Edoxaban nei pazienti con episodi aritmici atriali ad alta frequenza

Risultati del trial NOAH-AFNET 6

Background

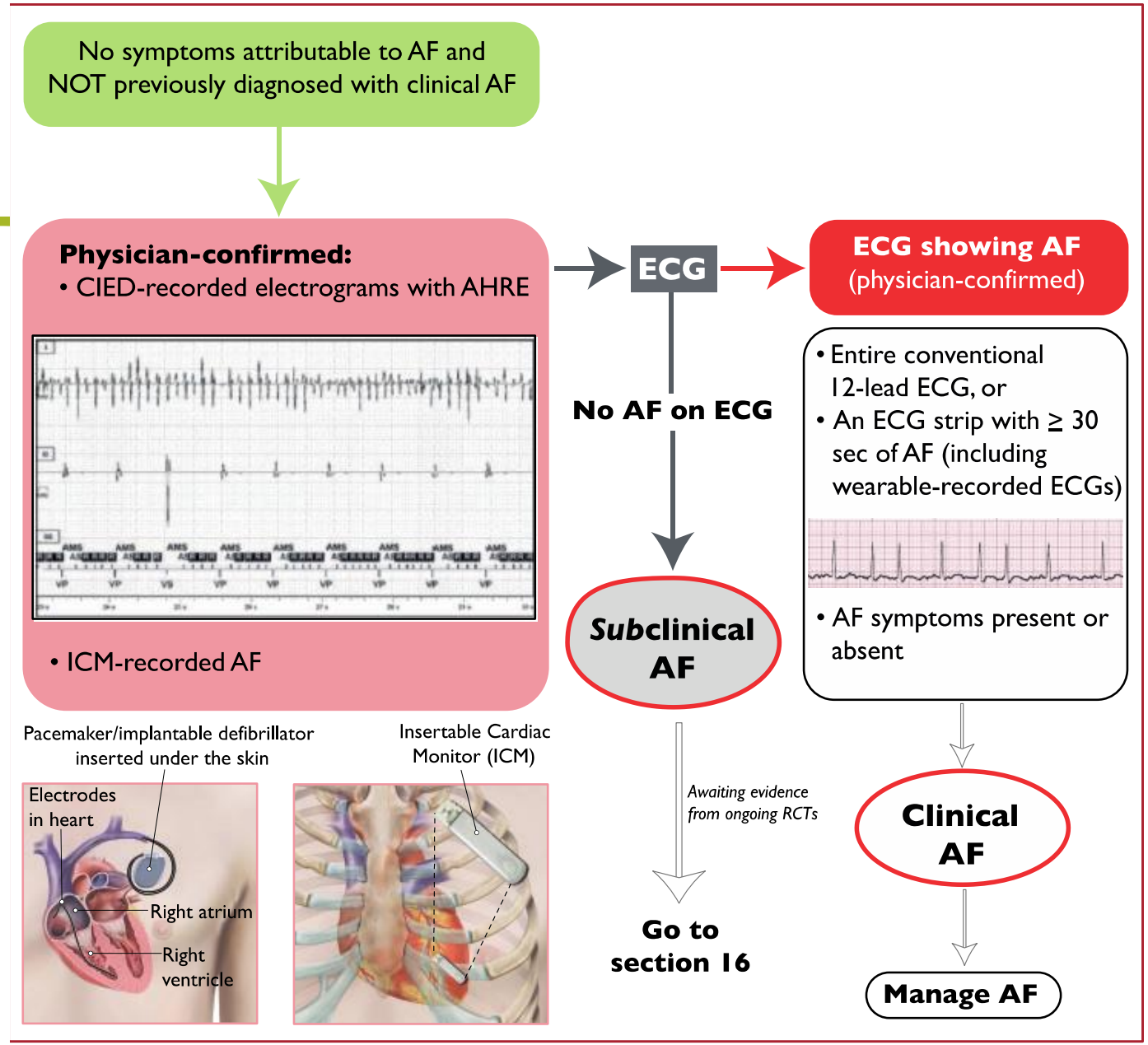
- Oral anticoagulation with the use of vitamin K antagonists or direct-acting, non–vitamin K antagonist oral inhibitors of factor II or Xa (NOACs) reduces the risk of ischemic stroke among patients with atrial fibrillation (AF).
- Implanted cardiac devices can record short episodes of atrial arrhythmias, which are referred to as subclinical atrial fibrillation or atrial high-rate episodes (AHREs).
- Because cardiac electrical activity recorded during AHREs resembles that recorded during AF, some clinicians have initiated anticoagulant therapy in patients with AHREs, especially in those who have several clinical risk factors for stroke or in those who have AHREs that last longer than 24 hours.
- In the absence of AF, oral anticoagulation has generally not been effective for the prevention of stroke in patients who have had an embolic stroke of unknown source or in those with heart failure.

