Brief Report

Vitamin K Antagonists and Cognitive Impairment: Results From a Cross-Sectional Pilot Study Among Geriatric Patients

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Background. Vitamin K is involved in brain physiology, suggesting that its deficiency induces cognitive decline. Our objective was to determine whether using vitamin K antagonists (VKAs) was associated with cognitive impairment among geriatric patients.

Methods. Two hundred sixty-seven older patients (mean, 83.4 ± 8.1 years; 56.9% female) were categorized according to cognitive impairment (ie, Mini-Mental State Examination ≤ 25). The regular use of VKAs was sought by questioning the patients, relatives, and family physicians. Age, gender, body mass index, comorbidity burden, mood and executive functioning, history of atrial fibrillation, ischemic stroke, intracranial hemorrhage and transient ischemic attack, use of other anticoagulants and antiplatelet medications, and severe renal failure were used as potential confounders.

Results. Compared with participants without cognitive impairment (n = 70), those with Mini-Mental State Examination ≤ 25 used more frequently VKAs (p = .038). The risk of cognitive impairment was 15% higher with VKAs, specifically with fluindione. Using VKAs was independently associated with cognitive impairment (fully adjusted odds ratio = 17.4 [95% CI: 1.4–224.2], p = .028).

Conclusions. We found more frequent cognitive impairment associated with the use of VKAs, specifically fluindione, among geriatric patients.

Key Words: Vitamin K—Vitamin K antagonists—Cognition—Dementia—Neurobiology—Older adults.

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Vitamin K antagonists (VKAs) are the most commonly used drugs for the prophylaxis and treatment of thromboembolic events (1), especially in elderly populations (2). The VKAs are not strictly pharmacological antagonists of vitamin K, but inhibitors of the enzymatic conversion of inactive vitamin K epoxide to its reduced active form, thus resulting in a relative state of vitamin K deficiency (1). Importantly, vitamin K has demonstrated, apart from its classical role in blood coagulation, actions in the central nervous system (CNS) (3–8). Vitamin K is involved in the regulation of sphingolipids synthesis—a major constituent of the myelin sheath and neuronal membranes (3,4)—and biological activation of vitamin K-dependent proteins implicated in neuron physiology and survival (3,4). The plausibility of an involvement of vitamin K in human brain functioning has been strengthened by the finding of CNS abnormalities in newborns exposed in utero to VKAs (5), and by the finding of an association between increased serum phylloquinone concentrations and better episodic memory performance in older adults (8). Based on these findings, and because VKAs deplete the active form of vitamin K (1), we hypothesized that the use of VKAs may result in cognitive impairment. The objective of this cross-sectional pilot study was to determine whether the use of VKAs was associated with cognitive impairment among geriatric patients.
Methods

Participants

We studied all patients ≥65 years hospitalized or seen in consultation in the Division of Geriatric Medicine of Angers University Hospital, France, who were consecutively recruited in the WARHOL study (Who is At Risk of Hypovitaminosis in Older individuals) study from March 2, 2013 to May 16, 2013. The WARHOL study is an observational, cross-sectional study designed to examine lipophilic vitamins and cognition in older in- and outpatients. The sampling and data collection procedures have been described elsewhere in detail (9). Exclusion criteria for our analysis were age <75 years, and delirium at the time of assessment diagnosed with the Confusion Assessment Method (10). All participants received a full medical examination consisting of structured questionnaires, a standardized clinical examination and a blood test, after having given their informed consent or the agreement of the trusted person, as appropriate. The entire study protocol was approved by Angers Ethical Committee.

Use of Vitamin K Antagonists

The regular use of VKAs was systematically noted from the primary care physicians’ prescriptions and sought by questioning the patients and their relatives. The type of VKA used (ie, warfarin, acenocoumarol, or fluindione) was specified, whatever the indication, length of treatment, and history of international normalized ratio.

Cognitive Impairment

Cognitive performance, as a whole, was assessed with Folstein’s Mini-Mental State Examination (MMSE), which shows good test–retest and interrater reliability (11). Consistent with the literature, cognitive impairment was defined as MMSE score ≤ 25 (12).

Covariables

The following covariables were included as potential confounders: age, gender, body mass index, comorbidity burden, depressed mood and executive functioning, history of atrial fibrillation, ischemic stroke, intracranial hemorrhage and transient ischemic attack, use of anticoagulants other than VKAs and use of antiplatelet medications, and severe renal failure.

