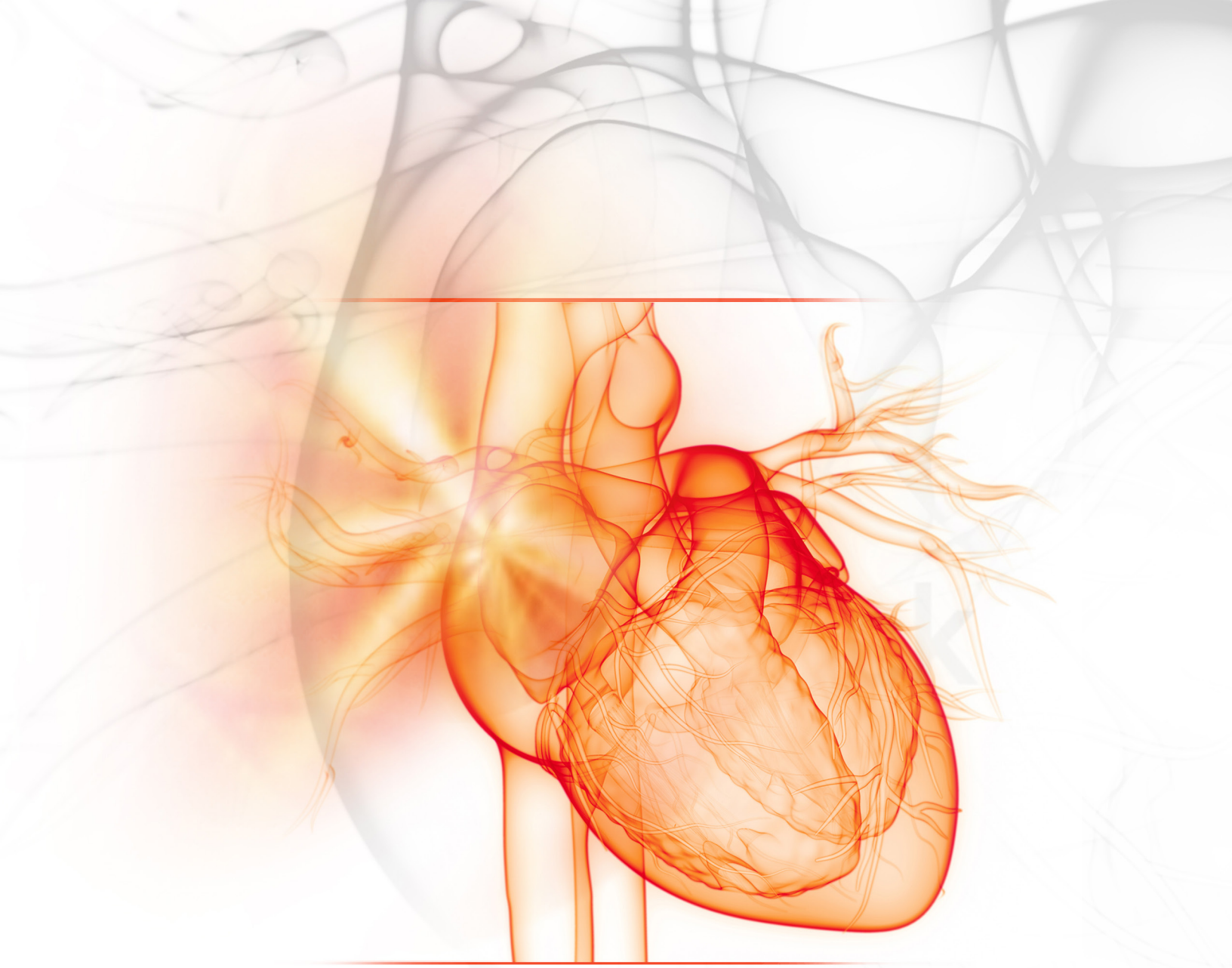

Using Antiarrhythmic Drugs for the Early Management of Rhythm Control in Atrial Fibrillation:

WHICH OF YOUR PATIENTS MAY BENEFIT FROM THIS APPROACH?

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This activity is supported by an educational grant from Sanofi US.

Using Antiarrhythmic Drugs for the Early Management of Rhythm Control in Atrial Fibrillation: Which of Your Patients May Benefit from This Approach?

PROGRAM CHAIR

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PROGRAM OVERVIEW

This live virtual activity targets healthcare gaps related to the treatment and management of atrial fibrillation (AF), impacting outcomes through guidelines and best practices, appropriate antiarrhythmic use, and shared decision-making.

- By addressing these gaps, you can assess whether your approach to AF management through utilization of current treatment guidelines, individualization of antiarrhythmic use and strategies for shared decision making – could be modified to help close these gaps.
- Expert discussion will guide you in analyzing and identifying appropriate candidates for antiarrhythmic intervention, utilizing clinical trial and real-world data on efficacy, and safety to affect patient outcomes.
- You will also be immersed in dynamic animations utilizing a whiteboard platform to memorably highlight key points related to antiarrhythmic mechanisms of action and consequences related to interactions with other cardiovascular agents.

TARGET AUDIENCE

This activity is designed to meet the educational needs of US-based general cardiologists, internal medicine physicians, and primary care physicians involved in the care of patients with AF.

LEARNING OBJECTIVES

After completing the CME activity, learners should be better able to:

- Discuss current guidelines and best practices to improve outcomes for patients with AF in clinical practice
- Review clinical trial and real-world data on the efficacy and safety of antiarrhythmic drugs used for the management of AF
- Adopt shared decision-making approaches aimed at improving patient outcomes in clinical practice

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Purpose: This program would be beneficial for nurses involved and/or interested in the care of patients with atrial fibrillation.

Credits: 1.0 ANCC Contact Hour

CNE Accreditation Statement: Ultimate Medical Academy/Complete Conference Management (CCM) is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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Dr. Kenneth Ellenbogen has nothing to disclose.

Dr. Peter Kowey has received consulting fees from Sanofi, and Medtronic; he also has ownership interest in Biotelemetry.

Dr. John Osborne has nothing to disclose.

Dr. James Reiffel has received consulting fees from Medtronic, Sanofi, Janssen/J&J, Correvio, and Amarin; he has also served on the speakers' bureau for Sanofi, and provides research support to Janssen/J&J.

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The reviewer of this activity has nothing to disclose.

CNE Content Review

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The reviewer of this activity has nothing to disclose.

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2. Participate in the live virtual activity; and
3. Complete pre-and-post surveys and evaluation.

You will receive your certificate as a downloadable file.

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Program Agenda

I. **Pharmacotherapeutic Management of AF**
   a. Rhythm control as goal of pharmacotherapy
   b. Unique MOAs and clinical profiles of currently available AADs for the management of patients with AF ***(Animated Theme: MOAs of AADs used for the management of patients with AF)***

II. Individualizing Patient Management
   a. Goals: Decrease symptoms, improve patient QoL and clinical outcomes, relieve AF-associated economic burdens (eg, hospitalizations)
   b. Recommendations for the selection of AADs based on patient-specific factors
   c. Effects of early rhythm-control therapy on patient outcomes in patients with AF
   d. Implications for placement of AADs in evidence-based management guideline recommendations and treatment algorithms
   e. Important considerations in AAD selection ***(Animated Theme: pathophysiologic consequences of interactions between AADs and other cardiovascular drugs)***

III. **SDM as an Additional Component of Individualizing Patient Management**
   a. Goals of SDM approaches to the management of patients with AF
   b. Applying SDM approaches to the management of patients with AF in clinical practice
   c. Barriers to implementation and strategies to overcome them

IV. Conclusions

Using Antiarrhythmic Drugs for the Early Management of Rhythm Control in Atrial Fibrillation:
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Gerald V. Naccarelli, MD
Bernard Trabin Chair of Cardiology
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Disclosures

- Please see Program Overview for specific speaker disclosure information.
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- This educational activity is applicable for CME and CNE credits. Please complete the necessary electronic evaluation to receive credit.