ESC guidelines

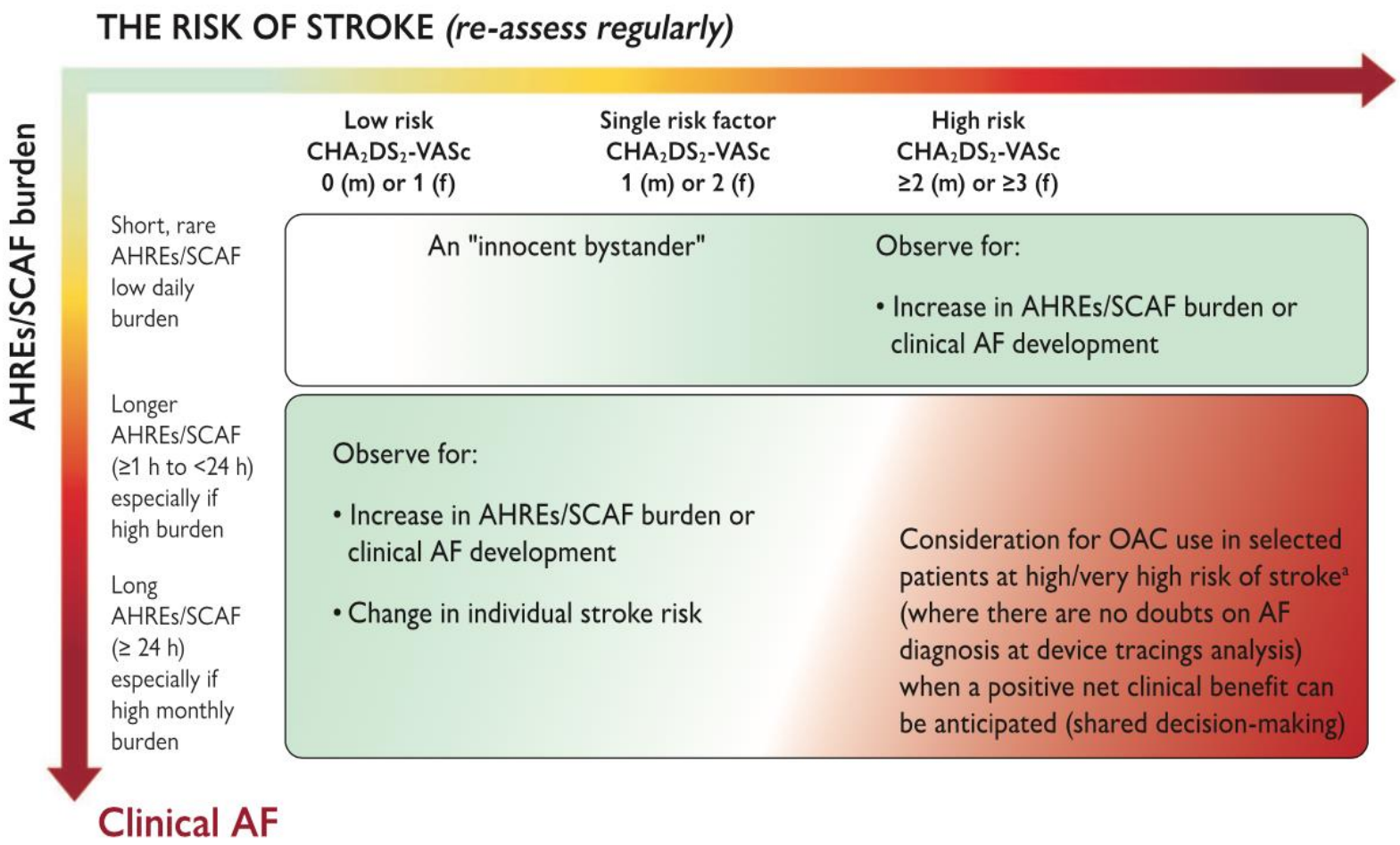
2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)

