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Risk of Bleeding and Thrombosis in Patients 70 Years or Older Using Vitamin K Antagonists

Hilde A. M. Kooistra, PhD; Agneta H. Calf, MD; Margriet Piersma-Wichers, MD; Hanneke C. Kluin-Nelemans, PhD; Gerbrand J. Izaks, PhD; Nic J. G. M. Veeger, PhD; Karina Meijer, PhD

IMPORTANCE Previous studies have shown that, despite the higher risk of bleeding, the elderly still benefit from taking anticoagulants if they have a stringent indication. However, owing to the relatively low number of patients older than 90 years in these studies, it is unknown whether this benefit is also seen with the eldest patients.

OBJECTIVE To determine how the risk of bleeding and thrombosis is associated with age in patients older than 70 years who were treated with a vitamin K antagonist (VKA).

DESIGN, SETTING, AND PARTICIPANTS A matched cohort study was conducted of patients at a thrombosis service who were treated with a VKA between January 21, 2009, and June 30, 2012. All 1109 patients 90 years or older who were treated with a VKA were randomly matched 1:1:1 with 1100 patients aged 80 to 89 years and 1104 patients aged 70 to 79 years based on duration of VKA treatment. Data analysis was conducted from April 2015 to April 2016.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of clinically relevant nonmajor and major bleeding. Secondary outcomes included thromboses and quality of VKA control.

RESULTS During 6419 observation-years, 713 of the 3313 patients (1394 men and 1919 women) had 1050 bleeding events. The risk of bleeding was not significantly increased in patients aged 80 to 89 years (event rate per 100 patient-years [ER], 16.7; hazard ratio [HR], 1.07; 95% CI, 0.89-1.27) and mildly increased in patients 90 years or older (ER, 18.1; HR, 1.26; 95% CI, 1.05-1.50) compared with patients aged 70 to 79 years (ER, 14.8). The point estimates for major bleeding (including fatal) were comparable for patients aged 80 to 89 years (ER, 1.0; HR, 1.09; 95% CI, 0.60-1.98) and those 90 years or older (ER, 1.1; HR, 1.20; 95% CI, 0.65-2.22) compared with those aged 70 to 79 years (ER, 0.9). The increase in bleeding risk was sharper in men than in women. Eighty-five patients (2.6%) developed a thrombotic event. Risk of thrombosis was higher for patients in their 90s (HR, 2.14; 95% CI, 1.22-3.75) and 80s (HR, 1.75; 95% CI, 1.002-3.05) than for patients in their 70s. Vitamin K antagonist control became significantly poorer with rising age, which partly explained the increased bleeding risk in patients 90 years or older, but most of the increased risk of thrombosis was not mediated by VKA control.

CONCLUSIONS AND RELEVANCE These clinical practice data of patients considered eligible for anticoagulation show that the bleeding risk with a VKA only mildly increases after the age of 80 years, while there is a sharp increase in the risk of thrombosis in the same age group.

Editor's Note page 1184

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Hilde A. M. Kooistra, PhD, Division of Hemostasis and Thrombosis, Department of Hematology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands (h.a.m.kooistra@umcg.nl).

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Vitamin K antagonists (VKAs) are effective in the prevention of venous and arterial thrombosis, but their major complication is bleeding.[1,2] Several studies have shown that the risk of bleeding among patients taking a VKA increases with age.[3-5] This increased risk might be partly explained by poorer control of the VKA.[6-8] Other possible explanations are the increased comorbidities, comedications, fall risks, and susceptibility for gastrointestinal bleeding with increasing age.[9]

The higher bleeding risk in the elderly makes physicians reluctant to prescribe VKAs.[10,11] However, the clinical decision to initiate anticoagulation should be modeled as a balance between the risks of bleeding and thrombosis. As the risk of thrombosis is higher in the elderly,[12] more thrombotic events can be prevented by the use of anticoagulants. Consequently, it could be that a higher risk of bleeding should be accepted in favor of fewer thrombotic events.

