Managing Stroke Prevention in AF:
"A Closer Look at Non-surgical Interventions"

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Disclosure Statement of Financial Interest

- Consultant to: Boston Scientific; Medtronic; St. Jude; Biosense Webster; ELA Sorin; Boehringer Ingelheim; Bayer; Abbott; Pfizer
- Speaker's Bureau: Boston Scientific; Medtronic; St. Jude; Biosense Webster; BARD; Sanofi; Boehringer Ingelheim; Bayer; Abbott
- Investigator: Medtronic; Biosense Webster; Sanofi; Cameron Health, BARD; Bayer; Abbott; Pfizer
- Grants: Boston Scientific; Medtronic; St. Jude; Biosense Webster; BARD; ELA Sorin
- Equity and Intellectual Property Rights: Cameron Health

A Closer Look at Non-surgical Intervention for SPAF

Case Report

- Mr. John Reed is a 67-year old gentleman with
  - post-MI CAD in Canadian Class I and NYHA I under oral B-blocker, ASA and statin therapy
  - hypertension under ACE and dyhropyridine oral therapy (125/80)
  - type 2 diabetes mellitus in good oral therapy control

Mr J. Reed is a 67 year old man with atrial fibrillation

Personal Information	
Sex	Male
Age	67
Weight	84 kg
BMI	30 kg/m^2
Blood Pressure	130/85 mm Hg
Pulse	104 bpm

Medical History

- NVAF of first onset
- Hypertension (controlled)
- Diabetes mellitus (type 2)

Medications

- β-blockers
- ACE inhibitors
- Dihidropyridine agents
- Anti-diabetic agents

Mr J. Reed is at Intermediate Risk for Stroke

$CHADS_2$

Risk Factors[1]		Points
C	Congestive heart failure (recent)	1
H	Hypertension	1
A	Age ≥75 years	1
D	Diabetes mellitus	1
S_2	Stroke or TIA (history)	2
	Maximum score	**6**

Assessment:
- $CHADS_2 = 1$
- CHA_2DS_2-VASc = 2

CHA_2DS_2-VASc

Risk Factors[2]		Points
C	Congestive heart failure/LV dysfunction	1
H	Hypertension	1
A_2	Age ≥75 years	2
D	Diabetes mellitus	1
S_2	Stroke/TIA/thromboembolism	2
V	Vascular disease[a]	1
A	Age 65 to 74 years	1
Sc	Sex category (female)	1
	Maximum score	**9**

1. Gage BF et al. *JAMA*. 2001;285(22):2864-2870.
2. Camm AJ et al. *Eur Heart J*. 2010;31(19):2369-2429.

A Closer Look at Non-surgical Intervention for SPAF

Case Report

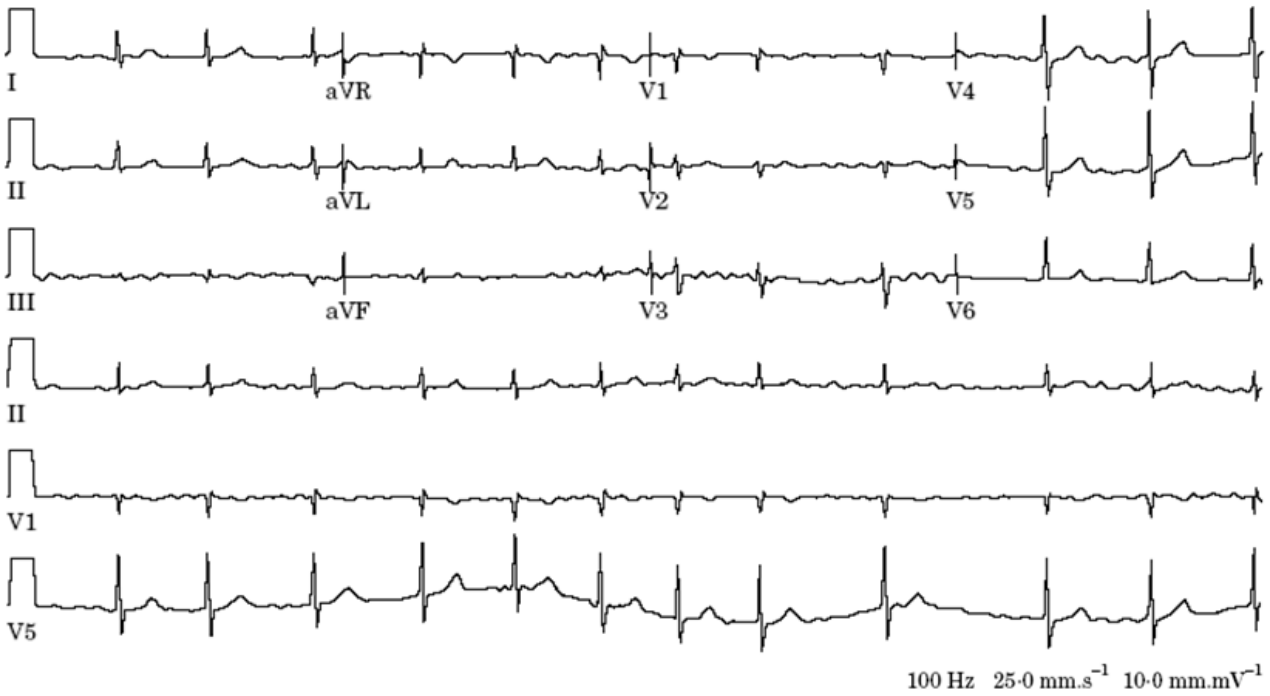
- On Saturday May 21 2014, for the first time in his life, he suddenly experienced an episode characterized by
  - irregular palpitation
  - shortness of breath
  - hyperdiaforesis
  - chest pain (not the first time, but different from prior MI)
- During the same day he seeked for help in the ED of the local city

A Closer Look at Non-surgical Intervention for SPAF

Case Report

- The ECG performed at the ED showed AF with narrow QRS (85 ms) left axis deviation, and a mean heart rate of 125 bpm

Mrs. J. Reed's Baseline ECG



Question 1

- What would you do in this patient?
  1. Cardioversion
  2. Leave the patient in atrial fibrillation

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Question 2

- In case of cardioversion, what would you consider as your first strategy?
  1. Electrical cardioversion
  2. Pharmacological cardioversion

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  2. **Pharmacological cardioversion**

Question 2

- In case of cardioversion, what would you consider as your first strategy?
  1. **Electrical cardioversion**
  2. Pharmacological cardioversion

Question 3

- After selecting for cardioversion, how would you proceed with regards to the peri-operative thromboembolic risk?
  1. Vitamin K antagonist (VKA)
  2. Novel oral anticoagulants (NOAC)
  3. No anti-platelet/anticoagulation protection; it is just the first episode!
  4. Either 1 or 3

Question 3

- After selecting for cardioversion, how would you proceed with regards to the peri-operative thromboembolic risk?
  1. Vitamin K antagonist (VKA)
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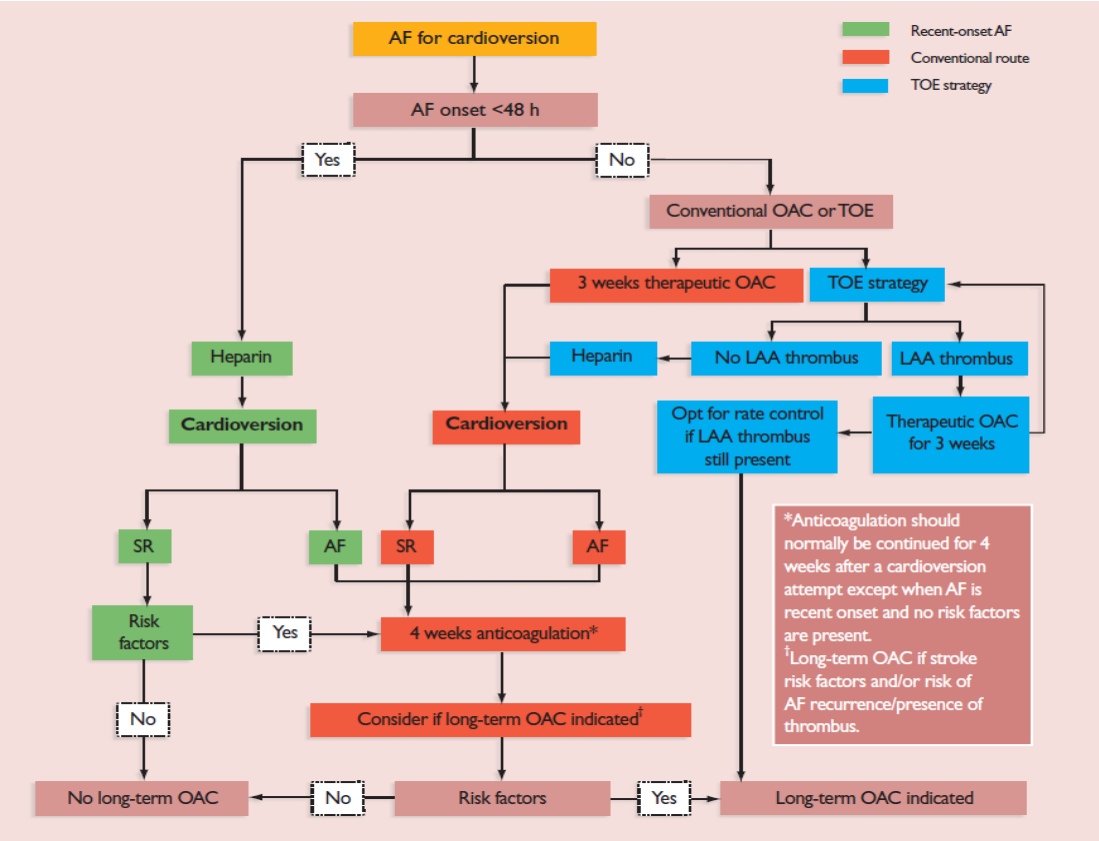
Guidelines for Cardioversion of Atrial Fibrillation