Educational Objectives

- Discuss current guidelines and best practices to improve outcomes for patients with atrial fibrillation (AF) in clinical practice
- Review clinical trial and real-world data on the efficacy and safety of antiarrhythmic drugs used for the management of AF
- Adopt shared decision-making approaches aimed at improving patient outcomes in clinical practice

AF: A Significant Healthcare Issue

AF affects ~ **3–6 million people** in the US; it is important to differentiate:

- AF is associated with increases in aging and chronic heart disease, especially HF
- **Median age 75 yrs**, although *70% are between 65 and 85 yrs and 84% >65 yrs*

AF *frequently* presents with comorbidities; does this complicate AF management?	→	Comorbidities complicate AF management ⟷ AF complicates comorbidity management
Is hospitalization for AF common or uncommon?	→	*Most common arrythmia* requiring hospitalization (454,000 hospital hospitalizations with AF as primary diagnosis)
AF is associated with stroke, HF, and death. How many deaths does **AF contribute to per year**?	→	**158,000** patient deaths/year
Is AF incidence over, under, or appropriately estimated?	→	**Underestimated** due to lack of symptoms; silent AF (45% of SPAF III study had AF detected incidentally)

AF = atrial fibrillation; HF = heart failure; yr(s) = year(s).

Fuster V, et al. *Circulation*. 2006;114:700-752. Thom T, et al. *Circulation*. 2006;113:e85-e151. Feinberg WM, et al. *Arch Intern Med*. 1995;155:469-473. Waktare JE, Camm AJ. *Am J Cardiol*. 1998;81:3C-15C. Benjamin EJ, et al. *Circulation*. 1998;98:946-952. Wang TJ, et al. *Circulation*. 2003;107:2920-2925. Miyasaka Y, et al. *Circulation*. 2006;114:119-125. Chugh SS, et al. *J Am Coll Cardiol*. 2001;37:371-378. Centers for Disease Control and Prevention (CDC). What is AF, 2020 (www.cdc.gov/heartdisease/atrial_fibrillation.htm). American College of Cardiology (ACC). Impact and consequences of AF, 2018 (www.acc.org/latest-in-cardiology/articles/2018/08/06/12/42/cover-story-impact-and-consequences-of-atrial-fibrillation). URLs accessed 10/19/2020.

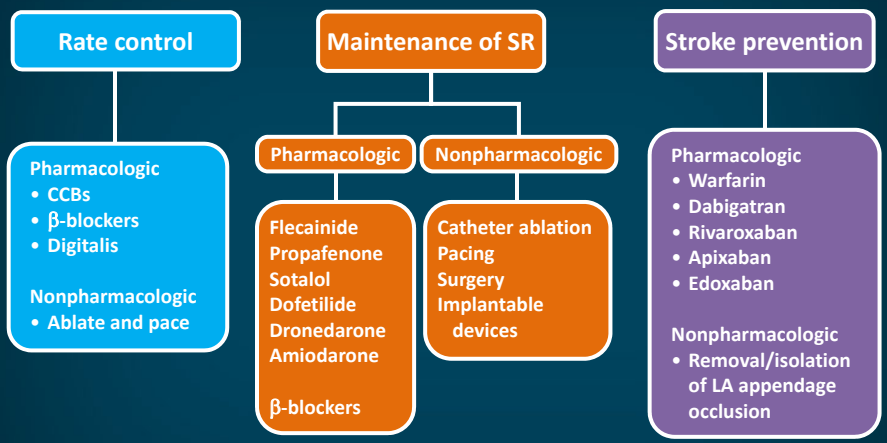
AF-Related Outcomes

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/HF	In 20–30% of patients with AF	Excessive ventricular rate, irregular ventricular contractions; primary underlying cause of AF
Cognitive decline/ vascular dementia	HR = 1.4 to 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 QoL	>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; HR = hazard ratio; MI = myocardial infraction.

Hindricks G, et al. *Eur Heart J*. 2021;42:373-498.

Treatment Options for AF



CCB = calcium channel blocker; SR = sinus rhythm; LA = left atrial.

ACC. 2014 guidelines. (http://eguideline.guidelinecentral.com/i/387793-atrial-fibrillation/0?m4=). Accessed 10/5/2020. January CT, et al. *J Am Coll Carciol.* 2019;74:104-132.

Anticoagulant, Antiplatelet, or Neither
Current Guidelines

Risk Factor	Recommended Therapy	
	ESC	AHA/ACC/HRS
No risk factors CHA_2DS_2-VASc = 0 in men CHA_2DS_2-VASc = 1 in women	Prefer neither, or OAC vs antiplatelet (consider bleeding complications and patient preferences)	Neither
CHA_2DS_2-VASc = 1 in men CHA_2DS_2-VASc = 2 in women	Prefer OAC, or ASA 75–325 mg daily	Neither or ASA or OAC
CHA_2DS_2-VASc ≥2 in men CHA_2DS_2-VASc ≥3 in women	TSOAC > VKA	TSOAC or VKA
Mechanical valve (modern)	VKA: INR 2.0–3.0 (AVR) VKA: INR 2.5–3.5 (MVR)	

ESC = European Society of Cardiology; AHA = American Heart Association; HRS = Heart Rhythm Society; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 yrs (doubled), diabetes mellitus, prior stroke or transient ischemic attack thromboembolism (doubled), vascular disease, age 65–74 yrs, sex category (female); ASA = acetylsalicylic acid; OAC = oral anticoagulant; TSOAC = target-specific OAC; VKA = vitamin K antagonist (eg, warfarin); AVR = aortic valve replacement; MVR = mitral valve replacement; INR = international normalized ratio.

January CT, et al. *J Am Coll Cardiol.* 2014;64:e1-e76. January CT, et al. *Circulation.* 2019;74:104-132. Nishimura RA, et al. *J Am Coll Cardiol.* 2017;70:252-289. Hindricks G, et al. *Eur Heart J.* 2021;42:373-498.

AF: Heart Rate Goal

- Resting (apical) heart rate ≤80 bpm
- In RACE II (HR = 0.84, 95% CI, 0.58–1.21)
  - Strict rate control was 76 ± 14 bpm
  - Lenient rate control was 85 ± 14 bpm
- 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

CI = confidence interval; bpm = beats per minute.

Wyse DG, et al. *N Engl J Med*. 2002;347:1825-1833. Van Gelder IC, et al. *N Engl J Med*. 2010;362:1363-1373.

Rhythm and Rate Control in AF
AFFIRM, RACE, AF-CHF, PIAF, STAF, and HOT CAFÉ Trials

Major overall findings

- Rhythm control was **NOT** superior to rate control in terms of morbidity/mortality
- *Rate* control is **acceptable primary therapeutic option**
- Patients with AF and risk factors for stroke should receive anticoagulation indefinitely, even when SR appears to be restored and maintained

Both strategies are acceptable *but*…

Rate control does not apply to all patients with AF

- Particularly those who are symptomatic despite rate control
- Patients in whom exercise tolerance is important
- Patients in whom rate control failed
- Some patients with depressed LV function

Clinicians should adapt the therapeutic strategy to the individual

Hohnloser SH, et al. *Lancet*. 2000;356:1789-1794. Wyse DG, et al. *N Engl J Med*. 2002;347:1825-1833. Van Gelder IC, et al. *N Engl J Med*. 2002;347:1834-1840. Opolski G, et al. *Chest*. 2004;126:476-486. Vora A, et al. *J Cardiovasc Pharmacol Ther*. 2004;9:65-73. Ogawa S, et al. *Circ J*. 2009;73:242-248. Carlsson J, et al. *J Am Coll Cardiol*. 2003;41:1690-1696. Roy D, et al. *N Engl J Med*. 2008;358:2667-2677. Reiffel, J. *J Atr Fibrillation*. 2008;1:40-52.

