On Treatment Analysis

…a work in progress!

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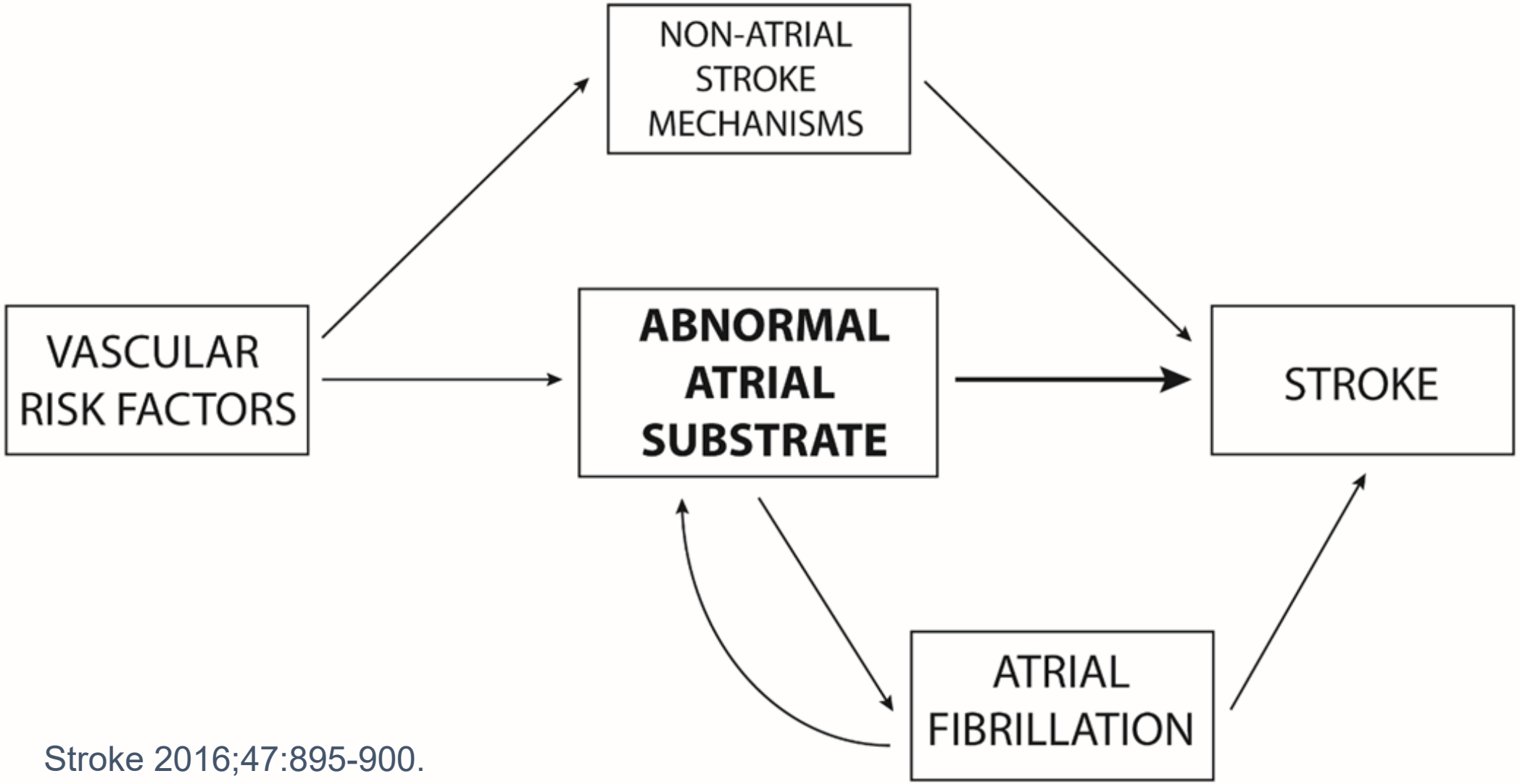
Table I Definition of atrial cardiomyopathy

'Any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations'.

