

Supplementary Table 1 Definition of variables outcomes according to international classification of diseases 9th and international classification of diseases 10th revision from Med-Echo databases

	ICD-9 codes	ICD-10 codes
Thromboembolic events		
-Stroke		
Hemorrhagic stroke intracranial (non-traumatic)	430, 431, 432.x	I60, I61, I62
Ischaemic stroke	433.xx, 434.xx, 436.0, 436.9	I63 except I63.6, I64 (primary diagnosis only using Med-Echo)
-Systemic embolism	444.x, 557.0, 362.31, 362.32, 598.31	I74 (primary only) (primary diagnosis only using Med-Echo)
Arterial embolism and thrombosis	444.x (primary diagnosis only using Med-Echo)	I74.0, I74.1, I74.2, I74.3, I74.5, I74.8, I74.9 (primary diagnosis only using Med-Echo)
Ischemic colitis or mesenteric thromboembolism	557.0 (primary diagnosis only using Med-Echo)	K55.0 (primary diagnosis only using Med-Echo)
Retinal artery thromboembolism	362.31, 362.32 (primary diagnosis only using Med-Echo)	H34.1, H34.2 (primary diagnosis only using Med-Echo)
Renal artery thromboembolism	593.81 (primary diagnosis only using Med-Echo)	N28.0 (primary diagnosis only using Med-Echo)
All-cause of deaths		
Myocardial infarction	410	I21
Major bleeding		
-Intracranial major bleeding		
Intracranial bleeding	430, 431, 432.x, 852.x, 853.x	I60, I61, I62, S06.3, S06.4, S06.5, S06.6 (primary diagnosis or the first secondary diagnosis using Med-Echo)

-Major gastrointestinal bleeding

Upper gastrointestinal bleeding (only using Med-Echo) 456.1, 530.7, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.1, 578.0 (primary diagnosis only using Med-Echo) I85.0, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K92.0 (primary diagnosis only using Med-Echo)

Upper gastrointestinal bleeding (only using RAMQ) 456.1, 530.7, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.1, 578.0 RAMQ ICD-9 at an emergency room and procedure endoscopic control of gastric or duodenal bleeding or upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate with control of bleeding, any method (code 00691) within 7 d I85.0, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K92.0 RAMQ ICD-9 at an emergency room and procedure endoscopic control of gastric or duodenal bleeding or upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate with control of bleeding, any method (00691) within 7 d

Lower gastrointestinal bleeding 562.02, 562.03, 562.12, 562.13, 569.3x, 569.85, 578.1x, 578.9 (primary diagnosis only using Med-Echo) K57.11, K57.13, K57.31, K57.33, K62.5, K55.21, K92.1, K92.2 (primary diagnosis only using Med-Echo)

-Other critical sites of major bleeding

Gross hematuria 599.7 (primary diagnosis only using Med-Echo) R31 (primary diagnosis only using Med-Echo)

Hemoptysis 786.3x (primary diagnosis only using Med-Echo) R04.2, R04.89, R04.9 (primary diagnosis only using Med-Echo)

Vitreous hemorrhage 379.23 (primary diagnosis only) H43.13 (primary diagnosis only)

	using Med-Echo)	using Med-Echo)
Urogenital bleed	626.2x and 280.0 (primary only), 285.1 (principal diagnosis or the first secondary diagnosis) or 285.9 (principal diagnosis or the first secondary diagnosis using Med-Echo)	N92.0 and D50.0 (primary only), D62 (principal diagnosis or the first secondary diagnosis), D64.9 (principal diagnosis or the first secondary diagnosis using Med-Echo)
Hemarthrosis	719.1x (primary diagnosis only using Med-Echo)	M25.0x (primary diagnosis only using Med-Echo)
Hemopericardium	423.0 (primary diagnosis only using Med-Echo)	I31.2 (primary diagnosis only using Med-Echo)
Hemoperitoneum	568.8 (primary diagnosis only using Med-Echo)	K66.1 (primary diagnosis only using Med-Echo)
Hemorrhage not specified	459.0x (primary diagnosis only using Med-Echo)	R58.0 (primary diagnosis only using Med-Echo)
Acute posthemorrhagic anemia	285.1x (primary diagnosis only using Med-Echo)	D62 (primary diagnosis only using Med-Echo)

ICD-9: International classification of diseases 9th revision; ICD-10: International classification of diseases 10th revision; RAMQ: Régie de l'assurance maladie du Québec.

Supplementary Table 2 Risk score definition for CHADS₂ and modified HAS-BLED

Risk score definition	Points if present
CHADS ₂	
Congestive heart failure or left ventricular dysfunction	1
Hypertension	1
Age ≥ 75 yr	1
Diabetes mellitus	1
Stroke (ischemic stroke, transient ischemic disease or systemic embolism)	2
Modified HAS-BLED	
Hypertension	1
Abnormal renal function	1
Abnormal hepatic function	1
Abnormal stroke (ischemic stroke, transient ischemic disease)	1
Bleeding	1
Older than > 65 yr	1
Labile international normalized ratio (not available)	1
Drugs (acetylsalicylic acid, clopidogrel, prasugrel, ticagrelor, ticlopidine, or nonsteroidal anti-inflammatory drugs) in the one month preceding the intracranial hemorrhage hospitalization or one month after discharge	1
Alcohol intake	1

