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ORIGINAL RESEARCH ARTICLE

Use of Vitamin K Antagonist Therapy in Geriatrics: A French National Survey from the French Society of Geriatrics and Gerontology (SFGG)

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Abstract

Objective We aimed to evaluate the quality and determinants of vitamin K antagonists (VKA) control among very elderly patients in geriatric settings.

Methods A national cross-sectional survey was conducted among patients aged ≥80 years who were hospitalized in rehabilitation care or institutionalized in a nursing home and who were treated by VKA. Time in therapeutic range (TTR) was computed according to Rosendaal's method.

Results A total of 2,633 patients were included. Mean [± standard deviation (SD)] age was 87.2 ± 4.4 years and 72.9 % were women. The main indication for VKA therapy was atrial fibrillation (AF; 71.4 %). Mean (±SD) TTR was 57.9 ± 40.4 %. After backward logistic regression, poorer VKA control (TTR <50 vs. ≥50 %) was associated with being hospitalized in rehabilitation care [odds ratio $(OR)_{\text{rehab. vs. nursing home}} = 1.41$; 95 % CI 1.11–1.80], the indication for VKA treatment ($OR_{\text{prosthetic heart valve vs. AF}} = 4.76$; 95 % CI 2.83–8.02), a recent VKA prescription ($OR_{<1 \text{ vs. } >12 \text{ months}} = 1.70$; 95 % CI 1.08–2.67), the type of VKA ($OR_{\text{fluindione vs. warfarin}} = 1.22$; 95 % CI 1.00–1.49), a history of international normalized ratio >4.5 (OR = 1.50; 95 % CI 1.21–1.84), a history of major bleeding (OR = 1.88; 95 % CI 1.00–3.53), antibiotic use (OR = 1.83; 95 % CI 1.24–2.70), and falls ($OR_{\geq 2 \text{ falls during the past year vs. } <2} = 1.26$; 95 % CI 1.01–1.56).

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Conclusion Overall, VKA control remains insufficient in very old patients. Poorer VKA control was associated with taking VKA for a prosthetic heart valve, a recent VKA prescription, the use of other VKAs than warfarin, a history of overcoagulation and major bleeding, antibiotic use, and falls.

1 Introduction

Oral anticoagulation therapy by vitamin K antagonists (VKA) has proven efficacy against thromboembolic disorders such as stroke prevention in atrial fibrillation (AF), venous thromboembolic disease (VTE), or heart valve replacement with mechanical prosthesis [1–3]. These diseases are very common in the elderly, and thus this particular population is more prone to being treated by VKA [4, 5]. However, VKA therapy increases bleeding complications, especially in older patients [6–9]. The effectiveness of VKA is challenged by its variable dose response, narrow therapeutic windows, and the need for frequent monitoring of the international normalized ratio (INR). This is particularly true among elderly patients in whom specific characteristics may influence the safety of anticoagulation therapy, such as impaired renal function, co-morbidities, or the use of multiple medications [10]. The most recognized way to measure therapeutic effectiveness of VKA treatment over time is to measure the proportion of time spent in the therapeutic range (TTR) [11, 12]. TTR has been shown to strongly correlate with the principal clinical outcomes of hemorrhage and thrombosis and, thus, is a reliable measure of high-quality anticoagulation management [11]. Moreover, increased TTR has also been associated with decreased mortality, myocardial infarction, and stroke rates [13–15]. In this way, the latest AF European Guidelines (2012) indicate that stroke prevention with a VKA is effective where the individual mean TTR is $\geq$70 % [16]. However, observational studies reported that older warfarin-treated AF patients spent only half (50 %) of their time in the therapeutic INR range [17–27]. Most of these studies have been performed in patients from community settings [17–20] and few studies have concerned very old and frail populations in a geriatrics setting [21–27]. Our objectives were to evaluate the quality of VKA control in very elderly patients hospitalized in rehabilitation care or institutionalized in nursing homes and to assess the characteristics associated with VKA control. These two questions were addressed using data from a large National French Survey on VKA use conducted by the French Society of Geriatrics and Gerontology (Société Française de Gériatrie et Gérontologie—SFGG).

