SUPPLEMENTARY DATA

Definition and adjudication of adverse events

Two data managers independently reviewed the clinical history of each patient to identify events. All suspected events were independently reviewed by 2 specialists in the clinically relevant areas of cardiology and internal medicine. Both data managers and specialists underwent a study-specific training course on event definitions and the adjudication process. Finally, an independent clinical events committee revised and adjudicated all events.

- Cardiovascular death includes death resulting from acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, death due to cardiovascular hemorrhage, and death due to other cardiovascular causes.
- Ischemic stroke was defined as sudden onset of a focal deficit consistent with occlusion of a major cerebral artery (documented by means of magnetic resonance imaging or computed tomography). Signs or symptoms had to last > 24 hours, unless supported by clear evidence of cerebral infarction on imaging techniques (eg, diffusion-weighted magnetic resonance imaging).
- Transient ischemic attack was defined as a temporary neurologic deficit presumably due to reduced blood flow in a specific cerebral artery lasting for ≤ 24 hours with complete resolution of the neurologic deficit and no acute infarction.
- Pulmonary embolism was considered verified and recorded when the presence of clinical signs and symptoms of pulmonary embolism was combined with objective confirmatory tests (spiral

computed tomography, perfusion-ventilation scan, pulmonary angiography, or autopsy) and resulted in a diagnosis of pulmonary embolism.

- Systemic embolism (SE) was defined as any end-organ ischemia other than in the brain, heart, eyes, and lungs caused by abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of another likely mechanism (eg, atherosclerosis, instrumentation, or trauma), and objectively documented by duplex scanning, computed tomography, magnetic resonance imaging, or angiography. SE included arterial embolism in the lower extremities, upper extremities, and visceral-mesenteric system.
- Major bleeding (MB) episodes were defined as fatal bleeding, symptomatic bleeding in a critical area or organ, or bleeding causing a reduced hemoglobin level of 2 g/dL or more or leading to transfusion of 2 or more units of whole blood or red cells.
- Clinically relevant nonmajor bleeding (non-MB) was defined as any sign or symptom of hemorrhage that did not fit the criteria for the International Society on Thrombosis and Haemostatis definition of major bleeding but that required medical intervention by a health care professional, led to hospitalization or an increased level of care, or prompted a face-to-face evaluation.

Table 1 of the supplementary data

Univariate analysis for all-cause mortality

Variables	HR	95%CI	*P*
Patient characteristics			
Age, per y	1.13	1.12-1.14	< .001
Female sex	0.91	0.85-0.98	.012
Obesity[a]	0.64	0.59-0.69	< .001
Cardiovascular risk factors			
Hypertension	0.92	0.86-0.98	.019
Diabetes mellitus	1.15	1.06-1.26	.001
Dyslipidemia	0.65	0.61-0.70	< .001
Peripheral artery disease	1.75	1.49-2.04	< .001
Ischemic heart disease	1.21	1.09-1.35	< .001
Prior heart failure	2.12	1.90-2.36	< .001
Prior ischemic stroke	1.44	1.28-1.62	< .001
Prior non-CNS embolic events	1.93	1.44-2.58	< .001
Comorbidities			
Prior bleeding admission	1.07	0.91-1.27	.395
Anemia in previous year[b]	2.27	2.11-2.43	< .001
GFR < 60 mL/min/1.73 m^2[c]	1.78	1.66-1.91	< .001
COPD	1.30	1.18-1.44	<.001
Cancer	1.22	1.08-1.39	.002
Dementia	1.54	1.40-1.70	< .001
Malnutrition[d]	1.88	1.75-2.02	< .001

Echocardiographic data			
LVEF < 40%	1.59	1.39-1.82	< .001
Severe aortic valve disease	1.53	1.34-1.75	< .001
Severe mitral valve disease	1.41	1.21-1.64	< .001
Medical therapy			
Anticoagulation	0.55	0.51-0.60	< .001
Antiplatelet therapy	1.61	1.48-1.75	< .001
Antiarrhythmic drug	0.71	0.60-0.83	< .001
Beta-blocker	0.79	0.73-0.85	< .001
Verapamil/diltiazem	0.73	0.60-0.88	.0001
Digoxin	1.48	1.36-1.62	< .001
ACEI/ARB	0.78	0.73-0.83	< .001
Statin	0.67	0.62-0.72	< .001
Risk scores			
CHA_2DS_2-VASc, per 1 point	1.12	1.09-1.16	< .001
HAS-BLED, per 1 point	1.20	1.16-1.24	< .001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction.