Supplementary Table 3 Definition of variables used in the risk score definition of CHADS₂ according to international classification of diseases 9th revision and international classification of diseases 10th revision from Med-Echo databases

	ICD-9 codes	ICD-10 codes
CHADS ₂		
Congestive heart failure	402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93, 425.4, 428.0	I11.0, I13.0, I13.2, I42.0, I50
Left ventricular dysfunction	428.1, 428.9	I50.1, I50.9
Hypertension	401	I10
Diabetes	250.x	E08, E10, E11, E13
Ischemic stroke	433.xx, 434.xx, 436	I63 except 63.6, I67.89
Systemic embolism	444.x, 557.0, 362.31, 362.32, 598.31	I74, K55.0, H34.1, H34.2, N28.0
Transient ischemic stroke	435.x	G45

ICD-9: International classification of diseases 9th revision; ICD-10: International classification of diseases 10th revision.

Supplementary Table 4 Definition of variables used in the risk score definition of modified HAS-BLED based on associated morbidities and concomitant drugs

	ICD-9	ICD-10
Modified HAS-BLED		
Ischemic stroke	433.xx, 434.xx, 436	I63 except I63.6, I67.89
Transient ischemic attack	435.x	G45
Moderate to severe renal disease	404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 580.0, 580.4, 581.0, 581.1, 581.2, 581.3, 581.89, 581.9, 582.0, 582.1, 582.2, 582.89, 582.9, 583.0, 583.1, 583.2, 583.4, 583.7, 583.6, 583.89, 583.9, 584.5, 584.6, 584.7, 584.8, 584.9, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 586, 590.0, 590.01, 590.80	I12, I13, N00, N01, N02, N03, N04, N05, N07, N11, N12, N14, N17, N18, N19
Moderate to severe liver disease	570, 572.3, 070.0, 070.21, 070.20, 070.60	K7200, K762, K766, B150, B160, B162, B190, K704, I85
Haemorrhagic intracranial (non-traumatic)	430, 431, 432.x	I60, I61, I62
Extracranial major or unclassified major bleeding	<u>Upper GI:</u> 456.1, 530.7, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 537.83, 578.0 <u>Lower GI:</u> 562.02, 562.03, 562.12, 562.13, 569.3x, 569.85, 578.1x, 578.9 <u>Other sites:</u> 626.2x and 280.0, 285.1 or 285.9, 599.7, 786.3x, 379.23, 719.1x, 423.0x, 568.8, 459.0x, 285.1x	<u>Upper GI:</u> I850, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K2901, K290, K31811, K920 <u>Lower GI:</u> K921, K922, K5711, K5713, K5731, K5733, K625, K5521 <u>Other sites:</u> N92.0 and D50.0 or D62 or D64.9, R31, R042, R0489, R049, H43.13, M250x, I31.2, K66.1, R58.0, D62
Gastrointestinal bleeding	<u>Upper GI:</u> 531.0x, 531.2x, 531.4x,	<u>Upper GI:</u> K250, K252, K254, K256,

		531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 537.83, 578.0	K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K2901, K290, K31811, K920
		578.0	Lower GI: 562.02, 562.03, K921, K922, K5711, K5713, K5731, 562.12, 562.13, 569.3x, 569.85, 578.1x, K5733, K625, K5521
		578.9	
Traumatic bleeding	intracranial	852x, 853x	S063, S064, S065, S066
Clopidogrel, prasugrel, ticagrelor	ticlopidine,	46486, 47307, 45617, 47402, 47834, 47866	46486, 47307, 45617, 47402, 47834, 47866
Low-dose acid	acetylsalicylic	00143, 46353 (daily dose < 100 mg)	00143, 46353 (daily dose < 100 mg)
Nonsteroidal inflammatory drugs	anti-	46353, 38184, 47327, 47078, 41694, 47059, 43150, 47122, 33803, 44749, 04745, 46654, 47506, 04810, 38691, 44359, 47385, 47084, 19752, 47890, 07462, 42019, 47346, 47107, 40381, 45592, 45407, 03766	46353, 38184, 47327, 47078, 41694, 47059, 43150, 47122, 33803, 44749, 04745, 46654, 47506, 04810, 38691, 44359, 47385, 47084, 19752, 47890, 07462, 42019, 47346, 47107, 40381, 45592, 45407, 03766
Alcohol		331.7, 359.4, 425.5, 577.1	E224, E529A, F10, G312, G612, G721, I426, K292, K70, K860, L278A, O354, T51, Z714, Z721

ICD-9: International classification of diseases 9th revision; ICD-10: International classification of diseases 10th revision; GI: Gastrointestinal.