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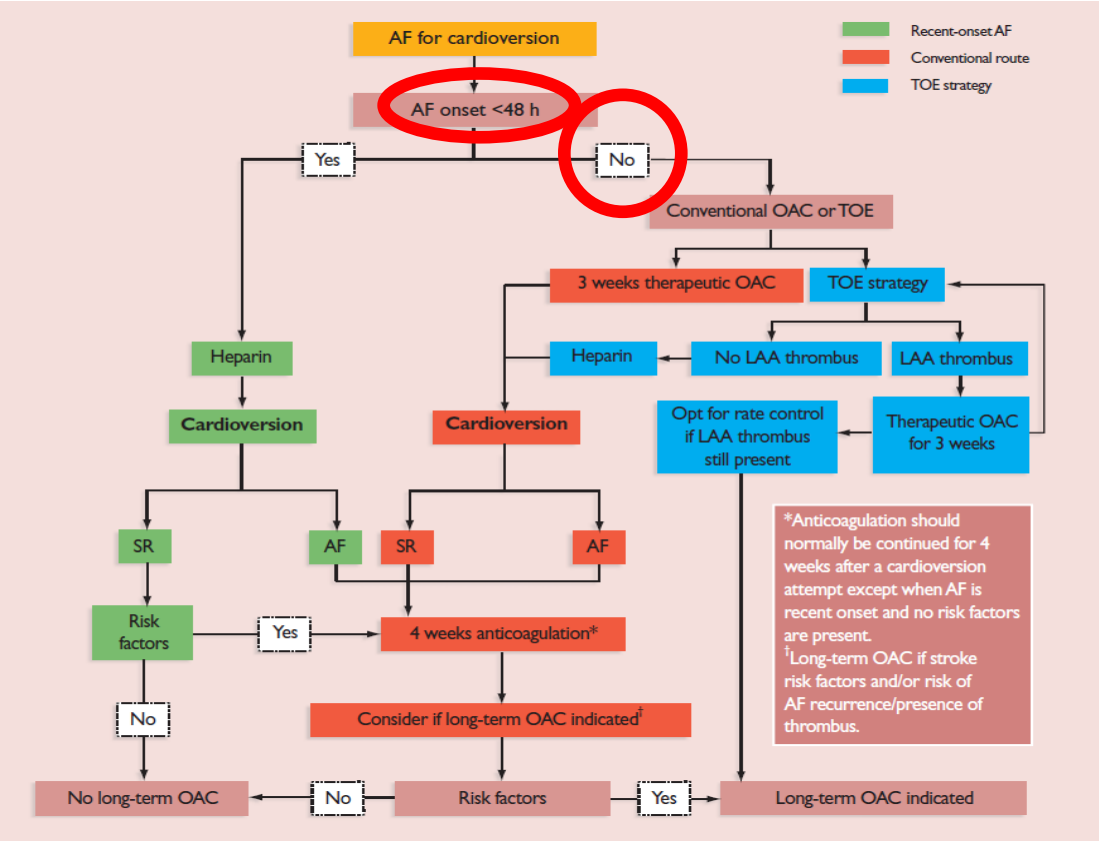

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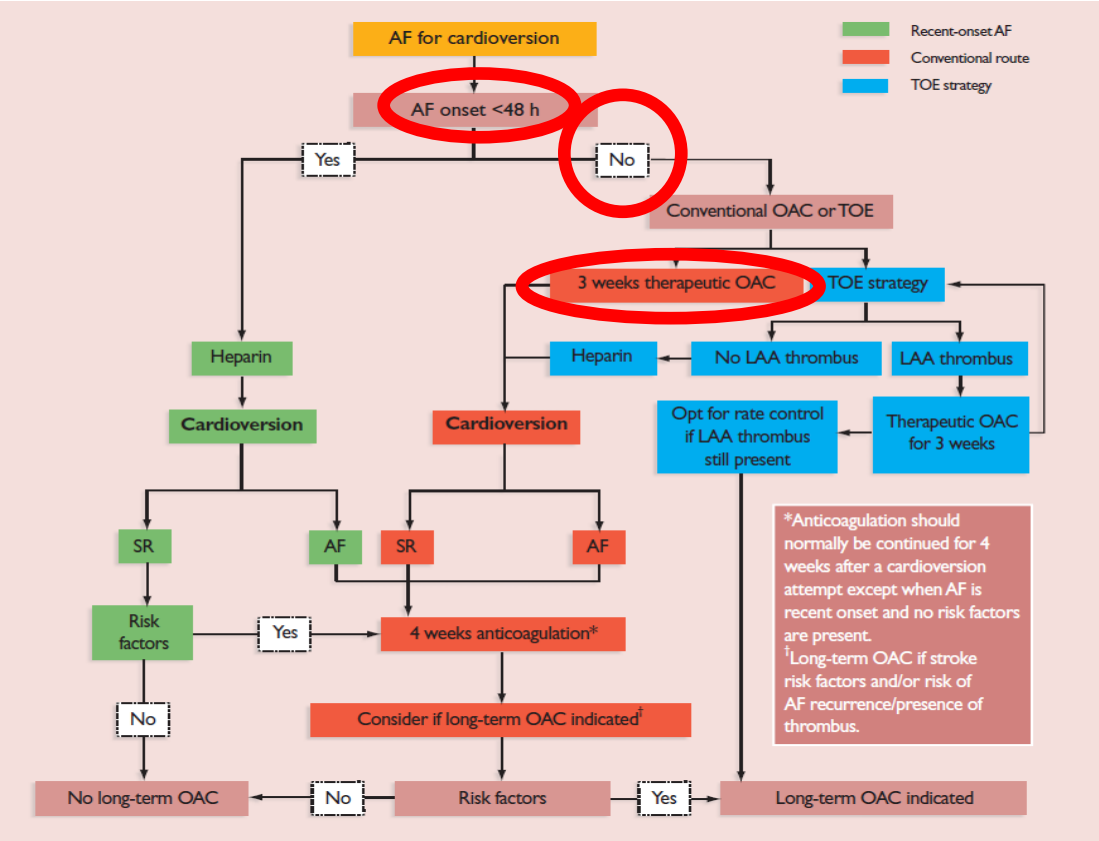
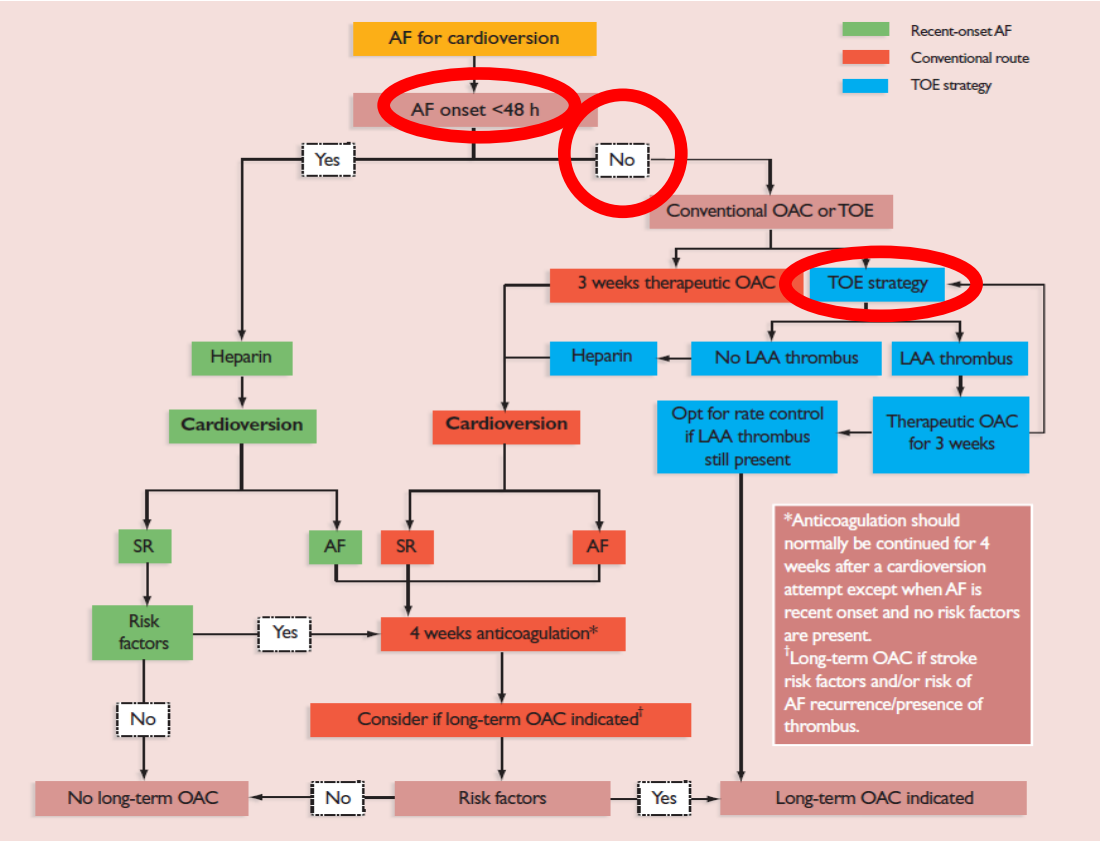


Nonrandomized Trials Comparing Cardioversion in AF Patients With vs Without Anticoagulation

