Apixaban versus Heparin/Vitamin K Antagonist in Anticoagulation-naïve Patients with Atrial Fibrillation Scheduled for Cardioversion: The EMANATE Trial

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Disclosures

- Michael D. Ezekowitz has received consulting fees from Boehringer Ingelheim, Armetheon, Pfizer, Sanofi, Bristol-Myers Squibb, Portola, Daiichi-Sankyo, Medtronic, Johnson & Johnson, and Janssen Scientific Affairs; grant support from Boehringer Ingelheim, Pfizer, and Bristol-Myers Squibb
- Co-PI PETRO, RE-LY, X-VeRT, EMANATE; Executive Committee ENSURE-AF, ENGAGE-AF.

Background

- The goal of anticoagulation in the setting of cardioversion is to prevent stroke and systemic embolism without causing bleeding.
- Post hoc analyses of cardioversions in the RE-LY, ARISTOTLE, ROCKET-AF and ENGAGE-AF trials found low event rates .[1-4] A limitation was the prolonged period of pre-cardioversion anticoagulation.
- To evaluate more immediate cardioversion , prospective trials comparing rivaroxaban (X-VeRT)[5] and edoxaban (ENSURE-AF)[6] against heparin/VKA in patients undergoing cardioversion found comparable efficacy and safety with low event rates.

1. Nagarakanti R, Ezekowitz M, et al. *Circulation.* 2011;123:131-136. 2. Flaker G, et al. *J Am Coll Cardiol*. 2014;63:1082-1087. 3. Piccini JP, et al. *J Am Coll Cardiol.* 2013;61:1998-2006. 4. Plitt A, et al. *Clin Cardiol.* 2016;39:345-346. 5. Cappato R, Ezekowitz M, et al. *Eur Heart J.* 2014;35:3346-3355. 6. Goette A, et al. *Lancet.* 2016;388:1995-2003.

Objectives of EMANATE

- To prospectively compare the outcomes of stroke, systemic embolism, major bleeding, and clinically relevant non-major (CRNM) bleeding in patients with < 48 hrs anticoagulation who were randomized to apixaban or heparin/VKA in an open-label trial with blinded endpoint adjudication.

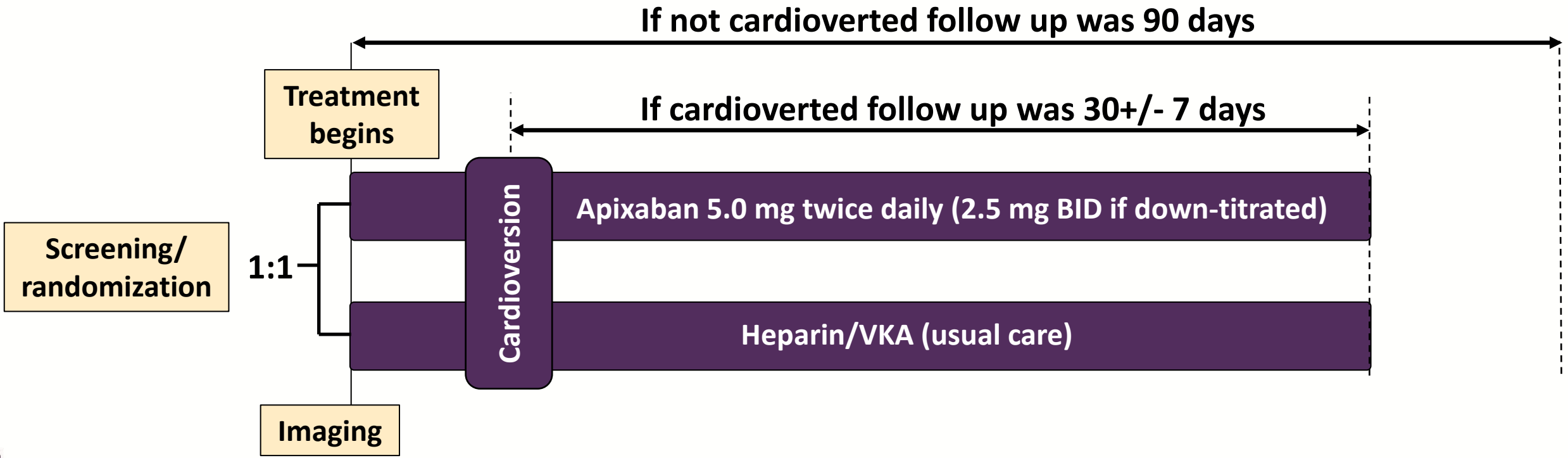
- To gain insight into the role of image guidance.