Comorbidity burden was estimated with the Cumulative Illness Rating Scale-Geriatrics score (range 0–60, worst) (13). Depressive symptoms were investigated using the four-item Geriatric Depression Scale with a score ranging between 0 and 4 (worst) (14). The efficiency of executive functioning was evaluated using the Frontal Assessment Battery score (range 0–18, best) (15). History of continuous or paroxysmal atrial fibrillation was sought from the family physician correspondence and the patient’s file, by questioning the patient or relatives, and with systematic electrocardiograms. History of stroke and transient ischemic attack was also sought by questioning the patients and the family physicians, and reviewing the patients’ files. Stroke was defined according to the World Health Organization criteria as rapidly developed signs of focal or global disturbance of cerebral function lasting longer than 24 hours, with no apparent nonvascular cause (16). In case of clinical suspicion, computed tomography or magnetic resonance imaging scan was necessary to confirm the diagnosis and to distinguish among ischemic stroke and intracranial hemorrhage. The diagnosis of transient ischemic attack was retained if symptoms lasted ≤1 hour. In addition, the use of anticoagulants other than VKAs (ie, heparin, enoxiparin, tinzaparin, nadroparin, dalteparin, fondaparinux, danaparoid, enoxaparin, and direct oral anticoagulants) and antiplatelet medications (ie, aspirin, clopidogrel, ticlopidin, and dipyridamole) was systematically noted from the primary care physician’s prescription and sought by questioning the patient and relatives. Finally, severe renal failure was defined as estimated glomerular filtration rate <30 mL/min, according to Cockcroft–Gault formula.

Statistical Analysis

The participants’ characteristics were summarized using mean ± SD or proportion ± SD, as appropriate. Firstly, comparisons between participants separated into two groups based on cognitive impairment (ie, MMSE score ≤25 or >25) were performed using t test or chi-square test, as appropriate. Secondly, the risk difference (ie, absolute risk reduction) of cognitive impairment was calculated for participants with blood-thinning drugs compared with those without, using the following formula: \( \text{RD} = \frac{a}{n_1} - \frac{b}{n_2} \), where \( a \) is the number of participants with the event (ie, cognitive impairment) in the group using blood-thinning drugs, \( n_1 \) the total number of participants using blood-thinning drugs, \( b \) the number of participants with the event in the group without blood-thinning drugs, and \( n_2 \) the total number of participants without blood-thinning drugs (17).

Thirdly, logistic regressions were used to examine the association between the use of VKAs (independent variable) and cognitive impairment (dependent variable). \( p \) values < .05 were considered significant. All statistics were performed using SPSS (v19.0, IBMcorp, Chicago, IL) and RevMan (v5.1, Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Two hundred sixty-seven participants were included in this analysis (mean, 83.4 ± 8.1 years; 56.9% female). The mean MMSE score was 19.8 ± 6.8. As illustrated in Table 1, 133 participants (49.8%) were regularly using blood-thinning drugs, including 44 (16.5%) using VKAs. No participant was using direct oral anticoagulants. Among 197 participants with cognitive impairment, the use of blood-thinning drugs was more frequently retrieved than among 70 participants without cognitive impairment (53.8% vs
Our results show that the use of VKA, irrespective of all studied covariables, was positively associated with cognitive impairment among geriatric patients.

This finding is in line with previous reports that fetal exposure to warfarin derivatives during the first trimester of pregnancy results in mental retardation (5). Case-control studies in adults are also consistent and have reported that the dietary intakes (6) and serum concentrations (8) of phylloquinone (ie, vitamin K1) were lower among AD cases compared with cognitively healthy controls. Recently, a cross-sectional study has showed that increased serum phylloquinone concentrations were associated with better episodic memory performance among older community-dwellers (8). Compared with the last two studies, no information on serum phylloquinone concentrations was available here, but our results consistently report that the use of VKAs, a drug class that generates a relative state of vitamin K deficiency (1), was associated with greater prevalence of cognitive disorders. Specifically, we found that the use of fluindione, but not that of warfarin and

### Table 1. Characteristics and Comparison of Participants Separated into Two Groups Based on Cognitive Impairment* (n = 267)

