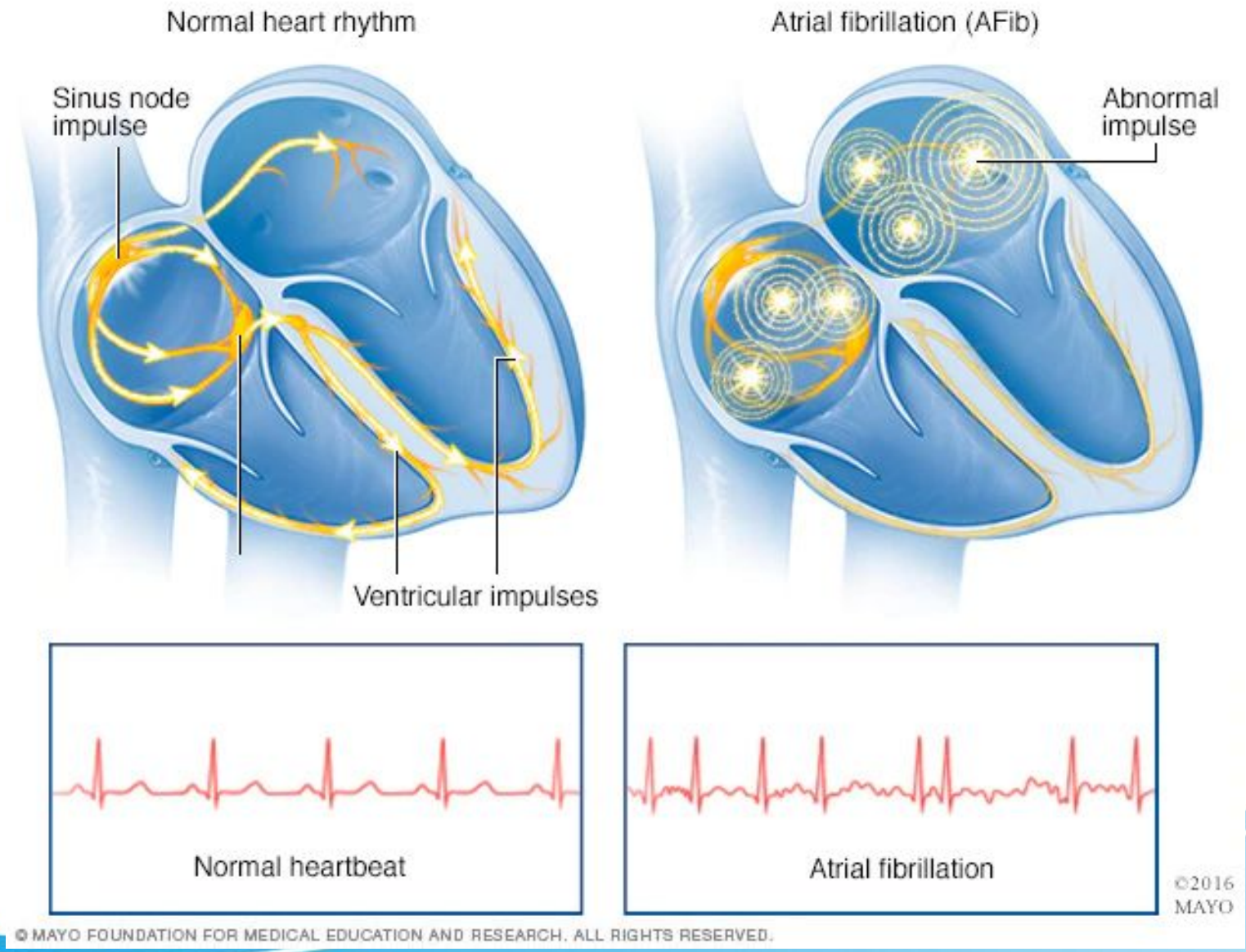
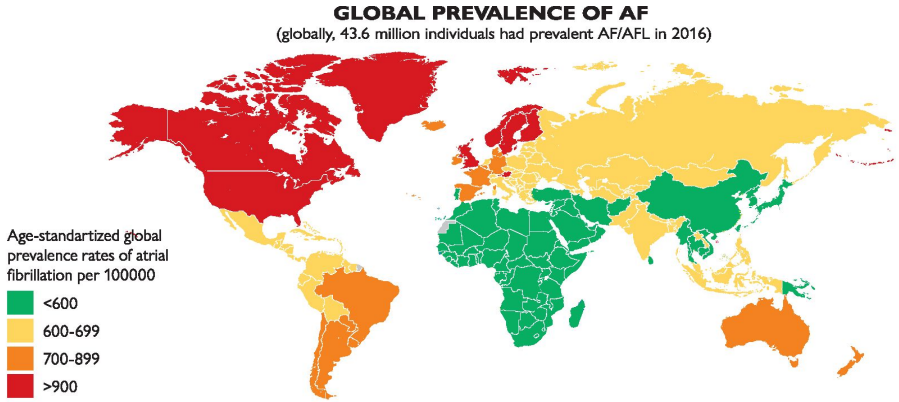
Lixarit (Flecainide)

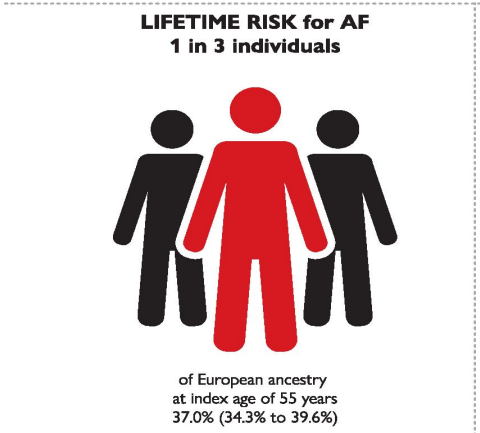
Approach to Management of
Atrial Fibrillation

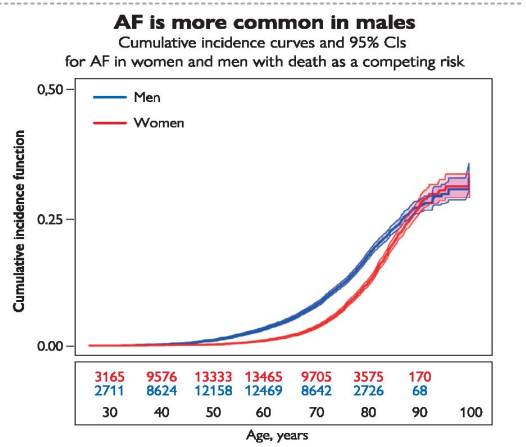
What is atrial fibrillation?

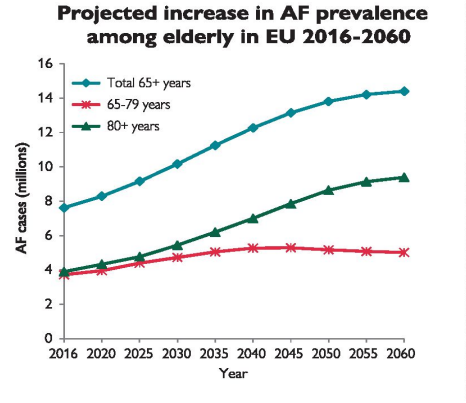


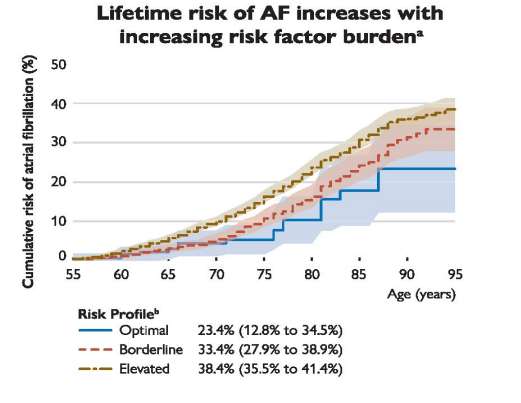
AF is the most common sustained cardiac arrhythmia in adults worldwide