Rate vs Rhythm-Control Studies: Other Findings

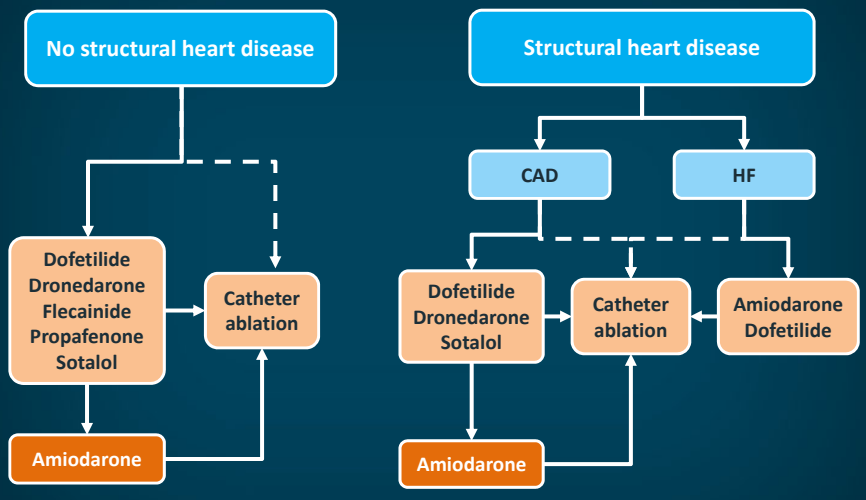
Study	Findings
J-RHYTHM*	Rhythm control improved primary endpoint (*P*= .0128)
SAFE-T	• Maximal exercise duration better in SR group at 8 wks (*P*= .01) and 1 yr (*P*= .02) • QoL more likely to improve in symptomatic patients
STAF	Remaining in AF had higher risk for embolic events (pNS rate vs rhythm)
PIAF	Exercise tolerance better in NSR group
Gillinov A et al	No difference in outcomes after cardiac surgery
ORBIT-AF	• No difference in outcomes • Rhythm control was associated with more CV hospitalizations hazard ratio = 1.24 (1.10-1.39), *P* = .0003
RACE	In sinus rhythm, LV function significantly improved (*P* <.05)

***Studied composite of total mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalization for HF, or physical/psychological disability requiring alteration of treatment strategy.**

wk(s) = week(s); pNS = P-value not significant; NSR = normal sinus rhythm.

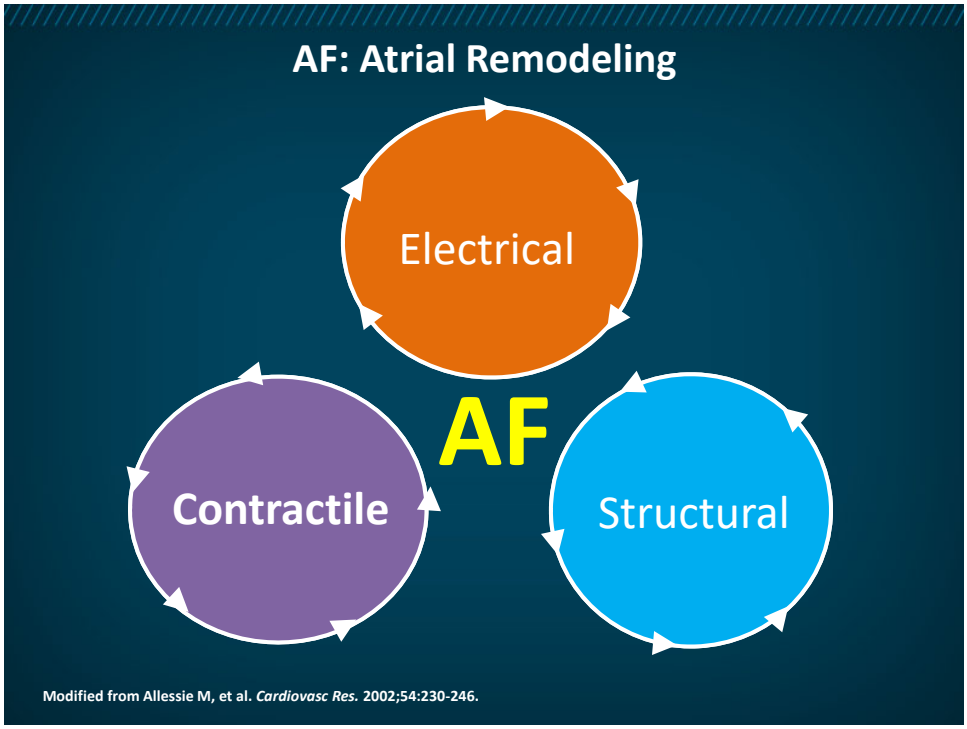
Ogawa S, et al. *Circ J.* 2009;73:242-248. Singh SN, et al. *J Am Coll Cardiol.* 2006;48:721-730. Hagens VE, et al. *Heart Rhythm.* 2005;2:19-24. Carlsson J, et al. *J Am Coll Cardiol.* 2003;41:1690-1696. Gillinov AM, et al. *N Engl J Med.* 2016;374:1911-1921. Noheria A, et al. *JACC Clin Electrophysiol.* 2016;2:221-229. Hohnsloser SH, et al. *Lancet.* 2000;356:1789-1794.

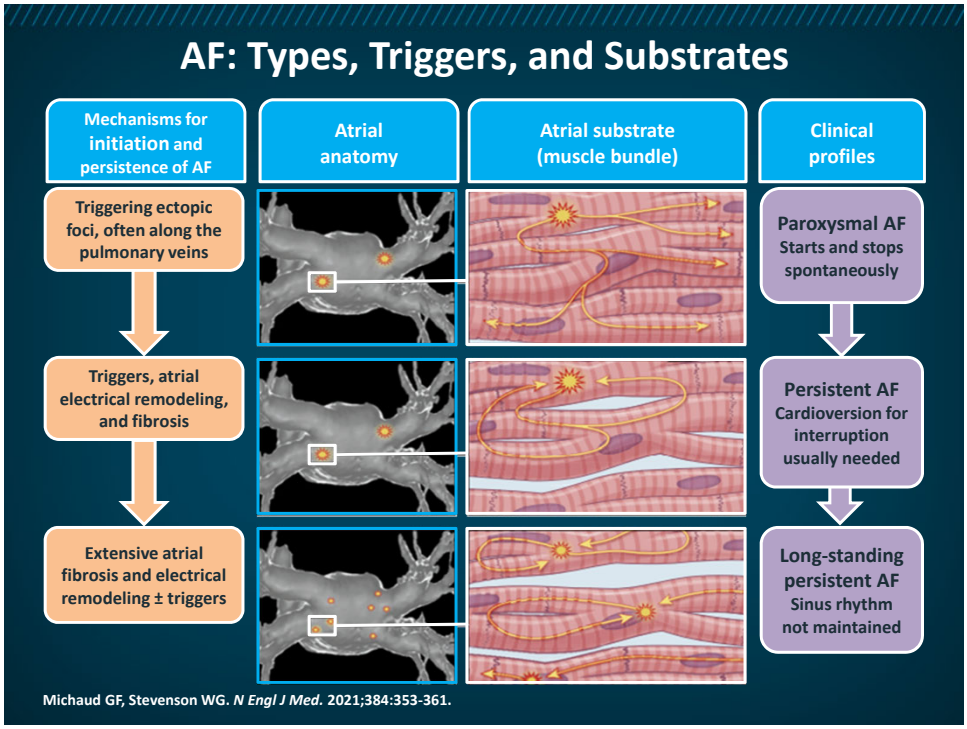
AHA/ACC/HRS: AF Rhythm Control



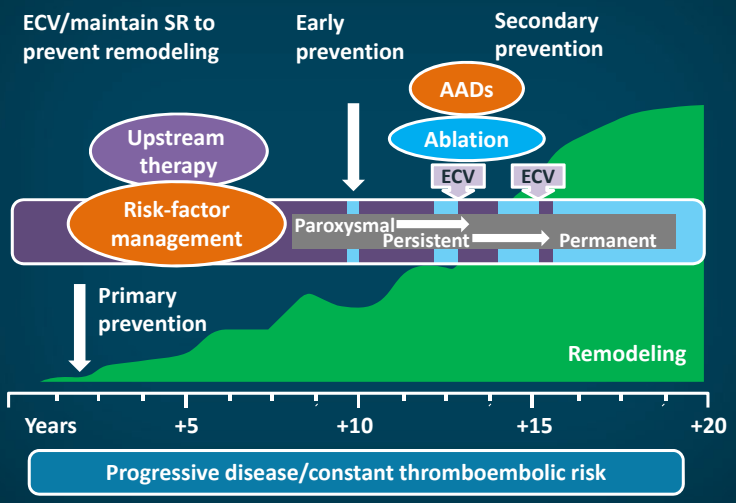
CAD -= coronary artery disease.

ACC. 2014 ACC guidelines. (http://eguideline.guidelinecentral.com/i/387793-atrial-fibrillation/17?m4=). Accessed 10/5/2020.
January CT, et al. *J Am Coll Cardiol.* 2014;64:e1-e76.