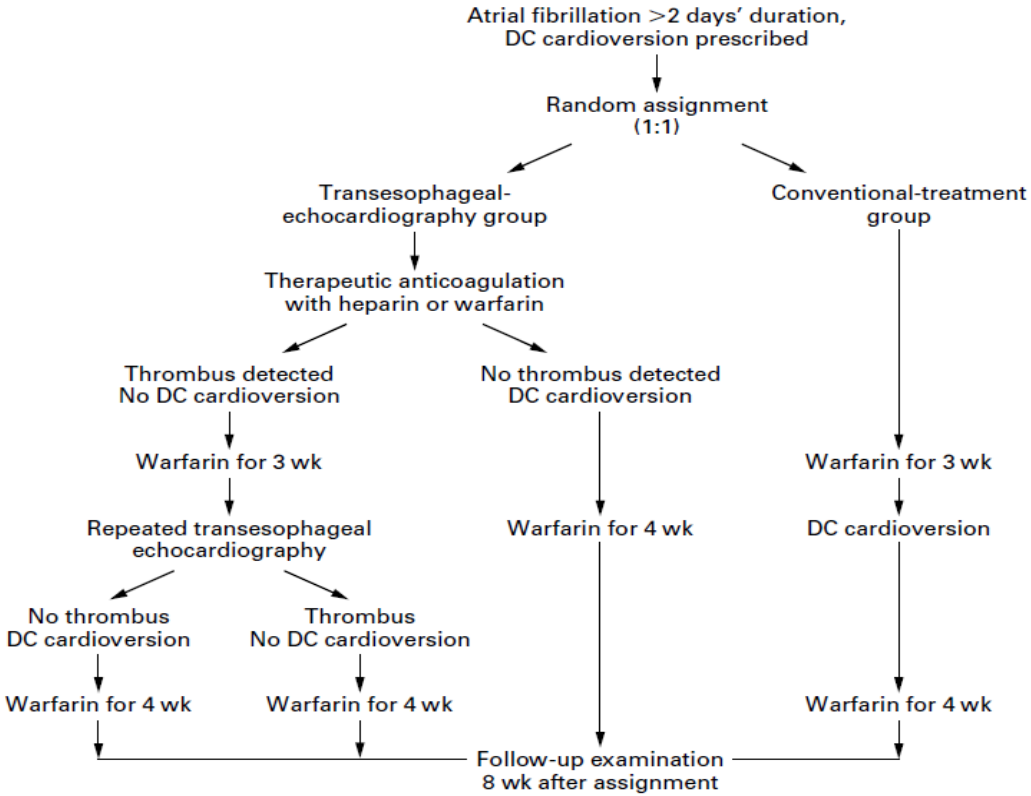
Source	N	Anticoagulation	No anticoagulation	P value
		Thromboembolic Events, n/N (%)		
Bjerkelund and Orning, 1969	437	2/228 (0.8)	11/209 (5.3)	0.016
Weinberg and Mancini, 1989	79	0/51 (0)	2/28 (7)	0.12
Arnold et al, 1992	332	0/153 (0)	6/179 (3.3)	0.026
Total	848	2/432 (0.5)	19/416 (4.6)	-

Guidelines for Cardioversion of Atrial Fibrillation



ACUTE Study

Assessment of Cardioversion Using TEE



- **Primary outcome:** composite of cerebrovascular accident, TIA, peripheral embolism
- **Secondary outcomes:** bleeding, death, success of cardioversion, functional status

Klein et al. 2001

ACUTE Study

TABLE 2. CLINICAL OUTCOMES AT EIGHT WEEKS AMONG PATIENTS WITH ATRIAL FIBRILLATION OF MORE THAN TWO DAYS' DURATION IN THE TRANSESOPHAGEAL-ECHOCARDIOGRAPHY GROUP AND THE CONVENTIONAL-TREATMENT GROUP.*

VARIABLE	TRANSESOPHAGEAL-ECHOCARDIOGRAPHY GROUP (N=619)	CONVENTIONAL-TREATMENT GROUP (N=603)	RELATIVE RISK (95% CI)	P VALUE
All embolic events — no. (%)	5 (0.8)	3 (0.5)	1.62 (0.39–6.76)	0.50
Cerebrovascular accident	4 (0.6)	2 (0.3)	1.95 (0.36–10.60)	0.43
Transient ischemic attack	1 (0.2)	1 (0.2)	0.97 (0.06–15.54)	0.99
Peripheral embolism	0	0	—	—
Hemorrhagic events — no. (%)	18 (2.9)†	33 (5.5)	0.53 (0.30–0.93)	0.03
Major	5 (0.8)	9 (1.5)	0.54 (0.18–1.61)	0.26
Minor	14 (2.3)	24 (4.0)	0.57 (0.30–1.09)	0.08
Death from all causes — no. (%)	15 (2.4)	6 (1.0)	2.44 (0.95–6.24)	0.06
Cardiac-related	8 (1.3)	4 (0.7)	1.95 (0.59–6.44)	0.27
Noncardiac-related	5 (0.8)	2 (0.3)	2.44 (0.47–12.50)	0.27
Unknown cause	2 (0.3)	0	4.87 (0.23–101.25)	0.16
Sinus rhythm — no. (%)				
Restored immediately after DC cardioversion	370/461 (80.3)	266/333 (79.9)	1.01 (0.94–1.08)	0.90
Restored within 8 wk	440 (71.1)	393 (65.2)	1.09 (1.01–1.18)	0.03
Maintained at 8-wk follow-up	326 (52.7)	304 (50.4)	1.05 (0.95–1.16)	0.43
Functional status at 8 wk — DASI score‡	27.4±18.3	26.7±18.6	—	0.50

Klein et al. 2001

Question 4

- After selecting for electrical cardioversion and assuming the patient was not on prior anticoagulation therapy (it is just the first episode!), which strategy would you use in this patient?
  1. Early cardioversion no TEE
  2. Early cardioversion yes TEE
  3. Delayed cardioversion no TEE
  4. Delayed cardioversion yes TEE

Question 4

- After selecting for electrical cardioversion and assuming the patient was not on prior anticoagulation therapy (it is just the first episode!), which strategy would you use in this patient?
  1. Early cardioversion no TEE
  2. **Early cardioversion yes TEE**
  3. Delayed cardioversion no TEE
  4. Delayed cardioversion yes TEE

Question 4

- After selecting for electrical cardioversion and assuming the patient was not on prior anticoagulation therapy (it is just the first episode!), which strategy would you use in this patient?
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  2. Early cardioversion yes TEE
  3. **Delayed cardioversion no TEE**
  4. Delayed cardioversion yes TEE

A Closer Look at Non-surgical Intervention for SPAF

Case report

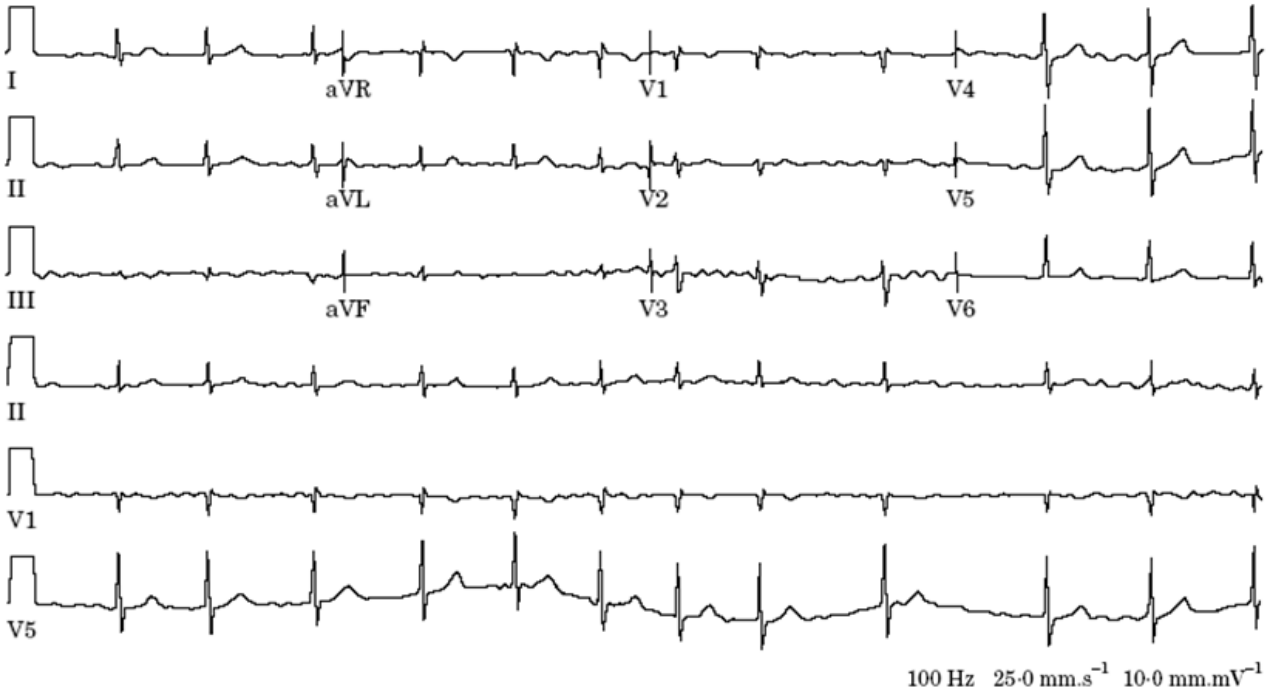
- On Tuesday May 24 2014, he underwent successful (electrical) cardioversion of his first episode of atrial fibrillation

A Closer Look at Non-surgical Intervention for SPAF

Case report

- During the following 12 months, he developed about 2 to 3 episodes of atrial fibrillation per month in spite of oral flecainide administered at 100 mg twice daily
- A pill-in-the-pocket approach was helpful to terminate most, but not all episodes within hours from onset of symptoms
- Access to an ED for CV was required 4 times in one year FU

Mr. J. Reed's Baseline ECG



Question 1

- Did Mr. J. Reed require anticoagulation therapy after CV?
  1. Yes
  2. No
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S_2	Stroke or TIA (history)	2
	Maximum score	**6**