<table>
<thead>
<tr>
<th>Characteristics and Comparison of Participants Separated into Two Groups Based on Cognitive Impairment* (n = 267)</th>
<th>Total Cohort (n = 267)</th>
<th>Yes (n = 197)</th>
<th>No (n = 70)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographical measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD, years)</td>
<td>83.37±8.09</td>
<td>85.10±7.44</td>
<td>78.49±7.90</td>
<td>&lt;.001</td>
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<tr>
<td>Female gender</td>
<td>56.9±5.9</td>
<td>57.9±6.9</td>
<td>54.3±11.7</td>
<td>.603</td>
</tr>
<tr>
<td>Body mass index (mean ± SD, kg/m²)</td>
<td>25.28±4.61</td>
<td>25.16±4.71</td>
<td>25.61±4.33</td>
<td>.485</td>
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<tr>
<td>Clinical measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIRS-G score (mean ± SD, /60)</td>
<td>8.40±3.97</td>
<td>8.73±3.87</td>
<td>7.49±4.13</td>
<td>.024</td>
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<tr>
<td>Atrial fibrillation</td>
<td>21.7±4.9</td>
<td>25.6±6.1</td>
<td>11.4±7.5</td>
<td>.014</td>
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<tr>
<td>Ischemic stroke</td>
<td>18.4±4.7</td>
<td>22.1±5.8</td>
<td>8.6±6.6</td>
<td>.013</td>
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<td>Intracranial hemorrhage</td>
<td>1.5±1.5</td>
<td>2.1±2.0</td>
<td>0</td>
<td>.227</td>
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<td>Transient ischemic attack</td>
<td>6.0±2.9</td>
<td>5.6±5.2</td>
<td>7.1±6.0</td>
<td>.651</td>
</tr>
<tr>
<td>GDS score (mean ± SD, /4)</td>
<td>1.26±1.47</td>
<td>1.50±1.56</td>
<td>0.6±0.91</td>
<td>&lt;.001</td>
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<td>FAB score (mean ± SD, /18)</td>
<td>12.7±3.10</td>
<td>11.38±2.87</td>
<td>14.67±2.32</td>
<td>&lt;.001</td>
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<tr>
<td>Biological measures</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe renal failure</td>
<td>11.2±3.8</td>
<td>12.2±4.6</td>
<td>9.0±6.7</td>
<td>.472</td>
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<td>Use of blood-thinning drugs</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>49.8±6.0</td>
<td>53.8±7.0</td>
<td>38.6±11.4</td>
<td>.029</td>
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<tr>
<td>Vitamin K antagonists</td>
<td>16.5±4.5</td>
<td>19.3±5.5</td>
<td>8.6±6.6</td>
<td>.038</td>
</tr>
<tr>
<td>Other anticoagulants</td>
<td>3.0±2.1</td>
<td>3.0±2.4</td>
<td>2.9±3.9</td>
<td>.937</td>
</tr>
<tr>
<td>Antiplalet agents</td>
<td>33.7±5.7</td>
<td>35.0±6.7</td>
<td>30.0±10.7</td>
<td>.445</td>
</tr>
</tbody>
</table>

Notes: Data presented as proportion ± SD when applicable. CIRS-G = Cumulative Illness Rating Scale for Geriatrics; FAB = Frontal Assessment Battery; GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Examination.

*MMSE ≤ 25/30, in the absence of delirium; p values < .05 indicated in bold.

### Discussion

Our results show that the use of VKA, irrespective of all studied covariables, was positively associated with cognitive impairment among geriatric patients.

This finding is in line with previous reports that fetal exposure to warfarin derivatives during the first trimester of pregnancy results in mental retardation (5). Case-control studies in adults are also consistent and have reported that the dietary intakes (6) and serum concentrations (8) of phylloquinone (ie, vitamin K1) were lower among AD cases compared with cognitively healthy controls. Recently, a cross-sectional study has showed that increased serum phylloquinone concentrations were associated with better episodic memory performance among older community-dwellers (8). Compared with the last two studies, no information on serum phylloquinone concentrations was available here, but our results consistently report that the use of VKAs, a drug class that generates a relative state of vitamin K deficiency (1), was associated with greater prevalence of cognitive disorders. Specifically, we found that the use of fluindione, but not that of warfarin and

### Figure 1

Forest plot for the crude risk difference of cognitive impairment according to the use of blood-thinning drugs. Horizontal lines correspond to the 95% CI. The vertical line corresponds to a risk difference of 0.00, equivalent to no between-group difference. BT drugs = blood-thinning drugs.
acenocoumarol, was associated with cognitive impairment. Two main explanations may be offered for this drug-specific association. Firstly, a drug-specific effect was likely. Fluindione is an indandione derivative, whereas both warfarin and acenocoumarol are coumarin derivatives (1). Previous studies have suggested that indanedione VKAs may cause unpredictable and sometimes severe immunological adverse effects (18). Secondly, since fluindione is the most prescribed VKA in France (2), it is also possible that the absence of association between coumarinic VKAs and cognitive impairment was the result of the small size of the treated sample that may have exposed to lack of statistical power with the risk of missing significant differences.

