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VITAMIN K ANTAGONIST USE AND MORTALITY IN DIALYSIS PATIENTS

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Abstract

Introduction: The risk-benefit ratio of vitamin K antagonists for different CHA_2DS_2-VASc scores in patients with end-stage renal disease treated with dialysis is unknown. The aim of this study was to investigate the association between vitamin K antagonist use and mortality for different CHA_2DS_2-VASc scores in a cohort of end-stage renal disease patients receiving dialysis treatment.

Methods: We prospectively followed 1718 incident hemodialysis patients. Hazard ratios (HRs) were calculated for all-cause and cause-specific (stroke, bleeding, cardiovascular and other) mortality associated with vitamin K antagonist use.

Results: Vitamin K antagonist use as compared with no vitamin K antagonist use was associated with a 1.2-fold (95% CI 1.0-1.5) increased all-cause mortality risk, a 1.5-fold (95% CI 0.6-4.0) increased stroke mortality risk, a 1.3-fold (95% CI 0.4-4.2) increased bleeding mortality risk, a 1.2-fold (95% CI 0.9-1.8) increased cardiovascular mortality risk and a 1.2-fold (95% CI 0.8-1.6) increased other mortality risk after adjustment. Within patients with a CHA_2DS_2-VASc score of equal to or less than one, vitamin K antagonist use was associated with a 2.8-fold (95% CI 1.0-7.8) increased all-cause mortality risk as compared with no vitamin K antagonist use, while vitamin K antagonist use within patients with a CHA_2DS_2-VASc score of two or more was not associated with an increased mortality risk after adjustment.

Conclusion: Vitamin K antagonist use was not associated with a protective effect on mortality in the different CHA_2DS_2-VASc scores. The lack of knowledge on the indication for vitamin K antagonist use could lead to confounding by indication.

Introduction

Vitamin K antagonists are used to prevent stroke in patients with an increased risk of stroke due to atrial fibrillation [1,2]. Current American College of Cardiology/American Heart Association atrial fibrillation guidelines and European Society of Cardiology guidelines for the management of atrial fibrillation suggest the consideration of vitamin K antagonist prescription for those with high stroke risks based on increased CHA_2DS_2-VASc scores (score of two or more) [1,2]. These guidelines are based on several clinical trials in the general population, in which benefits of vitamin K antagonists outweigh the risks of bleeding for patients with an increased stroke risk [3,4].

The risk-benefit ratio of vitamin K antagonists in patients with end-stage renal disease treated with dialysis and atrial fibrillation is unknown. This is under scribed by the 2016 European Society of Cardiology guideline stating the need for research in this patient group [2]. Previous studies that investigated the effect of vitamin K antagonists in dialysis patients showed conflicting results [5-13]. Only two of these studies showed a decreased risk of stroke [5] or survival benefit [6] for vitamin K antagonist use as compared with no vitamin K antagonist use in dialysis patients, while all other studies did not show a protective effect of vitamin K antagonists on stroke risk or all-cause mortality [9-14]. The studies showing a decreased risk had several limitations, including limited adjustment for confounders. Furthermore, these studies also included transplantation patients. A meta-analysis performed in over 9800 dialysis patients with atrial fibrillation showed that vitamin K antagonist treatment was associated with a 1.2-fold (95% CI 0.8-1.9) increased stroke risk [7]. Several studies showed an increased bleeding risk for vitamin K antagonists [13,15]. It is plausible that pre-existing platelet dysfunction, routine heparin use during hemodialysis treatment and a suboptimal time in therapeutic range leads to increased risks of bleeding complications in dialysis patients [16,17]. Because of the higher bleeding risk in dialysis patients compared to the general population, it could be that vitamin K antagonists are only beneficial in higher CHA_2DS_2-VASc scores (i.e. higher stroke risks) than the cut-off score of two used in the general population. However, studies investigating the association between vitamin K antagonist use and mortality for different CHA_2DS_2-VASc scores in dialysis patients are lacking.

Therefore, the aim of this study was to investigate the association between vitamin K antagonist use and mortality for different CHA_2DS_2-VASc scores in a cohort of end-stage renal disease patients with and without atrial fibrillation receiving dialysis treatment.