2 Methods

2.1 Patient Selection

The present study was conducted by the SFGG. A standardized questionnaire was sent by email to the 1,500 SFGG members, covering the entire French mainland and also overseas territories. Practitioners were asked to include every patient aged 80 years and over, hospitalized in a rehabilitation care unit (hospital-based setting for non-acute patients with multiple chronic co-morbidities and requiring specific medical and nursing care) or living in a nursing home (community-based setting for disabled subjects with a stable medical condition otherwise) and who were treated by VKA on 21 June 2011 or who had received VKA treatment during the previous 7 days. The questionnaires were emailed or faxed back to the SFGG office.

In total, 482 geriatricians participated to the survey (participation rate 32 %), representing a total population of 20,170 patients ($n = 4{,}249$ in rehabilitation care units and $n = 15{,}921$ in nursing homes). Thirteen percent (13.4 %) of these patients ($n = 2{,}707$) met the inclusion criteria (VKA use) as defined above.

2.2 Data Collection

For each patient, the following information was collected: age, gender, the type of care structure, characteristics of the VKA treatment (indication for VKA, type of VKA, time since institution of VKA, results and dates of the last two INRs, history of INR >4.5, and history of major bleeding), current co-medications known to interact with VKA [aspirin, clopidogrel, NSAIDs, statins (HMG-CoA reductase inhibitors), antibiotics, antifungal drugs, proton pump inhibitors, selective serotonin reuptake inhibitors (SSRIs), and acetaminophen], and co-morbidities (Charlson's score [28]). Plasma creatinine and bodyweight were also recorded and glomerular filtration rate was assessed using the Cockroft–Gault formula.

2.3 Data Analysis

The quality of VKA control was assessed by the TTR as defined by Rosendaal et al. [12]. This method estimates the ratio of time spent within the target range, assuming that INR values vary linearly over time. In the present study, we used different target ranges according to the indication for VKA. The target range was 2.0–3.0 for AF and VTE/pulmonary embolism (PE), and 3.0–4.5 for prosthetic heart valve [29]. The patients' characteristics and the aspects of VKA treatment were compared according to the type of care structure using Chi-square tests and ANOVA for categorical and continuous variables, respectively. Because

of a skewed distribution, TTR values were divided into four categories: 0, 0–49, 50–99, and 100 %. Differences in patients' characteristics and in aspects of VKA treatment were assessed across the four TTR categories by non-adjusted Chi-square tests or by non-adjusted general linear models as appropriate. The associations between patients' characteristics, VKA treatment, and the quality of VKA control were estimated from logistic models using the median-TTR cutoff (TTR <50 vs. ≥50 %) as the dependant variable. All models were adjusted for age and gender. Other covariates were included in the full model if their p value was <0.10. The final full-adjusted model included the following covariates: age, sex, care setting, indication for VKA, the time since VKA initiation, type of VKA, history of INR >4.5, history of major bleeding, antibiotic use, and falls. All analyses were two-sided and the statistical significance was set at $p < 0.05$. Statistical analyses were performed using SAS® version 9.3 (SAS Institute, Cary, NC, USA).

A total of 2,707 patients were included in the survey. TTR was available for 97.3 % of the population, yielding a sample size of $n = 2{,}633$ patients for the present analysis.

3 Results

3.1 Characteristics of the Patients

The mean [± standard deviation (SD)] age was 87.2 ± 4.4 years, 72.9 % ($n = 1{,}912$) were women, and 74.9 % ($n = 1{,}971$) were in nursing homes. AF (71.4 %) and VTE/PE (22.6 %) represented 94 % of the indications for VKA therapy. As shown in Table 1, 51.5 % ($n = 1{,}356$) of the patients had at least three associated co-morbidities, of which the more frequent were dementia (53.4 %), heart failure (43.9 %), and depression (36.2 %). The mean (±SD) number of co-medications was 8.7 ± 3.2. The more frequently associated drugs were paracetamol (58.1 %), proton pump inhibitors (40.6 %), and SSRIs (32.1 %).

