Farmaci antiaritmici nella FA:terapia personalizzata

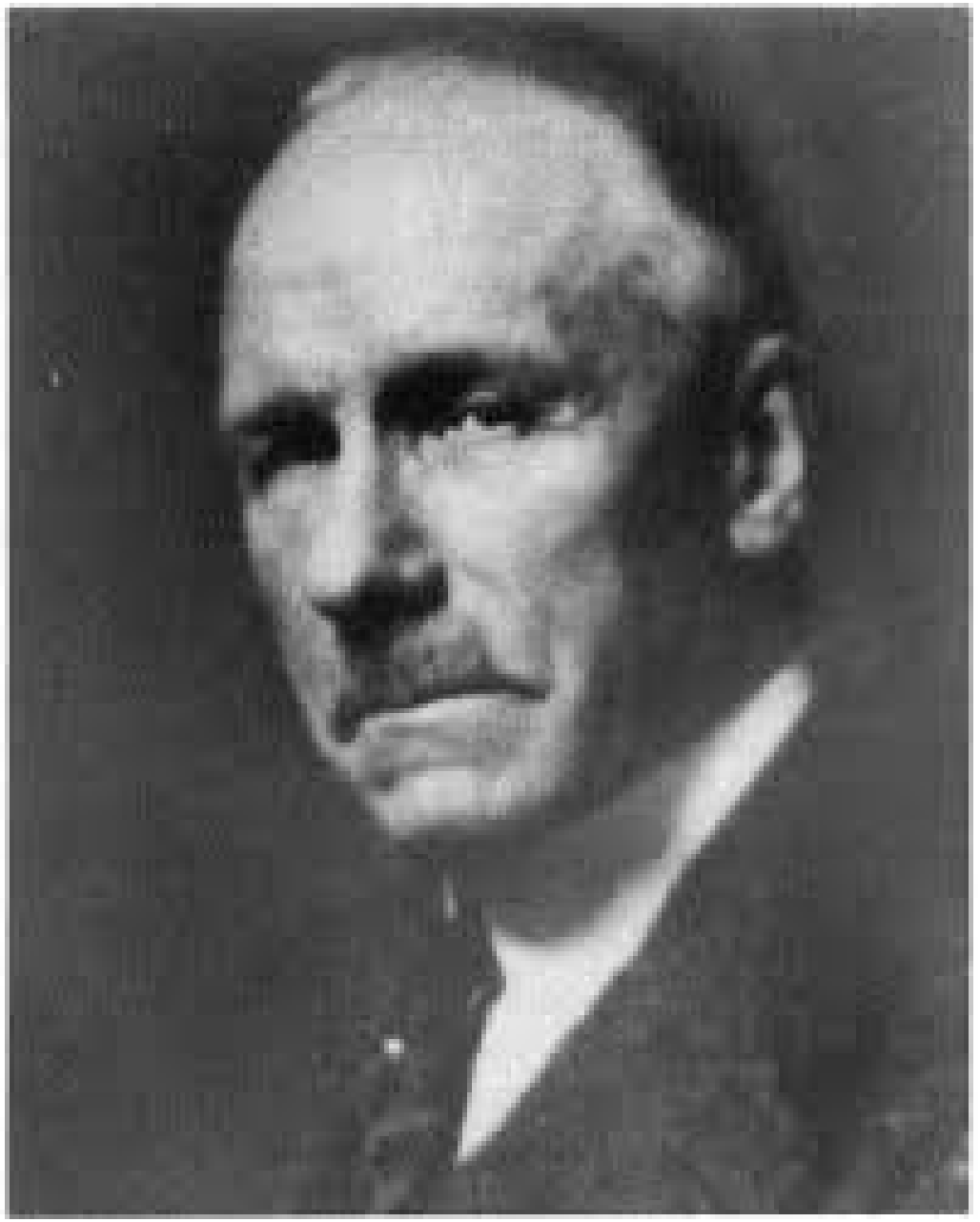
- Prof Alessandro Capucci, MD,FESC,FACC

PLACE IX Edizione Roma 29sett-1 ott, 2022

CINCHONA DERIVATIVES IN THE TREATMENT OF HEART DISORDERS *

K. F. WENCKEBACH
VIENNA, AUSTRIA

The first arrhythmia in which I had complete success with small doses of quinin (from 0.3 to 0.4 gm.) was extrasystole. It is well known that until that time we had no generally satisfying drug or method of treatment of this very common and innocuous, but at the same time very disagreeable, form of arrhythmia. For



Present situation – Davit vs Goliath

Fleca: 7.98€
Propa: 4,09 €
Amio: 5,81 €

- AADs are “cheap old (generic) drugs”
  - Generics do not receive support from anyone
  - Pivotal trials were performed “in the old times” (before 2008) when treatment of AF and comorbidities was very different from today´s
- *Nobody gives a nickel* for the AADs, particularly cardiac electrophysiologists
  - They “need ADDs” to maintain many patients free from recurrences following ablation
- Meetings interested only NOACs, catheters, techniques, devices and procedures but ….. forget AADs
- So, it's not a surprise <u>how bad we use AADs</u>

Personal disclosures

Speaker fees from:

- Abbot
- Bayer
- Boheringer
- Medtronic
- Sanofi
- Boston Scientific
- Liva Nova
- Part of steering committee in sponsored studies: Pfizer,Biotronik,Boston.

Conoscenza delle proprietà dei farmaci

- Effetto elettrofisiologico

Classificazione farmacologica secondo Vaughan-Williams

La più utilizzata classificazione dei farmaci antiaritmici individua 4 fondamentali classi in relazione al principale meccanismo con cui le molecole interferiscono con le correnti ioniche (e di conseguenza con le fasi del potenziale d'azione)

Classe I: **Farmaci che bloccano i canali veloci del Na^+**

Classe Ia – ripolarizzazione ritardata

Classe Ib – ripolarizzazione accelerata (riduzione pda)

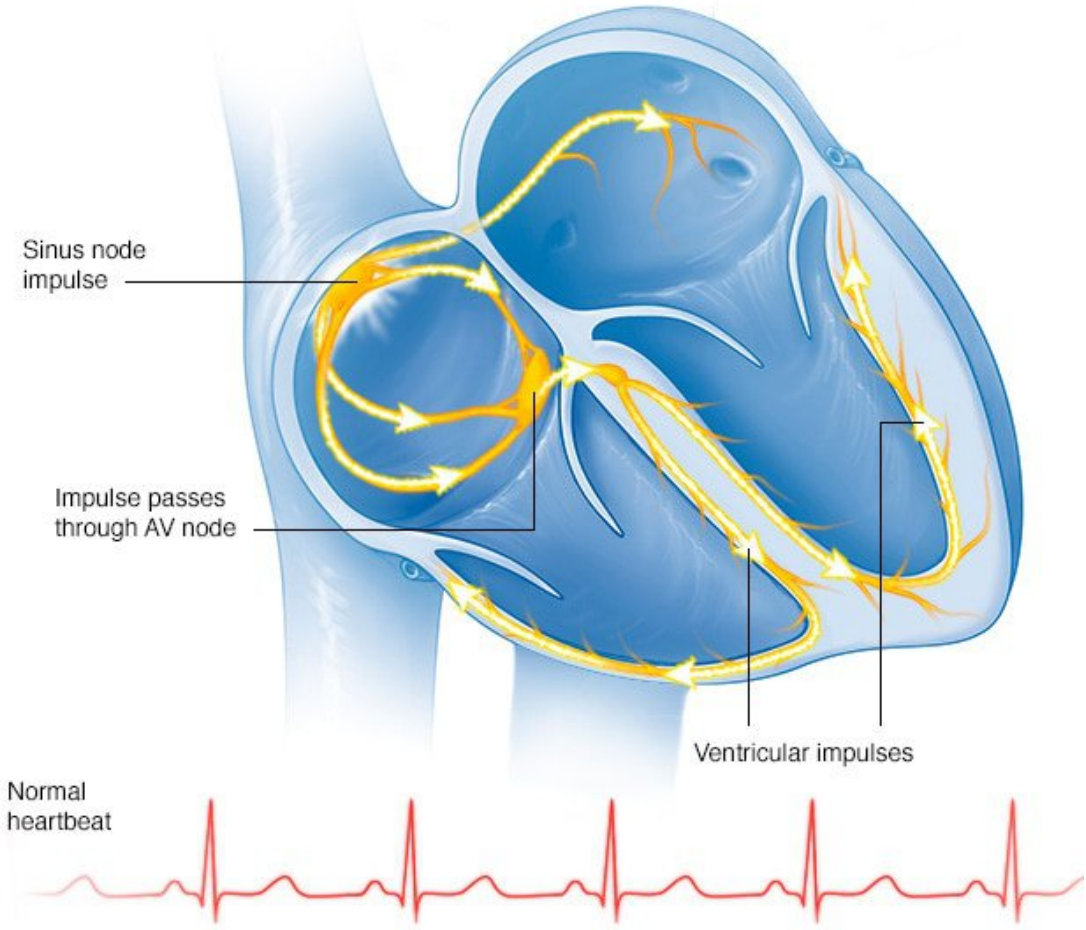
Classe Ic – ripolarizzazione marginalmente influenzata

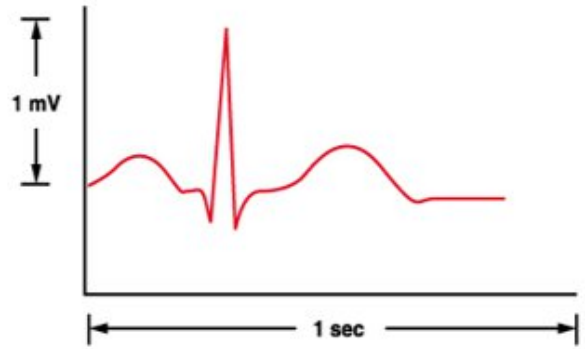
Classe II: **Farmaci β-bloccanti**

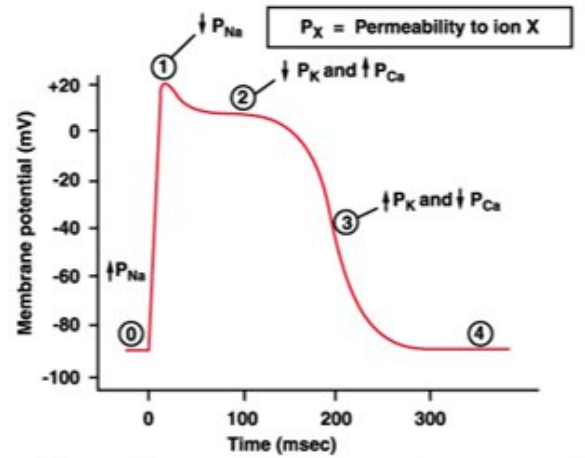
Classe III: **Antagonisti dei canali del K^+**

prolungamento del periodo refrattario

Classe IV: **Farmaci bloccanti dei canali del Ca^{2+}**







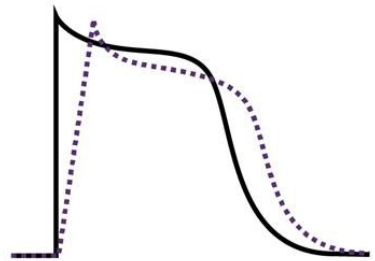
Phase	Membrane channels
⓪	Na^+ channels open
①	Na^+ channels close
②	Ca^{2+} channels open; fast K^+ channels close
③	Ca^{2+} channels close; slow K^+ channels open
④	Resting potential

Class I

Decreased slope of phase 0 depolarization

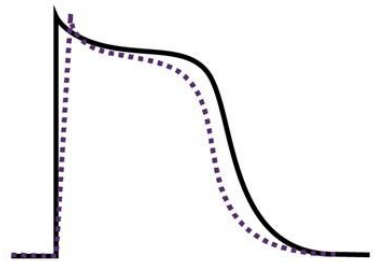
Class IA

↑ ERP
↑ AP duration



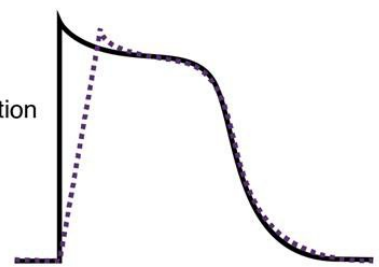
Class IB

↓ ERP
↓ AP duration



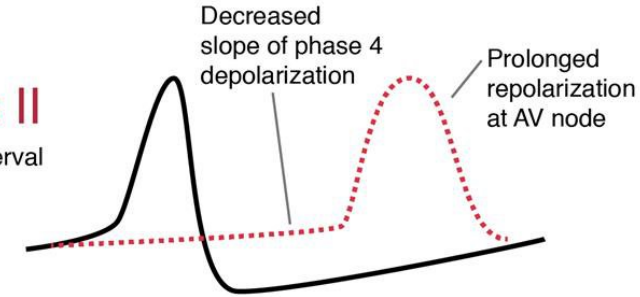
Class IC

Normal ERP
Normal AP duration



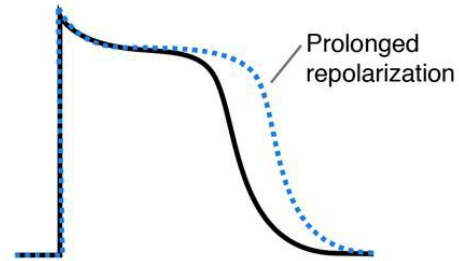
Class II

↑ PR interval



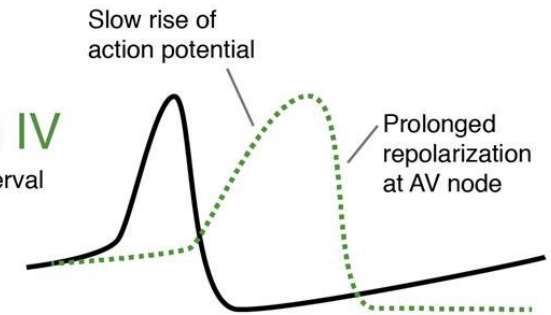
Class III

↑ ERP
↑ AP duration



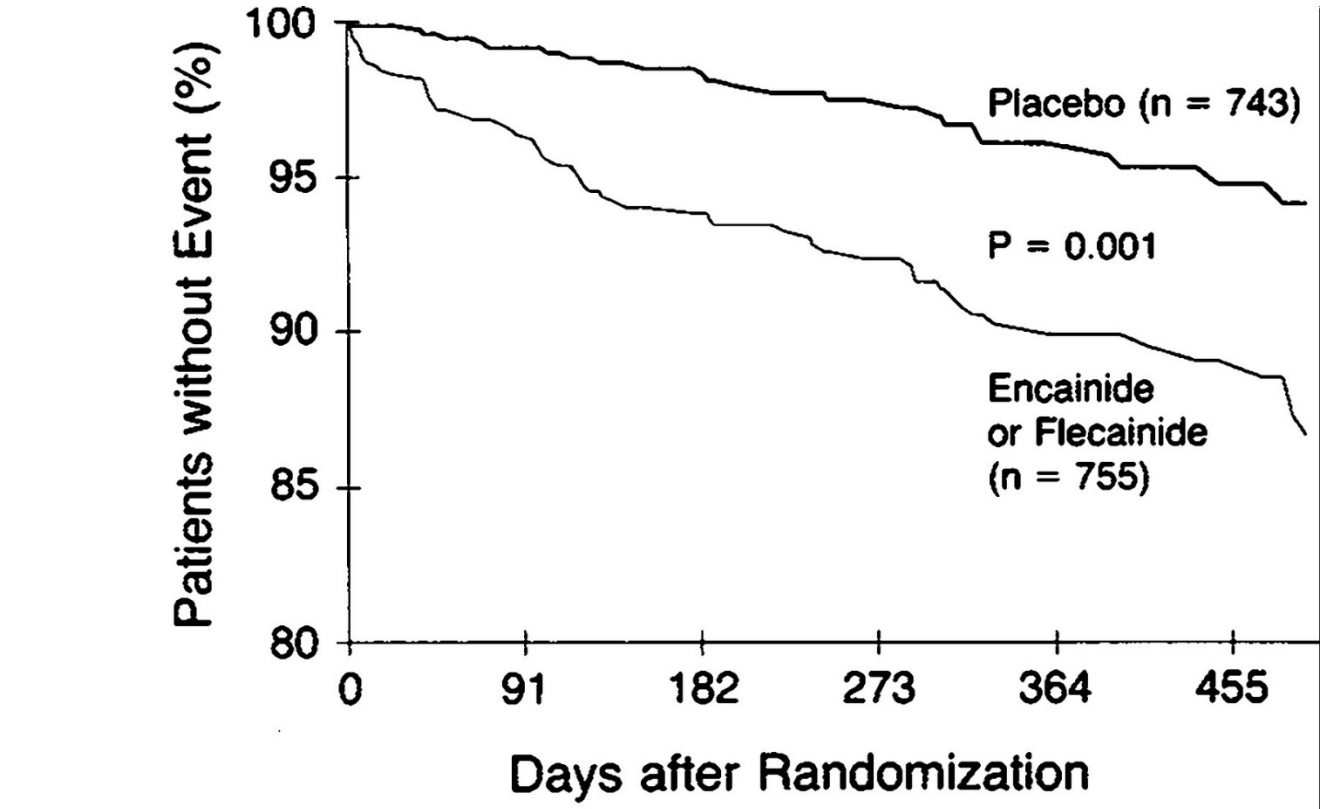
Class IV

↑ PR interval
↑ ERP



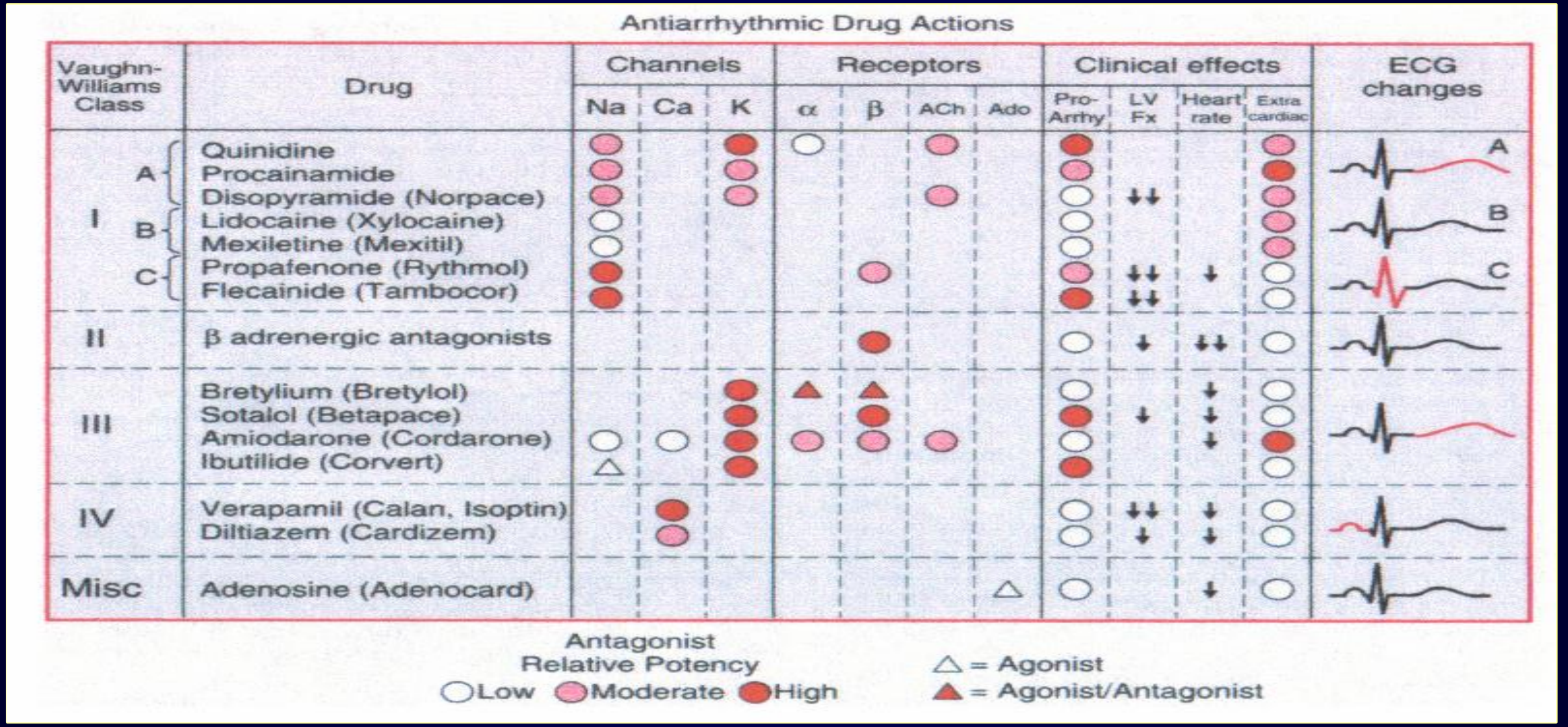
Nel 1989 lo studio CAST (Cardiac Arrhythmias Suppression Trial)

ha dimostrato che i farmaci antiaritmici possono essere potenzialmente pericolosi, sopratutto in presenza di cardiopatie strutturali e a dosi elevate.