AF: Atrial Remodeling
Electrical
AF
Contractile
Structural
Modified from Allessie M, et al. Cardiovasc Res. 2002;54:230-246.


AF: Types, Triggers, and Substrates
Mechanisms for initiation and persistence of AF
Atrial anatomy
Atrial substrate (muscle bundle)
Clinical profiles
Triggering ectopic foci, often along the pulmonary veins
Triggers, atrial electrical remodeling, and fibrosis
Extensive atrial fibrosis and electrical remodeling ± triggers
Paroxysmal AF
Starts and stops spontaneously
Persistent AF
Cardioversion for interruption usually needed
Long-standing persistent AF
Sinus rhythm not maintained
Michaud GF, Stevenson WG. N Engl J Med. 2021;384:353-361.

Maintaining NSR May Slow Down AF Disease Progression



AAD = antiarrhythmic drug; ECV = extracellular volume fraction.

Modified from Cosio FG, et al. *Europace*. 2008;10:21-27.

Case Study

- A 66-y-old male has 2-year history of symptomatic PAF (causing palpitations and dyspnea) with episodes lasting 2–6 hours
- He has a history of HTN managed with metoprolol succinate 100 mg daily; he also has hyperlipidemia
- His ventricular rate during PAF dropped from 125 to 80 bpm after metoprolol succinate was increased to 150 mg daily
- Family history is positive for CAD and MI (father at age 55 years)
- Past history is negative for DM, stroke, CAD, or CHF; he quit smoking 20 years ago
- Other medications: simvastatin 20 mg daily, losartan 50 mg daily, and rivaroxaban 20 mg daily with evening meal

PAF = paroxysmal atrial fibrillation; HTN = hypertension; MI = myocardial infarction; DM = diabetes mellitus; CHF = congestive heart failure.

Case Study: Question 1

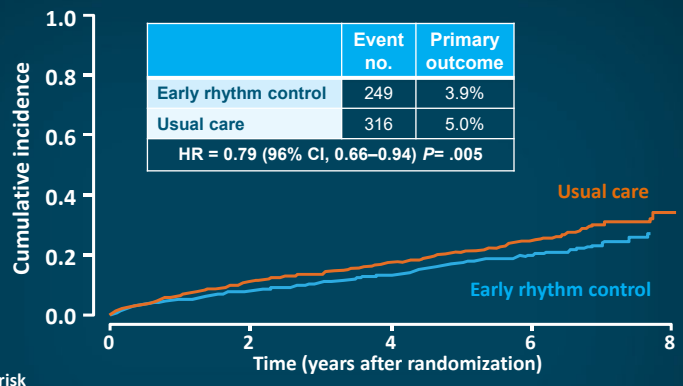
- Labs: TSH is normal; CrCl = 88 ml/min
- ECG: sinus rhythm with rate of 64 bpm; normal with QT interval corrected for heart rate (QTc) of 438 msec
- Echocardiogram: LVEF = 60%; LV wall thickness = 1.2 cm; LA diameter = 4.1 cm
- Stress nuclear study in last year: normal LVEF (60%) with no evidence of ischemia

What is the best first option for rhythm control in this patient?

a) Flecainide
b) Sotalol
c) Amiodarone
d) Catheter ablation

TSH = thyroid-stimulating hormone; CrCl = creatinine clearance; ECG = electrocardiogram; LVEF = left ventricular ejection fraction

EAST-AFNET: Primary Safety Outcome*



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

*Composite of death, stroke, or serious adverse events related to rhythm-control therapy.

Kirchhof P, et al. *N Engl J Med.* 2020;383:1305-1316.

EAST-AFNET 4

Outcome	Patients With Event		Uncorrected HR (95% CI]
	Early Rhythm Control (n = 1395)	Usual Care (n = 1394)	
CV death	67/6915 (1.0%)	94/6988 (1.3%)	0.72 (0.52–0.98)
Stroke	40/6813 (0.6%)	62/6856 (0.9%)	0.65 (0.44–0.97)
Hospitalization with worsening of HF	139/6620 (2.1%)	169/6558 (2.6%)	0.81 (0.65–1.02)
Hospitalization with ACS	53/6762 (0.8%)	65/6816 (1.0%)	0.83 (0.58–1.19)

The primary safety outcome was a composite of death, stroke, or serious adverse events related to rhythm-control therapy

CV = cardiovascular; ACS = acute coronary syndrome.

Kirchhof P, et al. *N Engl J Med*. 2020;383:1305-1316.

EAST-AFNET 4 and AFFIRM: Main Differences

	AFFIRM	EAST-AFNET
Early initiation of rhythm control		X
More persistent AF	X	
Higher % HTN, valvular heart disease		X
Dronedarone and catheter ablation use		X
High digoxin, sotalol, and amiodarone use	X	
Non-vitamin K anticoagulants (NOAC) use Oral anticoagulant use similar in both study arms		X
All-cause mortality primary endpoint	X	
Composite endpoint: CV death, stroke, hospitalization with worsening HF or ACS		X
Rhythm control: higher hospitalizations	X	
Safety outcomes no different in both study arms		X

Wyse DG, et al; AFFIRM Investigators. *N Engl J Med*. 2002;347:1825-1833. Kirchhof P, et al. *N Engl J Med*. 2020;383:1305-1316.

EAST-AFNET 4: Conclusions

- Early initiation of rhythm-control therapy reduced CV outcomes in patients with early AF and CV conditions without affecting nights spent in hospital
- As expected, early rhythm control strategy was associated with more adverse events related to rhythm-control therapy, but overall safety of both treatment strategies was comparable
- Superiority of early rhythm control may be secondary to refinement of AF therapies
- These results have the potential to inform the future use of rhythm-control therapy, further improving the care of patients with early AF

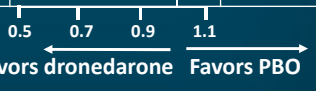
Kirchhof P, et al. *N Engl J Med*. 2020;383:1305-1316. Yang, E, et al. *Heart Rhythm* 2021;18:674-681.

Post-Hoc Analysis of ATHENA

2859 patients with known duration of AF

First CV hospitalization or death due to any cause

Length of AF/AFL history	Dronedarone Event No.	Dronedarone Event Rate	Placebo Event No.	Placebo Event Rate	HR (95% CI)
<3 mos	670	29.3%	626	35.5%	0.79 (0.65–0.96)
3 to <24 mos	416	26.0%	429	34.3%	0.72 (0.56–0.92)
≥24 mos	355	33.8%	363	38.0%	0.84 (0.66–1.07)



The results of this analysis suggest that treatment with an antiarrhythmic drug such as dronedarone should commence at an early stage of disease; prospective trials are warranted to confirm these findings

AFL = atrial flutter; PBO = placebo.

Blomström-Lundqvist C, et al. *Clin Cardiol.* 2020;43:1469-1477

AAD Classification and Pharmacokinetics

Antiarrhythmic class		Agent	CYP substrate	P-gp	Enzymes/transporters inhibited
Class I	Class Ia	Quinidine	3A4	Yes	3A4, 2D6, P-gp
		Procainamide	No	No	None known
		Disopyramide	3A4	No	None known
	Class Ib	Lidocaine	1A2, 2B6, 2D6	No	1A2
		Mexiletine	2D6. 1A2	No	1A2
	Class Ic	Flecainide	2D6	No	2D6
		Propafenone	1A2, 2D6, 3A4	No	2D6
Class II		Propranolol	2D6, 1A2, 2C19	Yes	P-gp, weakly 2D6
		Bisoprolol	3A4 (minor: 2D6)	Possibly	None known
		Metoprolol	2D6	No	None known
		Carvedilol	2D6, 2C9 (minor: 3A4, 1A1, 1A2, 2C19, 2E1)	No	P-gp
Class III		Amiodarone	3A4, 2C8	No	1A2, 2D6, 2C9, 3A4, P-gp
		Dronedarone	3A4	No	3A4, 2d6, P-gp
		Sotalol	No	No	None known
		Ibutilide	No	No	None known
		Dofetilide	Insignificant	No	None known
Class IV		Verapamil	3A4, 3A5, 2C8 (minor: 1A2, 2C9, 2D6, 2E1)	Yes	3A4, P-gp
		Diltiazem	3A4, 2C8, 2C9, 2C19	Yes	3a4, possibly 2D6, P-gp

CYP = cytochrome P-450; P-gp = P-glycoprotein.