Table 1 Population characteristics

Characteristic	Total population ($n = 2{,}633$)
Age, years [mean (SD)]	87.2 (4.4)
Women [% (no.)]	72.9 (1,912)
Nursing home [% (no.)]	74.9 (1,971)
Number of medications [mean (SD)]	8.7 (3.2)
Associated medications [% (no.)]	
Paracetamol	58.1 (1,526)
Proton pump inhibitors	40.6 (1,061)
Selective serotonin reuptake inhibitors	32.1 (842)
Statins (HMG-CoA reductase inhibitors)	19.4 (508)
Antiplatelet agents	8.8 (232)
Antibiotics	5.8 (152)
Antifungal drugs	2.7 (72)
NSAIDs	1.5 (38)
Associated co-morbidities [% (no.)]	
Charlson's score ≥3	51.5 (1,356)
Dementia	53.4 (1,399)
Heart failure	43.9 (1,150)
Depression	36.2 (950)
Stroke	33.1 (872)
≥2 falls during the past year	23.7 (619)
Peripheral artery disease	18.6 (486)
Diabetes mellitus	18.2 (479)
Renal failure[a]	
CL_{CR} >60 mL/min	24.6 (601)
CL_{CR} >30 and ≤60 mL/min	59.3 (1,469)
CL_{CR} ≤30 mL/min	16.4 (407)
Myocardial infarction	14.1 (369)
Cancer	10.3 (272)
Gastroduodenal ulcer	9.3 (243)
Chronic hepatic disease	2.7 (71)

CL_{CR} creatinine clearance, *SD* standard deviation

[a] CL_{CR} derived from the Cockroft–Gault formula

3.2 General Aspects of Vitamin K Antagonists (VKA) Treatment and Control

The characteristics of VKA management are presented in Table 2. The most prescribed VKA was fluindione (64.9 %) and 31.3 % of the patients received warfarin. VKA treatment had been initiated more than 12 months prior in 77.8 % of patients. On average, INR values were in therapeutic range 57.9 % of the time. Only 34.9 % ($n = 919$) of patients had both INR values in therapeutic range (100 % TTR) whereas 22.3 % (588) of patients were never in therapeutic range (0 % TTR). Among the 1,714 patients who spent less than 100 % of TTR, INR values were more often below the therapeutic target than above (first INR test: 31.9 vs. 16.4 %; $p < 0.001$, and second INR test: 29.9 vs. 14.7 %; $p < 0.001$). One quarter of the patients ($n = 657$) had a history of INR >4.5 but only 2.1 % ($n = 55$) had a history of major bleeding.

3.3 Factors Associated with VKA Control

As shown in Table 3, poorer VKA control was associated with being in rehabilitation care, antibiotic use, and falls. Proton pump inhibitor use was more frequent in the lower TTR categories, although this association did not reach

Table 2 Aspects of anticoagulation control and management

VKA control and management	Total population (n = 2,633)
Indication for VKA [% (no.)]	
Atrial fibrillation	71.4 (1,922)
VTE/PE	22.6 (591)
Cardiac valve	4.1 (106)
Other/unknown	2.0 (51)
Type of VKA [% (no.)]	
Fluindione	64.9 (1,708)
Warfarin	31.3 (823)
Acenocoumarol	3.8 (99)
VKA since [% (no.)]	
>12 months	77.8 (1,898)
1–12 months	17.4 (424)
<1 month	4.9 (119)
First INR test in range [% (no.)]	
Below therapeutic range	31.9 (839)
Within therapeutic range	51.8 (1,363)
Above therapeutic range	16.4 (431)
Second INR test in range [% (no.)]	
Below therapeutic range	29.9 (787)
Within therapeutic range	56.4 (1,485)
Above therapeutic range	14.7 (435)
INR in therapeutic range [% (no.)]	
None	26.7 (704)
At least one INR	38.4 (1,010)
Both INR values	34.9 (919)
Test interval, days [mean (SD)]	15.3 (12.7)
% TTR [mean (SD)]	57.9 (40.4)
% of patients across TTR categories [% (no.)]	
0 % TTR	22.3 (588)
0–50 % TTR	17.7 (466)
50–100 % TTR	25.1 (660)
100 % TTR	34.9 (919)
History of INR >4.5 [% (no.)][a]	25.4 (657)
History of major bleeding [% (no.)][a]	2.1 (55)