Placebo	743	625	516	412	292	181
Active drug	755	619	507	392	286	186

AZIONE DEI FARMACI ANTIARITMICI



Nel 1991, il “Sicilian Gambit” ha proposto una nuova e più realistica classificazione degli anti-aritmici

MECCANISMI ARITMOGENI	ARITMIA	PARAMETRO VULNERABILE	FARMACI
1. AUTOMATISMO			
- Normale esaltato	T Sinusale T Ventr Id	Dep diast	β-Bloccanti Ca bloccanti
- Anomalo	TA, R Id accel	Dep diast	Na, Ca bloccanti
2. ATTIVITÀ TRIGGER			
- EAD *(Early After Depolar)*	Tors. Punta	Durata PA	β-Agonisti, vagolitici Ca, Na bloccanti
- DAD *(Delayed After Depolarization)*	A Digitale TV ↑ T Simp	↑ Ca^{++} ↑Ipert Simp	Na bloccanti Ca bloccanti β, Ca bloccanti
3. RIENTRO DIPENDENTE DA CANALI DEL SODIO			
- Alterata conduzione	Flutter A (I) T in WPW	Eccitabilità Conduzione	Na bloccanti (non attivi atrio)
- Alterata refrattarietà	Flutter A (II) FA, FV	Periodo refrattario	K bloccanti
4. RIENTRO DIPENDENTE DA CANALI DEL CALCIO			
	rientro AV WPW	Conduzione Eccitabilità	Ca bloccanti

Editorials

Redefining the Role of Antiarrhythmic Drugs

THE growing recognition of the potentially harmful effects of antiarrhythmic drugs[1] and the subsequent proof from controlled trials that some of these drugs can increase the risk of death in some patients have led to a decline in their use.[2,3] This change in practice has been fueled by the widespread application of nonpharmacologic therapies, such as implantable defibrillators and radio-frequency catheter ablation, which have now become the dominant

currence of arrhythmias was substantially lower in the sotalol group.[8]

The study by Pacifico and coworkers in this issue of the *Journal* confirms and extends those findings in a placebo-controlled trial of 302 patients who received an implantable cardioverter–defibrillator and who were then randomly assigned to receive sotalol or placebo.[9] As compared with placebo, sotalol was associated with a significant (48 percent) reduction in the risk of the primary end point (death from any cause or the delivery of a first shock for any reason), primarily as a result of a reduction in the frequency of shocks due to any cause. In a subgroup analysis, sotalol reduced the frequency of death and appropriate shocks by 44 percent and of death and inappropriate shocks by 64 percent, and it was equally effective whether the left ventricular ejection frac-

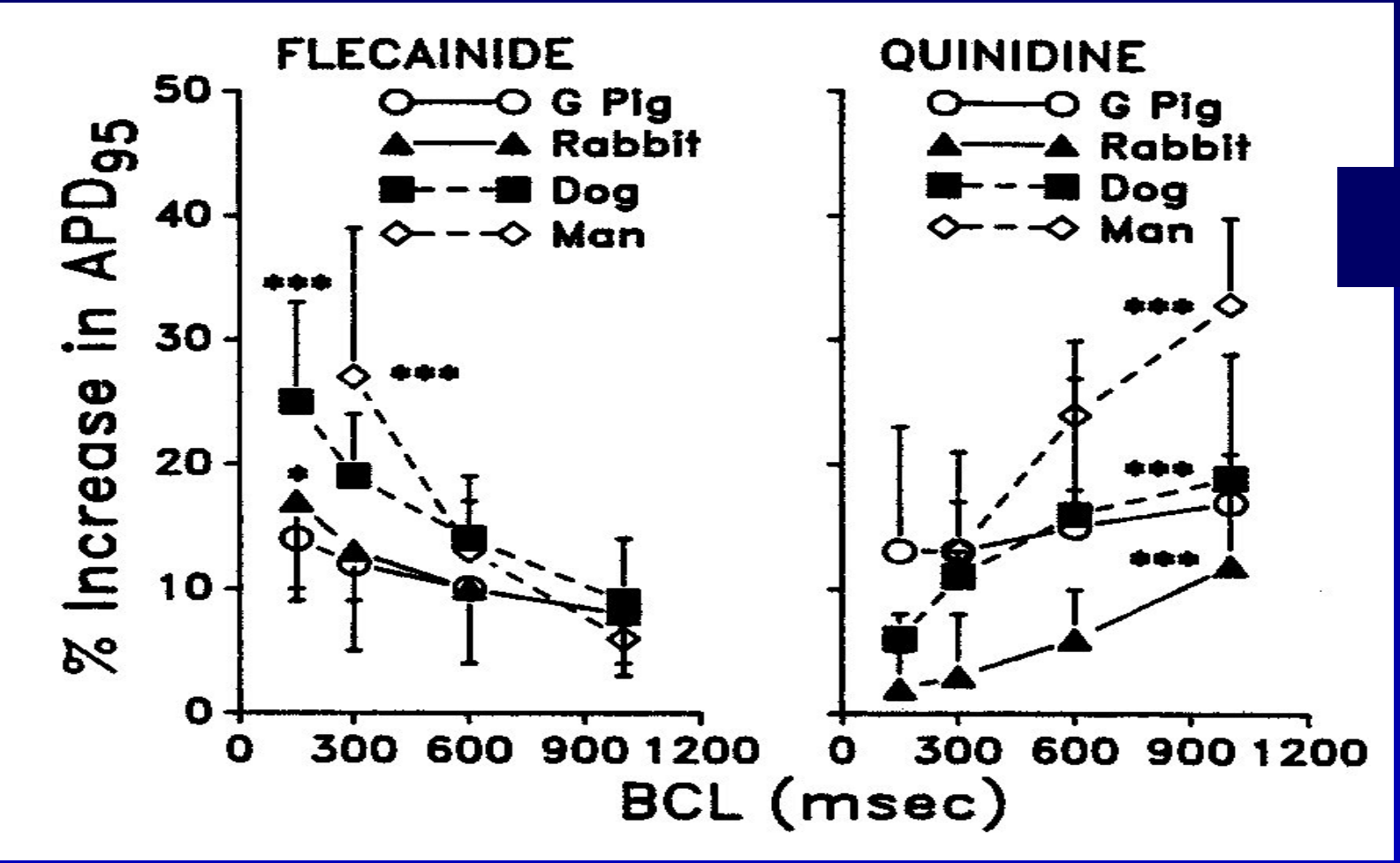
"The growing recognition of the potentially harmful effects of antiarrhythmic drugs and the subsequent proof from controlled trials that some of these drugs can increase the risk of death in some patients have led to a decline in their use. This change in practice has been fueled by the widespread application of nonpharmacologic therapies, such as implantable defibrillators and radio-frequency catheter ablation, which have now become the dominant types of therapy for many patients with ventricular and supraventricular arrhythmias."

the adjunctive use of antiarrhythmic drugs in this situation is an attractive idea, there are few data from controlled trials to support this approach. In one study, patients with ventricular arrhythmias who had no response to sotalol received an implantable defibrillator and were then randomly assigned to continue sotalol therapy or to receive no additional treatment. During follow-up, the rate of re-

toration of sinus rhythm is important in some patients, such as those with congestive heart failure, which may be exacerbated by atrial fibrillation, even when the heart rate is controlled. Although internal cardioversion (i.e., with the use of a catheter) is often effective when external cardioversion fails to restore sinus rhythm, this invasive procedure is not widely available and is associated with potentially se-

PHILIP J. PODRID - 1999

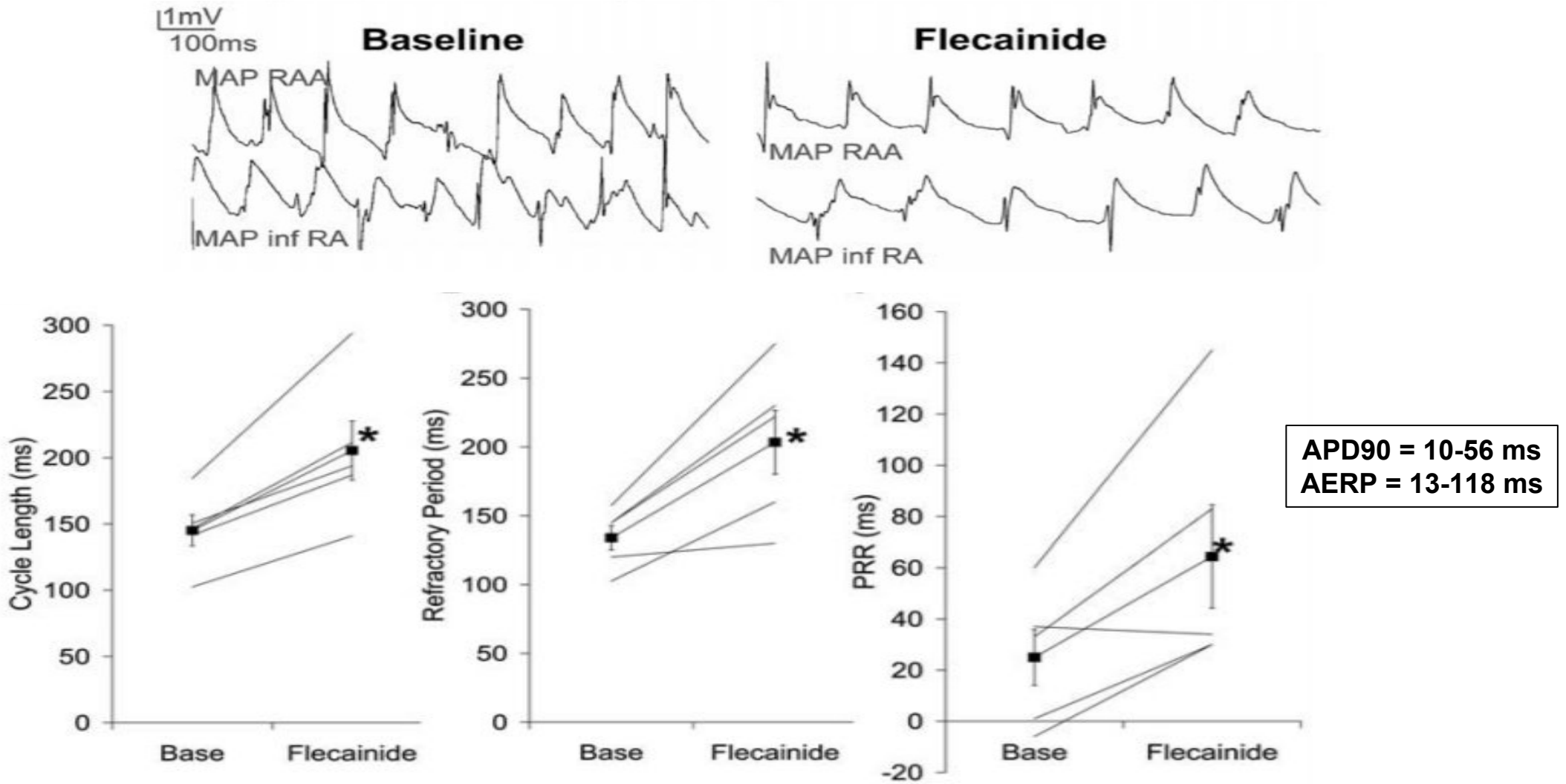
Flecainide prolongs atrial APD and refractoriness at fast rates (Wang et al. Circ Res 1992;71:271-287)



Reverse use-dependence

1. Flecainide has no effect on QT interval, but produces a rate-dependent prolongation in atrial APD and refractoriness (exerts a class III effect)
- Slows the recovery kinetics of Na^+ channels at fast rates

Flecainide prolong atrial cycle length and refractoriness and induces atrial postrepolarization refractorines in patients with persistent AF



APD90 = 10-56 ms
AERP = 13-118 ms

Kirchhof P et al. Basic Res Cardiol 2005;100:112-21.

Indicazioni all’ impiego dei farmaci

- Valutazioni cliniche

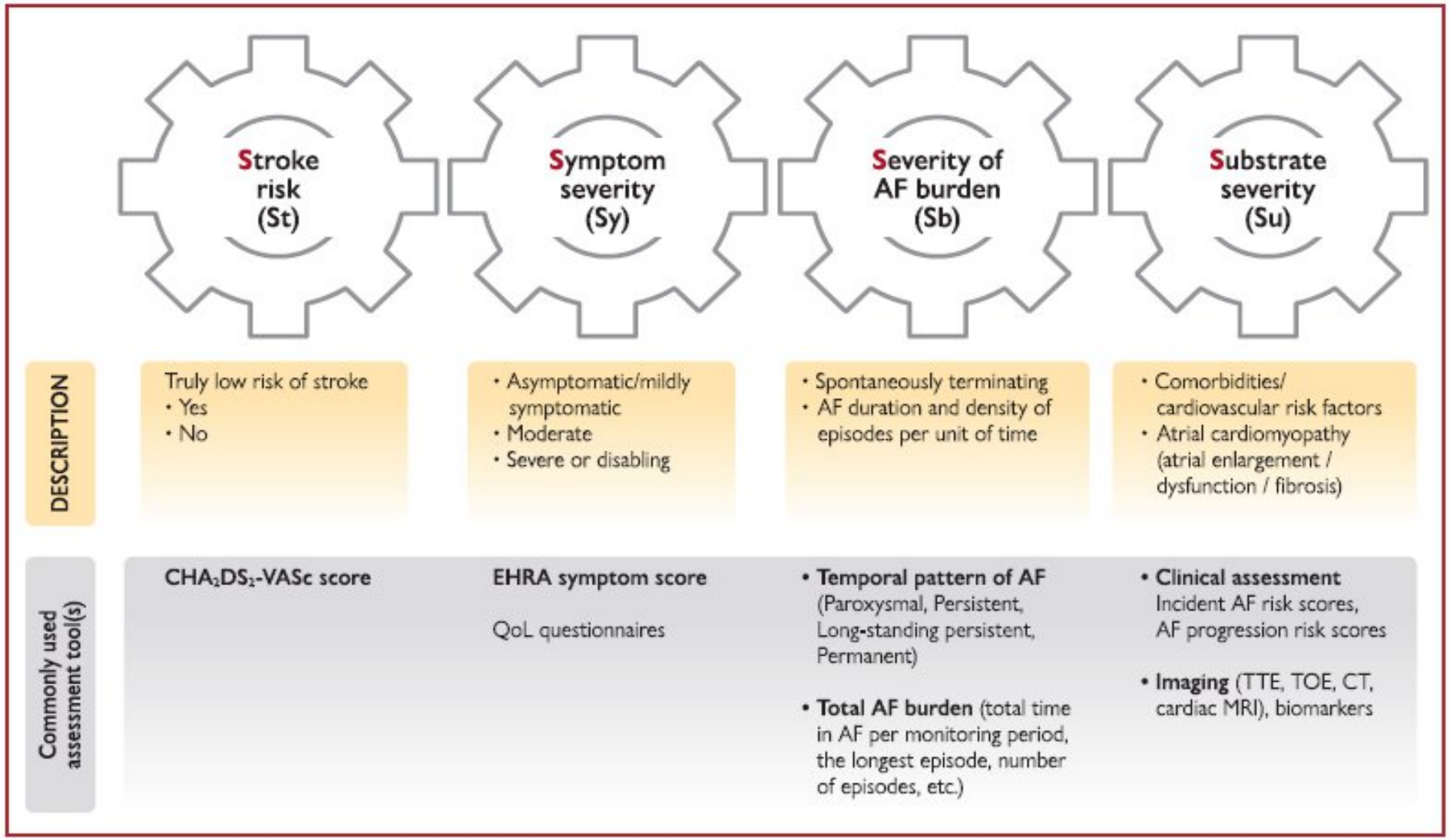


Figure 5 4S-AF scheme as an example of structured characterization of AF.[151] AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); CT = computed tomography; EHRA = European Heart Rhythm Association; LA = left atrium; MRI = magnetic resonance imaging; QoL = quality of life; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

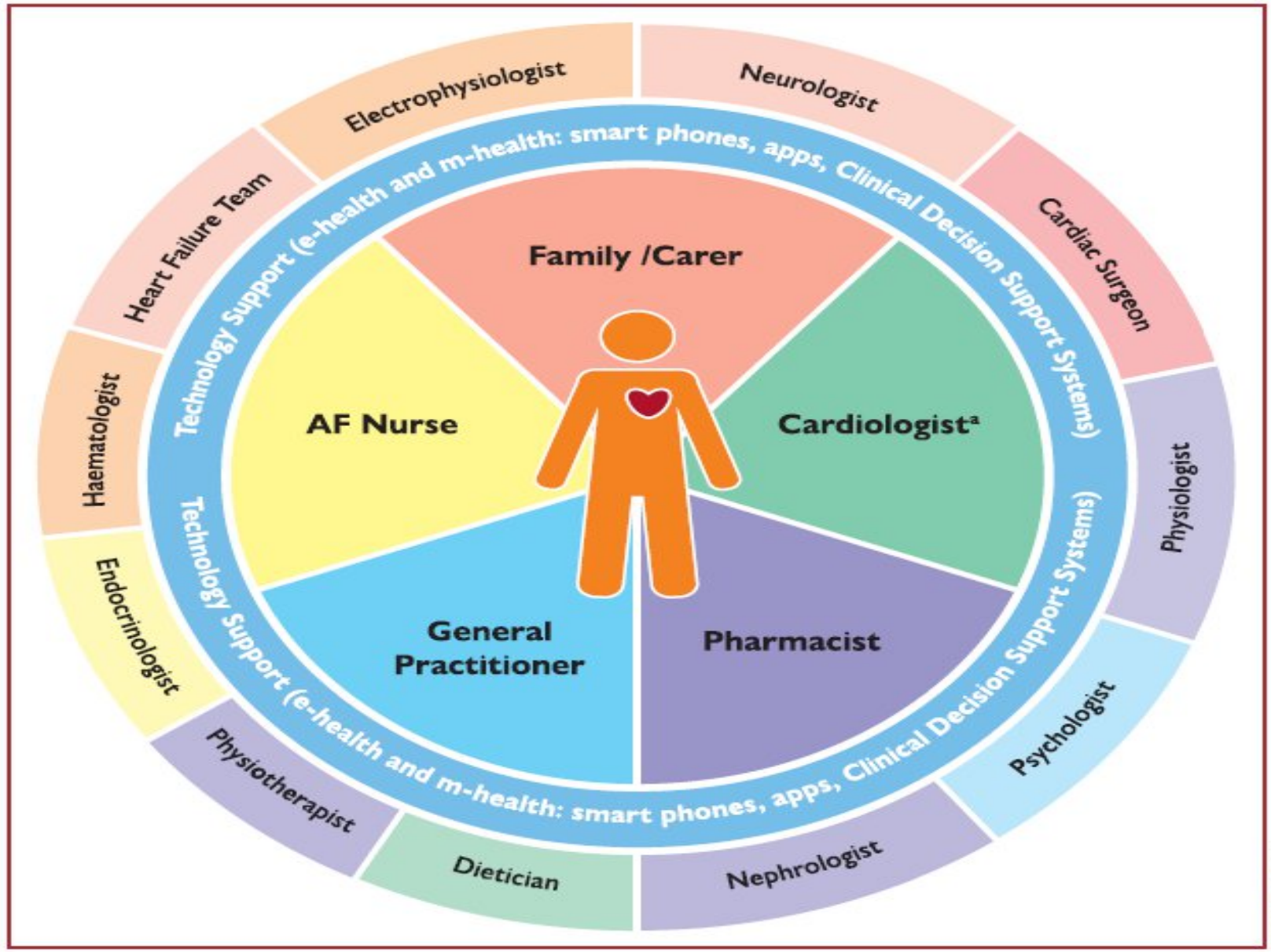


Figure 11 Integrated AF management team (an example). The figure gives an example on the potential composition of AF teams showing a varie different specialists supporting individual patients as needed. AF = atrial fibrillation. [a]According to local standards, this could be a general cardiologist special interest in arrhythmias/AF or an electrophysiologist.

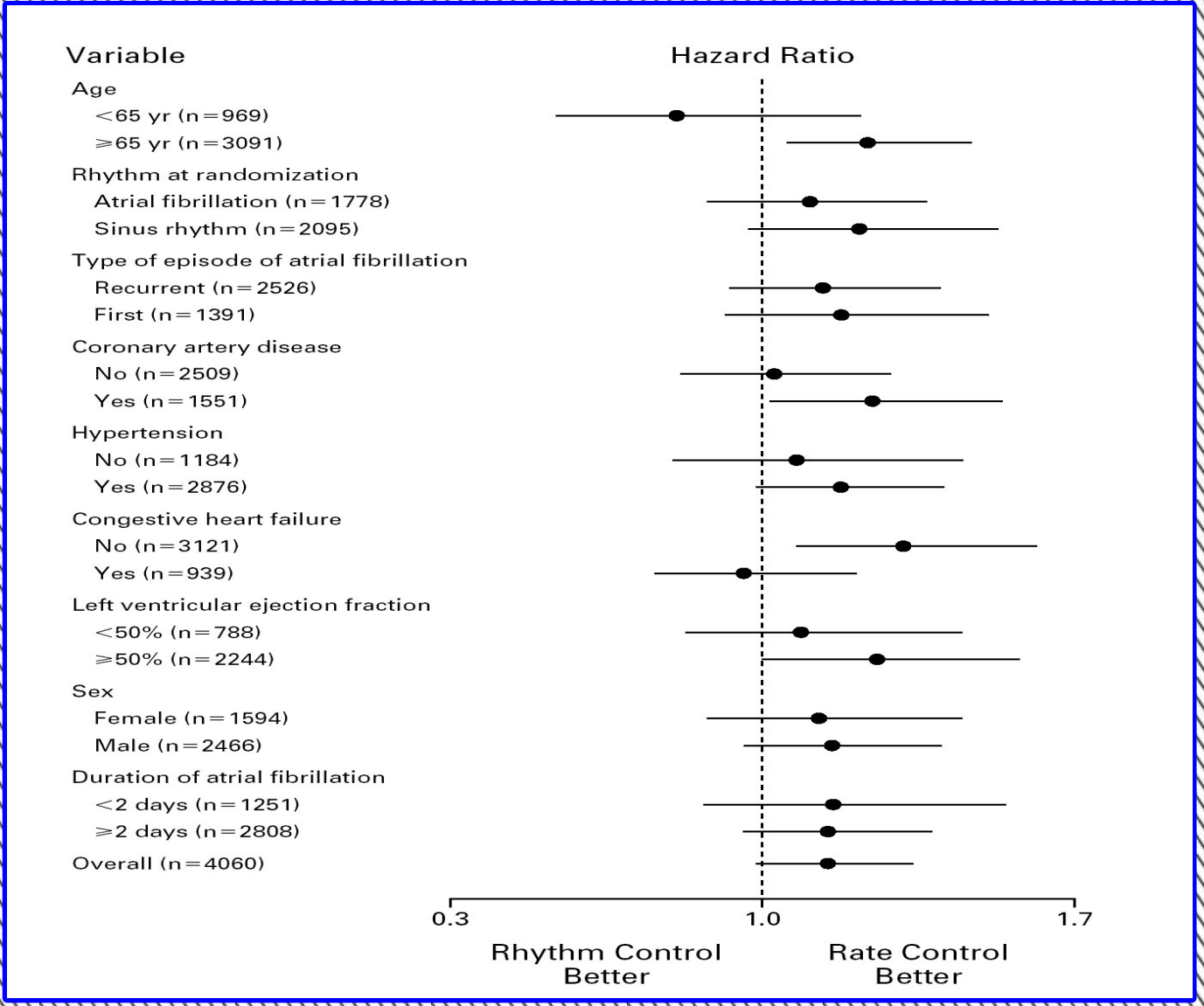
Table 18 Principles of antiarrhythmic drug therapy[143]

Principles
AAD therapy aims to reduce AF-related symptoms
Efficacy of AADs to maintain sinus rhythm is modest
Clinically successful AAD therapy may reduce rather than eliminate AF recurrences
If one AAD 'fails', a clinically acceptable response may be achieved by another drug
Drug-induced proarrhythmia or extracardiac side-effects are frequent
Safety rather than efficacy considerations should primarily guide the choice of AAD

AAD = antiarrhythmic drug; AF = atrial fibrillation.

A COMPARISON OF RATE CONTROL AND RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

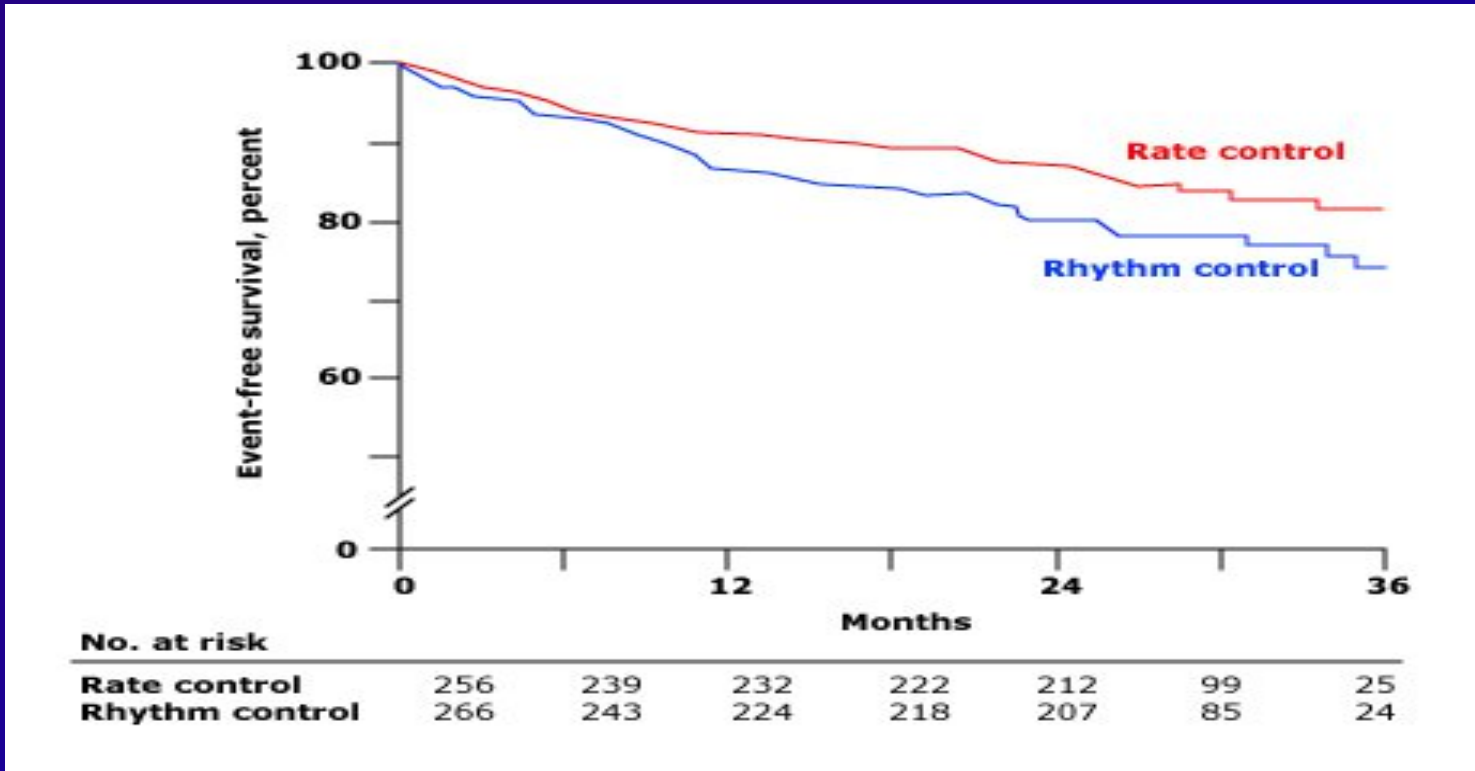
THE ATRIAL FIBRILLATION FOLLOW-UP INVESTIGATION OF RHYTHM MANAGEMENT (AFFIRM) INVESTIGATORS*



RACE trial: Rate control vs rhythm control

- 522 patients with recurrent persistent atrial fibrillation (AF) were randomly assigned to rhythm or rate control.
- Primary end point: composite of cardiovascular death, heart failure, thromboembolism, bleeding, pacemaker placement, and antiarrhythmic drug side effects.
- The primary end point occurred in 44 patients (17.2 percent) in the rate-control group and in 60 (22.6 percent) in the rhythm-control group (hazard ratio 0.73, 90 percent CI 0.53 to 1.01).