Methods

Patients

The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) is a prospective multicenter cohort study in which incident adult end-stage renal disease patients in the

Netherlands were included. Eligibility included age older than 18 years, and no previous renal replacement therapy. All patients gave informed consent and the study was approved by all local medical ethics committees. We followed patients until death or censoring, i.e. transfer to a nonparticipating dialysis center, withdrawal from the study, transplantation, or end of the follow-up period (February 2015).

Demographic and clinical data

Data on age, sex, primary kidney disease, dialysis modality, gastro-intestinal problems including bleeding, malignancy and cardiovascular disease (angina pectoris, myocardial infarction, heart failure, ischemic stroke, or claudication) were collected at the start of dialysis treatment. Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) [18]. We grouped patients into four classes of primary kidney disease: glomerulonephritis, diabetes mellitus, renal vascular disease, and other kidney diseases. Antiplatelet drug use, vitamin K antagonist use, blood pressure and laboratory data were collected at three months after the start of dialysis, which was defined as baseline. Blood pressure was measured in the sitting position. Hypertension was defined as a systolic blood pressure ≥140mmHg or use of anti-hypertensive agents. CHA_2DS_2-VASc scores were calculated (Congestive heart failure=1 point, hypertension=1 point, age ≥75 years=2 points, age 65-74 years=1 point, diabetes mellitus=1 point, prior stroke=2 point, vascular disease including peripheral artery disease or myocardial infarction=1 point and female sex=1 point) [19,20], as were HAS-BLED scores (hypertension=1 point, kidney disease=1 point, liver cirrhosis=1 point, prior stroke=1 point, prior bleeding=1 point, age >65 years=1 point, predisposing medication use=1 point, drug or alcohol abuse history=1 point). The HAS-BLED score lacks 1 possible point for labile International Normalized Ratio (INR), since we had no data on INR. We had no data on the presence of atrial fibrillation. Serum hemoglobin, urea and creatinine were routinely measured in the dialysis centers at three months after start of dialysis. Residual glomerular filtration rate (GFR) was calculated as the mean of creatinine and urea clearance corrected for body surface area (ml/min per 1.73 m^2).

Mortality

We classified causes of death according to the codes of the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA) which is a standardized classification of death causes in dialysis patients [18]. We grouped death causes into stroke, bleeding, cardiovascular and other. Stroke mortality was defined as death due to cerebrovascular accident (code 22). Bleeding mortality was defined as death due to hemorrhagic pericarditis (code 13), gastro-intestinal hemorrhage (code 23), hemorrhage from graft site (code 24), hemorrhage from vascular access or dialysis circuit (code 25), hemorrhage from ruptured vascular aneurysm (code 26), hemorrhage from surgery (code 27), other hemorrhage (code 28) and perforation of peptic ulcer (code 71). Cardiovascular

mortality was defined as death due to myocardial ischemia and infarction (code 11), cardiac arrest/ sudden death (code 15), cardiac failure/ fluid overload/ pulmonary edema (codes 14,16,18), hyperkalemia /hypokalemia (code 12,17), pulmonary embolism (code 21), mesenteric infarction (code 29) and cause of death uncertain/unknown (code 0). Other mortality was defined as death caused by pulmonary infection (code 31-33), infections elsewhere (code 34), septicemia (code 35), tuberculosis (code 36-37), generalized viral infection (code 38), peritonitis (code 39), suicide (code 52), treatment cessation (code 51, 53-54), cachexia (code 64), malignancies (codes 66-68) and miscellaneous (codes 41-46, 61-63, 69-70, 72-73, 81-82, 99-102).