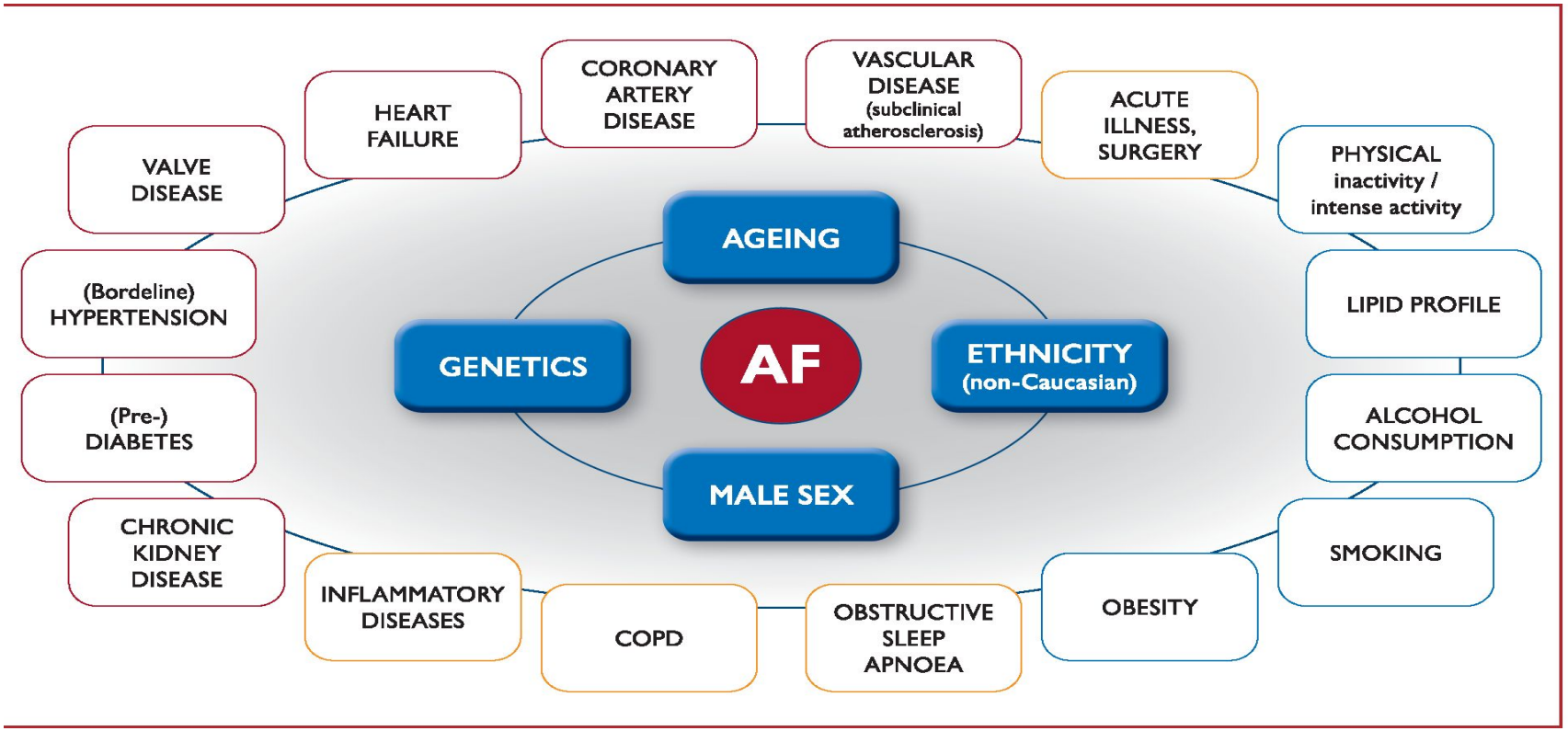






- AF is associated with substantial morbidity and mortality
- prevalence of AF in adults is between 2% and 4%
- Increasing age is a prominent AF risk factor
- lifetime risk of AF are lower in women vs. men
- lifetime risk of AF are lower in non-Caucasian vs. Caucasian cohorts
- lifetime AF risk estimate of 1 in 3 individuals age of 55 years
- by 2030 in EU diagnosed with atrial fibrillation will reach

Risk factors for AF



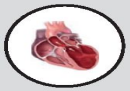
Control of modifiable risk factors could reduce the incidence of AF

Risk of AF significantly increasing from 23.4% among individuals with an optimal clinical risk factor profile to 33.4% and 38.4% in those with borderline and elevated clinical risk factors

Magnussen C, Niiranen TJ, Ojeda FM, Gianfagna F, Blankenberg S, Njolstad I, Vartiainen E, Sans S, Pasterkamp G, Hughes M, Costanzo S, Donati MB, Jousilahti P, Linneberg A, Palosaari T, de Gaetano G, Bobak M, den Ruijter HM, Mathiesen E, Jorgensen T, Soderberg S, Kuulasmaa K, Zeller T, Iacoviello L, Salomaa V, Schnabel RB; BiomarCaRE Consortium. Sex differences and similarities in atrial fibrillation epidemiology, risk factors, and mortality in community cohorts: results from the BiomarCaRE Consortium (Biomarker for Cardiovascular Risk Assessment in Europe). Circulation 2017;136:1588-1597

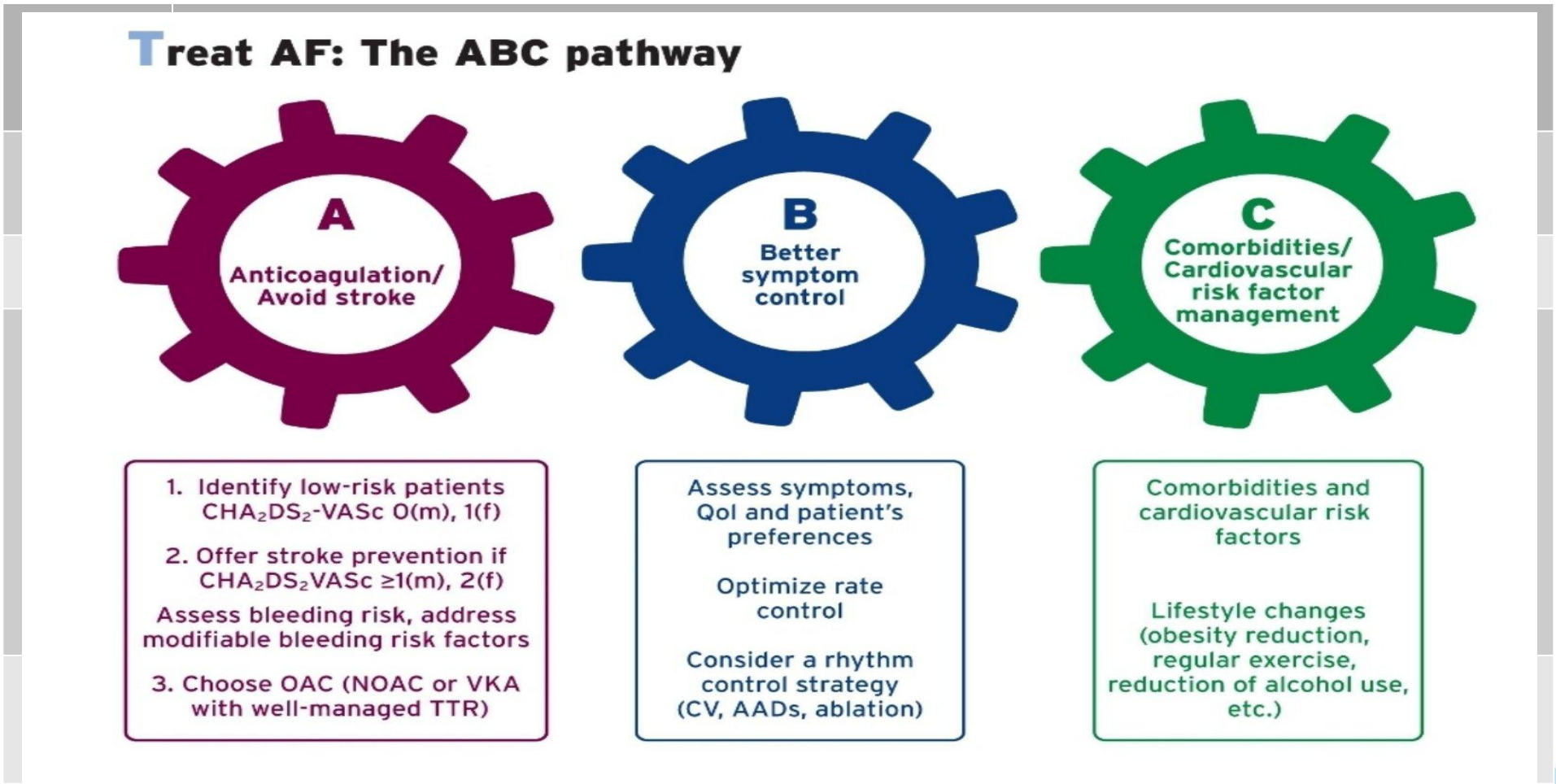
Why AF is dangerous?

AF-related OUTCOMES

AF-Related Outcome	Frequency in AF	Mechanism(s)
Death 	1.5 - 3.5 fold increase	Excess mortality related to: • HF, comorbidities • Stroke
Stroke 	20-30% of all ischaemic strokes, 10% of cryptogenic strokes	• Cardioembolic, or • Related to comorbid vascular atheroma
LV dysfunction / Heart failure 	In 20-30% of AF patients	• Excessive ventricular rate • Irregular ventricular contractions • A primary underlying cause of AF
Cognitive decline / Vascular dementia 	HR 1.4 / 1.6 (irrespective of stroke history)	• Brain white matter lesions, inflammation, • Hypoperfusion, • Micro-embolism
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

1. Cardioembolic **stroke** accompanied by high disability and mortality;
2. Development of **heart failure** (HF) - the main complication of AF, also leading to death.
3. Symptoms which negatively impact **quality of life**
4. Hospitalization rate

Patient management: the integrated ABC pathway (Atrial fibrillation Better Care) ASC 2020