INR international normalized ratio, *SD* standard deviation, *TTR* time in therapeutic range according to the Rosendaal's method, *VKA* vitamin K antagonists, *VTE/PE* venous thromboembolic disease/pulmonary embolism

[a] During the time spent in the care structure

statistical significance. SSRI use was significantly associated with TTR, but without a clear trend across TTR categories. Regarding the aspect of VKA treatment (Table 4), poorer VKA control was associated with the prosthetic heart valve indication, a recent VKA prescription, a history of INR ≥4.5, and a history of major bleeding. Warfarin use was associated with higher TTR than fluindione or acenocoumarol use.

Results from logistic models using the median-TTR as the dependant variable (TTR <50 vs. ≥50 %) are presented in Table 5. The associations observed across TTR categories were mostly consistent after adjustment for age and gender except for SSRI use, the number of co-medications, and dementia (not shown). After backward selection, the covariates that remained independently associated with poorer VKA control were being hospitalized in a rehabilitation care unit [odds ratio $(OR)_{\text{rehab. vs. nursing home}} = 1.41$; 95 % CI 1.11–1.80; $p = 0.005$], the indication for VKA treatment ($OR_{\text{prosthetic heart valve vs. AF}} = 4.76$; 95 % CI 2.83–8.02; $p < 0.001$), a recent VKA prescription ($OR_{<1 \text{ vs. } >12 \text{ months}} = 1.70$; 95 % CI 1.08–2.67; $p = 0.02$), the use of fluindione ($OR_{\text{fluindione vs. warfarin}} = 1.22$; 95 % CI 1.00–1.49; $p = 0.05$), a history of INR >4.5 ($OR_{\text{yes vs. no}} = 1.50$; 95 % CI 1.21–1.84; $p \leq 0.001$), a history of major bleeding ($OR_{\text{yes vs. no}} = 1.88$; 95 % CI 1.00–3.53; $p = 0.05$), antibiotic use ($OR_{\text{yes vs. no}} = 1.83$; 95 % CI 1.24–2.70; $p = 0.002$), and falls ($OR_{\geq 2 \text{ falls during the past year vs. } <2} = 1.26$; 95 % CI 1.01–1.56; $p = 0.04$).

3.4 Sensitivity Analyses

As we did not have further information on the nature or the position of the prosthetic heart valve, the recommended therapeutic range might not be as high as 3.0–4.5 for all prosthetic heart valve carriers. However, setting the therapeutic range between 2.0 and 3.0 for all patients regardless of the indication for VKA did not substantially change our results and even strengthened the association ($OR_{\text{prosthetic heart valve vs. AF}} = 5.28$; 95 % CI 2.95–9.46).

In the present work, VKA control was poorer among rehabilitation care patients than in those in nursing homes (TTR 48.8 vs. 60.9 %; $p < 0.001$). As expected, institutionalized patients were older and had more chronic comorbidities, dementia, depression, and history of stroke, while those in rehabilitation care showed a more "acute" profile (higher mean number of medications, more frequent use of paracetamol, proton pump inhibitors, statins, antiplatelets agents, and antibiotics) (Supplementary Table 1). Also, the VKA prescription was more recent ($VKA_{<1 \text{ vs. } \geq 1 \text{ month}} = 18.6$ vs. 0.9 %; $p < 0.001$) and acenocoumarol use was more frequent (5.5 vs. 3.2 %; $p = 0.02$) in rehabilitation care than in nursing homes (Supplementary Table 2). However, the factors associated with VKA control in our main analysis had similar effects in both care settings (all $p_{\text{for interation}} > 0.12$; Supplementary Table 3).

Lastly, restricting our analysis to the 1,922 patients who were taking VKA for AF did not change these findings (not shown).