The Computerized Registry of Patients with Venous Thromboembolism (RIETE) study showed that patients older than 80 years with venous thromboembolism (VTE) have a higher risk of death from recurrent VTE than from fatal bleeding while taking a VKA.[13] Moreover, the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial demonstrated that patients older than 75 years with atrial fibrillation still benefit from anticoagulant treatment.[14] These data confirm that elderly patients should be treated with anticoagulants if they have a stringent indication. However, it is unclear whether these recommendations can be extrapolated to patients older than 90 years as well, as such patients were still underrepresented in these studies. Therefore, it is essential to know how the risk of bleeding and thrombosis during VKA therapy develops after the age of 70 years. This risk was analyzed in a large cohort study of patients treated with VKAs at Certe Thrombosis Service Groningen, Groningen, the Netherlands.

Key Points

Question Are risk of bleeding and thrombosis associated with age in patients older than 70 years who were treated with a vitamin K antagonist?

Findings In this cohort study of 3313 patients using a vitamin K antagonist, the bleeding risk only mildly increased in patients 90 years or older, and the increase was more pronounced in men than in women. There was a profound increase in the risk of thrombosis among patients 90 years or older.

Meaning Our data suggest that the recommendations to use anticoagulants in patients older than 80 years can be safely extrapolated to the eldest patients as well, but evidence is stronger for women than for men.

Methods

Study Design

From the patients treated at Certe Thrombosis Service Groningen between January 21, 2009, and June 30, 2012, we selected all patients 90 years or older. This thrombosis service managed VKA therapy for all noninstitutionalized patients and the patients of many nursing homes in the area of Groningen. All referred patients were actually being treated with VKAs; thus, there was no selection bias as the thrombosis service had no role in screening or selecting patients. Blood was drawn for international normalized ratio (INR) measurements by thrombosis service personnel at a local laboratory or at patients' homes for those with mobility issues. Vitamin K antagonist doses were determined using a computerized algorithm. Dosing cards and follow-up appointments were sent by postal mail or email. The location where blood was drawn did not influence the frequency, intensity, or nature of medical care.

We formed 2 cohorts: 1 of newly referred patients (inception cohort) and 1 with all other patients (long-term cohort). We used a matched cohort design to include all information of the patients 90 years or older while limiting the total number of patients to enable thorough adjudication of end points. Every patient 90 years or older was randomly matched to 1 patient aged 80 to 89 years and 1 patient aged 70 to 79 years. Matching was based on whether the patient belonged to the inception or long-term cohort, as previous research has shown that the risk of bleeding is highest during the beginning of treatment.[15] To equalize the potential follow-up time, we also matched patients on the date that the study follow-up started for that individual patient. To select a group of patients representative for their age group, we did not match on other characteristics. There were no exclusion criteria to optimize generalizability.

Data Collection

Patient and treatment characteristics were collected from the computerized records of the thrombosis service. The physicians of the thrombosis service prospectively registered all bleeding events, thrombotic events, permanent treatment discontinuations at Thrombosis Service Groningen (including patients who migrated and left the service to be treated elsewhere), and deaths. Also, additional information was routinely requested from the general practitioner in case of death or if there was any indication of stroke or major bleeding. Subsequently, strokes were classified into hemorrhagic, ischemic, or unspecified. In addition, it was registered if death was caused by bleeding, VTE, stroke, or myocardial infarction. The therapeutic INR range for atrial fibrillation and VTE was 2.0 to 3.5, as routinely applied in the Netherlands.[16] Individual patients could have a therapeutic INR range of 2.5 to 4.0 if they were being treated for another indication.

As this study concerns retrospective research, no institutional review board approval or patient consent was needed according to Dutch law. Protection of the patients' identity was guaranteed by assigning study-specific unique patient numbers as deidentifiers.

Outcome Definition

The primary end point was a composite of clinically relevant nonmajor and major bleeding. The secondary end points were major bleeding, including hemorrhagic stroke, death related

