect of VKA treatment (12). Recently, some coauthors of our group have reported a higher frequency of treatment with VKAs in older geriatric patients with cognitive impairment (MMSE < 25) (11). Finally, a randomized controlled trial compared the effect of warfarin and aspirin for prevention of cognitive decline over 33 months in older patients with atrial fibrillation (24). No significant difference was found between the two antithrombotic agents for both cognitive performance and decline, as measured by the MMSE.

One interpretation of our findings could be that participants who were given VKAs had modestly poorer cognitive performance because of their higher burden of cardiovascular diseases, especially cardiac arrhythmia, which cannot be totally controlled for by multivariate adjustments. However, patients treated with PAIs did not have poorer cognitive performance at baseline when adjusting for their similar cardiovascular morbidity. Moreover, in spite of poorer cognitive performance at baseline, treatment with VKAs was not associated with accelerated subsequent cognitive decline because their slope of decline was parallel to that of participants not taking any antithrombotic drug (no significant interaction with time). Indeed, in light of their suppressive effects on the coagulation cascade, VKAs could theoretically be protective for cognition over the long term by lowering the risk of thrombosis associated with atrial fibrillation, which is a risk factor for cognitive decline (25).

Another interpretation of our findings showing modestly poorer cognitive performance at baseline with VKA treatment could lie in a detrimental impact of VKA on cognition by interfering with vitamin K-dependent proteins not involved in hemostasis. Mechanistically, VKA interferes with the vitamin K cycle decreasing the availability of the active form of vitamin K (hydroquinone) in the body. This results in the decreased activation of the vitamin K-dependent clotting factors (anticoagulation) and of all vitamin K-dependent proteins. In the brain, two vitamin K-dependent proteins are targeted, namely, Gas6 (growth arrest–specific gene 6) and protein S (1). Gas6 is a regulator of cell survival, cell growth, and myelination processes, whereas protein S is known for its neuroprotective effects during hypoxic and/or ischemic injury. Whether warfarin treatment alters the activation of these two vitamin K-dependent proteins in brain has not yet been investigated in humans. However, in rodent studies, warfarin treatment has been shown to decrease brain vitamin K levels (4,8), alter sphingolipid profile (8,9), and be detrimental to spatial learning performances (8). Diminished levels of active vitamin K in the brain could also interfere with the neuroprotective properties of vitamin K observed in primary cultures of oligodendrocytes, neurons, and neuroblastoma cells subjected to oxidative injury (26–28).

The anticoagulant effect of warfarin occurs within 24 hours and gradually decreases over the next few days. As a result, VKAs have to be taken on a daily basis to sustain a stable anticoagulant effect over time. Whether VKAs operate in a similar manner in the brain, reducing vitamin K status and cognitive performance at the onset of treatment without impacting cognition over time, remains to be determined. Our data also suggest that vitamin K may target specific cognitive functions over global cognition because no associations were found between VKAs and cognitive functioning as assessed by the MMSE. This is in line with our recent cross-sectional study in 320 healthy older adults where higher serum vitamin K concentrations were associated with better verbal episodic memory, while being unrelated to nonverbal episodic memory, executive functions, and speed of processing (7). Given that verbal episodic memory strongly depends on the hippocampus, we hypothesized that vitamin K is especially important for this brain region where one ligand of Gas6, Tyro3, is highly expressed (29). In the present report, we found an association with both verbal fluency and visual working memory, two cognitive functions involving the hippocampus (30,31). Our findings are thus consistent with this hypothesis, providing support for the emerging role of vitamin K in brain and revealing a possible side effect of VKAs on cognition. However, the effect of VKAs on cognitive performance was relatively small, and VKAs were not associated with cognitive decline.

