Cardioversion of AF : Anticoagulation in the Modern Era

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Disclosure

Michael D. Ezekowitz, MBChB, DPhil, FACC, FAHA, FRCP, MA

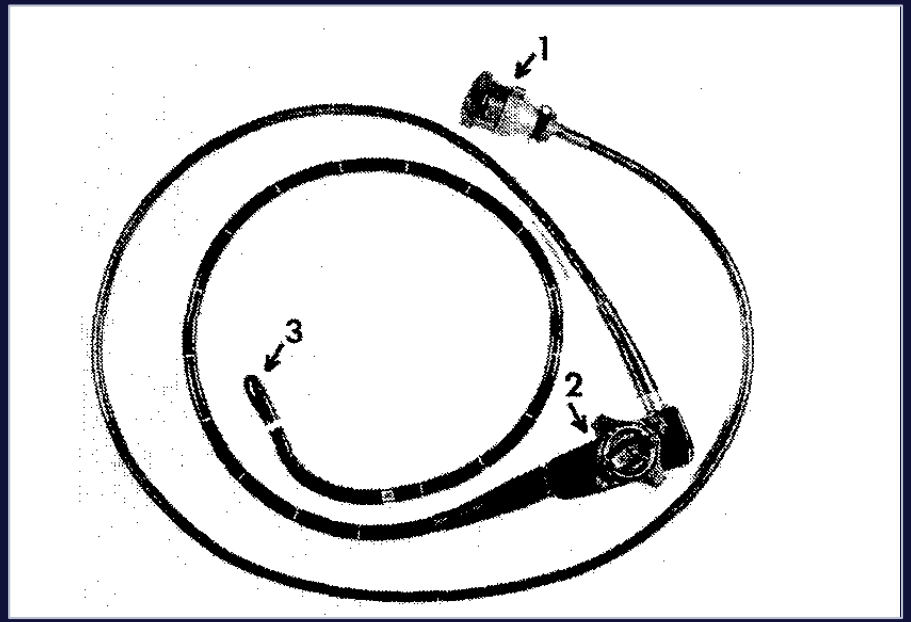
- Consultant: Armetheon, AstraZeneca, Boehringer Ingelheim, BMS, Daiichi Sankyo, Medtronic, Portola, sanofi-aventis, Merck, Pfizer, J&J, Coherex Gilead, St Jude Medical , Biogen
- Grants: ARYx Therapeutics, Boehringer Ingelheim, Daiichi Sankyo, Portola, sanofi-aventis
- CO-PI Petro and RELY : Executive committee Engage AF : Co–PI Explore Xa , X-Vert and EMANATE

One of the First Outpatient TEE's

A modified Model D Olympus fiberoptic gastroscope.

1. Attachment to Varian 3400 2-dimensional echocardiograph
2. Mechanism for up and down and lateral movement of gastroscope tip
3. Gastroscope tip to which is attached a 3.5 m Hz transducer

Maximum width of tip is 1.2 cm.



Ezekowitz MD et al. Left atrial mass: Diagnostic value of transesophageal 2-dimensional echocardiography and indium-111 platelet scintigraphy . *Am J Cardiol.* 1983;51:1563-64.

Dabigatran: RE-LY cardioversion Post Hoc Analysis

Background/rationale

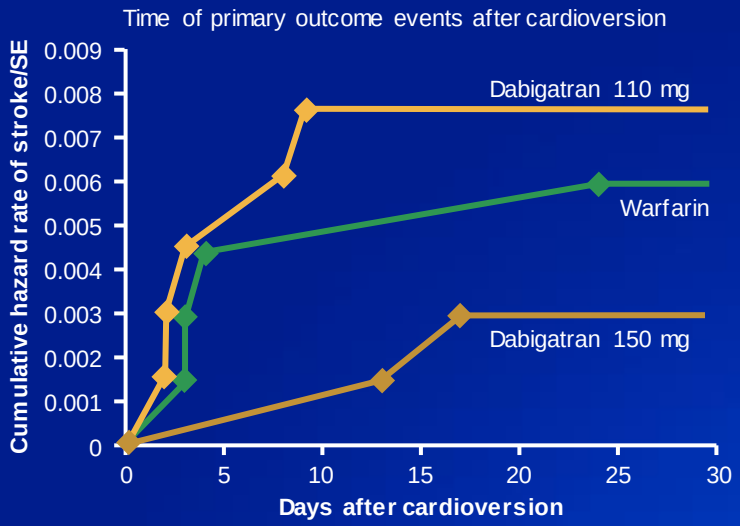
- This was a post hoc analysis of 647 dabigatran 110 mg bid, 672 dabigatran 150 mg bid and 664 warfarin patients undergoing cardioversion