Statistical analysis

Continuous variables are presented as median and interquartile range (IQR). Categorical variables are presented as percentages. Survival curves were determined with the Kaplan-Meier method and mortality rates per 1000 person-years were calculated for vitamin K antagonist users and vitamin K antagonist non-users. We calculated crude and adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) for all-cause and cause-specific (stroke, bleeding, cardiovascular and other) mortality within five-years of follow-up using Cox proportional hazard regression analysis. In an additional analysis, we calculated HRs with 95% CIs for all-cause and cause-specific mortality for dialysis patients with a CHA_2DS_2-VASc score of two, a CHA_2DS_2-VASc score of three and a CHA_2DS_2-VASc score of four or more as compared with a CHA_2DS_2-VASc score of equal to or less than one. Furthermore, we calculated crude and adjusted HRs with 95% CIs for all-cause mortality within five-years of follow-up for vitamin K antagonist users as compared with vitamin K antagonist non-users within patients with a CHA_2DS_2-VASc score of equal to or less than one, a CHA_2DS_2-VASc score of two, a CHA_2DS_2-VASc score of three and a CHA_2DS_2-VASc score of four or more. Finally, we calculated HR's with 95% CIs for all-cause mortality for vitamin K antagonist users as compared with vitamin K antagonist non-users for patients with a low CHA_2DS_2-VASc score (<2) and a low HAS-BLED score (≤3), a low CHA_2DS_2-VASc score and a high HAS-BLED score, a high CHA_2DS_2-VASc score and a low HAS-BLED score, and a high CHA_2DS_2-VASc score and a high HAS-BLED score. As a sensitivity analysis we repeated the analyses for all-cause mortality stratifying for dialysis modality. HRs were adjusted for age, sex, primary kidney disease, dialysis modality, hypertension, antiplatelet drug use, gastro-intestinal problems including bleeding, malignancy, cardiovascular disease (angina pectoris, myocardial infarction, heart failure, ischemic stroke, or claudication), GFR and hemoglobin levels. All analyses were performed in SPSS statistical software version 23.0 (IBM SPSS Statistics).

Results

Baseline characteristics

Baseline characteristics are shown in Table 1. Of the 1718 patients, 244 patients used vitamin K antagonists and 1474 patients did not use vitamin K antagonists. Vitamin K antagonist users were older, had more often hemodialysis as dialysis modality, had higher CHA_2DS_2-VASc scores, had more often cardiovascular diseases, less often used antiplatelet drugs and had lower hemoglobin levels than patients who did not use vitamin K antagonists.

Table 1. Baseline characteristics

	Vitamin K antagonist users N=244		Vitamin K antagonist non-users N=1474	
Age (years) (IQR)	67.6	(56.4-75.2)	61.3	(48.3-71.0)
Sex, female (%)	40.2		38.4	
Primary kidney disease (%)				
Diabetes mellitus	17.6		15.8	
Glomerulonephritis	7.0		14.9	
Renal vascular disease	32.8		16.3	
Other	42.6		53.0	
Dialysis modality				
Hemodialysis	87.3		60.6	
Peritoneal dialysis	12.7		39.4	
CHA_2DS_2-VASc score				
0-1	10.7		28.9	
2	22.1		29.2	
3	22.1		20.6	
≥4	45.1		21.2	
Cardiovascular disease (%)	59.0		31.7	
Malignancy (%)	12.4		9.1	
Gastro-intestinal diseases (%)	6.2		5.7	
Hypertension (%)	88.1		89.1	
Antiplatelet drugs use (%)	9.8		25.7	
GFR (ml/min) (IQR)	3.4	(1.6-5.2)	3.3	(1.7-5.3)
Hemoglobin (mmol/L) (IQR)	6.7	(6.1-7.3)	6.9	(6.3-7.6)

IQR; interquartile range, GFR; glomerular filtration rate

Vitamin K antagonist use and mortality

During the five-years of follow-up, 141 of the 244 vitamin K antagonist users and 540 of the 1476 vitamin K antagonist non-users died, 66 vitamin K antagonist users and 700 vitamin K antagonist non-users were censored. Figure 1 shows the Kaplan-Meier survival curve with