Rate control is not inferior to rhythm control for the prevention of death and morbidity from cardiovascular causes



Data from Van Gelder IC, Hagens VE, Bosker *HA*, et al. N Engl J Med 2002; 347:1834.

Euro Heart survey on AF

	No HF	HF
Pts n.	3482	1816
Age (yrs)	66±13	69±12

No difference in mortality was found between a rate and rhythm control strategy. Probably sinus rhythm simply reflects a better hemodynamic cardiac situation and might therefore be an independent prognostic marker rather than a treatment target.

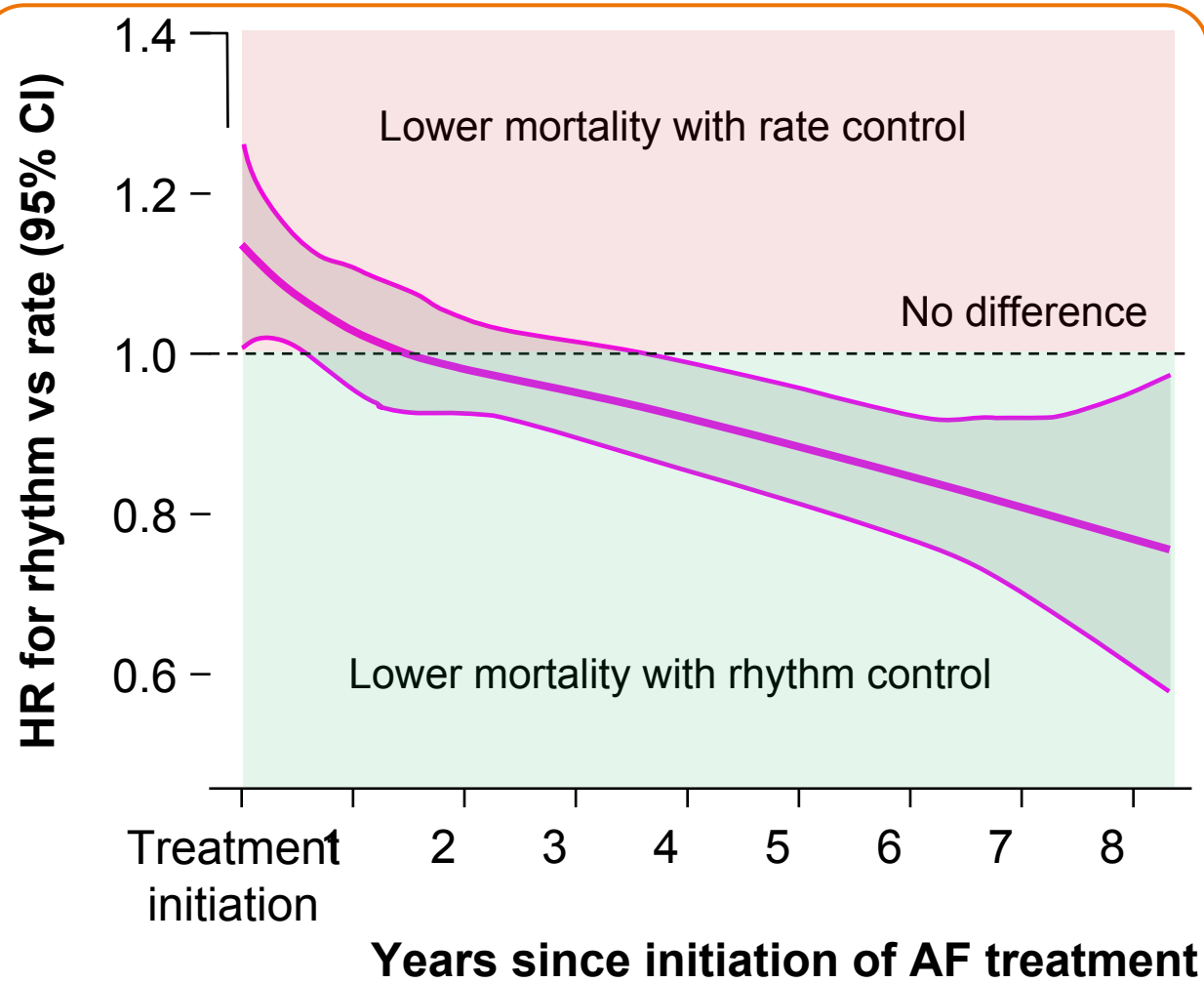
Nieuwlaat et al. JACC 2009;53(18):1690-8

Rhythm control and mortality in AF
Longterm benefit

- Population-based administrative databases, Quebec
- 26,130 patients
- 1999 to 2007

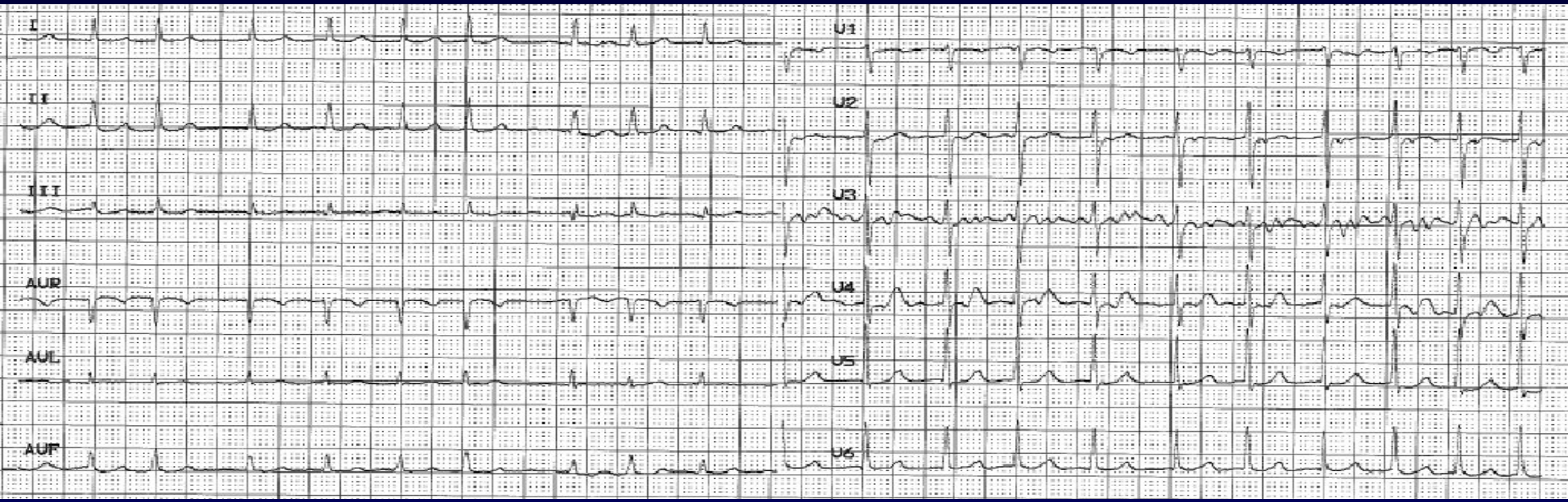
- > 65 years
- AF hospitalization
- No AF-related drug prescriptions < 1year < admission (first documented AF)
- AAD < 7 days > discharge

AAD = antiarrhythmic drug.



Effect of rhythm vs rate control therapy on mortality. Point estimates and 95% CIs can be reported at selected time points during the follow-up. The adjusted hazard ratio (HR) at a corresponding point in time quantifies the relative risks of immediate death, for rhythm vs rate control drugs, among patients who were followed until that time (ie, had not died and were not censored until that time).

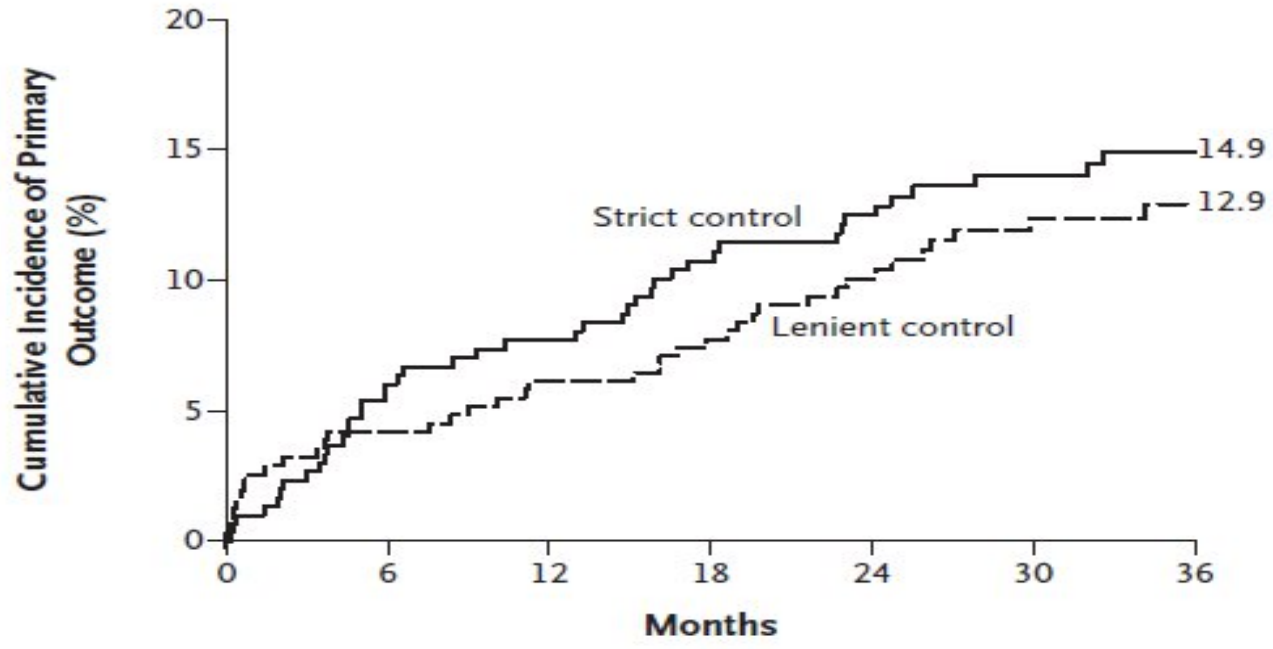
Ionescu-Ittu R, et al. Arch Intern Med. 2012;172:997-1004.


I
II
III
AUR
AUL
AUF
U1
U2
U3
U4
U5
U6

62 anni, maschio; BMI index 34; iperteso

- I episodio FA persistente
- Classe EHRA III
- PA 150 /100 mmHg
- FE 38%; Asn di volume moderatamente aumentato; Ppolm 40 mmHg
- Terapia: Triatec 5 mg; Lixiana 60 mg; Atenololo 75+ 50 mg/die

Kaplan–Meier Estimates of the cumulative incidence of death from CV causes, hospitalization for heart failure, and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events



CONCLUSIONS

In patients with permanent AF, lenient RC is as effective as strict RC and is easier to achieve

Strict HR control

≠

Clinical Impact

Isabelle C. Van Gelder
N Engl J Med 2010;362:1363-73

62 anni, maschio: 2 mesi dopo

- BMI index 28
- Classe EHRA I
- PA 120/80 mmHg
- FE 50%; Asn lievemente aumentato di vol; Ppolm 25 mmHg
- FC media in FA 56/min
- CVE con ripristino di RS

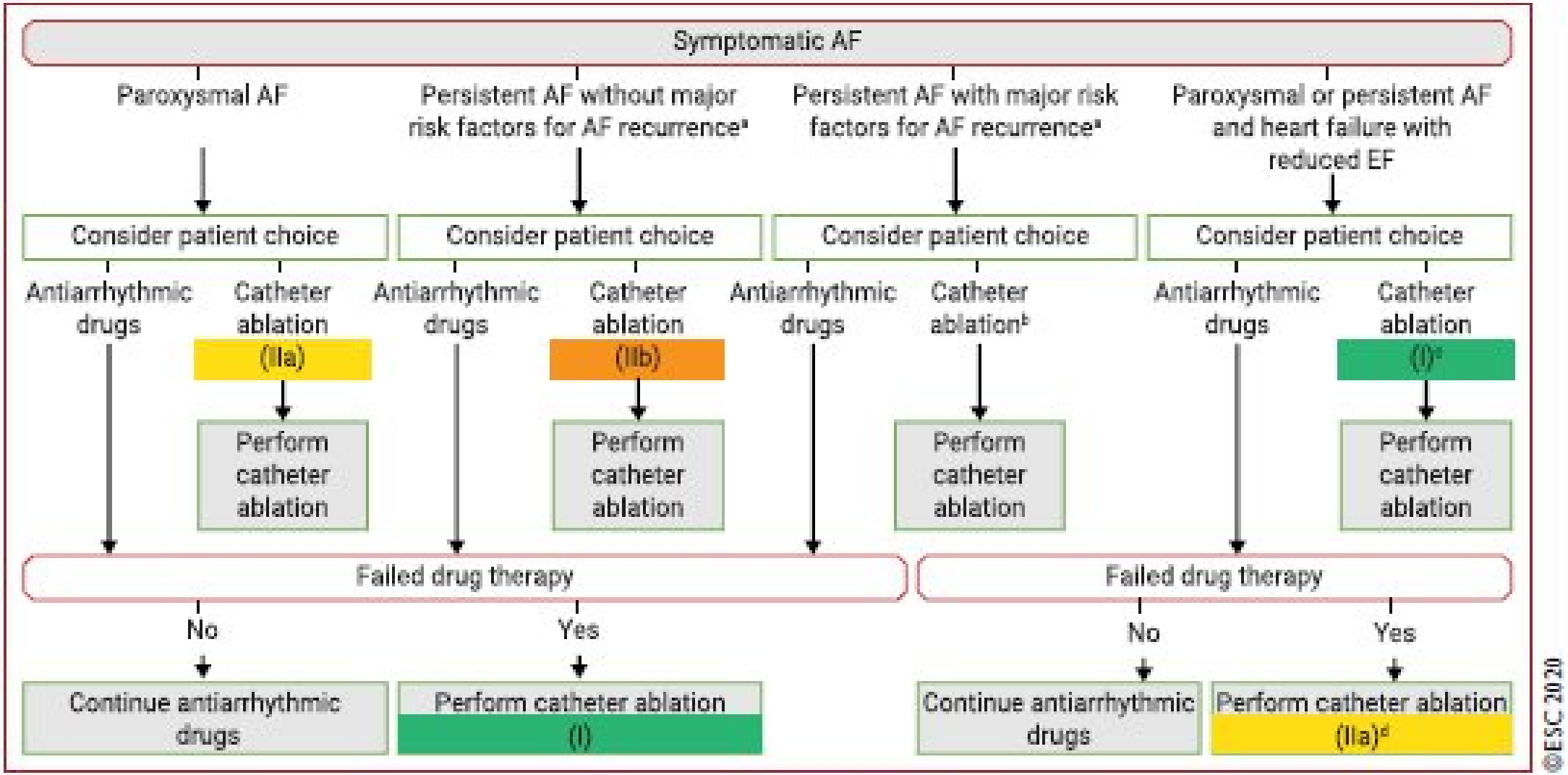


Figure 17 Indications for catheter ablation of symptomatic AF. The arrows from AAD to ablation indicate failed drug therapy. AAD = antiarrhythmic drug; AF = atrial fibrillation; EF = ejection fraction; LA = left atrial. [a]Significantly enlarged LA volume, advanced age, long AF duration, renal dysfunction, and other cardiovascular risk factors. [b]In rare individual circumstances, catheter ablation may be carefully considered as first-line therapy. [c]Recommended to reverse LV dysfunction when tachycardiomyopathy is highly probably. [d]To improve survival and reduce hospitalization.

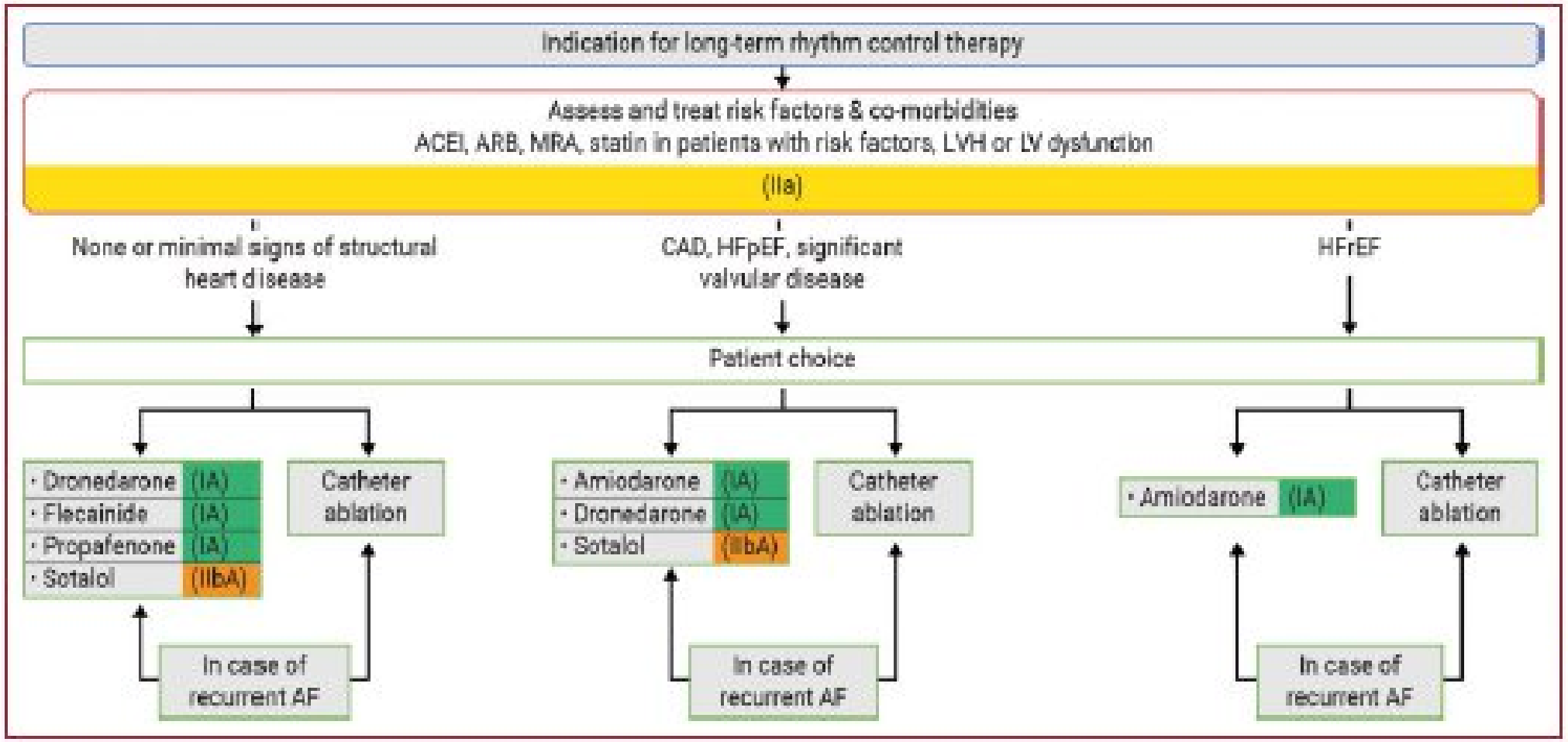


Figure 19 Long-term rhythm control therapy. ACEi = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CAD=coronary artery disease; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; LVH = left ventricular hypertrophy; MRA=mineralocorticoid receptor antagonist.

Table 16 Procedure-related complications in catheter ablation and thoracoscopic ablation of AF[771]

Complication severity	Complication type	Complication rate	
		Catheter ablation	Thoracoscopic ablation
Life-threatening complications	Periprocedural death	<0.1%	<0.1%
	Oesophageal perforation/fistula	<0.5%	N/A
	Periprocedural thromboembolic event	<1.0%	<1.5%
	Cardiac tamponade	≈1%	<1.0%
Severe complications	Pulmonary vein stenosis	<1.0%	N/A
	Persistent phrenic nerve palsy	<1.0%	N/A
	Vascular complications	2-4%	N/A
	Conversion to sternotomy	N/A	<1.7%
	Pneumothorax	N/A	<6.5%
Moderate or minor complications	Various	1-2%	1-3%
Complications of unknown significance	Asymptomatic cerebral embolism	5-15%	N/A

N/A = not available.

Quando e come utilizzare gli AADs

- Sempre utilizzati correttamente?