Recommendations for rhythm control

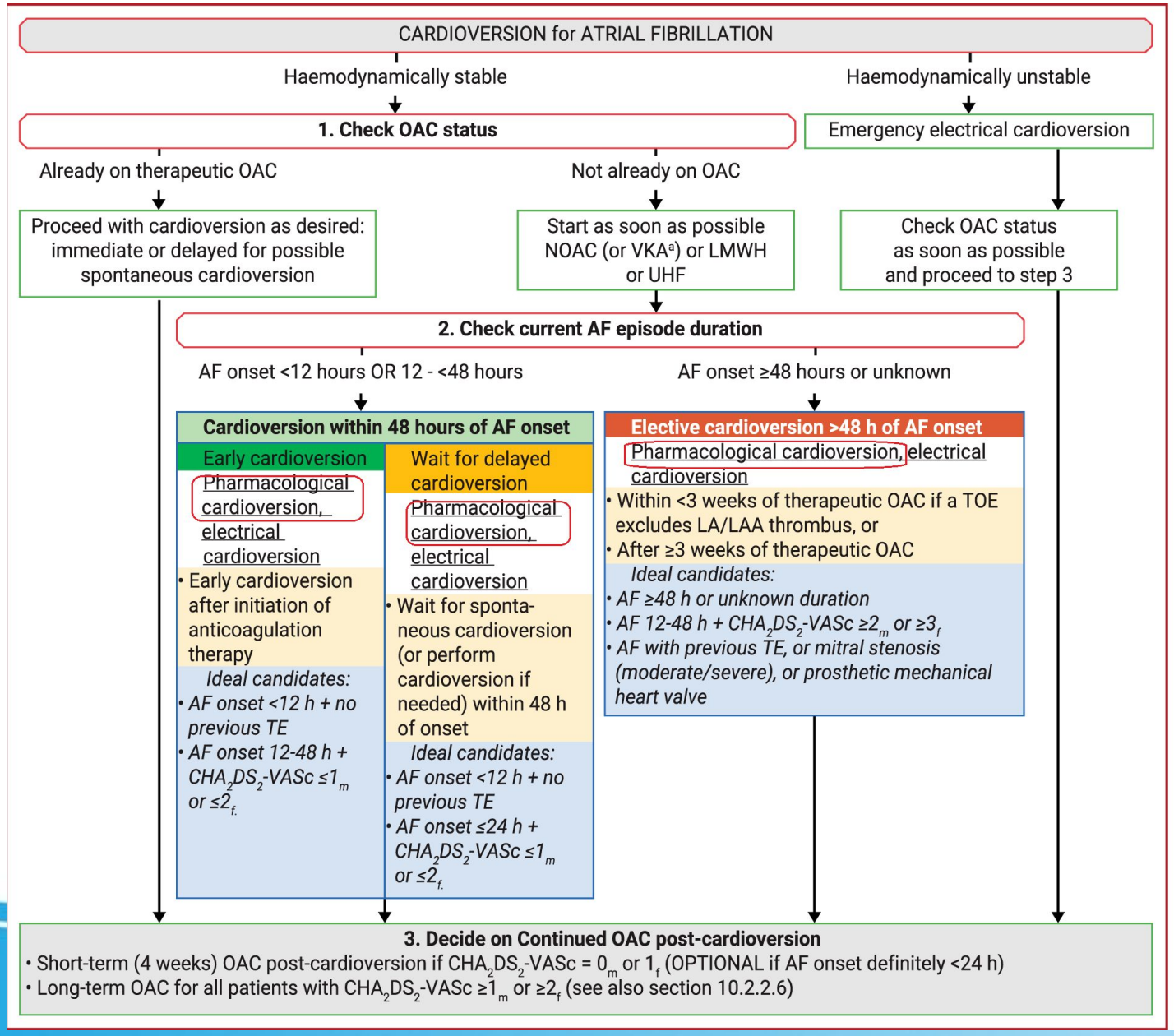
Recommendations	Class[a]	Level[b]
Rhythm control therapy is recommended for symptom and QoL improvement in symptomatic patients with AF.[551–553]	I	A

Classification of AF ESC 2020

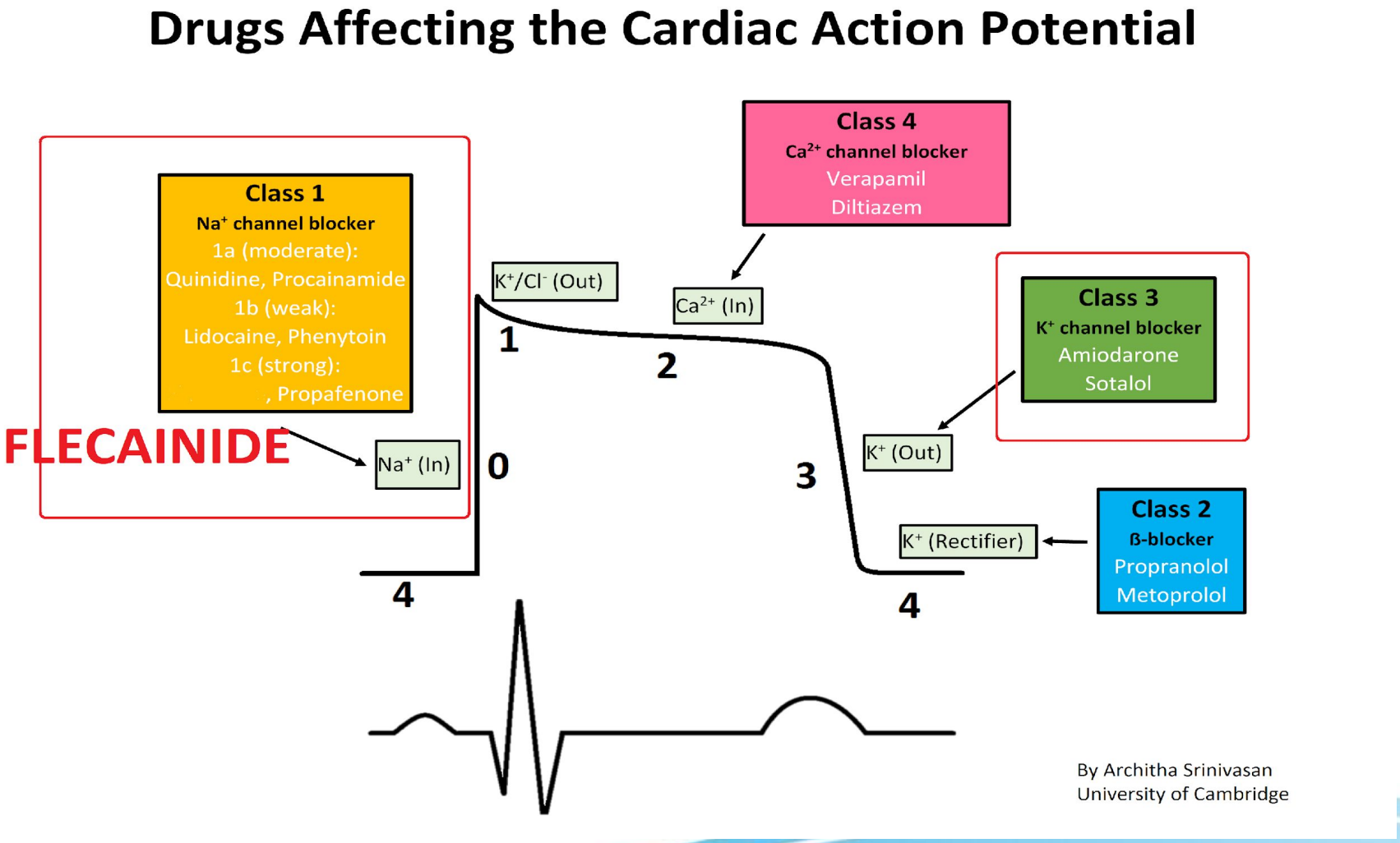
First diagnosed	AF not diagnosed before, irrespective of its duration or the presence/severity of AF-related symptoms.
Paroxysmal	AF that terminates spontaneously or with intervention within 7 days of onset.
Persistent	AF that is continuously sustained beyond 7 days, including episodes terminated by cardioversion (drugs or electrical cardioversion) after ≥7 days
Long-standing persistent	Continuous AF of >12 months' duration when decided to adopt a rhythm control strategy
Continuous AF of >12 months' duration when decided to adopt a rhythm control strategy.	AF that is accepted by the patient and physician, and no further attempts to restore/maintain sinus rhythm will be undertaken. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as 'long-standing persistent AF'.

rhythm control strategy

Cardioversion of AF to sinus rhythm (ESC 2020)



AAD classification



Class 1 and Class 3 used for pharmacological cardioversion

Recommendations for pharmacological cardioversion ESC 2020

NO REVALENT STRUCTURAL HEART DISEASE MEAN:

- **no history of Q-MI;**
- **absence of hypertrophic and dilated cardiomyopathy;**
- **LVEF> 40%;**
- **no signs of congestive or progressive HF;**
- **HF stage no more than IIA;**
- **absence of congenital or rheumatic heart defects;**
- **absence of severe LVH (thickness of one of the walls of the LV is ≥14 mm).**

Symptomatic, haemodynamically stable

Cardioversion of AF (either electrical or pharmacological) is recommended in symptomatic patients with persistent AF as part of rhythm control therapy.[232,233,593,594]	I	B
Pharmacological cardioversion of AF is indicated only in a haemodynamically stable patient, after consideration of the thromboembolic risk.[595]	I	B

No severe structural HD

For pharmacological cardioversion of recent-onset AF, i.v. vernakalant (excluding patients with recent ACS or severe HF) or flecainide or propafenone (excluding patients with severe structural heart disease) is recommended.[569,573,579,582,588–590]	I	A

