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An Overview of Atrial Fibrillation Diagnosis and Management

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Presentation overview

- **Introduction**
  - Why atrial fibrillation matters? Epidemiology and risk factors
- **Diagnosis and screening**
  - Symptoms and screening
  - Monitors and wearable technologies
  - Classifying atrial fibrillation
- **Risk stratification**
  - Thromboembolic risk
  - Bleeding risk
- **Treatment**
  - Life style changes
  - Rate vs. Rhythm Control
  - Strategies for stroke prevention
    - Medications
    - Non-pharmacological

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Introduction

Why atrial fibrillation matters? Epidemiology and risk factors

- Affects 6 million patients in USA (43.6 million worldwide) associated with increase in aging and chronic heart disease, especially heart failure
- Responsible for > 454,000 hospitalizations and >158,000 deaths annually in the US.
- Frequently seen with comorbidities
  - AF complicates management of comorbidity
  - Comorbidity complicates management of AF
- Associated with stroke, heart failure, and death
  - 71,000 patients die/year from complications of AF or atrial flutter (AFL)
- Most common arrhythmia requiring hospitalization
  - 416,000 hospital discharges/year (most common arrhythmia discharge diagnosis)
- Median age is 75 y.o.
  - 70% of patients are between age 65-85 y.o.
  - 84% older than 65 y.o.
- Underestimated due to lack of symptoms, silent AF *(45% in SPAF-III)*

	AF Related Outcome	Frequency in AF	Mechanism(s)
	**Death**	1.5- to 3.5-fold increase	Excess mortality related to: • HF, comorbidities • Stroke
	**Stroke**	20-30% of all ischemic strokes, 10% of cryptogenic strokes	• Cardioembolic or • Related to comorbid vascular atheroma
	**LV dysfunction/ heart failure**	In 20-30% of patients with AF	• Excessive ventricular rate • Irregular ventricular contractions • A primary underlying cause of AF
	**Cognitive decline/ vascular dementia**	Hazard ratio 1.4/1.6 (irrespective of stroke history)	• Brain white matter lesions, inflammation • Hypoperfusion • Microembolism
	**Depression**	Depression in 16-20% (even suicidal ideation)	• Severe symptoms and decreased QoL • Drug side effects
	**Impaired quality of life**	>60% of patients	• Related to AF burden, comorbidities, psychological functioning, and medication • Distressed personality type
	**Hospitalizations**	10-40% annual hospitalization rate	• AF management, related to HF, MI, or AF related symptoms • Treatment-associated complications

LV = left ventricular; QoL = quality of life; MI = myocardial infraction.
Hindricks G, et al. 2020 ESC Guidelines. *Eur Heart J.* 2020;00:1-125.

Introduction

Why atrial fibrillation matters? Epidemiology and risk factors

- *Non-modifiable risk factors*

  - Age: The single strongest risk factor.

  - Family History and Genetics: Family history of AF increase the risk. Certain genetic mutations are also associated with a higher risk.

  - Sex: Men are at a higher risk of developing AF than women.

  - Race/Ethnicity: Individuals of European descent have a higher incidence of AF. However, Black, Hispanic, and Asian populations with AF may have a higher risk of stroke.

Introduction

Why atrial fibrillation matters? Epidemiology and risk factors

- *Modifiable risk factors*
  - **Hypertension:** This is the most common modifiable risk factor.
  - **Heart Disease:** Mitral valve disease, systolic heart failure, etc.
  - ***Obesity:*** Higher inflammation, Higher atrial pressure, sleep apnea.
  - **Sleep apnea:** Hypoxia, autonomic dysfunction, inflammation
  - **Diabetes:** Inflammation, atrial fibrosis, autonomic dysregulation
  - **Hyperthyroidism:** Altering calcium handling
  - **Physical inactivity**
  - **Alcohol consumption:** Alters electrical signal, oxidative stress, hormonal changes electrolyte imbalances
  - **Smoking:** Inflammation, oxidative stress, alters electrical signal

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Diagnosis and screening

Symptoms and screening

- *Symptoms of atrial fibrillation:* Palpitations, chest discomfort or pressure, shortness of breath (especially with exertion), Dizziness or lightheadedness, syncope.
- Many are asymptomatic (silent AF - *45% in SPAF-III).*
- *EKG is the most important test for diagnosis.*
- “The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for atrial fibrillation”.
- Possible harm with screening secondary to overprescribing of oral anticoagulants.

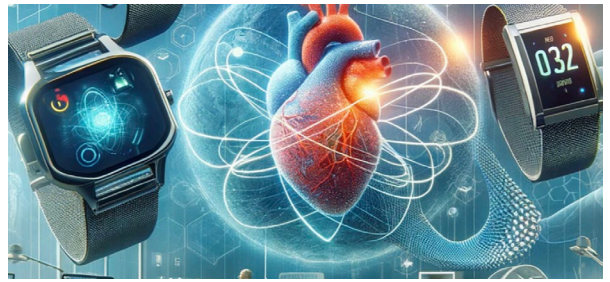
US Preventive Services Task Force JAMA. 2022;327(4):360-367.

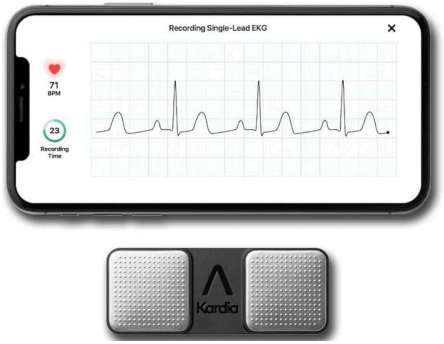
Mandrola J, Foy A, Naccarelli GV. JAMA Intern Med 2018;178(10):1296-1298

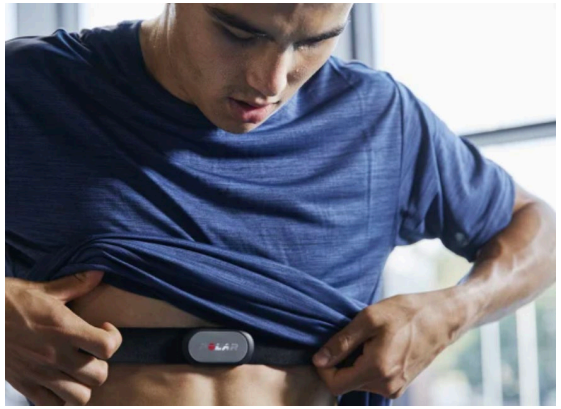
Diagnosis and screening

Monitors and wearable technologies

- False positives
- How should you treat?







Diagnosis and screening

Classifying atrial fibrillation

Based on duration

- **First diagnosed AF:** AF that has not been diagnosed before.
- **Paroxysmal AF:** AF that terminates spontaneously within 7 days or with the assistance of an intervention (most terminate spontaneously with 48 hours).
- **Persistent AF:** Continuous for more than 7 days.
- **Long-standing persistent AF:** Continuous for 12 months or more.
- **Permanent AF:** When *both patient and physician accept AF as permanent*, and no further attempts at rhythm control are pursued.

Diagnosis and screening

Classifying atrial fibrillation

Valvular atrial fibrillation

- A term used to describe patients with atrial fibrillation for whom current evidence supports anticoagulation with warfarin rather than direct oral anticoagulants
    - Presence of mechanical heart valves
    - Moderate or severe rheumatic mitral stenosis

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Risk stratification

Thromboembolic risk

- The major adverse events associated with AF are stroke and systemic thromboembolism, with risks ~5 times higher than for age-matched patients without AF.
- Furthermore, AF-associated strokes are more severe, have a higher recurrence rate (~2 times more likely to reoccur than non-AF-associated strokes).

Wolf PA, Abbott RD, Kannel WB. Archives of Internal Medicine. 1987;147(9):1561-1564.

Menke J, Lüthje L, Kastrup A, et al. The American journal of cardiology. 2010;105(4):502-10.

Britton M, Gustafsson C. Stroke. 1985;16(2):182-8.

Lin H-J, Wolf PA, Kelly-Hayes M, et al. Stroke. 1996;27(10):1760-1764.

Risk stratification

Thromboembolic risk

- The most widely use score is the CHA_2DS_2-VASc score.

Risk Factor	Points
Congestive heart failure	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke / TIA / thromboembolism history	2
Vascular disease	1
Age 65–74 years	1
Sex category (female)	1

CHA_2DS_2-VASc Score	Risk of ischemic stroke	Risk of stroke/TIA/systemic embolism
0	0.2%	0.3%
1	0.6%	0.9%
2	2.2%	2.9%
3	3.2%	4.6%
4	4.8%	6.7%
5	7.2%	10.0%
6	9.7%	13.6%
7	11.2%	15.7%
8	10.8%	15.2%
9	12.2%	17.4%

Lip GY, Nieuwlaat R, Pisters R, et al. Chest. 2010;137(2):263-72.
Friberg L, Rosenqvist M, Lip GY. Eur Heart J. 2012;33(12):1500-10.