Supplementary Table 5 Demographic and clinical characteristics of the initial cohort and the cohort after inverse probability of treatment weighting of new oral anticoagulant users with stage III chronic kidney disease (CKD) in warfarin *vs.* rivaroxaban 15 mg users with stage III CKD from 2013 to 2017

	Initial cohort			Cohort after IPTW		
	Warfarin (<i>n</i> = 3335)	Rivaroxaban 15 mg (<i>n</i> = 744)	Absolute standard ized difference	Warfarin (<i>n</i> = 3335)	Rivaroxaban 15 mg (<i>n</i> = 744)	Absolute standardi zed difference
Age (mean ± SD)	83.0 ± 8.5	82.6 ± 7.8	0.04	82.9 ± 8.6	82.8 ± 7.7	0.01
Female sex (%)	56.6	55.8	0.02	56.5	56.5	< 0.01
CHADS ₂ score (mean ± SD)	3.1 ± 1.2	2.8 ± 1.2	0.22	3.0 ± 1.2	3.0 ± 1.2	0.02
HAS-BLED score (mean ± SD)	3.6 ± 1.3	3.2 ± 1.3	0.29	3.5 ± 1.3	3.5 ± 1.3	< 0.01
Charlson-Deyo Comorbidity Index (mean ± SD)	6.1 ± 3.4	5.3 ± 3.5	0.22	5.9 ± 3.4	6.0 ± 3.6	0.02
Frailty score (mean ± SD)	18.9 ± 6.0	17.2 ± 6.5	0.29	18.6 ± 6.2	18.6 ± 5.9	< 0.01
Comorbidities (including the index hospitalization and the three years prior to cohort entry)						
Hypertension (%)	87.0	82.8	0.12	86.2	86.5	0.01
Coronary artery disease (%)	65.9	59.1	0.14	64.7	65.1	0.01
Acute myocardial infarction (%)	22.0	17.1	0.12	21.1	20.3	0.02
Chronic heart failure (%)	58.0	48.1	0.20	56.2	56.7	0.01
Cardiomyopathy (%)	7.9	7.8	< 0.01	7.9	8.3	0.02
Other cardiac dysrhythmias (%)	19.2	16.7	0.07	18.8	19.0	0.01
Valvular heart disease (%)	27.4	19.6	0.18	26.1	27.1	0.02
Stroke/transient ischemic attack (%)	17.4	14.9	0.07	16.9	17.2	0.01
Peripheral vascular disease (%)	29.2	20.6	0.20	27.7	27.5	<0.01
Dyslipidemia (%)	56.0	47.9	0.16	54.4	53.3	0.02
Diabetes (%)	46.7	37.6	0.18	45.1	46.1	0.02
Major bleeding (%)	40.2	31.1	0.19	38.5	38.3	<0.01

Major intracranial bleeding (%)	3.6	3.8	0.01	3.7	3.7	< 0.01
Major gastrointestinal bleeding (%)	8.6	6.7	0.07	8.3	9.5	0.04
Other sites of major bleeding (%)	33.5	25.5	0.17	32.0	30.9	0.02
Liver disease (%)	2.7	2.0	0.04	2.6	2.8	0.02
Chronic obstructive pulmonary disease/asthma (%)	44.3	42.1	0.04	44.0	44.2	0.01
Depression (%)	11.9	11.8	< 0.01	11.8	11.5	0.01
Medical procedures (three years prior to cohort entry)						
Cardiac catheterization (%)	5.2	4.3	0.04	5.0	5.4	0.02
Percutaneous coronary intervention-stent (%)	4.1	3.9	0.01	4.1	3.9	0.01
Coronary artery bypass grafting (%)	0.7	0.4	0.04	0.6	0.5	0.02
Implantable cardiac device (%)	0.1	0.1	0.02	0.1	0.1	0.01
Medications (two weeks prior to cohort entry)						
Statin (%)	51.7	48.1	0.07	51.0	51.2	< 0.01
Antiplatelet (%)	9.2	6.3	0.11	8.7	8.5	0.01
Low-dose acetylsalicylic acid (%)	36.0	32.3	0.08	35.3	35.5	< 0.01
Proton pump inhibitors (%)	50.9	44.0	0.14	49.7	49.6	< 0.01
Nonsteroidal anti-inflammatory drugs (%)	0.8	1.5	0.06	0.9	0.9	< 0.01
Digoxin (%)	9.5	8.3	0.04	9.3	10.6	0.04
Amiodarone (%)	9.8	8.7	0.04	9.6	9.3	0.01
Antidepressants (%)	10.5	10.4	0.01	10.5	10.1	0.01
Beta-blockers (%)	62.9	60.8	0.04	62.5	63.1	0.01
Calcium channel blockers (%)	44.0	38.6	0.11	42.9	42.6	0.01
Inhibitors of the renin-angiotensin system (%)	37.3	38.6	0.03	37.5	36.9	0.01

Diuretics (%)	61.3	57.1	0.08	60.5	60.3	0.01
Loop diuretics (%)	57.1	52.6	0.09	56.2	55.8	0.01
Antidiabetics (%)	28.3	23.7	0.11	27.4	28.0	0.01
Health medical services (one year prior to cohort entry)						
Consultations with specialist physicians (mean ± SD)	1.1 ± 2.3	1.3 ± 2.0	0.05	1.2 ± 2.4	1.2 ± 1.9	< 0.01
Consultations with family physicians (mean ± SD)	1.3 ± 3.3	1.4 ± 2.8	0.03	1.3 ± 3.3	1.3 ± 2.8	0.01
Emergency visits (mean ± SD)	3.5 ± 3.2	3.1 ± 2.8	0.07	3.4 ± 3.1	3.4 ± 2.9	0.02
Health hospital services (three years prior to cohort entry)						
All-cause hospital admission (mean ± SD)	2.5 ± 2.1	2.3 ± 2.1	0.09	2.5 ± 2.1	2.5 ± 2.0	0.02

IPTW: Inverse probability of treatment weighting.