Structural HD or HF

Intravenous amiodarone is recommended for cardioversion of AF in patients with HF or structural heart disease, if delayed cardioversion is consistent with clinical situation.[515,591,592]	I	A

Pill in the pocket approach

In selected patients with infrequent and recent-onset AF and no significant structural or ischaemic heart disease, a single self-administered oral dose of flecainide or propafenone ('pill in the pocket' approach) should be considered for patient-led cardioversion, but only following efficacy and safety assessment.[574,586,600,601]	IIa	B

Antiarrhythmic drugs for restoration of sinus rhythm (pharmacological cardioversion) ASC 2020

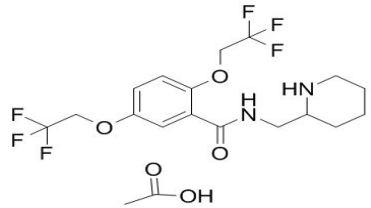
Drug	Administration route	Initial dose for cardioversion	Further dosing for cardioversion	Acute success rate and expected time to sinus rhythm	Contraindications/precautions/comments
Flecainide[a]	Oral[b] i.v.	200-300 mg 2 mg/kg over 10 min	-	Overall: 59-78% (51% at 3 h, 72% at 8 h)	• Should not be used in ischaemic heart disease and/or significant structural heart disease • May induce hypotension, AFL with 1:1 conduction (in 3.5-5.0% of patients) • Flecainide may induce mild QRS complex widening • Do NOT use for pharmacological cardioversion of AFL
Propafenone[a]	Oral[b] i.v.	450-600 mg 1.5-2 mg/kg over 10 min	-	Oral: 45-55% at 3 h, 69-78% at 8 h; i.v.: 43-89% Up to 6 h	
Vernakalant[c]	i.v.	3 mg/kg over 10 min	2 mg/kg over 10 min (10-15 min after the initial dose)	<1 h (50% conversion within 10 min)	• Should not be used in patients with arterial hypotension (SBP <100 mmHg), recent ACS (within 1 month), NYHA III or IV HF, prolonged QT, or severe aortic stenosis • May cause arterial hypotension, QT prolongation, QRS widening, or non-sustained ventricular tachycardia
Amiodarone[a]	i.v.	5-7 mg/kg over 1-2 h	50 mg/h (maximum 1.2 g for 24 h)	44% 8-12 h to several days	• May cause phlebitis (use a large peripheral vein, avoid i.v. administration >24 hours and use preferably volumetric pump) • May cause hypotension, bradycardia/atrioventricular block, QT prolongation • Only if no other options in patients with hyperthyroidism (risk of thyrotoxicosis)
Ibutilide[c]	i.v.	1 mg over 10 min 0.01 mg/kg if body weight <60 kg	1 mg over 10 min (10-20 min after the initial dose)	31-51% (AF) 63-73% (AFL) ~1 h	• Effective for conversion of AFL • Should not be used in patients with prolonged QT, severe LVH, or low LVEF • Should be used in the setting of a cardiac care unit as it may cause QT prolongation, polymorphic ventricular tachycardia (torsades de pointes) • ECG monitoring for at least 4 hours after administration to detect a -proarrhythmic event

not registered in Ukraine

not registered in Ukraine

AAD = antiarrhythmic drug; ACS = acute coronary syndrome; AF = atrial fibrillation; AFL = atrial flutter; b.i.d. = bis in die (twice a day); CrCl = creatinine clearance; CYP2D6 = cytochrome P450 2D6; ECG = electrocardiogram; EHRA = European Heart Rhythm Association; HCM = hypertrophic cardiomyopathy; HF = heart failure; i.v. = intravenous; LV = left ventricular; LVEF = left ventricular ejection fraction; LVH = LV hypertrophy; NYHA = New York Heart Association; QRS = QRS interval; QT = QT interval; SA = sinoatrial; SBP = systolic blood pressure; VKA = vitamin K antagonist.

[a]Most frequently used for cardioversion of AF, available in most countries.
[b]May be self-administered by selected outpatients as a 'pill-in-the-pocket' treatment strategy.
[c]Not available in some countries. For more details regarding pharmacokinetic or pharmacodynamic properties refer to EHRA antiarrhythmic drugs (AADs) clinical use and clinical decision making: a consensus document.



Flecainide (Lexarit)

Flecainide acetate is an oral class Ic antiarrhythmic drug (AAD) which blocks cardiac Na+ channels and was approved by the FDA in 1984.

Mechanism of Action

Flecainide acts on the fast-inward Na+ ion channel and has a high affinity to activated or open Na+ channels.

It prolongs the depolarization and increases refractoriness due to slow release from its binding site.

Flecainide is shown to block ryanodine receptor opening, which reduces calcium release from sarcoplasmic reticulum resulting in after depolarization and triggered activity. Hence, indications for flecainide include catecholaminergic polymorphic ventricular tachycardia (CPVT).

Initial dose for cardioversion 300 mg for patients more than 70 kg or 200 mg otherwise

Acute success rate and expected time to sinus rhythm 59–78% (51% at 3 h, 72% at 8 h)*

Contraindications/precautions/comments

- Should not be used in ischaemic heart disease and/or significant structural heart disease
- May induce hypotension, AFL with 1:1 conduction (in 3.5 − 5.0% of patients)
- Flecainide may induce mild QRS complex widening
- Do NOT use for pharmacological cardioversion of AFL

* ESC 2020

Efficacy of Flecainide for the Treatment of acute AF

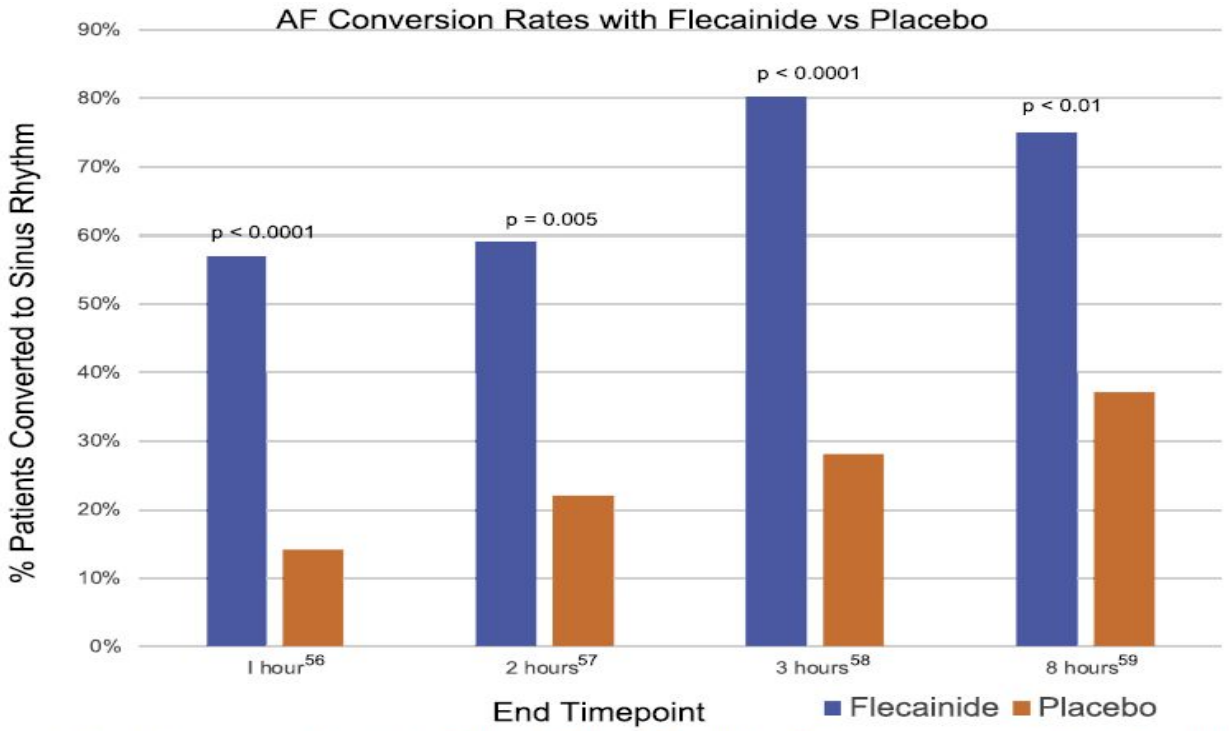
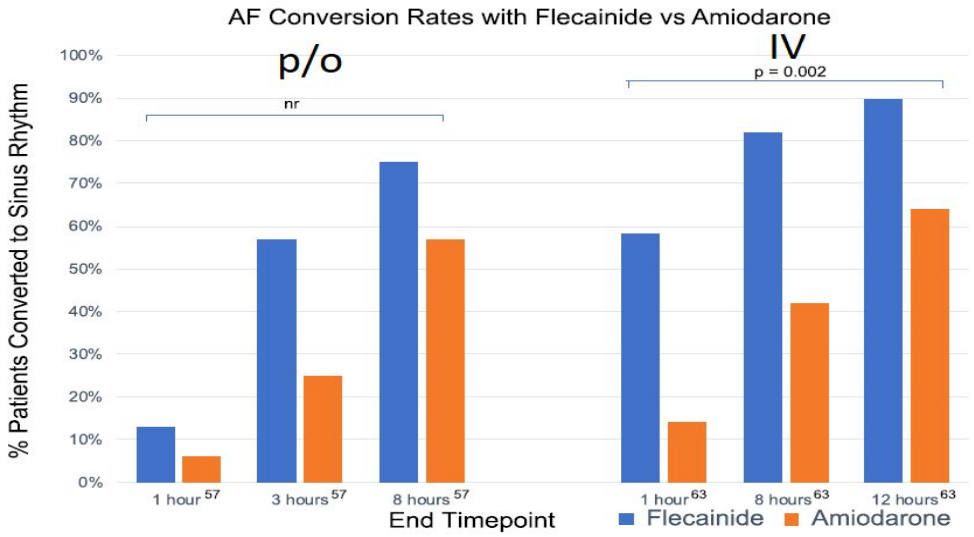


Figure 1. Acute AF conversion rates at 1 hour,[56] 2 hours,[57] 3 hours,[58] and 8 hours[59] after administration of flecainide or placebo.

