Apixaban nella prevenzione dell’ictus nei pazienti con fibrillazione atriale subclinica

Risultati del trial ARTESIA

Background

- Atrial fibrillation is typically diagnosed by means of electrocardiography in patients with symptoms.
- Clinical atrial fibrillation is a leading cause of stroke, particularly among older persons.
- Vitamin K antagonists and direct-acting oral anticoagulants reduce the risk of stroke among patients with clinical atrial fibrillation while increasing the risk of bleeding.
- Pacemakers and implantable cardioverter–defibrillators that could continuously detect and characterize atrial arrhythmias may document short episodes of asymptomatic atrial fibrillation, even in patients with no other evidence of clinical atrial fibrillation.

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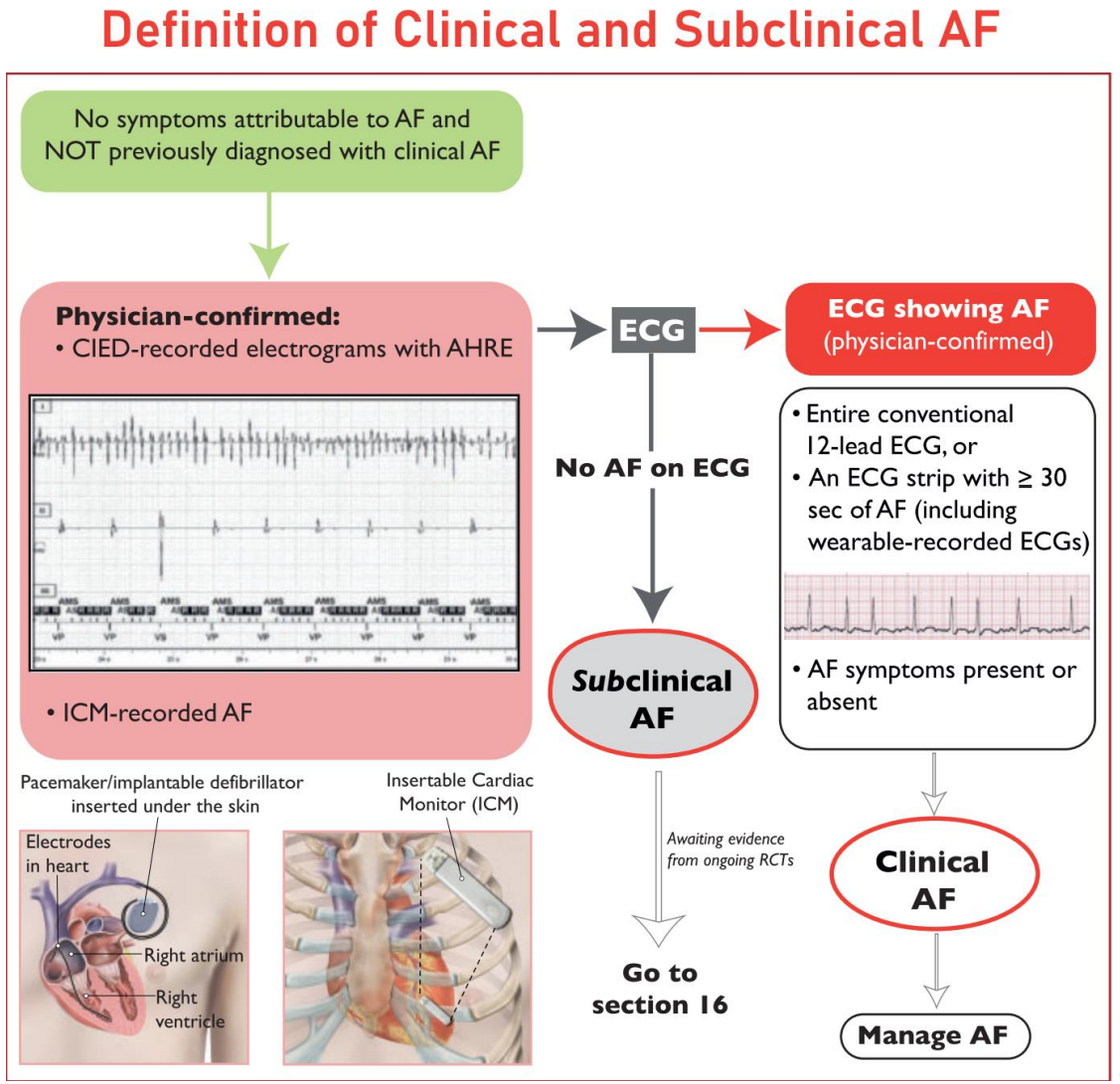
Subclinical AF