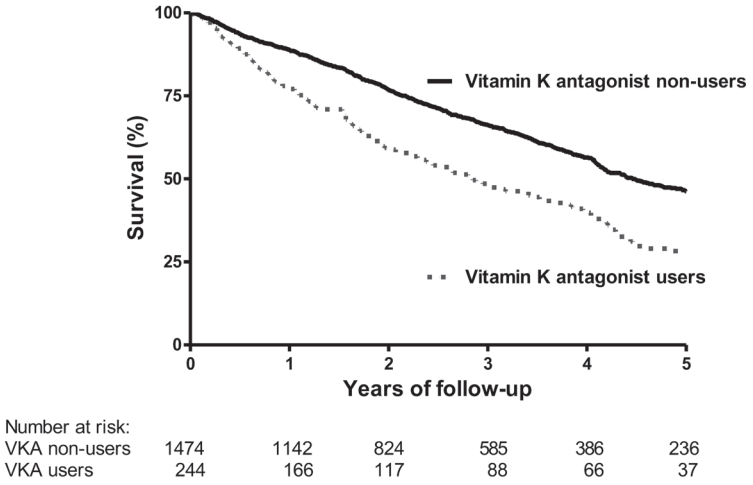

Figure 1. Kaplan–Meier curves for mortality of vitamin K antagonist users and non–users

five-years mortality as outcome. The five-year cumulative survival was 27.9% for vitamin K antagonist users and 46.2% for vitamin K antagonist non-users.

The mortality rate was 250 per 1000 person-years for vitamin K antagonist users and 144 per 1000 person-years for vitamin K antagonist non-users. Vitamin K antagonist use as compared with no vitamin K antagonist use was associated with a 1.2-fold (95% CI 1.0-1.5) increased five-years mortality risk after adjustment for age, sex, primary kidney disease, dialysis modality, cardiovascular disease, hypertension, malignancy, gastro-intestinal disease, antiplatelet drug use, GFR and hemoglobin levels (Table 2). Table 3 shows adjusted hazard ratios for patients who used vitamin K antagonists as compared with patients who did not use vitamin K antagonists for stroke mortality (HR 1.5; 95% CI 0.6-4.0), bleeding mortality (HR 1.3; 95% CI 0.4-4.2), cardiovascular mortality (HR 1.2; 95% CI 0.9-1.8), and for other mortality (HR 1.2; 95% CI 0.8-1.6).

Table 2. Vitamin K antagonist use versus no vitamin K antagonist use and all–cause mortality

		Mortality rate per 1000 person-years	Crude HR (95% CI)	Adjusted* HR (95% CI)	Adjusted** HR (95% CI)	
Vitamin K antagonist non-users	(N=1474)	144	1 (reference)	1 (reference)	1 (reference)	(reference)
Vitamin K antagonist users	(N=244)	250	1.7 (1.4-2.1)	1.3 (1.0-1.5)	1.2 (1.0-1.5)	(1.0-1.5)

HR; hazard ratio, CI; confidence interval. *Adjusted for age, sex, primary kidney disease, dialysis modality, cardiovascular disease, hypertension, malignancy, gastro-intestinal disease, antiplatelet drug use **Additionally adjusted for laboratory measurements (GFR and hemoglobin)

Table 3. Vitamin K antagonist use versus no vitamin K antagonist and cause–specific mortality

			Stroke Mortality	Bleeding Mortality	Cardiovascular Mortality	Other mortality
Vitamin K antagonist non-users	(N=1474)		1 (reference)	1 (reference)	1 (reference)	1 (reference)
Vitamin K antagonist users	(N=244)	Crude HR (95% CI)	1.7 (0.8-3.7)	2.3 (0.8-6.4)	1.6 (1.2-2.2)	1.8 (1.4-2.4)
		Adjusted* HR (95% CI)	1.5 (0.6-4.0)	1.3 (0.4-4.2)	1.2 (0.9-1.8)	1.2 (0.8-1.6)

HR; hazard ratio, CI; confidence interval. *Adjusted for age, sex, primary kidney disease, dialysis modality, cardiovascular disease, hypertension, malignancy, gastro-intestinal disease, antiplatelet drug use, GFR and hemoglobin levels

Vitamin K antagonist use and mortality in patients with low and high CHA2DS2–VASc scores