End point time of **2 hours** flecainide administration was associated with a **69%** conversion rate compared with 16% with placebo.

Acute AF conversion rates at various time points after administration of p/o flecainide or IV amiodarone and IV flecainide or IV amiodarone

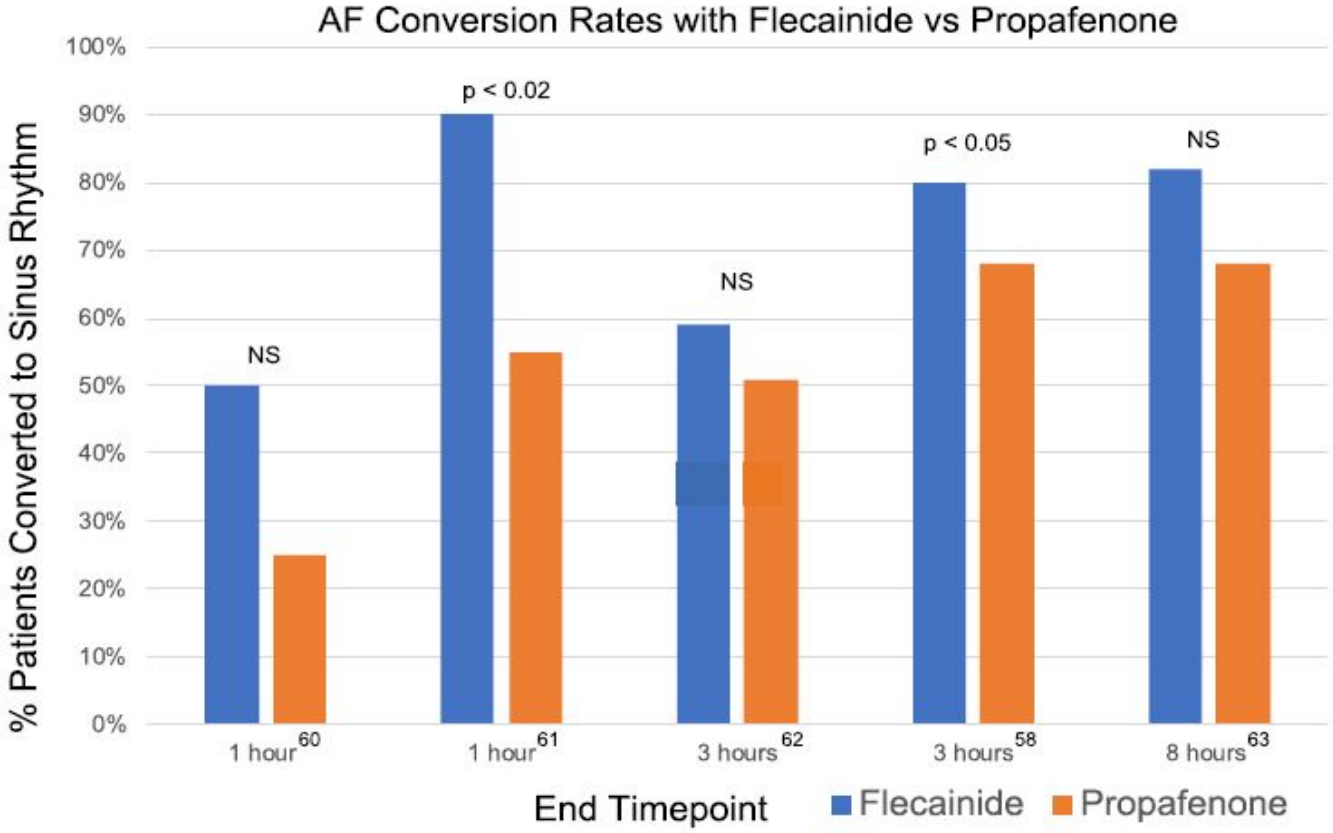


AF conversion rate within **3 hours** to be higher **with p/o flecainide 66%** compared with the IV amiodarone

Time point **8h** AF conversion rates higher **with p/o flecainide** vs IV amiodarone (73% vs 53%, p <0.05)

Echt D.S., Ruskin J.N. Use of Flecainide for the Treatment of Atrial Fibrillation. The Am. J. of Card. Vol. 125(7), 1 April 2020, Pages 1123-1133

Acute AF conversion rates at various time points after administration of flecainide or propafenone



In 5 randomized controlled studies, the conversion rate with **flecainide (range 50% to 90%)** was higher than with propafenone (range 25% to 72%)

Echt D.S., Ruskin J.N. Use of Flecainide for the Treatment of Atrial Fibrillation. The Am. J. of Card. Vol. 125(7), 1 April 2020, Pages 1123-1133

Pill-in-the-Pocket Approach

patients who are able to reliably self-identify symptomatic episodes of AF or are able to obtain confirmation from a wearable, implantable, or portable ECG monitoring device.

- **Propafenone 600 mg (single dose)**
- **Flecainide 300 mg (single dose)**

Recommendations	Class[a]	Level[b]
In selected patients with infrequent and recent-onset AF and no significant structural or ischaemic heart disease, a single self-administered oral dose of flecainide or propafenone ('pill in the pocket' approach) should be considered for patient-led cardioversion, but only following efficacy and safety assessment.[574,586,600,601]	IIa	B

PIP significantly reduced:
-number of emergency room visits;
-need for electrical cardioversion;
-the need for hospitalization

Andrade J.G. 2018
- In 165 patients subsequently self-treating 618 episodes of AF with flecainide or propafenone, the conversion rate was 94% and the mean AF duration was 113 ± 84 minutes.
- In 84% of the 165 patients, self-treatment was successful for all AF recurrences.

Chronic Suppression of AF

The primary role of chronic therapy with flecainide and other AADs is to delay the time to AF recurrence and reduce AF burden.

Outcome	Early Rhythm Control	Usual Care	Treatment Effect
First primary outcome — events/person-yr (incidence/100 person-yr)	249/6399 (3.9)	316/6332 (5.0)	0.79 (0.66 to 0.94)†
Components of first primary outcome — events/person-yr (incidence/100 person-yr)			
Death from cardiovascular causes	67/6915 (1.0)	94/6988 (1.3)	0.72 (0.52 to 0.98)‡
Stroke	40/6813 (0.6)	62/6856 (0.9)	0.65 (0.44 to 0.97)‡
Hospitalization with worsening of heart failure	139/6620 (2.1)	169/6558 (2.6)	0.81 (0.65 to 1.02)‡
Hospitalization with acute coronary syndrome	53/6762 (0.8)	65/6816 (1.0)	0.83 (0.58 to 1.19)‡

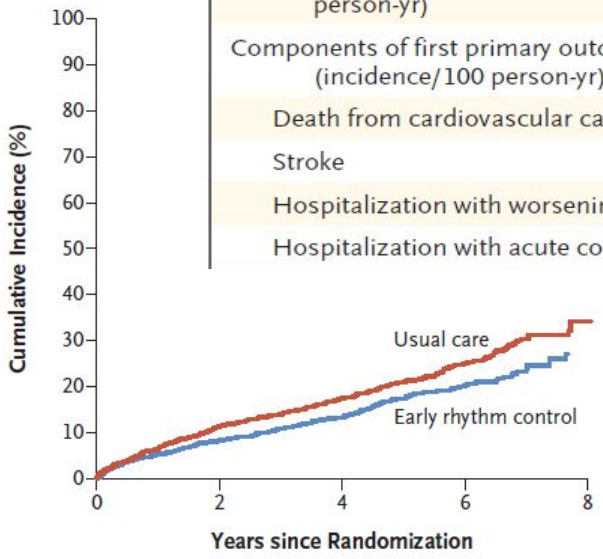


Figure 2. Aalen–Johansen Cumulative-Incidence Curves for the First Primary Outcome.

The first primary outcome was a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome.