Table 1. Patient Characteristics by Age Group

Characteristic	Age Group, y[a]		
	70-79	80-89	≥90
Patients, No.	1104	1100	1109
Mean age, y	75.1	84.4	92.6
Female sex, No. (%)	458 (41.5)	651 (59.2)	810 (73.0)
Primary indication for VKA, No. (%)			
Atrial fibrillation	704 (63.8)	786 (71.5)	795 (71.7)
Venous thromboembolism	148 (13.4)	124 (11.3)	136 (12.3)
Myocardial infarction or coronary disease	68 (6.2)	43 (3.9)	30 (2.7)
Heart failure	24 (2.2)	21 (1.9)	21 (1.9)
Valve disorder	57 (5.2)	34 (3.1)	14 (1.3)
Stroke or TIA without atrial fibrillation	18 (1.6)	23 (2.1)	18 (1.6)
Arrhythmia other than atrial fibrillation	19 (1.7)	11 (1.0)	22 (2.0)
Prophylaxis	10 (0.9)	15 (1.4)	23 (2.1)
Other	56 (5.1)	43 (3.9)	50 (4.5)
Therapeutic range, No. (%)			
INR 2.0-3.5	856 (77.5)	918 (83.5)	1001 (90.3)
INR 2.5-4.0	248 (22.5)	182 (16.5)	108 (9.7)
Acenocoumarol, No. (%)	1063 (96.3)	1069 (97.2)	1085 (97.8)
Comorbidity and comedication of inception cohort at time of referral[b]			
Comorbidity, No. (%)			
History of stroke or TIA	15 (3.9)	30 (7.8)	34 (8.8)
Coronary artery disease	29 (7.5)	25 (6.5)	13 (3.4)
Heart failure	21 (5.5)	29 (7.5)	35 (9.1)
Diabetes type 1 and type 2	49 (12.7)	41 (10.6)	28 (7.3)
Recent surgery	18 (4.7)	15 (3.9)	9 (2.3)
Comedication, No. (%)			
1 Platelet aggregation inhibitor	62 (16.1)	51 (13.2)	44 (11.4)
2 Platelet aggregation inhibitors	13 (3.4)	8 (2.1)	6 (1.6)
Corticosteroids	21 (5.5)	25 (6.5)	29 (7.5)
Selective serotonin reuptake inhibitor	4 (1.0)	8 (2.1)	12 (3.1)
Nonsteroidal anti-inflammatory drugs	15 (3.9)	10 (2.6)	8 (2.1)
Antibiotic	34 (8.8)	37 (9.6)	57 (14.8)
Proton pump inhibitor	107 (27.8)	127 (33.0)	114 (29.6)
Location of first appointment, No. (%)			
At home	201 (52.2)	309 (80.3)	360 (93.5)
Outpatient clinic	184 (47.8)	76 (19.7)	25 (6.5)

Abbreviations: INR, international normalized ratio; TIA, transient ischemic attack; VKA, vitamin K antagonist.

[a] Percentages may not total 100 because of rounding.

[b] N=385 in all 3 age groups.

to bleeding or thrombosis, thrombotic events (myocardial infarction, ischemic and unspecified stroke, and VTE), permanent treatment discontinuation owing to bleeding problems, and quality of VKA control (individual time in the therapeutic range and variability of the INR).

Clinical events were adjudicated by 2 experienced physicians (H.A.M.K. and A.H.C.) who were blinded to age. In case of doubt, a third physician (M.P.-W.) was consulted. Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical organ, bleeding causing a decrease in the hemoglobin level of 2.0 g/dL or more (to convert to grams per liter, multiply by 10.0), and/or bleeding leading to transfusion of 2 U or more of blood.[17] Clinically relevant bleeding was defined as bleeding events that did not meet the criteria for major bleeding but did lead to a medical intervention, unscheduled contact with a physician, and/or cessation of anticoagulant therapy. Strokes and deaths related to bleeding or thrombosis were adjudicated according to the registry of the thrombosis service, as these events were already prospectively adjudicated by their physicians. Venous thromboembolism and myocardial infarction were adjudicated based on the information in the patient record. Information on whether permanent discontinuation of the VKA was associated with bleeding problems was received from the general practitioner and adjudicated accordingly. Individual time in the therapeutic range was calculated by the method of Rosendaal et al[18] based on the patient-specific therapeutic range (INR 2.0-3.5 or 2.5-4.0). Recently, it has become clear that not only the intensity (individual time in the therapeutic range) of