Strengths of the present study include the large population-based cohort, the longitudinal cognitive assessment over 10 years, the adjustment for many potential confounding variables including vascular risk factors and indication biases, and the concomitant analysis of the effect of PAIs. Moreover, present results are robust while performing several sensitivity analyses as excluding participants with baseline history of stroke or performing additional adjustment for antidementia drugs. As the length of follow-up was slightly lower among participants with

Table 3. Multivariate Mixed Linear Models of the Association Between Treatment With Vitamin K Antagonists or Platelet Aggregation Inhibitors With Each Cognitive Test Score

	MMSE				BVRT				IST			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	β (*SE*)	*p* Value	β (*SE*)	*p* Value	β (*SE*)	*p* Value	β (*SE*)	*p* Value	β (*SE*)	*p* Value	β (*SE*)	*p* Value
VKA	0.08 (0.04)	.026	0.03 (0.04)	.41	−0.369 (0.111)	.0009	−0.29 (0.12)	.02	−1.875 (0.382)	<.0001	−1.37 (0.41)	.0009
VKA × time	0.001 (0.007)	.93	0.003 (0.008)	.73	0.011 (0.022)	.60	0.015 (0.024)	.53	−0.009 (0.059)	.88	−0.010 (0.063)	.87
PAI	0.046 (0.019)	.014	0.02 (0.02)	.39	−0.123 (0.054)	.022	−0.04 (0.06)	.53	−0.424 (0.187)	.023	−0.09 (0.21)	.65
PAI × time	0.0002 (0.0035)	.95	0.0008 (0.0039)	.83	−0.014 (0.010)	.15	−0.017 (0.011)	.13	−0.041 (0.027)	.13	−0.040 (0.030)	.18

Note: BVRT = Benton Visual Retention Test; IST = Isaacs Set Test; MMSE = Mini Mental State Examination (square root of the number of errors); PAI = platelet aggregation inhibitor; *SE* = standard error; VKA = vitamin K antagonist. The Three-City study, *N* = 7,133 at baseline (1999–2000) with at least one cognitive follow-up over 10 years.

Model 1 on each cognitive score was adjusted for age, sex, education, study center, their interactions with time, and learning effect.

Model 2 on each cognitive score was adjusted for age, sex, education, study center, marital status, vascular diseases (in five categories), depressive symptoms, *APOE4*, BMI, smoking, hypercholesterolemia, high blood pressure, glycemia (in three classes), fruit and vegetable intake, their interactions with time, and learning effect.

VKAs or PAIs who suffered from a poorer health status at baseline, we can speculate that our results may be underestimated. Among limitations, dietary vitamin K intakes and serum vitamin K levels were not available for the study participants, although mixed models were adjusted for the consumption of vegetables, the primary dietary source of vitamin K. Also, data did not include detailed information on VKA treatments such as doses, exposure prior the entry into the cohort, and values of international normalized ratio. However, medication data from the study follow-ups indicated that most VKA-treated participants underwent long-term anticoagulation therapy. Therefore, VKA status at baseline seems a fair assumption of VKA status over time. Regarding outcomes, the limited number of cognitive tests available at each follow-up prevented us to investigate more in depth specific cognitive domains. Moreover, results of the present study should be interpreted with caution, as the clinical impact of the low mean difference on cognitive tasks observed at baseline among older adults treated with VKAs may be modest. This is particularly true for IST scores because almost half of the participants with low educational level had lower performances than normative data. Finally, we cannot dismiss potential residual confounding and reverse causality for the cross-sectional association at baseline.

In the present report, treatment with VKAs was associated with modestly poorer performance in visual working memory and verbal fluency at baseline, but not with global cognitive functioning and subsequent cognitive decline. Clearly, the potential role of vitamin K in brain warrants further investigation as does the risk–benefit balance of VKA treatment. These findings need replication in prospective cohorts of older patients treated with various antithrombotic agents.

Supplementary Material

Please visit the article online at http://gerontologist.oxfordjournals.org/ to view supplementary material.

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Conflict of Interest

N. Presse, S. Lorrain, F. Bazin, C. Helmer, C. Berr, C. Annweiler, and G. Ferland report no conflict of interest. P. Barberger-Gateau reports grants and nonfinancial support from Danone Research and Vifor Pharma, personal fees and nonfinancial support from Nutricia and Pileje, grants and nonfinancial support from Groupe Lipides et Nutrition, and nonfinancial support from ILSI Europe. C. Féart reports fees for conferences from Danone Research and Nutricia. O. Rouaud reports board participation for Novartis. J.-F. Dartigues reports grants research from IPSEN and Novartis and honorarium for board participation from Novartis and Newron. A. Fourrier-Réglat has participated as coinvestigator in clinical studies for Janssen-Cilag, Pfizer, Merck-Serono, and Novartis.

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