#AHA23

ARTESiA

THE ARTESIA TRIAL

Apixaban for Stroke Prevention in Subclinical Atrial Fibrillation

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On behalf of the ARTESIA steering committee and investigators

American Heart Association.

DISCLOSURES

Dr. J. Healey:

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ARTESIA study funding

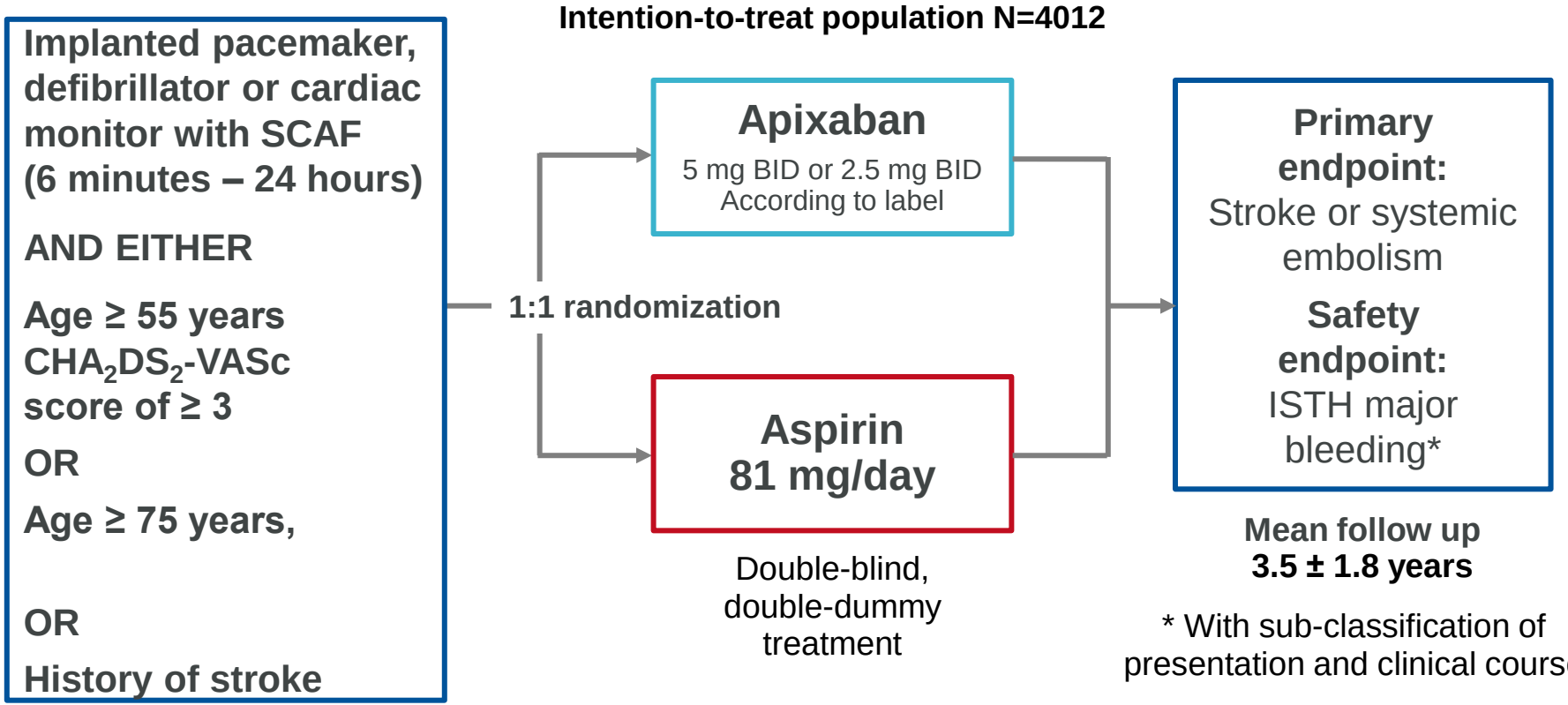
Canadian Institutes for Health Research (201610PTJ-378238), the Bristol-Myers Squibb-Pfizer Alliance, the Heart and Stroke Foundation of Canada, the Canadian Stroke Prevention Intervention Network (CSPIN), Hamilton Health Sciences, the Accelerating Clinical Trials (ACT) Network and the Population Health Research Institute (PHRI).

SUBCLINICAL AF (SCAF)