Table 2. Clinical End Points

Characteristic	70-79 Years			80-89 Years			≥90 Years		
	Inception Cohort	Long-Term Cohort	Event Rate[a]	Inception Cohort	Long-Term Cohort	Event Rate[a]	Inception Cohort	Long-Term Cohort	Event Rate[a]
Patients, No.	385	719		385	715		385	724	
Observation-years	424	1962		432	1832		365	1404	
Total bleeding events, No. (major bleeding events, No.)	90 (6)	263 (16)	14.8 (0.9)	87 (9)	290 (13)	16.7 (1.0)	93 (4)	227 (16)	18.1 (1.1)
Skin	22 (0)	67 (0)	3.7	26 (0)	94 (0)	5.3	32 (1)	86 (0)	6.7
Nose	21 (0)	46 (0)	2.8	13 (0)	66 (0)	3.5	30 (0)	40 (0)	4.0
Urogenital tract	20 (0)	57 (0)	3.2	16 (0)	51 (1)	3.0	11 (1)	30 (0)	2.3
Gastrointestinal tract	7 (1)	52 (5)	2.5	19 (4)	40 (3)	2.6	10 (1)	44 (11)	3.1
Conjunctiva	9 (0)	9 (0)	0.8	4 (0)	13 (0)	0.8	8 (0)	7 (0)	0.8
Lung	2 (0)	8 (0)	0.4	3 (0)	12 (1)	0.7	1 (0)	10 (1)	0.6
Intracranial	2 (2)	9 (9)	0.5	2 (2)	8 (8)	0.4	1 (1)	4 (4)	0.3
Others	7 (3)	15 (2)	0.9	4 (3)	6 (0)	0.4	0 (0)	6 (0)	0.3
Total thrombotic events, No.	2	18	0.8	10	23	1.5	10	22	1.8
Ischemic stroke	0	8	0.3	3	7	0.4	4	10	0.8
Unspecified stroke	0	1	0.0	4	3	0.3	4	6	0.6
Venous thromboembolism	1	0	0.0	0	0	0.0	1	1	0.1
Myocardial infarction	1	9	0.4	3	13	0.7	1	5	0.3
Total deaths, No.	34	138	7.2	65	207	12.0	129	353	27.2
Related to bleeding or thromboses	6	12	0.8	3	15	0.8	10	26	2.0
Bleeding	4	7	0.5	3	9	0.5	1	11	0.7
Thrombosis	2	5	0.3	0	6	0.3	9	15	1.4
Permanent discontinuations of VKA owing to bleeding, No.	3	7	0.4	7	13	0.9	6	17	1.3

Abbreviation: VKA, vitamin K antagonist.

[a] Event rate per 100 patient-years for all patients (inception and long-term cohort).

the INRs but also the variability of the INRs determine the risk of bleeding and thrombosis while using a VKA.[6] Variability—the degree to which INRs differ from the previous INR—was determined by the formula of Cannegieter.[7]

Statistical Analysis

Data analysis was conducted from April 2015 to April 2016. We described the baseline characteristics stratified by age group. The association of age with the time to first event was analyzed using Cox proportional hazards regression, with patients aged 70 to 79 years as the reference group. We checked visually for violations of the Cox proportional hazards regression assumption and found none. Follow-up ended at permanent discontinuation of treatment, death, or June 30, 2012, whichever came first. For all end points, subgroup analyses for the inception and long-term cohort were performed. For the primary end point, subgroup analyses with respect to the indication for VKA (atrial fibrillation and VTE), sex, and the target INR range were also performed. These predefined subgroup analyses were chosen based on literature and clinical experience. We performed a sensitivity analysis using the robust sandwich method to determine whether a matched analysis would have led to different findings and found highly comparable results.