Risk stratification

Thromboembolic risk

- Other important risk factors for stroke beside what's included in the CHA_2DS_2-VASc score include: Proteinuria and advanced kidney disease.
- Guidelines recommend anticoagulation if CHA_2DS_2-VASc is ≥2 in men or ≥3 in women, if no high risk for bleeding (The 2023 ACC/AHA/ACCP/HRS guidelines).
- In patients with AF and cardiac amyloidosis or hypertrophic cardiomyopathy, anticoagulation is recommended regardless of the CHA_2DS_2-VASc score.

Risk stratification

Bleeding risk

- The most widely used score is HAS-BLED

Risk Factor	Points
Hypertension (SBP >160 mmHg)	1
Abnormal renal function (dialysis, transplant, Cr >2.26 mg/dL)	1
Abnormal liver function (cirrhosis, bilirubin >2x, AST/ALT/AP >3x normal)	1
Stroke history	1
Bleeding history or predisposition (e.g., prior major bleed, anemia)	1
Labile INR (if on warfarin: TTR <60%)	1
Elderly (age >65 years)	1
Drugs predisposing to bleeding (antiplatelets, NSAIDs)	1
Alcohol use (≥8 drinks/week)	1

HAS-BLED Score	Risk group	Risk of major bleeding**	Bleeds per 100 patient-years***
0	Low	0.9%	1.13
1		3.4%	1.02
2	Moderate	4.1%	1.88
3	High	5.8%	3.72
4		8.9%	8.70
5		9.1%	12.50
>5*	Very high	-	-

Pisters R, Lane DA, Nieuwlaat R, et al. Chest. 2010;138 (5):1093-100.
Lip GY, Frison L, Halperin JL, et al. J Am Coll Cardiol. 2011;57(2):173-80.

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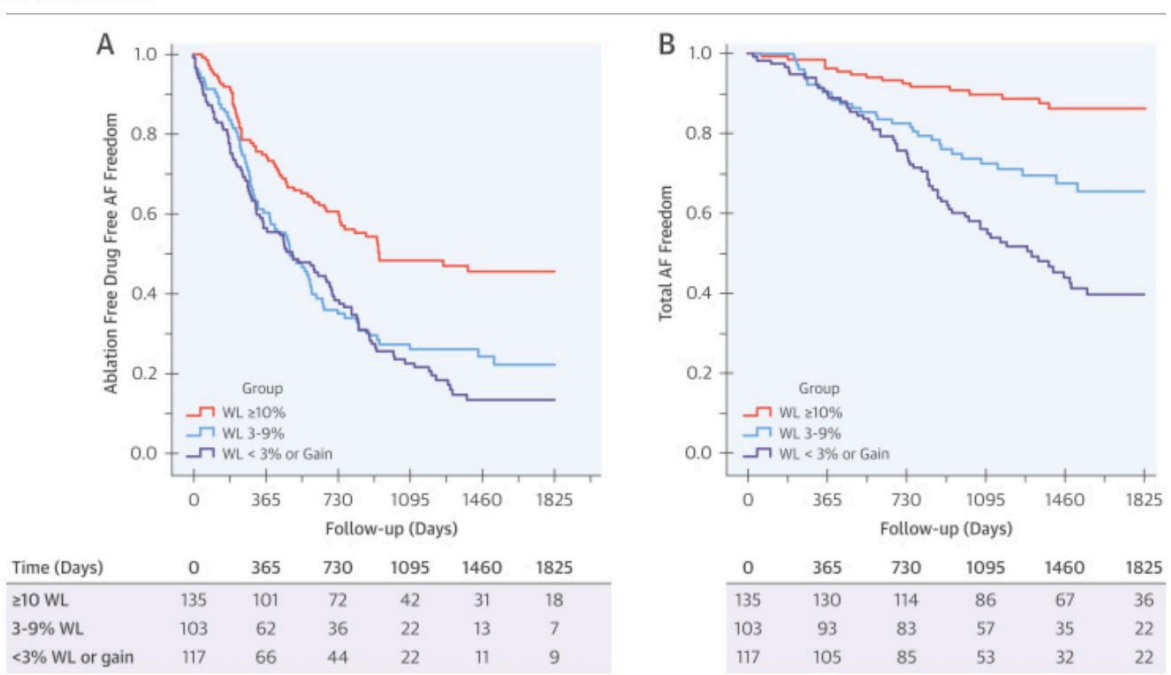
Treatment

Life style changes

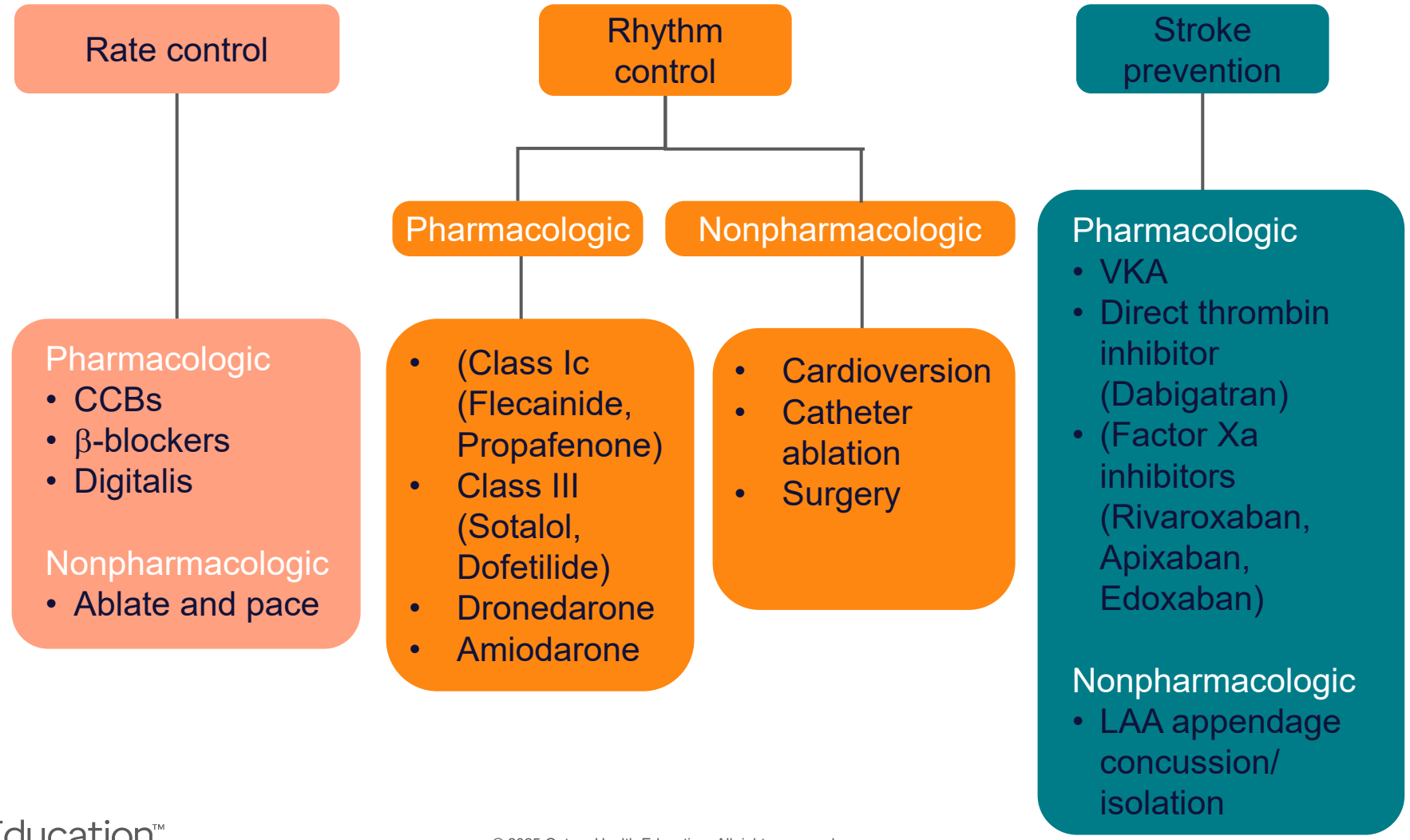


Time (Days)	0	365	730	1095	1460	1825
≥10 WL	135	101	72	42	31	18
3-9% WL	103	62	36	22	13	7
<3% WL or gain	117	66	44	22	11	9

0	365	730	1095	1460	1825
135	130	114	86	67	36
103	93	83	57	35	22
117	105	85	53	32	22

Pathak RK et al. J Am Coll Cardiol. 2015;65(20):2159-69.

