Safety and efficacy of vitamin K antagonists versus rivaroxaban in hemodialysis patients with atrial fibrillation: a multicenter randomized controlled trial

Supplementary Appendix

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Supplemental methods

Definition of secondary endpoints

Sudden death was defined as sudden and unexpected death within an hour of symptom onset. If unwitnessed, the patient was seen alive and clinically stable less than 24 hours prior to being found dead without any evidence supporting a specific cause of death.

Stroke was defined as the sudden onset of a focal neurological deficit lasting at least 24 hours, consistent with the territory of a major cerebral artery, and categorized as ischemic, hemorrhagic, or of uncertain type. Hemorrhagic transformation of ischemic stroke was not deemed to be hemorrhagic stroke. An event matching this definition but lasting less than 24 hours was considered to be a transient ischemic attack. Systemic embolism was defined as an acute vascular occlusion of a limb or organ documented by imaging, surgery, or autopsy.

Acute coronary syndrome was defined by typical symptoms and cardiac biomarker elevation above the upper limit of normal or new pathological Q waves in at least 2 contiguous electrocardiogram leads.

Symptom-driven revascularization was defined as an acute coronary syndrome or symptoms suggestive of coronary insufficiency leading to invasive coronary artery assessment and a subsequent revascularization procedure (percutaneous coronary intervention or coronary artery bypass grafting).

Hospitalization for heart failure was defined as an unscheduled hospital admission for heart failure, characterized by typical signs and symptoms and diagnostic testing consistent with a diagnosis of heart failure, including elevated natriuretic peptides, radiological evidence of congestion or echocardiographic evidence of elevated filling pressures.

Symptomatic aortic valve stenosis was defined as aortic valve stenosis resulting in symptoms such as angina, syncope or heart failure, and leading to the consideration of surgical aortic valve replacement or transcatheter aortic valve implantation.

Death from cardiac cause was defined as death resulting from acute coronary syndrome, sudden cardiac death, death due to heart failure or death due to an identified arrhythmia (captured on an electrocardiogram, witnessed on a monitor, or recorded on an implantable cardioverter-defibrillator).

Symptomatic lower limb ischemia was defined as clinical evidence of limb ischemia due to atherosclerotic vascular disease requiring revascularization or amputation. In patients undergoing multiple consecutive revascularization or amputation procedures, only the first episode was considered.

Calciphylaxis was defined as (an) active skin lesion(s) with a morphological appearance consistent with calciphylaxis (including but not limited to livedo, induration, ulceration, necrosis) or

histological features consistent with calciphylaxis (including but not limited to soft tissue calcification, arteriolar thrombosis, medial calcific necrosis of terminal arterioles).

Bowel ischemia was defined as clinical (abdominal pain), biochemical (lactic acidosis) or imaging evidence of interruption of the blood supply to a segment of the intestine.

Calculation of risk scores

The CHA_2DS_2-VASc score was calculated by assigning 1 point each for age between 65 and 74 years, history of hypertension, diabetes, congestive heart failure, vascular disease (defined as prior myocardial infarction, aortic plaque or peripheral artery disease) and female gender, and 2 points each for a history of stroke/TIA and age ≥75 years.

The HAS-BLED score was calculated by assigning automatically 1 point for abnormal renal function and 1 point each for uncontrolled hypertension (systolic blood pressure >160 mmHg), abnormal liver function, history of stroke/TIA, history of bleeding, age ≥65 years, concomitant use of drugs that enhance bleeding risk and excessive use of alcohol. Labile INR was not included in the HAS-BLED score as this would hamper comparison of patients on VKA and not on VKA.

Supplemental Tables

Supplemental Table 1: Baseline characteristics by anticoagulant discontinuation

Baseline characteristics	Anticoagulant discontinuation (n=33)	No anticoagulant discontinuation (n=99)	P[3]
Age – yr.	77.2 (68.6-82.9)	80.6 (76.1-84.1)	P=0.033
Male – % (no.)	69.7% (23/33)	65.7% (65/99)	P=0.832
History of stroke – % (no.)	27.3% (9/33)	31.3% (31/99)	P=0.827
History of gastrointestinal bleeding – % (no.)	36.4% (12/33)	25.3% (25/99)	P=0.264
Diabetes – % (no.)	48.5% (16/33)	46.5% (46/99)	P=0.844
History of AMI – % (no.)	45.5% (15/33)	46.5% (46/99)	P=0.999
Congestive heart failure – % (no.)	27.3% (9/33)	32.3% (32/99)	P=0.668
Preexisting vascular disease – % (no.)	42.4% (14/33)	56.6% (56/99)	P=0.166
Dialysis vintage – yr.	2.4 (0.8-5.9)	2.6 (0.6-5.7)	P=0.838
Incident dialysis (<3 mo.) – % (no.)	12.1% (4/33)	18.2% (18/99)	P=0.591
$CHAD_2D_2$-VASc score[1]			
Mean ± SD	4.3 (1.3)	4.8 (1.4)	
Median score ± IQR	4.0 (3.5-5.0)	5.0 (4.0-6.0)	P=0.061
Number ≥2 (men) or ≥3 (women)	100% (33/33)	100% (99/99)	--
HAS-BLED score[2]			
Mean ± SD	4.8 (1.0)	4.6 (0.9)	
Median score ± IQR	5.0 (4.0-5.5)	5.0 (4.0-5.0)	P=0.257
VKA vintage – yr.	0.9 (0.0-4.4)	1.2 (0.0-4.6)	P=0.693
VKA naïve (<3 mo.) – % (no.)	42.4% (14/33)	33.3% (33/99)	P=0.524
Aspirin – % (no.)	42.4% (14/33)	32.3% (32/99)	P=0.300