Assessment:
- $CHADS_2 = 1$
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Risk Factors[2]		Points
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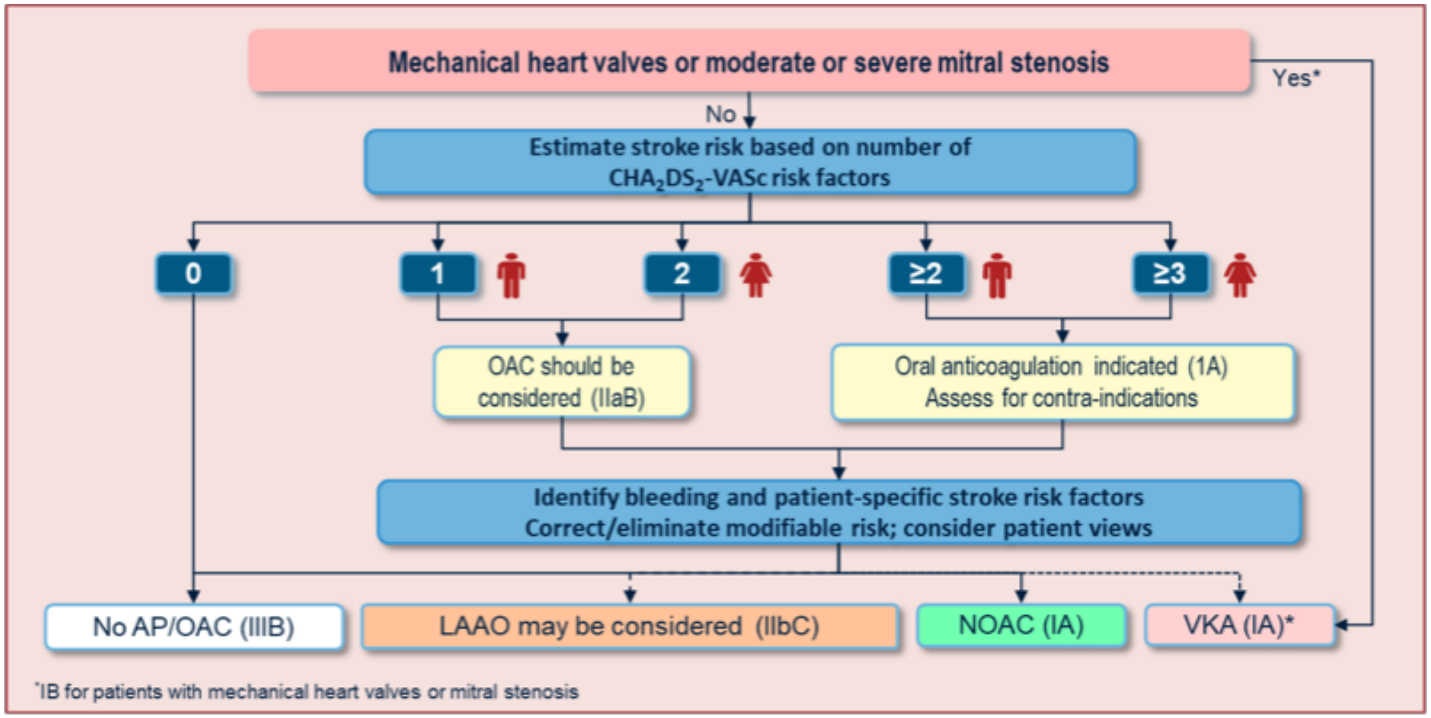
$CHADS_2$
Stroke risk threshold favouring anticoagulation

Score (points)	Risk of stroke (%/year)
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2

Approximate risk threshold for anticoagulation **3%/year**

1. Van Walraven C, et al. Arch Intern Med 2003; 163:936. 2. Go A, et al. JAMA 2003; 290: 2685. 3. Gage BF, et al. Circulation 2004; 110: 2287.

ESC guidelines:
Anticoagulation for stroke prevention



Modified from Kirchhof P, et al. Eur Heart J 2016; 37(38):2893-962.

Anticoagulants according to CHA_2DS_2-VASc

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score		
CHA_2DS_2-VASc score	Patients (n=7329)	Adjusted stroke rate (%/year)[b]
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

Camm AJ, et al. Eur Heart J 2010; 31(19):2369-429. Lip GY, et al. Stroke 2010; 41(12):2731-8

Anticoagulants according to CHA_2DS_2-VASc

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CHA_2DS_2-VASc score	Patients (n=7329)	Adjusted stroke rate (%/year)[b]	
0	1	0%	0%
1	422	1.3%	0.6% (0.0-3.4)
2	1230	2.2%	1.6% (0.3-4.7)
3	1730	3.2%	3.9% (1.7-7.6)
4	1718	4.0%	1.9% (0.5-4.9)
5	1159	6.7%	3.2% (0.7-9.0)
6	679	9.8%	3.6% (0.4-12.3)
7	294	9.6%	8.0% (1.0-26.0)
8	82	6.7%	11.1% (0.3-48.3)
9	14	15.2%	100% (2.5-100)

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  1. Yes
  2. No
  3. Uncertain

Question 1

- Did Mr. J. Reed require anticoagulation therapy after CV?
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  2. **No**
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Question 2

- At this point, what would you do in this patient?
  1. Change AAD
  2. Propose catheter ablation of atrial fibrillation

Question 2

- At this point, what would you do in this patient?
  1. Change AAD
  2. **Propose catheter ablation of atrial fibrillation**

Question 3

- Does Mr. J. Reed require anticoagulation therapy peri-ablation?
  1. Yes
  2. No
  3. Uncertain

Trends in Complications for AF Ablation

	Overall	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	*P* Value
Any procedural complications	6.29	5.33	5.53	6.01	7.17	6.32	5.10	6.17	6.66	5.93	6.49	7.48	0.108
In hospitalization death	0.42	0.44	0.55	0.63	0.30	0.61	0.15	0.45	0.53	0.27	0.52	0.47	0.492
Vascular complications	1.53	0.89	0.66	1.16	1.12	0.95	1.31	0.60	0.97	1.02	0.97	1.33	0.500
Postop hemorrhage	3.38	1.78	2.54	2.53	2.39	3.38	2.77	3.13	3.52	3.75	3.46	4.90	<0.001
Postop hemorrhage requiring transfusion	0.58	0.30	0.22	0.32	0.30	0.61	0.34	0.45	0.87	0.65	0.44	1.03	0.020
Vascular complications including	1.01	0.30	0.11	0.21	0.22	0.26	0.34	0.05	0.10	0.03	0.04	0.04	0.060
Cardiac complications	2.54	1.63	1.66	1.37	2.69	2.42	1.90	1.69	2.90	2.90	3.06	3.53	<0.001
Iatrogenic cardiac complications	1.18	1.33	0.88	0.63	1.19	1.13	0.83	0.90	1.54	1.33	0.93	1.76	0.050
Pericardial complications	1.52	0.74	0.44	0.63	1.49	0.87	1.31	1.00	1.83	1.84	2.14	2.24	<0.001
Myocardial infarction	0.37	0.30	0.55	0.32	0.60	0.69	0.29	0.30	0.34	0.37	0.32	0.26	0.650
Requiring open heart surgery	0.28	0.44	0.22	0.11	0.07	0.09	0.24	0.30	0.24	0.24	0.36	0.47	0.460
Respiratory complications	1.3	1.48	1.66	1.27	1.79	1.21	1.12	1.59	1.79	1.16	1.09	0.77	0.109
Pneumothorax	0.39	0.59	0.66	0.63	0.82	0.52	0.44	0.50	0.29	0.31	0.24	0.04	0.020
Postop respiratory failure	0.77	0.74	0.88	0.53	0.75	0.61	0.49	0.90	1.16	0.68	0.85	0.73	0.575
Other iatrogenic respiratory complications	0.18	0.15	0.33	0.11	0.30	0.09	0.24	0.20	0.43	0.20	0.00	0.00	0.030
Neurological complications (postop stroke/TIA)	1.02	0.89	1.11	1.79	1.57	1.13	0.68	1.39	0.53	0.78	0.93	1.20	0.013
Postop infectious complications	0.38	0.15	0.11	0.21	0.45	0.43	0.29	0.50	0.72	0.24	0.40	0.43	0.235

AF indicates atrial fibrillation; Postop, postoperative; and TIA, transient ischemic attack.

Deshmukh et al, 2013

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Vascular complications	1.53	0.89	0.66	1.16	1.12	0.95	1.31	0.60	0.97	1.02	0.97	1.33	0.500
Postop hemorrhage	3.38	1.78	2.54	2.53	2.39	3.38	2.77	3.13	3.52	3.75	3.46	4.90	<0.001
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Postop infectious complications	0.38	0.15	0.11	0.21	0.45	0.43	0.29	0.50	0.72	0.24	0.40	0.43	0.235