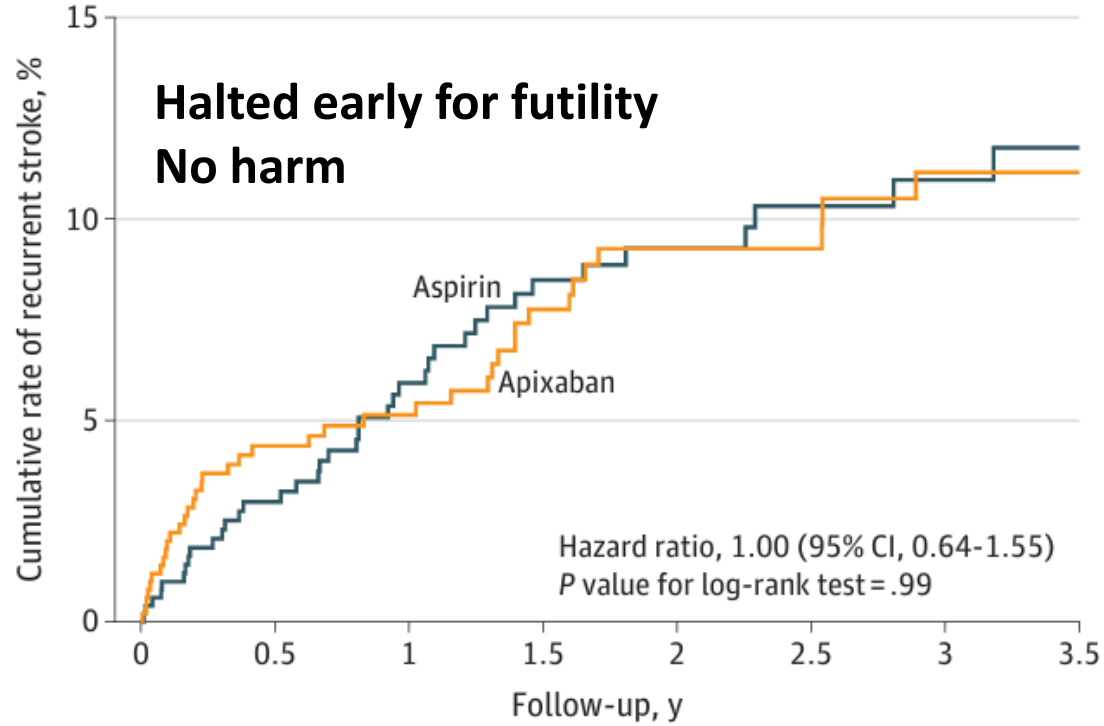
J Arrhythm. 2016 Aug;32(4):247-78



Stroke 2016;47:895-900.

ARCADIA Trial – Overview, ITT results

- Double blind RCT
- Recent cryptogenic stroke
- Atrial Cardiopathy
  - Serum marker (NT-proBNP)
  - ECG marker (PWTFV1)
  - ECHO marker (LADI)
- Aspirin vs. Apixaban
- 1° Outcome: time to recurrent stroke of any type
- ITT survival analysis



No. at risk								
Apixaban	507	400	327	256	188	146	121	74
Aspirin	508	395	317	262	195	145	119	74

Recurrent stroke included stroke of ischemic, hemorrhagic, or unknown type. The mean (SD) follow-up period in both groups was 1.8 (1.3) years.

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JAMA.2024;331(7):573-581

Intention to Treat (ITT) vs. On Treatment

- On Treatment ~= “per protocol” (PP)
- In a perfect trial, these are the same; the hypothesis is the effect of the treatment on outcomes, presumes patients take the treatment
- Begin to diverge when adherence to intervention decreases
  - Likely more relevant in trials with prolonged interventions
- ITT may give a smaller estimate of true effect, but better generalizability
  - On treatment effect may be more relevant to individual patient decision
  - Positive trial result may effect/increase adherence in clinical practice, thus making the ITT effect inaccurate
- On treatment estimates vulnerable to post randomization selection bias and confounding; may require adjustment

NEJM 2017. 377;14: 1391-1398

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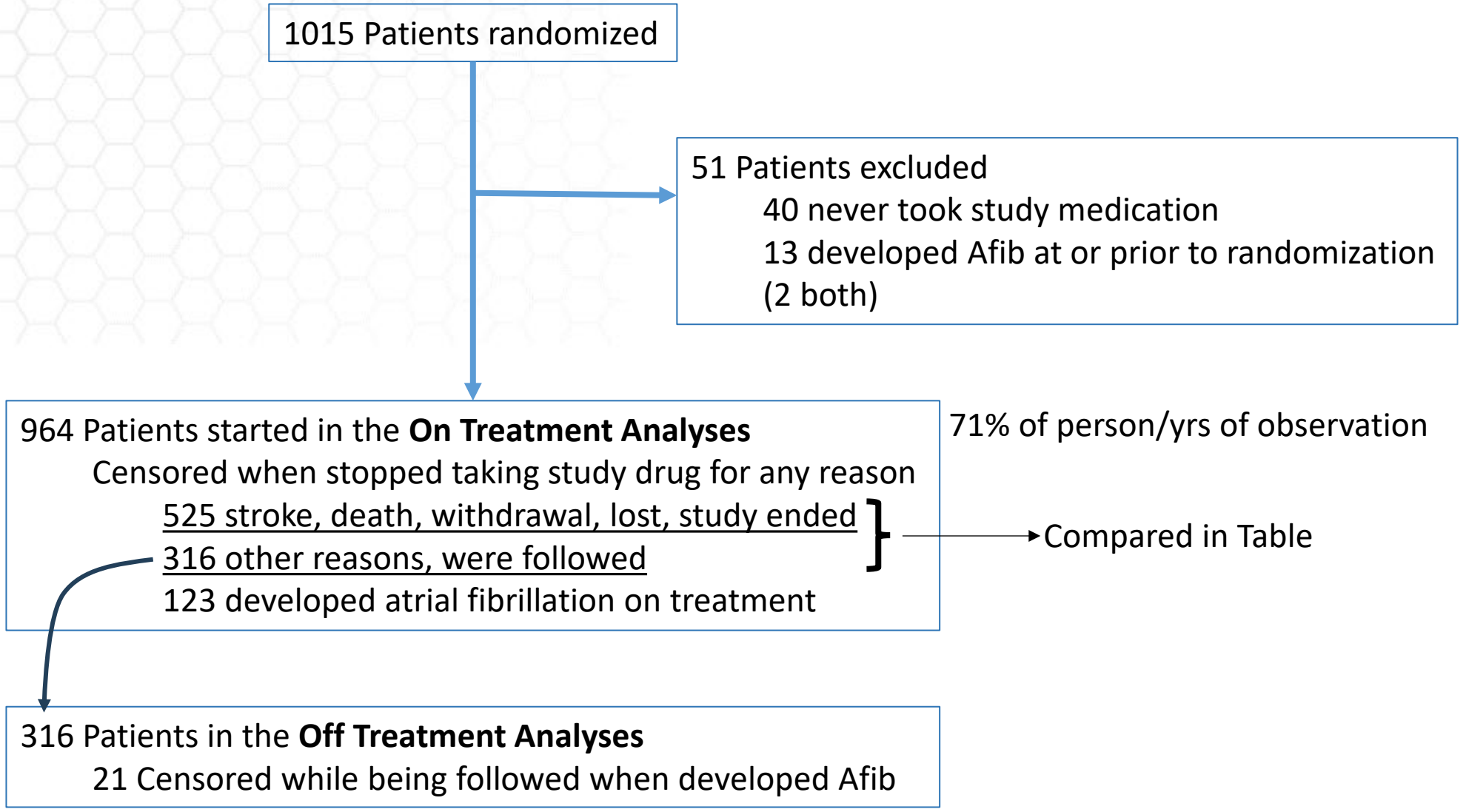
On Treatment Population