Results

- Stroke and SE 30-day event rates: 0.8%, 0.3% and 0.6% for dabigatran 110 mg, dabigatran 150 mg and warfarin, respectively; *p*=0.71 and *p*=0.45
- Major bleeding rates: 1.7%, 0.6% and 0.6% for dabigatran 110 mg, dabigatran 150 mg and warfarin, respectively

Conclusion

- Dabigatran have comparable rates with warfarin for stroke/SE and major bleeding within 30 days of cardioversion



Outcome	Dabigatran 110 mg bid	Dabigatran 150 mg bid	Warfarin
Major bleeding	11 (1.7%)	4 (0.6%)	4 (0.6%)

Nagarakanti R, Ezekowitz MD *et al*, Circulation 2011

Post Hoc Analysis ROCKET AF: Rivaroxaban in patients after cardioversion or catheter ablation. Low event rates.

Background/rationale

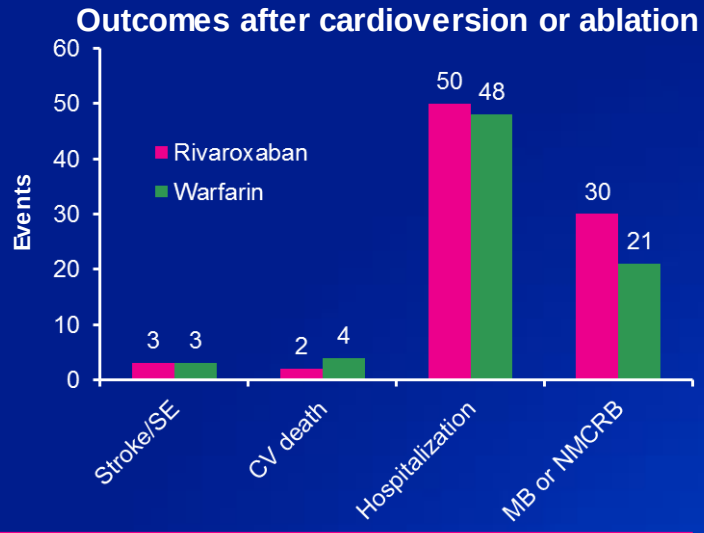
- There are limited data on patient outcomes following cardioversion or catheter ablation in patients with AF treated with rivaroxaban

Results

- In ROCKET AF, the overall incidence of cardioversion or ablation procedures on treatment was 1.45%/year (n=321)
- Despite an increase in hospitalization, there was no significant difference in long-term stroke rates or survival following cardioversion or ablation

Conclusion

- Outcomes following cardioversion or ablation were similar in both study arms



Outcome	HR (95% CI) before vs after procedure	*p*-value
Stroke/SE	1.38 (0.61–3.11)	0.4423
CV death	1.57 (0.69–3.55)	0.2793
Hospitalization	2.01 (1.51–2.68)	<0.0001
MB/NMCRB	1.51 (1.12–2.05)	0.0072

Piccini *et al*, 2013

ROCKET AF

Clinical Events in the First 30 days After First Cardioversion While on Treatment Post Hoc Analysis of the Engage AF Trial

	Warfarin, n = 114	HDE, n = 140	LDE, n = 111
Stroke or SEE, n (%)	0	0	2(1.81)
Major bleeding, n	0	0	0
Death, n (%)	0	1(0.71)	0

Plitt A, Ezekowitz MD, et al. "Cardioversion of Atrial Fibrillation in ENGAGE AF-TIMI 48". Clin. Cardiol. 39, 6, 345-346 (2016)

Limitations of phase III Post Hoc -analyses

- *Post-hoc* analyses of prospectively collected clinical trial data
- The sample size and statistical power were limited
- TEE data were incomplete or not collected
- Prolonged period of anticoagulation prior to the cardioversion