- Brief (minutes-hours), asymptomatic AF
- Detected only with long-term continuous monitoring
  - 1/3 of patients with pacemakers and ICDs
- 2.5-fold increased risk of stroke (ASSERT, TRENDS)
- Stroke risk appears lower than with clinical AF (4-5-fold)[1]
- Value of oral anticoagulation is unknown



Apixaban for Stroke Prevention in Subclinical Atrial Fibrillation

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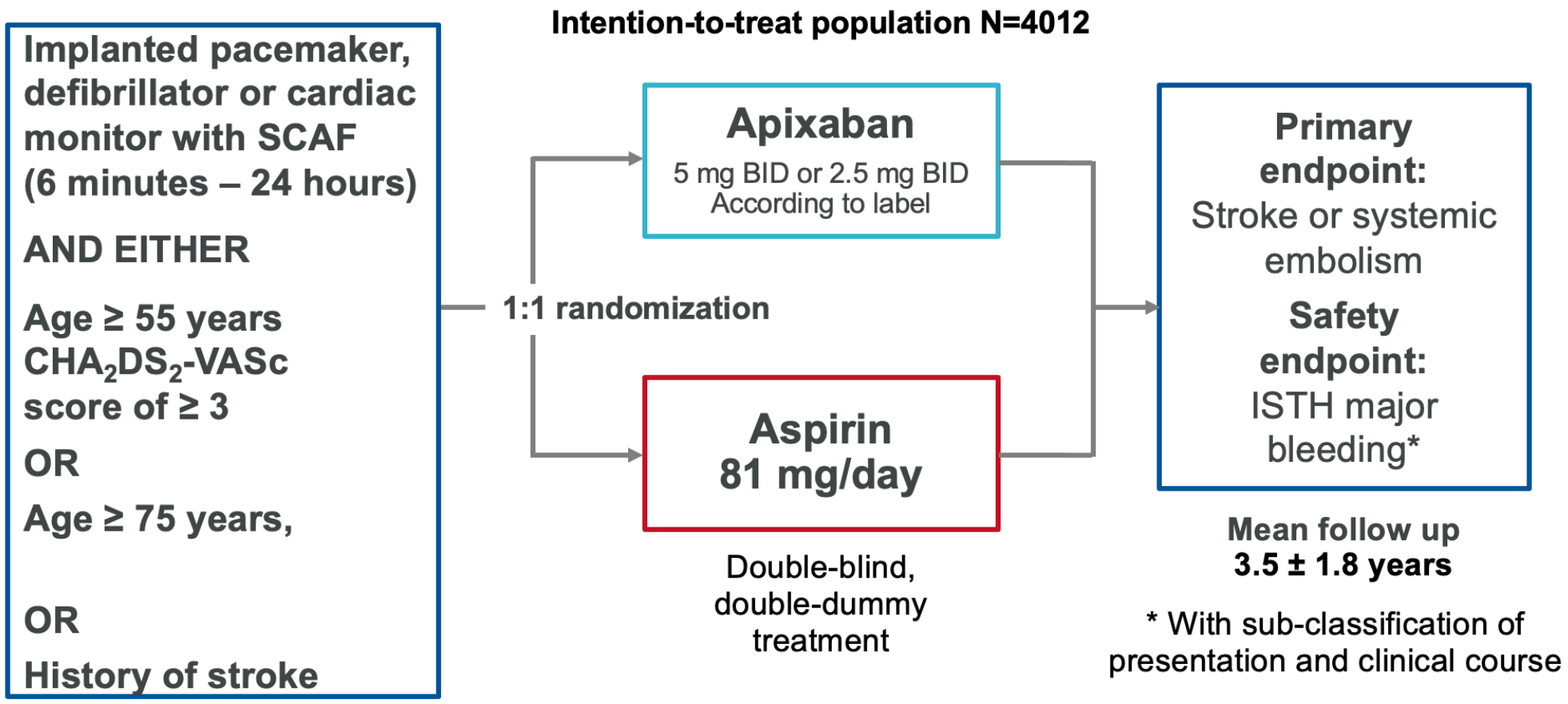
ARTESIA Study design



Lopes RD, et al. *American Heart Journal* 2017

Patient disposition

- 4012 patients randomized at 247 centers in 16 countries
- 99% received at least one dose of study medication
  - 24% of patients stopped study medication due to SCAF>24 or clinical AF at median follow up of 1.5 years
  - 35% of patients stopped study medication for other reasons
- 22% of patients died
- 2.9% withdrew or were lost to follow-up