Analyses

- On treatment group
  - censored at time of Afib or when stopped study medication for any reason
- Off treatment group
  - Enter when study treatment stopped, censored at time of Afib, reached end point or study ended
- Additional analyses
  - Adherence
  - Subgroup analyses
- Cox models for HRs, interaction testing

Table 1. Demographics, patients **Never Followed Off Study Drug** vs. **Followed Off Study Drug**

Patient Characteristic	Never Followed Off Study Drug (N = 525)	Off Study Drug Followed (N = 316)	P value
Aspirin/Apixaban	269/256	160/156	.86
Age (yrs), mean (SD)	67 (11)	67 (11)	.95
Gender, N (% Female)	278 (53%)	176 (56%)	.41
Race, N (%)			
Asian	9 (1.7%)	7 (2.3%)	
Black	98 (19%)	81 (26%)	.08
White	401 (78%)	221 (71%)	
Other	7 (1.4%)	2 (.64%)	
Medical History N (%)			
TIA/Stroke	99 (19%)	67 (21%)	.4
Heart Failure	**24 (4.6%)**	**34 (11%)**	**<.001**
Ischemic Heart Disease	52 (10%)	31 (9.9%)	.98
Hypertension	399 (76%)	251 (80%)	.25
Diabetes	**142 (27%)**	**118 (37%)**	**.0019**
Smoker	219 (42%)	142 (45%)	.34
Weight (kg), mean (SD)	85 (20)	84 (21)	.54
SBP (mm Hg), mean (SD)	134 (18)	137 (19)	.082
Baseline NIHSS, median (IQR)	1 (0-3)	1 (0-3)	.75
Baseline mRS, median (IQR)	1 (0-2)	1 (0-2)	.42
Atrial Cardiopathy Biomarkers			
NT-proBNP, median (IQR)	**488 (864)**	**689 (1512)**	**.015**
PWTFV1, median (IQR)	4915 (2593)	4803 (2872)	.56
LADI, median (IQR)	1.9 (.34)	1.9 (.38)	.4

Main On Treatment Survival Analysis (1289 pyrs)

Table. Efficacy outcomes while patients were on study drug with censoring when atrial fibrillation first detected

Outcome	*number (rate per person years)* Aspirin Group (N = 488)	Apixaban Group (N = 476)	Hazard Ratio (95% CI)
On Study Drug			
Primary Outcome: Recurrent stroke of any type	32 (0.050)	23 (0.036)	0.73 (0.43, 1.25)
Components of primary efficacy outcome			
Ischemic stroke	30 (0.046)	22 (0.034)	0.74 (0.43, 1.29)
Hemorrhagic stroke	2 (0.003)	0 (0.000)	
Stroke of undetermined type	0	1 (0.001)	
Secondary efficacy outcomes			
Recurrent ischemic stroke or systemic embolism	30 (0.046)	22 (0.034)	0.74 (0.43, 1.29)
Recurrent stroke of any type or death from any cause	35 (0.054)	28 (0.044)	0.81 (0.49,1.34)