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Deshmukh et al, 2013

Trends in Complications for AF Ablation

	Overall	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	*P* Value
Any procedural complications	6.29	5.33	5.53	6.01	7.17	6.32	5.10	6.17	6.66	5.93	6.49	7.48	0.108
In hospitalization death	0.42	0.44	0.55	0.63	0.30	0.61	0.15	0.45	0.53	0.27	0.52	0.47	0.492
Vascular complications	1.53	0.89	0.66	1.16	1.12	0.95	1.31	0.60	0.97	1.02	0.97	1.33	0.500
Postop hemorrhage	3.38	1.78	2.54	2.53	2.39	3.38	2.77	3.13	3.52	3.75	3.46	4.90	<0.001
Postop hemorrhage requiring transfusion	0.58	0.30	0.22	0.32	0.30	0.61	0.34	0.45	0.87	0.65	0.44	1.03	0.020
Vascular complications including	1.01	0.30	0.11	0.21	0.22	0.26	0.34	0.05	0.10	0.03	0.04	0.04	0.060
Cardiac complications	2.54	1.63	1.66	1.37	2.69	2.42	1.90	1.69	2.90	2.90	3.06	3.53	<0.001
Iatrogenic cardiac complications	1.18	1.33	0.88	0.63	1.19	1.13	0.83	0.90	1.54	1.33	0.93	1.76	0.050
Pericardial complications	1.52	0.74	0.44	0.63	1.49	0.87	1.31	1.00	1.83	1.84	2.14	2.24	<0.001
Myocardial infarction	0.37	0.30	0.55	0.32	0.60	0.69	0.29	0.30	0.34	0.37	0.32	0.26	0.650
Requiring open heart surgery	0.28	0.44	0.22	0.11	0.07	0.09	0.24	0.30	0.24	0.24	0.36	0.47	0.460
Respiratory complications	1.3	1.48	1.66	1.27	1.79	1.21	1.12	1.59	1.79	1.16	1.09	0.77	0.109
Pneumothorax	0.39	0.59	0.66	0.63	0.82	0.52	0.44	0.50	0.29	0.31	0.24	0.04	0.020
Postop respiratory failure	0.77	0.74	0.88	0.53	0.75	0.61	0.49	0.90	1.16	0.68	0.85	0.73	0.575
Other iatrogenic respiratory complications	0.18	0.15	0.33	0.11	0.30	0.09	0.24	0.20	0.43	0.20	0.00	0.00	0.030
Neurological complications (postop stroke/TIA)	1.02	0.89	1.11	1.79	1.57	1.13	0.68	1.39	0.53	0.78	0.93	1.20	0.013
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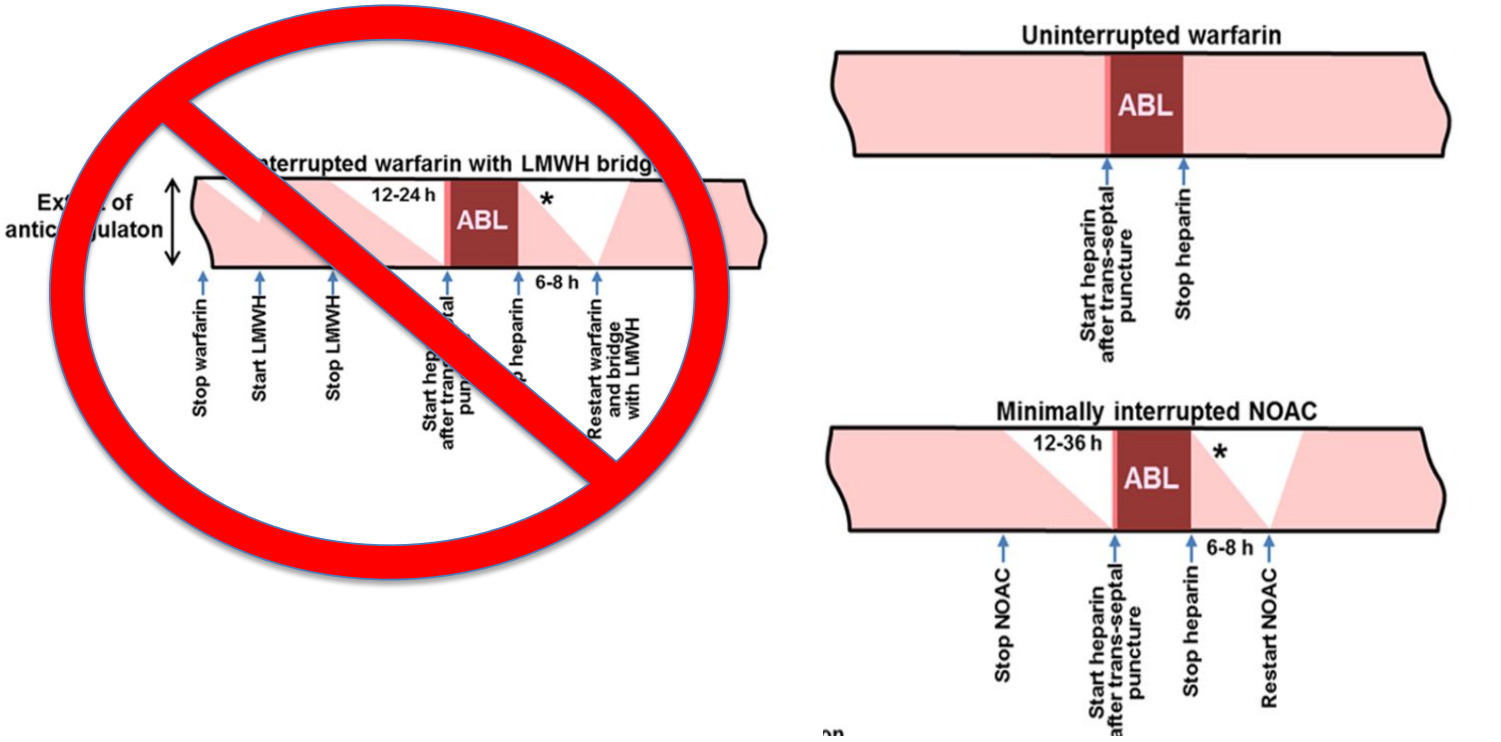
Deshmukh et al, 2013

AF Ablation: Interrupted Vs. Uninterrupted Vs. Minimally Interrupted Anticoagulation



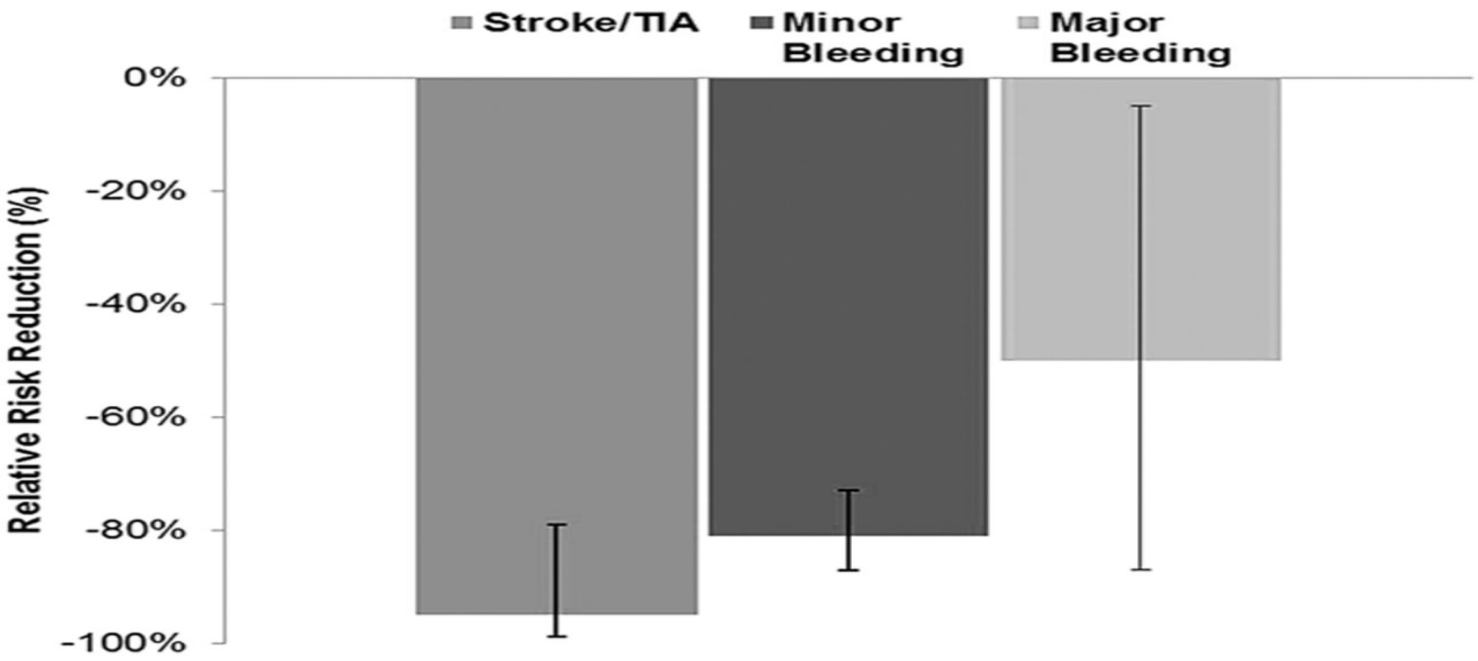
EHRA survey – 71.6% use uninterrupted approach

Weitz J I. Circulation. 2014;129:1688-1694

Incidence of periprocedural thromboembolic events and bleeding complications were more frequent in the off-warfarin population (group 1).

Periprocedural Stroke & Bleeding: AF Ablation with Different Anticoagulation Management (COMPARE)

Lower event rates in continuous vs. interrupted warfarin groups



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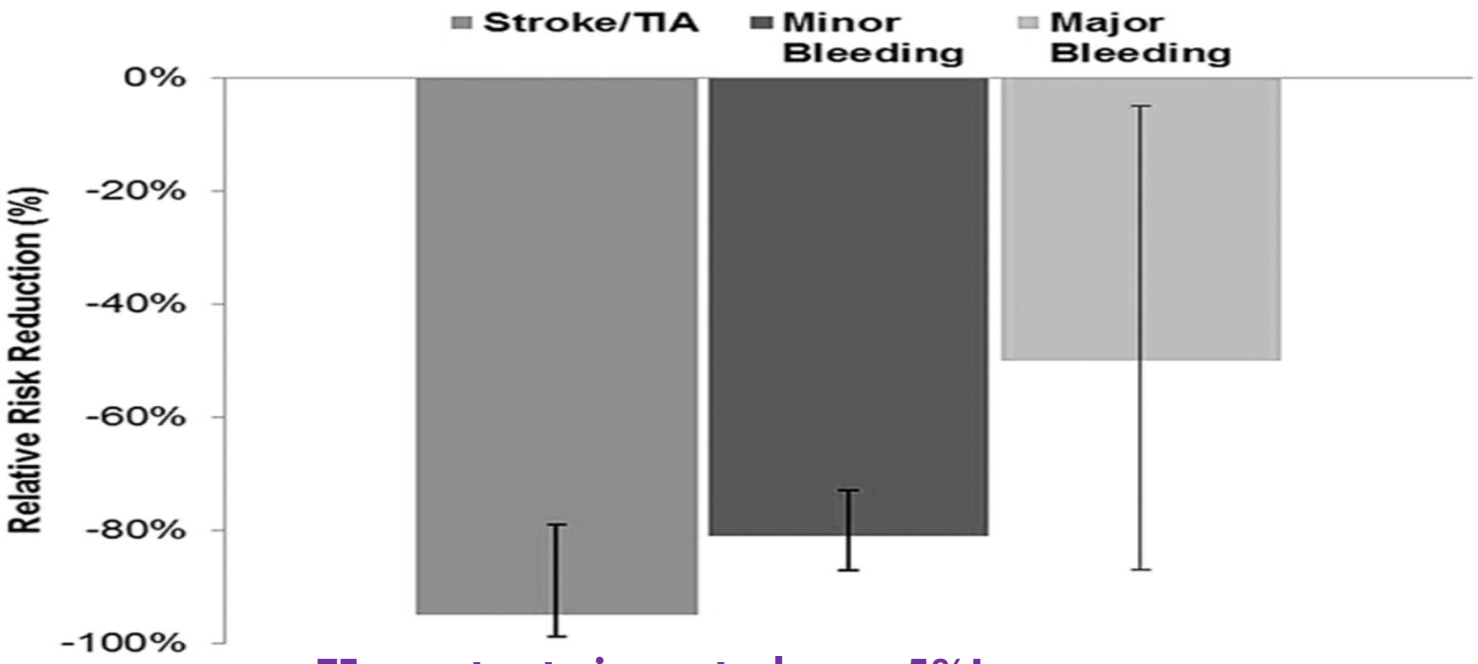

TE event rate in control arm, 5%!