Treatment Options for AF



Treatment

Rate vs Rhythm control

- One of the most debated topics in cardiology.
- Rhythm control include drugs, cardioversion or ablation procedures.

Treatment

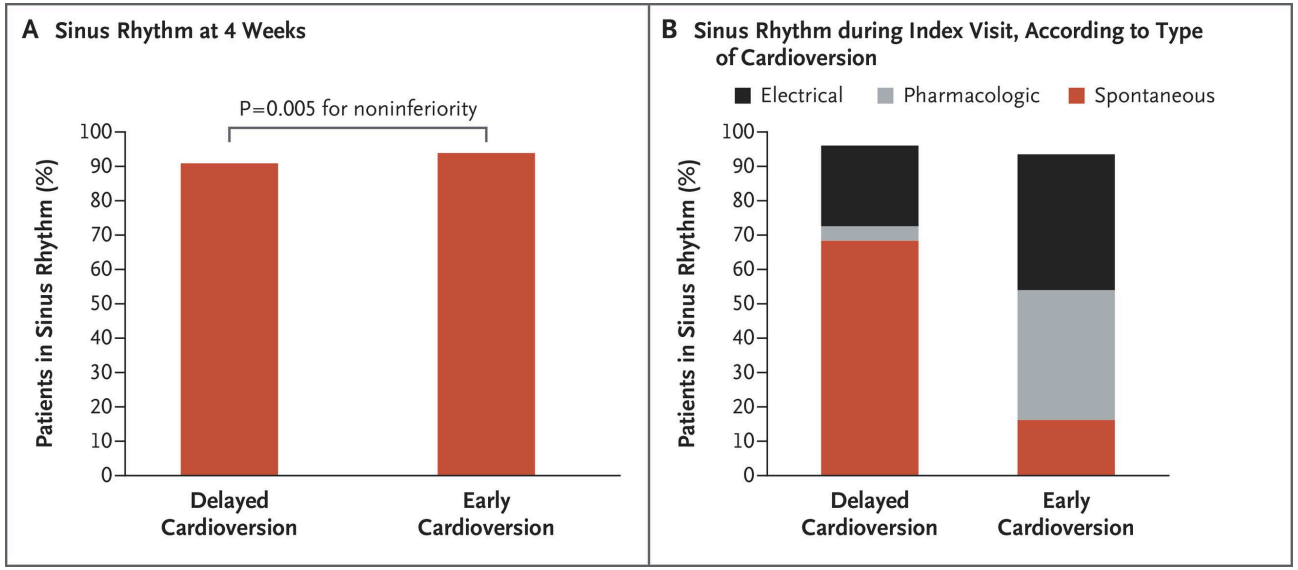
Rate vs Rhythm control

- Electrical cardioversion is successful at restoring sinus rhythm in the vast majority of patients, BUT it does not prevent AF recurrence
- Pharmacological therapy
    - Pill-in-pocket cardioversion
    - Chronic treatment
- Ablation may increase atrial arrhythmia burden first 3 months but reduces it after that

Treatment

Rate vs Rhythm control

- 437 patients with hemodynamically stable, recent-onset (<36 hours), symptomatic atrial fibrillation were randomized to a wait-and-see approach (delayed-cardioversion group) or early cardioversion.



N Engl J Med 2019;380:1499-1508

Treatment

Rate vs Rhythm control

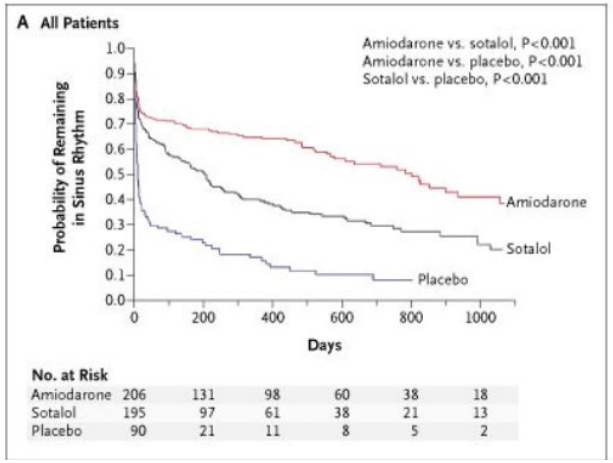
- Chemical cardioversion with pill-in-pocket approach (Flecainide 300 mg if the patient weighed ≥ 70 kg or more and200 mg otherwise; Propafenone 600 mg if the patient weighed ≥ 70 kg and 450 mg otherwise) has success rate of 94%.

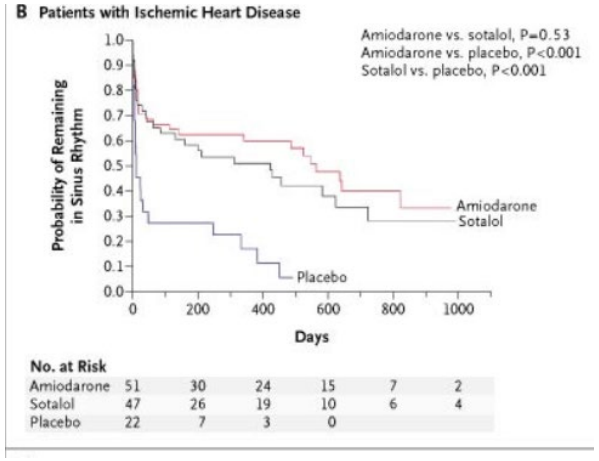
N Engl J Med 2004;351:2384-2391

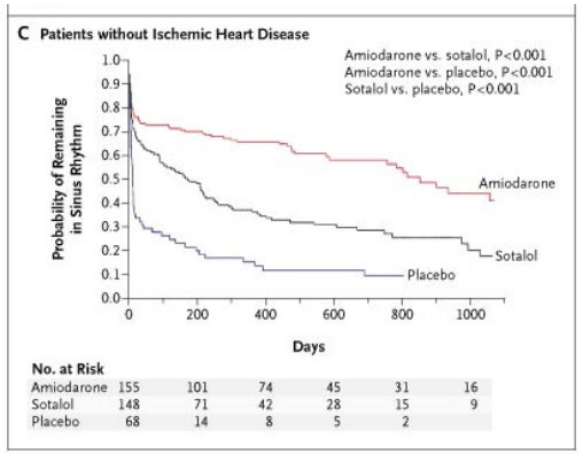
Treatment

Rate vs Rhythm control

- 665 patients with persistent atrial fibrillation were randomized to receive amiodarone (267 patients), sotalol (261 patients), or placebo (137 patients).