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Statistical analysis

- Primary efficacy analysis
  - Used intention to treat (ITT)
  - Patients censored at time of discontinuation for SCAF>24 hours or clinical AF
- ITT, without censoring also performed
- Primary analysis for bleeding
  - Used on-treatment analysis, as pre-specified

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Baseline characteristics

Baseline Characteristics - 1	Apixaban (N = 2015)	Aspirin (N = 1997)
Age years (mean ± SD)	76.9 ± 7.6	76.7 ± 7.7
Sex, % female	35.7	36.5
CHA_2DS_2-VASc Score (mean ± SD)	3.9 ± 1.1	3.9 ± 1.1
CHA_2DS_2-VASC ≥ 4 (%)	60.5	60.8
History of Hypertension (%)	81.5	81.4
History of Coronary Artery Disease (%)	36.3	37.8
Peripheral Arterial Disease (%)	8.3	8.3
Diabetes Mellitus (%)	28.9	29.2
History of Heart Failure	27.3	29.4
History of Stroke, Systemic Embolism or TIA (%)	8.9	9.1
Creatinine Clearance mL/min (mean ± SD)	70.8 ± 26.7	72.1 ± 30.6

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Baseline characteristics

Baseline Characteristics - 2	Apixaban (N = 2015)	Aspirin (N = 1997)
Baseline Anti-Platelet Usage (%)		
Aspirin	57.8	56.9
Other Single or Dual Anti-Platelet Agents	7.1	7.6
Longest episode of SCAF in past 6 months	1.4 (0.2-4.9) hours	1.5 (0.2-4.8) hours
No episodes (%)	15.7	15.8
< 6 min (%)	2.1	2.2
6 min - < 1 hour (%)	26.6	24.9
1 hour – < 6 hours (%)	33.8	37.2
6 hours – < 12 hours (%)	14.2	13.2
12 hours – < 24 hours (%)	7.5	6.7

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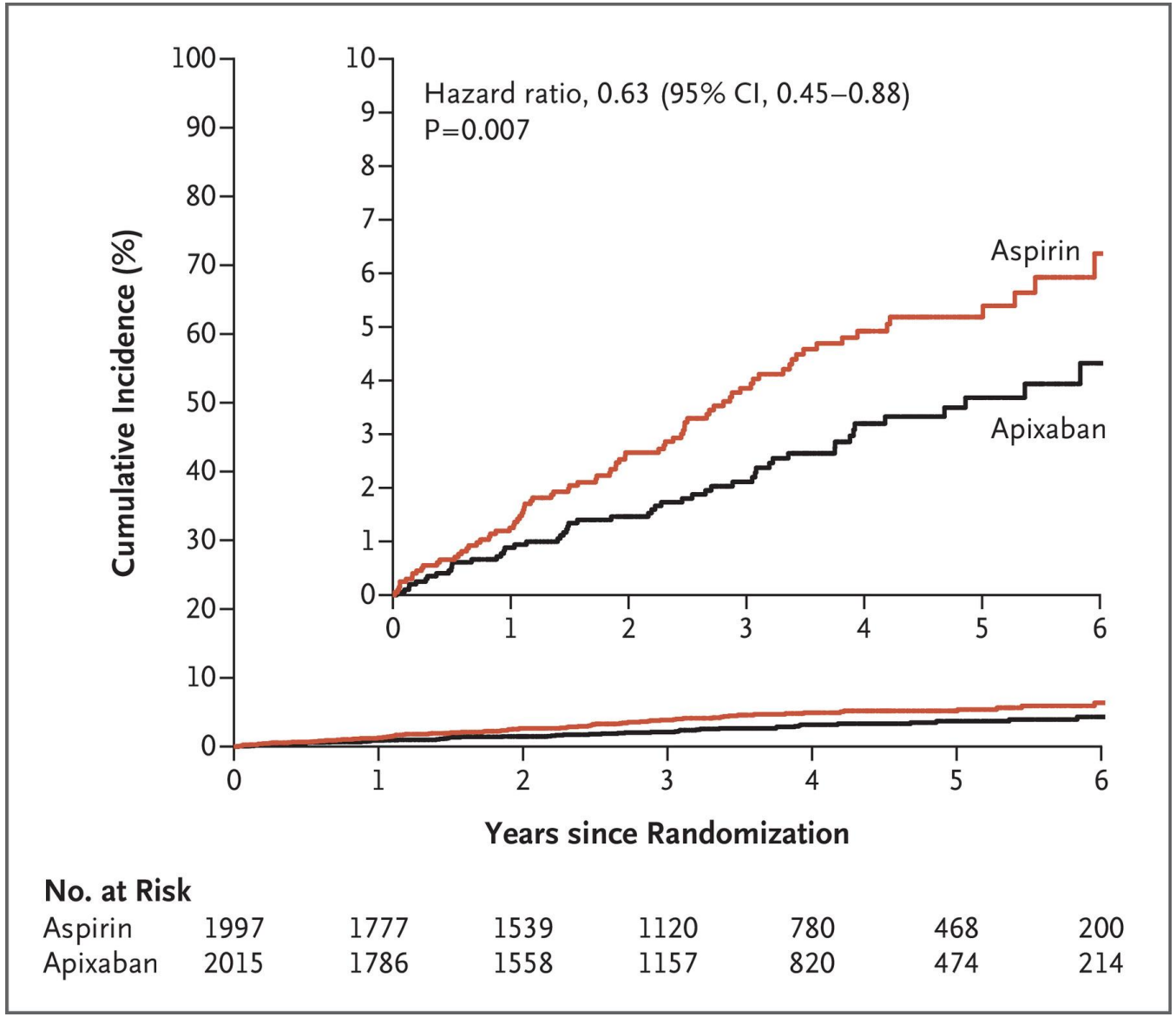
Stroke or Systemic Embolism (Primary Efficacy Outcome)