AADs outside of Guidelines recommendations

Education, education and Education

Study	n	Non concordance
Chiang et al. Europace 2013;15:1733-40	10,523	• Amiodarone was not recommended for ~50% of the patient population enrolled in the study
Allen LaPointe et al. Am Heart J 2013;166:871-8	331,274	• 45% of AAD use in patients with concomitant HF and 31% of AAD use in patients with CAD did not conform with guideline recommendations
Allen LaPointe et al. J Atr Fibrillation 2014;7:1062	79,232	• <65 ys without structural heart disease: only 16% received rhythm-control
Kirchhof P, et al (PREFER in AF). Europace 2014;16:6–14	7,243	• More than 50% of highly symptomatic patients did not receive adequate rate control
EORP-AF Pilot registry. Lip et al. Eur Heart J 2014;35:3365-76	3,113	• 36% of patients with PAF received digoxin • 29% of patients with long-standing AF received class III AADs
Qin D et al. *J Am Heart Assoc*. 2015;4:e001793	5,976	• 49-60% (1445 on amiodarone when not indicated) • If rhythm control is prescribed in accordance with guidelines - less AF recurrences, hospitalizations and AF-related procedures
Holmqvist et al (FORBIT-AF). J Am Heart Assoc 2015;4:e001901	10,137	• After ablation 46% were still on AADs (56% for Class IC in CAD)
Barnett et al (ORBIT-AF). Circ Arrhythm Electrophysiol. 2017;10:e005051	9,570	• One third of patients with AF receive care that is not in agreement with at least one guideline recommendation

Class I AADs – Safety considerations

Drug	NOT/Cautions	Drug Interactions
Flecainide	• Sinus or AV node dysfunction • QRS >25% baseline • HF or CAD • Infranodal conduction disease • Brugada syndrome • Renal or liver disease • Asthma (P)	• Metabolized by CYP2D6 – inhibitors ⊠ Pc (amiodarone, quinidine, fluoxetine, paroxetine, quinidine, ritonavir, sertraline, TADs) • Cimetidine and amiodarone ⊠ Pc of flecainide • Flecainide ⊠ digoxin Pc • PM: 7-10% of population • Renal excretion
Propafenone		• Metabolized by CYP2D6 • Increases the Pc of digoxin, metoprolol, propranolol and warfarin (INR) • PM have beta-blockade • CYP3A4 inhibitors (erythromyxin, ritonavir, saquinavir, or grapefruit juice) can increase propafenone Pc

4. Hybrid therapy (no algorithms in Guidelines)

4. When AAD therapy for AF is ineffective, a "hybrid" approach, combining both a pharmacologic and non-pharmacologic approaches, may work

a. Use combinations of AADs:
   - 🚲-blocker + AAD (Class IC); dronedarone + ranolazine...
   - Widely used for rate control

b. AAD after AF ablation:
   - In daily practice, RCTs and national databases, a short regimen of AAD is commonly prescribed to prevent early recurrence during the first 3 months post-ablation
   - This includes AADs previously reported as ineffective
   - 2016 ESC Guidelines: RCTs to confirm this are desirable

c. AADs combined with PM implantation, ICD or AF surgery

Combination Therapy for Cardiac Arrhythmias

SAMUEL LÉVY, MD

Combinations of antiarrhythmic agents are often used when single agents are ineffective, only partly effective or poorly tolerated. The theoretical and experimental basis for combination therapy for arrhythmias is the dissimilar electrophysiologic properties of antiarrhythmic agents. Until more is known about the mechanism of drug synergism and drug interactions, the experience gained clinically remains essential to our understanding. Published reports contain numerous data on the effectiveness of various combinations of antiarrhythmic agents, including combinations of class I agents, the combination of a class I agent and a β-blocking agent or amiodarone, and combinations including a calcium-antagonist agent. Adverse drug interactions, however, can occur, and combinations of certain agents must be avoided or used with caution.

(Am J Cardiol 1988;61:95A–101A)

Il razionale della combinazione di più farmaci antiaritmici è nel loro diverso meccanismo elettrofisiologico di azione. La terapia di associazione con antiaritmici può essere utile per:

- Ridurre le dosi dei farmaci utilizzati;
- Minimizzare i possibili effetti collaterali dei singoli farmaci.

Associazioni di antiaritmici per tachicardie ventricolari – I primi case report

Combined mexiletine and amiodarone treatment of refractory recurrent ventricular tachycardia

A. Waleffe, M.D., Ph.D.
L. Mary-Rabine, M.D., F.A.C.C.
V. Legrand, M.D.
J. Cl. Demoulin, M.D.
H.E. Kulbertus, M.D., F.A.C.C.
Liège, Belgium

Waleffe, A., Mary-Rabine, L., Legrand, V., Demoulin, J. C., & Kulbertus, H. E. Combined mexiletine and amiodarone treatment of refractory recurrent ventricular tachycardia. American Heart Journal (1980).

The role of beta blocking agents as adjunct therapy to membrane stabilizing drugs in malignant ventricular arrhythmia

Antiarrhythmic drugs are often either partially or totally ineffective for the suppression of ventricular arrhythmias in a given patient. Drug combinations afford an additional therapeutic option. We report the role of beta-blocking agents as adjunct therapy to membrane stabilizing drugs in the management of patients with malignant ventricular arrhythmias. The study group included 54 patients who were evaluated by 24-hour ambulatory monitoring and symptom-limited exercise testing. Patients underwent control studies without antiarrhythmic drugs, were evaluated on membrane stabilizing drugs and beta blocking agents separately, and were then tested on combination therapy. The combination of a beta-blocking agent and a membrane stabilizing drug abolished ventricular tachycardia and couplets in 83% and 86% of exercise tests in patients with this arrhythmia present during therapy with membrane drugs alone ($p < 0.01$). The addition of a beta blocker to a membrane drug, as evaluated by ambulatory monitoring, resulted in an abolition of ventricular tachycardia and couplets in 43% and 20% of studies ($p < 0.05$). Ventricular premature beat frequency was reduced by more than 50% in 65% of exercise tests and in 52% of monitoring studies ($p < 0.05$). In this population, beta-blocking agents failed to reduce ventricular arrhythmias when used alone. Thus the addition of a beta blocker to a membrane stabilizing drug significantly enhances the suppression of ventricular arrhythmia, especially when assessed by exercise testing. This results from synergistic drug effects of the combination rather than from the effect of the individual drugs. (Am Heart J 111:852, 1986.)

Hirsowitz, G., Podrid, P. J., Lampert, S., Stein, J., & Lown, B. The role of beta blocking agents as adjunct therapy to membrane stabilizing drugs in malignant ventricular arrhythmia. American Heart Journal (1986).

Associazioni di antiaritmici per tachicardie ventricolari – I Trials

Treatment of patients with left ventricular dysfunction and sustained recurrent monomorphic ventricular tachycardia

Recommendations	Class[a]	Level[b]	Ref.[c]
Optimization of HF medication according to current HF guidelines is recommended in patients with LV dysfunction and sustained VT.	I	C	8
Amiodarone treatment should be considered to prevent VT in patients with or without an ICD.	IIa	C	64

MADIT-II study: patients with ICD treated with the highest doses of beta-blockers experienced a significant reduction in recurrent episodes of VT or VF necessitating ICD intervention compared with patients not taking beta-blockers [HR 0.48 (95% CI 0.26, 0.89),P=0.02].

OPTIC (Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients) study: beta-blockers vs sotalol vs beta-blockers plus amiodarone for the prevention of ICD shocks. Amiodarone plus beta-blocker therapy significantly reduced the risk of shock compared with betablocker treatment alone [HR 0.27 (95% CI 0.14, 0.52),P=0.001] and sotalol [HR 0.43 (95% CI 0.22, 0.85),P=0.02].

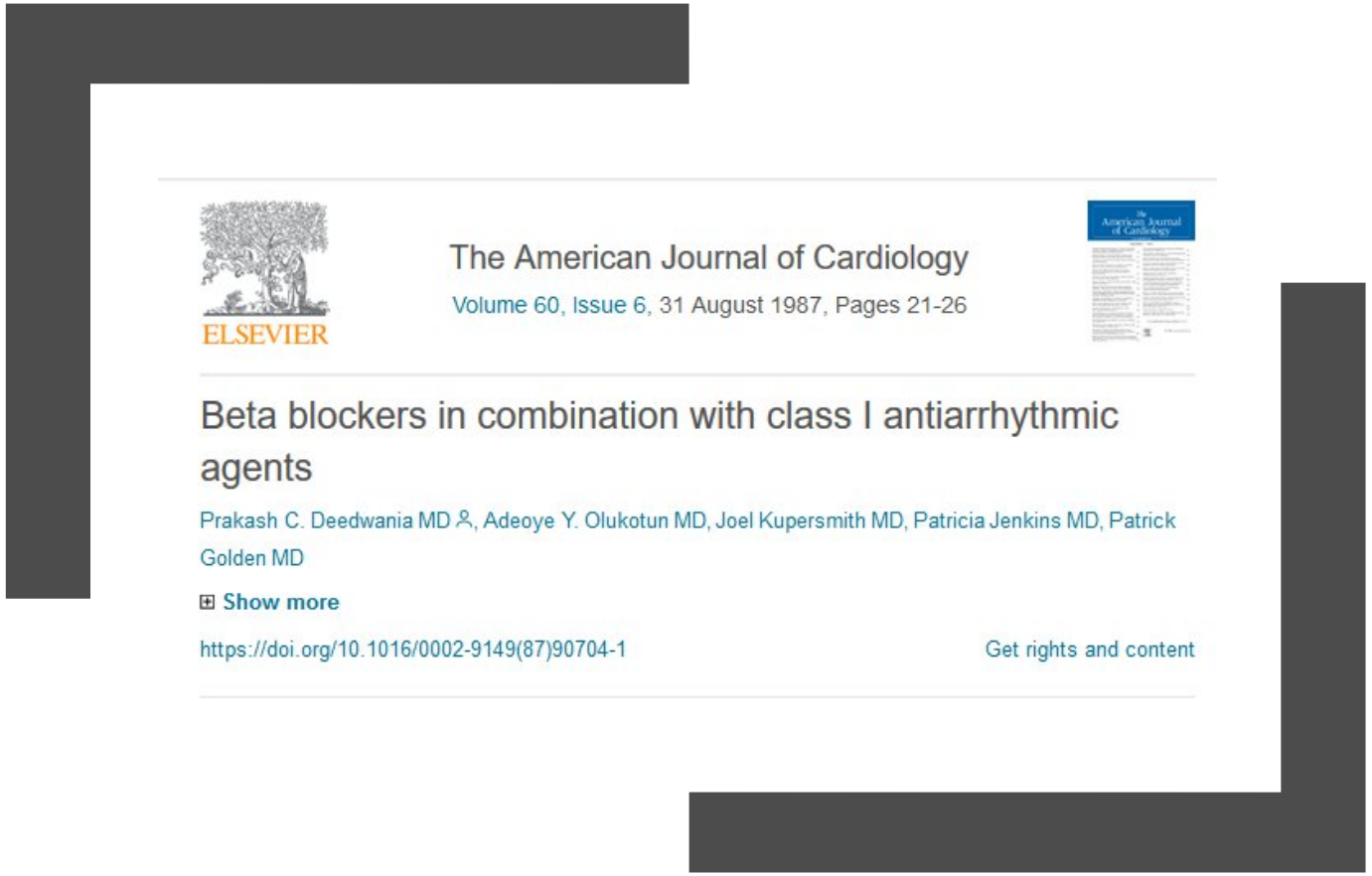
- Not only is the **adjunct of amiodarone to b-blockers not hazardous**, but b-blocker therapy should be continued if possible in patients in whom amiodarone is indicated.

- *"Patients receiving beta-blockers and amiodarone had a lower relative risk for all-cause mortality, cardiac death, arrhythmic cardiac death, nonarrhythmic cardiac death, and arrhythmic death or resuscitated cardiac arrest compared with those not receiving beta-blockers".*

Amiodarone Interaction With β-Blockers

Analysis of the Merged EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) Databases

Florent Boutitie, PhD; Jean-Pierre Boissel, MD; Stuart J. Connolly, FRCPC; A. John Camm, MD; John A. Cairns, MD; Desmond G. Julian, MD; Michael Gent, DSc; Michiel J. Janse, MD; Paul Dorian, MD; Gerald Frangin, MD; and the EMIAT and CAMIAT Investigators



- "In patients with ventricular arrhythmias remained poorly controlled (≥10 ventricular premature complexes/hr) with the class I agent alone and with a left ventricular ejection fraction > 30% combination therapy with **nadolol and class I** antiarrhythmic agents is safe and effective in the management of patients whose ventricular arrhythmias are refractory to therapeutic doses of class I agents alone"

Ad oggi, nessun antiaritmico ha dimostrato una riduzione della sudden cardiac death (SCD) e la diffusione degli ICD ha contribuito a ridurre l'interesse nei confronti della terapia farmacologica.

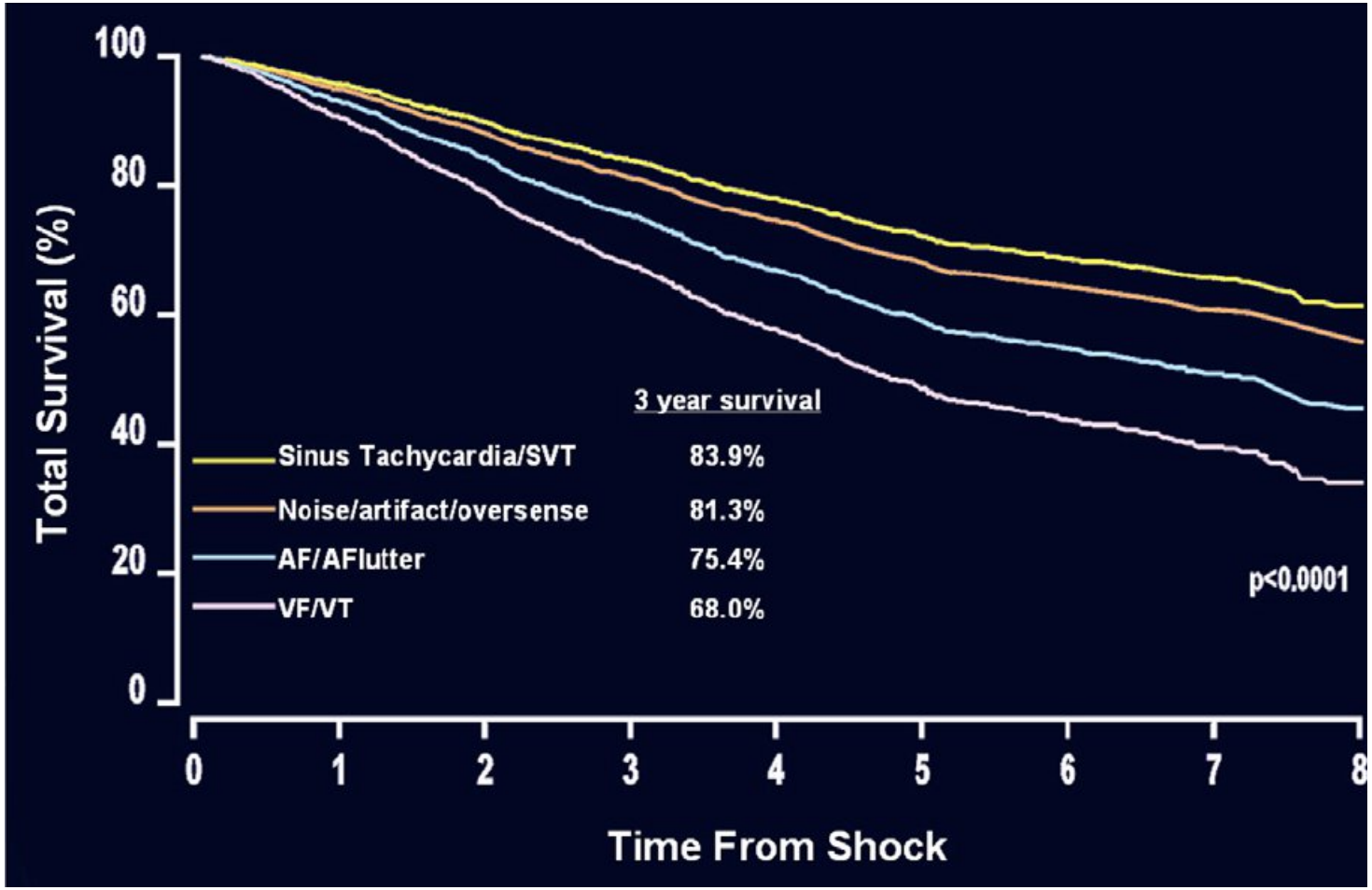
L'obiettivo della terapia anti-aritmica durante il follow-up quindi è…

Riduzione della frequenza e della durata degli episodi aritmici

Riduzione degli accessi in ospedale connessi ad episodi aritmici

Survival After Shock Therapy in Implantable Cardioverter-Defibrillator and Cardiac Resynchronization Therapy-Defibrillator Recipients According to Rhythm Shocked

The ALTITUDE Survival by Rhythm Study



Contemporary Management of Electrical Storm

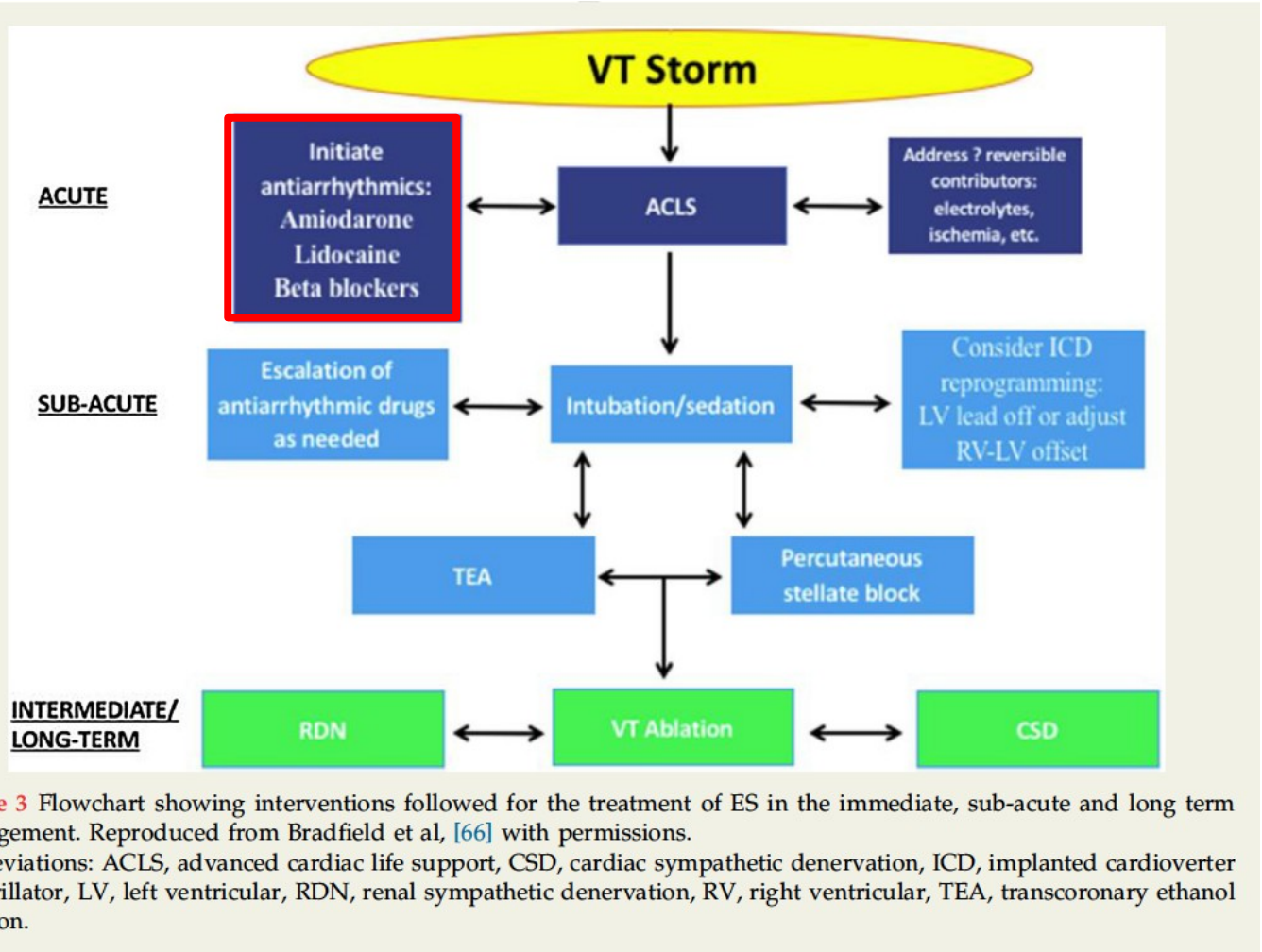


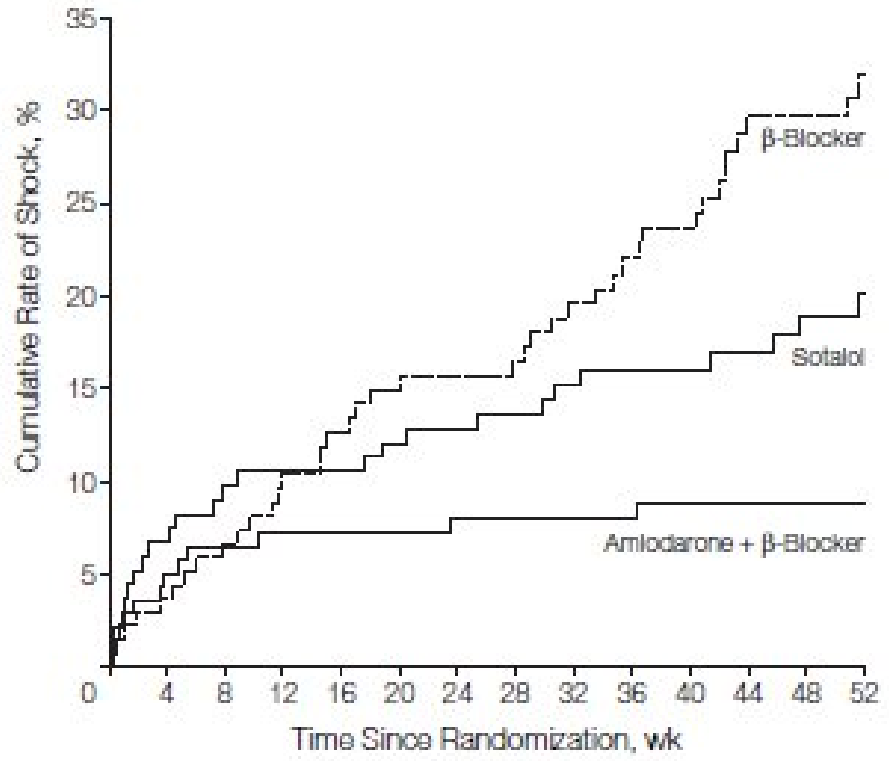
Figure 3 Flowchart showing interventions followed for the treatment of ES in the immediate, sub-acute and long term management. Reproduced from Bradfield et al, [66] with permissions.
Abbreviations: ACLS, advanced cardiac life support, CSD, cardiac sympathetic denervation, ICD, implanted cardioverter defibrillator, LV, left ventricular, RDN, renal sympathetic denervation, RV, right ventricular, TEA, transcoronary ethanol ablation.

- Beta-blokers
- Amiodarone
- Lidocaine

Lucy Geraghty et al Heart, Lung and Circulation (2018)

Comparison of β-Blockers, Amiodarone Plus β-Blockers, or Sotalol for Prevention of Shocks From Implantable Cardioverter Defibrillators

The OPTIC Study: A Randomized Trial



Outcome	β-Blocker (n = 138)	Amiodarone + β-Blocker (n = 140)	Sotalol (n = 134)	*P* Value: Amiodarone + β-Blocker vs β-Blocker	*P* Value: Sotalol vs β-Blocker
Any shock					
No. of events	41	12	26		
Annual event rate, %	38.5	10.3	24.3		
HR (95% CI)	1.00	0.27 (0.14-0.52)	0.61 (0.37-1.01)	<.001	.055
Appropriate shock					
No. of events	25	8	17		
Annual event rate, %	22.0	6.7	15.1		
HR (95% CI)	1.00	0.30 (0.14-0.68)	0.65 (0.36-1.24)	.004	.18
Inappropriate shock					
No. of events	18	4	11		
Annual event rate, %	15.4	3.3	9.4		
HR (95% CI)	1.00	0.22 (0.07-0.64)	0.61 (0.29-1.30)	.006	.20

Amiodarone in conjunction with a β-blocker reduces the risk of both appropriate and inappropriate ICD shocks

- Lo «storm aritmico», definito da 3 o più episodi di TV o FV nell'arco di 24h, è associato a un aumento della mortalità improvvisa e della mortalità complessiva.