Clinical AF	*Symptomatic* or *asymptomatic* AF that is documented by surface ECG. The minimum duration of an ECG tracing of AF required to establish the diagnosis of clinical AF is at least 30 seconds, or entire 12-lead ECG.[1,2]
AHRE, subclinical AF	Refers to individuals *without symptoms attributable to AF*, in whom *clinical AF is NOT previously detected (that is, there is no surface ECG tracing of AF)*, see also *section 3.3*. **AHRE** - events fulfilling programmed or specified criteria for AHRE that are detected by CIEDs with an atrial lead allowing automated continuous monitoring of atrial rhythm and tracings storage. CIED-recorded AHRE need to be visually inspected because some AHRE may be electrical artefacts/false positives. **Subclinical AF** includes AHRE confirmed to be AF, AFL, or an AT, or AF episodes detected by insertable cardiac monitor or wearable monitor and confirmed by visually reviewed intracardiac electrograms or ECG-recorded rhythm.

ESC guidelines



ESC guidelines



Anticoagulation with Edoxaban in Patients with Atrial High-Rate Episodes

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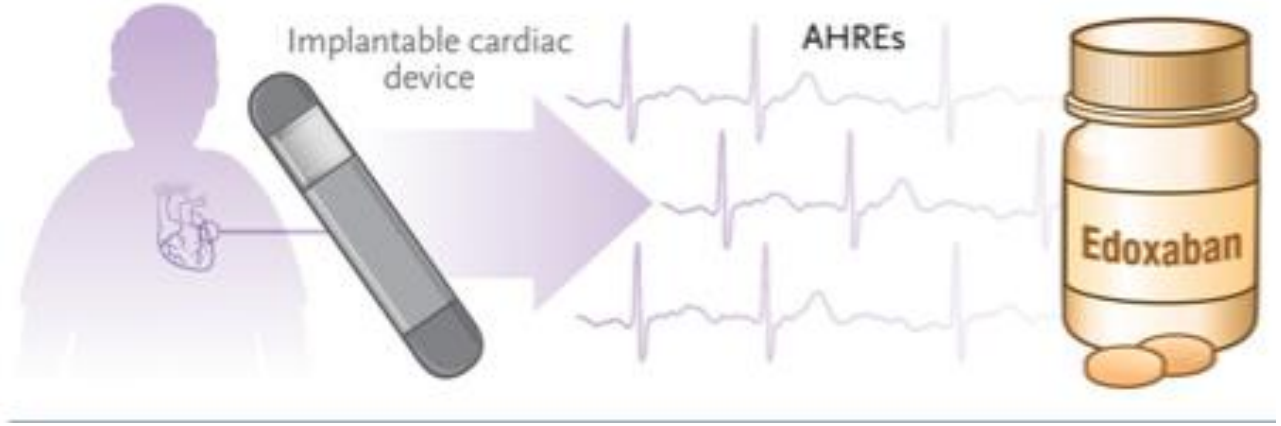
Aim of the study