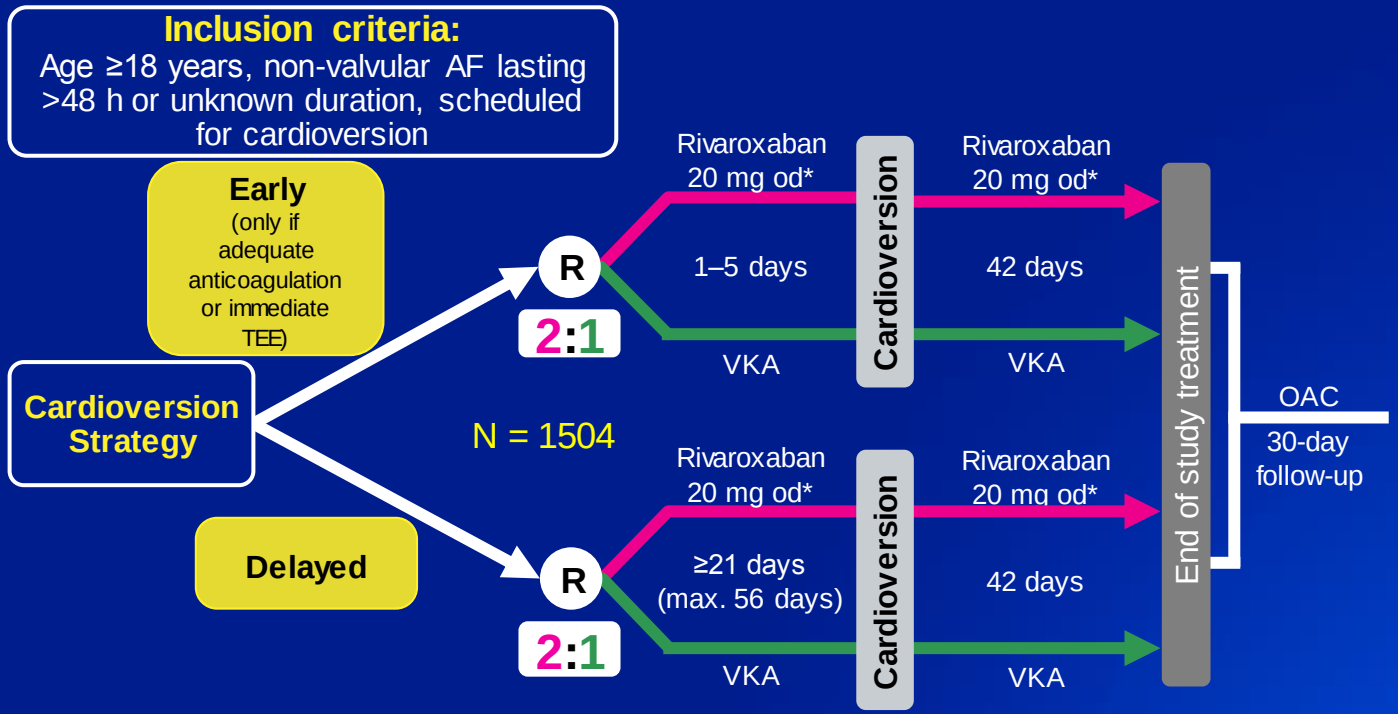
1. Nagarakanti *et al*, 2011; 2. Flaker *et al,* 2014; 3. Piccini *et al*, 2013

Prospective Cardioversion Studies.

- Cardiovascular advances have lead to low event rates thus
- Sample size to establish non-inferiority estimated at between 25,000 and 45,000 patients assuming
  - 1% periprocedural risk of 1.5 risk ratio, power 90%

- Trials of this size not feasible
- A comparison of 1,500 to 2000 patients would give clinically meaningful information if events rates low

The First : Xvert Randomized, open-label, Comparison of Rivaroxaban vs Usual care



*15 mg if CrCl 30–49 ml/min; VKA with INR 2.0–3.0

Ezekowitz, Cappato *et al*, 2014; www.clinicaltrials.gov. NCT01674647

X-VeRT: Study treatment

- Rivaroxaban 20 mg od
  - First dose should be started ≥4 hours before cardioversion (OAC-naïve/untreated)
  - Dose reduction to 15 mg od for patients with moderate renal impairment (CrCl 30–49 ml/min)
  - In the delayed group, compliance was ≥80% before cardioversion
- VKA with target INR 2.5 (range 2.0–3.0)
  - VKA type according to local treatment standards
  - Weekly INR monitoring required throughout the study to ensure INR remained within the target range
  - Three consecutive weekly INR measurements >2.0 before cardioversion

Ezekowitz, Cappato *et al*, 2014; www.clinicaltrials.gov. NCT01674647

Primary efficacy outcome

	Rivaroxaban (N=978)		VKA (N=492)		Risk ratio (95% CI)
	%	n*	%	n*	
Primary efficacy outcome	**0.51**	**5**	**1.02**	**5**	**0.50 (0.15–1.73)**
Stroke	0.20	2	0.41	2	
Haemorrhagic stroke	0.20	2		0	
Ischaemic stroke		0	0.41	2	
TIA		0		0	
Non-CNS SE		0	0.20	1	
MI	0.10	1	0.20	1	
Cardiovascular death	0.41	4	0.41	2	