- To assess the value of a loading dose of apixaban in patients rapidly transitioned to cardioversion.

Key Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
▪ Anticoagulation-naïve patients with AF (<48 hours of parenteral and/or oral anticoagulation) indicated for cardioversion.	▪ Contraindications to apixaban or heparin/VKA ▪ Mitral stenosis or previous valve surgery ▪ Other conditions requiring anticoagulation ▪ Dual antiplatelet therapy

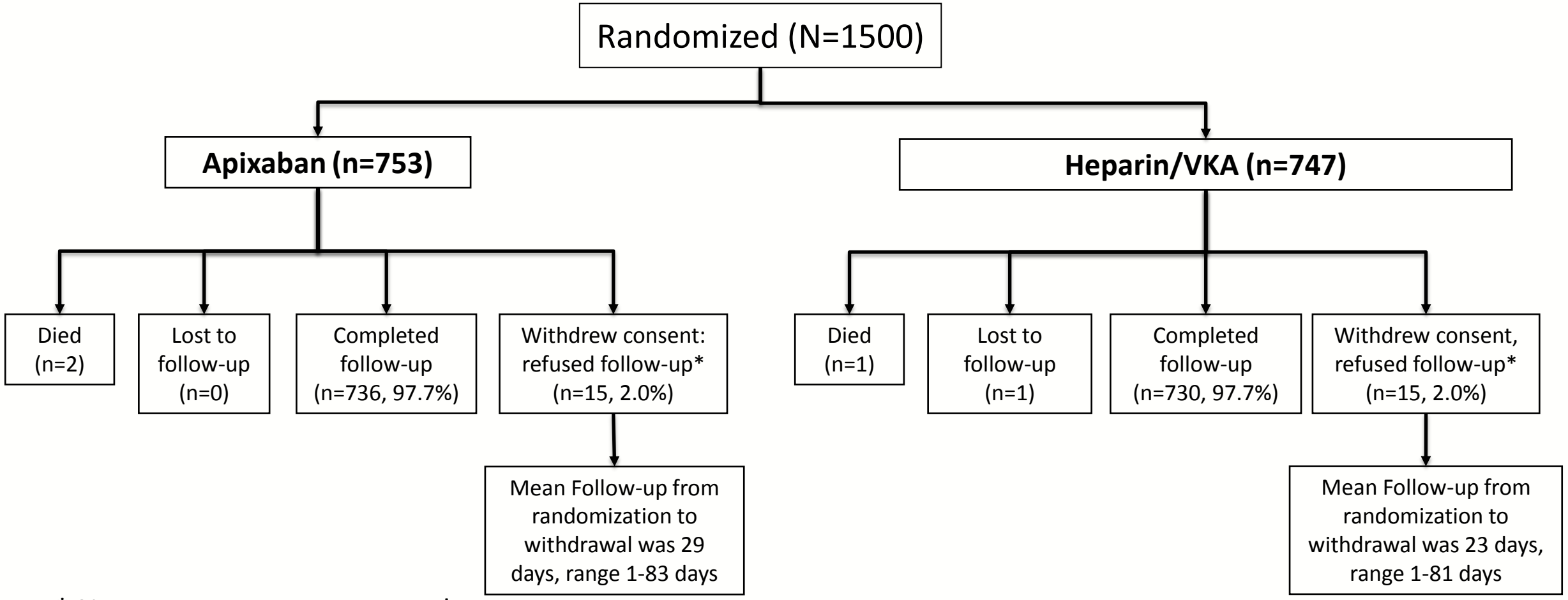
Study Design



Apixaban Loading Dose Option

- In patients randomized to apixaban, cardioversion could be performed 2 hours after a loading dose of 10 mg (reduced to 5 mg if 2 of the following present: age ≥ 80, weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dl [133 micromol/L).