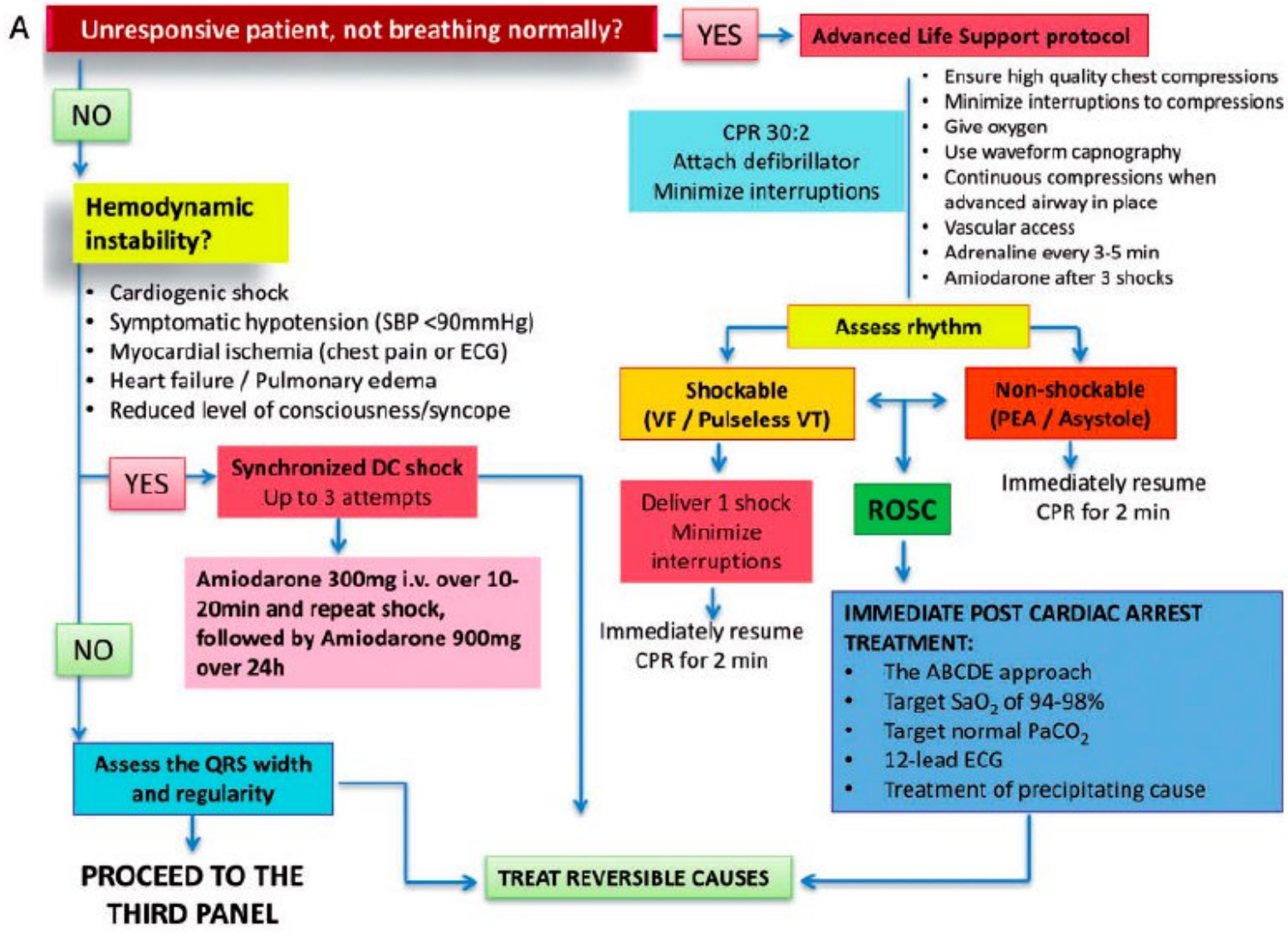
- "Electrical storm can be acutely treated with the combination of **a class III** and a **class Ic** antiarrhythmic agent when a class III agent alone is insufficient and when radiofrequency ablation is not an option"

Use of a Combination of Class III and Class Ic Antiarrhythmic Agents in Patients with Electrical Storm

Therese Fuchs M.D., Rima Groysman, Ilia Meilichov M.D.

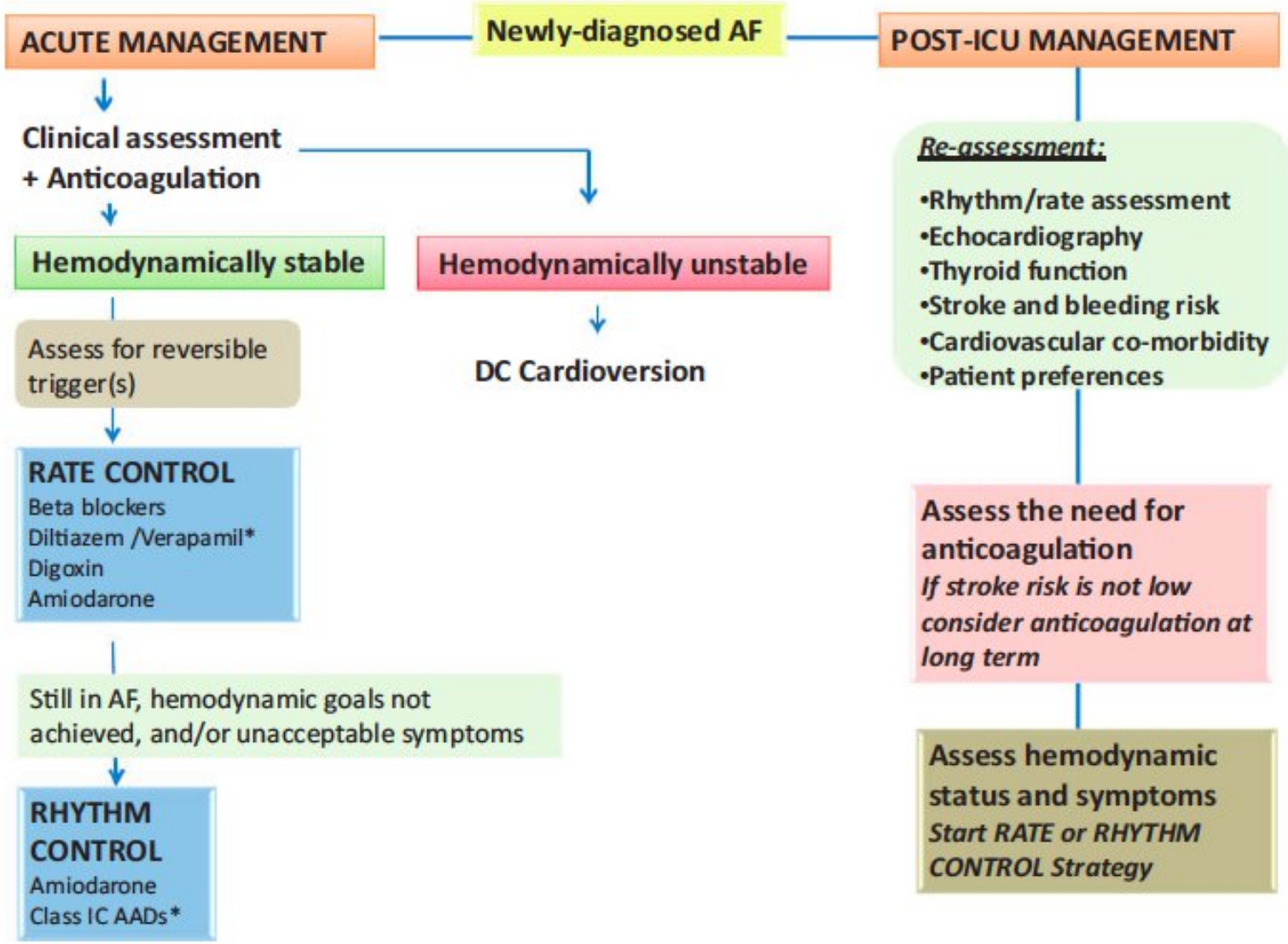
First published: 06 January 2012 | https://doi.org/10.1592/phco.28.1.14 | Cited by: 4

Management of tachyarrhythmias in critically ill and post-surgery patients



Boriani et al, Europace, 2018

Management of AF in critically ill patients



Boriani et al, Europace, 2018

How should AAD therapy be used?

Recommendations	References
• To prevent frequent shocks or electrical storm in ICD patients	7

AAD, antiarrhythmic drugs; ICD, implantable cardioverter-defibrillator.

Where does AAD therapy still play a central role?

Atrial Fibrillation

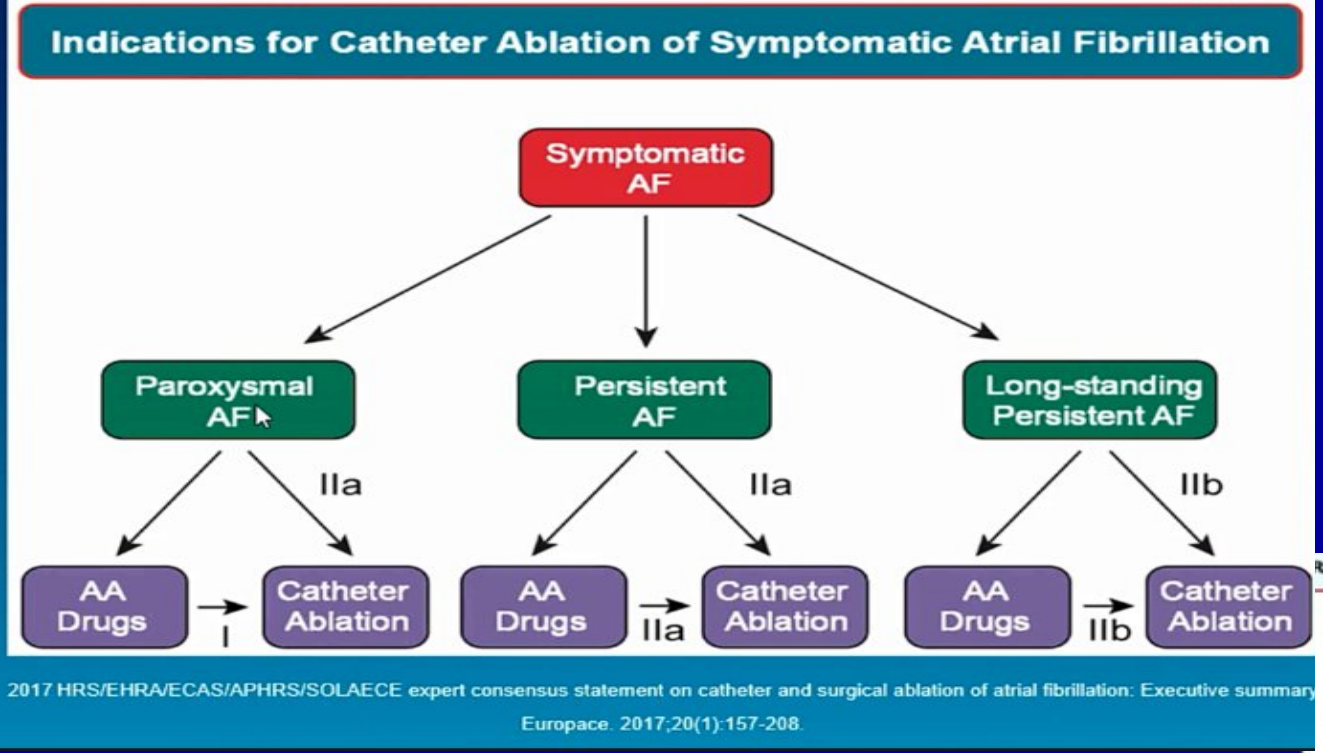
- Pharmacological cardioversion
- Facilitating electrical cardioversion
- Out of Hospital cardioversion -Pill in the pocket strategy
- Initial therapy in paroxysmal AF as alternative of RF ablation
- Before and/or after catheter ablation

Ventricular Arrhythmias

Prevent ICD shocks

Channellophaties

- Prevent sudden death or arrhythmic storm



2017 HRS/EHRA/ECAS/APHRS/SOLAECE: expert consensus document

Recommendation | Class | LOE | References

Calkins et al. Heart Rhythm 2017

Recommendations for catheter ablation of atrial fibrillation and atrial fibrillation surgery

Recommendations	Class[a]	Level[b]	Ref[c]
Catheter ablation of symptomatic paroxysmal AF is recommended to improve AF symptoms in patients who have symptomatic recurrences of AF on antiarrhythmic drug therapy (amiodarone, dronedarone, flecainide, propafenone, sotalol) and who prefer further rhythm control therapy, when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced centre.	I	A	585–587, 713, 727
Ablation of common atrial flutter should be considered to prevent recurrent flutter as part of an AF ablation procedure if documented or occurring during the AF ablation.	IIa	B	827
Catheter ablation of AF should be considered as first-line therapy to prevent recurrent AF and to improve symptoms in selected patients with symptomatic paroxysmal AF as an alternative to antiarrhythmic drug therapy, considering patient choice, benefit, and risk.	IIa	B	585
All patients should receive oral anticoagulation for at least 8 weeks after catheter (IIaB) or surgical (IIaC) ablation.	IIa	B C	727
Anticoagulation for stroke prevention should be continued indefinitely after apparently successful catheter or surgical ablation of AF in patients at high-risk of stroke.	IIa	C	
When catheter ablation of AF is planned, continuation of oral anticoagulation with a VKA (IIaB) or NOAC (IIaC) should be considered during the procedure, maintaining effective anticoagulation.	IIb	B C	760, 768
Catheter ablation should target isolation of the pulmonary veins using radiofrequency ablation or cryothermy balloon catheters.	IIa	B	585, 715, 716, 734, 735
AF ablation should be considered in symptomatic patients with AF and heart failure with reduced ejection fraction to improve symptoms and cardiac function when tachycardiomyopathy is suspected.	IIa	C	185, 226–228, 720, 777–779, 828
AF ablation should be considered as a strategy to avoid pacemaker implantation in patients with AF-related bradycardia.	IIa	C	829, 830
Catheter or surgical ablation should be considered in patients with symptomatic persistent or long-standing persistent AF refractory to AAD therapy to improve symptoms, considering patient choice, benefit and risk, supported by an AF Heart Team.	IIa	C	468, 735, 777, 831, 832, 1040
Minimally invasive surgery with epicardial pulmonary vein isolation should be considered in patients with symptomatic AF when catheter ablation has failed. Decisions on such patients should be supported by an AF Heart Team.	IIa	B	468 812, 819, 823
Maze surgery, possibly via a minimally invasive approach, performed by an adequately trained operator in an experienced centre, should be considered by an AF Heart Team as a treatment option for patients with symptomatic refractory persistent AF or post-ablation AF to improve symptoms.	IIa	C	808, 832
Maze surgery, preferably biatrial, should be considered in patients undergoing cardiac surgery to improve symptoms attributable to AF, balancing the added risk of the procedure and the benefit of rhythm control therapy.	IIa	A	461, 466, 790, 791, 796, 797
Concomitant biatrial maze or pulmonary vein isolation may be considered in asymptomatic AF patients undergoing cardiac surgery.	IIb	C	796, 797, 833

NB. Only in symptomatic patients…

In asymptomatic patients class IIb
Only in case of concomitant cardiac surgery

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Anti-arrhythmic drugs for the long-term maintenance of sinus rhythm/prevention of recurrent AF			
The choice of AAD needs to be carefully evaluated, taking into account the presence of comorbidities, cardiovascular risk and potential for serious proarrhythmia, extracardiac toxic effects, patient preferences, and symptom burden.	I	A	41, 580
Dronedarone, flecainide, propafenone, or sotalol are recommended for prevention of recurrent symptomatic AF in patients with normal left ventricular function and without pathological left ventricular hypertrophy.	I	A	581, 583, 584, 588, 601
Dronedarone is recommended for prevention of recurrent symptomatic AF in patients with stable coronary artery disease, and without heart failure.	I	A	583, 588
Amiodarone is recommended for prevention of recurrent symptomatic AF in patients with heart failure.	I	B	596–598
Amiodarone is more effective in preventing AF recurrences than other AAD, but extracardiac toxic effects are common and increase with time. For this reason, other AAD should be considered first.	IIa	C	596–598
Patients on AAD therapy should be periodically evaluated to confirm their eligibility for treatment.	IIa	C	583, 588, 657, 658, 660

Class IC AADs for maintaining sinus rhythm after cardioversion of AF – AF recurrence

	Drug/s studied	Studies	Events No/Total		Peto Odds Ratio (95% CI)	p
Comparing an antiarrhythmic versus control			Anti-arrhythmic	Control	0.10 1	
Class IC	flecainide	3	31 / 71	56 / 78	0.31 (0.16 – 0.60)	<0.001
	propafenone	5	376 / 720	276 / 378	0.37 (0.28 – 0.48)	<0.001
	all class IC IA	9	443 / 843	342 / 466	0.36 (0.28 – 0.45)	<0.001
Comparing two antiarrhythmics			Drug A	Drug B		
flecainide *versus* propafenone		2	49 / 145	56 / 152	0.87 (0.54 – 1.40)	ns
amiodarone *versus* class I drugs		5	142 / 311	229 / 332	0.36 (0.26 – 0.50)	<0.001

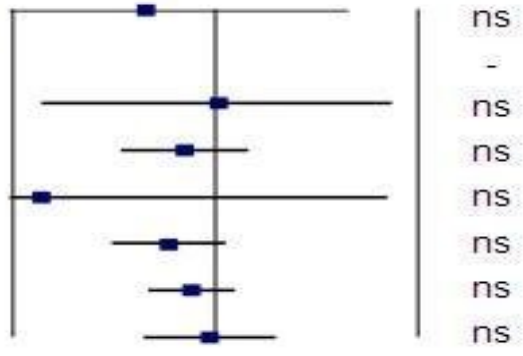
1. Determine inpatients who have recovered SR affter having AF, the effects of long-term treatment with AADs on recurrence of AF, death, stroke, embolism and adverse effects
2. Class IC (flecainide, propafenone) AADs significantly reduced recurrence of AF (NNT to beneft 4-5)

- Clinically successful AAD therapy reduces rather than eliminate the recurrences of AF

Lafuente-Lafuente et al. Cochrane Database of Systematic Reviews 2015:CD005049

Antiarrhythmics for maintaining sinus rhythm after cardioversion of AF – Overall mortality

Drug/s studied		Studies (n)	Events No/Total: Anti-arrhythmic	Events No/Total: Control	Peto Odds Ratio (95% CI)	p
Comparing an antiarrhythmic *vs.* control						
Class IA	disopyramide	2	2 / 75	0 / 71	7.56 (0.47 – 122)	ns
	quinidine	7	21 / 1128	4 / 548	2.26 (0.93 – 5.45)	ns
	all class IA	8	23 / 1203	4 / 594	**2.39 (1.03 – 5.59)**	**0.04**
Class IC	flecainide	4	0 / 352	0 / 159	no event	-
	propafenone	5	0 / 720	2 / 378	no event	-
Comparing two antiarrhythmics			Drug A	Drug B		
disopyramide *versus* other class I drugs		2	1 / 60	2 / 53	0.46 (0.05 - 4.52)	ns
quinidine *versus* flecainide		2	0 / 132	0 / 137	no event	-
	other class I drugs	4	2 / 258	2 / 268	1.04 (0.14 – 7.46)	ns
	sotalol	6	13 / 1109	17 / 869	0.71 (0.34 – 1.46)	ns
flecainide *versus* propafenone		2	0 / 145	1 / 152	0.14 (0.01 – 6.96)	ns
amiodarone *versus* class I drugs		5	16 / 311	28 / 332	0.59 (0.31 – 1.11)	ns
	sotalol	6	34 / 606	39 / 562	0.77 (0.47 – 1.25)	ns
sotalol *versus* class I except quinidine		4	15 / 243	17 / 251	0.94 (0.44 – 1.99)	ns



- **Class IA drugs (pooled data) significantly increased all-cause mortality at 1 year FU.**
- **They are less commonly used for rhythm control in AF. It is prudent lo limit their use to specific situations**

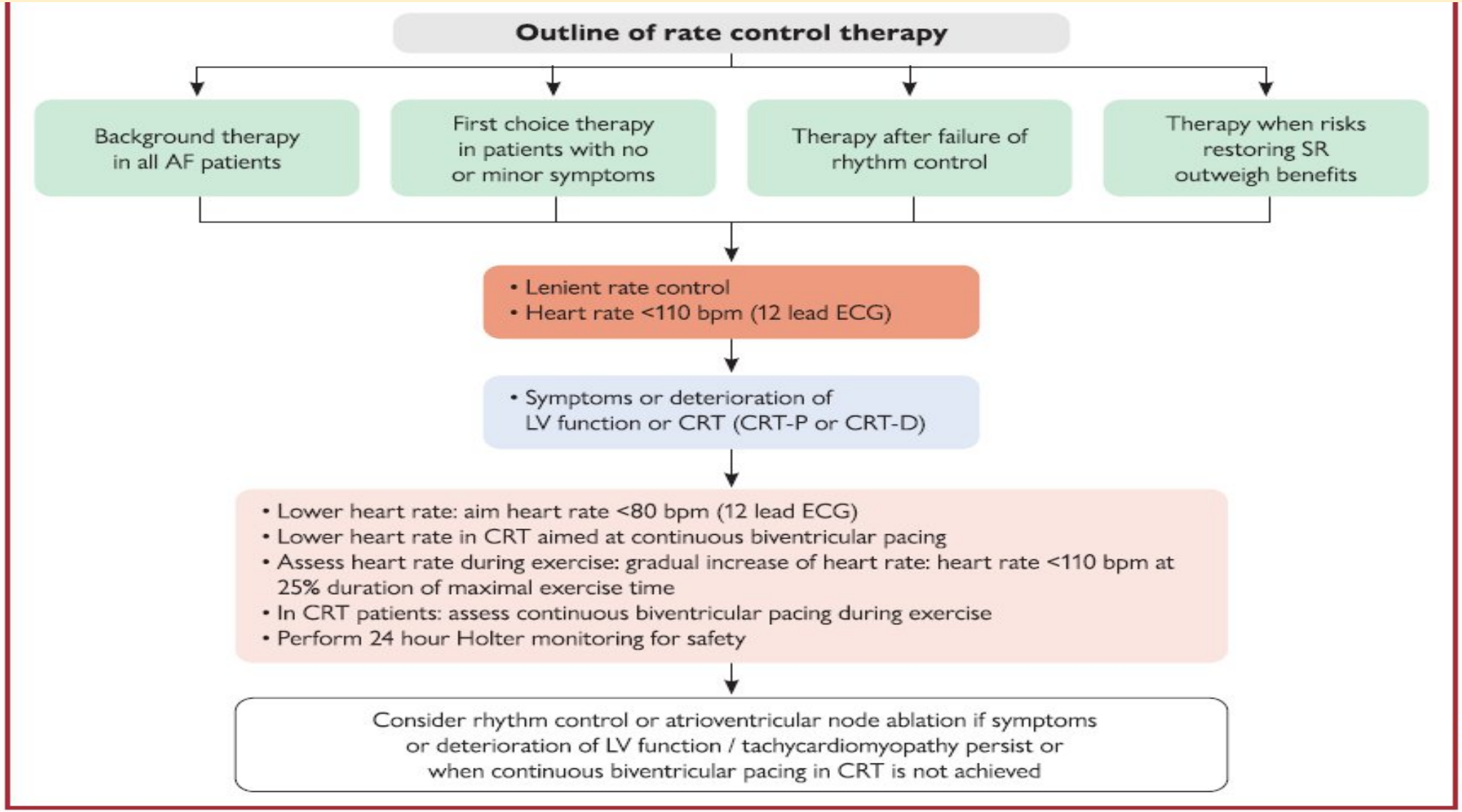


Figure 13 Outline of rate control therapy.[490] AF = atrial fibrillation; AVN = atrioventricular node; bpm = beats per minute; BV = biventricular; CRT = cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; ECG = electrocardiogram; LV = left ventricular; SR = sinus rhythm.