The risk of all-cause mortality, stroke mortality, bleeding mortality, cardiovascular mortality, and other mortality increased with increasing CHA_2DS_2-VASc scores (Table 4). The risk of all-cause mortality increased with increasing CHA_2DS_2-VASc scores in both vitamin K antagonist users and non-users. Within patients with a low CHA_2DS_2-VASc score (score of equal to or less than one), vitamin K antagonist use was associated with a 2.8-fold (95% CI 1.1-7.9) increased mortality risk as compared with no vitamin K antagonist use after adjustment. There was no association between vitamin K antagonist use as compared with no vitamin K antagonist use within patients with a high CHA_2DS_2-VASc score (score of two and more). Within dialysis patients with a high CHA_2DS_2-VASc score, HRs were 0.9 (95% CI 0.5-

Table 4. CHA_2DS_2–VASc scores and mortality

CHA_2DS_2-VASc Scores		All-cause Mortality		Stroke Mortality		Bleeding Mortality	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
0-1	(N=452)	1	(reference)	1	(reference)	1	(reference)
2	(N=485)	2.2	(1.6-3.0)	10.6	(1.4-81.2)	3.5	(0.4-31.6)
3	(N=358)	4.4	(3.2-6.0)	15.4	(2.0-118.3)	6.5	(0.8-55.7)
≥4	(N=423)	7.6	(5.7-10.1)	18.8	(2.5-142.8)	12.0	(1.5-94.8)

CHA_2DS_2-VASc Scores		Cardiovascular mortality		Other mortality	
		HR	(95% CI)	HR	(95% CI)
0-1	(N=452)	1	(reference)	1	(reference)
2	(N=485)	1.9	(1.1-3.1)	2.2	(1.4-3.4)
3	(N=358)	4.0	(2.5-6.4)	4.3	(2.8-6.4)
≥4	(N=423)	7.6	(4.9-11.8)	7.0	(4.7-10.4)

HR; crude hazard ratio, CI; confidence interval

1.6) for patients with a CHA_2DS_2-VASc score of two, 1.2 (95% CI 0.7-2.0) for patients with a CHA_2DS_2-VASc score of three and 1.2 (95% CI 0.8-1.6) for patients with a CHA_2DS_2-VASc score of four or more (Table 5). Due to a low number of events it was not possible to investigate the association between vitamin K antagonists and cause-specific mortality for the different CHA_2DS_2-VASc scores.

Table 5. Hazard ratios for vitamin K antagonist use versus no vitamin K antagonist use for different CHA_2DS_2–VASc scores

CHA_2DS_2-VASc Scores			All-cause mortality	
			HR	(95% CI)
0-1	Vitamin K antagonist non-users		1	(reference)
	Vitamin K antagonist users	Crude HR	1.8	(0.8-4.2)
		Adjusted* HR	2.8	(1.0-7.8)
2	Vitamin K antagonist non-users		1	(reference)
	Vitamin K antagonist users	Crude HR	1.5	(1.0-2.4)
		Adjusted* HR	0.9	(0.5-1.6)
3	Vitamin K antagonist non-users		1	(reference)
	Vitamin K antagonist users	Crude HR	1.5	(1.0-2.1)
		Adjusted* HR	1.2	(0.7-2.0)
≥4	Vitamin K antagonist non-users		1	(reference)
	Vitamin K antagonist users	Crude HR	1.1	(0.8-1.4)
		Adjusted* HR	1.1	(0.8-1.6)

HR; hazard ratio, CI; confidence interval. *Adjusted for age, sex, primary kidney disease, dialysis modality, cardiovascular disease, hypertension, malignancy, gastro-intestinal disease, antiplatelet drug use, GFR and hemoglobin

We calculated the all-cause mortality risks for vitamin K antagonist users as compared with vitamin K antagonist non-users for low and high CHA_2DS_2-VASc and HAS-BLED scores. The adjusted HR for all-cause mortality in patients with a CHA_2DS_2-VASc score<2 and a HAS-BLED score ≤3 was 2.8 (95% CI 1.0-7.8), in patients with a CHA_2DS_2-VASc score≥2 and a HAS-BLED score ≤3 this was 1.2 (95% CI 0.9-1.5) and in patients with a CHA_2DS_2-VASc score≥2 and a HAS-BLED score >3 this was 1.0 (95% CI 0.3-2.9). There were no patients with a CHA_2DS_2-VASc score<2 and a HAS-BLED score >3.