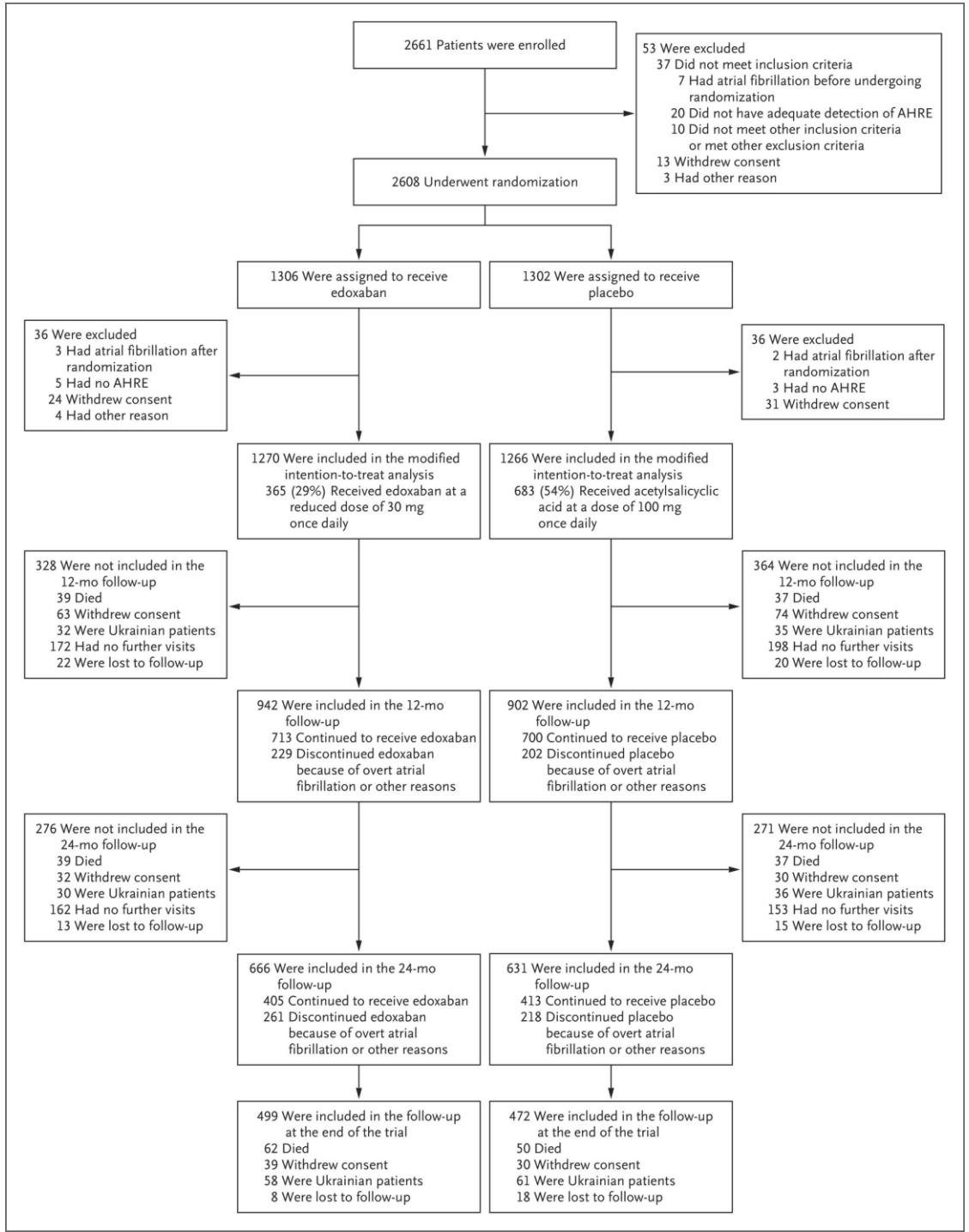
- The NOAH-AFNET 6 trial (Non–Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes) was conducted to compare the efficacy and safety of oral anticoagulant therapy with the non–vitamin K antagonist edoxaban with the efficacy and safety of no anticoagulation in patients with AHREs who had clinical risk factors for stroke.

Methods

- **Design**: An event-driven, double-blind, double-dummy, randomized trial was conducted to assess the efficacy and safety of oral anticoagulation among patients ≥65 years of age who had AHREs lasting for ≥6 minutes and who had at least one risk factor for stroke and no history of AF.
- **Intervention**: 2608 patients received either the oral anticoagulant edoxaban (60 mg) or placebo once daily.
- **Primary efficacy outcome:** first occurrence of a composite of cardiovascular death, stroke, or systemic embolism
- **Safety outcome:** composite of death from any cause or major bleeding.