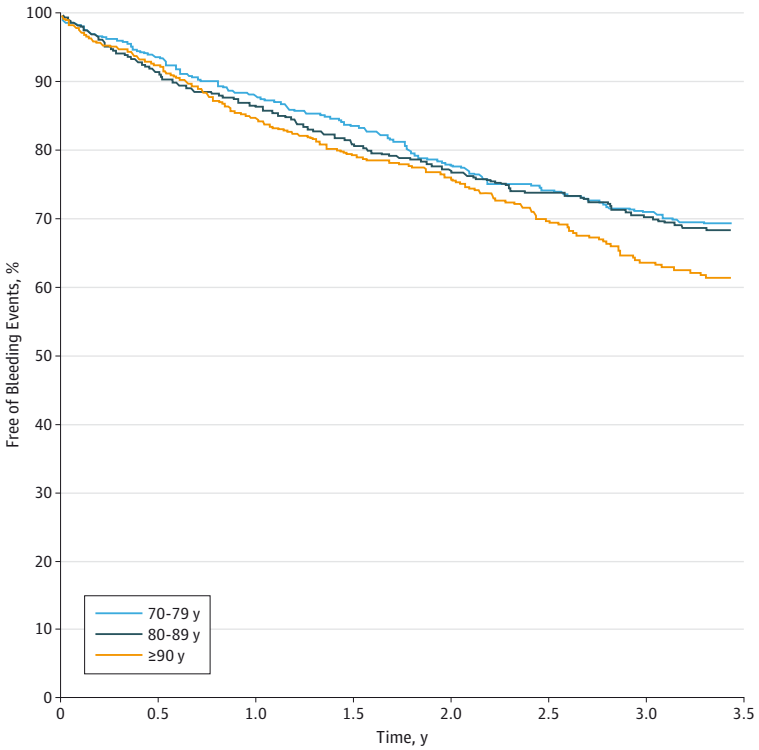
Differences between age groups in quality of VKA control were analyzed using one-way analysis of variance or the Kruskal-Wallis test. In addition, we determined whether the potential association between age and the risk of bleeding and thrombosis was mediated by VKA control.

Results

Patient Characteristics

Of the 26 089 patients who were treated between January 21, 2009, and June 30, 2012, at Certe Thrombosis Service Groningen, 1109 were 90 years or older. Of these patients, 385 (34.7%) belonged to the inception cohort and 724 (65.3%) to the long-term cohort. The long-term patients in their 70s (n = 1104), 80s (n = 1100), and 90s had a median treatment duration at the start of the study of 4.4, 4.8, and 5.0 years, respectively. As expected, with rising age, the proportion of women increased (**Table 1**). Atrial fibrillation was the most prevalent indication for all ages.

Figure 1. Kaplan-Meier Curve for Free of Bleeding Events, Stratified by Age Group



No. at risk

70-79 y	1104	857	717	609	513	455	389	0
80-89 y	1100	836	681	562	480	413	344	0
≥90 y	1109	776	567	428	335	243	178	0

The risk of bleeding in patients 90 years and older is mildly increased compared with patients aged 70 to 79 years. Patients in their 80s have a risk of bleeding comparable with that of patients in their 70s.

Comparison of Bleeding Events Between Age Groups

The 713 patients (21.5%) with at least 1 bleeding event had a total of 986 clinically relevant nonmajor and 64 major bleeding events (**Table 2**). The event rate per 100 patient-years was based on all 1050 bleeding events and was lowest for the patients aged 70 to 79 years (14.8), followed by the patients aged 80 to 89 years (16.7), and was highest in the patients 90 years or older (18.1) (Table 2). Bleeding was most often localized at the skin (327 events [31.1%]), nose (216 events [20.6%]), urogenital tract (185 events [17.6%]), and gastrointestinal tract (172 events [16.4%]), which was the same for all ages. In the inception cohort, a disproportional number of bleeding events (32 of the 270 bleeds [11.9%]) occurred in the first 30 days, which accounted for only 7% of the total follow-up time (1221 observation-years).

Patients 90 years or older had a mildly increased risk of bleeding (hazard ratio [HR], 1.26; 95% CI, 1.05-1.50) compared with patients aged 70 to 79 years (**Figure 1**). The risk of bleeding for patients aged 80 to 89 years (HR, 1.07; 95% CI, 0.89-1.27) was comparable with that for the patients in their 70s. Outcomes of several subgroup analyses regarding indication, treatment duration, and target range did not differ essentially from the main analysis. We observed a sharper increase in risk of bleeding for men than women with rising age (**Figure 2**). We also found that there was a slightly increased risk of bleeding (HR, 1.20; 95% CI, 1.03-1.39) in men overall. Of the 1394 men, 340 (24.4%) had at least 1 bleeding event, while 373 of the 1919 women (19.4%) developed at least 1 bleeding event.