Dialysis modality stratification

Stratifying for dialysis modality did not show any differences in the five-years mortality risk between the two modalities for all-cause mortality. In hemodialysis patients the adjusted HR was 1.2 (95% CI 0.9–1.5) and in peritoneal dialysis patients the adjusted HR was 1.4 (0.8-2.6). The risk of all-cause mortality increased in both dialysis modalities with increasing CHA_2DS_2-VASc scores (Table 6).

Table 6. CHA_2DS_2–VASc scores and all–cause mortality separated by dialysis modality

CHA_2DS_2-VASc		All-cause mortality			
Scores		Hemodialysis		Peritoneal dialysis	
		HR	(95% CI)	HR	(95% CI)
0-1	(N=452)	1	(reference)	1	(reference)
2	(N=485)	2.3	(1.5-3.5)	1.9	(1.2-3.1)
3	(N=358)	4.0	(2.6-6.0)	4.9	(3.0-7.8)
≥4	(N=423)	6.7	(4.5-10.0)	9.0	(5.7-14.2)

HR; crude hazard ratio, CI; confidence interval

Discussion

In this prospective cohort study of 1718 incident dialysis patients with and without atrial fibrillation, we did not find a protective effect on mortality of vitamin K antagonists. Furthermore, we showed that the mortality risk increased with increasing CHA_2DS_2-VASc scores. In addition, it was shown that within patients with a CHA_2DS_2-VASc score equal to or less than one, vitamin K antagonist use was associated with an increased mortality risk as compared with no vitamin K antagonist use, while vitamin K antagonist use within patients with a CHA_2DS_2-VASc score of two or more was not associated with a protective effect on mortality.

Most of the previous studies that investigated the effect of vitamin K antagonists in dialysis patients with atrial fibrillation did not show a protective effect of vitamin K antagonists on stroke risk or survival [7-13], while only two studies showed a decreased risk of stroke [5] or survival benefit [6] for vitamin K antagonist in dialysis patients with atrial fibrillation. The different conclusion in these two studies might be due to the lack of adjustment for confounding, and the inclusion of transplant patients in both studies. In our study, we found an increased all-cause mortality risk.

As recommended by international guidelines, the CHA_2DS_2-VASc score is frequently used as risk stratification for stroke and to guide the decision to start oral anticoagulation therapy [1,2]. These guidelines advise vitamin K antagonist use in patients with atrial fibrillation and a CHA_2DS_2-VASc score of two or more [1,2]. In our study, we found that stroke risks increased with increasing CHA_2DS_2-VASc scores which is in line with previous studies in the general population [19,20]. Since dialysis patients have an increased stroke risk, the same CHA_2DS_2-VASc scores probably reflect higher stroke risks in dialysis patients than subjects in the general population [21-23]. In our study, we found an increased mortality risk for vitamin K antagonist use in dialysis patients with a low CHA_2DS_2-VASc score. To our knowledge, we are the first to report an increased mortality risk for vitamin K antagonist use in dialysis patients with a CHA_2DS_2-VASc score of equal to or less than one. We did not find an association between vitamin K antagonist use and mortality in patients with a CHA_2DS_2-VASc score of two of more.

Unfortunately, we had no data on the indication for vitamin K antagonist use to investigate whether differences were influenced by the indication for vitamin K antagonist use.

Stratification based on HAS-BLED scores did not show a change in mortality risk for the vitamin K antagonist users as compared with non-users. Vitamin K antagonist use versus non-use was not associated with a protective effect on mortality for patients with a low CHA_2DS_2-VASc score (<2) and a low HAS-BLED score ≤3, for patients with a high CHA_2DS_2-VASc score (≥2) and a low HAS-BLED score ≤3 and for patients with a high CHA_2DS_2-VASc score (≥2) and a high HAS-BLED score (>3).

Since hemodialysis patients receive heparin during dialysis sessions, this might influence the mortality risk. However, we did not find different effects of vitamin K antagonist use in the different dialysis modalities on all-cause mortality.