Table 2 Relapse rates for different antiarrhythmic drugs reported in the literature[a]

	Mean relapse rate (range)	Studies (*n*)
No drug	69% (44–85)	10
Quinidine	59% (46–89)	11
Disopyramide	51% (46–56)	3
Propafenone	61% (54–70)	3
Flecainide	38% (19–51)	3
Sotalol	58% (51–63)	3
Amiodarone	47% (17–64)	4

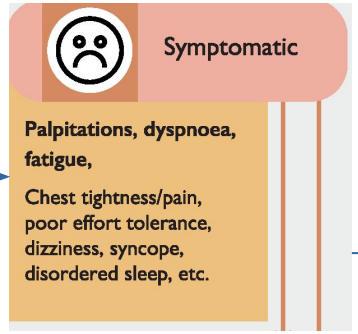
[a]Minimum 6-months follow-up.
Adapted from Levy et al.[108]

P. Kirchhof 2020 (In 135 centers, 2789 patients)

Etienne Aliot, 2011

Selection of AAD for Long-term therapy

Indication for AAD



Classification of AF-related symptoms (EHRA score)

EHRA class	Explanation
EHRA I	'No symptoms'
EHRA II	'Mild symptoms'; normal daily activity not affected
EHRA III	'Severe symptoms'; normal daily activity affected
EHRA IV	'Disabling symptoms'; normal daily activity discontinued

When to start AAD

→ Usually not for the first episode, but it may enhance efficacy of cardioversion

How to choose among AADs

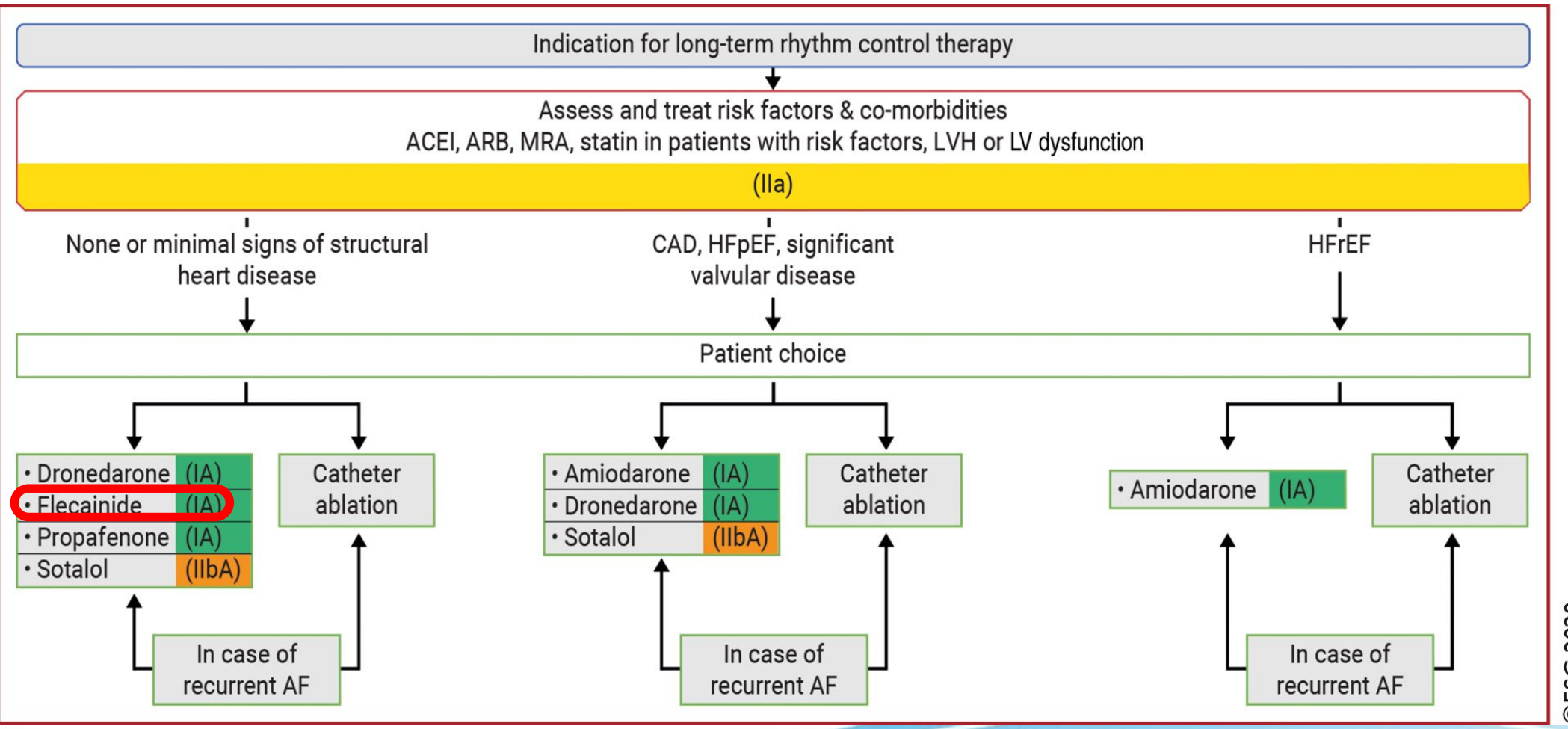
→ Minimize proarrhythmic risk and organ toxicity
- basal ECG abnormalities (QRS duration, PR, Qtc)
- LV function
- Risk factors for proarrhythmia may be dynamic and change over time

How to minimize proarrhythmic risk

→ - Evaluate ECG after the treatment
- Evaluate periodically for organ toxicity (amiodarone)
- Long-term Holter monitoring and exercise test in selected cases

Avoid AAD combinations

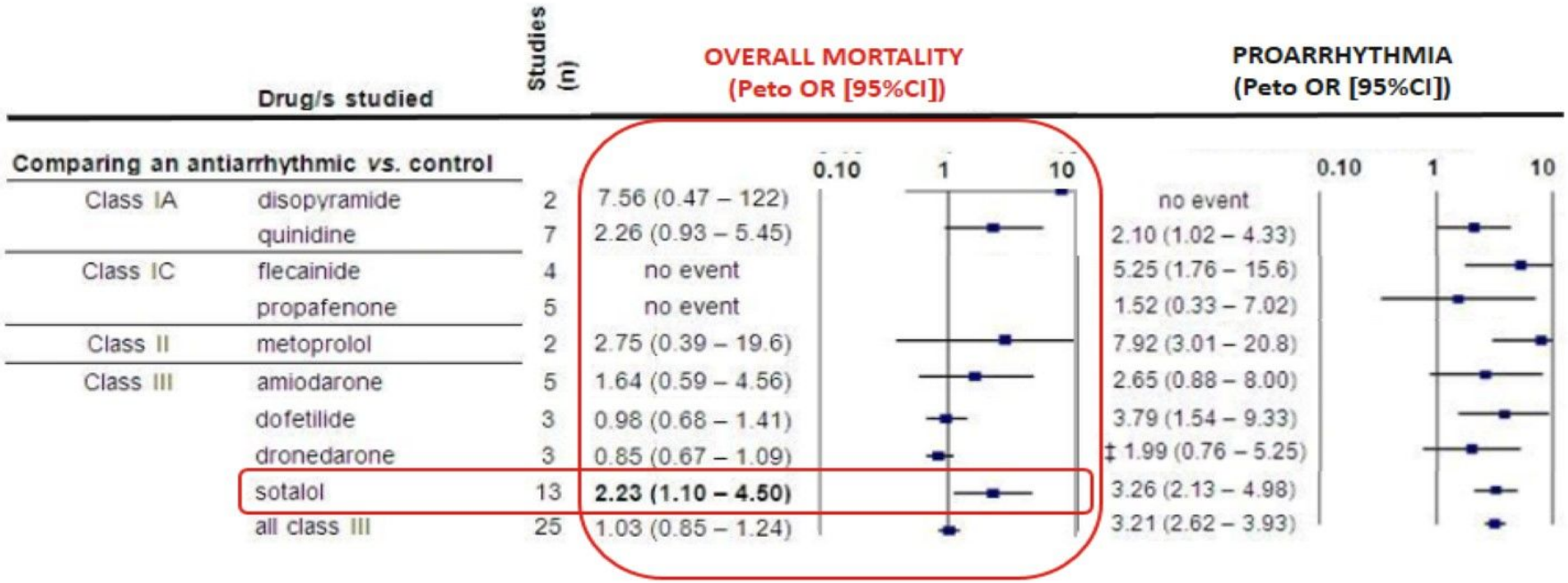
Adopted from guidelines ASC 2020


Indication for long-term rhythm control therapy
Assess and treat risk factors & co-morbidities
ACEI, ARB, MRA, statin in patients with risk factors, LVH or LV dysfunction
(IIa)
None or minimal signs of structural heart disease
CAD, HFpEF, significant valvular disease
HFrEF
Patient choice
• Dronedarone (IA)
• Flecainide (IA)
• Propafenone (IA)
• Sotalol (IIbA)
Catheter ablation
In case of recurrent AF
• Amiodarone (IA)
• Dronedarone (IA)
• Sotalol (IIbA)
Catheter ablation
In case of recurrent AF
• Amiodarone (IA)
Catheter ablation
In case of recurrent AF

Cochrane Review

- Review of AADs for maintaining sinus rhythm after cardioversion of AF
- Included RCTs comparing AADs with either control or another AAD
  - 59 RCTs
  - ~21,000 participants
  - Mean follow-up of 10.2 months