The mechanism linking the use of VKAs with cognitive impairment is not firmly established. Of course, the association could be explained by the fact that using blood-thinning drugs like VKAs implies underlying conditions, such as atrial fibrillation or ischemic strokes, which result themselves in greater risks of cognitive impairment (1,2). However, this first assumption should be balanced by the fact that the association between VKAs and cognitive impairment was still significant after adjustment for these conditions, and also after adjustment for the use of other blood-thinning drugs, which were in turn not associated to cognition. This may indicate a VKA-specific effect on cognition, independent of the underlying conditions and anticoagulant effect.

Basic research precisely supports a role of vitamin K in the CNS. Vitamin K is present, mostly as menaquinone-4, in the brain (4). Vitamin K modulates the synthesis and metabolism of sphingolipids (5), which are key players in neuronal proliferation, differentiation, senescence, cell–cell interaction, and transformation (3,4). Recent research has linked alterations in sphingolipid metabolism to the aging process and neurodegenerative disorders such as Alzheimer’s disease (AD) (4). In parallel, two vitamin K-dependent proteins, Gas6 (growth arrest-specific gene 6) and protein S, are also closely associated with the CNS (3,4). Gas6 is involved in chemotaxis, mitogenesis, cell growth, and myelination, and has further been shown to rescue cortical neurons from amyloid β-induced apoptosis, a hallmark of AD (4). Protein S offers neuronal protection during ischemic/hypoxic injury, both in vivo and in vitro (4). It may also protect neurons from N-methyl-D-aspartate–induced toxicity and apoptosis (4). This suggests that the less available the vitamin K is—due to VKAs for example—the less protected and effective the CNS is, with subsequent greater risks of brain changes and cognitive decline.

The strengths of our study include the originality of the research question on a drug used in clinical routine, the standardized collection of data from a single research center, and the detailed description of the participants’ characteristics allowing the use of regression models to measure adjusted associations. Regardless, a number of limitations should be acknowledged. Firstly, the study cohort was restricted to a relatively small number of geriatric patients, which leads to large standard error and confidence interval for the odds ratio, and likely made our sample unrepresentative of the population of all seniors. Secondly, the generalizability of our findings was limited by the fact that fluindione is not currently approved by the US Food and Drug Administration. Thirdly, cognitive impairment was defined here using only the MMSE score, which is a widely used cognitive screening instrument for detecting dementia, but lacks sensitivity to early signs of dementia, possibly resulting in false-negative diagnosis (12). Fourthly, the association we found between cognitive impairment and the use of VKAs accounted neither
for the length of VKA treatment, nor for the history of international normalized ratio. Fifthly, at present, our study is cross-sectional, which limits conclusions regarding causality. Finally, although we were able to control for important characteristics likely to modify the association, it would have been valuable to consider additional characteristics such as serum phylloquinone concentration or education level.

Despite these limitations, we were able to show more frequent cognitive impairments associated with VKAs among geriatric patients, specifically with fluindione. This question is all the more crucial as the use of VKAs is widespread in older adults. Further prospective studies with different senior cohorts are warranted to clarify whether older adults using VKAs are more likely to experience cognitive decline and/or dementia than the others, including in comparison with direct oral anticoagulants whose indications are similar but whose mechanism is independent of vitamin K (19).

ACKNOWLEDGMENTS
C.A. has full access to all of the data in the study, takes responsibility for the data, the analyses, and interpretation and has the right to publish any and all data, separate and apart from the attitudes of the sponsor. All authors meet all of the following criteria: (i) contributing to the conception and design, or analyzing and interpreting data; (ii) drafting the article or revising it critically for important intellectual content; and (iii) approving and design, or analyzing and interpreting data; (iii) approving and final version to be published.

REFERENCES