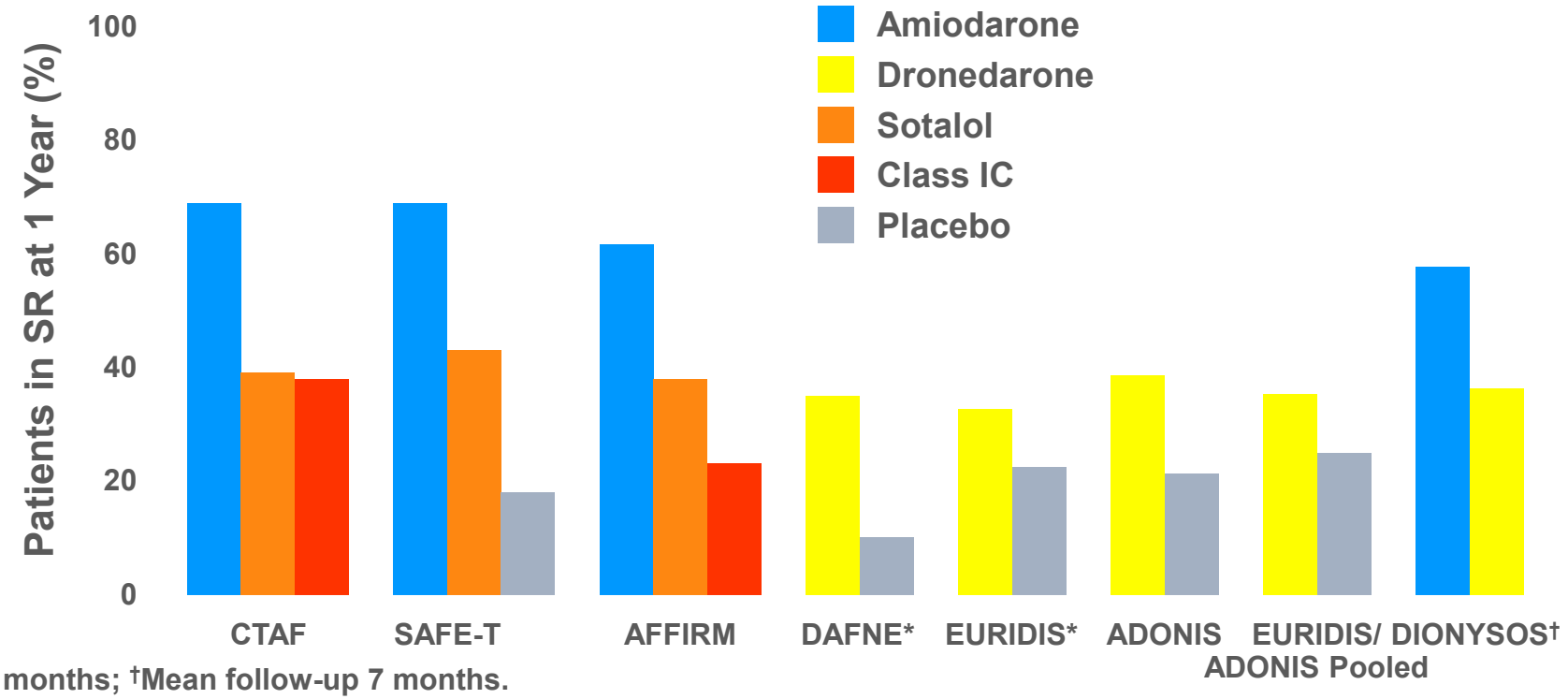






N Engl J Med 2005;352:1861-1872

Efficacy of anti-arrhythmic drugs in AF Trials



*At 6 months; †Mean follow-up 7 months.
CTAF = Canadian Trial of Atrial Fibrillation; SAFE-T = Sotalol Amiodarone Atrial Fibrillation Efficacy Trial; DAFNE = Dronedarone Atrial Fibrillation Study after Electrical Cardioversion; EURIDIS = European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm; ADONIS = American-Australian-African Trial with Dronedarone in Atrial Fibrillation or Flutter for the Maintenance of Sinus Rhythm; DIONYSOS = Randomized, Double-blind Trial to Evaluate the Efficacy and Safety of Dronedarone vs Amiodarone for at Least 6 Months for the Maintenance of Sinus Rhythm in Patients with AF.

Naccarelli G., et al. Clin Med Insights Cardiol 2011;5: 103-119; Roy D, et al. Am J Cardiol. 1997;80:464-468. Singh BN, et al. N Engl J Med. 2005;352(18):1861-1872. AFFIRM Investigators. J Am Coll Cardiol. 2003;42:20-29. Touboul P, et al. Eur Heart J. 2003;24:1481-1487. Singh BN, et al. N Engl J Med. 2007;357(10):987-999. Le Heuzey JY, et al. J Cardiovasc Electrophysiol. 2010;21:597-605.

Treatment

Rate vs Rhythm control

- Special consideration for anti-arrhythmic drugs

  - Class Ic (flecainide and propafenone): Use only in patients with no or mild structural heart disease, and no prior myocardial infarction.

  - Class III (sotalol and Dofetilide): Main concern is QTc prolongation (reverse-use dependence). Sotalol is usually initiated inpatient but can be initiated outpatient under certain conditions. Dofetilide can only be initiated as inpatient.

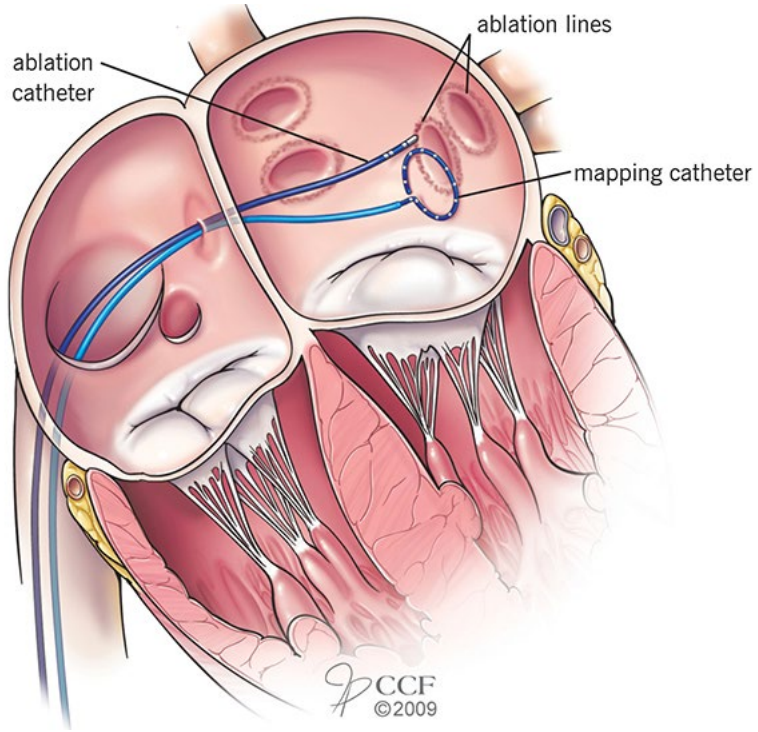
  - Amioderone (rate and rhythm control): Many extra-cardiac side effects. Causes QTc prolongation but does not increase risk of torsade de pointes

  - Dronedarone: Less side effects compared to amiodarone. It increases risk of death and adverse outcomes in patients with permanent atrial fibrillation who are at risk for major vascular events.

Treatment

Rate vs Rhythm control

- Ablation has been extensively studied (radiofrequency, cryoablation and pulse field ablation)
- Less studies on surgical ablation.

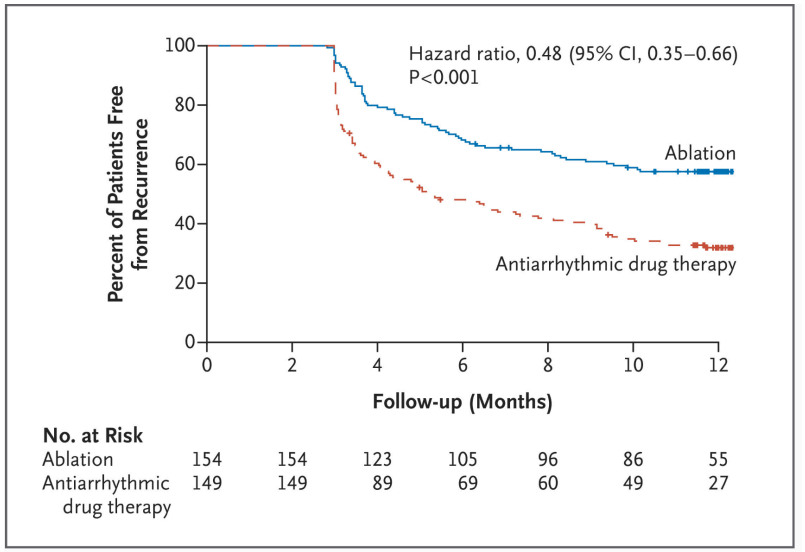


Treatment

Rate vs Rhythm control

- Trials of AF ablation commonly exclude the first 3 months after AF ablation, referred to as the blanking period). AF ablation reduces AF recurrence compared to placebo when excluding the first three months after the procedure.

Ablation	Sham procedure
60.31%	35.0%
AF burden changed from 78.52 to 18.21	AF burden changed from 78.19 to 43.19



Treatment

Rate vs Rhythm control

We have several strategies to terminate atrial fibrillation, but the questions is:

Which one is better? Rate or rhythm control?