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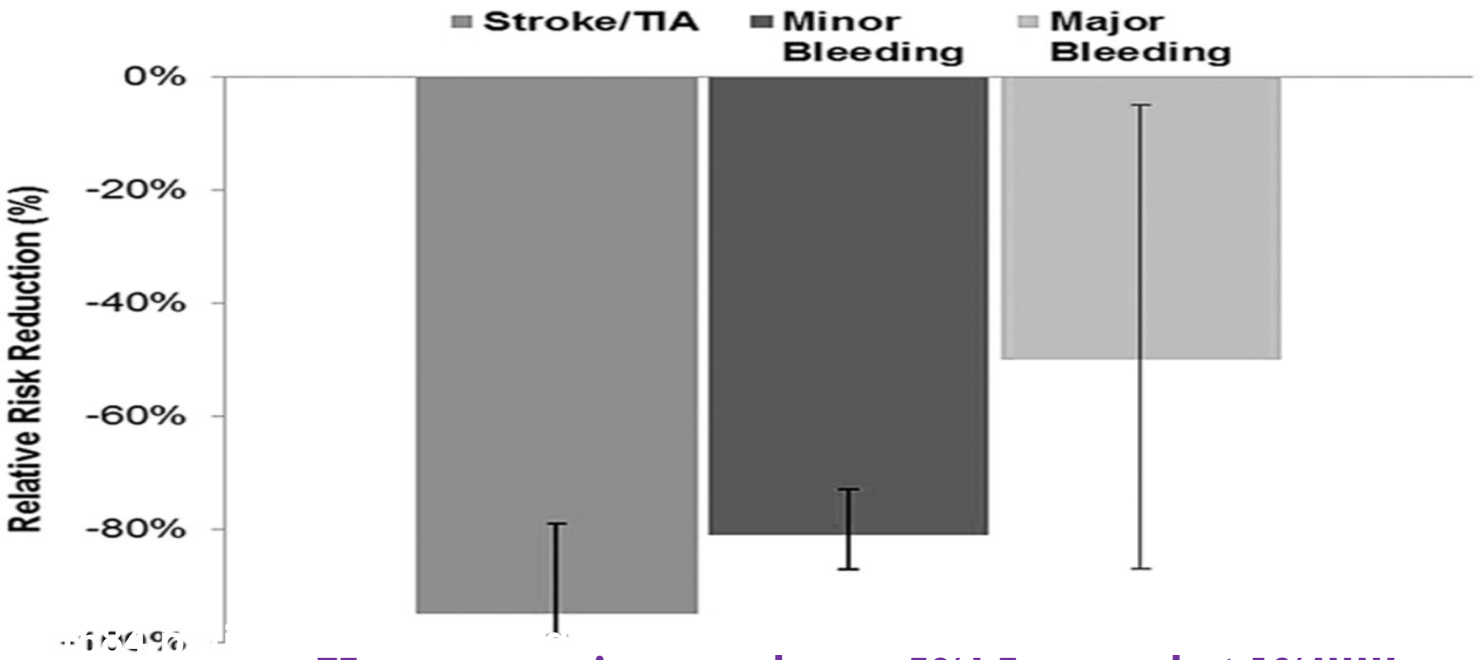

TE event rate in control arm, 5%! Expected: < 1%!!!!!!

Incidence of periprocedural thromboembolic events and bleeding complications were more frequent in the off-warfarin population (group 1).

Periprocedural Stroke & Bleeding: AF Ablation with Different Anticoagulation Management (COMPARE)

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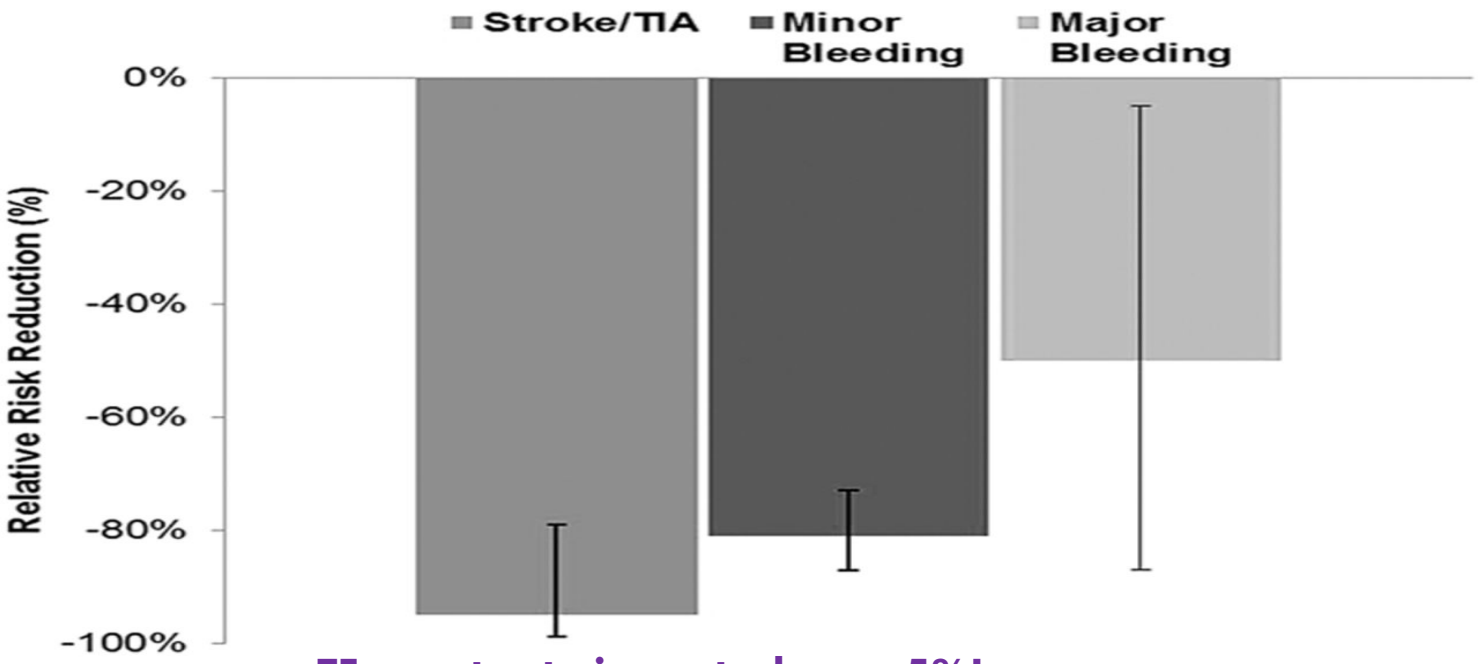

TE event rate in control arm, 5%!
No pre-determined working hypothesis driving the sample size!

Question 3

- Does Mr. J. Reed require anticoagulation therapy peri-ablation?
  1. Yes
  2. No
  3. Uncertain

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  1. **Yes**
  2. No
  3. Uncertain

Question 4

- Which anticoagulant would you use for peri-procedural protection?
  1. VKA
  2. NOACs
  3. 1 or 2

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- Which anticoagulant would you use for peri-procedural protection?
  1. VKA
  2. NOACs
  3. **1 or 2**

VENTURE-AF

BACKGROUND

- Catheter ablation was first reported in 1996 and is now used routinely to establish rhythm control in AF patients[1]
- The traditional approach is to interrupt oral vitamin K antagonist (VKA; eg, warfarin) and use heparin bridging
- EP evidence suggests that the uninterrupted anticoagulation strategy may be safer[2,3]
- This clinical trial extends findings from a catheter ablation subgroup analysis of the pivotal Phase III ROCKET AF study of nonvalvular AF patients using rivaroxaban, a selective oral direct factor Xa inhibitor NOAC[4]

Cappato R, et al. *Eur Heart J.* 2015;36:1805-11.

METHODS

- This is a prospective randomized, open-label, comparative Phase IIIb international exploratory trial
- After traditional sample size estimation indicated an unfeasibly large number of patients needed to establish non-inferiority or superiority, trial size was administratively set at 250, the protocol-specified target
- We randomized 248 patients 1:1 to uninterrupted rivaroxaban 20 mg once-daily or to an uninterrupted VKA prior to catheter ablation and for 4 weeks afterwards
- Pre-specified thromboembolic and bleeding events were independently and blindly-adjudicated by a CEC

Naccarelli GV, Cappato R, Hohnloser SH, et al. *J Interv Card Electrophysiol*. 2014 Nov;41(2):107-16.
CEC = clinical events committee

VENTURE AF: Key Inclusion and Exclusion Criteria

Key inclusion criteria*	Key exclusion criteria#
◆ Scheduled for catheter ablation for NVAF ◆ Prior paroxysmal (<1 week) or persistent (>1 week and <1 year or requiring pharmacological or electrical cardioversion) or long-standing persistent (≥1 year) NVAF ◆ Suitable for anticoagulant therapy and catheter ablation	◆ Prior stroke, TIA or non-convulsive status epilepticus ≤6 months ◆ Prior major bleeding or a thromboembolic event ≤12 months ◆ Major surgery ≤6 months before screening/planned during study ◆ MI ≤2 months or CABG surgery ≤6 months ◆ Non-cardiac or reversible NVAF ◆ CrCl ≤50 ml/min†

*Including but not limited to; #any other exclusion criteria in conjunction with the local product information and any other contraindication listed in the local labeling for rivaroxaban or the comparator have to be considered; †owing to the small size of the study, patients with a CrCl ≤50 ml/min were excluded to avoid the need for separate data analysis in two different patient cohorts