Supplementary Table 6 Demographic and clinical characteristics of the initial cohort and the cohort after inverse probability of treatment weighting of new oral anticoagulant users with stage III chronic kidney disease (CKD) in warfarin *vs.* rivaroxaban 20 mg new users with stage III CKD from 2013 to 2017

	Initial cohort			Cohort after IPTW		
	Warfarin (<i>n</i> = 3335)	Rivaroxaban 20 mg (<i>n</i> = 1064)	Absolute standardized difference	Warfarin (<i>n</i> = 3335)	Rivaroxaban 20 mg (<i>n</i> = 1064)	Absolute standardized difference
Age (mean ± SD)	83.0 ± 8.5	74.2 ± 9.2	1.02	80.1 ± 10.8	79.1 ± 8.2	0.09
Female sex (%)	56.6	46.2	0.21	54.8	52.3	0.05
CHADS ₂ score (mean ± SD)	3.1 ± 1.2	2.3 ± 1.2	0.62	2.8 ± 1.3	2.9 ± 1.2	0.04
HAS-BLED score (mean ± SD)	3.6 ± 1.3	2.7 ± 1.3	0.65	3.3 ± 1.5	3.4 ± 1.4	0.06
Charlson-Deyo Comorbidity Index (mean ± SD)	6.1 ± 3.4	4.7 ± 3.5	0.39	5.7 ± 3.5	5.9 ± 3.6	0.05
Frailty score (mean ± SD)	18.9 ± 6.0	14.5 ± 7.1	0.68	17.7 ± 6.7	17.6 ± 6.3	0.03
Comorbidities (including the index hospitalization and the three years prior to cohort entry)						
Hypertension (%)	87.0	77.2	0.26	83.9	85.2	0.03
Coronary artery disease (%)	65.9	52.9	0.27	62.0	62.7	0.02
Acute myocardial infarction (%)	22.0	11.5	0.28	18.9	17.5	0.04
Chronic heart failure (%)	58.0	41.9	0.33	53.4	54.2	0.02
Cardiomyopathy (%)	7.9	7.1	0.03	7.7	8.7	0.03
Other cardiac dysrhythmias (%)	19.2	14.5	0.13	17.8	16.4	0.04
Valvular heart disease (%)	27.4	14.9	0.31	24.9	24.6	0.01
Stroke/transient ischemic attack (%)	17.4	11.0	0.18	16.0	17.3	0.03
Peripheral vascular disease (%)	29.2	20.2	0.21	26.6	25.9	0.01
Dyslipidemia (%)	56.0	50.3	0.11	54.2	55.8	0.03
Diabetes (%)	46.7	46.2	0.01	46.4	49.9	0.07

Major bleeding (%)	40.2	26.9	0.28	37.0	39.3	0.05
Major intracranial bleeding (%)	3.6	2.8	0.04	3.5	5.7	0.10
Major gastrointestinal bleeding (%)	8.6	6.7	0.07	7.9	7.7	0.01
Other sites of major bleeding (%)	33.5	21.2	0.28	30.9	32.4	0.03
Liver disease (%)	2.7	2.7	< 0.01	2.9	2.9	< 0.01
Chronic obstructive pulmonary disease/asthma (%)	44.3	48.5	0.08	46.0	49.7	0.07
Depression (%)	11.9	11.8	< 0.01	12.2	11.8	0.01
Medical procedures (three years prior to cohort entry)						
Cardiac catheterization (%)	5.2	5.9	0.03	5.2	5.3	< 0.01
Percutaneous coronary intervention-stent (%)	4.1	3.4	0.04	3.8	4.1	0.01
Coronary artery bypass grafting (%)	0.7	1.3	0.01	0.8	0.7	0.01
Implantable cardiac device (%)	0.1	0.1	0.01	< 0.1	< 0.1	0.01
Medications (two weeks prior to cohort entry)						
Statin (%)	51.7	49.7	0.04	51.1	52.9	0.04
Antiplatelet (%)	9.2	5.3	0.15	8.1	8.9	0.03
Low-dose acetylsalicylic acid (%)	36.0	34.6	0.03	34.8	35.2	0.01
Proton pump inhibitors (%)	50.9	38.8	0.24	47.8	46.9	0.02
Nonsteroidal anti-inflammatory drugs (%)	0.8	2.0	0.10	1.3	1.6	0.03
Digoxin (%)	9.5	8.4	0.04	9.1	10.1	0.03
Amiodarone (%)	9.8	5.7	0.15	8.6	6.1	0.09
Antidepressants (%)	10.5	9.3	0.04	10.4	10.5	< 0.01
Beta-blockers (%)	62.9	59.1	0.08	61.4	61.1	0.01
Calcium channel blockers (%)	44.0	38.8	0.10	41.9	39.8	0.04