Konieczny KM, Dorian P. *J Innov Card Rhythm Manag.* 2019;10:3552-3559.

Case Study: New Symptoms

- The patient was started on flecainide 100 mg BID and had excellent control of his PAF for 3 years
- He now presents with new exertional chest pain; his resting ECG shows NSR and no new ST-T wave changes
- A stress nuclear study is performed and after 6 minutes on a Bruce protocol, he develops chest pain and 1.5 mm horizontal inferior ST-segment depression
- Nuclear study: evidence of inferior-wall myocardial ischemia, LVEF = 60%
- His flecainide is discontinued
- Cardiac catheterization performed: 90% right coronary artery occlusion, which is treated successfully with a PCI and drug-eluting stent
- Aspirin 81 mg a day and clopidogrel 75 mg a days are added to his regimen, and his simvastatin is increased to 40 mg a day

BID = twice daily; PCI = percutaneous coronary intervention.

Case Study: Question 2

What is the best option for rhythm control, given his CAD ?

a) Propafenone

b) Amiodarone

c) Dronedarone

d) Catheter ablation

Antiarrhythmic Therapy With AADs

What is the goal?

AF is usually recurrent and rarely lethal →

Keep goals realistic

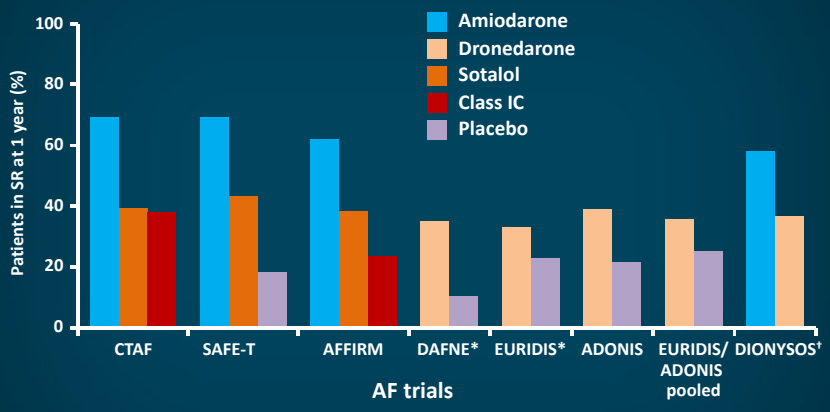
- Reduce frequency, duration, and severity of events
- Minimize the risks of treatment (drug, ablation, etc)

AAD therapy (per the AHA/ACC/HRS and ESC algorithmic guidelines) *must be selected based on:*

- **Anticipated efficacy**
- **Tolerance**
- **Proarrhythmic risk**
- **Organ toxicity**
- **Effects on SN and conduction system**
- **LV dysfunction**

Camm AJ, et al; European Heart Rhythm Association. *Eur Heart J.* 2010:31;2369-2429. Fuster V, et al. *J Am Coll Cardiol*. 2006;48:e149-e246. Naccarelli GV, et al. *Bus Brief: US Cardiol*. 2004;1-5.

Efficacy of AADs in AF Trials



*At 6 months; †Mean follow-up 7 months.

Naccarelli GV, 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;352:1861-1872. 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;357:987-999. Le Heuzey JY, et al. *J Cardiovasc Electrophysiol*. 2010;21:597-605.

Amiodarone: Adverse Effects

- Well tolerated hemodynamically with **minimal negative inotropic effects**
- Drug interactions: digoxin, warfarin, quinidine, procainamide, and flecainide

System	Adverse Effect
Cardiac	• Bradycardia may require backup permanent pacing; but ***low-dose amiodarone may minimize*** • Prolongs APD; however, TdP and development of incessant sustained VT are *rare* • Raises defibrillation threshold
Dermatologic	Skin photosensitivity Bluish-gray discoloration
Endocrine	Hypothyroidism requires addition of thyroid replacement Hyperthyroidism may require therapy discontinuation
Hepatic	Asymptomatic, transient ↑ of hepatic enzymes and drug-induced hepatitis (2%)
Neurologic	Peripheral neuropathy and myopathy Usually resolve with ↓ dose
Ocular	Corneal microdeposits
Pulmonary	Interstitial pneumonitis
Vascular	Venous sclerosis can be minimized if IV amiodarone is given via central venous line

APD = action potential duration; TdP = torsade de pointes; VT = ventricular tachycardia; IV = intravenous.

Naccarelli GV, et al. *Pharmacotherapy.* 1985;5:298-313.

Propafenone vs Flecainide

	Propafenone	Flecainide
Metabolism	Hepatic (P450D6)	Hepatic—70% Renal—30%
Active metabolites	5-OH propafenone	None
β-blocking activity	Yes	No
Drug interactions	Digoxin Warfarin	Amiodarone
Onset/offset kinetics	Fast/slow	Slow/slow
K-channel blocker	No	Low
Saturated pharmacokinetics	Yes	No

Lei M, et al. *Circulation.* 2018;138:1879-1896. Flecainide (Tambocor™) prescribing information (PI) (www.drugs.com/pro/tambocor.html). Accessed 10/19/2020.

Amiodarone vs Dofetilide and Sotalol

	Dofetilide	Sotalol
AF termination efficacy	Greater than amiodarone	Similar to amiodarone
Sinus node or AV node effects	Much less than amiodarone	Similar to amiodarone
Maintaining sinus rhythm	Amiodarone superior	Amiodarone superior
Safety	**Requires in-hospital initiation** due to TdP risk Minimize use in chronic renal failure	**In-hospital initiation *preferred*** due to TdP risk Minimize use in chronic renal failure

AV = atrioventricular.

Wolbrette DL, et al. *J Cardiovasc Pharmacol Ther.* 2019;24:3-10. Piccini JP, et al. *Am J Cardiol.* 2014;114:716-722. Singh BN, et al. *N Engl J Med.* 2005;352:1861-1872. Sotalol PI. 2011. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021151s010lbl.pdf. Accessed 5.26.21. Atti V, et al. *ACC.* 2020. https://www.acc.org/latest-in-cardiology/articles/2020/01/06/07/55/safety-of-rapid-switching-from-amiodarone-to-dofetilide-in-patients-with-af-with-an-icd. Accessed 5.26.21.

Clinical Profiles for Amiodarone and Dronedarone

	Amiodarone	Dronedarone
Iodine moiety	Yes	No
Half-life	53 days	14–30 hours
Blocks I_{Kr}; I_{Ks}; β_1; $I_{ca\text{-}L}$; I_{Na} ; I_{Kl}; $I_{K\text{-}ACh}$	Yes	Yes
Dosing	Daily after loading	BID with meals
Food effect	Yes	Yes
CYP450 3A4 metabolism	No	Yes
Inhibits tubular secretion of creatinine	Yes	Yes
Increase QT but low TdP	Yes	Yes
Efficacy in suppressing AF	65%	50%
Efficacy in suppressing VT	Yes	Not well studied
Decreases CV hospitalization	No	Yes
Warfarin interaction	Yes	No
Pulmonary/thyroid toxicity	Yes	No
Safety concerns in CHF	SCD-HeFT (NYHA III)	ANDROMEDA

NYHA = New York Heart Association.

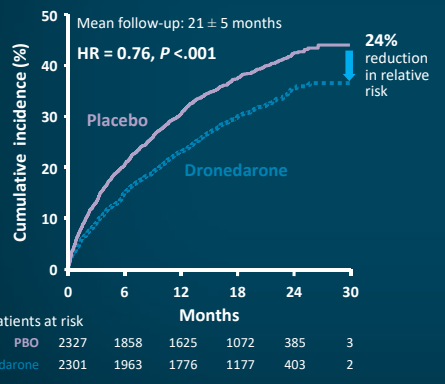
Wolbrette D, et al. *Vasc Health Risk Manag*. 2010;6:517-523.