Table 13 Drugs for rate control in AF[a]

	Intravenous administration	Usual oral maintenance dose	Contraindicated
Beta-blockers[b]			
Metoprolol tartrate	2.5 - 5 mg i.v. bolus; up to 4 doses	25 - 100 mg *b.i.d.*	In case of asthma use beta-1-blockers Contraindicated in acute HF and history of severe bronchospasm
Metoprolol XL (succinate)	N/A	50 - 400 mg *o.d.*	
Bisoprolol	N/A	1.25 - 20 mg *o.d.*	
Atenolol[c]	N/A	25 - 100 mg *o.d.*	
Esmolol	500 µg/kg i.v. bolus over 1 min; followed by 50 - 300 µg/kg/min	N/A	
Landiolol	100 µg/kg i.v. bolus over 1 min; followed by 10 - 40 µg/kg/min[505]	N/A	
Nebivolol	N/A	2.5 - 10 mg *o.d.*	
Carvedilol	N/A	3.125 - 50 mg *b.i.d.*	
Non-dihydropyridine calcium channel antagonists			
Verapamil	2.5 - 10 mg i.v. bolusover 5 min	40 mg b.i.d. to 480 mg (extended release) o.d.	Contraindicated in HFrEF Adapt doses in hepatic and renal impairment
Diltiazem	0.25 mg/kg i.v. bolus over 5 min, then 5 - 15 mg/h	60 mg t.i.d. to 360 mg (extended release) o.d.	
Digitalis glycosides			
Digoxin	0.5 mg i.v. bolus (0.75 - 1.5 mg over 24 hours in divided doses)	0.0625 - 0.25 mg o.d.	High plasma levels associated with increased mortality Check renal function before starting and adapt dose in CKD patients
Digitoxin	0.4 - 0.6 mg	0.05 - 0.1 mg o.d.	High plasma levels associated with increased mortality
Other			
Amiodarone	300 mg i.v. diluted in 250 mL 5% dextrose over 30 - 60 min (preferably via central venous cannula), followed by 900 - 1200 mg i.v. over 24 hours diluted in 500 - 1000 mL via a central venous cannula	200 mg o.d. after loading 3 × 200 mg daily over 4 weeks, then 200 mg daily[536] [d](reduce other rate controlling drugs according to heart rate)	In case of thyroid disease, only if no other options

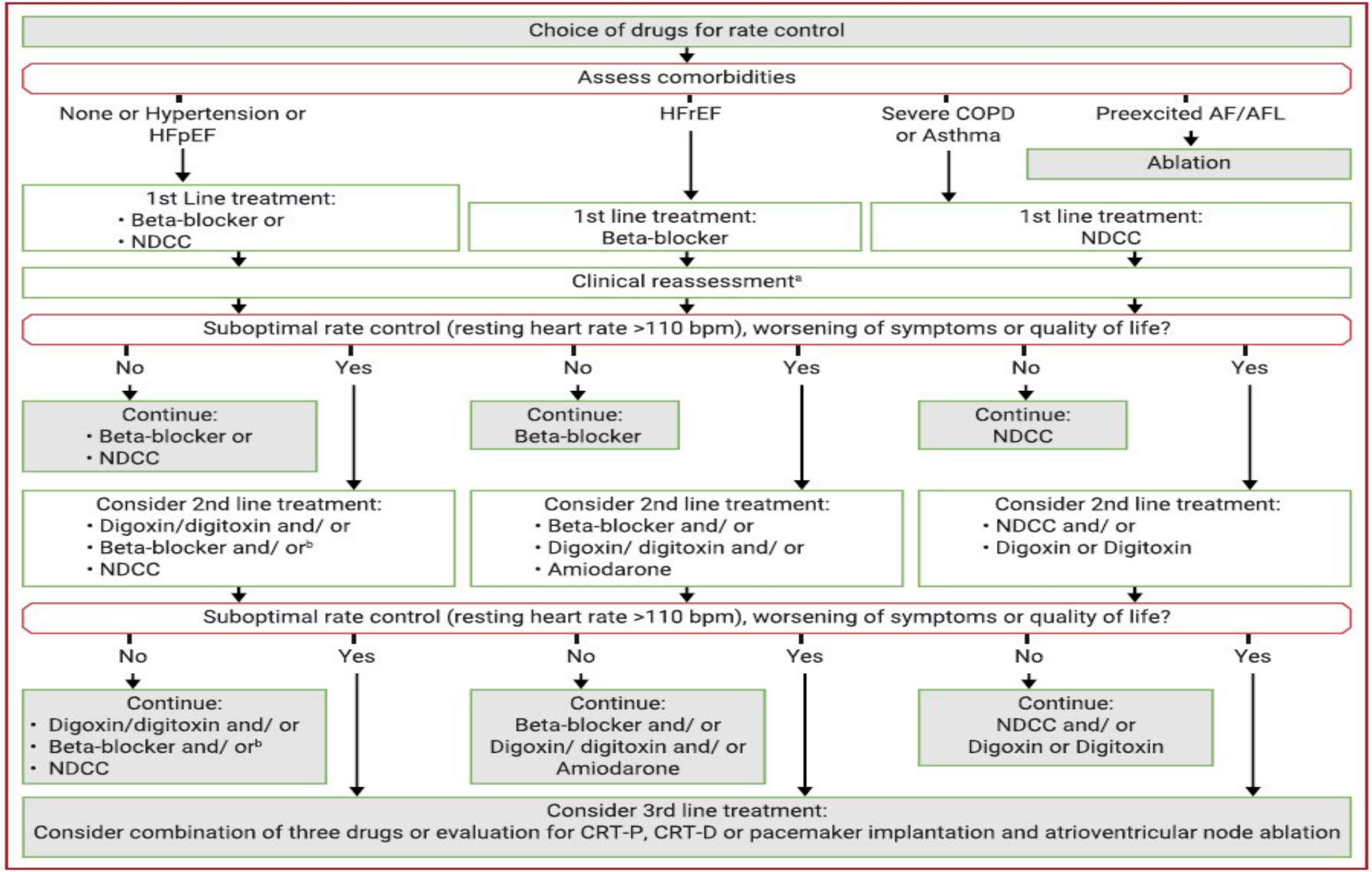
AF = atrial fibrillation; b.i.d. = *bis in die* (twice a day); CKD = chronic kidney disease; HF = heart failure; HFrEF = HF with reduced ejection fraction; i.v. = intravenous; min = minutes; N/A = not available or not widely available; o.d. = *omni die* (once daily); t.i.d. = *ter in die* (three times a day).

[a]All rate control drugs are contraindicated in Wolff-Parkinson-White syndrome, also i.v. amiodarone.

[b]Other beta-blockers are available but not recommended as specific rate control therapy in AF and therefore not mentioned here (e.g. propranolol and labetalol).

[c]No data on atenolol; should not be used in HFrEF.

[d]Loading regimen may vary; i.v. dosage should be considered when calculating total load.


Choice of drugs for rate control
Assess comorbidities
None or Hypertension or HFpEF
HFrEF
Severe COPD or Asthma
Preexcited AF/AFL
Ablation
1st Line treatment:
• Beta-blocker or
• NDCC
1st line treatment:
Beta-blocker
1st line treatment:
NDCC
Clinical reassessment[a]
Suboptimal rate control (resting heart rate >110 bpm), worsening of symptoms or quality of life?
No
Yes
No
Yes
No
Yes
Continue:
• Beta-blocker or
• NDCC
Continue:
Beta-blocker
Continue:
NDCC
Consider 2nd line treatment:
• Digoxin/digitoxin and/ or
• Beta-blocker and/ or[b]
• NDCC
Consider 2nd line treatment:
• Beta-blocker and/ or
• Digoxin/ digitoxin and/ or
• Amiodarone
Consider 2nd line treatment:
• NDCC and/ or
• Digoxin or Digitoxin
Suboptimal rate control (resting heart rate >110 bpm), worsening of symptoms or quality of life?
No
Yes
No
Yes
No
Yes
Continue:
• Digoxin/digitoxin and/ or
• Beta-blocker and/ or[b]
• NDCC
Continue:
Beta-blocker and/ or
Digoxin/ digitoxin and/ or
Amiodarone
Continue:
NDCC and/ or
Digoxin or Digitoxin
Consider 3rd line treatment:
Consider combination of three drugs or evaluation for CRT-P, CRT-D or pacemaker implantation and atrioventricular node ablation

Europace (2016) **18**, 1698–1704
doi:10.1093/europace/euv462

CLINICAL RESEARCH
Atrial fibrillation

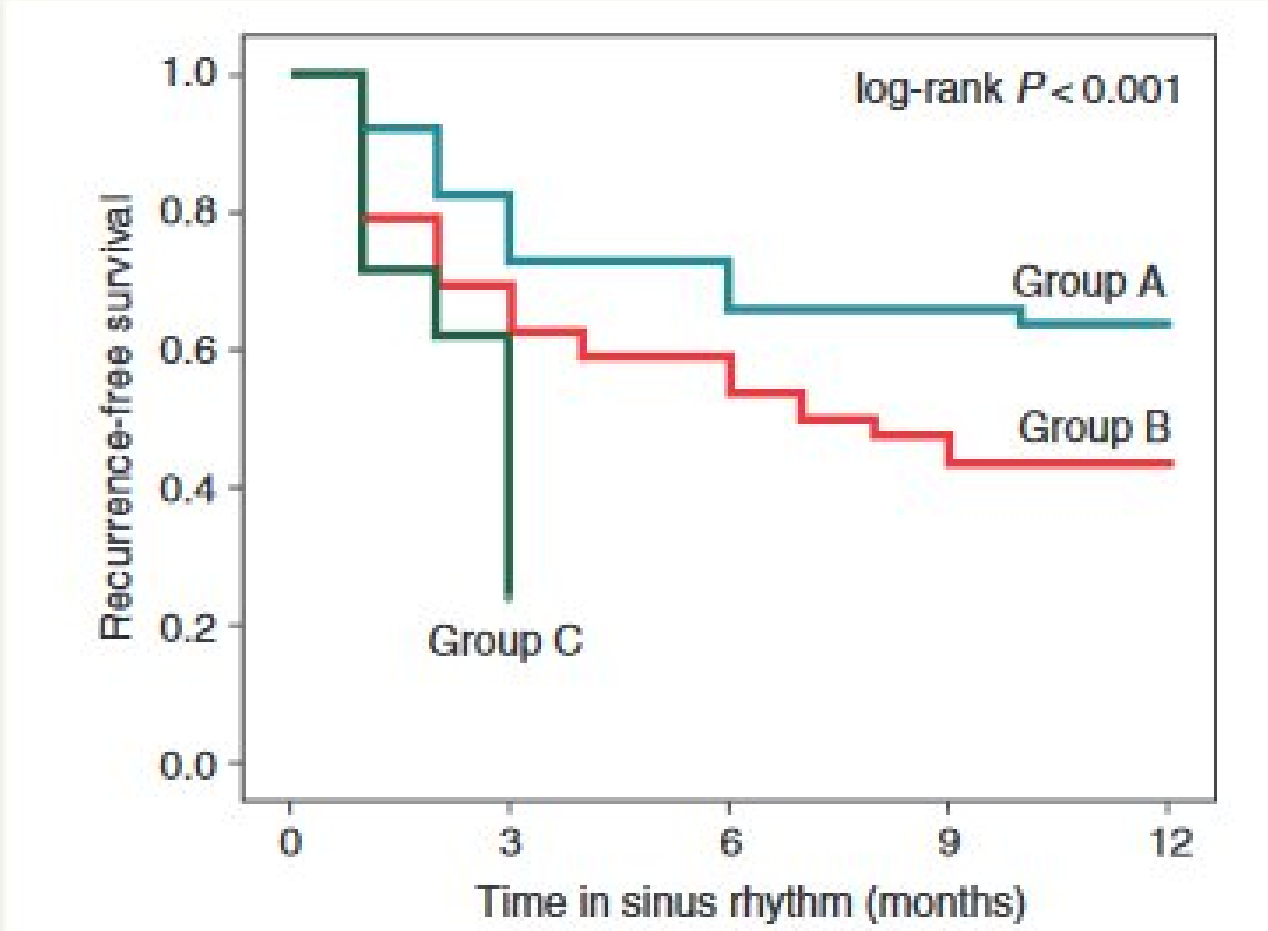
Flecainide–metoprolol combination reduces atrial fibrillation clinical recurrences and improves tolerability at 1-year follow-up in persistent symptomatic atrial fibrillation

Alessandro Capucci[1], Luca Piangerelli[1], Jenny Ricciotti[1], Domenico Gabrielli[2], and Federico Guerra[1]*

[1]Cardiology and Arrhythmology Clinic, Marche Polytechnic University, University Hospital 'Ospedali Riuniti', Via Conca 71, Ancona, Italy; and
[2]Cardiology Department, 'Murri' Hospital, Fermo, Italy

Received 28 September 2015; accepted after revision 29 December 2015; online publish-ahead-of-print 17 February 2016

Flecainide (200—300 mg/day) and **propafenone** (450—900 mg/day) is considered first-line choices in patients with AF and no organic heart disease.



Group A	80	53 (0.73)	37 (0.69)	33 (0.69)	32 (0.67)
Group B	72	38 (0.63)	28 (0.54)	21 (0.47)	20 (0.47)
Group C	21	5 (0.76)	–	–	–

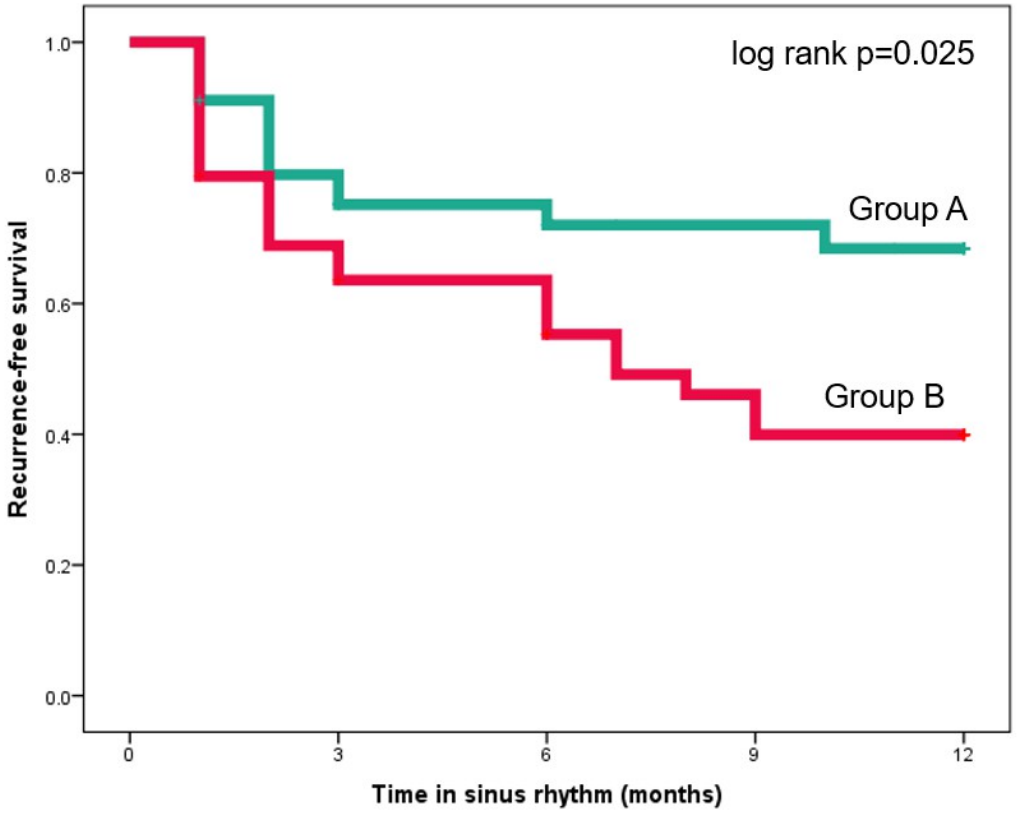
- During the 1-year follow-up period, **combination therapy with flecainide plus metoprolol was 20% more effective** than flecainide alone in preventing atrial fibrillation recurrences.

Flecainide–metoprolol combination reduces atrial fibrillation clinical recurrences and improves tolerability at 1-year follow-up in persistent symptomatic atrial fibrillation

Alessandro Capucci[1], Luca Piangerelli[1], Jenny Ricciotti[1], Domenico Gabrielli[2], and Federico Guerra[1]*

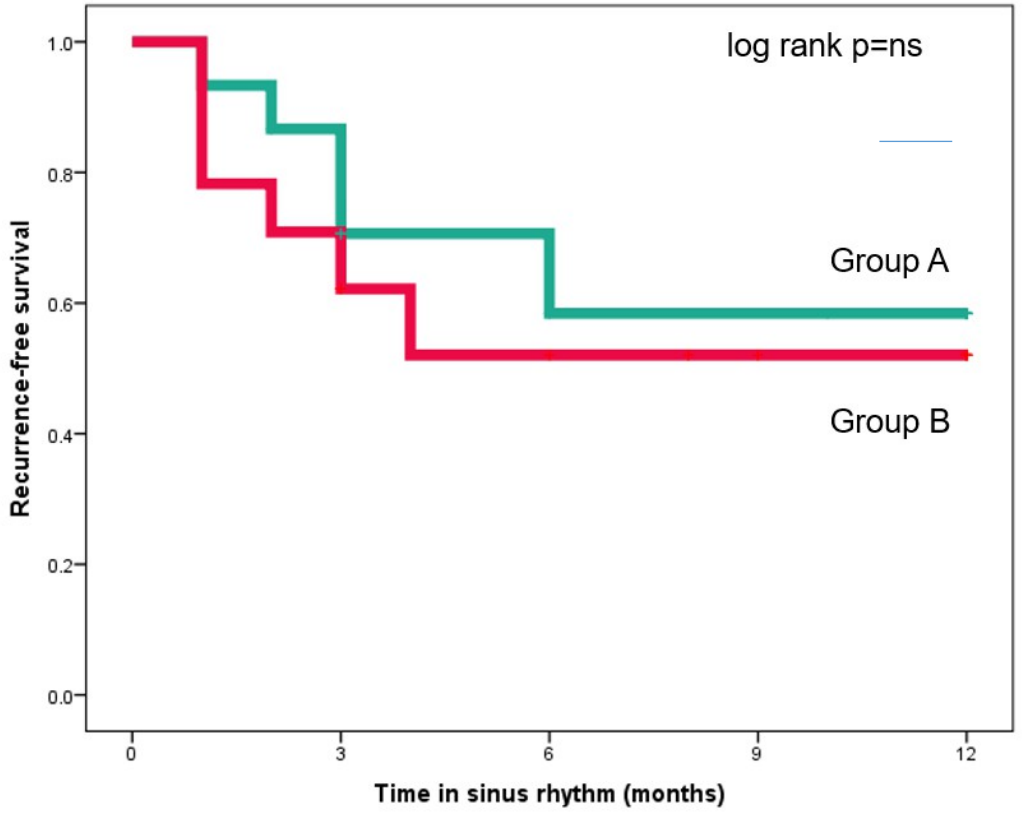
Capucci A et al. Europace 2016,

Persistent AF



Group A	47	34 (79.7)	23 (75.2)	19 (75.2)	17 (71.1)
Group B	45	26 (68.9)	18 (55.0)	15 (43.6)	13 (43.6)

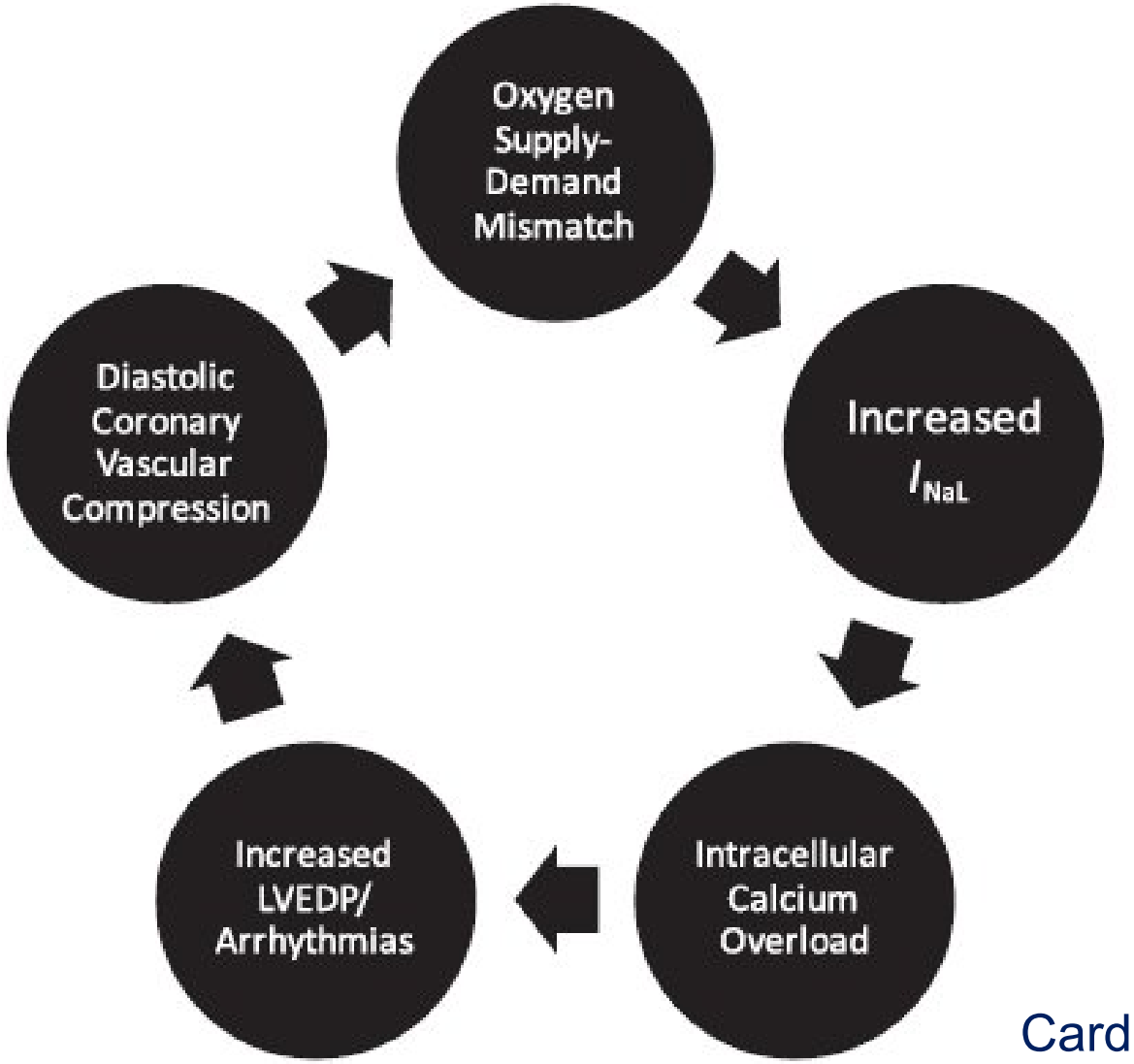
Paroxysmal AF



A	33	25 (0.87)	17 (0.60)	13 (0.60)	11 (0.60)
B	27	16 (0.69)	11 (0.52)	9 (0.52)	8 (0.52)