Inhibitors of the renin-angiotensin system (%)	37.3	44.6	0.15	38.1	38.5	0.01
Diuretics (%)	61.3	61.8	0.01	61.4	61.0	0.01
Loop diuretics (%)	57.1	56.8	0.01	57.0	54.4	0.05
Antidiabetics (%)	28.3	30.0	0.04	28.7	30.3	0.03
Health medical services (one year prior to cohort entry)						
Consultations with specialist physicians (mean ± SD)	1.1 ± 2.3	1.4 ± 3.2	0.08	1.2 ± 2.5	1.2 ± 2.3	< 0.01
Consultations with family physicians (mean ± SD)	1.3 ± 3.3	1.0 ± 2.6	0.08	1.2 ± 3.1	1.2 ± 2.5	0.01
Emergency visits (mean ± SD)	3.5 ± 3.2	3.1 ± 3.1	0.14	3.4 ± 3.4	3.5 ± 3.0	0.04
Health hospital services (three years prior to cohort entry)						
All-cause hospital admission (mean ± SD)	2.5 ± 2.1	2.2 ± 2.3	0.15	2.5 ± 2.4	2.6 ± 2.2	0.05

IPTW: Inverse probability of treatment weighting.

Supplementary Table 7 Demographic and clinical characteristics of the initial cohort and the cohort after inverse probability of treatment weighting of new oral anticoagulant users with stage III chronic kidney disease (CKD) in warfarin *vs.* apixaban 2.5 mg users with stage III CKD from 2013 to 2017

	Initial cohort			Cohort after IPTW		
	Warfarin (<i>n</i> = 3335)	Apixaban 2.5 mg (<i>n</i> = 1674)	Absolute standardi zed difference	Warfarin (<i>n</i> = 3335)	Apixaban 2.5 mg (<i>n</i> = 1674)	Absolute standardi zed difference
Age (mean ± SD)	83.0 ± 8.5	86.5 ± 6.3	0.42	84.3 ± 8.3	84.5 ± 7.2	0.02
Female sex (%)	56.6	61.7	0.10	58.2	59.0	0.02
CHADS ₂ score (mean ± SD)	3.1 ± 1.2	3.0 ± 1.1	0.08	3.0 ± 1.2	3.0 ± 1.1	< 0.01
HAS-BLED score (mean ± SD)	3.6 ± 1.3	3.3 ± 1.3	0.18	3.5 ± 1.3	3.5 ± 1.2	0.02
Charlson-Deyo Comorbidity Index (mean ± SD)	6.1 ± 3.4	5.4 ± 3.3	0.19	5.9 ± 3.4	5.8 ± 3.2	0.02
Frailty score (mean ± SD)	18.9 ± 6.0	18.4 ± 6.3	0.08	18.8 ± 6.2	18.8 ± 5.8	0.01
Comorbidities (including the index hospitalization and the three years prior to cohort entry)						
Hypertension (%)	87.0	86.0	0.03	86.9	86.9	< 0.01
Coronary artery disease (%)	65.9	61.1	0.10	64.1	62.5	0.04
Acute myocardial infarction (%)	22.0	18.3	0.09	20.9	20.9	< 0.01
Chronic heart failure (%)	58.0	52.1	0.12	56.1	56.6	0.01
Cardiomyopathy (%)	7.9	6.9	0.04	7.4	7.1	0.01
Other cardiac dysrhythmias (%)	19.2	18.5	0.02	19.2	19.4	0.01
Valvular heart disease (%)	27.4	22.6	0.11	25.7	25.6	< 0.01
Stroke/transient ischemic attack (%)	17.4	15.7	0.05	16.8	16.1	0.02
Peripheral vascular disease (%)	29.2	23.2	0.14	27.3	26.2	0.02
Dyslipidemia (%)	56.0	50.5	0.11	53.9	54.0	< 0.01
Diabetes (%)	46.7	33.9	0.26	43.1	42.7	0.01
Major bleeding (%)	40.2	34.3	0.12	38.3	37.0	0.03

Major intracranial bleeding (%)	3.6	3.5	< 0.01	3.9	3.5	0.02
Major gastrointestinal bleeding (%)	8.6	8.3	0.01	8.7	8.1	0.02
Other sites of major bleeding (%)	33.5	28.7	0.10	31.8	31.2	0.01
Liver disease (%)	2.7	1.7	0.07	2.5	2.4	0.01
Chronic obstructive pulmonary disease/asthma (%)	44.3	37.8	0.13	42.2	42.1	< 0.01
Depression (%)	11.9	11.4	0.01	11.7	11.4	0.01
Medical procedures (three years prior to cohort entry)						
Cardiac catheterization (%)	5.2	4.1	0.05	5.0	4.9	< 0.01
Percutaneous coronary intervention-stent (%)	4.1	3.2	0.05	3.8	4.0	0.01
Coronary artery bypass grafting (%)	0.7	0.2	0.07	0.5	0.5	< 0.01
Implantable cardiac device (%)	0.1	0.0	0.03	< 0.1	0.0	0.03
Medications (two weeks prior to cohort entry)						
Statin (%)	51.7	46.5	0.10	50.0	47.9	0.04
Antiplatelet (%)	9.2	7.6	0.06	8.3	7.4	0.03
Low-dose acetylsalicylic acid (%)	36.0	34.0	0.04	35.6	34.9	0.01
Proton pump inhibitors (%)	50.9	47.0	0.08	50.0	49.1	0.02
Nonsteroidal anti-inflammatory drugs (%)	0.8	1.5	0.06	0.9	1.0	< 0.01
Digoxin (%)	9.5	8.8	0.02	9.2	9.0	0.01
Amiodarone (%)	9.8	8.5	0.04	9.3	9.8	0.02
Antidepressants (%)	10.5	10.5	< 0.01	10.6	10.3	0.01
Beta-blockers (%)	62.9	64.5	0.03	63.8	62.8	0.02
Calcium channel blockers (%)	44.0	40.1	0.08	42.7	43.2	0.01
Inhibitors of the renin-angiotensin system (%)	37.3	39.6	0.05	38.0	36.5	0.03