Treatment

Rate vs Rhythm control

Numerous trials in this area (*AFFIRM, AF-CHF, PIAF, STAF, HOT CAFÉ, CASTLE AF, CABANA, EAST-AFENT 4, CASTLE HTx)*

- Mixed results but overall many trials were negative, and when positive, the absolute differences favoring rhythm control were generally not large.
  - Rate control is an acceptable primary therapeutic option for many patients.
- Rate control does not apply to all patients with AF:
  - Symptomatic patients despite rate control
  - Patients in whom exercise tolerance is important
  - Patients in whom rate control failed
  - Some patients with depressed LV function
- Adapt the therapeutic strategy to the individual

Treatment

Rate vs Rhythm control

- RACE II randomized patients with permanent atrial fibrillation to lenient rate-control strategy (resting heart rate <110 beats per minute) or a strict rate-control strategy (resting heart rate <80 beats per minute and heart rate during moderate exercise <110 beats per minute) and found no significant difference in outcomes.
- Resting heart rate <100 bpm (not a strict rule)
- In RACE II, and the end of the trial, strict rate control was 76 ± 14 bpm and Lenient rate control 85 ± 14 bpm [HR: 0.84 (0.58–1.21)]
- Ambulatory (Holter) heart rate ≤90 bpm
- Stress test: Peak heart rate 20% less than age-predicted maximum
- Rate to reverse tachycardia-induced cardiomyopathy not known

N Engl J Med 2010;362:1363-1373

Treatment

Rate vs Rhythm control

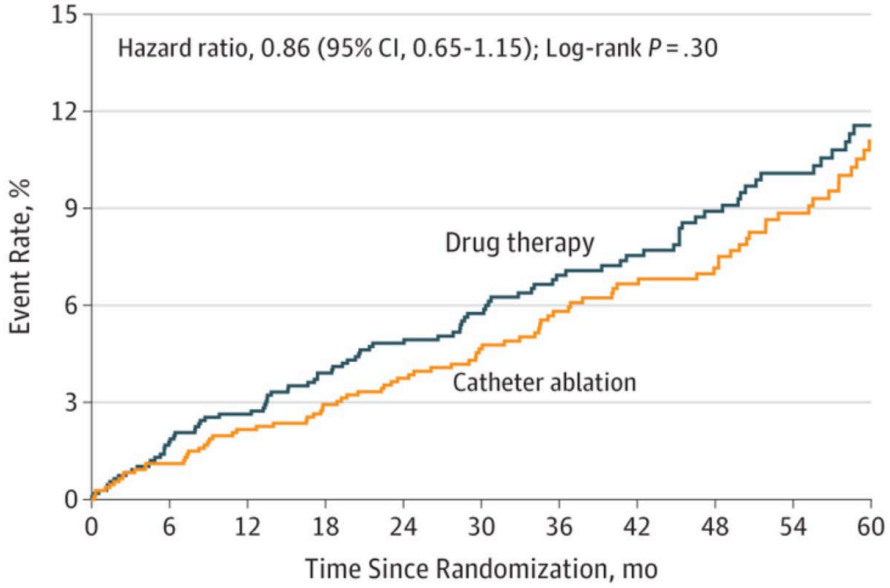
Original Investigation

Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation

The CABANA Randomized Clinical Trial

Douglas L. Packer, MD[1]; Daniel B. Mark, MD, MPH[2]; Richard A. Robb, PhD[1] ; et al

Figure 2. Kaplan-Meier Estimates of the Incidence of the Primary End Point



No. at risk											
Drug therapy	1096	1036	1006	970	880	763	652	578	499	418	312
Catheter ablation	1108	1045	1021	996	915	793	700	614	535	432	309

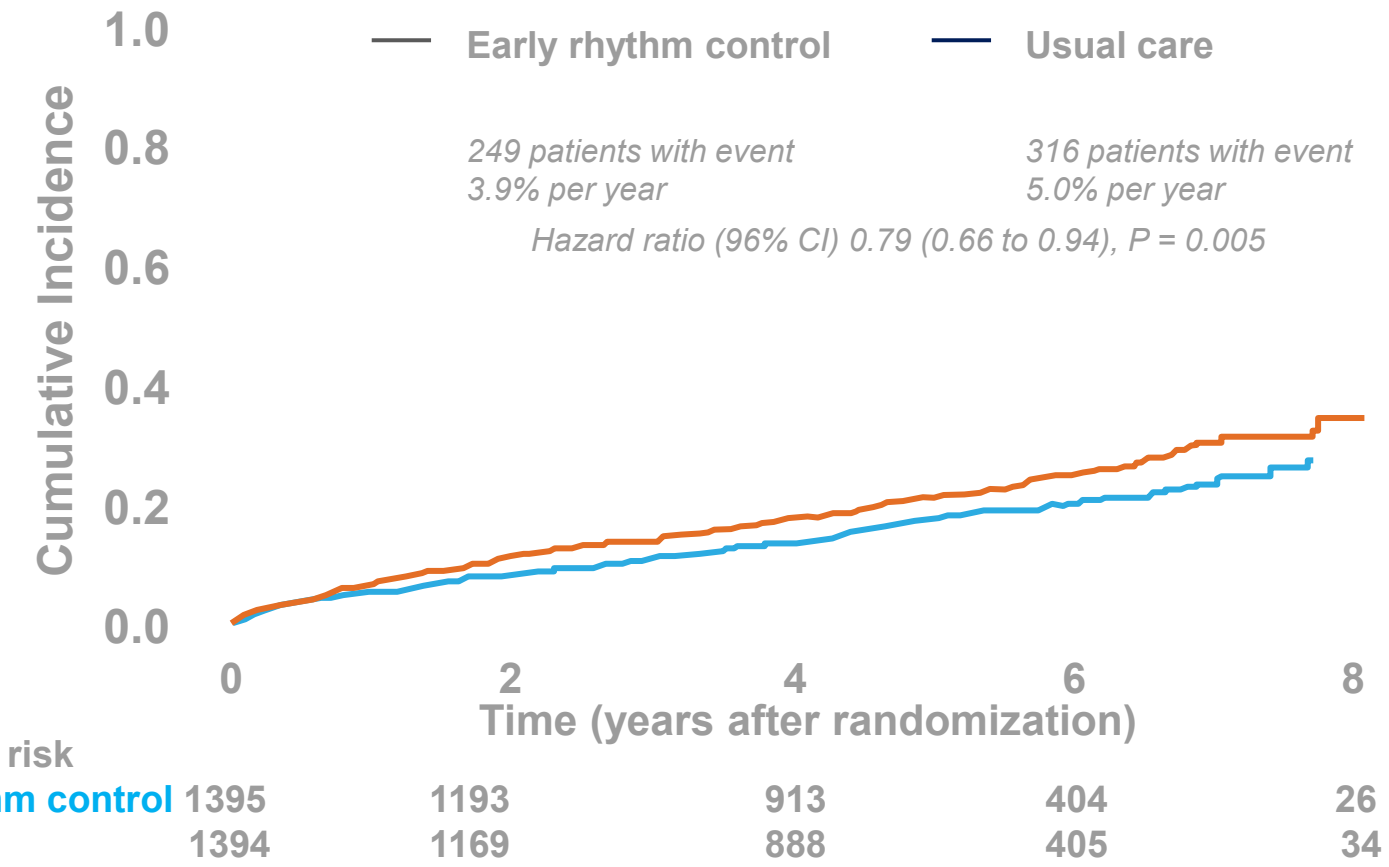
Treatment

Rate vs Rhythm control

EAST-AFNET 4 randomized patients with **early atrial fibrillation (diagnosed ≤1 year before enrollment)** to receive either early rhythm control(rhythm drugs or ablation) or usual care.

Primary outcome: **Composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome**

Sinus rhythm at 2 years: **82.1% in early rhythm control vs 60.5% in usual care study arm**



N Engl J Med 2020;383:1305-1316

Treatment

Rate vs Rhythm control (2023 American Guidelines)

COR	LOE	Recommendations
1	B-NR	1. In patients with AF, SDM with the patient is recommended to discuss rhythm- versus rate-control strategies (taking into consideration clinical presentation, comorbidity burden, medication profile, and patient preferences), discuss therapeutic options, and for assessing long-term benefits.[1–3]
2a	B-R	2. In patients with AF without HF who are candidates for select rate-control strategies, heart rate target should be guided by underlying patient symptoms, in general aiming at a resting heart rate of <100 to 110 bpm.[2,4–6]