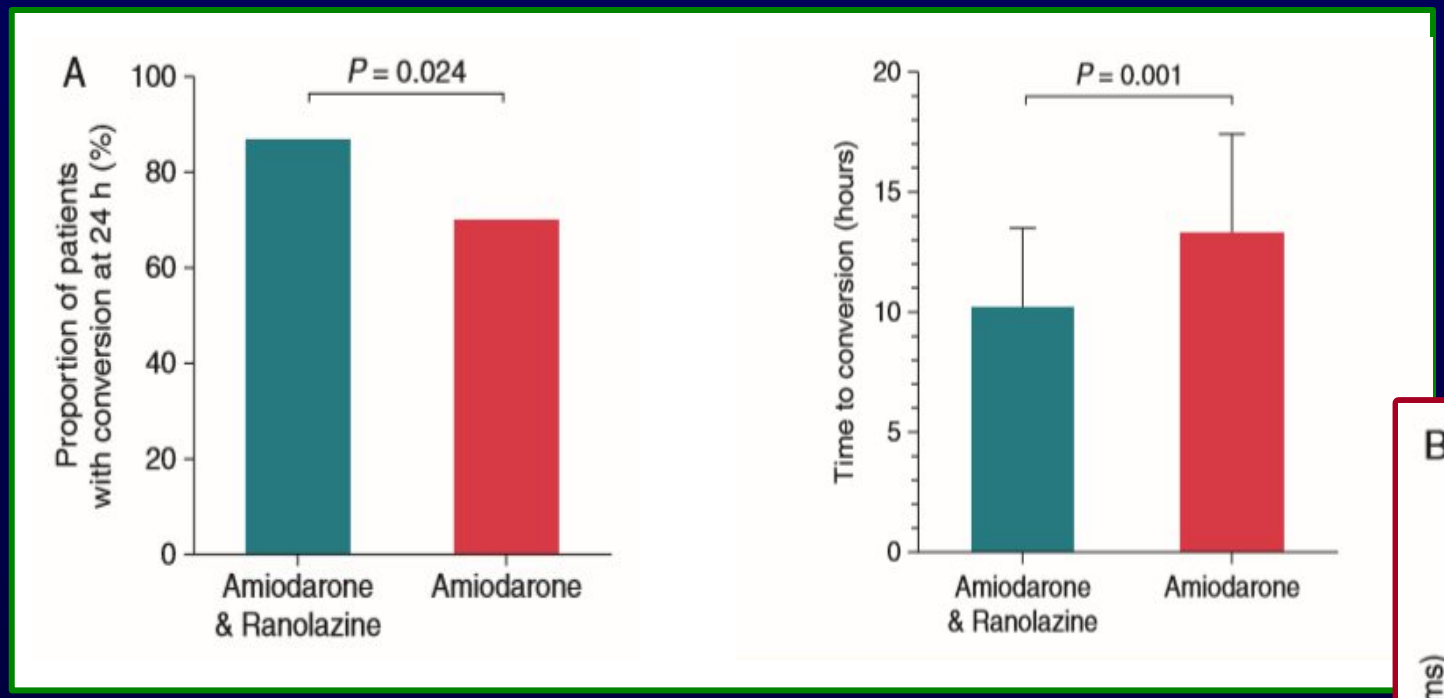
Presumed Effect of Ranolazine

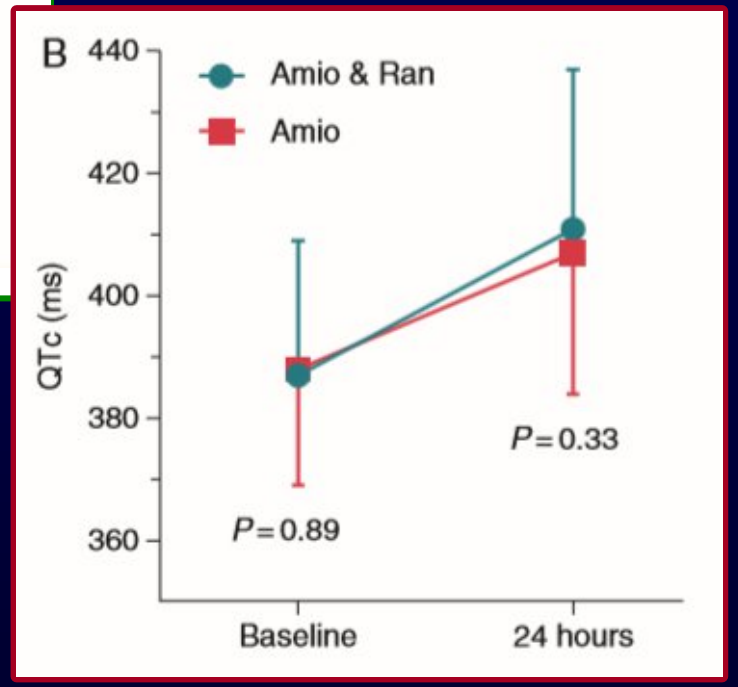
on Myocardial Oxygen Demand–Supply Mismatch



Stone PH.
Cardiol Clin 2008; 26: 603-614

Ranolazine Enhances the Efficacy of Amiodarone for Conversion of Recent-Onset AF

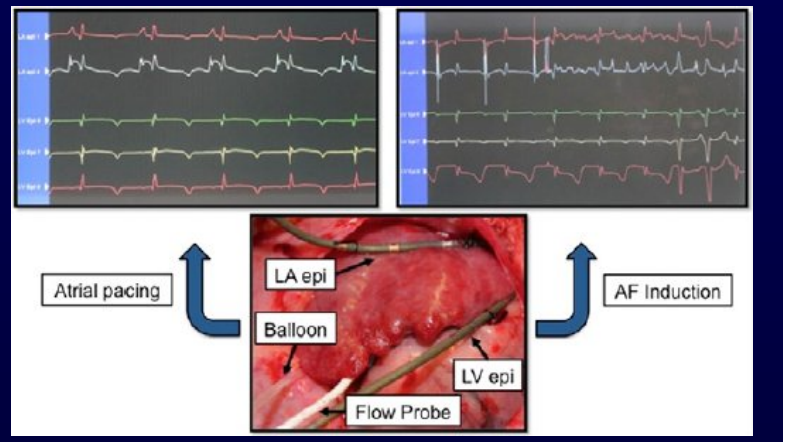




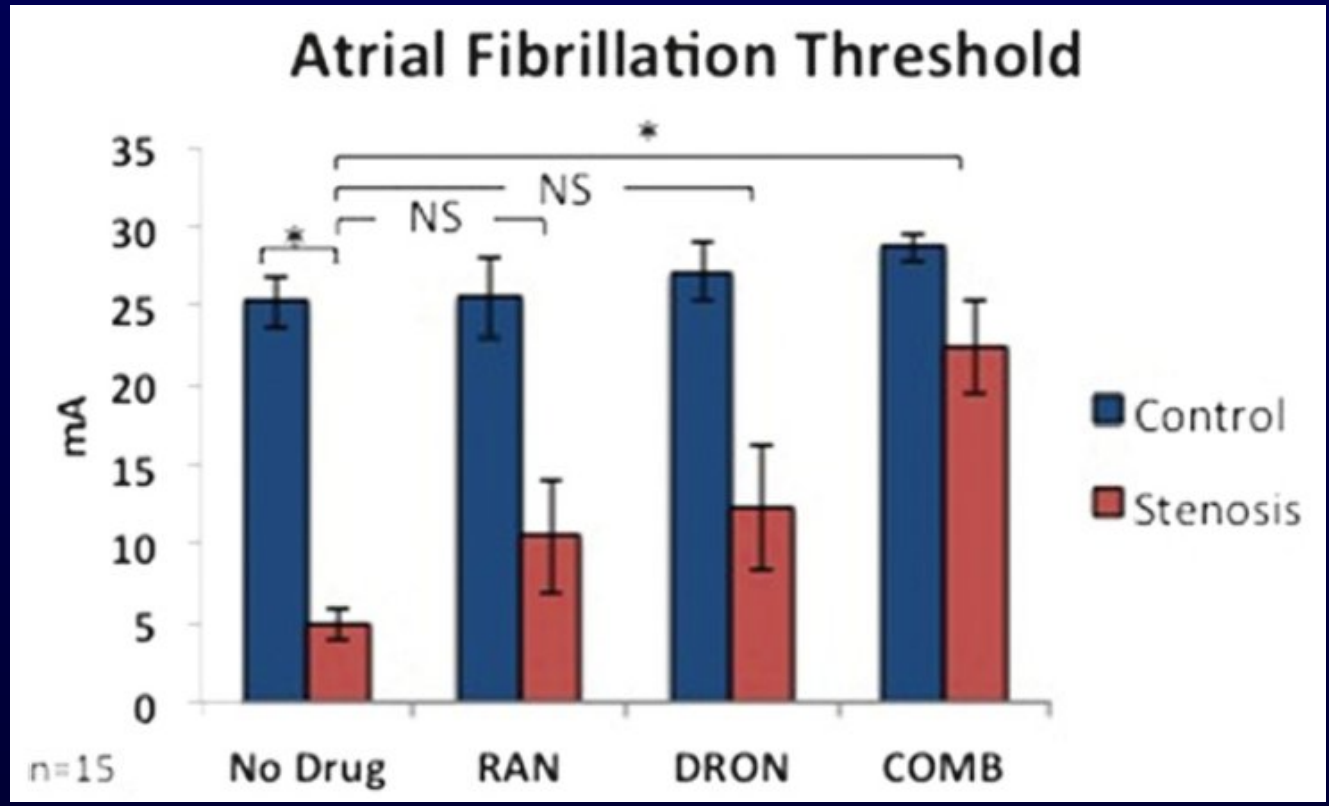
Koskinas KC Europace 2014; 16: 973–979

Low doses of ranolazine and dronedarone in combination exert potent protection against atrial fibrillation and vulnerability to ventricular arrhythmias during acute myocardial ischemia

Richard L. Verrier, PhD, FACC,[*†] Vitor P.F. Pagotto, BS,[*‡] Alexandre F. Kanas, BS,[*‡] Marcel F. Sobrado, BS,[*‡] Bruce D. Nearing, PhD,[*†] Dewan Zeng, PhD,[§] Luiz Belardinelli, MD[§]

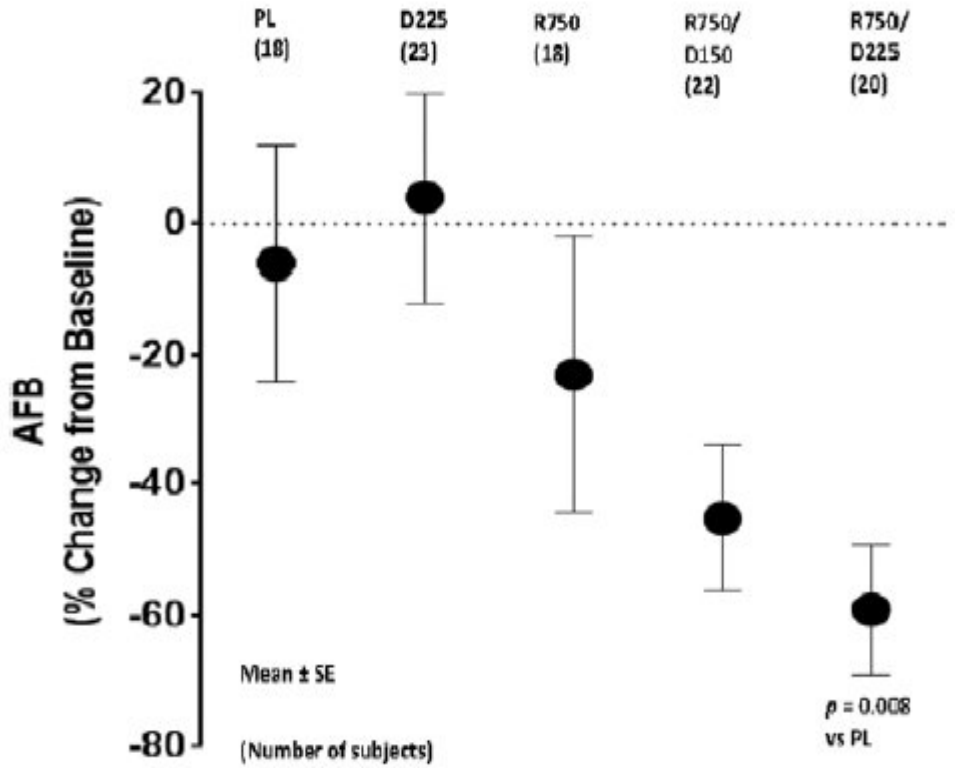


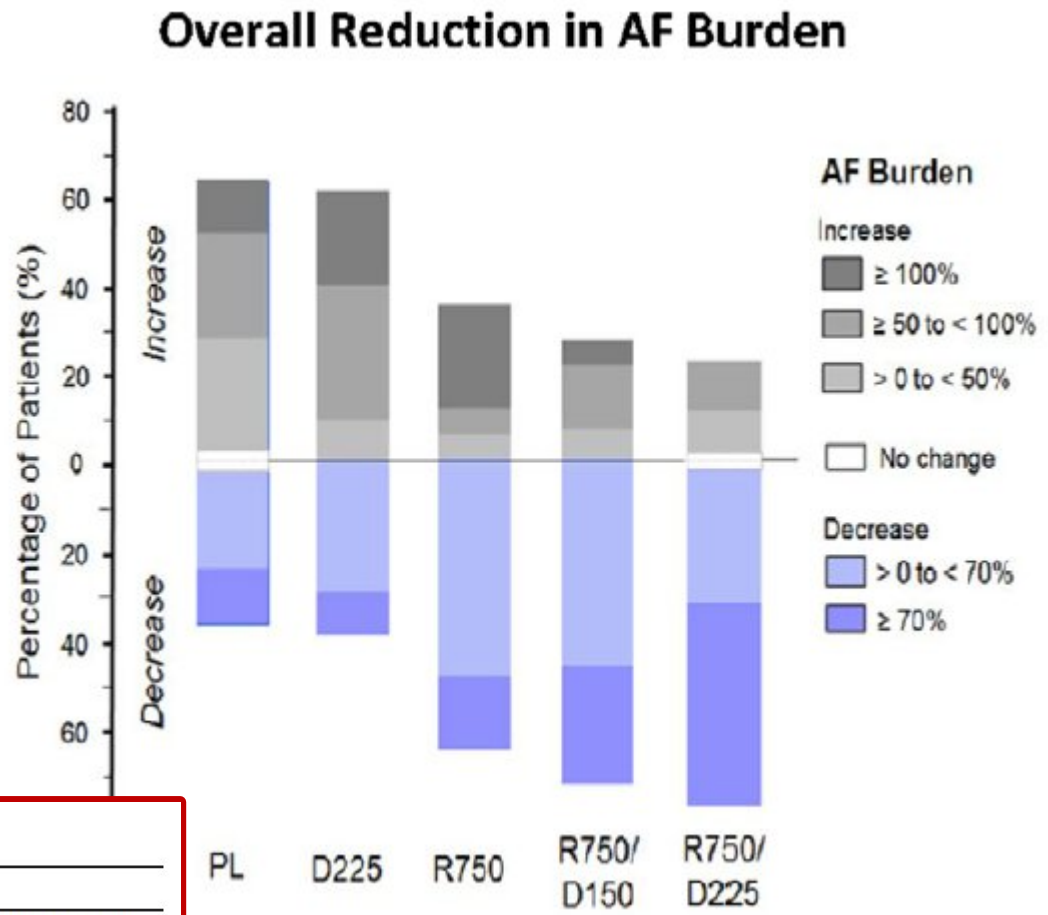
balloon occlusion of the LCx CA to reduce flow by 75% during AP @ 150 beats/min



Heart Rhythm 2013;10:121–127

Combined Ranolazine and Dronedarone in Paroxysmal AF: *The HARMONY Trial*

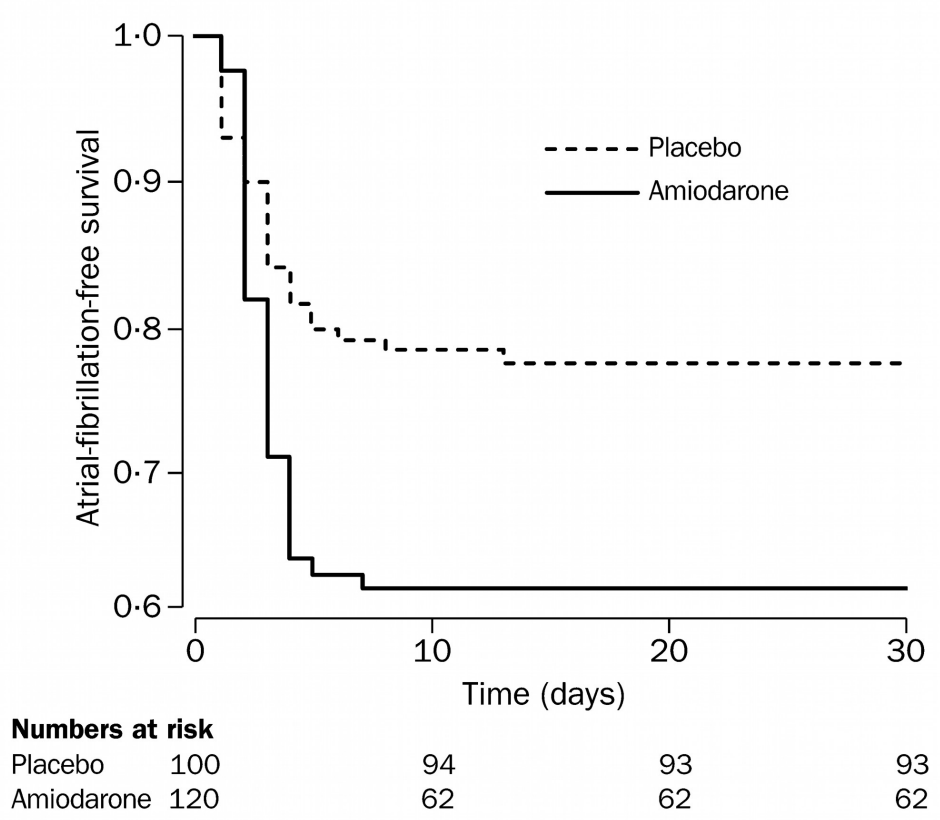




Summary of Treatment Emergent Adverse Events (TEAE)

	No (%) of Patients With Any Event				
	PL (N=26)	D225 (N=26)	R750 (N=26)	R750/D150 (N=26)	R750/D225 (N=27)
Patients with any TEAE					
AE	15 (58)	18 (69)	17 (65)	16 (62)	20 (74)
SAE	1 (4)	2 (8)	7 (27)	1 (4)	5 (19)
AE leading to discontinuation	3 (12)	4 (15)	5 (19)	5 (19)	5 (19)

Reiffel JA.
Circ AEP. 2015; 8: 1048-1056



- **Atrial Fibrillation Suppression Trial (AFIST):** The combination of amiodarone with a beta-blocker may be useful in prolonging the time to first recurrence and postsurgery AF: prophylaxis with oral amiodarone in combination with beta-blockers prevented AF and reduced the risk for cerebrovascular accidents in patients undergoing open-heart surgery (220 patients)

Amiodarone plus Flecainide combination therapy in patients with Amiodarone refractory paroxysmal atrial fibrillation

Darren R. Kagal *, Eugene Crystal, Ilan Lashevsky, Irving Tiong, Ching Lau, Atilio Costa Vitali, David Newman

Sunnybrook Health Sciences Centre, Toronto, ON, Canada
University of Toronto, Toronto, ON, Canada

"The **combination of Amiodarone and Flecainide was relatively safe.** There were no deaths or arrhythmia induced syncope but overall 37% of patients had to discontinue their medications due to adverse effects"

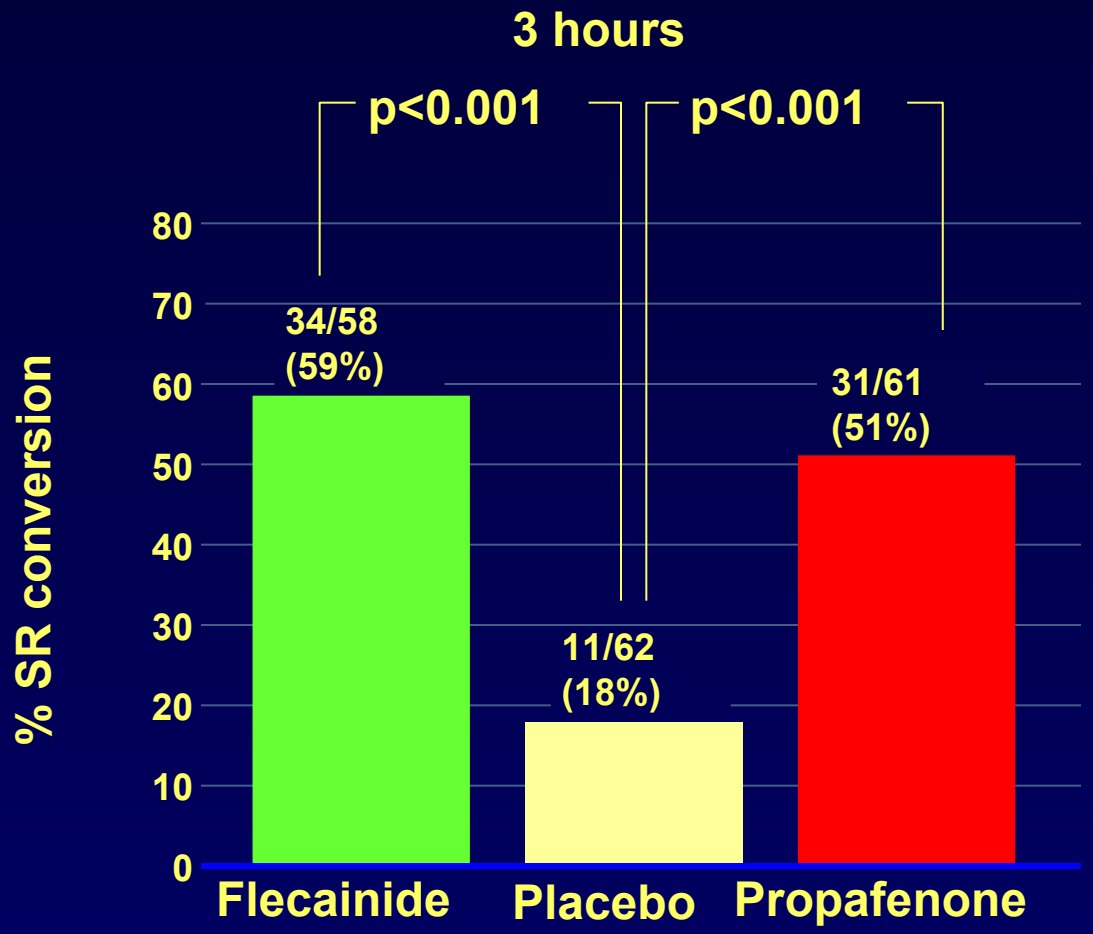
VErapamil Plus Antiarrhythmic drugs Reduce Atrial Fibrillation recurrences after an electrical cardioversion (VEPARAF Study)

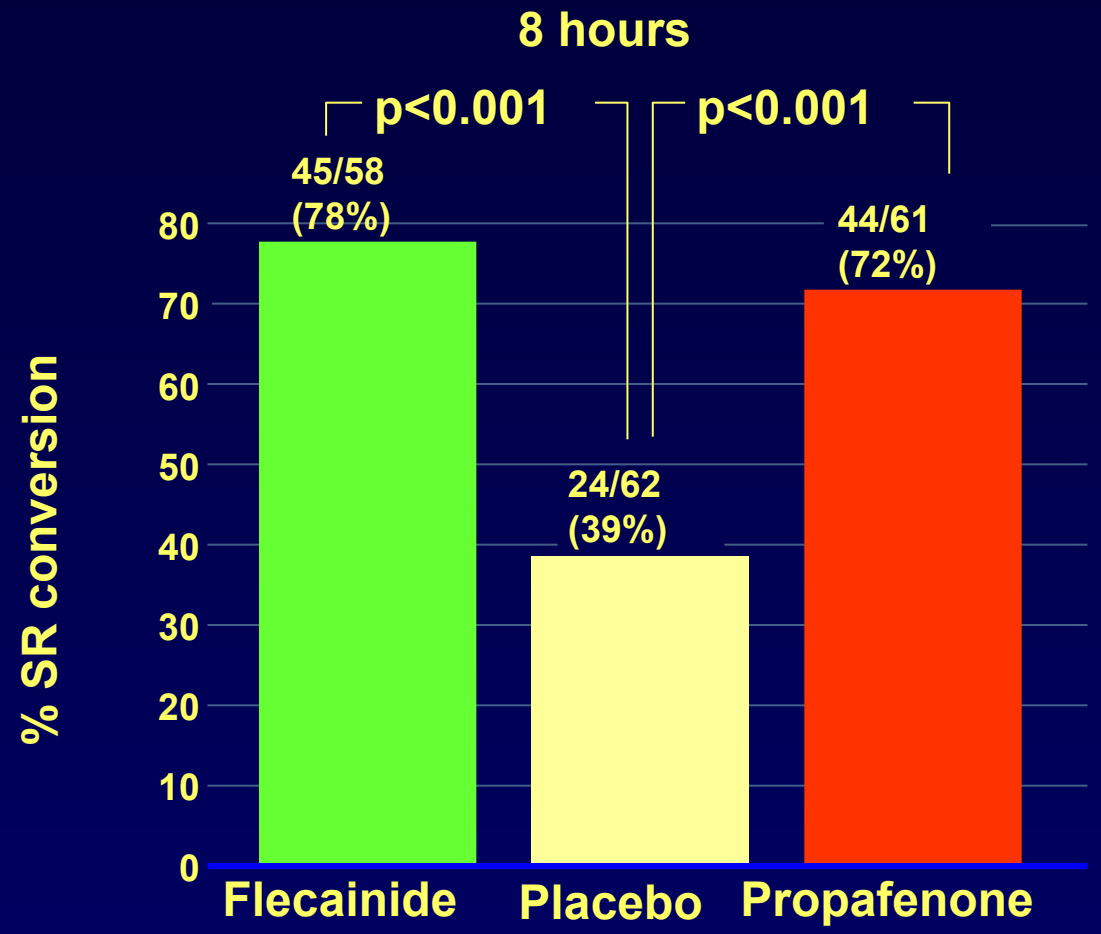
Antonio De Simone[a], Michele De Pasquale[b], Carmine De Matteis[c], Michelangelo Canciello[d], Michele Manzo[e], Luigi Sabino[f], Ferdinando Alfano[g], Michele Di Mauro[a], Andrea Campana[e], Giuseppe De Fabrizio[g], Dino Franco Vitale[h], Pietro Turco, Giuseppe Stabile[a]*