Diuretics (%)	61.3	59.9	0.03	61.0	60.8	< 0.01
Loop diuretics (%)	57.1	55.1	0.04	56.4	56.7	0.01
Antidiabetics (%)	28.3	20.8	0.17	26.5	25.8	0.02
Health medical services (one year prior to cohort entry)						
Consultations with specialist physicians (mean ± SD)	1.1 ± 2.3	1.3 ± 2.6	0.07	1.2 ± 2.4	1.2 ± 2.2	0.01
Consultations with family physicians (mean ± SD)	1.3 ± 3.3	1.4 ± 3.1	0.03	1.3 ± 3.4	1.4 ± 3.0	0.01
Emergency visits (mean ± SD)	3.5 ± 3.2	3.3 ± 2.9	0.07	3.4 ± 3.1	3.5 ± 2.9	0.01
Health hospital services (three years prior to cohort entry)						
All-cause hospital admission (mean ± SD)	2.5 ± 2.1	2.2 ± 1.9	0.16	2.4 ± 2.0	2.5 ± 1.9	0.01

IPTW: Inverse probability of treatment weighting.

Supplementary Table 8 Demographic and clinical characteristics of the initial cohort and the cohort after inverse probability of treatment weighting of new oral anticoagulant users with stage III chronic kidney disease (CKD) in warfarin vs. apixaban 5.0 mg users with stage III CKD from 2013 to 2017

	Initial cohort			Cohort after IPTW		
	Warfarin (<i>n</i> = 3335)	Apixaban 5.0 mg (<i>n</i> = 2082)	Absolute standardi zed difference	Warfarin (<i>n</i> = 3335)	Apixaban 5.0 mg (<i>n</i> = 2082)	Absolute standardi zed difference
Age (mean ± SD)	83.0 ± 8.5	78.0 ± 8.4	0.58	80.4 ± 10.2	80.2 ± 7.8	0.02
Female sex (%)	56.6	49.1	0.15	54.3	53.9	0.01
CHADS ₂ score (mean ± SD)	3.1 ± 1.2	2.6 ± 1.2	0.36	2.9 ± 1.3	2.8 ± 1.1	0.02
HAS-BLED score (mean ± SD)	3.6 ± 1.3	3.0 ± 1.3	0.42	3.3 ± 1.4	3.3 ± 1.2	0.03
Charlson-Deyo Comorbidity Index (mean ± SD)	6.1 ± 3.4	5.1 ± 3.5	0.26	5.7 ± 3.5	5.7 ± 3.4	0.01
Frailty score (mean ± SD)	18.9 ± 6.0	15.8 ± 6.7	0.49	17.7 ± 6.6	17.5 ± 6.1	0.03
Comorbidities (including the index hospitalization and the three years prior to cohort entry)						
Hypertension (%)	87.0	82.0	0.14	84.5	84.0	0.01
Coronary artery disease (%)	65.9	54.8	0.23	61.2	58.4	0.06
Acute myocardial infarction (%)	22.0	13.0	0.24	18.8	15.8	0.08
Chronic heart failure (%)	58.0	46.4	0.23	53.3	53.6	0.01
Cardiomyopathy (%)	7.9	8.1	0.01	8.2	7.8	0.01
Other cardiac dysrhythmias (%)	19.2	18.1	0.03	18.2	18.0	< 0.01
Valvular heart disease (%)	27.4	15.6	0.29	23.5	22.3	0.03
Stroke/transient ischemic attack (%)	17.4	13.1	0.12	15.9	15.0	0.03
Peripheral vascular disease (%)	29.2	21.2	0.18	25.6	23.2	0.06
Dyslipidemia (%)	56.0	53.3	0.05	55.5	53.8	0.03
Diabetes (%)	46.7	46.3	0.01	47.3	46.9	0.01
Major bleeding (%)	40.2	29.2	0.23	36.2	34.8	0.03
Major intracranial bleeding (%)	3.6	3.4	0.01	4.2	3.8	0.02