Dronedarone: ATHENA and PALLAS

ATHENA: PAF or persistent AF

Primary outcome: time to first CV hospitalization or death

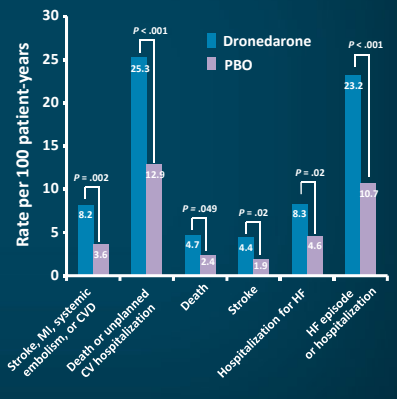
N = 4628 (PAF or persistent AF) randomized
≥75 yrs ± additional RF *or* ≥70 yrs and ≥1 RF
(HTN, DM, prior stroke/TIA, LA diameter ≥50 mm, LVEF ≤0.40)



PALLAS: permanent AF

N = 3236; ≥65 yrs with >6 mos h/o permanent AF and risk factors for major vascular event

Study stopped for safety reasons



RF = risk factor; h/o = history of.

Hohnloser SH, et al. *N Engl J Med*. 2009;360:668-678. Connolly SJ, et al. *N Engl J Med*. 2011:365:2268-2676. Singh D, et al. *J Am Coll Cardiol*. 2010;55:1569-1576.

US Department of Defense Real-World Outcomes
Dronedarone vs Other Antiarrhythmic Drugs

Outcomes	Dronedarone (n = 6349)		Other AAD (n = 12,698)		Dronedarone vs Other ADD HR (95% CI)
	N (%)	Event Rate	N (%)	Event Rate	
CV hospitalization	586 (9.23%)	149.48	1315 (10.36%)	173.57	0.87 (0.79–0.96) *P* = .006
CV hospitalization/ death from any cause	598 (9.42%)	151.32	1364 (10.74%)	178.60	0.86 (0.78–0.95) *P* = .002

Goehring EL jr, et al. *Am J Cardiol.* 2020;135:77-83.

Other AAD Real-World Data

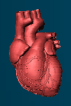
- ORBIT-AF and AF: Focus on Effective Clinical Treatment Strategies (AFFECTS) registry demonstrated amiodarone was often used even when more front-line guideline-recommended drugs were available
- The Retrospective Evaluation and Assessment of Therapies in AF (TREAT-AF) study demonstrated that class IC AADs (flecainide or propafenone) as initial treatment for AF were associated with lower risk of hospitalization and cardiovascular events than class III drugs (sotalol or dofetilide)

Reiffel JA, et al. *Am J Cardiol* .2010;105:1122-1129. Pokorney SD, et al. *Am Heart J.* 2020;220:145-154. Kipp R, et al. *JACC Clin Electrophysiol*. 2019;5:231-241.

Considerations in Choosing an AAD


Efficacy


Safety
(end-organ toxicity, mortality, proarrhythmic risk)


Morbidity
(bradyarrhythmias, negative inotropy, subjective toxicity)


Outpatient initiation


Interactions
(drug-drug, drug-device)


Dosing convenience
(patient compliance)


Metabolism


Quality of life


Cost
(drug, follow-up)

Naccarelli GV, et al. *Bus Briefing: US Cardiol.* 2004;1-5. Zimetbaum P. *Circulation.* 2012;125;381-389.

All Antiarrhythmics Are Not Alike

- Binding characteristics
  - Onset-offset kinetics
  - Open or inactivated state blockade
- Additional channel or autonomic blocking properties
- Proarrhythmic incidence
- Inotropic actions
- Organ toxicity and nuisance symptoms
- Drug interactions
- Metabolism
  - Active metabolites with a different mechanism of action

Lei M, et al. *Circulation,* 2018;138:1879-1896.

Significant AADs and Their CV Drug Interactions

Amiodarone	Dronedarone	Quinidine	Verapamil
↑ INR (warfarin) ↑ digoxin level ↑ therapeutic levels: • quinidine • procainamide • flecainide Theoretic increase in DOAC levels Increase in simvastatin levels	↑ digoxin level Theoretic increase in DOAC levels Increase simvastatin levels	↑ digoxin level	Can ↑ therapeutic levels of dofetilide

DOAC = direct oral anticoagulant.

Amiodarone (Nesterone®) PI, 2016 (https://baxterpi.com/pi-pdf/Nexterone_PI.pdf). Dronedarone (Multaq) PI, 2009 (www.accessdata.fda.gov/drugsatfda_docs/label/2009/022425lbl.pdf). Quinidine (Qualaquin) PI, 2019 (www.accessdata.fda.gov/drugsatfda_docs/label/2019/021799s029lbl.pdf). Verapamil (Verelan) PI, 2011 (www.accessdata.fda.gov/drugsatfda_docs/label/2011/020943s028lbl.pdf). Konieczny K, Dorian P. *J Innov Cardiac Rhythm Manag.* 2019;10:3552-3559. Wiggins BS, et al. *Circulation.* 2016;134:e468-e495. Frommeyer G, et al. *Int J Cardiol.* 2017;22:74-79.

Outpatient vs Inpatient Initiation of AADs for AF

Agents	In AF		In NSR	
	Hospital	Outpatient	Hospital	Outpatient
Class IA*	X		X	
Class IC*		X†		X†
Sotalol	X		X	X‡
Dofetilide	X		X	
Dronedarone		X		X
Amiodarone		X		X

*After rate control; †No SHD or sinus node/conduction abnormalities; ‡No risk factors for TdP (QT <450 ms, normal electrolytes).

SHD = structural heart disease; TdP = Torsade de pointes.

Fuster V, et al. *Circulation.* 2006;114:e257-e354.

AADs: Follow-Up Protocols

Proarrhythmia

- May occur ***late***
  - Risk factors develop
  - Drug clearance impaired
- Organ toxicity is ongoing risk with amiodarone
- Permanent AF: discontinue membrane-active AADs

Class IC
Flecainide, propafenone

- Coronary artery disease, ventricular disorders
  - ECG, exercise test

Class III
Dofetilide, sotalol
Dronedarone
Amiodarone

- QT interval
- Renal function/chemistry profiles
- ECG if long-lasting and persistent AF suspected
- LFTs and TSH every 6 months, chest x-rays annually, PFTs (if pulmonary toxicity suspected)

LFT = liver-function test; PFT = pulmonary function test.

Dan GA, et al. *Europace.* 2018;20:731-732an. January CT, et al. *J Am Coll Cardiol.* 2014;64:e1-e76.

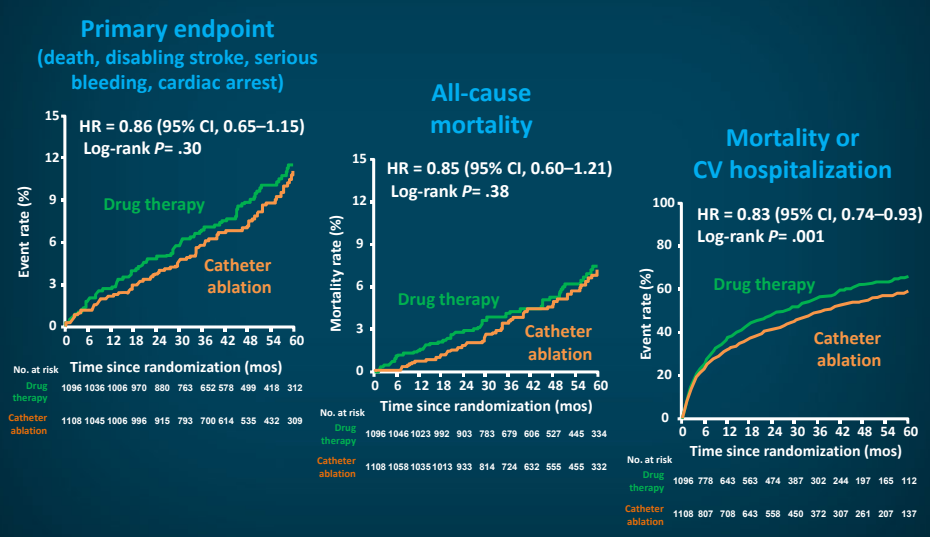
Case Study: Question 3

- The patient is started on dronedarone 400 mg BID with meals with no AF recurrences for 6 months; after 1 month, his aspirin is discontinued
- When he presents for follow-up, he is asymptomatic without any adverse side effects from his medical regimen; however, on physical exam, his heart rate is 80 bpm and irregularly irregular. An ECG confirms atrial fibrillation
- He has been faithful in taking his medications as prescribed, including his daily rivaroxaban

Considering the above changes, what would the best treatment option?