Table 3 Characteristics of the patients according to percentage of time in therapeutic range

Characteristic	% of time in therapeutic range				*p* value[a]
	0 % ($n = 588$)	0–49 % ($n = 466$)	50–99 % ($n = 660$)	100 % ($n = 919$)	
Age, years [mean (SD)]	87.2 (4.6)	87.4 (4.4)	87.2 (4.4)	87.2 (4.3)	0.86
Women [% (no.)]	70.7 (414)	72.3 (334)	76.3 (502)	72.1 (662)	0.13
Number of medications [mean (SD)]	8.8 (3.1)	8.8 (3.4)	8.7 (3.2)	8.6 (3.1)	0.45
Care setting [% (no.)]					
Nursing home	66.8 (393)	72.1 (336)	75.5 (498)	81.0 (744)	<0.001
Rehabilitation care	33.2 (195)	27.9 (130)	24.6 (162)	19.0 (175)	
Associated medications [% (no.)]					
Paracetamol	58.1 (340)	59.9 (279)	60.0 (395)	55.9 (512)	0.34
Proton pump inhibitors	42.5 (248)	44.5 (207)	37.8 (247)	39.3 (359)	0.08
Selective serotonin reuptake inhibitors	28.2 (164)	36.1 (168)	29.2 (193)	34.6 (317)	0.006
Statins (HMG-CoA reductase inhibitors)	20.6 (120)	17.8 (83)	20.7 (136)	18.4 (169)	0.47
Antiplatelet agents	9.5 (56)	10.8 (50)	7.3 (48)	8.5 (78)	0.28
Antibiotics	8.4 (49)	8.6 (40)	4.6 (30)	3.6 (33)	<0.001
Antifungal drugs	3.8 (22)	3.2 (15)	2.4 (16)	2.1 (19)	0.21
NSAIDs	1.5 (9)	1.7 (8)	2.0 (13)	0.9 (8)	0.29
Associated co-morbidities [% (no.)]					
Charlson's score ≥3	55.3 (325)	49.4 (230)	51.2 (338)	50.4 (463)	0.20
Dementia	51.3 (300)	50.5 (235)	53.9 (354)	55.7 (510)	0.20
Heart failure	45.9 (268)	44.6 (208)	43.0 (283)	42.8 (391)	0.63
Depression	32.8 (192)	39.5 (183)	34.9 (230)	37.7 (345)	0.09
Stroke	34.7 (204)	29.2 (136)	32.2 (212)	34.9 (320)	0.14
≥2 falls during the past year	28.7 (167)	25.2 (116)	22.4 (147)	20.7 (189)	0.003
Diabetes mellitus	17.6 (103)	18.1 (84)	19.3 (127)	18.0 (165)	0.87
Peripheral artery disease	22.1 (129)	16.4 (76)	17.5 (115)	18.2 (166)	0.08
Creatinine clearance ≤30 mL/min[b]	18.7 (105)	15.8 (69)	16.1 (100)	15.5 (133)	0.26
Myocardial infarction	14.7 (86)	16.0 (74)	13.2 (87)	13.4 (122)	0.52
Cancer	10.0 (59)	11.8 (55)	10.9 (72)	9.4 (86)	0.51
Gastroduodenal ulcer	8.3 (48)	11.7 (54)	8.7 (57)	9.2 (84)	0.24
Chronic hepatic disease	2.9 (17)	3.2 (15)	3.0 (20)	2.1 (19)	0.52

SD standard deviation

[a] *p* values for the difference in characteristics according to percentage of time in therapeutic range from non-adjusted Chi-square tests for categorical variables and from non-adjusted linear regressions for continuous variables

[b] Creatinine clearance derived from the Cockroft–Gault formula

4 Discussion

In this large French National Survey of VKA use in hospitalized/institutionalized older adults, the first indication for VKA was AF (71.4 %) and the most widely VKA used was fluindione (64.9 %). Although the mean TTR was 57.9 %, only 34.9 % of the patients achieved 100 % of TTR, whereas 22.3 % were never within the therapeutic range. Moreover, we found that poorer VKA control was associated with being hospitalized in a rehabilitation care unit, taking VKA for a prosthetic heart valve, a recent VKA prescription, the use of VKAs other than warfarin, a history of overcoagulation or major bleeding, antibiotic use, and the occurrence of two or more falls during the past year.