Cochrane Review
All-Cause Mortality



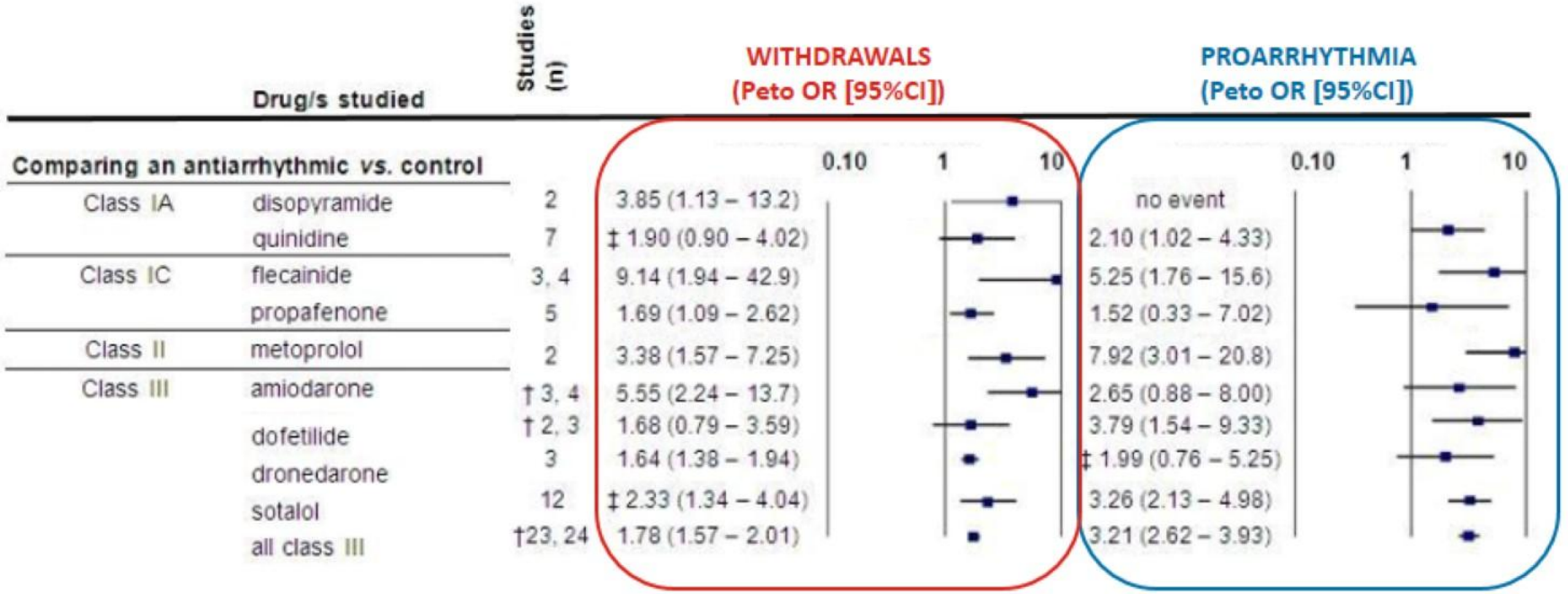
Drug/s studied		Studies (n)	OVERALL MORTALITY (Peto OR [95%CI])	PROARRHYTHMIA (Peto OR [95%CI])
Comparing an antiarrhythmic *vs.* control				
Class IA	disopyramide	2	7.56 (0.47 – 122)	no event
	quinidine	7	2.26 (0.93 – 5.45)	2.10 (1.02 – 4.33)
Class IC	flecainide	4	no event	5.25 (1.76 – 15.6)
	propafenone	5	no event	1.52 (0.33 – 7.02)
Class II	metoprolol	2	2.75 (0.39 – 19.6)	7.92 (3.01 – 20.8)
Class III	amiodarone	5	1.64 (0.59 – 4.56)	2.65 (0.88 – 8.00)
	dofetilide	3	0.98 (0.68 – 1.41)	3.79 (1.54 – 9.33)
	dronedarone	3	0.85 (0.67 – 1.09)	‡ 1.99 (0.76 – 5.25)
	sotalol	13	**2.23 (1.10 – 4.50)**	3.26 (2.13 – 4.98)
	all class III	25	1.03 (0.85 – 1.24)	3.21 (2.62 – 3.93)

- Sotalol is associated with increased all-cause mortality (RR = 2.23)
  - NNTH = 102 participants treated for 1 year to have 1 additional death

Lafuente-Lafuente et al. *Cochrane Database Syst Rev*. 2015;3:CD005049.
Valembois, et al. *Cochrane Database Syst Rev*. 2019;9:CD005049.

Sotalol

Cochrane Review
Adverse Effects and Proarrhythmia



- All analyzed drugs reduced the recurrence of AF
- All analyzed drugs also increased withdrawals due to side effects
- Virtually all analyzed drugs showed increased proarrhythmic effects

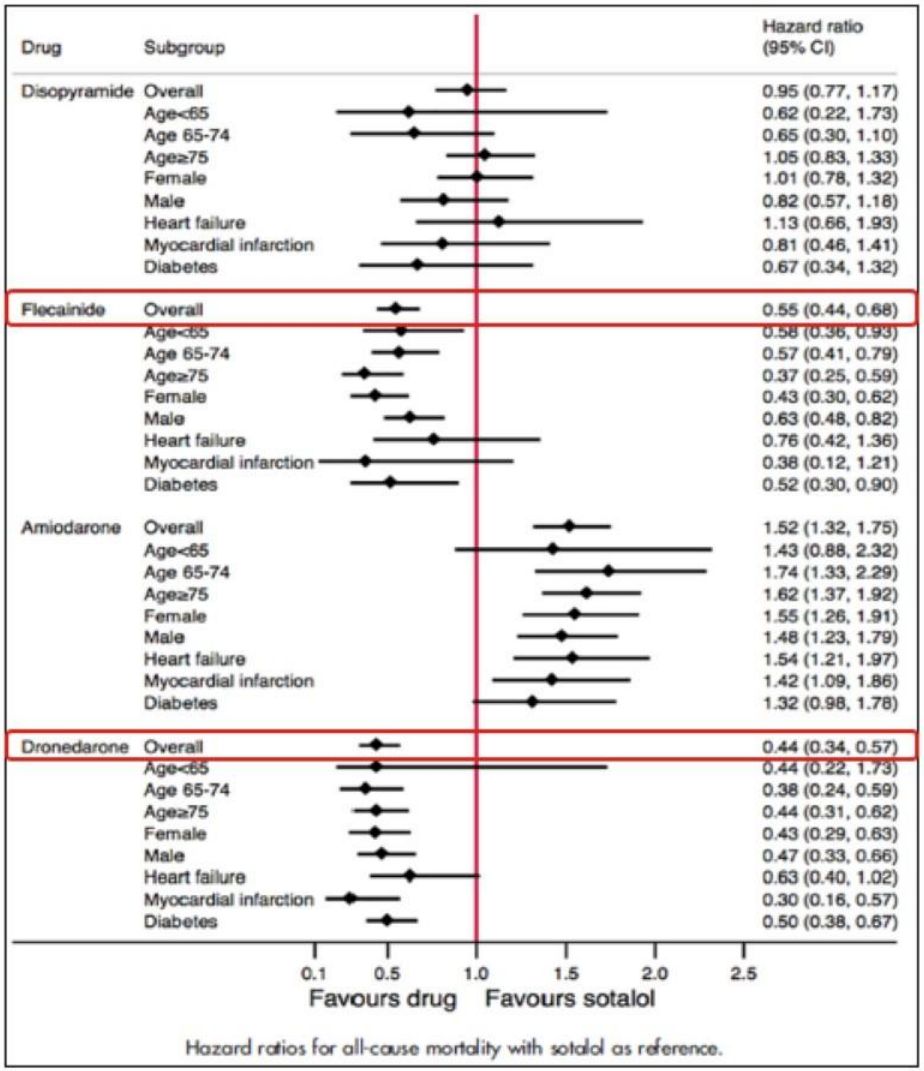
Lafuente-Lafuente et al. *Cochrane Database Syst Rev*. 2015;3:CD005049.
Valembois, et al. *Cochrane Database Syst Rev*. 2019;9:CD005049.

Real-World Data
Erlich, et al. 2019

- Real-world data from Germany
- ~ 3500 patients prescribed dronedarone and ~ 17,000 patients on other AADs (amiodarone, flecainide, propafenone, or sotalol)
- Spanned 1258 general and 62 cardiology practices (IQVIA database) during 2010-2017

Ehrlich JR, et al. *Int J Cardiol*. 2019;278:126-132.