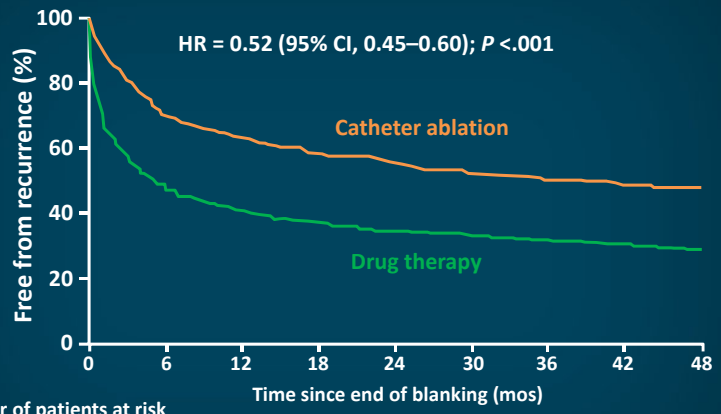
a) Perform a DC cardioversion and, if successful, keep patient on dronedarone
b) Switch to dofetilide or sotalol
c) Switch to amiodarone
d) Stop dronedarone and schedule for a catheter ablation procedure

CABANA: Catheter Ablation vs Drug Therapy
Intention-to-Treat Population



Packer DL, et al. *JAMA*. 2019;321:1261-1274.

CABANA: Recurrent AF
ITT after blanking period



Number of patients at risk									
Drug therapy	629	304	252	212	181	157	131	115	94
Catheter ablation	611	432	381	328	291	241	201	163	134

ITT = intention-to-treat (population).

Packer DL, et al. *JAMA*. 2019;321:1261-1274.

CABANA Trial: Conclusion

- Ablation compared with drug therapy (ITT)
  - **Did not** produce a significant reduction in primary endpoint and all-cause mortality
  - **Ablation significantly reduced mortality or CV hospitalization by 17%**
  - There was **48% reduction in recurrent AF** with ablation
- Ablation compared with drug therapy (treatment received)
  - 14% reduction in primary endpoint and 17% reduction in mortality or CV hospitalization

Ablation is an acceptable treatment strategy for the treatment of AF, with low adverse event rates

Packer DL, et al. *JAMA*. 2019;321:1261-1274.

CASTLE-AF

Catheter ablation vs conventional drug therapy for AF in HF

397 patients w/LVEF <35% and ICD randomized to CA vs drug therapy Modified ITT approach

Symptomatic PAF (30%) Persistent AF (35%)

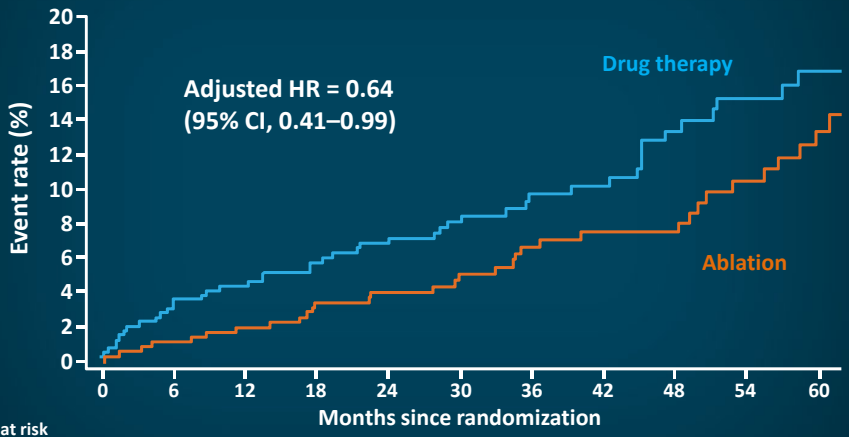
- **Primary endpoint**: TM + HF hospitalization ***reduced by CA*** (28.5% vs 44.6%, RRR = 38%, *P*= .007) with mean follow-up of 37 mos
- **Secondary endpoints**: TM (13.4% vs 25%, RRR = 47%), HF hospitalization (20.7% vs 35.9%, RRR = 44%), CV mortality (RRR = 51%) and CV hospitalization (RRR = 28%)
- ***LVEF increased more with ablation*** (8%) than drugs (0.2%, *P*= .005)
- ***AF reduced with ablation at 3 mos***; gradually increased over 60 mos of follow-up

ICD = implantable cardioverter-defibrillator; TM = total mortality; CA = catheter ablation; RRR = relative risk reduction.

Marrouche NF, et al. *N Engl J Med*. 2018;378:417-427. ESC. European Heart Rhythm Association (EHRA) 2018 Congress News. (www.escardio.org). Accessed 10/21/2020. Stiles S. *Medscape*, 2018 (www.medscape.com/viewarticle/892189). Accessed 5/23/2021.

CABANA Heart Failure Patients: ITT

Primary composite endpoint
(death, disabling stroke, serious bleeding, or cardiac arrest)



No. at risk											
Drug therapy	400	371	359	345	317	264	210	179	149	121	97
Ablation	378	353	344	332	311	265	228	193	171	137	108

Packer DL, et al. *Circulation* 2021;143:14:1377-1390.

How Lifestyle Affects AF

Smoking

Quitting *decreased AF by 36%*

Alcohol

10% ↑ **risk** with 1 drink/day

Impact of comorbidities on AF

- OSA treatment can *reduce* AF
- HTN control can *reduce* AF
- DM ↑ **risk** of AF
- Obesity ↑ **risk** of *new onset* AF by 40%; **weight loss** *reduces* AF burden and recurrences

Lifestyle choices can affect AF

- Stimulants (caffeine, adrenergic drugs)
- Mediterranean diet may *reduce* AF
- Mindset and stress (yoga *reduced* AF by 24%)
- Physical activity *reduces* AF

OSA = obstructive sleep apnea.

Sabzwari SR, et al. *Cureus.* 2018;10:e2682. Foy AJ, et al. *Am J Cardiol.* 2018;121:1072-1075. Pathak RK, et al. *J Am Coll Cardiol.* 2015;65:2159-2169.

Shared Decision-Making (SDM) in AF

While SDM in AF frequently centers around anticoagulation, it is reasonable to apply SDM to all aspects of AF management

Remind patient why treatment is important

Ensure original treatment decisions are still appropriate to current patient situation and priorities

Identify adherence factors
Accessibility (cost barriers, delayed prescription fill)
Organization (fixed packaging, pill boxes)
Administration (reminders)

- Ongoing process that starts during initial treatment discussion
- Evolves over time as a series of "problem-solving" discussions that refine individualized care plans to live well with treatment
- Can uncover which aspects of an individual situation need intervention *as well as* the situation-specific action required

Brand-McCarthy SR, et al. *Circ Cardiovasc Qual Outcomes.* 2020;13:e006080.

Goals of SDM

Primary goal is to help patients and clinicians make shared and informed decisions that integrate:

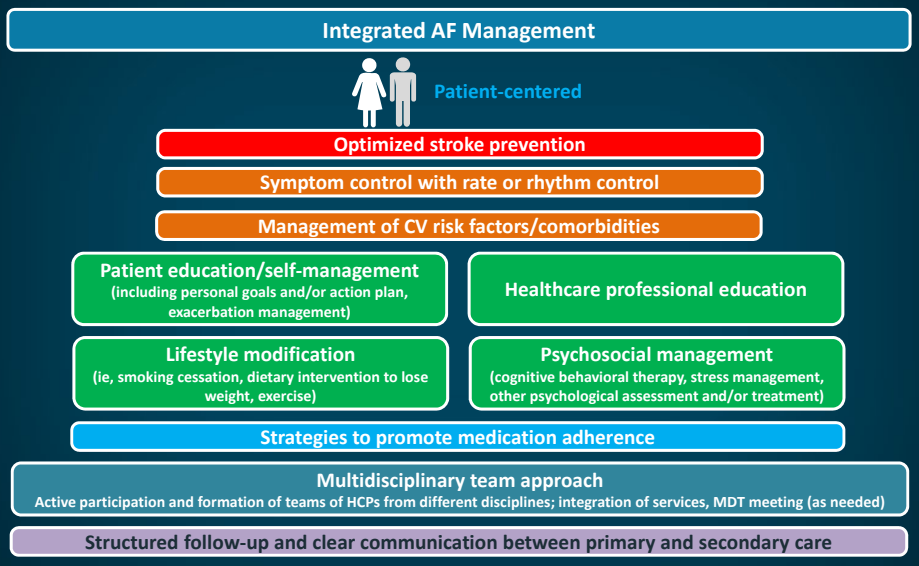
- Known risks and benefits of treatment
- Pertinent patient-specific situations
- Patient preferences

What SDM does → **Enhances communication**
Facilitates identification of individualized treatment options

What SDM is ***not*** → **A checklist of tasks to be completed**

Noseworthy PA, et al. *J Interv Card Electrophysiol.* 2019;56:159-163.