Patient Disposition (ITT Population)

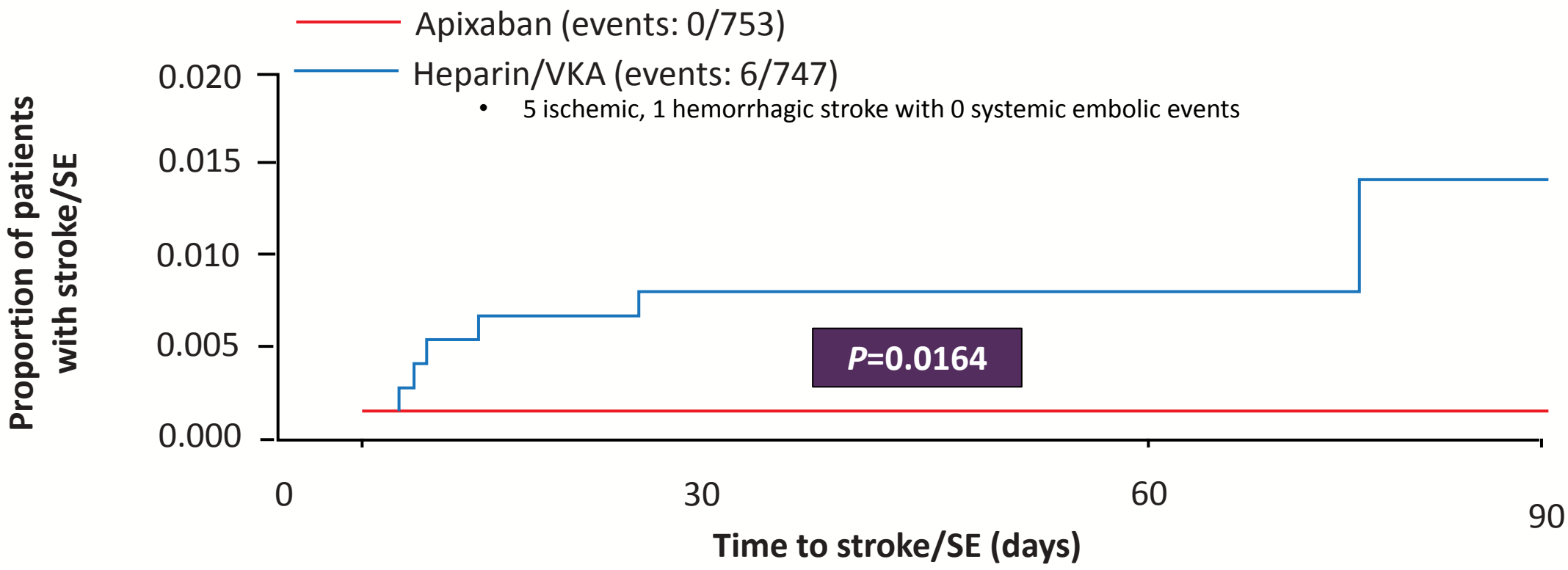


* No outcome events occurred.

Key Baseline Patient Demographics

	Apixaban			Heparin/VKA
	All (n=753)	5-mg loading dose (n=11)	10-mg loading dose (n=331)	(n=747)
Age, years, mean (SD)	64.7 (12.2)	80.5 (7.4)	63.2 (12.2)	64.5 (12.8)
Sex, female, n (%)	248 (32.9)	4 (36.4)	123 (37.2)	250 (33.5)
Race, white, n (%)	654 (86.9)	10 (90.9)	322 (97.3)	648 (86.7)
Weight, kg, mean (SD)	87.9 (20.6)	69.1 (15.5)	90.2 (21.0)	86.3 (19.8)
Hypertension, n (%)	496 (65.9)	9 (81.8)	221 (66.8)	481 (64.4)
LVEF <40, n (%)	45 (6.0)	0	21 (6.3)	54 (7.2)
Diabetes, n (%)	154 (20.5)	1 (9.1)	75 (22.7)	140 (18.7)
CHA_2DS_2-VASc score, mean (SD)	2.4 (1.7)	4.4 (1.8)	2.3 (1.7)	2.4 (1.7)
Creatinine clearance, mL/min, mean (SD)	79.2 (50.6)	41.0 (13.4)	91.7 (52.1)	78.5 (49.0)