*Number of patients with events; patients may have experienced more than one primary efficacy event
mITT population

Principal safety outcome

	Rivaroxaban (N=988)		VKA (N=499)		Risk ratio (95% CI)
	%	n*	%	n*	
Major bleeding	**0.61**	**6**	**0.80**	**4**	**0.76 (0.21–2.67)**
Fatal	0.1	1	0.4	2	
Critical-site bleeding	0.2	2	0.6	3	
Intracranial haemorrhage	0.2	2	0.2	1	
Hb decrease ≥2 g/dl	0.4	4	0.2	1	
Transfusion of ≥2 units of packed RBCs or whole blood	0.3	3	0.2	1	

*Number of patients with events; patients may have experienced more than one primary safety event
Safety population

Edoxaban vs Enoxaparin/Warfarin in Subjects Undergoing Cardioversion of Atrial Fibrillation

The Randomized ENSURE-AF Study

Andreas Goette, Jose L. Merino, Michael D. Ezekowitz, Dmitry Zamoryakhin, Michael Melino, James Jin, Michele F. Mercuri, Michael A. Grosso, Victor Fernandez, Naab Al-Saady, Natalya Pelekh, Bela Merkely, Sergey Zenin, Mykola Kushnir, Jindrich Spinar, Valeriy Batushkin, Joris R. de Groot, Gregory Y. H. Lip

Thromboembolic and Cardiovascular Event Rates[a]

	Total by Treatment			TEE		Non-TEE	
	Edoxaban n = 1095	Enoxaparin + Warfarin n = 1104	OR (95% CI)	Edoxaban (n = 589)	Enoxaparin + Warfarin (n = 594)	Edoxaban (n = 506)	Enoxaparin + Warfarin (n = 510)
Stroke	2 (0.2)	3 (0.3)	0.67 (0.06–5.88)	0	2 (0.3)	2 (0.4)	1 (0.2)
SEE	1 (0.1)	1 (0.1)	NC	1 (0.2)	1 (0.2)	0	0
MI	2 (0.2)	3 (0.3)	0.67 (0.06–5.88)	0	2 (0.3)	2 (0.4)	1 (0.2)
CV mortality	1 (0.1)	5 (0.5)	0.20 (0–1.80)	1 (0.2)	0	0	5 (1.0)

All values are n's except where indicated

[a] ITT population during overall period

CI = confidence interval; CV = cardiovascular; ITT = intent-to-treat; MI = myocardial infarction; NC = not calculated; OR = odds ratio; SEE = systemic embolic event; TEE = transesophageal echocardiography

Major Bleeding Event Rates[a]

	Total by Treatment		TEE		Non-TEE	
	Edoxaban (n = 1067)	Enoxaparin + Warfarin (n = 1082)	Edoxaban (n = 570)	Enoxaparin + Warfarin (n = 577)	Edoxaban (n = 497)	Enoxaparin + Warfarin (n = 505)
ICH	0	0	0	0	0	0
Gastrointestinal Bleeding	1	1	1	0	0	1
Fatal Non-ICH	0	1	0	0	0	1
Life threatening	1	1	1	1	0	0
Other[b]	1	2 (0.2%)	1	1	0	1

All values are n's except where indicated

[a] In the safety population assessed during the on-treatment period
[b] Other included hematuria in the edoxaban arm and intra-articular bleeding in the warfarin/enoxaparin arm
ICH = intracranial hemorrhage; TEE = transesophageal echocardiography

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

Michael D. Ezekowitz, Professor, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA and Lankenau Heart Center, Wynnewood, PA and Bryn Mawr Hospital, Bryn Mawr, PA;