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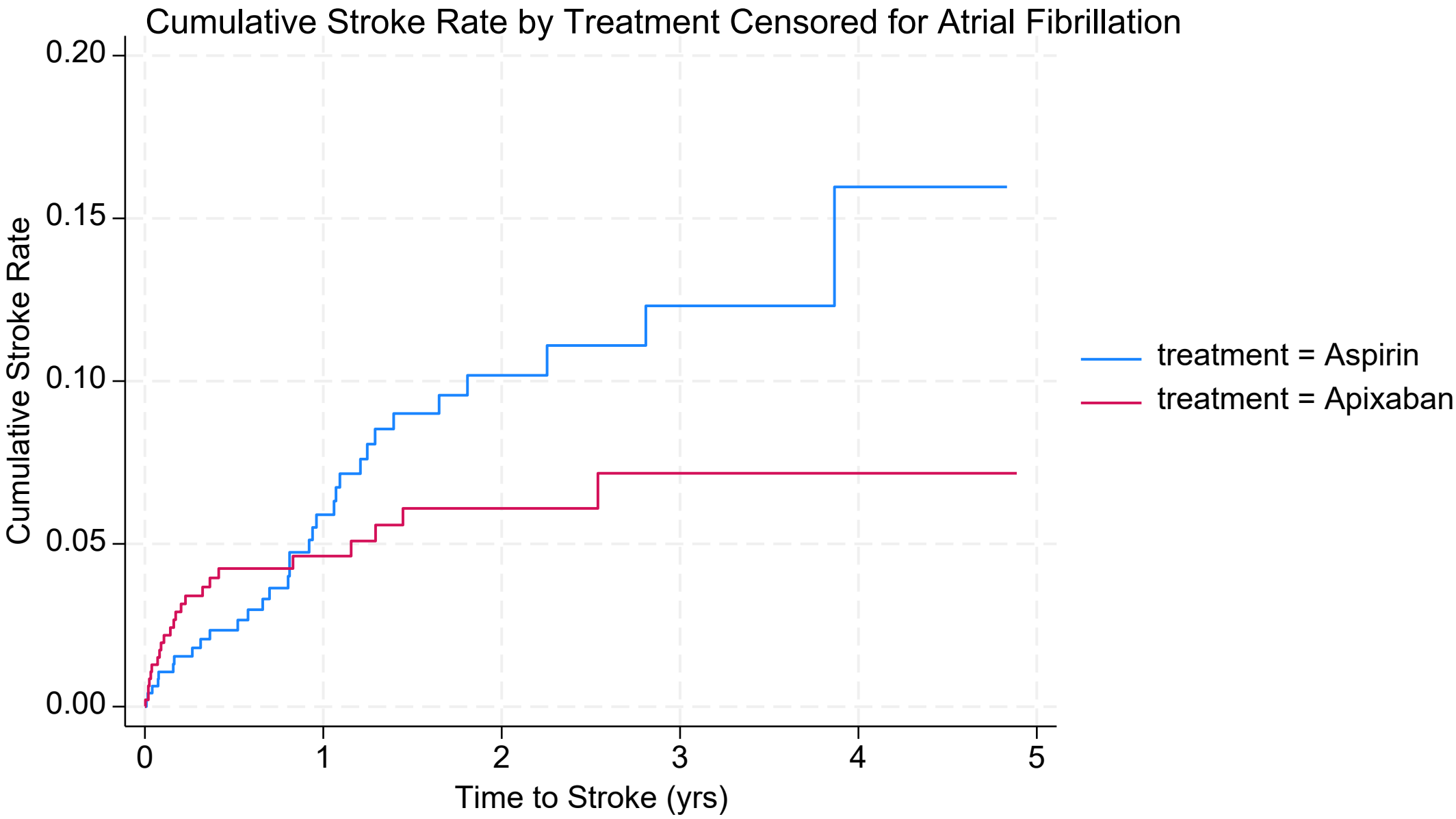
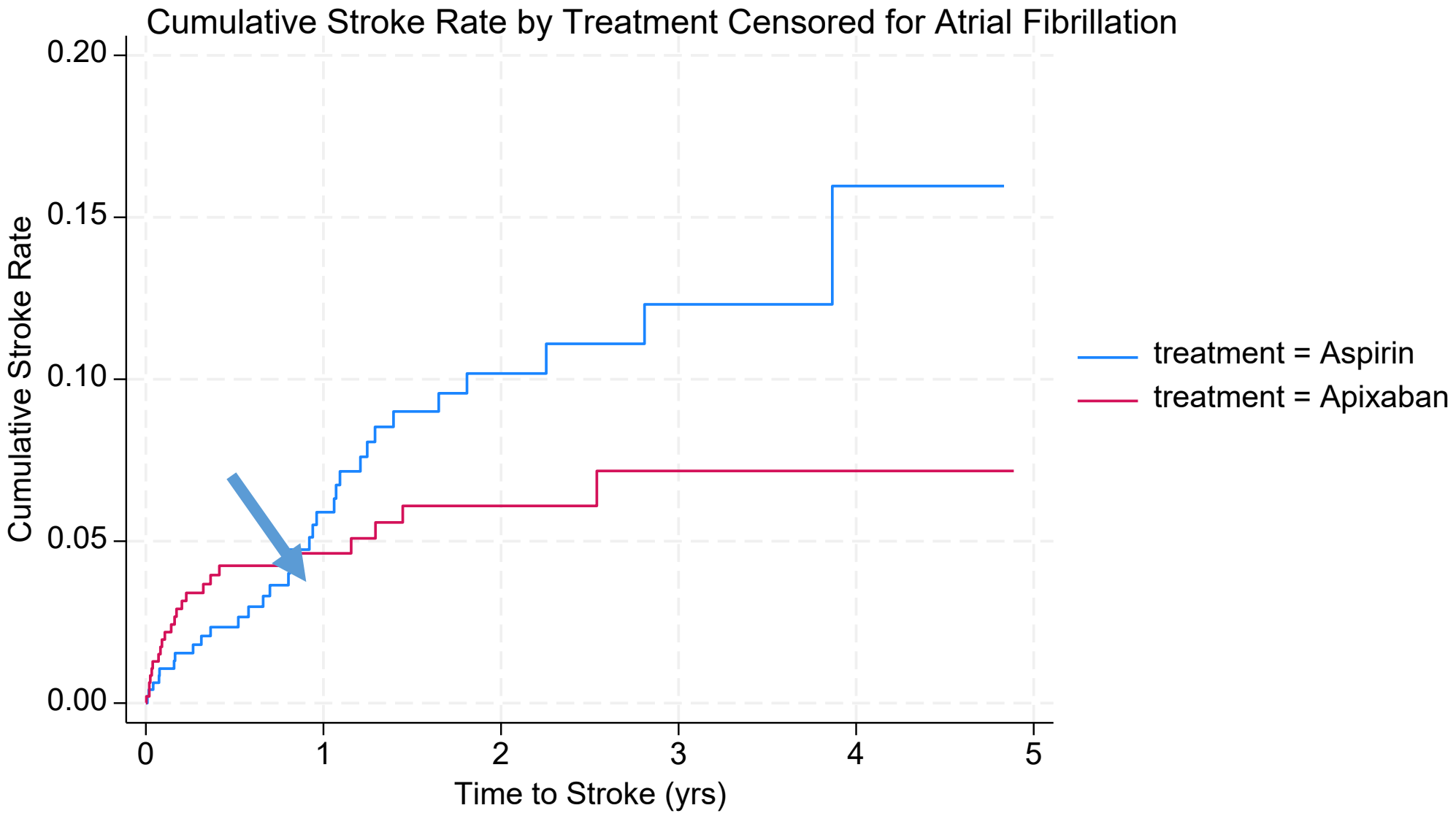