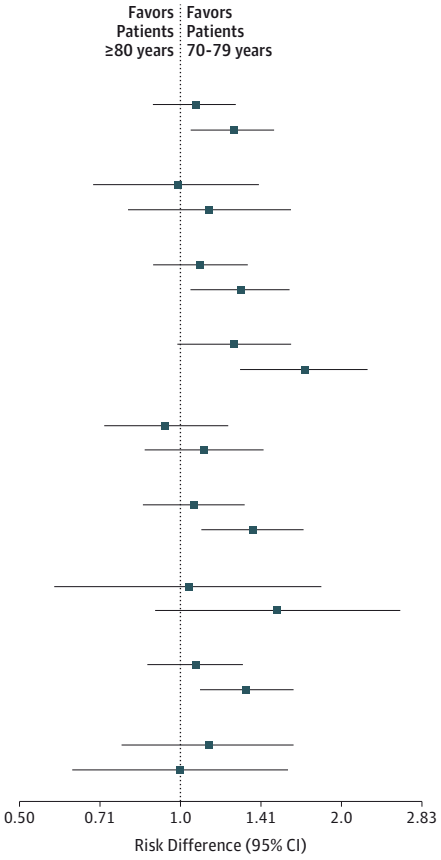
The event rate (per 100 patient-years) of major bleeding was 0.9, 1.0, and 1.1 for patients in their 70s, 80s, and 90s, respectively (Table 2). The occurrence of major bleeding was not significantly higher in patients 90 years or older (HR, 1.20; 95% CI, 0.65-2.22) or those between 80 and 89 years (HR, 1.09; 95% CI, 0.60-1.98) than in patients aged 70 to 79 years, and there was no interaction between age and sex. The risk of fatal bleeding was also not increased in patients in their 90s (HR, 1.32; 95% CI, 0.58-3.01). Bleeding events led more often to discontinuation of the VKA in patients in their 80s (HR, 2.07; 95% CI, 0.97-4.42) and 90s (HR, 2.83; 95% CI, 1.34-5.95) than in patients in their 70s.

Comparison of Thrombotic Events Between Age Groups

Eighty-five patients (2.6%) had a thrombotic event; no patient had multiple thromboses. The event rate (per 100 patient-years) was 0.8, 1.5, and 1.8 for patients in their 70s, 80s, and 90s, respectively (Table 2). The risk of developing a thrombosis was higher for patients in their 90s (HR, 2.14; 95% CI, 1.22-3.75) and 80s (HR, 1.75; 95% CI, 1.002-3.05) than for patients in their 70s. The subgroup analyses showed a more pronounced risk in the inception cohort (HR, 5.57; 95% CI, 1.22-25.4 and HR, 5.00; 95% CI, 1.10-22.8, respectively) than in the

Figure 2. Subgroup Analysis of Relative Risk of Bleeding for Patients Aged 80 to 89 Years and 90 Years or Older vs Patients Aged 70 to 79 Years

		No. of Bleeding Events	HR (95% CI)
Total cohort	70-79 y	239	Reference
	80-89 y	242	1.07 (0.89-1.27)
	≥90 y	232	1.26 (1.05-1.50)
Inception cohort	70-79 y	62	Reference
	80-89 y	63	0.99 (0.69-1.40)
	≥90 y	63	1.13 (0.80-1.61)
Long-term cohort	70-79 y	177	Reference
	80-89 y	179	1.09 (0.89-1.34)
	≥90 y	169	1.30 (1.05-1.60)
Male	70-79 y	144	Reference
	80-89 y	115	1.26 (0.99-1.61)
	≥90 y	81	1.71 (1.30-2.24)
Female	70-79 y	95	Reference
	80-89 y	127	0.94 (0.72-1.23)
	≥90 y	151	1.11 (0.86-1.43)
Atrial fibrillation	70-79 y	151	Reference
	80-89 y	173	1.06 (0.85-1.32)
	≥90 y	177	1.37 (1.10-1.70)
Venous embolism	70-79 y	26	Reference
	80-89 y	21	1.04 (0.58-1.84)
	≥90 y	31	1.52 (0.90-2.57)
Therapeutic INR range 2.0-3.5	70-79 y	174	Reference
	80-89 y	190	1.07 (0.87-1.31)
	≥90 y	208	1.33 (1.09-1.63)
Therapeutic INR range 2.5-4.0	70-79 y	65	Reference
	80-89 y	52	1.13 (0.78-1.63)
	≥90 y	24	1.00 (0.63-1.59)



Subgroup analyses regarding indication, treatment duration, and target range showed outcomes comparable with those of the main analysis. However, a sharper increase in the risk of bleeding with age was observed in men than in women. HR indicates hazard ratio; INR, international normalized ratio.

long-term cohort (HR, 1.74; 95% CI, 0.93-3.25 and HR, 1.38; 95% CI, 0.74-2.55, respectively). We found no interaction between age group and sex.