Enrollment, Randomization, and Follow-up



Demographic and Clinical Characteristics of the Patients at Baseline

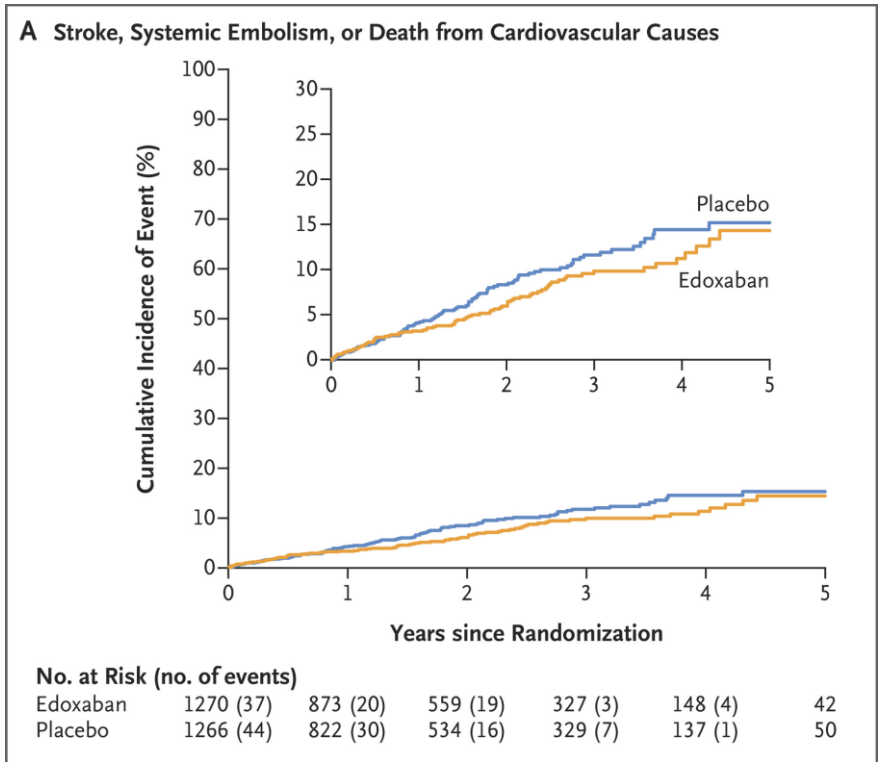
- mean age: 78 years.
- median duration of AHREs: 2.8 hours
- median number of AHREs: 2.8
- median CHA2DS2-VASc score: 4