Real-World Data
Friberg 2018

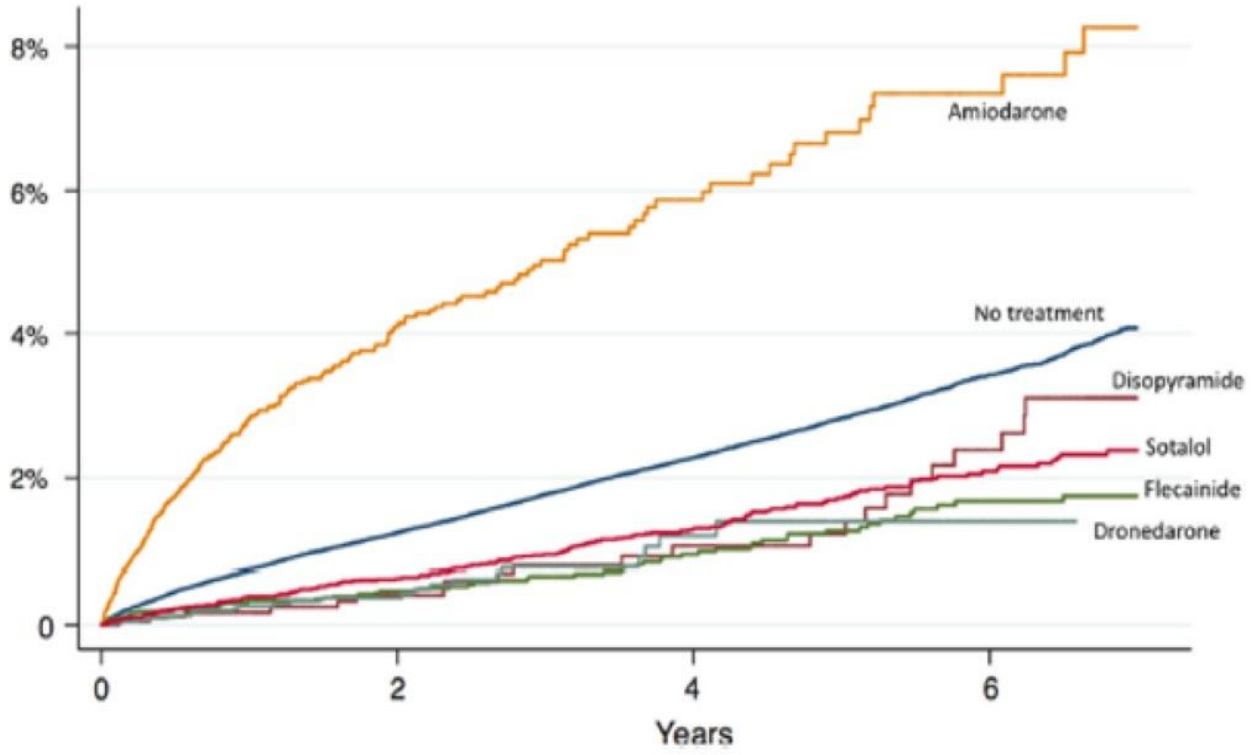


- Mortality compared with sotalol:
  - Dronedarone: HR = 0.44
  - Flecainide: HR = 0.55
  - Amiodarone: HR = 1.52

Friberg L. *Am Heart J.* 2018;205:118-127.

Real-World Data
Friberg 2018

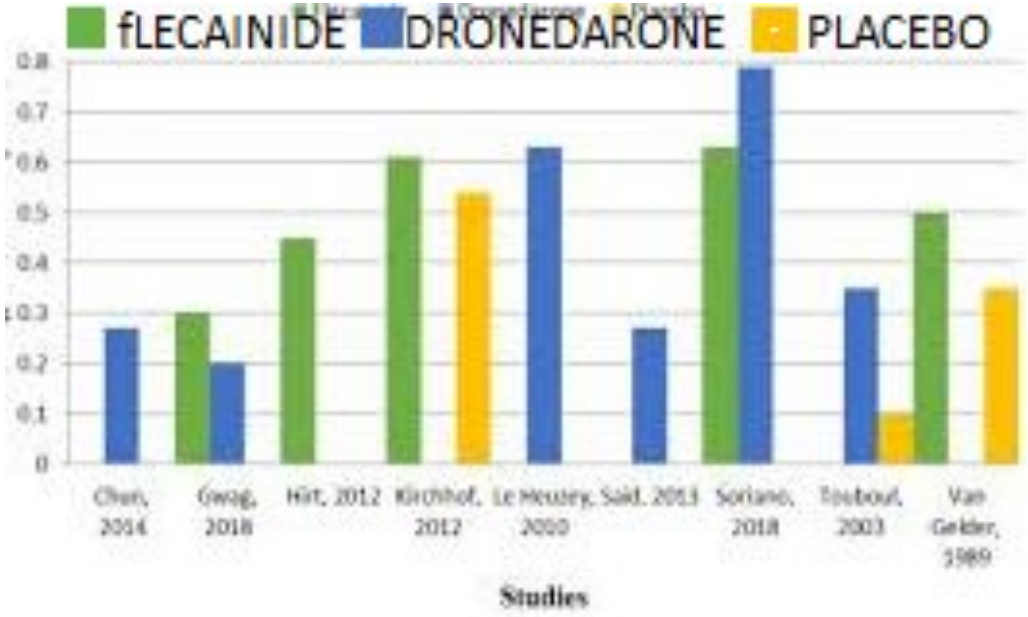
- Risk of main arrhythmic endpoint, compared with sotalol:
  - Flecainide: HR 0.95
  - Amiodarone: HR 2.61



Friberg L. *Am Heart J.* 2018;205:118-127.

Comparison of dronedarone vs. flecainide in the maintenance of sinus rhythm, following electrocardioversion in adults with persistent atrial fibrillation: a systematic review and meta-analysis

Hannah Wilson, 2020



Encompassing 1349 persistent AF dronedarone and flecainide displayed similar efficacy in maintaining SR in patients following electrocardioversion for persistent AF (p>0,05).

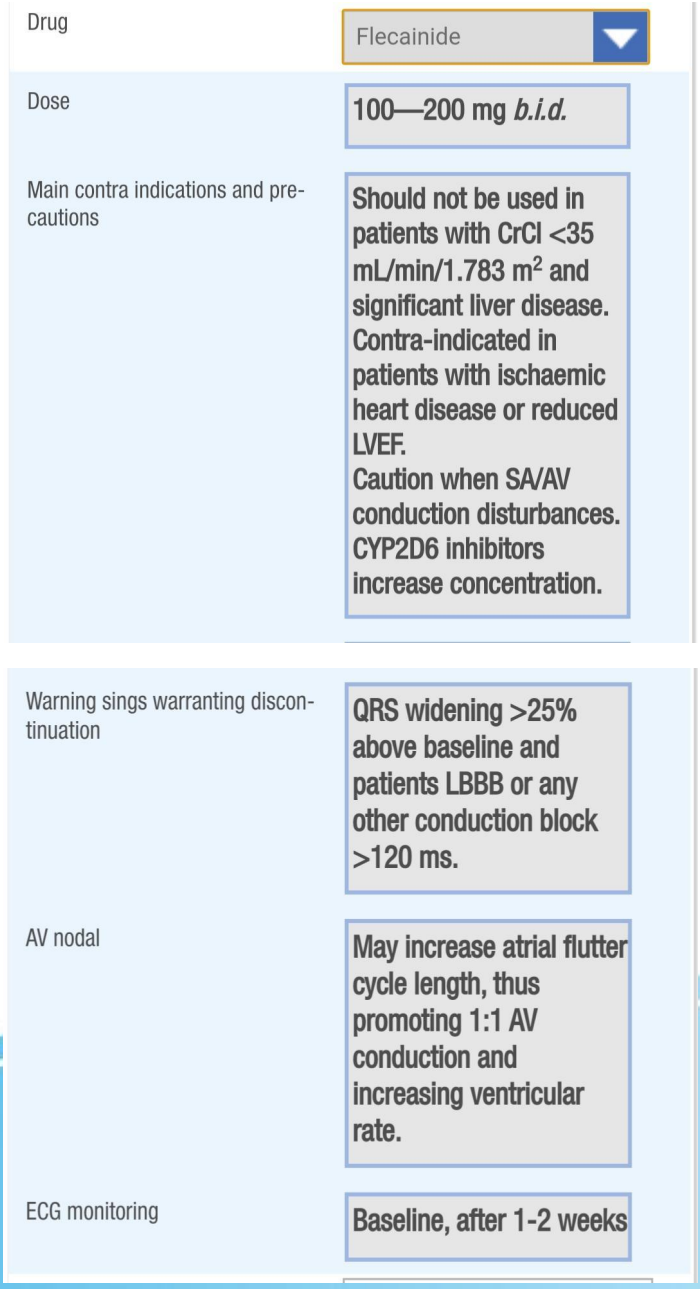
Flecainide for chronic suppression of AF

1. For the chronic prevention of AF recurrence, it is not necessary to hospitalize the patient for initiation of therapy.

2. important to obtain 12-lead ECGs at baseline, at steady state and before increasing the dosage.

3. echocardiogram to document the presence of normal LV function and exercise stress testing to rule out the presence of inducible myocardial ischemia before the initiation of chronic oral therapy.

4. Flecainide is usually initiated at 100 mg bid, though a minority of patients will respond to doses as low as 50 mg BID.



Drug	Flecainide
Dose	100—200 mg *b.i.d.*
Main contra indications and pre-cautions	Should not be used in patients with CrCl <35 mL/min/1.783 m^2 and significant liver disease. Contra-indicated in patients with ischaemic heart disease or reduced LVEF. Caution when SA/AV conduction disturbances. CYP2D6 inhibitors increase concentration.
Warning sings warranting discon-tinuation	QRS widening >25% above baseline and patients LBBB or any other conduction block >120 ms.
AV nodal	May increase atrial flutter cycle length, thus promoting 1:1 AV conduction and increasing ventricular rate.
ECG monitoring	Baseline, after 1-2 weeks

Conclusion

1. Flecainide acetate is highly effective for the acute termination of recent onset AF and is moderately effective for the chronic suppression of AF.

2. The drug has an excellent safety profile when administered to patients with minimal or no structural heart disease.

3. The PiP approach avoids the need for these patients to seek emergency care.

4. Prophylactic AAD flecainide therapy during the blanking period following catheter ablation has been found to be an effective strategy even in previously drug refractory patients.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