Major gastrointestinal bleeding (%)	8.6	7.4	0.04	7.9	7.9	< 0.01
Other sites of major bleeding (%)	33.5	23.2	0.23	29.8	28.8	0.02
Liver disease (%)	2.7	2.3	0.03	2.7	2.5	0.01
Chronic obstructive pulmonary disease/asthma (%)	44.3	44.3	< 0.01	44.5	45.3	0.01
Depression (%)	11.9	11.1	0.02	12.1	11.9	0.01
Medical procedures (three years prior to cohort entry)						
Cardiac catheterization (%)	5.2	6.8	0.07	6.4	6.4	< 0.01
Percutaneous coronary intervention-stent (%)	4.1	3.8	0.02	4.1	4.0	0.01
Coronary artery bypass grafting (%)	0.7	1.6	0.09	1.2	1.2	< 0.01
Implantable cardiac device (%)	0.1	0.0	0.03	< 0.1	0.0	0.03
Medications (two weeks prior to cohort entry)						
Statin (%)	51.7	50.1	0.03	50.6	50.4	< 0.01
Antiplatelet (%)	9.2	6.1	0.12	8.1	7.9	0.01
Low-dose acetylsalicylic acid (%)	36.0	29.9	0.13	33.9	33.4	0.01
Proton pump inhibitors (%)	50.9	41.6	0.19	46.4	44.7	0.03
Nonsteroidal anti-inflammatory drugs (%)	0.8	1.3	0.05	1.2	1.2	< 0.01
Digoxin (%)	9.5	8.6	0.03	8.9	8.7	0.01
Amiodarone (%)	9.8	7.4	0.08	8.8	8.0	0.03
Antidepressants (%)	10.5	9.6	0.03	10.2	10.4	0.01
Beta-blockers (%)	62.9	63.6	0.02	62.4	62.5	<0.01
Calcium channel blockers (%)	44.0	39.8	0.08	41.4	41.0	0.01
Inhibitors of the renin-angiotensin system (%)	37.3	42.6	0.11	38.0	38.3	0.01
Diuretics (%)	61.3	57.9	0.07	60.3	60.4	< 0.01

Loop diuretics (%)	57.1	53.7	0.07	55.4	56.3	0.02
Antidiabetics (%)	28.3	29.8	0.03	29.2	29.3	< 0.01
Health medical services (one year prior to cohort entry)						
Consultations with specialist physicians (mean ± SD)	1.1 ± 2.3	1.3 ± 2.1	0.08	1.2 ± 2.6	1.2 ± 1.8	< 0.01
Consultations with family physicians (mean ± SD)	1.3 ± 3.3	1.1 ± 2.8	0.05	1.2 ± 3.2	1.2 ± 2.6	0.01
Emergency visits (mean ± SD)	3.5 ± 3.2	3.3 ± 3.0	0.08	3.4 ± 3.3	3.3 ± 2.8	0.02
Health hospital services (three years prior to cohort entry)						
All-cause hospital admission (mean ± SD)	2.5 ± 2.1	2.3 ± 2.2	0.12	2.5 ± 2.3	2.4 ± 2.0	0.03

IPTW: Inverse probability of treatment weighting.

Supplementary Table 9 Distribution of follow-up time and level of adherence at one-year follow-up of new oral anticoagulant users with stage III chronic kidney disease in an on-treatment analysis

	Follow-up time (days)		Level of adherence (%)	
	Mean (95% CI)	Median (Q ₁ -Q ₃)	Mean (95% CI)	Median (Q ₁ -Q ₃)
Warfarin	236.0 (231.0-40.0)	320.0 (83.0-365.0)	64.5 (63.2-65.9)	87.7 (22.7-100.0)
Rivaroxaban 15 mg	256.0 (246.0-266.0)	365.0 (109.0-365.0)	70.0 (67.3-72.8)	100.0 (29.9-100.0)
Rivaroxaban 20 mg	286.0 (279.0-294.0)	365.0 (196.0-365.0)	78.4 (76.3-80.5)	100.0 (53.7-100.0)
Apixaban 2.5 mg	260.0 (253.0-266.0)	365.0 (120.0-365.0)	71.2 (69.4-72.9)	100.0 (32.9-100.0)
Apixaban 5.0 mg	280.0 (274.0-285.0)	365.0 (181.0-365.0)	76.6 (75.1-78.1)	100.0 (49.6-100.0)

CI: Confidence interval; Q1: Quartile 1; Q3: Quartile 3.

Supplementary Table 10 Distribution of follow-up time and level of adherence at one-year follow-up of new oral anticoagulant users with stage III chronic kidney disease in an intent-to-treat analysis

	Follow-up time (days)		Level of adherence (%)	
	Mean (95% CI)	Median (Q ₁ -Q ₃)	Mean (95% CI)	Median (Q ₁ -Q ₃)
Warfarin	273.0 (268.0-277.0)	365.0 (156.0-365.0)	56.9 (55.5-58.2)	57.8 (14.0-100.0)
Rivaroxaban 15 mg	284.0 (275.0-293.0)	365.0 (193.0-365.0)	66.7 (63.9-69.5)	99.7 (24.9-100.0)
Rivaroxaban 20 mg	313.0 (307.0-320.0)	365.0 (365.0-365.0)	71.9 (69.7-74.1)	100.0 (34.7-100.0)
Apixaban 2.5 mg	281.0 (275.0-287.0)	365.0 (184.0-365.0)	68.1 (66.3-69.9)	100.0 (27.1-100.0)
Apixaban 5.0 mg	305.0 (300.0-310.0)	365.0 (335.0-365.0)	71.1 (69.5-72.7)	100.0 (31.5-100.0)

CI: Confidence interval; Q1: Quartile 1; Q3: Quartile 3.