Cumulative Stroke Rate by Treatment Censored for Atrial Fibrillation
Cumulative Stroke Rate
0.20
0.15
0.10
0.05
0.00
0
1
2
3
4
5
Time to Stroke (yrs)
treatment = Aspirin
treatment = Apixaban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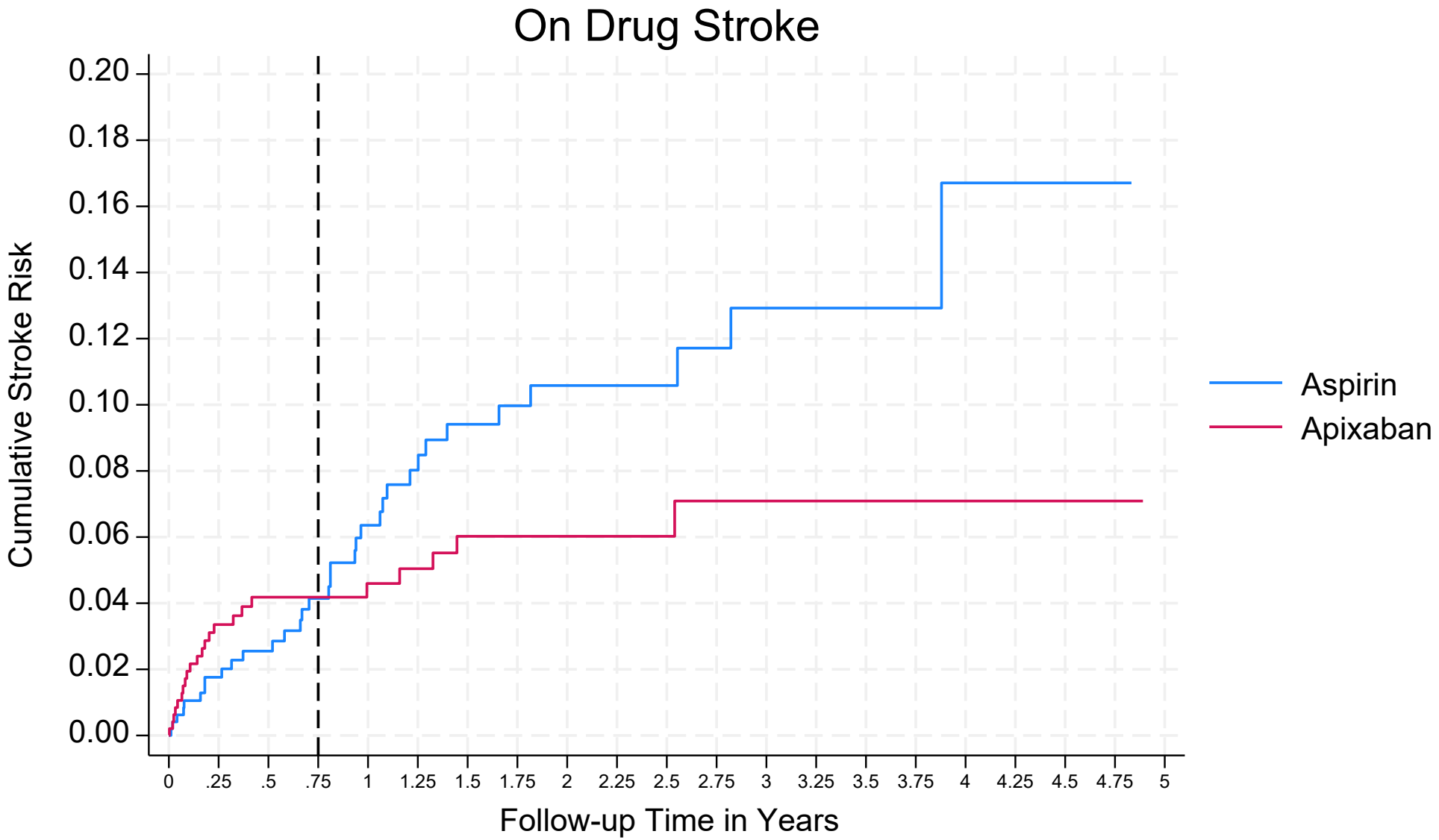
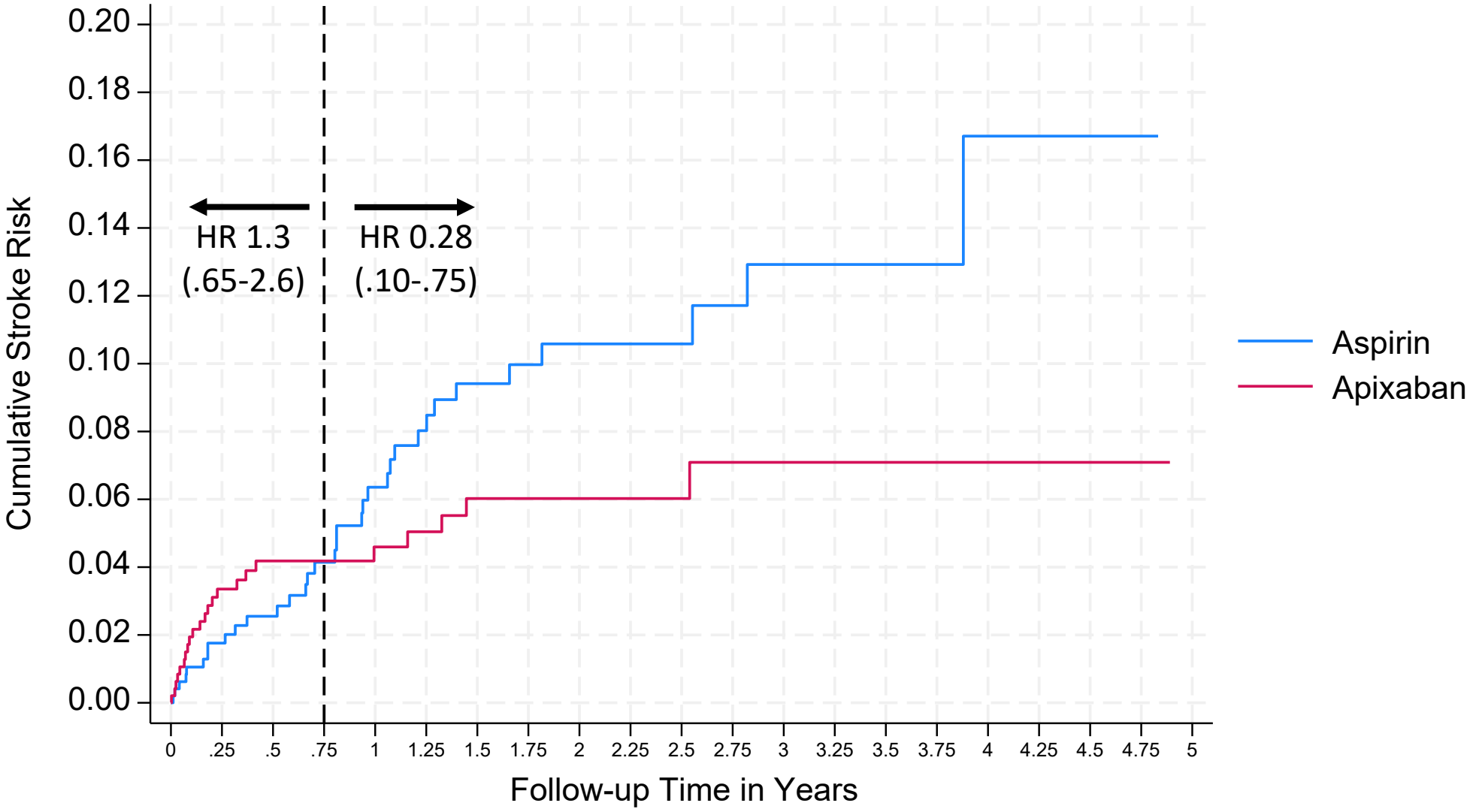