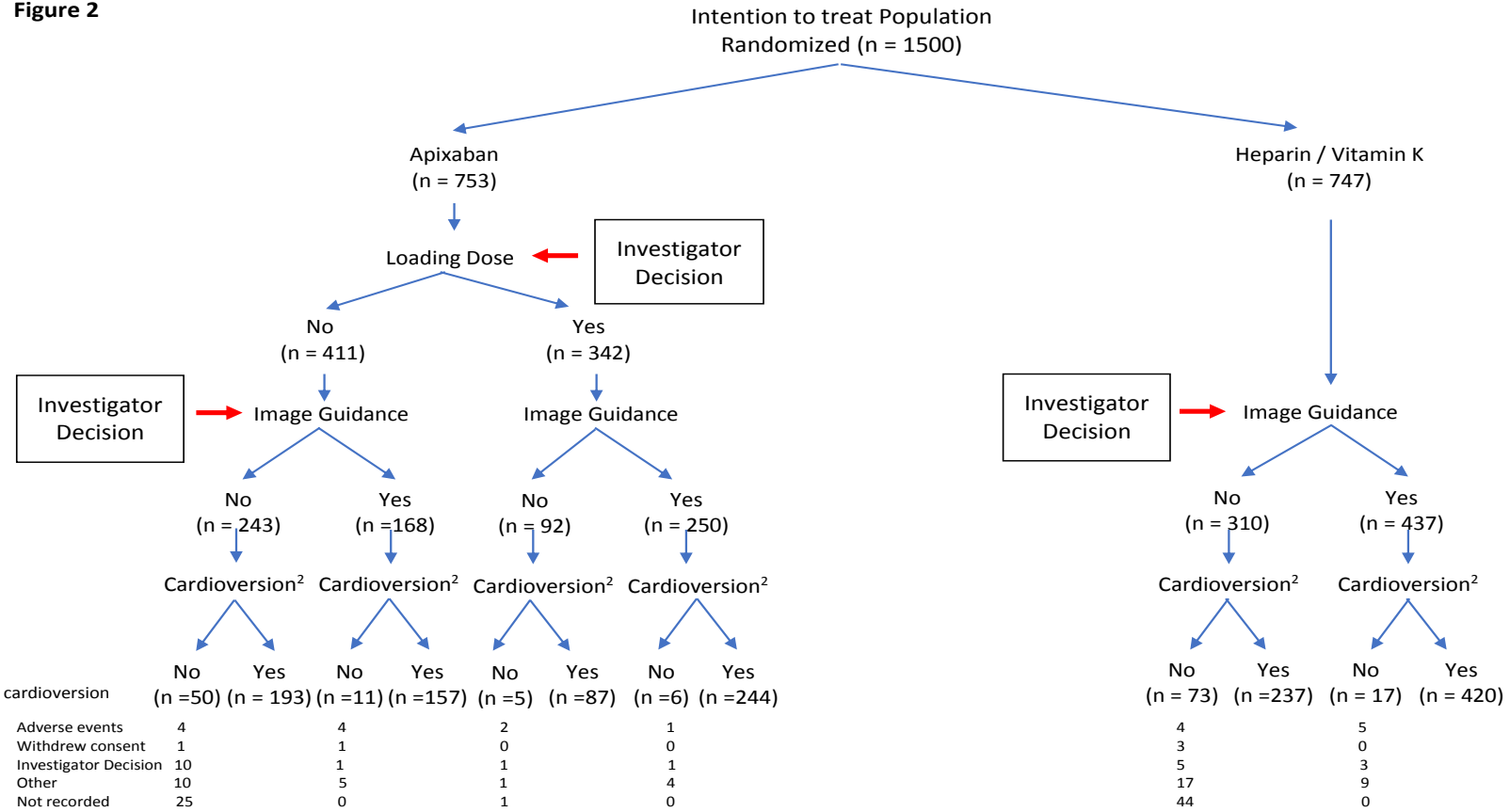
Co Chair EMANATE Committee Executive on behalf of co-authors

Charles V. Pollack, Jonathan L. Halperin, Richard D. England, Sandra VanPelt Nguyen, Judith Spahr, Maria Sudworth, Nilo Cater, Andrei Breazna, Jonas Oldgren, Paulus Kirchhof, for the EMANATE investigators

Objective of EMANATE

- To compare apixaban to heparin/VKA, in an open-label, randomized trial of efficacy outcomes of stroke, systemic embolization, and death and safety outcomes of major and CRNM bleeding in patients with recent onset AF (78 % < 3 months) scheduled for cardioversion
- All patients had < 48 hrs. anticoagulation prior to randomization (62 % no anticoagulation)
- To gain insight into the role of image guidance and the value of a loading dose of apixaban 10mgs (cardioversion > 2 hrs) in patients scheduled for immediate cardioversion

Figure 2



Reason for no cardioversion								
Adverse events	4	4	2	1	4	5		
Withdrew consent	1	1	0	0	3	0		
Investigator Decision	10	1	1	1	5	3		
Other	10	5	1	4	17	9		
Not recorded	25	0	1	0	44	0		

Figure 2: Intention to treat population (ITT).
[1] < 48 hours of anticoagulation for current episode of atrial fibrillation. [2]Includes active and first spontaneous cardioversions.