When focusing on the thrombotic events for which VKAs are most effective (VTE and stroke), the risk estimates of patients 90 years or older (HR, 3.45; 95% CI, 1.66-7.18) and those aged 80 to 89 years (HR, 1.79; 95% CI, 0.82-3.92) did not essentially change. Again, this risk was more pronounced in the inception cohort (HR, 9.93; 95% CI, 1.26-78.4 and HR, 7.00; 95% CI, 0.86-56.9, respectively) than in the long-term cohort (HR, 2.72; 95% CI, 1.21-6.12 and HR, 1.20; 95% CI, 0.49-2.94, respectively). The risk of thrombosis-related death was also increased in patients 90 years or older (HR, 4.53; 95% CI, 1.94-10.5) compared with those aged 70 to 79 years.

Comparison of VKA Control Among Age Groups

The control of individual time in the therapeutic range and variability of the INRs became significantly worse with rising age (**Table 3**). A higher perceived risk of bleeding in the eldest patients could have led to a more cautious anticoagulant treatment with a lower target INR and consequently more underanticoagulation. However, the time under and above the target INR range remained well balanced, and the mean INR was highly comparable for all ages.

As expected, poorer VKA control was associated with worse clinical outcome (eTable in the Supplement). Adding variability of the INRs and individual time in the therapeutic range to the bleeding model reduced the HR of the patients 90 years or older from 1.26 to 1.11 (95% CI, 0.92-1.33). Hence, part of the increased bleeding risk was mediated by poorer VKA control. In contrast, most of the increased risk of thrombosis was not mediated by VKA control, as the HR remained 1.85 (95% CI, CI 1.04-3.27) for patients 90 years or older and 1.64 (95% CI, 0.94-2.87) for patients aged 80 to 89 years after adding VKA control to the Cox proportional hazards regression model.

Discussion

This large cohort study showed that the frequency of bleeding events was not significantly increased in patients aged 80 to 89 years and only mildly increased in patients 90 years or older compared with patients in their 70s. The subgroup analyses showed that the risk of bleeding increased more with age in men than in women. The severity and location of bleeding were the same for patients of all ages. The risk of thrombosis of patients in their 90s and 80s was higher and more often fatal than in patients aged 70 to 79 years, especially in patients

Table 3. Comparison of VKA Control Among Age Groups

Characteristic	Age, y			*P* Value
	70-79	80-89	≥90	
Mean iTTR, %	73.5	71.1	66.4	<.001
Mean time above the therapeutic INR range, %	14.5	15.1	17.4	<.001
Mean time below the therapeutic INR range, %	12.0	13.7	16.2	<.001
Mean INR	2.93	2.90	2.93	.32
Median variability of the INR	0.61	0.78	1.01	<.001
Mean time between INR measurements, wk	2.6	2.5	2.3	<.001
Mean No. of VKA tablets per day	2.3	1.9	1.6	<.001

Abbreviations: INR, international normalized ratio; iTTR, individual time in the therapeutic range; VKA, vitamin K antagonist.

who just started VKA treatment. Additional analyses regarding the role of VKA control showed that the increased risk of bleeding in patients 90 years or older was partly explained by poorer VKA control. In contrast, the increased risk of thrombosis was mostly independent of VKA control.

The rate of nonmajor clinically relevant bleeding was comparable with that in the Italian Study on Complications of Oral Anticoagulant Therapy (ISCOAT).[4] The rate of major bleeding events was relatively low in our study, which could be explained by the inclusion of a large proportion of patients with long-term VKA use and the relatively broad criteria for major bleeding in some of the other studies.[4,5,13,14]

We compared 3 well-defined age groups and showed that the risk of bleeding stabilized in patients aged 80 to 89 years and subsequently only mildly increased above the age of 90 years. This result was in line with the findings by Poli and colleagues,[5] but they compared only 2 age groups. Many other studies compared patient groups with wide ranges of age[13,19] or had too few patients within the age strata.[14]

The higher risk of bleeding in patients 90 years or older compared with that of patients aged 70 to 79 years became nonsignificant after adjustment for quality of VKA control. Thus, the higher risk seemed to be partly associated with poorer VKA control and partly with age-associated fragility. The increased risk of thrombosis in patients in their 90s and 80s persisted after adjustment. It is unlikely that this high risk of thrombosis was caused by a general lack of efficacy of VKAs.[14] Thus, physicians probably prescribed VKAs to a selection of patients older than 80 years with a relatively high risk of thrombosis.