On Drug Stroke
Cumulative Stroke Risk
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0
.25
.5
.75
1
1.25
1.5
1.75
2
2.25
2.5
2.75
3
3.25
3.5
3.75
4
4.25
4.5
4.75
5
Follow-up Time in Years
Aspirin
Apixaban

On Drug Stroke



Main Off Treatment Survival Analysis (254 pyrs)

Table. Primary efficacy outcomes during period when the patients were off study drug with censoring for atrial fibrillation

Outcome	*number (rate per person years)* Aspirin Group (N = 160)	Apixaban Group (N = 156)	Hazard Ratio (95% CI)
Off Study Drug			
Primary Outcome: Recurrent stroke of any type	3 (0.024)	12 (0.094)	4.32 (1.22, 15.32)
Components of primary efficacy outcome			
Ischemic stroke	3 (0.024)	11 (0.086)	3.96 (1.10, 14.20)
Hemorrhagic stroke	0 (0.000)	1 (0.008)	
Stroke of undetermined type	0	0	
Secondary efficacy outcomes			
Recurrent ischemic stroke or systemic embolism	5 (0.040)	11 (0.086)	2.36 (0.82,6.80)
Recurrent stroke of any type or death from any cause	16 (0.13)	27 (0.21)	1.72 (0.93,3.21)
Death	13 (0.10)	15 (0.12)	1.14 (0.54,2.40)

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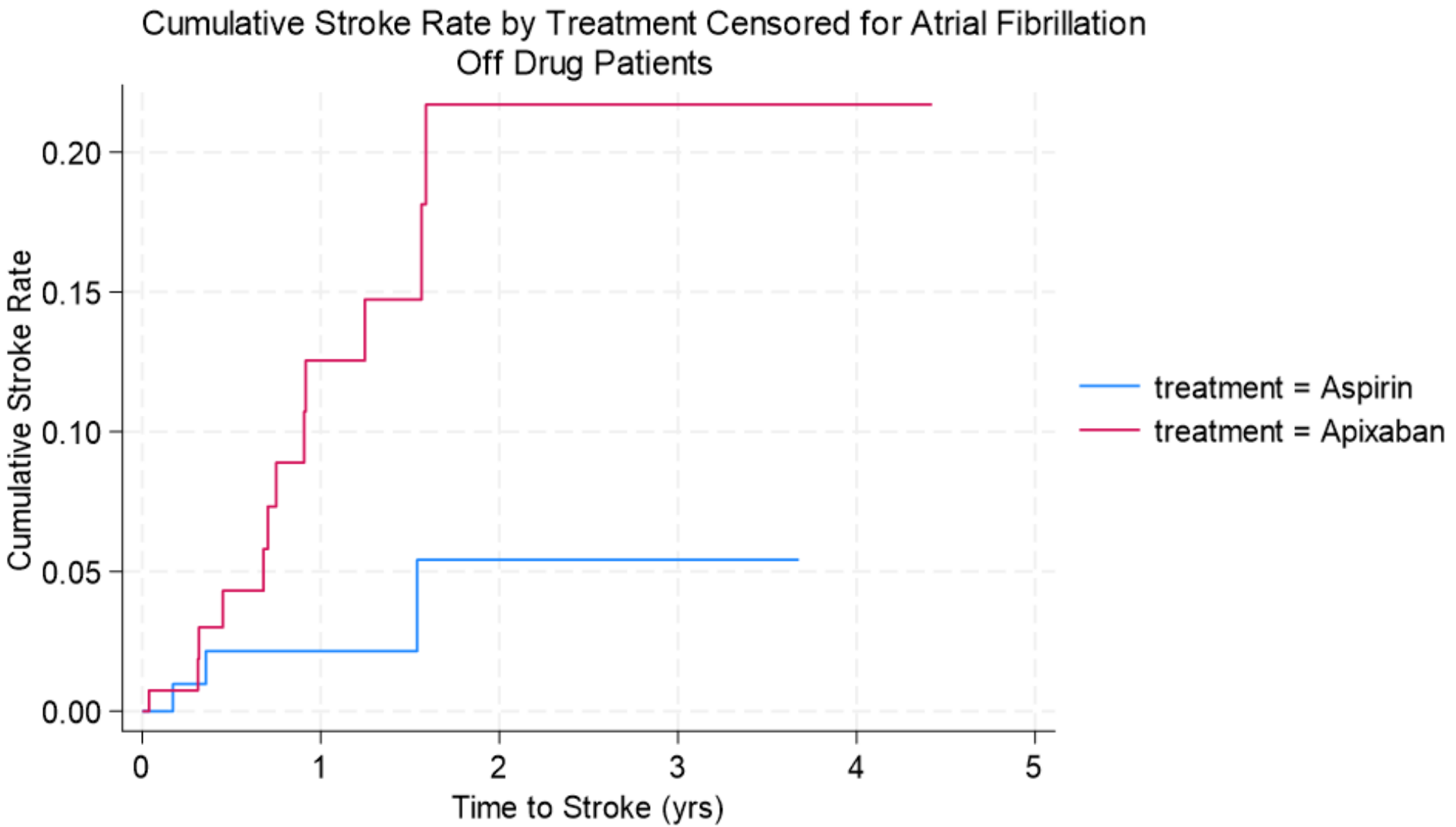

Cumulative Stroke Rate by Treatment Censored for Atrial Fibrillation
Off Drug Patients
Cumulative Stroke Rate
0.00
0.05
0.10
0.15
0.20
0
1
2
3
4
5
Time to Stroke (yrs)
treatment = Aspirin
treatment = Apixaban