Time from first dose to active cardioversion (days)

	Apixaban						Heparin/Vitamin K Antagonist		
	Loaded Dose			Non-Loaded Dose					
	With Image Guidance	Without Image Guidance	Overall	With Image Guidance	Without Image Guidance	Overall	With Image Guidance	Without Image Guidance	Overall
n	238	34	272	155	92	247	407	111	518
Mean	3.3	4.1	3.4	21.7	32.5	25.7	11.5	40.7	17.8
Median	1	1	1	15	30	27	2	43	2
p-value[1]			0.6214			<0.0001			<0.0001
p-value[2]						<0.0001			

CI: 95% confidence interval for mean time to cardioversion. [1] t-test for comparison of time to cardioversion with and without image guidance in each treatment group. 2 t-test for comparison of time to cardioversion with and without a loading dose (apixaban-treated patients)

Efficacy Outcomes (ITT Population, N=1500)

	Apixaban Total (n=753)	Apixaban loading dose Total (n=342)	Heparin/VKA Total (n=747)
Strokes	0	0	6
Ischemic			5
Hemorrhagic			1
Systemic embolism	0	0	0
Death	2	1	1

P=0.0151

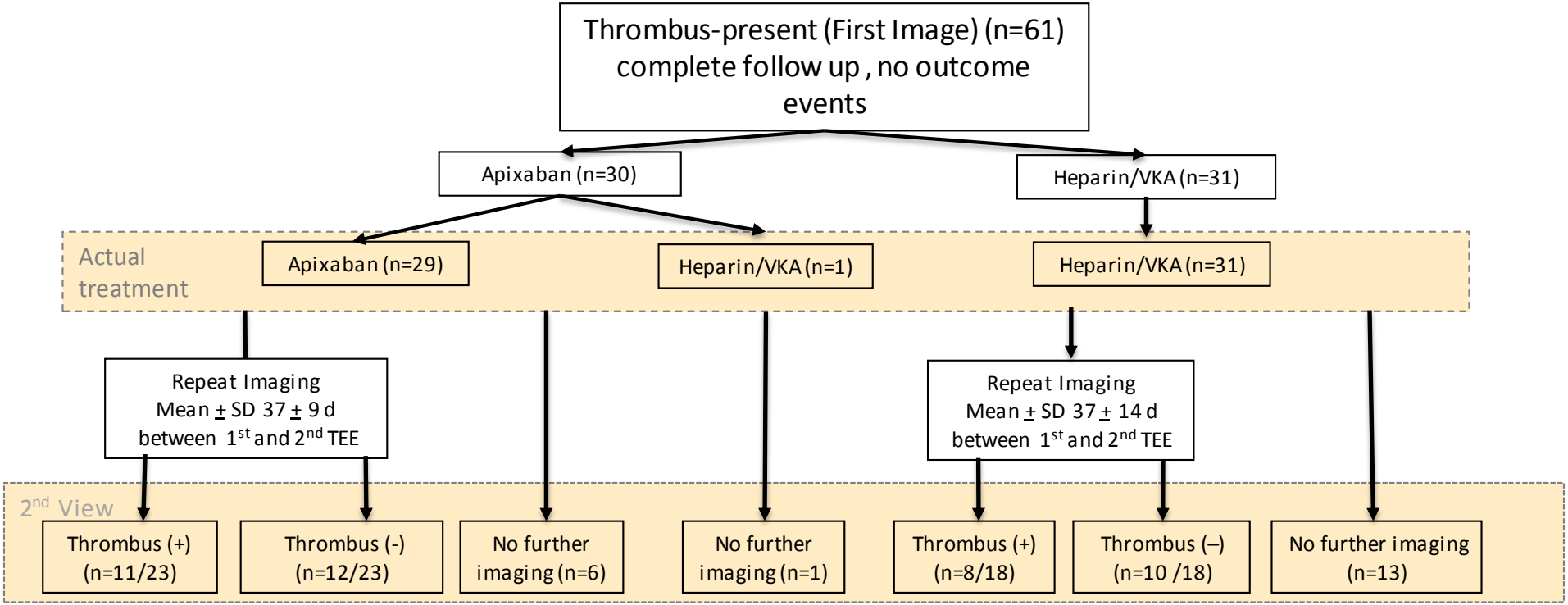
*Fisher's exact test (nominal).

Safety Outcomes (Safety Population*, N=1456)

	Apixaban Total (n=735)	Apixaban Loading Dose Total (n=342)	Heparin/VKA Total (n=721)
Major bleeds	3	1	6
CRNM bleeds	11	4	13

*Randomized and received at least one dose of study medication (summarized by treatment actually received).