[a] Obesity was defined as a body mass index ≥ 30 kg/m^2.

[b] According to the World Health Organization, anemia was defined as hemoglobin levels < 12.0 g/dL in women and < 13.0 g/dL in men. We did not include anemia following traumatic injuries or surgical treatments.

[c] Glomerular filtration rate was estimated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

[d] Risk of malnutrition was defined as a Controlling Nutritional Status (CONUT) score ≥ 3 points.

Table 2 of the supplementary data

Bleeding and embolic events in the study population, considering the number (No.), percentage (%), incidence rate (per 100 patients/y), and treatment with anticoagulant drugs at the time of the event

Event	Number of patients	%	Incidence rate (95%CI)
Embolic events	922	9.8	2.8 (2.6-3.0)
Major embolism	698	7.5	2.1 (1.9-2.2)
Stroke	538	5.7	1.6 (1.5-1.7)
Non-CNS embolism	178	1.9	0.5 (0.4-0.6)
TIA	276	2.9	0.8 (0.7-0.9)
Bleeding	2,822	30.1	10.0 (9.6-10.4)
MB	827	8.8	2.5 (2.3-2.7)
ICH	269	2.9	0.8 (0.7-0.8)
Non-ICH MB	579	6.2	1.7 (1.6-1.9)
Non-MB	2,368	25.3	8.2 (7.9-8.5)

CNS, central nervous system; DOAC, direct oral anticoagulants; ICH, intracranial hemorrhage; MB: major bleeding; TIA, transient ischemic attack.

Table 3 of the supplementary data

Association between risk of death and bleeding and embolic events by anticoagulation status at the time of each respective event

Covariate	Incidence rate of death[a] (95%CI)		Adjusted HR for death[b]	*P*
	With event	Without event	(95%CI)	
Embolism				
ON anticoagulation	22.2 (19.5-25.4)	8.8 (8.5-9.1)	2.47 (2.13-2.85)	< .001
VKA	20.5 (17.5-24.1)	8.9 (8.6-9.2)	2.36 (1.99-2.80)	< .001
DOAC	27.6 (21.6-35.1)	9.0 (8.7-9.4)	2.66 (2.06-3.43)	< .001
OFF anticoagulation	31.7 (26.2-38.5)	8.9 (8.6-9.3)	1.94 (1.56-2.42)	< .001
Bleeding				
ON anticoagulation	12.1 (11.3-13.1)	8.6 (8.3-8.9)	1.84 (1.67-2.03)	< .001
VKA	11.2 (10.3-12.2)	8.8 (8.5-9.2)	1.70 (1.53-1.89)	< .001
DOAC	15.9 (13.3-18.2)	9.0 (8.7-9.3)	1.97 (1.63-2.39)	< .001
OFF anticoagulation	19.2 (16.1-22.8)	9.0 (8.6-9.3)	1.58 (1.30-1.93)	< .001

95%CI, confidence interval; CNS, central nervous system; DOAC, direct oral anticoagulants; HR, hazard ratio; ICH, intracranial hemorrhage; MB, major bleeding; TIA, transient ischemic attack; VKA, vitamin K antagonist.

[a] Incidence rate per 100 patients per year.

[b] Adjustments were finally applied for the significant influential characteristics of age, female sex, obesity, cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia), peripheral artery disease, ischemic heart disease, prior heart failure, prior embolic events (ischemic stroke and

extracranial embolism), comorbidities (anemia in the last year, glomerular filtrate rate according to Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation < 60 mL/min/1.73 m^2, chronic obstructive pulmonary disease, history of cancer, dementia, risk of malnutrition [Controlling Nutritional Status—CONUT—score ≥ 3]), echocardiographic data (left ventricular ejection fraction < 40%, severe aortic and mitral valve disease), medical therapies (anticoagulation, antiplatelet therapy, antiarrhythmic drugs, beta-blockers, verapamil/diltiazem, digoxin, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins), and risk scores (CHA_2DS_2-VASc and HAS-BLED).

Figure 1 of the supplementary data. Differential impact of embolism vs bleeding (MB) on mortality according to anticoagulant therapy. Blue rhombuses and circles represent the magnitude (adjusted hazard ratio [HR]) of the impact on mortality of embolic events (on and off anticoagulation), while red rhombuses and circles represent that of bleeding events (on and off anticoagulation). For patients who received anticoagulation, we analyzed separately those patients treated with vitamin K antagonists (on VKA), and those treated with direct oral anticoagulants (on DOAC). We report the estimate of the relative risk (ratio of the HR) for each comparison. The estimates of the impact of events on mortality are derived from a multivariate model (table 2). DOAC, direct oral anticoagulants; VKA, vitamin K antagonist.