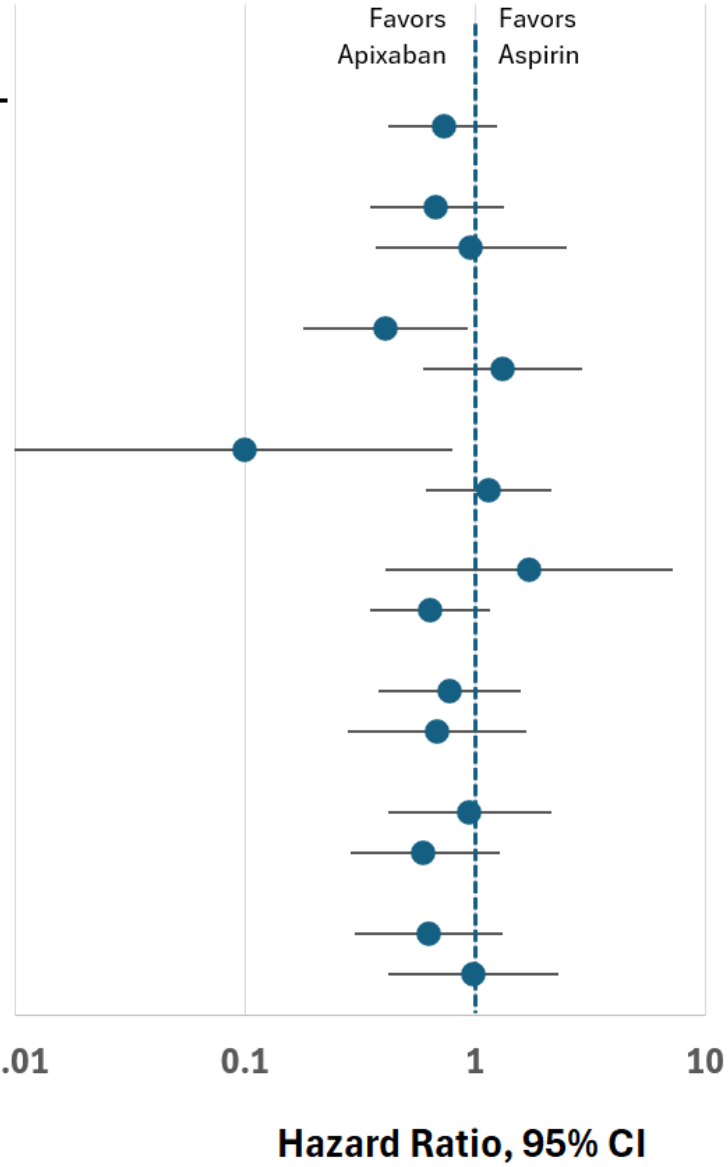
Adherence On Treatment

- Data difficult to work with, contain errors
- Good/poor adherence = 90-110% of pills taken/<90%
  - 206 cases dropped due to values >110%

Group	HR (95% CI)	Interaction P value
Good adherence	0.56 (0.25 – 1.3)	0.046
Poor adherence	5.6 (0.67 – 46.2)	

- Small N in poor adherence group
- Hypothesis: Aspirin half life longer, so poor adherence retains protection better

Subgroup	HR	95% CI lower/	upper	Interaction P value
All Patients	0.73	0.42	1.25	
Age, yrs				
<75	0.68	0.35	1.34	0.6
≥75	0.96	0.37	2.5	
Sex				
Male	0.41	0.18	0.93	0.044
Female	1.32	0.6	2.92	
Race				
Asian, Black, Other	0.1	0.01	0.8	0.021
White	1.15	0.61	2.16	
Weight, kg				
<70	1.73	0.41	7.25	0.21
≥70	0.64	0.35	1.17	
NT-proBNP level, pg/mL				
Below median (<304)	0.78	0.38	1.58	0.81
Above median (≥304)	0.69	0.28	1.67	
PTFV1, μV × ms				
Below median (<5200)	0.95	0.42	2.16	0.42
Above median (≥5200)	0.6	0.29	1.28	
Left atrial diameter index, cm/m2				
Below median (<1.89)	0.63	0.3	1.32	0.46
Above median (≥1.89)	0.98	0.42	2.31	



Summary

- 71%/29% of observed person years On/Off Treatment
- On Treatment
  - HR suggests possible benefit, underpowered
  - Proportional Hazards assumption violation: effect varies over time
- Off Treatment
  - Increased rate in apixaban group: previously protective?
- Adherence: better lowers HR
- Subgroups: sex

Discussion points…

- Many hypotheses generated, all exploratory
- ITT v PP/on treatment, explanatory vs pragmatic, efficacy vs effectiveness
  - Both approaches have value, and should be considered for reporting
  - ITT: generalizable, industry std, but may be biased if much lack of adherence
  - OT: more directly tests hypothesis, less generalizable, may need adjustment
- Even stronger focus on adherence
  - Pandemic – did us no favors
  - How much Off Treatment is acceptable?
- Should PP/On Treatment analysis be part of standard SAP, DSMB monitoring?
  - Especially relevant if no safety issues?
- Better markers of atrial cardiopathy needed?
- Is the development of Afib a special censoring event?
  - How to deal with a loss of equipoise for some patients during trial
- How to move forward…

Thank you

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