Image-Guided Strategy (n=855*)



Conclusion

- Explore Xa ,X-Vert and EMANATE provide evidence that the non- vitamin K antagonists are alternatives to heparin /VKA in the setting of Cardioversion especially is the cardioversion is early

Conclusion

FOCUS SHOULD CHANGE IN PATIENTS WITH AF

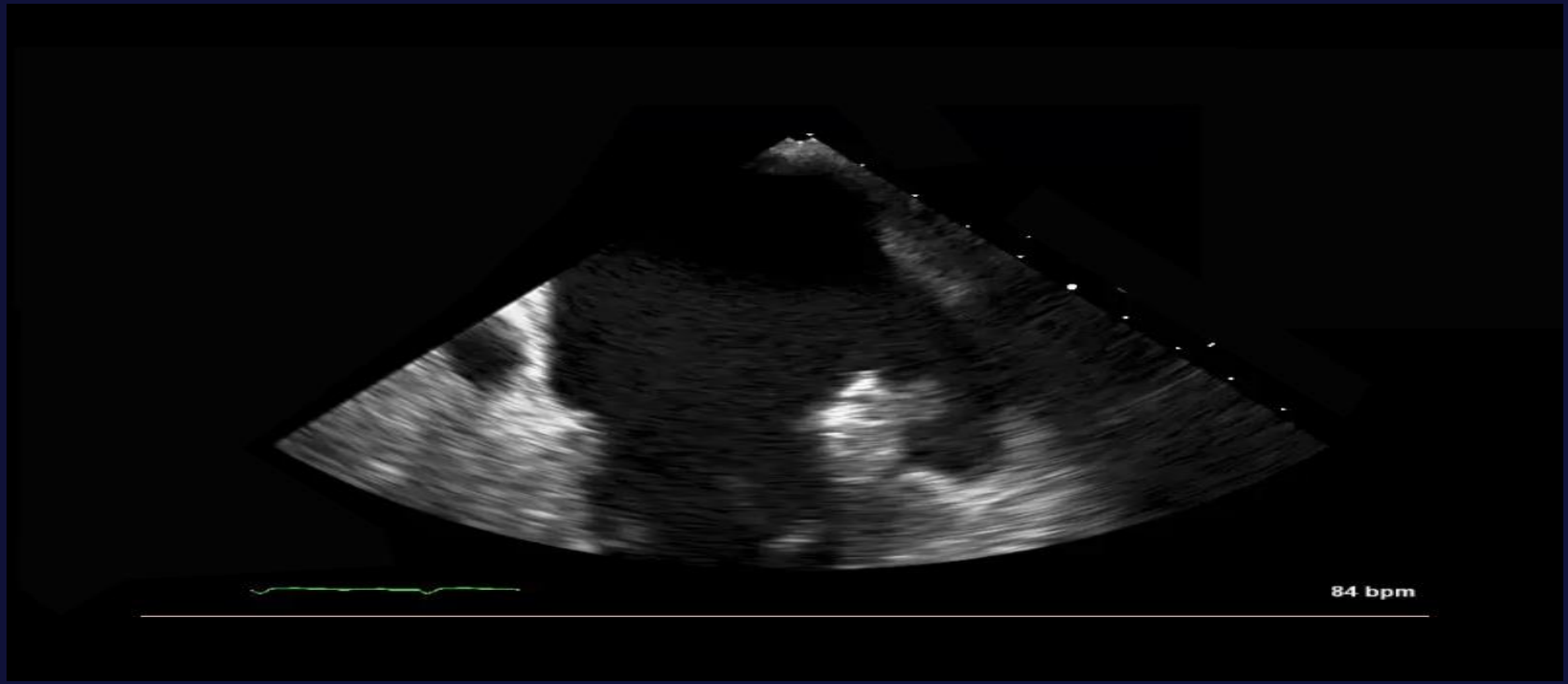
FROM

STROKE PREVENTION

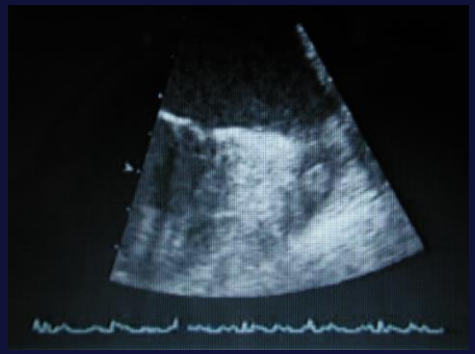