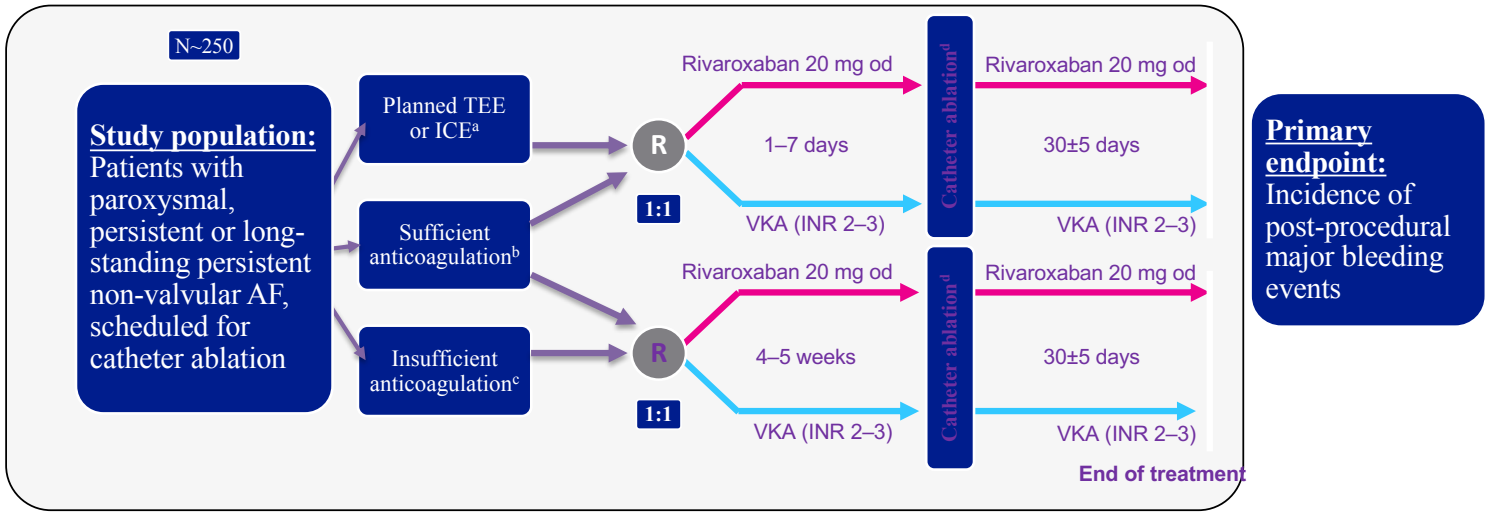
Naccarelli GV *et al, J Interv Card Electrophysiol* 2014;41:107–116

VENTURE AF

Study Design

Randomized, open-label, active-controlled study

Objective: To assess the safety of rivaroxaban vs VKA in patients with AF undergoing catheter ablation



AF, atrial fibrillation; ICE, intracardiac echocardiography; TEE, transesophageal echocardiogram; R, randomization VKA, vitamin K antagonist od, once daily;
INR, international normalized ratio

1. Naccarelli *et al*, 2014; 2. www.clinicaltrials.gov/ct2/show/NCT01729871

Demographics (ITT)

	Rivaroxaban (N=124)	VKA (N=124)	Total (N=248)	*p* Value
Mean age, years (SD)	58.6 (9.9)	60.5 (10.5)	59.6 (10.2)	0.211
Age ≥75, n (%)	5 (4.0)	10 (8.1)	15 (6.0)	0.183
Age 65-75	34 (27.4)	41 (33.1)	75 (30.2)	0.183
Male	86 (69.4)	90 (72.6)	176 (71.0)	0.576
Caucasian	112 (90.3)	116 (93.5)	228 (91.9)	0.351
Non-Hispanic/Latino	90 (72.6)	94 (75.8)	184 (74.2)	0.562
Paroxysmal AF	95 (76.6)	87 (70.2)	182 (73.4)	0.250
Prior cardioversion	47 (37.9)	54 (43.5)	101 (40.7)	0.366
Prior catheter ablation	11 (8.9)	11 (8.9)	22 (8.9)	0.563
Mean BMI, kg/m^2 (SD)	29.8 (5.7)	28.9 (5.5)	29.4 (5.6)	0.231

Note: Units are listed as n(%) unless otherwise indicated
Note: BMI = body mass index; BP = blood pressure; CHF = congestive heart failure; ITT = intention-to treat; SD = standard deviation

Cappato R, et al. *Eur Heart J.* 2015;36:1805-11.

Demographics (ITT)

	Rivaroxaban (N=124)	VKA (N=124)	Total (N=248)	*p* Value
CHF	12 (9.7)	9 (7.3)	21 (8.5)	0.494
Hypertension	59 (47.6)	57 (46.0)	116 (46.8)	0.799
Mean systolic BP, mm Hg (SD)	133 (16)	131 (18)	132 (17)	0.325
Mean diastolic BP, mm Hg (SD)	81 (10)	79 (11)	80 (10)	0.233
Diabetes mellitus	8 (6.5)	14 (11.3)	22 (8.9)	0.180
Prior Stroke/TIA/embolism	0	3 (2.4)	3 (1.2)	0.081
Vascular disease	22 (17.7)	25 (20.2)	47 (19.0)	0.627
Mean CHADS2 Score (SD)	0.7 (0.7)	0.8 (0.9)	0.7 (0.8)	0.179
Mean CHA2DS2-VASc Score (SD)	1.5 (1.3)	1.7 (1.4)	1.6 (1.3)	0.277
Beta blocker, selective	65 (52.4)	61 (49.2)	126 (50.8)	0.611
Antiarrhythmic, class IC	51 (41.1)	49 (39.5)	100 (40.3)	0.796
Antiarrhythmic, class III	30 (24.2)	39 (31.5)	69 (27.8)	0.202
Vitamin K antagonist	36 (29.0)	37 (29.8)	73 (29.4)	0.889
Rivaroxaban	23 (18.5)	29 (23.4)	52 (21.0)	0.349
Dabigatran	12 (9.7)	10 (8.1)	22 (8.9)	0.655
Antiplatelet agent	37 (29.8)	29 (23.4)	66 (26.6)	0.250
Proton pump inhibitor	26 (21.0)	18 (14.5)	44 (17.7)	0.184

Note: Units are listed as n(%) unless otherwise indicated; medications are baseline (pre-randomization)
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Cappato R, et al. *Eur Heart J*. 2015;36:1805-11.

VENTURE AF
Primary and secondary endpoints

	Rivaroxaban	VKA	Total
Any adjudicated event	26	25	51
	n=123	n=121	N=244
Any bleeding event* (SAFETY)	21	18	39
Major bleeding event (Primary endpoint)	0	1	1
Vascular pseudoaneurysm	0	1	1
Non-major bleeding event	21	17	38
Most relevant:			
Arteriovenous fistula	0	1	1
Catheter/puncture site haemorrhage	1	1	2
Haematoma/vessel puncture haematoma	8	10	18
Vascular pseudoaneurysm	3	1	4
	n=124	n=124	N=248
Any thromboembolic events (EFFICACY)#	0	2	2
Ischaemic stroke	0	1	1
Vascular death	0	1	1
	n=114	n=107	N=221
Any other procedure-attributable event†	5	5	10
Pericardial effusion without tamponade	0	1	1

*safety population; #ITT population; †per-protocol population

For full list see publication or back-up-slide
Adapted from Cappato R, et al. Eur Heart J. 2015;36:1805-11.

CEC-adjudicated Complications

	Rivaroxaban	VKA	Total
Any CEC-adjudicated Event	26	25	51
	N=124	N=124	N=248
Any Thromboembolic Events (Composite)[a]	0	2	2
Ischemic stroke	0	1	1
Vascular death	0	1	1
	n=123	n=121	n=244
Any Bleeding Events[b]	21	18	39
Major bleeding event			
Vascular pseudoaneurysm	0	1	1
Non-major bleeding events			
Arteriovenous fistula	0	1	1
Catheter/puncture site haemorrhage	1	1	2
Ecchymosis	0	1	1
Epistaxis	2	1	3
Eye haemorrhage (non-intraocular)	1	0	1
Gingival bleeding	1	0	1
Groin bruising	1	1	2
Haematoma/vessel puncture site haematoma	8	10	18
Haematuria	2	0	2
Haemorrhagic stomatitis	0	1	1
Mouth haemorrhage	1	0	1
Urinary tract infection	1	0	1
Vascular pseudoaneurysm	3	1	4

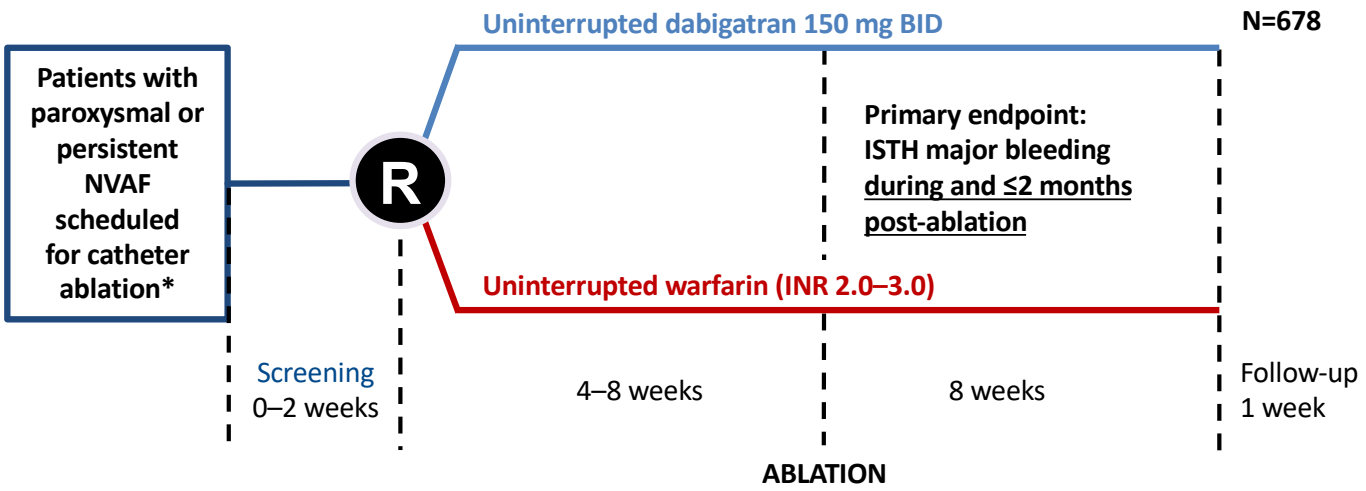
Cappato R, et al. *Eur Heart J.* 2015;36:1805-11.