Integrated AF Management



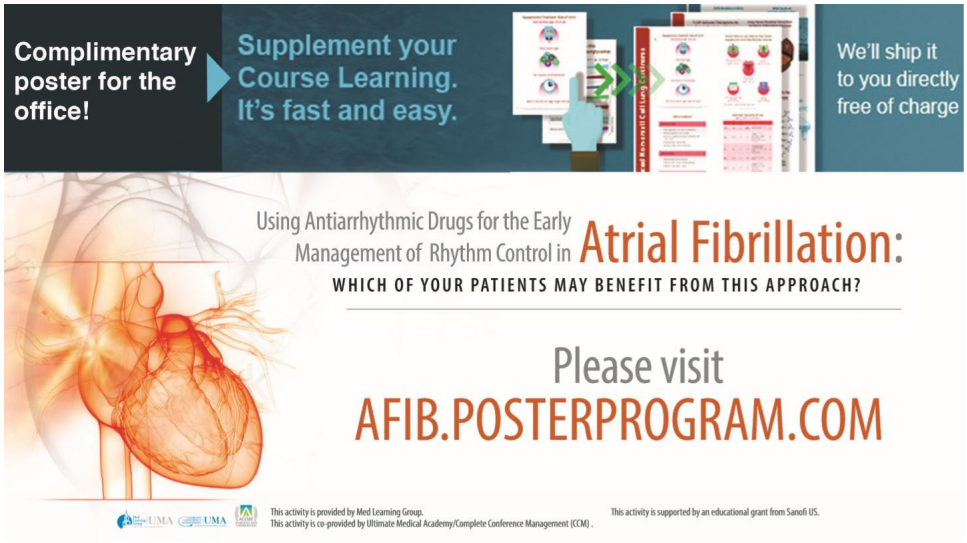
HCPs = healthcare professionals; MDT = multidisciplinary team.

Hindricks G, et al. *Eur Heart J.* 2021;42:373-498.

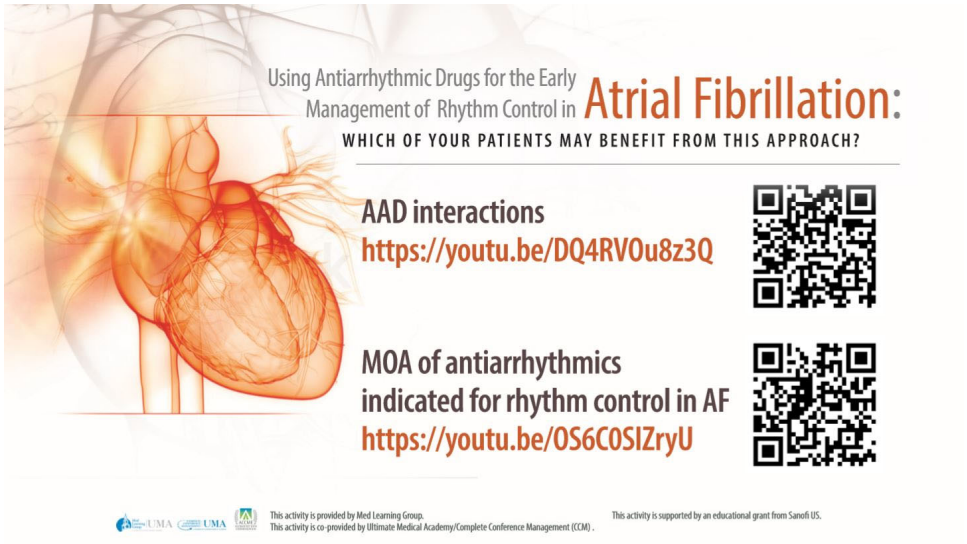
Atrial Fibrillation: "The Gift That Keeps on Giving"

- AF is chronic so you will get to be good friends with your long-term patients
- Keep goals realistic; total prevention with AADs is unlikely in the absence of correctable underlying disorder
- AAD therapy selection should be based on anticipated efficacy, proarrhythmic risk, organ toxicity, and effects on nodal, conductive system, and LV function
  - AF can be refractory to amiodarone, which can also have significant long-term toxicity
- No new antiarrhythmic agents near FDA approval in near future
- Catheter ablation can be effective and is growing but still has limitations
- Rate control has similar long-term efficacy on mortality
- Lifestyle modifications may be part of the treatment approach for patients with AF but will not be a panacea
- If you remember nothing else, remember this: "Protect the brain" with proper antiembolic strategies in high-risk patients with AF

Poster Program



Whiteboard Animations



Thank you!

Overview of Atrial Fibrillation and Guidelines

Resource	Address
American College of Cardiology (ACC). Impact and consequences of atrial fibrillation. Published August 16, 2018.	https://www.acc.org/latest-in-cardiology/articles/2018/08/06/12/42/cover-story-impact-and-consequences-of-atrial-fibrillation
Benjamin EJ, et al. Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. *Circulation*. 1998;98:946-952.	https://www.ahajournals.org/doi/epub/10.1161/01.CIR.98.10.946
Centers for Disease Control (CDC). What is atrial fibrillation? Reviewed September 8, 2020.	https://www.cdc.gov/heartdisease/atrial_fibrillation.htm
Chugh SS, et al. Epidemiology and natural history of atrial fibrillation: Clinical implications. *J Am Coll Cardiol.* 2001;37:371-378.	https://www.sciencedirect.com/science/article/pii/S0735109700011074
Feinberg WM, et al. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med*. 1995;155:469-473.	https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/620157
Fuster V, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation—Executive Summary. *Circulation*. 2006;114:700-752.	https://www.ahajournals.org/doi/epub/10.1161/CIRCULATIONAHA.106.177031
Fuster V, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation. *J Am Coll Cardiol*. 2006;48:e149-e246.	http://www.lippman.org/ACC/clinicalguidelines/AFGuidelinesFullText.pdf
Hindricks G, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J.* 2021;42:373-498.	https://academic.oup.com/eurheartj/article/42/5/373/5899003
January CT, et al. 2019 AHA/ACC/HRS	https://www.sciencedirect.com/science/artic

focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*, 2019;74:104-132.	le/pii/S0735109719302098
January C, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2014;64:e1-e76.	https://www.sciencedirect.com/science/article/pii/S0735109714017409
Michaud GF, Stevenson WG. Atrial fibrillation. *N Engl J Med.* 2021;384:353-361.	https://www.nejm.org/doi/10.1056/NEJMcp2023658
Miyasaka Y, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119-125.	https://www.ahajournals.org/doi/epub/10.1161/CIRCULATIONAHA.105.595140
Thom T, et al. Heart disease and stroke statistics—2006 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2006;113:e85-e151.	https://www.ahajournals.org/doi/epub/10.1161/CIRCULATIONAHA.105.171600
Wang TJ, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: The Framingham Heart Study. *Circulation*. 2003;107:2920-2925.	https://www.ahajournals.org/doi/epub/10.1161/01.CIR.0000072767.89944.6E

Rate vs Rhythm Control

Resource	Address
AFFIRM First Antiarrhythmic Drug Substudy Investigators. Maintenance of sinus rhythm in patients with atrial fibrillation: An AFFIRM substudy of the first antiarrhythmic drug. *J Am Coll Cardiol.* 2003;42:20-29.	https://www.sciencedirect.com/science/article/pii/S073510970300559X

Blomström-Lundqvist C, et al. Efficacy and safety of dronedarone by atrial fibrillation history duration: Insights from the ATHENA study. *Clin Cardiol.* 2020;43:1469-1477.	https://onlinelibrary.wiley.com/doi/10.1002/clc.23463
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Shared Decision-Making and Interdisciplinary Care

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