TO

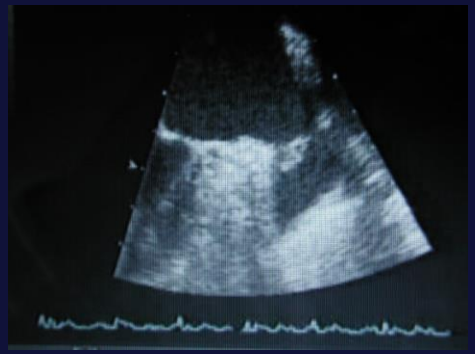
STROKE AND HEMORRAGE PREVENTION

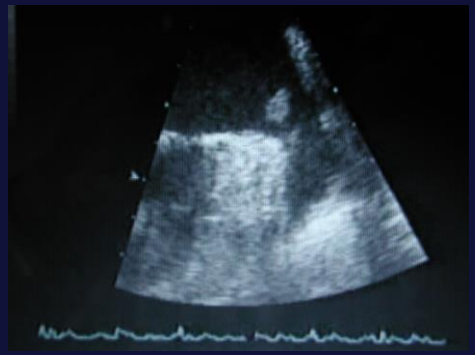
Mobile LAA Mass

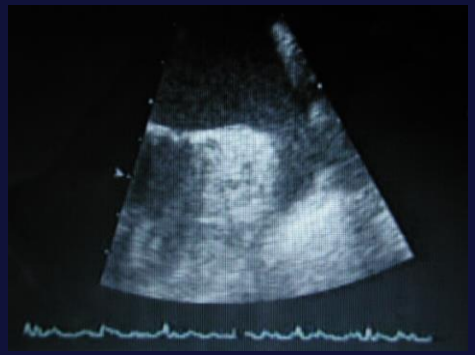


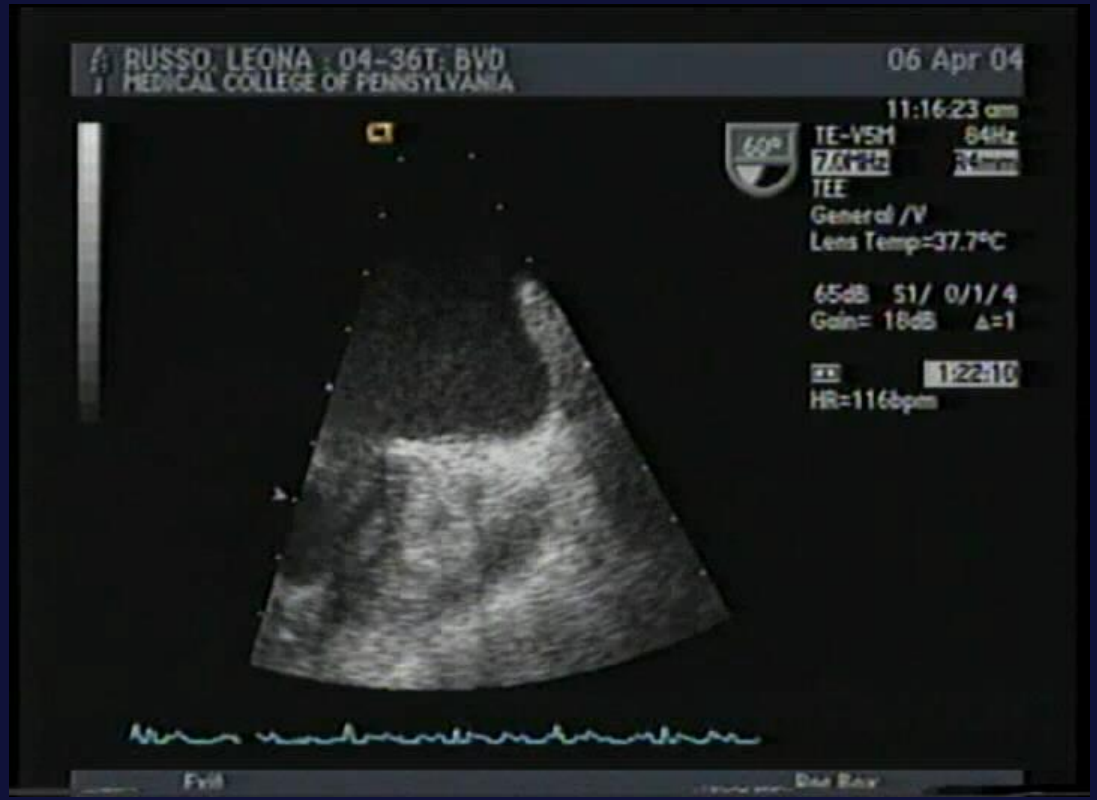
Case 3 :Left atrial appendage thrombus migration captured by TEE (Parekh…Ezekowitz Circ 06)







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