Few studies have addressed the quality of VKA anticoagulation in the very old population, particularly in a geriatrics setting [21–27]. Regarding the overall TTR value, our results are closer to those of studies conducted in community practice [17]. Recently, a meta-analysis that included warfarin-treated AF patients indicated a TTR of 55 % (95 % CI 51–58) [18]. Studies conducted among long-term care residents have been performed on small sample sizes and indicated INR levels in the therapeutic target for 48 % of the time (range 37–55 %) [30].

Table 4 Aspects of the anticoagulation control and management according to percentage of time in therapeutic range

Characteristic	% of time in therapeutic range				*p* value[a]
	0 % ($n = 588$)	0–49 % ($n = 466$)	50–99 % ($n = 660$)	100 % ($n = 919$)	
Indication for VKA [% (no.)]					
Atrial fibrillation	67.7 (388)	72.9 (333)	74.4 (482)	75.1 (668)	<0.001
VTE/PE	21.6 (124)	24.1 (110)	23.9 (155)	22.7 (202)	
Cardiac valve	10.7 (61)	3.1 (14)	1.7 (11)	2.3 (20)	
Type of VKA [% (no.)]					
Fluindione	64.5 (379)	68.3 (317)	65.5 (432)	63.2 (580)	0.01
Warfarin	31.6 (186)	26.5 (123)	30.0 (198)	34.4 (316)	
Acenocoumarol	3.9 (23)	5.2 (24)	4.6 (30)	2.4 (22)	
VKA since [% (no.)]					
>12 months	72.0 (391)	79.6 (343)	78.3 (473)	80.1 (691)	<0.001
1–12 months	20.4 (111)	13.7 (59)	16.7 (101)	17.7 (153)	
<1 month	7.6 (41)	6.7 (29)	5.0 (30)	2.2 (19)	
History of INR >4.5 [% (no.)][b]	29.9 (172)	31.8 (147)	21.6 (140)	22.0 (198)	<0.001
History of major bleeding [% (no.)][b]	3.9 (22)	2.0 (9)	1.2 (8)	1.8 (16)	0.01

INR international normalized ratio, *TTR* time in therapeutic range according to the Rosendaal's method, *VKA* vitamin K antagonists, *VTE/PE* venous thromboembolic disease/pulmonary embolism

[a] *p* values for the difference in characteristics according to percentage of time in therapeutic range derived from non-adjusted Chi-square tests for categorical variables and from non-adjusted general linear regressions for continuous variables

[b] During the time spent in the care structure

Poor compliance may be an important factor in INR instability [31]. However, in our study it is very unlikely that poor compliance explained the TTR we observed as we included hospitalized/institutionalized patients in whom compliance is monitored by a nurse.

Our results indicate that determinants other than drug compliance are involved in the complexity of VKA control in the elderly.

Although our results seem to be consistent with prior studies, it is difficult to raise any firm conclusion owing to differences in populations, settings, VKA control method assessment, and length of follow-up. Furthermore, most of the previous studies included only AF patients, with an INR target between 2 and 3. Nevertheless, we found similar results after the exclusion of patients with indications for VKA other than AF.

Interestingly, in the present work, the use of fluindione was associated with poorer INR control than warfarin. While warfarin is the standard treatment for VKA worldwide [32], fluindione is mainly used in France where it represents the first VKA used [17]. Accordingly, we found that fluindione was the most widely used VKA in our population of very old subjects. Fluindione is a long half-life indanedione-derived VKA [32]. Overall, the pharmacokinetics and pharmacodynamics of both fluindione and warfarin are influenced by the same environmental and genetic factors and these two VKAs share the same contraindications and drug–drug interactions [29, 33–35]. Furthermore, in a recent study including very old hospitalized patients with an INR ≥5.0, the reversal of overcoagulation was not related to the type of VKA used (fluindione vs. warfarin) [36]. However, some hypotheses could be suggested to explain the poorer INR control observed with fluindione than with warfarin. Fluindione has a slightly shorter half-life (31 h) than warfarin (36–42 h) and it is known that a longer half-life is associated with more stable anticoagulation [31, 32, 37, 38]. Besides this, the required doses of VKA are usually lower in elderly patients than in younger patients. For fluindione, it has been suggested that daily doses of 5–10 mg may be sufficient in elderly patients to maintain the INR in the therapeutic range [34, 39]. However, fluindione is still packaged as 20-mg pills, which may be difficult to divide for routine treatment [34, 40]. Lastly, the most studied and used VKA worldwide is warfarin and our results support the use of this particular VKA in elderly patients, although fluindione and warfarin have never been compared in a specific trial in terms of bleeding risk.