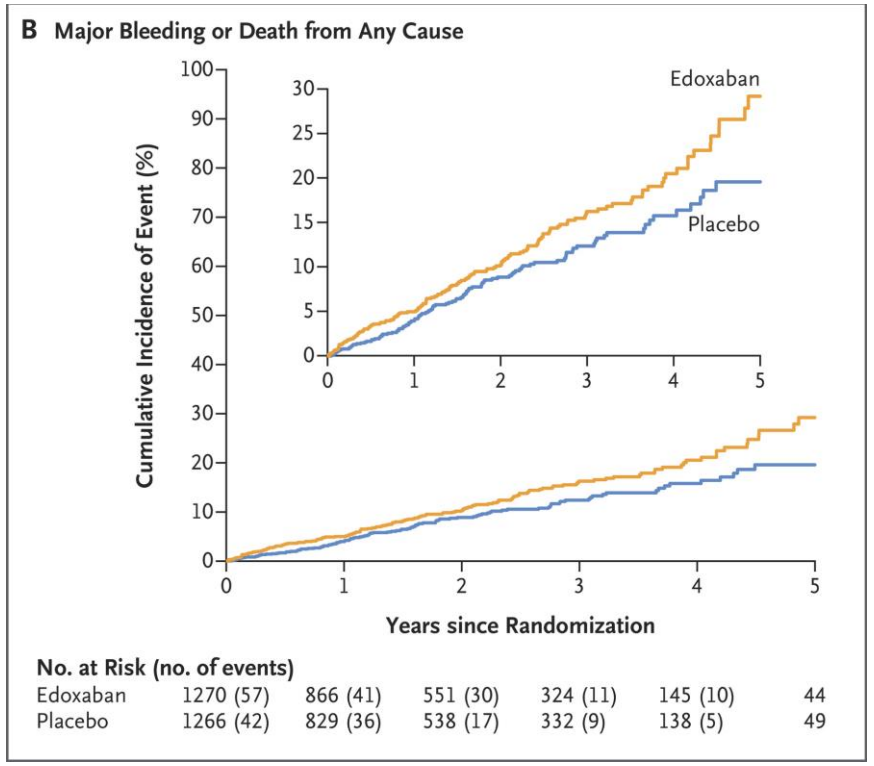
Characteristic	Edoxaban (N=1270)	Placebo (N=1266)	Total (N=2536)
Age — yr	77.4±6.5	77.5±6.8	77.5±6.7
Age ≥75 yr — no./total no. (%)	845/1270 (66.5)	855/1266 (67.5)	1700/2536 (67.0)
Female sex — no./total no. (%)	469/1270 (36.9)	480/1266 (37.9)	949/2536 (37.4)
Device used to record AHREs — no./total no. (%)			
Pacemaker	1017/1270 (80.1)	1055/1266 (83.3)	2072/2536 (81.7)
Defibrillator	100/1270 (7.9)	88/1266 (7.0)	188/2536 (7.4)
Cardiac resynchronization device	138/1270 (10.9)	113/1266 (8.9)	251/2536 (9.9)
Implanted loop recorder	15/1270 (1.2)	10/1266 (0.8)	25/2536 (1.0)
Median duration of AHREs (IQR) — hr†	2.8 (0.8–9.2)	2.8 (0.7–9.5)	2.8 (0.8–9.4)
AHREs with atrial rates >200 beats/ min — no./total no. (%)	918/944 (97.2)	896/925 (96.9)	1814/1869 (97.1)
Median CHA_2DS_2-VASc score (IQR)‡	4 (3–5)	4 (3–5)	4 (3–5)
Median CHA_2DS_2-VA score (IQR)‡	3 (3–4)	3 (3–4)	3 (3–4)
Heart failure — no./total no. (%)§	361/1270 (28.4)	335/1266 (26.5)	696/2536 (27.4)
Hypertension — no./total no. (%)¶	1096/1270 (86.3)	1109/1266 (87.6)	2205/2536 (86.9)
Diabetes mellitus — no./total no. (%)	350/1270 (27.6)	331/1266 (26.1)	681/2536 (26.9)
Previous stroke or transient ischemic attack — no./total no. (%)	122/1270 (9.6)	131/1266 (10.3)	253/2536 (10.0)
Previous myocardial infarction, PCI, or CABG — no./total no. (%)	353/1270 (27.8)	316/1266 (25.0)	669/2536 (26.4)
Indication for acetylsalicylic acid at randomization — no./total no. (%)‖	684/1270 (53.9)	683/1266 (53.9)	1367/2536 (53.9)
Indication for edoxaban dose reduction to 30 mg once daily — no./total no. (%)‖	365/1270 (28.7)	382/1266 (30.2)	747/2536 (29.5)
Estimated creatinine clearance — ml/min	66.4±23.6	65.7±23.2	66.0±23.4
Hemoglobin — g/liter**	138.9±17.5	138.6±16.9	138.8±17.2
Heart rate — beats/min††	68.9±10.8	68.4±10.8	68.6±10.8
Cardiovascular therapies — no./total no. (%)			
Beta-blockers	741/1263 (58.7)	735/1250 (58.8)	1476/2513 (58.7)
Antihypertensive therapy	1155/1263 (91.4)	1141/1250 (91.3)	2296/2513 (91.4)
ACE inhibitors, ARBs, or sacubitril–valsartan	889/1263 (70.4)	869/1250 (69.5)	1758/2513 (70.0)
Loop diuretics	325/1263 (25.7)	331/1250 (26.5)	656/2513 (26.1)
Mineralocorticoid-receptor antagonists	209/1263 (16. 5)	189/1250 (15.1)	398/2513 (15.8)
Statins	762/1263 (60.3)	732/1250 (58.6)	1494/2513 (59.5)