There could be several pathophysiological explanations why vitamin K antagonist use in dialysis patients is not associated with a protective effect on mortality. This could be explained by an accelerated vascular calcification in dialysis patients due to the inhibition of matrix Gla protein induced by vitamin K antagonists [24]. Therefore, it could be that vitamin K antagonists are less effective in preventing stroke events in dialysis patients than in the general population [25]. Furthermore, pre-existing platelet dysfunction, altered clot properties resulting in denser clots with thinner fibrin fibers, routine heparin use during hemodialysis treatment and a suboptimal time in therapeutic range of vitamin K antagonists could lead to an increased bleeding risk in dialysis patients [16,17,26].

Generally, the benefits of vitamin K antagonists for stroke prevention in atrial fibrillation needs to be outweighed against bleeding risks. Since there are no clinical trials that investigated stroke and bleeding outcomes associated with vitamin K antagonist use in dialysis patients, guideline recommendations of vitamin K antagonist use in dialysis patients are based on observational studies. These guidelines have reported conflicting recommendations for vitamin K antagonist use in dialysis patients [1,27,28]. Current American College of Cardiology/American Heart Association atrial fibrillation Guidelines report that in dialysis patients with a CHA_2DS_2-VASc score of two or more is reasonable to prescribe vitamin K antagonists. In contrast, the Canadian guidelines [27] and the Kidney Disease Improving Global Outcomes guidelines [28] do not recommend routine anticoagulation treatment for dialysis patients with atrial fibrillation for the primary prevention of stroke events. Therefore, randomized controlled trials comparing vitamin K antagonists with placebo or direct oral anticoagulants are needed.

The general strength of this study was the large and well-defined Dutch cohort of incident dialysis patients with available data on many patient characteristics, laboratory measurements, and death. However, our study has several potential limitations. The comparison between vitamin K antagonist use versus non-use in an observational design makes confounding-by-indication the most important limitation. In our analyses, we took this into account by correcting for several confounders, but this cannot exclude possible residual confounding. Furthermore, ERA-EDTA death codes make no distinction between death due

to ischemic or hemorrhagic stroke. Therefore, we could not investigate the association between vitamin K antagonist use and hemorrhagic or ischemic stroke separately and we could not evaluate whether there was a shift from ischemic stroke events towards hemorrhagic stroke events in patients with CHA_2DS_2-VASc scores of two and more. In addition, we had no information about the indication of vitamin K antagonist use in dialysis patients. Therefore, it could be that vitamin K antagonists were used for other indications than atrial fibrillation in dialysis patients with a low CHA_2DS_2-VASc score. However, based on the high risk of atrial fibrillation in dialysis patients, it is likely that an important proportion of these patients had atrial fibrillation[13]. In addition, it could be that at initiation of vitamin K antagonist use (before dialysis), the CHA_2DS_2-VASc score was higher than at baseline of start of dialysis. Furthermore, we had no information about the presence of atrial fibrillation in vitamin K antagonist non-users. However, more than one third of dialysis patients without a diagnosis of atrial fibrillation suffer from paroxysmal atrial fibrillation [29]. These patients with undiagnosed atrial fibrillation who do not use vitamin K antagonists probably have an increased stroke risk, since other therapeutic options such as electric cardioversion or medication for rhythm control are not considered. Therefore, it could be that we overestimated the risk of stroke for vitamin K non-users. Another potential limitation is that we included dialysis patients who already used vitamin K antagonists which could have led to an underestimation of the mortality risks associated with vitamin K antagonist use. Finally, we did not have enough power to investigate the association between vitamin K antagonists and cause-specific mortality for different CHA_2DS_2-VASc scores.

In conclusion, we showed that vitamin K antagonist use compared to no vitamin K antagonist use was associated with an increased all-cause mortality risk in dialysis patients. Furthermore, we showed that the mortality risk increased with increasing CHA_2DS_2-VASc scores. In addition, it was shown that within patients with a CHA_2DS_2-VASc score of equal to or less than one, vitamin K antagonist use was associated with an increased mortality risk as compared with no vitamin K antagonist use, while vitamin K antagonist use within patients with a CHA_2DS_2-VASc score of two or more was not associated with an increased mortality risk. Randomized controlled trials comparing vitamin K antagonists with placebo or direct oral anticoagulants are needed to provide better insight into the adverse effects of vitamin K antagonists and to provide more personalized prescription of anticoagulant drugs in dialysis patients.

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