Supplementary Table 11 Rates of effectiveness and safety outcomes in an on-treatment analysis after inverse probability of treatment weighting of new oral anticoagulant users with stage III chronic kidney disease

	Rate per 100 patient-years (95% CI)	Rate per 100 patient-years (95% CI)	Hazard ratio (95% CI)	P-value
	Rivaroxaban 15 mg	Warfarin		
Effectiveness composite	8.2 (5.6-10.7)	9.7 (8.4-11.1)	0.84 (0.60-1.18)	0.32
Stroke (Ischemic only)/SE	1.6 (0.5-2.7)	1.6 (1.1-2.1)	0.99 (0.46-2.16)	0.98
All-cause mortality	3.5 (1.8-5.1)	5.4 (4.5-6.4)	0.64 (0.39-1.06)	0.08
Safety composite	4.2 (2.4-6.0)	3.7 (2.9-4.6)	1.13 (0.70-1.83)	0.63
	Rivaroxaban 20 mg	Warfarin		
Effectiveness composite	7.4 (5.4-9.4)	9.1 (7.8-10.4)	0.83 (0.61-1.13)	0.23
Stroke (Ischemic only)/SE	2.2 (1.1-3.3)	1.5 (1.0-2.0)	1.52 (0.83-2.78)	0.18
All-cause mortality	3.4 (2.1-4.8)	5.1 (4.2-6.0)	0.68 (0.44-1.06)	0.09
Safety composite	4.4 (2.8-6.0)	3.5 (2.7-4.2)	1.29 (0.84-1.95)	0.24
	Apixaban 2.5 mg	Warfarin		
Effectiveness composite	9.6 (7.8-11.4)	9.7 (8.4-11.0)	1.00 (0.79-1.26)	1.00
Stroke (Ischemic only)/SE	2.1 (1.2-2.9)	1.5 (1.0-2.0)	1.38 (0.81-2.36)	0.23
All-cause mortality	4.5 (3.3-5.8)	5.5 (4.5-6.5)	0.83 (0.60-1.15)	0.26
Safety composite	2.7 (1.7-3.7)	4.1 (3.3-5.0)	0.65 (0.43-0.99)	0.04
	Apixaban 5.0 mg	Warfarin		
Effectiveness composite	5.8 (4.5-7.1)	8.7 (7.4-9.9)	0.76 (0.65-0.88)	< 0.01
Stroke (Ischemic only)/SE	1.0 (0.5-1.6)	1.5 (1.0-2.0)	0.72 (0.39-1.33)	0.29
All-cause mortality	2.9 (2.0-3.8)	4.7 (3.8-5.6)	0.61 (0.43-0.88)	< 0.01
Safety composite	3.3 (2.4-4.3)	3.6 (2.8-4.4)	0.94 (0.66-1.35)	0.75

P < 0.05 vs warfarin. CI: Confidence interval; SE: Systemic embolism.

Supplementary Table 12 Rates of effectiveness and safety outcomes in an intent-to-treat after inverse probability of treatment weighting of new oral anticoagulant users with stage III chronic kidney disease

	Rate per 100 patient-years (95% CI)	Rate per 100 patient-years (95% CI)	Hazard ratio* (95% CI)	P-value
	Rivaroxaban 15 mg	Warfarin		
Effectiveness composite	23.0 (19.0-27.0)	22.4 (20.6-24.3)	1.02 (0.84-1.24)	0.82
Stroke (ischemic only)/SE	1.8 (0.7-2.9)	1.9 (1.4-2.4)	0.94 (0.47-1.86)	0.86
All-cause mortality	18.6 (15.0-22.2)	18.2 (16.5-19.9)	1.02 (0.82-1.26)	0.86
Safety composite	4.6 (2.8-6.4)	4.1 (3.3-4.9)	1.11 (0.71-1.71)	0.65
	Rivaroxaban 20 mg	Warfarin		
Effectiveness composite	15.8 (13.1-18.7)	20.2 (18.5-22.0)	0.79 (0.65-0.96)	0.02
Stroke (ischemic only)/SE	2.2 (1.2-3.3)	1.7 (1.2-2.2)	1.31 (0.75-2.27)	0.34
All-cause mortality	11.6 (9.3-14.0)	16.2 (14.7-17.8)	0.72 (0.58-0.91)	0.01
Safety composite	4.0 (2.6-5.4)	3.8 (3.0-4.5)	1.07 (0.72-1.61)	0.73
	Apixaban 2.5 mg	Warfarin		
Effectiveness composite	21.5 (18.8-24.1)	23.7 (21.8-25.7)	0.90 (0.78-1.05)	0.18
Stroke (ischemic only)/SE	2.3 (1.4-3.1)	1.8 (1.3-2.3)	1.25 (0.78-2.01)	0.35
All-cause mortality	17.6 (15.2-20.0)	19.7 (17.9-21.4)	0.90 (0.76-1.05)	0.17
Safety composite	3.5 (2.4-4.5)	4.5 (3.7-5.4)	0.77 (0.54-1.10)	0.15
	Apixaban 5.0 mg	Warfarin		
Effectiveness composite	14.7 (12.8-16.7)	19.6 (17.9-21.4)	0.76 (0.65-0.88)	< 0.01
Stroke (ischemic only)/SE	1.0 (0.5-1.6)	1.7 (1.2 -2.2)	0.62 (0.35-1.09)	0.10
All-cause mortality	11.8 (10.1-13.6)	15.7 (14.2-17.2)	0.76 (0.64-0.90)	< 0.01
Safety composite	3.2 (2.3-4.1)	3.9 (3.2-4.7)	0.82 (0.58-1.15)	0.25

P < 0.05 vs warfarin. CI: Confidence interval; SE: Systemic embolism.