One of the limitations of this study was that patients who were considered to have too high of a risk of bleeding to use anticoagulants were not included in our study. However, this risk might only have been a problem if physicians could predict the bleeding risk. This issue can be questioned, as the predictive value of classic risk factors, such as history of bleeding or falls, proved very limited within the group of elderly patients.[20] However, we cannot rule out that clinical factors not included in the stratification models of risk of bleeding, such as cognitive function, are related to the risk of bleeding. If so, and if these factors influenced the decision of the physician to start anticoagulation therapy, the presented risks of bleeding only apply to patients considered eligible for anticoagulation therapy. Second, patients who started VKA therapy but died before their first appointment at the thrombosis service were not included in this study, which could have led to an underestimation of the bleeding risk. Third, the cause of some strokes remained unspecified despite thorough prospective adjudication. In line with common practice, the unspecified strokes were assumed in the analyses to be ischemic. Furthermore, the relatively low number of major bleeding events resulted in wide 95% CIs, which leaves some uncertainty regarding the true relative risk. On the other hand, the low number of major bleeding events is reassuring in itself. Moreover, minor bleeding alerts clinicians for subsequent major bleeding and therefore reflects the general tendency of the patient to experience bleeding events.[21] In this large cohort study, we found no indications that bleeding severity increased with age, while the frequency increased only mildly.

The strengths of this study included the real-life data, the thorough adjudication of end points, the lack of exclusion criteria, and the large cohort size. The latter enabled us to perform separate analyses in the inception and long-term cohort. In this way, we could analyze the effect of age in 2 situations: in elderly patients who started to use VKAs and in aging patients who were already using VKAs. Moreover, the inception cohort enabled us to estimate the risk of bleeding associated with initiation of VKAs without survivor bias. The lack of exclusion criteria and the comparable findings in most of the additional subanalyses endorse the generalizability of our findings.

Although physicians may believe that the risk of bleeding keeps rising with age, we found that the risk stabilized in patients aged 80 to 89 years and only mildly increased above 90 years. One of the possible explanations is that risk of bleeding rises steadily with age within patients but that the eldest patients are a natural selection of less frail individuals: a survivors cohort. Our data suggest that this selection results in fewer frail women than men, as the bleeding risk rises more sharply with age in men. The sex difference could also be explained by more extreme worsening of VKA control with age in men, but this possibility is not supported by our data. Last, the sex difference could also be a chance finding because we are not aware of any other study supporting this finding.

As men had a higher absolute bleeding risk, the large proportion of women in the eldest group could also partly explain the relatively low risk of bleeding in that group. Another explanation is that the risk of bleeding is counterbalanced by extra precautions, such as the instruction to use paracetamol instead of nonsteroidal anti-inflammatory drugs in case of pain.

Conclusions

Irrespective of the underlying mechanism, our data on patients considered eligible for anticoagulation therapy suggest that the recommendations to use anticoagulants in patients older than 80 years can be safely extrapolated to the eldest women as well. The stronger increase in risk of bleeding in the eldest men makes us more cautious to draw final conclusions for this group of patients.

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Author Affiliations: Division of Hemostasis and Thrombosis, Department of Hematology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands (Kooistra, Piersma-Wichers, Kluin-Nelemans, Meijer); Certe Thrombosis Service Groningen, Groningen, the Netherlands (Kooistra, Piersma-Wichers); Department of Internal Medicine, Medical Center Leeuwarden, Leeuwarden, the Netherlands (Calf); University Center for Geriatric Medicine, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands (Izaks); Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands (Veeger).

Author Contributions: Drs Kooistra and Veeger had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Kooistra, Izaks, Meijer.
Acquisition, analysis, or interpretation of data: Kooistra, Calf, Piersma-Wichers, Kluin-Nelemans, Veeger, Meijer.
Drafting of the manuscript: Kooistra, Piersma-Wichers.
Critical revision of the manuscript for important intellectual content: All authors.
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