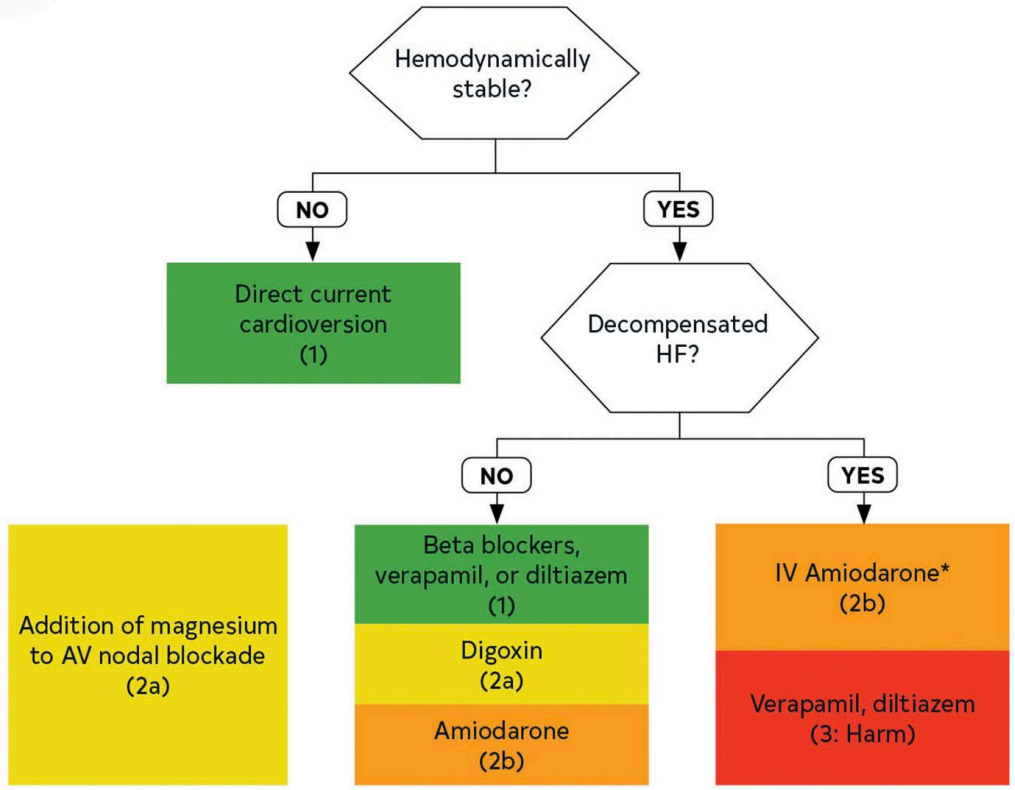
Treatment

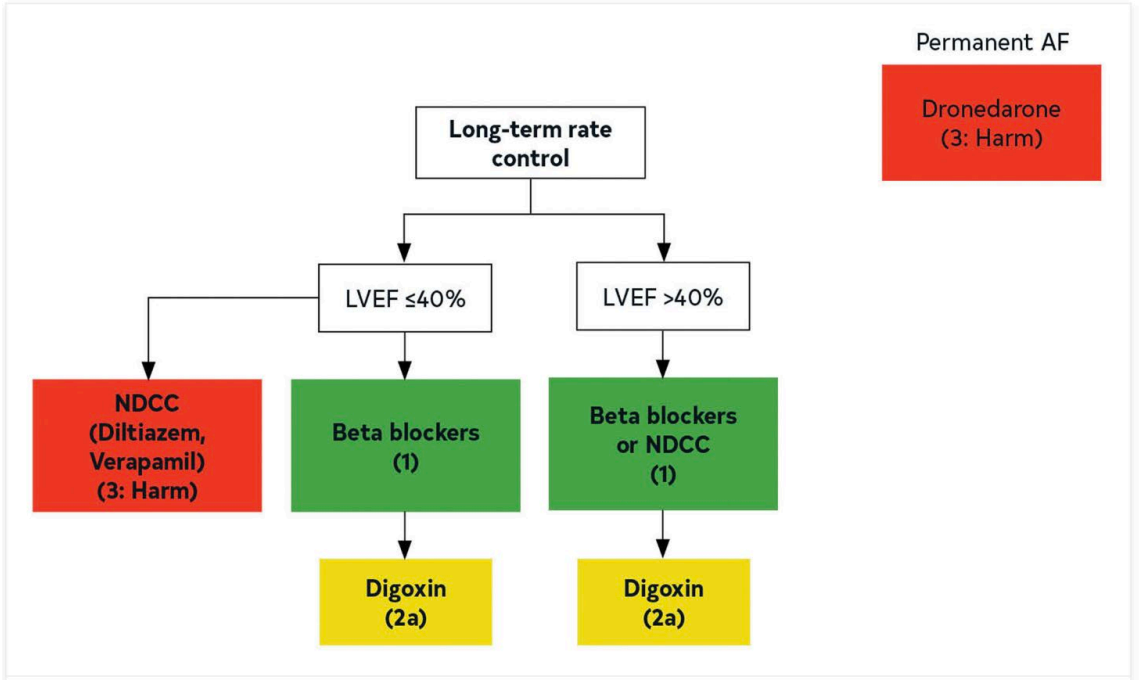
Rate vs Rhythm control (2023 American Guidelines)

COR	LOE	Recommendations
1	B-R	1. In patients with AF duration of ≥48 hours, a 3-week duration of uninterrupted therapeutic anticoagulation or imaging evaluation to exclude intracardiac thrombus is recommended before elective cardioversion.[1]
1	B-NR	2. In patients with AF undergoing cardioversion, therapeutic anticoagulation should be established before cardioversion and continued for at least 4 weeks afterwards without interruption to prevent thromboembolism.[2–7]
1	C-LD	3. In patients with AF in whom cardioversion is deferred due to LAA thrombus detected on precardioversion imaging, therapeutic anticoagulation should be instituted for at least 3 to 6 weeks, after which imaging should be repeated before cardioversion.[1,8]

Treatment

Rate vs Rhythm control (2023 American Guidelines)





Treatment

Rate vs Rhythm control (2023 American Guidelines)

COR	LOE	Recommendations
1	B-R	1. In patients with reduced LV function and persistent (or high burden) AF, a trial of rhythm control should be recommended to evaluate whether AF is contributing to the reduced LV function.[1–6]
2a	B-R	2. In patients with symptomatic AF, rhythm control can be useful to improve symptoms.[7–11]
2a	B-R	3. In patients with a recent diagnosis of AF (<1 year), rhythm control can be useful to reduce hospitalizations, stroke, and mortality.[12–14]
2a	B-R	4. In patients with AF and HF, rhythm control can be useful for improving symptoms and improving outcomes, such as mortality and hospitalizations for HF and ischemia.[15–19]
2a	B-NR	5. In patients with AF, rhythm-control strategies can be useful to reduce the likelihood of AF progression.[20–27]

Treatment

Strategies for stroke prevention - Medications

Risk Factor	Recommended Therapy based on guidelines
No risk factors CHA_2DS_2-VASc = 0 in men CHA_2DS_2-VASc = 1 in women	Nothing
CHA_2DS_2-VASc = 1 in men CHA_2DS_2-VASc = 2 in women	Nothing or DOACs (class 2a for DOACs)
CHA_2DS_2-VASc ≥2 in men CHA_2DS_2-VASc ≥3 in women	DOACs (preferred) or VKA
Mechanical valve and AF	VKA: INR 2.0-3.0 (AVR) VKA: INR 2.5-3.5 (MVR)
Moderate to severe rheumatic mitral stenosis and AF	VKA
Cardiac amyloidosis or hypertrophic cardiomyopathy	DOACs or VKA

Major Outcomes of DOACs vs warfarin

SUPERIOR INFERIOR NONINFERIOR

Outcome (RR ±95% CI)	RE-LY[1] (Dabigatran 150 mg BID)	ROCKET-AF[2] (Rivaroxaban 20 mg QDay)	ARISTOTLE[3] (Apixaban 5 mg BID)	ENGAGE-AF[4] (Edoxaban 60 mg QDay)
Stroke/SE	**0.66 (0.53-0.82)**	0.88 (0.75-1.03)	**0.79 (0.66-0.95)**	**0.79 (0.63-0.99)**
Ischemic stroke	**0.76 (0.60-0.98)**	0.94 (0.75-1.17)	0.92 (0.74-1.13)	1.00 (0.83-1.19)
Hemorrhagic stroke	**0.26 (0.14-0.49)**	**0.59 (0.37-0.93)**	**0.51 (0.35-0.75)**	**0.54 (0.38-0.77)**
Major bleeding	0.93 (0.81-1.07)	1.04 (0.90-1.20)	**0.69 (0.60-0.80)**	**0.80 (0.71-0.91)**
ICH	**0.40 (0.27-0.60)**	**0.67 (0.47-0.93)**	**0.42 (0.30-0.58)**	**0.47 (0.34 -0.63)**
GI	**1.50 (1.19–1.89)**	**1.39 (1.19–1.61)**	0.89 (0.70–1.15)	**1.23 (1.02–1.50)**
CV mortality	**0.85 (0.72-0.99)**	0.89 (0.73-1.10)	0.89 (0.76-1.04)	0.92 (0.83-1.01)
All-cause mortality	0.88 (0.77-1.00)	0.85 (0.70-1.02)	**0.89 (0.80-0.998)**	**0.86 (0.77-0.97)**

CV, cardiovascular; GI, gastrointestinal; ICH, intracranial hemorrhage. Black text indicates noninferior findings

1. Connolly SJ et al. *N Engl J Med*. 2009;363:1175-1176. 2. Patel MR et al. *N Engl J Med* 2011;365:883-891.
3. Granger CB et al. *N Engl J Med*. 2011;365:981-992. 4. Giugliano RP et al. *N Engl J Med*. 2013;369:2093-2104.