Numbers displayed are median (interquartile range) unless otherwise specified; [1]the $CHAD_2D_2$-VASc score ranges from 2 (minimum score to be included) to 9, with higher scores indicating an increased risk; [2]the HAS-BLED score ranges from 1 (as patients by definition have renal failure) to 8 (as we did not include labile INR), with higher scores indicating an increased risk; [3]according to the Fisher's exact test or the Kruskal-Wallis test.

Supplemental Table 2: Causes of death

	VKA (n=44)	Rivaroxaban (n=46)	Rivaroxaban+vit K2 (n=42)	P*
Death from any cause				
– no. (%)	32 (72.7%)	30 (65.2%)	27 (64.3%)	P=0.656
– per 100 person-years	33.7	28.3	30.2	
Sudden death – no.	5	7	4	
Cardiovascular disease				
Ischemic stroke – no.	1	0	1	
Acute coronary syndrome – no.	2	3	1	
Terminal heart failure – no.	3	1	1	
Ischemic colitis	0	2	2	
Limb ischemia – no.	1	0	1	
Bleeding				
Intracerebral bleeding – no.	1	0	0	
Gastrointestinal bleeding – no.	2	0	0	
Infectious disease				
Endocarditis – no.	1	0	1	
Sepsis – no.	3	6	2	
Respiratory infection – no.	1	3	2	
Malignancy – no.	1	2	4	
Multiorgan failure – no.	1	0	0	
Lactic acidosis – no.	1	0	0	
Accident – no.	0	0	2	
Withdrawal of dialysis – no.	9	6	6	

VKA, vitamin K antagonist; *according to Fisher's exact test.

Supplemental Table 3: Secondary efficacy outcomes for the VKA arm versus the pooled rivaroxaban arms

Outcome Parameter	VKA (n=44)	Pooled Rivaroxaban (n=88)	P**
Death from any cause – no. (%)	32 (72.7%)	57 (64.8%)	P=0.432
Sudden death – no.	5	11	P=0.850
Stroke or systemic embolism			
Ischemic or uncertain type of stroke – no.	7	6	P=0.124
Hemorrhagic stroke – no.	2	0	P=0.109
Systemic embolism – no.	0	0	--
Cardiac disease			
Acute coronary syndrome – no.	6	11	P=0.854
Symptom-driven revascularization* – no.	2	7	P=0.717
Hospitalization for heart failure – no.	5	4	P=0.159
Symptomatic aortic valve stenosis – no.	2	0	P=0.109
Death from cardiac cause – no.	5	6	P=0.505
Other vascular disease			
Symptomatic lower limb ischemia– no.	20	19	P=0.0080
Calciphylaxis – no.	4	2	P=0.095
Bowel ischemia – no.	1	4	P=0.664

*Including acute coronary syndrome; **according to Fisher's exact test; VKA, vitamin K antagonist

Supplemental Table 4: Bleeding outcomes for the VKA arm versus the pooled rivaroxaban arms

Outcome Parameter	VKA (n=44)	Pooled Rivaroxaban (n=88)	P_{Cox}	$P_{Cox\text{-}adj}$
Total bleeding	24 (49)	43 (72)	P=0.793	P=0.561
Life-threatening bleeding	11 (12)	9 (11)	P=0.036	P=0.033
Major bleeding	10 (18)	10 (12)	P=0.085	P=0.081
Life-threatening or major bleeding	17 (30)	17 (23)	P=0.017	P=0.015
Minor bleeding	13 (19)	32 (49)	P=0.379	P=0.407
Gastrointestinal bleeding	12 (23)	22 (35)	P=0.738	P=0.744

Cell entries are number of patients with at least one bleeding episode (total number of bleeding episodes); P_{Cox}, significance of differences in time to first bleeding episode according to Cox proportional hazard model analysis; $P_{Cox\text{-}adj}$, P_{Cox} adjusted for competing risk of death; VKA, vitamin K antagonist

Supplemental Figure

Supplemental Figure 1: Kaplan-Meier curve for the primary endpoint in the VKA arm versus the pooled rivaroxaban arms

Survival free of fatal and non-fatal cardiovascular events in the VKA (blue line) and pooled rivaroxaban (red line) groups. The primary endpoint occurred in 35 patients in the VKA group (63.8 per 100 person-years) and in 40 patients in the pooled rivaroxaban groups (23.8 per 100 person-years). The estimated competing risk adjusted hazard ratio (95% CI, P-value) was 0.37 (0.24-0.58, P<0.0001) in the pooled rivaroxaban groups in comparison to the VKA group.