The strongest association with low TTR was found for patients in whom VKA were prescribed for a prosthetic heart valve, with an increased odds of almost 5.0. In these patients, the proportion of INR values below the recommended therapeutic range (i.e., INR 3.0–4.5) was much higher than in other patients (first INR test: 65.9 vs. 30.5 %; $p < 0.001$, and second INR test: 67.0 vs. 28.3 %; $p < 0.001$). This may reflect that physicians might be

Table 5 Associations between patients' characteristics and vitamin K antagonists control

Characteristic	Multivariate model[a]		
	OR	95 % CI	*p* value
Age, per 1 year increase	1.01	0.99–1.03	0.33
Women vs. men	1.13	0.92–1.39	0.24
Care setting			
Nursing home	1.00	Ref.	
Rehabilitation care	1.41	1.11–1.80	0.005
Indication for VKA treatment			
Atrial fibrillation	1.00	Ref.	
VTE/PE	1.05	0.84–1.31	0.47
Cardiac valve	4.76	2.83–8.02	<0.001
VKA since			
>12 months	1.00	Ref.	
1–12 months	1.10	0.85–1.41	0.47
<1 month	1.70	1.08–2.67	0.02
Type of VKA			
Warfarin	1.00	Ref.	
Fluindione	1.22	1.00–1.49	0.05
Acenocoumarol	1.46	0.88–2.42	0.14
History of INR >4.5	1.50	1.21–1.84	<0.001
History of major bleeding	1.88	1.00–3.53	0.05
Antibiotic use	1.83	1.24–2.70	0.002
≥2 falls during the past year	1.26	1.01–1.56	0.04

INR international normalized ratio, *OR* odds ratio, *TTR* time in therapeutic range according to the Rosendaal's method, *VKA* vitamin K antagonists, *VTE/PE* venous thromboembolic disease/pulmonary embolism

[a] ORs and 95 % confidence intervals derived from logistic models using the median of TTR as the dependant variable (TTR <50 vs. ≥50 %). Multivariate model included age, sex, and covariates retained after backward selection

reluctant to maintain higher INR values in very elderly patients because of a fear of hemorrhagic complications. Of note, our sensitivity analysis after setting the INR range between 2 and 3 for the whole sample did not change our results.

In the multivariate analysis, of the other drugs and conditions known to be related to INR instability, only antibiotic use remained significantly associated with poorer VKA control. This might reflect the effects of acute illness overwhelming those of other chronic co-morbidities or co-medications pre-existing to the occurrence of the acute condition [41]. Unfortunately, we did not have information on the acute or chronic nature of co-morbidities or co-medications. However, we could hypothesize that antibiotic prescriptions were recent as they usually occur at the time of an acute episode, a period during which deterioration of chronic co-morbidities and changes in drug use are frequent, leading to INR instability [41, 42]. In line with this, patients hospitalized in a rehabilitation setting are usually still in the process of recovery after an acute event, and are therefore less stable than those who are institutionalized in a nursing home. However, firstly, we did not find any interaction between VKA control, the type of care setting, and the other factors associated with VKA control in our main analysis (e.g., VKA indication, length of VKA prescription, type of VKA, history of overcoagulation and of major bleeding, antibiotic use, and falls) and, secondly, those factors were associated with VKA control independent of the type of care setting. Therefore, it is unlikely that our results can be explained by the differences between patients in rehabilitation care and nursing homes.