Currently Approved DOACs

Agent	Dosing	Comments
Dabigatran (Thrombin inhibitor)	**150mg bid** (CrCl >30 mL/min) or **75 mg bid** (CrCl 15-30 mL/min)	• Contraindicated if CrCl <15 mL/min or dialysis • Avoid use with P-gp inducers • Consider 75 mg bid if CrCl 30-50 mL/min and dronedarone
Rivaroxaban (Factor Xa inhibitor)	**20mg qd** (CrCl >50mL/min) or **15mg qd** (CrCl 15-50mL/min) with evening meal	• Avoid use if CrCl <15 mL/min or dialysis • If a dose is missed, administer dose ASAP (but do not administer 2 doses on same day)
Apixaban (Factor Xa inhibitor)	**5mg bid** with or without food **2.5mg bid** for 2 of the following: • age ≥80 years • body weight ≤60 kg • serum Cr ≥1.5 mg/dL	• If co-administered with strong dual inhibitors of CYP3A4 and P-gp 2.5 mg bid recommended • If on 2.5 mg dose – avoid/do not use • Avoid concomitant use with strong dual inducers of CYP3A4 and P-gp
Edoxaban (Factor Xa inhibitor)	**60 mg qd** (CrCl >50 and ≤95 mL/min) **30 mg qd** (CrCl 15-50 mL/min)	• Do not use if CrCl >95 mL/min • Avoid use with rifampin • No dose reduction with P-gp inhibitors

Treatment

Strategies for stroke prevention – Medications

- Which DOAC is better? No randomized trial comparing DOACs to each other.
- This large observational study found better outcomes with apixaban vs rivaroxaban.

Original Investigation FREE

Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Patients With Atrial Fibrillation

Wayne A. Ray, PhD[1]; Cecilia P. Chung, MD, MPH[2]; C. Michael Stein, MB, ChB[2,3] ; et al

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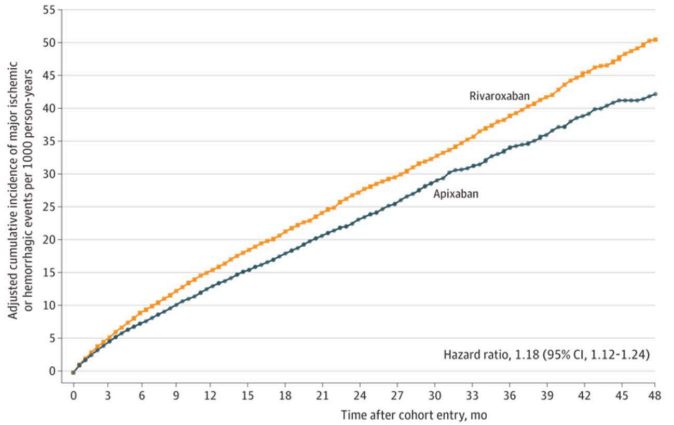
Figure 2. Primary Outcome in a Study of the Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Atrial Fibrillation



Treatment

Strategies for stroke prevention – Medications

- Trials of anticoagulation in atrial fibrillation included patients with paroxysmal or persistent atrial fibrillation documented on an EKG.

- The wide spread use of of monitoring devices created a new therapeutic question - What do we do for patients with asymptomatic atrial fibrillation caught on devices?

Treatment

Strategies for stroke prevention – Medications

The LOOP study

- Randomized controlled trial. Included individuals without AF, aged 70–90 years, with at least one additional stroke risk factor (ie, hypertension, diabetes, previous stroke, or heart failure).
- Participants were randomly assigned in a 1:3 ratio to ILR monitoring or usual care.
- In the ILR group, anticoagulation was recommended if AF episodes lasted ≥ 6 min.
- The primary outcome was time to first stroke or systemic arterial embolism.
- Atrial fibrillation was diagnosed in 31.8% in ILR group vs. 12.2% in the control group.
- Primary outcome was 4·5% in the ILR group vs. 5.6% in the control group (HR 0.80, 95% CI 0.61 - 1.05; p= 0.11).
- Major bleeding was 4·3% in the ILR group vs. 3·5% in the control group (HR 1.26, 95% CI 0.95 – 1.69; p= 0.11).

Svendsen JH et al. Lancet. 2021;398(10310):1507-1516.

Treatment

Strategies for stroke prevention – Medications

ARTESIA trial

- Enrolled patients with subclinical AF detected by an implanted pacemaker, defibrillator, or cardiac monitor, with at least one episode lasting ≥6 min but <24 hours.
- Eligible patients also had a CHA_2DS_2-VASc ≥ 3.
- Randomized to receive apixaban 5 mg BID (2.5 mg BID when indicated) or aspirin 81 mg daily.
- A total of 4,012 patients were randomized.
- The primary outcome of stroke or systemic embolism occurred in 0.78%/ patient-year with apixaban and 1.24%/ patient-year with aspirin (HR:0.63; 95% CI: 0.45 - 0.88; P=0.007).
- In the on-treatment population, major bleeding was 1.71%/ patient-year with apixaban vs 0.94%/ patient-year with aspiring (HR:1.80; 95% CI: 1.26 - 2.57; p=0.001).
- Subgroup analysis showed benefit only for CHA_2DS_2-VASc ≥ 5.

N Engl J Med 2024;390:107-117.

Lopes RD et al. J Am Coll Cardiol. 2024;84(4):354-364.

Treatment

Strategies for stroke prevention – Medications

NOAH-AFNET 6 trial

- Patients ≥65 years with atrial high rate episodes detected by implanted devices and no history of atrial fibrillation.
- Eligible patients also had a CHA_2DS_2-VASc ≥2.
- A qualifying event had to involve an atrial rate of ≥170 beats per minute and had to ≥6 minutes.
- Patients randomly assigned in a 1:1 ratio to receive edoxaban (anticoagulation) or placebo.
- The trial randomized 2,536 patients.
- A primary outcome (cardiovascular death, stroke, or systemic embolism) occurred in 3.2%/ patient-year in the edoxaban group vs 4.0%/ patient-year in the placebo group (HR: 0.81; 95% CI: 0.60 - 1.08; p= 0.15).
- A safety outcome (all-cause death or major bleeding) occurred in 5.9%/ patient-year in the edoxaban group vs. 4.5%/ patient-year in the placebo group (HR: 1.31; 95% CI, 1.02 - 1.67; P= 0.03).

N Engl J Med 2023;389:1167-1179.

Strategies for stroke prevention – Medications

What do we do after AF ablation? Still an area of ongoing research.

ALONE-AF trial

- A randomized trial including 840 adult patients who had no documented recurrence of atrial arrhythmia for at least 1 year after catheter ablation for AF.
- Patients were randomized to discontinue oral anticoagulant therapy or continue it.
- Ischemic stroke was 0.3% in the discontinuation group vs 0.8% in the continuation group.
- Major bleeding occurred in 0 patients in the discontinuation group vs 5 patients (1.4%) in the continuation group.

Kim D et al. JAMA. 2025 31:e2514679.

Treatment

Strategies for stroke prevention – Medications

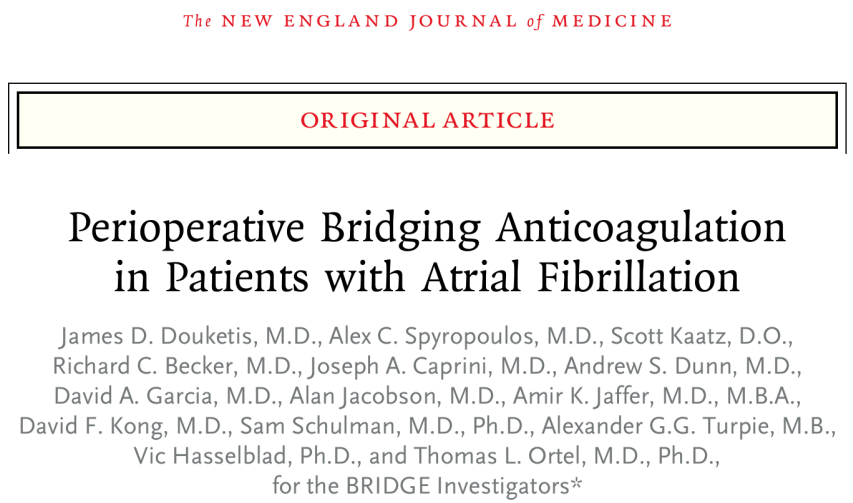
What do we do for patients with infrequent AF episodes? Also an area of ongoing research.

REACT-AF trial– ongoing

- Randomized (1:1 allocation), multi-center, trial enrolling patients with documented history of symptomatic or asymptomatic paroxysmal or persistent AF and a moderate risk of stroke.
- Patients randomized to the experimental arm will take DOAC for 30 consecutive days following a qualifying AF episode (I.e., greater than1 hour) detected by an Apple watch.
- Patients randomized to the standard of care (control) arm will remain on previously prescribed continuous DOAC throughout the study.
- A total of 5350 participants will be enrolled across up to 100 study sites.