Efficacy Outcomes

Outcome	Edoxaban (N=1270)	Placebo (N=1266)	Adjusted Hazard Ratio (95% CI)
	no. of patients with event/patient-yr (% per patient-yr)		
Primary composite efficacy outcome†	83/2557 (3.2)	101/2495 (4.0)	0.81 (0.60 to 1.08)‡
Ischemic stroke	22/2573 (0.9)	27/2519 (1.1)	0.79 (0.45 to 1.39)
Systemic embolism	14/2579 (0.5)	28/2515 (1.1)	0.51 (0.27 to 0.96)
Myocardial infarction	10/2589 (0.4)	16/2524 (0.6)	—
Pulmonary embolism	3/2589 (0.1)	9/2533 (0.4)	—
Peripheral limb embolism	1/2592 (<0.1)	3/2536 (0.1)	—
Abdominal embolism	0	1/2540 (<0.1)	—
Cardiovascular death	52/2595 (2.0)	57/2540 (2.2)	0.90 (0.62 to 1.31)
Death due to acute myocardial infarction	1/2595 (<0.1)	4/2540 (0.2)	—
Sudden cardiac death	18/2595 (0.7)	13/2540 (0.5)	—
Death due to heart failure	13/2595 (0.5)	15/2540 (0.6)	—
Death due to stroke	1/2595 (<0.1)	3/2540 (0.1)	—
Death due to cardiovascular hemorrhage	2/2595 (0.1)	1/2540 (<0.1)	—
Death due to other cardiovascular cause	1/2595 (<0.1)	4/2540 (0.2)	—
Death of unknown cause, counted as cardiovascular cause	16/2595 (0.6)	17/2540 (0.7)	—
Major adverse cardiovascular event§	92/2532 (3.6)	102/2485 (4.1)	0.89 (0.67 to 1.18)
Ischemic stroke or systemic embolism	25/2566 (1.0)	38/2509 (1.5)	0.65 (0.39 to 1.07)

Primary Efficacy Outcome and Safety Outcome





Safety Outcomes

Outcome	Edoxaban (N=1270)	Placebo (N=1266)	Adjusted Hazard Ratio (95% CI)	P Value
	no. of patients with event/patient-yr (% per patient-yr)			
Composite safety outcome†	149/2534 (5.9)	114/2508 (4.5)	1.31 (1.02 to 1.67)	0.03
Death from any cause	111/2595 (4.3)	94/2540 (3.7)	1.16 (0.88 to 1.53)	0.28
Cardiovascular death	52/2595 (2.0)	57/2540 (2.2)	—	—
Cancer-related death	22/2595 (0.8)	9/2540 (0.4)	—	—
Covid-19–associated death	15/2595 (0.6)	12/2540 (0.5)	—	—
Death due to acute infection or sepsis	12/2595 (0.5)	9/2540 (0.4)	—	—
Death due to frailty or old age	3/2595 (0.1)	2/2540 (0.1)	—	—
Death due to accident or poly-trauma	3/2595 (0.1)	1/2540 (<0.1)	—	—
Death due to lung disease	2/2595 (0.1)	1/2540 (<0.1)	—	—
Death due to acute abdomen	0	2/2540 (0.1)	—	—
Kidney-related death	1/2595 (<0.1)	0	—	—
Dementia-related death	0	1/2540 (<0.1)	—	—
Suicide	1/2595 (<0.1)	0	—	—
Major bleeding	53/2534 (2.1)	25/2508 (1.0)	2.10 (1.30 to 3.38)	0.002
Mean no. of major bleeding events per patient	0.06±0.35	0.02±0.16	3.06 (1.74 to 5.36)‡	<0.001

Limitations and remaining questions

- The trial was stopped early, so it did not have sufficient power to detect or rule out a small beneficial effect of oral anticoagulation on the prevention of stroke.
- Most of the patients were White and trom Europe, so the findings may not be generalizable to other racial and ethnic groups
- Whether other non-vitamin K antagonist oral anticoagulants would lead to results similar to those of this trial is unknown.

Conclusions

- Among patients with AHREs but without atrial fibrillation, the incidence of a composite of cardiovascular death, stroke, or systemic embolism with edoxaban was not significantly different from that with placebo, but treatment with edoxaban led to a higher incidence of a composite of death or major bleeding.