Cause of Death and Competing Risk in Patients with Device-Detected Atrial Fibrillation Treated with Apixaban or Aspirin: Insights from the ARTESiA Trial

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Background

- Device-detected subclinical atrial fibrillation (AF) is associated with a risk of stroke
- The ARTESiA trial found that, in patients with device-detected AF, apixaban, as compared to aspirin, reduced the primary efficacy outcome of stroke or systemic embolism.
- In a randomized trial, a competing event is any outcome that *precludes the potential subsequent occurrence of the outcome of interest.*
- In the primary analysis of ARTESiA, follow-up was censored at the first occurrence of either:
  - AF progression (defined as subclinical AF lasting >24 h or AF detected clinically), as participants transitioned to-open label oral anticoagulation, or
  - Death

Objectives

1) Describe causes of death in ARTESiA participants who died during follow-up

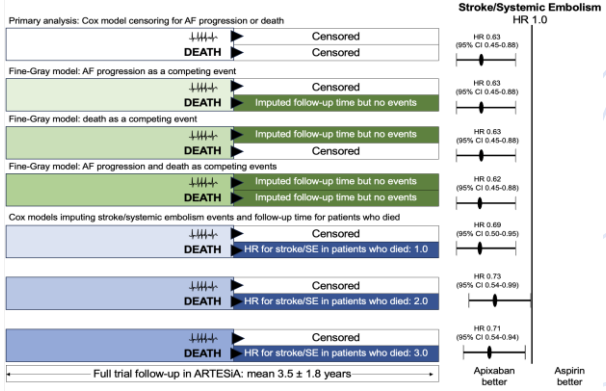
2) Test different assumptions regarding the statistical handling competing risk of death on the primary results of ARTESiA.

Methods

- ARTESiA enrolled patients with at least one episode of device-detected subclinical AF ≥6 minutes to <24 hours and and randomized them to apixaban or aspirin. The primary efficacy outcome of ARTESiA was stroke or systemic embolism
- Two adjudicators blinded to treatment allocation classified deaths occurring during follow-up using pre-specified criteria.
- In the intention-to-treat population, we used different models to compare the efficacy of apixaban to aspirin:
  - We tested Fine-Gray models.
  - We performed multiple imputations using Cox models that imputed a different hazard ratio (HR) of baseline risk of stroke/systemic embolism among trial participants with a competing death event as compared to those without. Each imputation model used 100 iterations. We censored participants at the time of AF progression

Hazard ratios for the effect of apixaban versus aspirin on stroke or systemic embolism using differing approaches to competing risk from AF progression and death

Intention-to-treat population



Conclusions

- **Among patients with device-detected AF who died during follow-up in ARTESiA, the largest proportion of deaths were non-cardiovascular. The most common causes of cardiovascular death were not anticoagulation-sensitive conditions.**
- **The observed reduction in stroke or systemic embolism with apixaban in ARTESiA is robust against a number of assumptions regarding the competing risk of death.**

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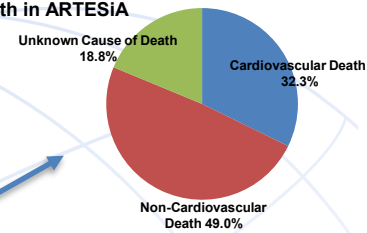
Causes of death in ARTESiA

A total of 896 of 4,012 study participants (22.3%) died during follow-up. There were no statistically significant differences in the proportion of any death type between the apixaban and aspirin arms



Cause of Death	N (%)
All-Cause Death	**896 (100.00%)**
Cardiovascular Death	**289 (32.3%)**
Ischemic stroke/SE	33 (3.7%)
Major bleeding	22 (2.5%)
Heart failure	133 (14.8%)
Myocardial infarction	7 (0.8%)
Sudden death	77 (8.6%)
Aortic dissection	1 (0.1%)
Bowel ischemia	2 (0.2%)
Major adverse limb event	2 (0.2%)
Pulmonary embolism	5 (0.6%)
Ruptured AAA	2 (0.2%)
Unspecified vascular	5 (0.6%)
Non-Cardiovascular Death	**439 (49.0%)**
Frailty/aging-associated	37 (4.1%)
Gastrointestinal	12 (1.3%)
Hepatobiliary	2 (2.1%)
Mass	1 (1.1%)
Neurodegenerative	16 (1.8%)
Pancreatitis	2 (0.2%)
Peri-operative	4 (0.4%)
Renal	14 (1.6%)
Suicide/Medically assisted	6 (0.7%)
Cancer	140 (15.6%)
Infection	138 (15.4%)
Liver failure	3 (0.3%)
Respiratory	35 (3.9%)
Trauma	29 (3.2%)
Unknown Cause of Death	**168 (18.8%)**

SE = Systemic Embolism
AAA = abdominal aortic aneurysm

Comparison between participants who died during ARTESiA with those who did not

	Patients without a Competing event	Patients with a Competing Death Event	P-value
Mean(±SD) or n(%)	2,471^ (100.0%)	644 (100.0%)	.
Age (years)	76.1 (±7.5)	79.4 (±7.8)	<.0001
Female sex	983 (39.8%)	196 (30.4%)	<.0001
DOAC Score	5.2 (±2.0)	5.9 (±2.0)	<.0001
CHA_2DS_2-VASc Score	3.9 (±1.1)	4.2 (±1.2)	<.0001
Hypertension	2,004 (81.1%)	528 (82.0%)	0.6
Coronary artery disease	859 (34.8%)	282 (43.8%)	<.0001
Peripheral arterial disease	188 (7.6%)	81 (12.6%)	<.0001
Diabetes mellitus	663 (26.8%)	224 (34.8%)	<.0001
Heart failure	618 (25.0%)	225 (34.9%)	<.0001
Prior stroke	112 (4.5%)	27 (4.2%)	0.7
Creatinine clearance (mL/min)	73.3 (±28.9)	61.7 (±26.9)	<.0001
Weight (kg)	82.7 (±18.0)	79.9 (±18.6)	0.0006
History of major bleeding	57 (2.3%)	15 (2.3%)	1.0
Device type			.
Pacemaker	1750 (70.8%)	434 (67.4%)	0.09
ICD	316 (12.8%)	96 (14.9%)	0.2
CRT	151 (6.1%)	20 (3.1%)	0.003
ICM	254 (10.3%)	94 (14.6%)	0.002

^ 897 participants are excluded form this comparison due to having experienced AF progression during the trial

Population Health Research Institute is affiliated with the academic teaching hospitals of Hamilton Health Sciences and McMaster University's Faculty of Health Sciences.