Patients on NOACs: Ablation of AF

Conclusions

- Uninterrupted rivaroxaban showed comparable efficacy and safety to uninterrupted VKA in NVAF patients undergoing ablation
- Results are consistent with real-life data with rivaroxaban in this setting
- Data from prospective randomized studies are awaited to confirm these preliminary observation before standard use of NOACs in this setting is recommended

RE-CIRCUIT™ assessed the safety of uninterrupted treatmentwith dabigatran vs warfarin in patients undergoing AF ablation

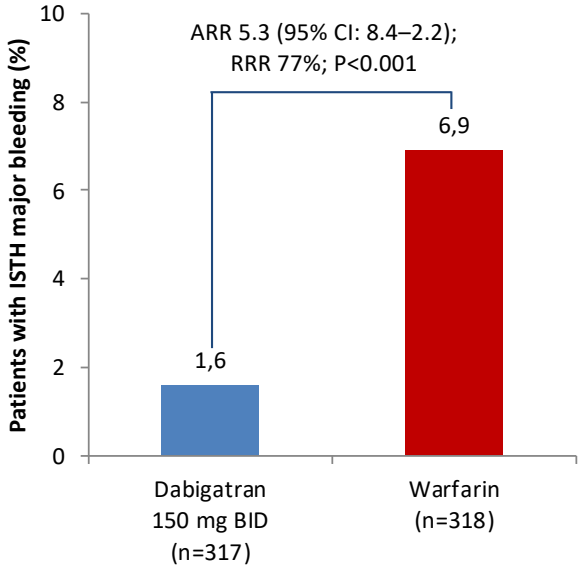


In line with current guidelines:[3] Continuous anticoagulation in both treatment arms; TEE performed on all patients ≤48 hrs before ablation; UFH administered before or immediately after transseptal puncture (adjusted to maintain ACT >300 s)

*Eligible for dabigatran 150 mg BID according to local label; ACT, activated clotting time; R, randomization;

Calkins et al. N Engl J Med 2017

RE-CIRCUIT™ showed a lower risk of major bleeding during and after ablation with dabigatran vs warfarin



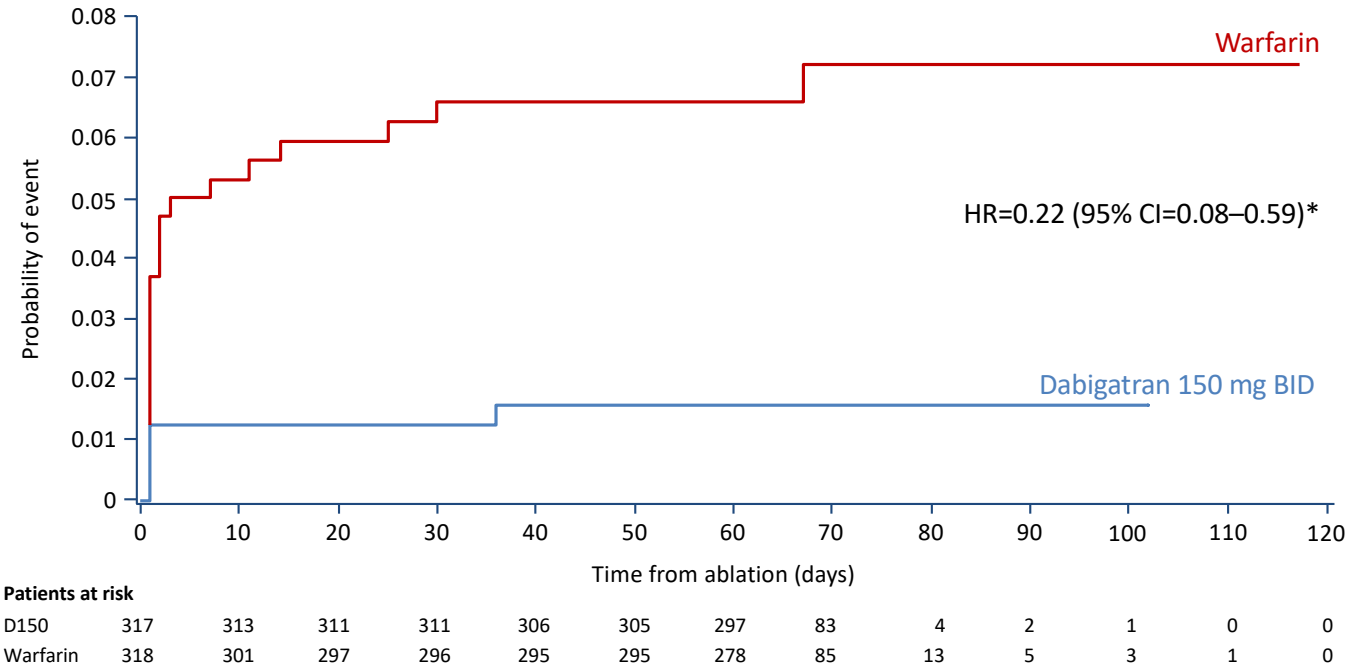
	Dabigatran	Warfarin
Patients with ISTH MBEs, n	**5**	**22**
ISTH MBEs, n*	**5**	**23†**
Pericardial tamponade	1	6
Pericardial effusion	1	0
Groin bleed	2	2
Groin haematoma	0	8
GI bleed	1	2
Intracranial bleed	0	2
Pseudoaneurysm	0	1
Haematoma	0	2
Required medical action	**4**	**21**
Intervention/procedure	1	11

*Based on number of events rather than number of patients; †One patient had two adjudicated ISTH MBEs;
MBEs during ablation and up to 2 months post-ablation; ARR, absolute risk reduction;
MBE, major bleeding event; RRR, relative risk reduction

Calkins et al. N Engl J Med 2017

RE-CIRCUIT™ showed fewer major bleeding events with dabigatran than with warfarin, particularly during the first 7 days post-ablation

Major bleeding events



Patients at risk

D150	317	313	311	311	306	305	297	83	4	2	1	0	0
Warfarin	318	301	297	296	295	295	278	85	13	5	3	1	0

*Cox proportional hazard model and Wald confidence limits;
Calkins et al. N Engl J Med 2017

RE-CIRCUIT™: fewer major bleeding and thromboembolic events with uninterrupted dabigatran than with uninterrupted warfarin

	Dabigatran 150 mg BID (n=317)	Warfarin (n=318)
Minor bleeding event, n (%)	59 (18.6)	54 (17)
Thromboembolic events, n (%) Stroke/SE TIA	 0 (0) 0 (0)	 0 (0) 1 (0.3)
Composite major bleeding and thromboembolic events, n (%)	5 (1.6)	23 (7.2)

TIA, transient ischaemic attack;
Calkins et al. N Engl J Med 2017

RE-CIRCUIT™: fewer adverse events with uninterrupted dabigatran than with uninterrupted warfarin

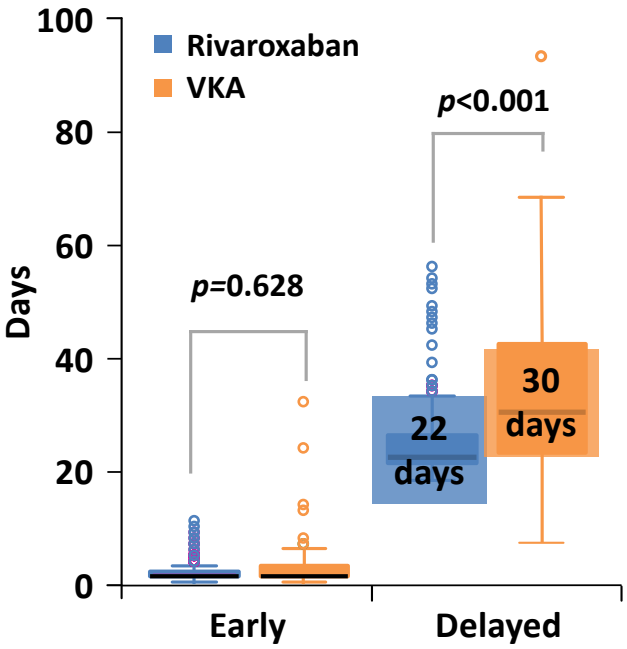
Adverse events, n (%)	Dabigatran 150 mg BID (n=338*)	Warfarin (n=338*)
Any	225 (66.6)	242 (71.6)
Severe	11 (3.3)	21 (6.2)
Serious	63 (18.6)	75 (22.2)
Fatal	0 (0)	0 (0)
Immediately life-threatening	1 (0.3)	2 (0.6)
Disabling/incapacitating	0 (0)	1 (0.3)
Leading to discontinuation	19 (5.6)	8 (2.4)
Requiring hospitalization	26 (7.7)	34 (10.1)
Prolonging hospitalization	13 (3.8)	22 (6.5)

*Treated patient set; TIA, transient ischaemic attack;
Calkins et al. N Engl J Med 2017

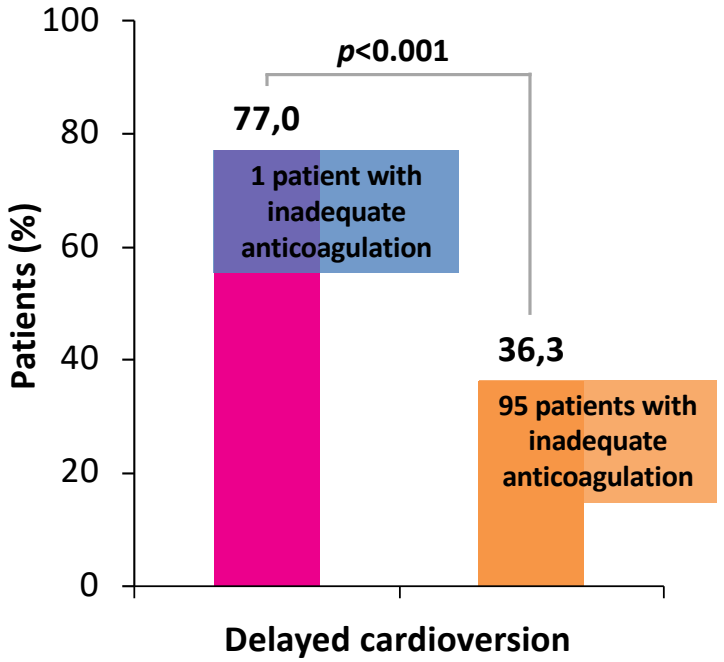
Practical Considerations for ATCG Rx in CV of AF

X-VeRT sub-analysis

Median time to cardioversion



Patients cardioverted as scheduled*



*Reason for not performing cardioversion as first scheduled from 21–25 days primarily due to inadequate anticoagulation (indicated by drug compliance <80% for rivaroxaban or weekly INRs outside the range of 2.0–3.0 for 3 consecutive weeks before cardioversion for VKA)

1. Cappato R *et al, Eur Heart J* 2014;35:3346–3355