Mean follow-up of 3.5±1.8 years



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Clinical outcomes (ITT)

The primary efficacy outcome, stroke or systemic embolism, was assessed in the intention-to-treat population (all the patients who had undergone randomization)

Table 2. Clinical Outcomes (Intention-to-Treat Population).*

Outcome	Apixaban (N=2015)		Aspirin (N=1997)		Hazard Ratio (95% CI)	P Value
	no. of patients with event	*%/patient-yr*	*no. of patients with event*	*%/patient-yr*		
Stroke or systemic embolism	55	0.78	86	1.24	0.63 (0.45–0.88)	0.007
Stroke	55	0.78	84	1.21	0.64 (0.46–0.90)	
Ischemic or unknown type†	45	0.64	71	1.02	0.62 (0.43–0.91)	
Hemorrhagic	10	0.14	13	0.18	0.76 (0.33–1.73)	
Severity according to score on modified Rankin scale‡						
0–2	31	0.44	45	0.65	0.68 (0.43–1.07)	
3–6	19	0.27	37	0.53	0.51 (0.29–0.88)	
Missing data	5	0.07	2	0.03	2.48 (0.48–12.80)	
Systemic embolism	0		2	0.03	NA	
Stroke, TIA, or systemic embolism§	82	1.17	107	1.56	0.75 (0.56–1.00)	
Stroke, systemic embolism, or death from cardiovascular causes	148	2.10	171	2.47	0.85 (0.68–1.06)	
Stroke, myocardial infarction, systemic embolism, or death	419	6.01	418	6.10	0.98 (0.86–1.12)	
Myocardial infarction	37	0.52	41	0.59	0.89 (0.57–1.40)	
Death	362	5.06	341	4.82	1.04 (0.90–1.21)	
Death from cardiovascular causes	105	1.47	108	1.53	0.96 (0.73–1.25)	
Major bleeding¶	106	1.53	78	1.12	1.36 (1.01–1.82)	0.04
Fatal bleeding	10	0.14	14	0.20	0.70 (0.31–1.57)	
Symptomatic intracranial hemorrhage	17	0.24	23	0.33	0.73 (0.39–1.36)	
Gastrointestinal bleeding	55	0.78	31	0.44	1.76 (1.13–2.74)	
Transfusion performed	35	0.49	31	0.44	1.11 (0.68–1.80)	

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Clinical outcome (On-Treatment)

The primary safety outcome, major bleeding, was assessed in the on-treatment population (all the patients who had undergone randomization and received at least one dose of the assigned trial drug, with follow-up censored 5 days after permanent discontinuation of trial medication for any reason