Stroke/Systemic Embolic Outcomes



Number at risk				
Apixaban	752	614	199	55
Heparin/VKA	747	565	231	88

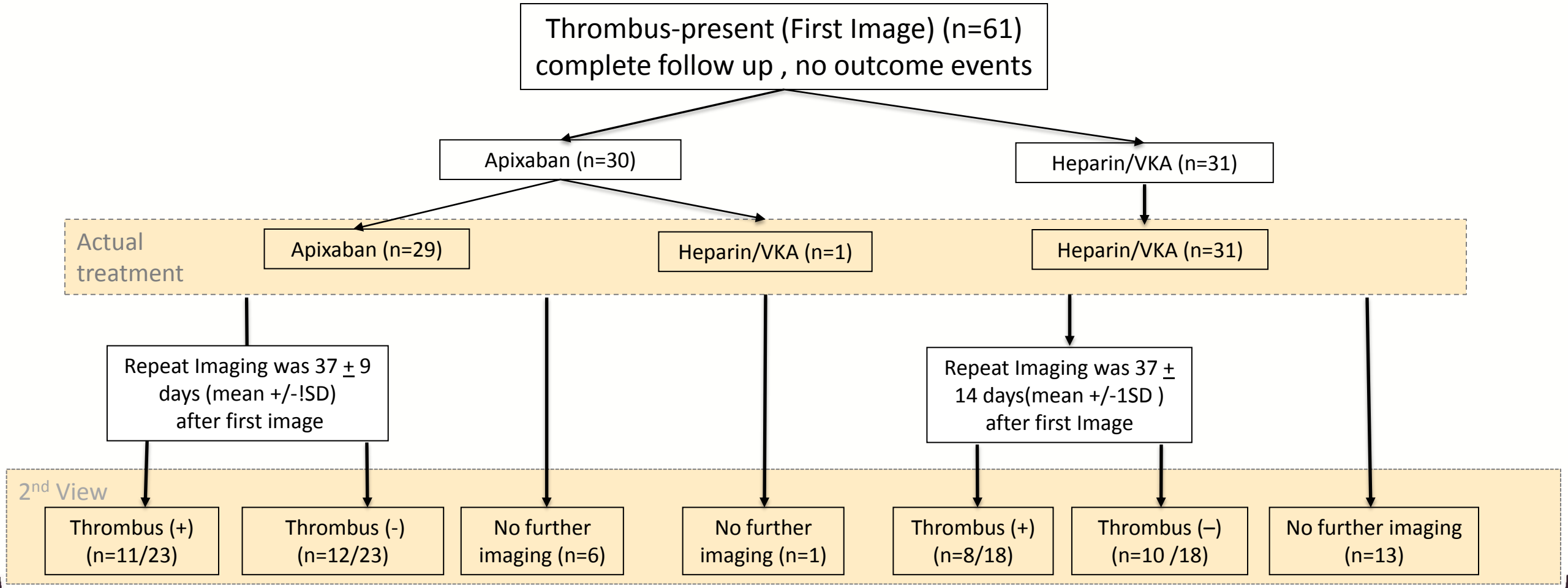
One patient's adjudicated stroke date was one day prior to randomization; thus at Day 0, only 1499 were at risk for stroke. No patients had SE.
ITT population. SE = systemic embolism

Safety Outcomes (Safety Population*, N=1456)

	Apixaban Total (n=735)	Apixaban Loading Dose Subset (n=342)	Heparin/VKA Total (n=721)
Major bleeds	3	(1)	6
Clinically relevant non-major bleeds	11	(4)	13

*Randomized and received ≥ 1 dose of study medication (by treatment received).

Image-Guided Strategy (n=840)



Summary and Conclusion

- EMANATE evaluated patients scheduled for cardioversion. All received < 48 hrs anticoagulation and 61% were not anticoagulated prior to randomization.
- There were 0 vs 6 strokes in the apixaban vs heparin/VKA group (p=0.0164*), 3 vs 6 major bleeds, 2 vs 1 deaths, and no systemic embolic events in either group.
- Among 342 patients receiving the loading dose of apixaban, there were 0 strokes, 1 major bleed, and 1 death.
- Imaging identified left atrial appendage thrombi in 61 patients; all continued anticoagulation. There were no outcome events. Among those with repeat imaging (37 ± 11 days after the initial imaging) thrombi resolved in 52% vs 56% in the apixaban and heparin/VKA groups.
- Limitation: Like the other prospective cardioversion studies, EMANATE was underpowered.
- We believe the findings observed in EMANATE support the use of apixaban in patients with AF undergoing cardioversion.

*log-rank test

The Executive Committee Acknowledge:

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BACK UP

Statistical Assumptions

- Using the ARISTOTLE hypothesis of a non-inferiority margin of 1.38 and accounting for the short follow-up of between 30 and 90 days, and the event rate of 0.75 – 1.00% we estimated that approximately 40,000 patients would have to be recruited to achieve a statistically valid study.