Regarding the other medical conditions, a history of overcoagulation and of major bleeding—two conditions reflecting INR instability—were understandably associated with poorer VKA control.

Frequent falls were associated with poorer VKA control. Falls or risk of falls are an important factor in VKA under-prescription in the elderly [30, 41, 43–47]. Nevertheless, current evidence suggests that among fallers, VKA prescription is not associated with a higher occurrence of intracranial hemorrhage but rather with its severity [45–47], and that a net clinical benefit remains in favor of VKA in this population [46].

In our study, as for prosthetic heart valve carriers, patients who experienced two or more falls during the past year were more frequently below the therapeutic range than "non-fallers", indicating that physicians may "lower the therapeutic range" in patients at risk of falls because of a fear of bleeding complications. Finally, frequent falls are also a marker of frailty and sarcopenia, a condition that could affect INR stability [48].

As previously reported [22], we found that poorer INR control was more frequent when VKA had recently been initiated (<1 month), reflecting the time necessary to obtain a stable dose response after VKA initiation.

Lastly, we did not find an association between increasing age and poorer VKA control as previously reported [49]. However, this association remains unclear and increasing age might be associated with increased risk of hemorrhage rather than with INR instability itself [20, 50, 51]. Furthermore, the current study included only very old patients, with a relatively narrow age range.

A number of limitations should be acknowledged. In the present study, the TTR values were computed from only two consecutive INRs. Although this could explain the large standard deviation that we observed, our TTR value (57.9 %) was still close to those reported in previous studies with more than two INR measurements [17, 18]. Furthermore, we were less likely to capture INR changes related to chronic co-morbidities or co-medications. However, our TTR results and the

characteristics associated with poorer VKA control remain consistent with those of previous works conducted in elderly populations. Our population consisted of hospitalized or institutionalized older individuals who might not be representative of the whole elderly population. However, the present survey included patients from all French territories. Furthermore, we found a prevalence of VKA use of 14 %, which was similar to that of data in a recent report from the French National Healthcare (13.2 % after 85 years) [52].

Our study also has several strengths, as it had a large sample size and included "real-life" elderly patients who were 80 years and older, with numerous co-morbidities such as dementia, falls, or heart failure. Furthermore, the inclusion of hospitalized/institutionalized patients allowed us to control for the potential confounding effect of poor compliance on our results.

The present work confirms that VKA control remains insufficient in very old people, even in hospitalized/institutionalized patients, so that there is an urgent need for measures to be taken to improve the anticoagulation quality in this population.

Based on our results, closer INR monitoring and possibly more frequent dose adjustments would be necessary among prosthetic heart valve carriers, fallers, patients taking VKAs other than warfarin, and those with a history of overcoagulation or major bleeding. Also, clinicians should be particularly cautious when concomitant antibiotic use is required and at the beginning of the VKA treatment. In line with this, the systematic use of low-dose VKA induction schemes specifically designed for older adults has been demonstrated to be safe and accurate in this particular population [53, 54]. More generally and regarding the long-term treatment, the risk/benefit ratio should be regularly re-evaluated and the frequency of monitoring should be adapted according to changes in the patient's condition over time (acute illness occurrence, severity of co-morbidities, co-medications, or diet) but also with their VKA treatment "history" (quality of adjustment-dose decision, INR stability) [32, 53]. In summary, rather than a fixed maximum INR recall, recall intervals might be tailored to the patient's characteristics and recent INR control [51].

5 Conclusion

Our findings suggest that overall VKA control remains insufficient in very old patients. The main factors associated with a poorer VKA control were the type of care setting, the indication for VKA (prosthetic heart valve), the use of other VKAs than warfarin, a history of overcoagulation and of major bleeding, antibiotic use, and falls.

The new oral anticoagulants (thrombin inhibitor or factor Xa inhibitor) may be a new alternative for oral anticoagulation in the elderly. However, no data are available concerning the use of these drugs in very old patients with multiple co-morbidities, renal impairment, and polymedication.

In conclusion, VKA control remains insufficient in very old people. Measures should be undertaken to improve the anticoagulation quality in this population.

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