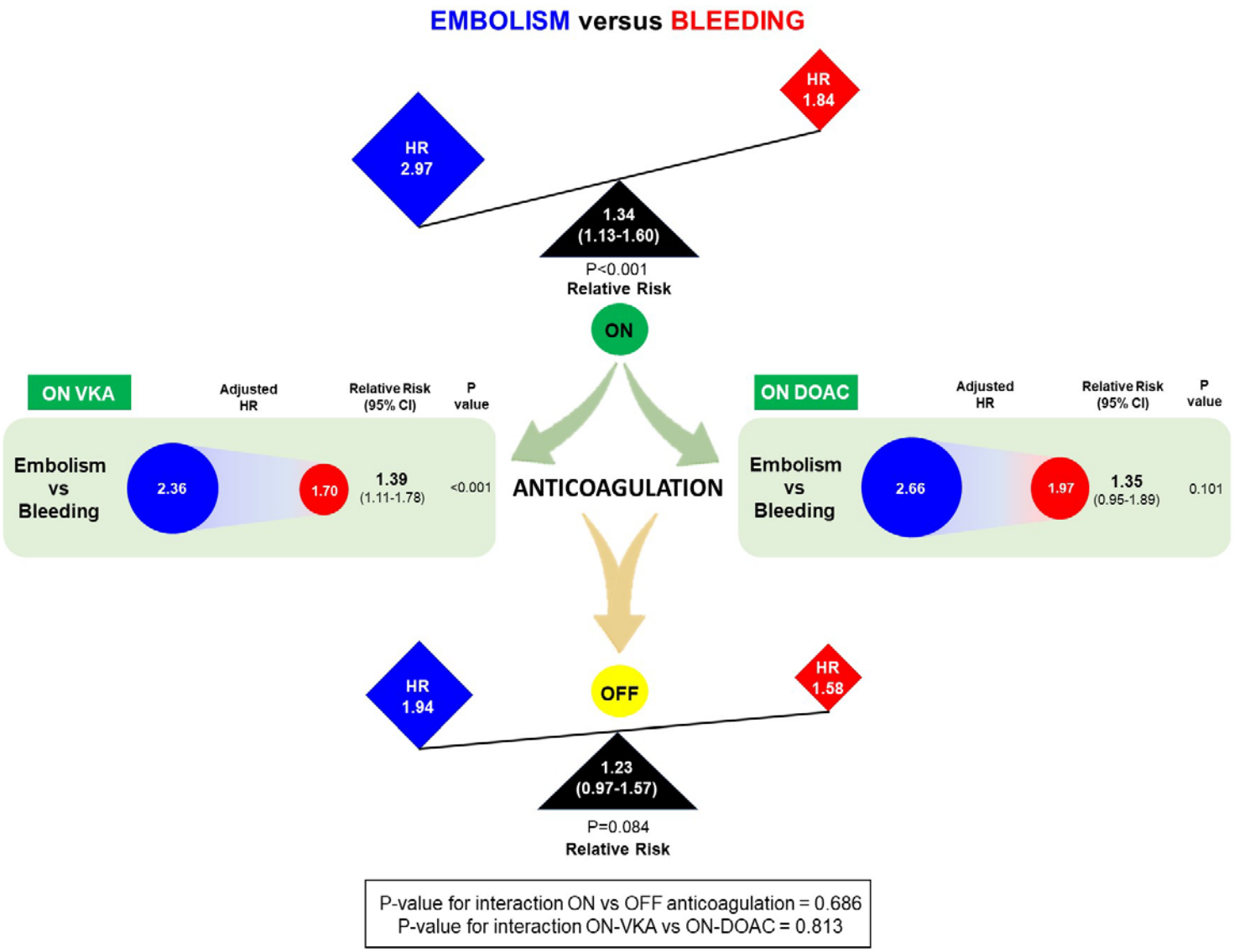

Figure 2 of the supplementary data. Differential impact of embolism and bleeding on mortality comparing treatment with vitamin K antagonists (on VKA) with treatment with direct oral anticoagulants (on DOAC). Blue rhombuses represent the magnitude (adjusted hazard ratio [HR]) of the impact on mortality of events on DOAC, while red rhombuses represent that of events on AVK. We report the estimate of the relative risk (ratio of the HR) for each comparison. The estimates of the impact of events on mortality are derived from a multivariate model (table 2). DOAC, direct oral anticoagulants; VKA, vitamin K antagonist.