- 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

[1]Wolf PA, Framingham Heart Study; Stroke 1991 Aug;22(8):983-8

ARTESIA STUDY DESIGN



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

STATISTICAL ANALYSIS

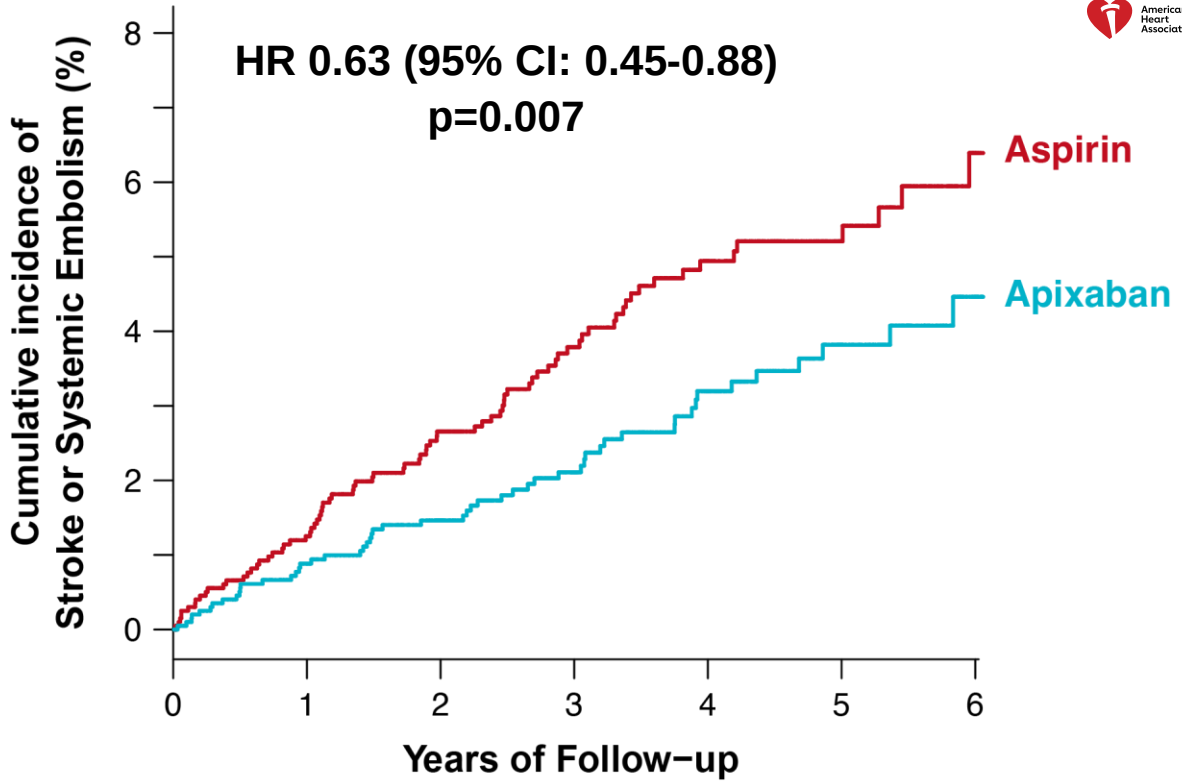
- Primary efficacy analysis
  - Used intention to treat (ITT)
  - Patients censored at time of discontinuation for SCAF>24 hours or clinical AF
- ITT, without censoring also performed
- Primary analysis for bleeding
  - Used on-treatment analysis, as pre-specified

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

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

PRIMARY OUTCOME

STROKE OR SYSTEMIC EMBOLISM



No. at Risk							
Aspirin	1997	1777	1539	1121	779	468	200
Apixaban	2015	1786	1556	1157	822	474	214

PRIMARY EFFICACY ANALYSIS (ITT)

	Apixaban (N = 2015)	Aspirin (N = 1997)	Hazard Ratio (95% CI)	P value
Stroke or systemic embolism n (% per year)	55 (0.78)	86 (1.24)	0.63 (0.45-0.88)	0.007
Total Stroke	55 (0.78)	84 (1.21)	0.64 (0.46-0.90)	
Ischemic stroke*	45 (0.64)	71 (1.02)	0.62 (0.43-0.91)	
Hemorrhagic stroke	10 (0.14)	13 (0.18)	0.76 (0.33-1.73)	
Mod. Rankin Score 0-2	31 (0.44)	45 (0.65)	0.68 (0.43-1.07)	
Mod. Rankin Score 3-6	19 (0.27)	37 (0.53)	0.51 (0.29-0.88)	
Cardiovascular death	105 (1.47)	108 (1.53)	0.96 (0.73-1.25)	

*includes stroke of unknown etiology

SAFETY ANALYSIS: MAJOR BLEEDING (ON-TREATMENT)

Major Bleeding (ISTH)	Apixaban (N = 2015)	Aspirin (N = 1997)	Hazard Ratio (95% CI)	P Value
Major Bleeding: n (% per year)	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)	
Transfusion required	26 (0.51)	18 (0.36)	1.43 (0.78-2.61)	
Major Bleeding (ITT)	106 (1.53)	78 (1.12)	1.36 (1.01-1.82)	0.04

Major Bleeding Events	Apixaban (N = 2015)	Aspirin (N = 1997)
Clinical course: n (% of major bleeds)		
1 (conservative measures)	21 (22.6)	16 (32.7)
2 (supportive care, transfusion)	54 (58.1)	22 (44.9)
3 (Immediate measures needed to avoid death)	9 (9.7)	4 (8.2)
4 (death unavoidable)	3 (3.2)	6 (12.2)

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

CONCLUSIONS

1. Apixaban reduces the risk of stroke or systemic embolism in patients with subclinical AF by 37%
   - Fatal and permanently disabling strokes reduced by 49%

2. Apixaban increases major bleeding
   - But no increase in fatal or intracranial bleeding was detected

3. Anticoagulation should be considered for patients with subclinical AF who have additional stroke risk factors

MANY THANKS!

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