At univariate analysis **verapamil significantly reduced the AF recurrences if added to amiodarone** or **flecainide** (from 35% to 20%, P=0.004)

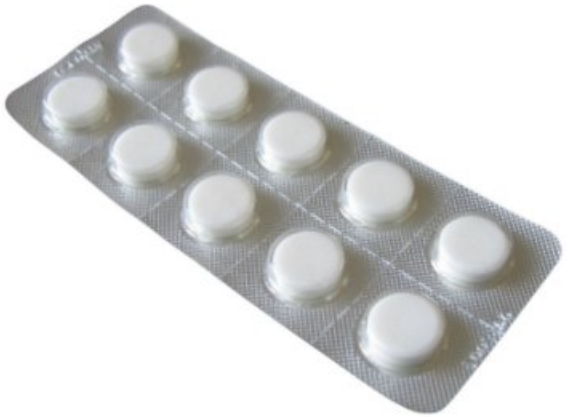
Comparative efficacy rate of 1C AAD in reverting PAF patients to SR (Oral loading dose)

(Capucci et al ,AJC 1992)





PILL IN THE POCKET



- Recidive infrequenti (<1/mese), sintomatiche
- Buona tolleranza emodinamica
- Assenza di cardiopatia organica e/o turbe della conduzione
- Proponibile dopo primo tentativo di cardioversione con farmaco per os in ambiente ospedaliero (safety assessment)

FLECAINIDE 300 mg per os (200 mg se < 70 kg)

PROPAFENONE 600 mg per os (450 mg se < 70 kg)

Reproducible efficacy of oral loading Propafenone in PAF

(Capucci et al. AJC 2003)

PAF episodes	87
Mean age	61±13 yrs
Mean follow-up	15±7 months
Time from onset	3.2±2.7 hrs
Time to SR within	2.8±2.2 hrs
Reproducible efficacy	93%
Side effects	None
Proarrhythmic events	None

Pill in the pocket

In selected patients with recent-onset AF and no significant structural heart disease, a single high oral dose of flecainide or propafenone (the 'pill-in-the-pocket' approach) should be considered, provided this treatment has proven safe during previous testing in a medically secure environment.	IIa	B

Systematic review and cost-effectiveness evaluation of 'pill-in-the-pocket' strategy for paroxysmal atrial fibrillation compared to episodic in-hospital treatment or continuous antiarrhythmic drug therapy

C Martin Saborido,[1] J Hockenhull,[1] A Bagust,[1] A Boland,[1] R Dickson[1]* and D Todd[2]

	Costs	QALYs	Time in NSR	Relapses
Pill in the pocket	£ 1512	9,21	3220	2422
AADs	£ 2389	9,23	2274	1403
In-hospital CV	£ 2340	9,29	2683	2153

- The pill-in-the-pocket is less effective in preventin recurrences
- Life expectancy adjusted for QoL is similar betwee both groups
- Pill in the pocket related costs are 40 % lower

Saborido CM et al. Health Technol Assess. 2010;14:1-75.

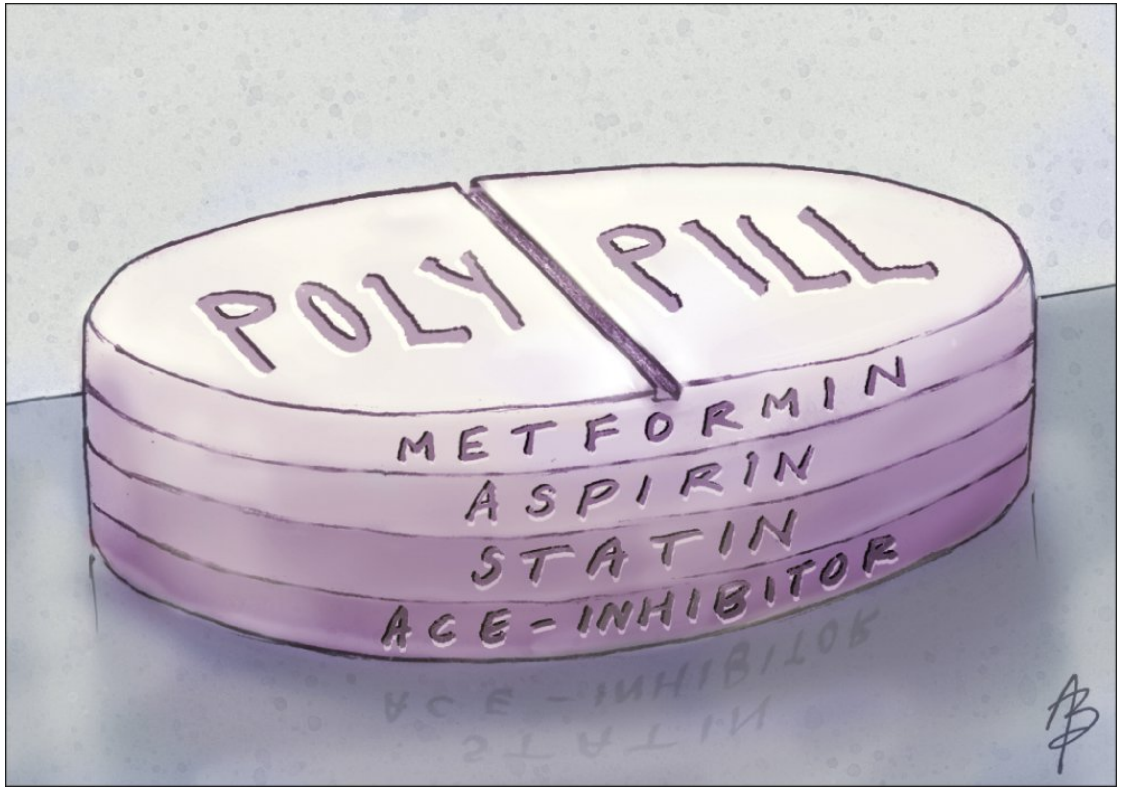
Recommendations for rate control

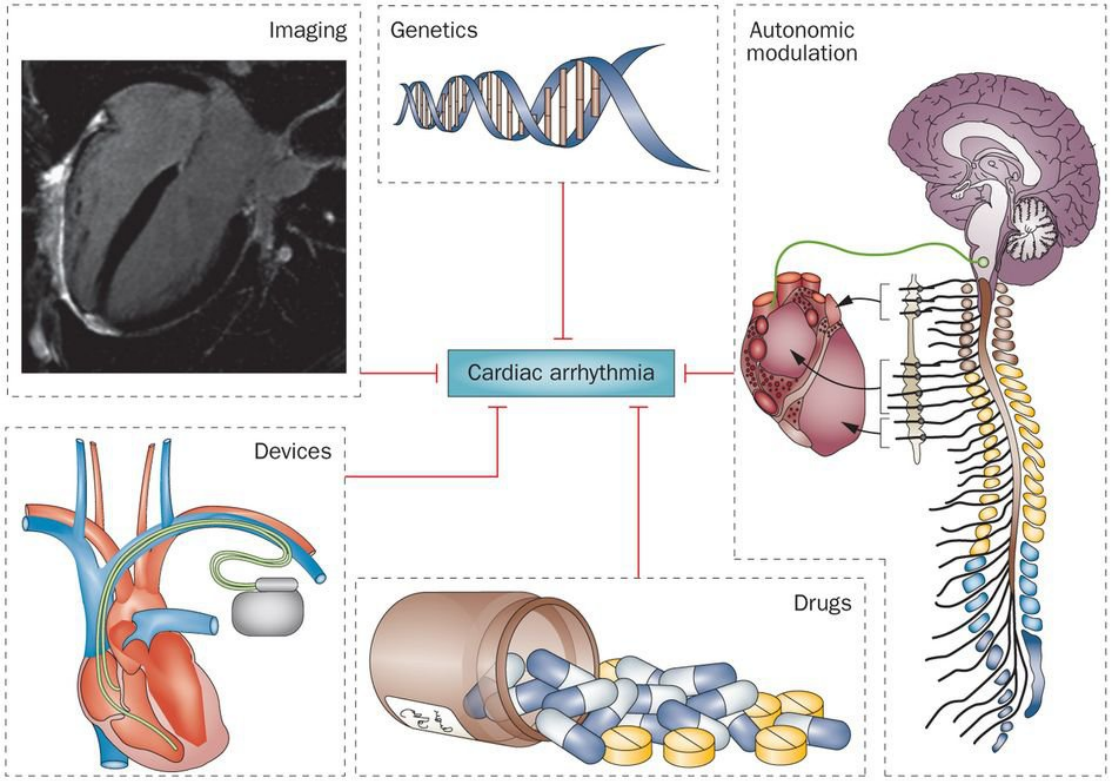
Recommendations	Class[a]	Level[b]	Ref[c]
Beta-blockers, digoxin, diltiazem, or verapamil are recommended to control heart rate in AF patients with LVEF ≥40%.	I	B	225, 526, 528, 531, 532, 541, 555, 575
Beta-blockers and/or digoxin are recommended to control heart rate in AF patients with LVEF <40%.	I	B	23, 225, 526, 533, 554, 575, 576
Combination therapy comprising different rate controlling agents should be considered if a single agent does not achieve the necessary heart rate target.	IIa	C	23, 554, 577
In patients with haemodynamic instability or severely depressed LVEF, amiodarone may be considered for acute control of heart rate.	IIb	B	536–538
In patients with permanent AF (i.e. where no attempt to restore sinus rhythm is planned), antiarrhythmic drugs should not routinely be used for rate control.	III (harm)	A	41, 578, 579
A resting heart rate of <110 bpm (i.e. lenient rate control) should be considered as the initial heart rate target for rate control therapy.	IIa	B	560
Rhythm rather than rate control strategies should be considered as the preferred management in pre-excited AF and AF during pregnancy.	IIa	C	

Drugs used for heart rate control are simple and generally safer than drugs used for maintenance of sinus rhythm.

Verapamil and diltiazem are considered the drugs of choice for heart rate control in the context of AF.

Digitalis (0.250—0.320 mg/day) and beta-blockers (metoprolol 50—200 mg/day, propranolol (80—240 mg/day) may be considered of secondary importance. In particular, the combinations of calcium channel blockers and digitalis, beta-blockers and digitalis, and calcium channel blockers and beta-blockers may be useful in reducing the dosage of single drugs and, consequently, dosage-dependent side-effects.


POLY PILL
METFORMIN
ASPIRIN
STATIN
ACE-INHIBITOR


Imaging
Genetics
Autonomic modulation
Cardiac arrhythmia
Devices
Drugs

Comorbidities represent an arrhythmogenic substrate and can modulate the efficacy/safety of AADs

Idiopathic AF (10-30%) → No evidence of cardiac disease

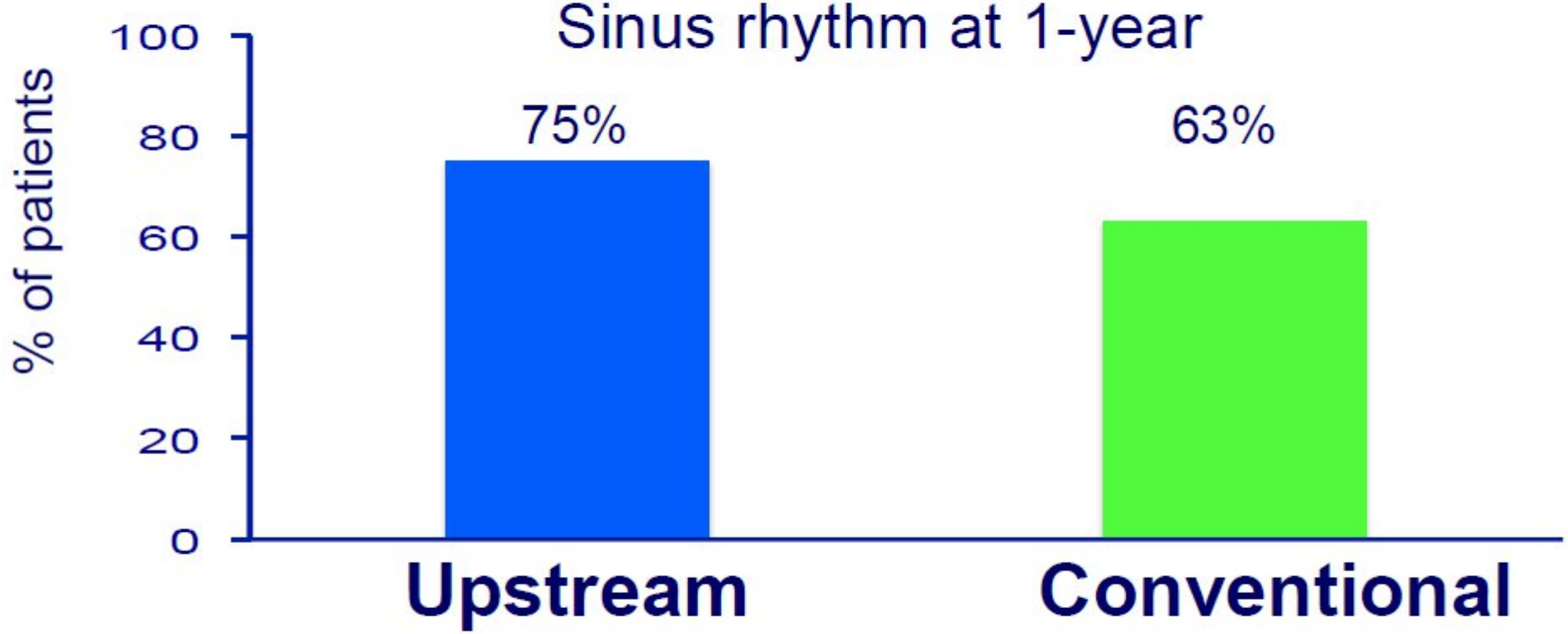
- Different co-morbidities – different substrates – different therapeutic strategies
  - "One size fits all" approach" is *doomed to failure*
  - Treatment should be individualized
  - **Goal:** to slow or arrest AF onset and progression

Recomendations	Class	Level
Management of cardiovascular risk factors and avoidance of AF triggers should be pursued in patients on rhythm control therapy to facilitate maintenance of sinus rhythm	IIa	B

umcg

RACE

Primary endpoint

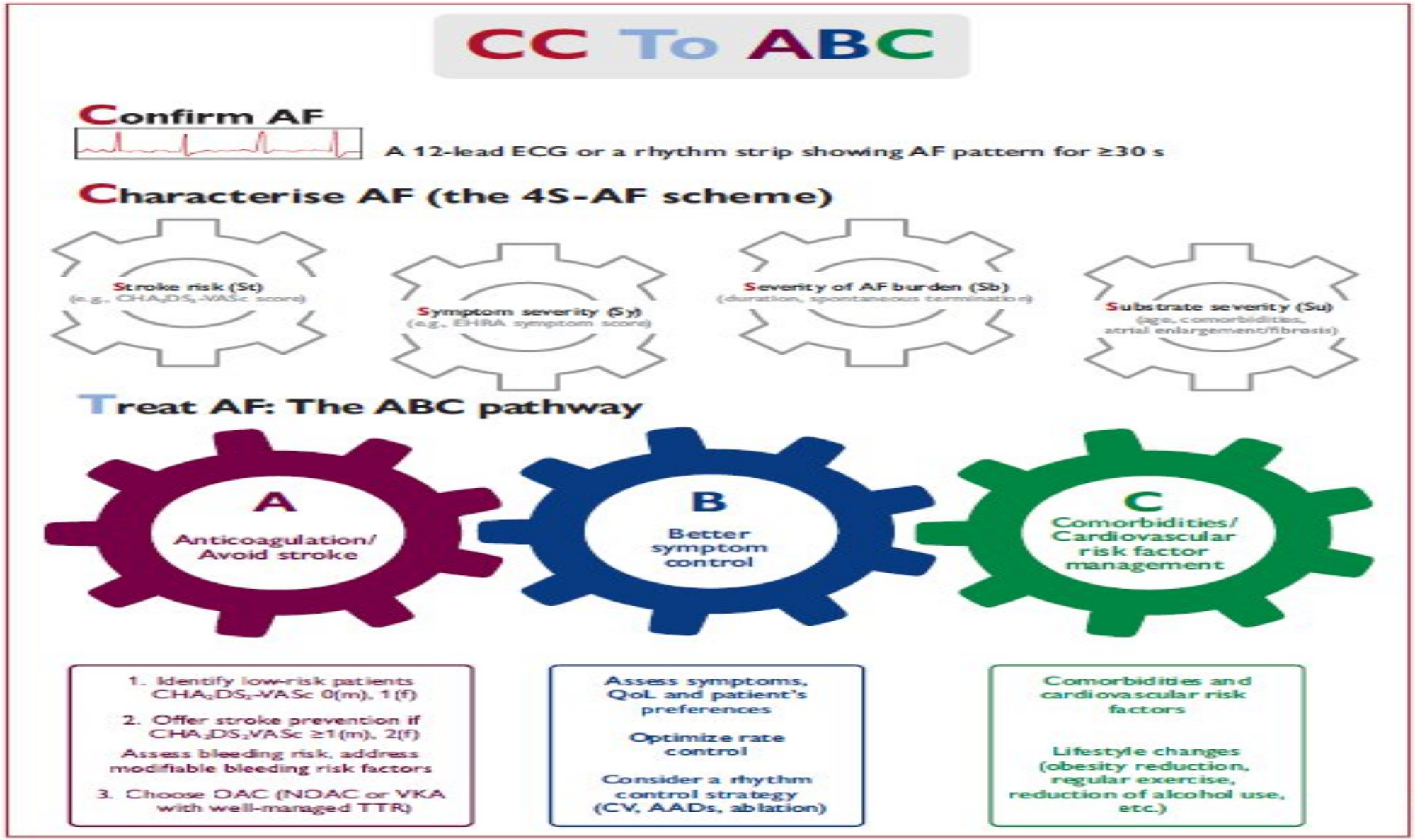


Odds ratio	1.765
Lower 95% confidence limit	1.115

Superiority hypothesis was proven (p=0.021)

Netherlands Heart Institute

funded by the dutch heart foundation
Hartstichting



Central Illustration Management of AF. AAD = antiarrhythmic drug; AF = atrial fibrillation; ECG = electrocardiogram; EHRA = European Heart Rhythm Association; CHA_2DS_2-VASc = Congestive HF, Hypertension, Age ≥75 years, diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); CV = cardioversion; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; TTR = time in therapeutic range; VKA = vitamin K antagonist.

Possible therapeutic targets (Great expectations?)

1. Atrial repolarization delaying agents	
• I_{Kur} blockers	• XEN-0D103*, BMS-394136/919373, MK0448*; MK-1832, KVI0201, F373280, BMS919373
• I_{KAchc} blockers**	• NIP-151, NTC-801, AZD-2927, XEN-R0702, KB130015, OPC-108459, A7071 (most abandoned)
• Late Na^+ current (I_{NaL}) blockers	• Ranolazine, Eleclazine (GS-458967)*
2. Other Selective channel blockers	
• Small conductance Ca^{2+}-activated K^+ (SK1-3) channels	• NS8593, AP14145, UCL1684, ICAGEN
• Two-pore K^+ (K2P) channels**	• TASK-1 (K2p3.1): A293, ML365 (amiodarone, vernakalant) • Also in the ventricles and other tissues
3. Transient receptor potential (TRP) channels**	• TRPC3, TRPM7: fibroblasts myofibroblasts • TRPC6/7, TRPM4
4. Multichannel blockers	• AVE1231, AZD1305, AZ13395438, S20951, S0100176
5. Abnormal intracellular Ca^{2+} handling	• RyR2-stabilizers: ivabradine, Rycals (Aladorian*) • RyR2 channel inhibitors: R-carvedilol, (l)-nebivolol, VK-II-86, flecainide, propafenone • CaMKII inhibitors**: KN-93 (CaMKII) • Restore SECRCA2a activity: allosteric modulators

** Selectivity (AEs) and/or undruggable

Conclusions

1. **AADs remain the mainstay therapy for MANY patients with paroxysmal/persistent AF**

(+) **Cheap generics, we know their efficacy/safety ration (?)**

- **Rhythm control improves symptoms and QoL and reduces hospitalizations**
- **Clearly improve the results of AF ablation**

(-) **Modest efficacy and safety concerns (structural heart disease)**

2. **A main limitation is to consider AF as a single entity**

- **Different co-morbidities – different substrates – different therapeutic strategies**
- **"One size fits all" approach" *is doomed to failure***

3. **There is a great opportunity to improve hybrid and combination therapy**

- **The "battle" against AF can only be won if both pharmacological and interventional antiarrhythmic therapies work together**

"*Marching apart, fighting together* (Helmut von Moltke, 1800-1891)

CONCLUSIONE

Table 19 **Rules to initiate antiarrhythmic drugs for long-term rhythm control in AF**

Consideration	Criteria
Indication for AAD	• **Is the patient symptomatic?** • Are AF symptoms severe enough (EHRA class) to justify AAD use? • Are there associated conditions predicting poor tolerance of AF episodes?
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**
	Evaluate for:
	  • basal ECG abnormalities (QRS duration, PR, QTc) and possible interference with AAD
	  • impact on LV function
	  • important pharmacokinetic and pharmacodynamic interactions (ie. antithrombotic drugs)
	• **Risk factors for proarrhythmia may be dynamic and change over time**

How to minimize proarrhythmic risk	• **Evaluate ECG after the treatment, as indicated in these Guidelines** • Evaluate periodically for organ toxicity (amiodarone) • Long-term Holter monitoring and exercise test in selected cases • Avoid AAD combinations
How to verify efficacy	• **Estimate AF burden under therapy (ask patient for noting episodes)** • If the patient is already on AAD and it was effective but was stopped because of intolerance, choose preferably from the same class
Adjuvant interventions and hybrid therapy	• **In patients with atrioventricular conduction abnormalities and/or sinus node dysfunction, pacemaker implantation should be considered if AAD therapy is deemed necessary** • Short-term AAD therapy could prevent early recurrences after AF ablation

AAD = antiarrhythmic drug; AF = atrial fibrillation; ECG = electrocardiogram; EHRA = European Heart Rhythm Association; LV = left ventricular; PR = PR interval; QRS = QRS interval; QTc = corrected QT interval.

Grazie per l'attenzione