Treatment

Strategies for stroke prevention – Medications



- Arterial thromboembolism: 0.3% LMWH vs. 0.4% placebo(p= 0.01; noninferiority)
- Major bleeding: 3.2% LMWH vs. 1.2% placebo(p= 0.005; superiority)

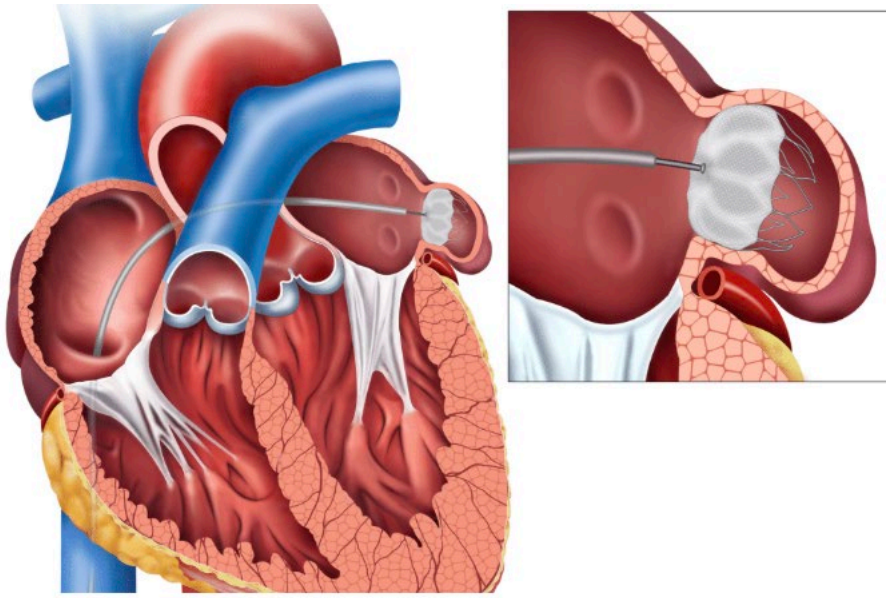
Treatment

Strategies for stroke prevention - Medications

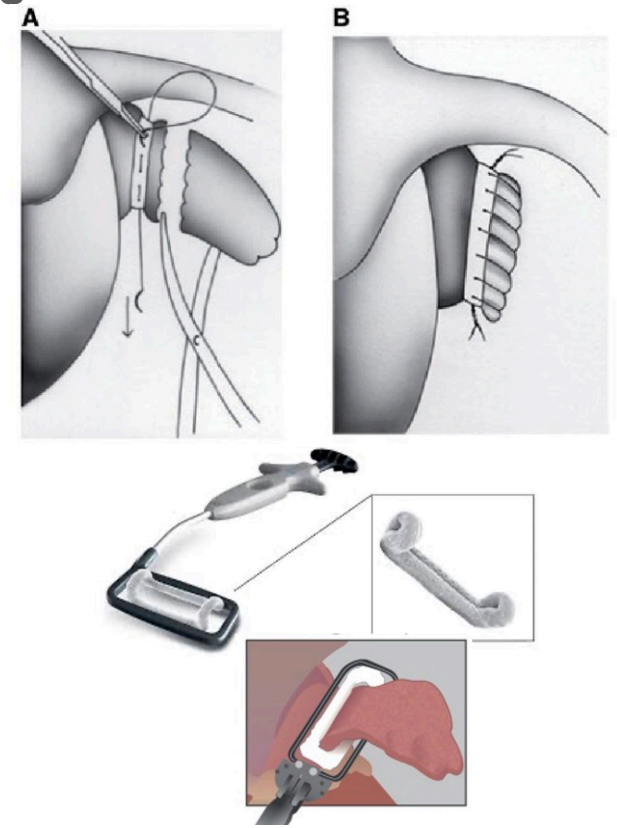
Recommendations for Periprocedural Management Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	**LOE**	**Recommendations**
1	B-R*	1. In patients with AF (excluding those with recent stroke or TIA, or a mechanical valve) and on oral anticoagulation with either warfarin* or DOAC† who are scheduled to undergo an invasive procedure or surgery, temporary cessation of oral anticoagulation without bridging anticoagulation is recommended.[1–4]
	B-NR†	
1	A	2. In patients with AF on warfarin anticoagulation and an annual predicted risk of thromboembolism of ≥5% undergoing pacemaker or defibrillator implantation or generator change, continued anticoagulation is recommended in preference to interruption of warfarin and bridging anticoagulation with heparin to reduce the risk of pocket hematoma.[5–7]

Treatment

Strategies for stroke prevention – non-pharmacological



Percutaneous



Surgical

Treatment

Strategies for stroke prevention – non-pharmacological

Recommendation	Class[a]	Level[b]
Percutaneous LAA occlusion may be considered in patients with AF and contraindications for long-term anticoagulant treatment to prevent ischaemic stroke and thromboembolism.[372,376,386,387]	IIb	C

AF, atrial fibrillation; LAA, left atrial appendage.
[a]Class of recommendation.
[b]Level of evidence.

Recommendations for Percutaneous Approaches to Occlude the LAA
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
2a	B-NR	1. In patients with AF, a moderate to high risk of stroke (CHA_2DS_2-VASc score ≥2), and a contraindication (Table 14) to long-term oral anticoagulation due to a nonreversible cause, percutaneous LAAO (pLAAO) is reasonable.[1–4]
2b	B-R	2. In patients with AF and a moderate to high risk of stroke and a high risk of major bleeding on oral anticoagulation, pLAAO may be a reasonable alternative to oral anticoagulation based on patient preference, with careful consideration of procedural risk and with the understanding that the evidence for oral anticoagulation is more extensive.[1–3,5,6]

Treatment

Strategies for stroke prevention – non-pharmacological

The percutaneous left atrial appendage occlusion (pLAAO) trials and recommendation are an area of considerable debate.

Things to know/ consider

- The five trials (PROTET-AF, PREVAIL, PRAGUE-17, WATCH-TAVR and OPTION, collectively randomized 3465 patients compared to the the initial four trials comparing DOACs to warfarin which collectively enrolled over 71,000 patients.
- The trials of pLAAO did not show significant reduction in major bleeding (when all are counted).
- Competing risks for stoke minimize the benefit of an isolated procedure.

Strategies for stroke prevention – non-pharmacological

More things to know/ consider

- In aspirin really safer than DOACs?

Major bleeding – DOACs vs aspirin

Trial	DOAC	Aspirin	P value
AVERROES (apixaban vs aspirin)	1.6%	1.4%	0.57
ARTESIA (apixaban vs aspirin)	5.3%	3.9%	0.04
EINSTEIN CHOICE (rivaroxaban vs aspirin)	0.5%	0.3%	0.32
NAVIGATE ESUS (rivaroxaban vs aspirin)	1.8%	0.7%	<0.001

Treatment

Strategies for stroke prevention – non-pharmacological

The pLAAO trials and recommendation are an area of considerable debate.

More things to know/ consider

- Patients may need anticoagulants/ antiplatelets for other reasons.

Medications after percutaneous LAA in Medicare beneficiaries

Medication	0-3 months	3-6 months	6-12 months
DOACs	47.0%	10.6%	7.4%
warfarin	42.4%	10.5%	2.2%
Antiplatelets (other than aspirin)	77.3%	75.2%	55.0%

Treatment

Strategies for stroke prevention – non-pharmacological

CLOSURE-AF trial (presented at the AHA in 2025)

- 888 patients randomized to pLAAO or best medication care.
- Average age 78 years.
- Over a median of 3 years, LAAO did not meet noninferiority criteria for the estimated cumulative incidence of the primary endpoint [a composite of stroke, systemic embolism, cardiovascular/unexplained death, or major bleeding (BARC ≥ 3)].
- Incidence was 16.83 per 100 person-years for LAAO and 13.27 per 100 person-years for standard (HR:1.28, 95% CI 1.01 - 1.62).

Treatment

Strategies for stroke prevention – non-pharmacological

Bottom line

We need a pragmatic trial of percutaneous LAA!

Treatment

Strategies for stroke prevention – non-pharmacological

Recommendations	Class[a]	Level[b]
Surgical closure of the left atrial appendage is recommended as an adjunct to oral anticoagulation in patients with AF undergoing cardiac surgery to prevent ischaemic stroke and thromboembolism.[400,401,408–412]	I	B

Recommendations for Cardiac Surgery—LAA Exclusion/Excision
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	A	1. In patients with AF undergoing cardiac surgery with a CHA_2DS_2-VASc score ≥2 or equivalent stroke risk, surgical LAA exclusion, in addition to continued anti-coagulation, is indicated to reduce the risk of stroke and systemic embolism.[1–3]