Table 3. Clinical Outcomes (On-Treatment Population).*

Outcome	Apixaban (N=1989)		Aspirin (N=1972)		Hazard Ratio (95% CI)	P Value
	no. of patients with event	*%/patient-yr*	*no. of patients with event*	*%/patient-yr*		
Stroke or systemic embolism	36	0.71	65	1.29	0.55 (0.37–0.83)	0.004
Stroke	36†	0.71	63	1.25	0.57 (0.38–0.85)	
Ischemic or unknown type	29	0.57	53	1.05	0.54 (0.35–0.86)	
Hemorrhagic	8	0.16	10	0.20	0.78 (0.31–1.98)	
Severity according to score on modified Rankin scale						
0–2	22	0.43	32	0.64	0.69 (0.40–1.18)	
3–6	11	0.22	29	0.58	0.37 (0.19–0.75)	
Missing data	3	0.06	2	0.04	1.43 (0.24–8.58)	
Systemic embolism	0		2	0.04	NA	
Stroke, TIA, or systemic embolism‡	53	1.04	86	1.71	0.61 (0.43–0.86)	
Stroke, systemic embolism, or death from cardiovascular causes	76	1.50	94	1.87	0.80 (0.59–1.09)	
Stroke, myocardial infarction, systemic embolism, or death	193	3.81	206	4.11	0.92 (0.75–1.12)	
Myocardial infarction	27	0.53	33	0.66	0.81 (0.49–1.35)	
Death	139	2.73	122	2.42	1.11 (0.87–1.42)	
Death from cardiovascular causes	42	0.83	37	0.73	1.13 (0.72–1.75)	
Major bleeding§	86	1.71	47	0.94	1.80 (1.26–2.57)	0.001
Fatal bleeding	5	0.10	8	0.16	0.63 (0.20–1.91)	
Symptomatic intracranial hemorrhage	12	0.24	15	0.30	0.77 (0.36–1.64)	
Gastrointestinal bleeding	45	0.89	20	0.40	2.23 (1.32–3.78)	
Transfusion performed	26	0.51	18	0.36	1.43 (0.78–2.61)	

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Clinical Presentation and Management of Major Bleeding

Table 4. Clinical Presentation and Management of Major Bleeding.*

Variable	Apixaban	Aspirin
No. of major bleeding events	93	49
Clinical presentation — no. (%)		
1: Without emergency	11 (12)	6 (12)
2: Need for some measures	57 (61)	27 (55)
3: Hemodynamic instability or neurologic symptoms	17 (18)	13 (27)
4: Fatal	2 (2)	2 (4)
Missing data	6 (6)	1 (2)
Clinical course — no. (%)		
1: Conservative measures	21 (23)	16 (33)
2: Supportive care, transfusion	54 (58)	22 (45)
3: Immediate measures needed to avoid death	9 (10)	4 (8)
4: Death unavoidable	3 (3)	6 (12)
Missing data	6 (6)	1 (2)

* Categorization is based on classification of bleeding used in previous publications.[17,18] Percentages may not total 100 because of rounding.

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Benefit to Risk Analysis

- ITT analysis (per thousand patient-years)
  - 4.6 fewer strokes/emboli
  - 4.1 more major bleeds

- 45% of strokes on aspirin were permanently disabling or fatal
  - Reduced by 49% with apixaban

- Fewer than 15% of major bleeds on apixaban progressed to death or required immediate measures to avoid death
  - Numerically fewer fatal or intracranial bleeds

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Comparison with NOAH-AFNET 6 trial

- The NOAH-AFNET 6 trial was stopped early, had relatively few stroke events, and was thus underpowered.
- The primary efficacy outcome of the NOAH-AFNET 6 trial included death from cardiovascular causes. Because deaths in this population of patients are rarely due to stroke and are commonly due to underlying cardiovascular disease and old age, adding death from cardiovascular causes to the primary outcome dilutes any potential signal related to stroke reduction.
- The control group in the NOAH-AFNET 6 trial was assigned to received placebo (and many received aspirin), whereas all the patients in the control group in the ARTESIA trial were assigned to receive aspirin. Aspirin is effective for stroke prevention in patients with previous stroke, but whether it reduces the risk of stroke among patients with atrial fibrillation is controversial. The use of aspirin in the control group in the ARTESIA trial probably had little effect on the signal for reduction in stroke but almost certainly mitigated the signal for harm, because aspirin is known to increase bleeding.
- However, the difference in the control groups of the two trials does not explain the fact that the ARTESIA trial showed a significant reduction in stroke and the NOAH-AFNET 6 trial did not.

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Conclusions

- Apixaban reduces the risk of stroke or systemic embolism in patients with subclinical AF by 37%
  - Fatal and permanently disabling strokes reduced by 49%
- Apixaban increases major bleeding
  - But no increase in fatal or intracranial bleeding was detected
- Anticoagulation should be considered for patients with subclinical AF who have additional stroke risk factors

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