Arythmies : focus, recommandation, consensus EHRA

Antiarythmiques
EHRA 2025

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Liens d’intérêt

Laurent Fauchier:

Orateur ou consultant:	AstraZeneca, Bayer, BMS Pfizer, Boehringer Ingelheim, Boston Scientific, Medtronic, Novartis, Novo Nordisk, Zoll

ESC European Society of Cardiology

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EHRA DOCUMENT

EHRA European Heart Rhythm Association

Practical compendium of antiarrhythmic drugs: a clinical consensus statement of the European Heart Rhythm Association of the European Society of Cardiology

Jose L. Merino [1,2,3]*, (Chair), Juan Tamargo [4], Carina Blomström-Lundqvist [5,6], Giuseppe Boriani [7], Harry J. G. M. Crijns [8], Dobromir Dobrev [9,10,11], Andreas Goette [12,13,14], Stefan H. Hohnloser [15], Gerald V. Naccarelli [16], James A. Reiffel [17], Jacob Tfelt-Hansen [18], Marcel Martínez-Cossiani [19], (Writing Group Coordinator), and A. John Camm [20]*, (Chair)

Merino et al., *Europace* 2025: epub on 30.03.2025, doi: 10.1093/europace/euaf076

The EHRA "ABC" of AADs: Why Still I Need Them?

Appropriate therapy: AADs are often the *appropriate* and, in many cases, the sole therapy required for managing cardiac arrhythmias, including terminating arrhythmias during their initial presentation, addressing acute or incessant episodes, and treating patients who respond well to pharmacological treatment and prefer it over invasive procedures.

Backup therapy: AADs are used as a *backup* therapy when other primary treatments, such as ablation or CIEDs, are unavailable, poorly tolerated, particularly risky, contraindicated, or ineffective in preventing or terminating arrhythmia episodes or their consequences.

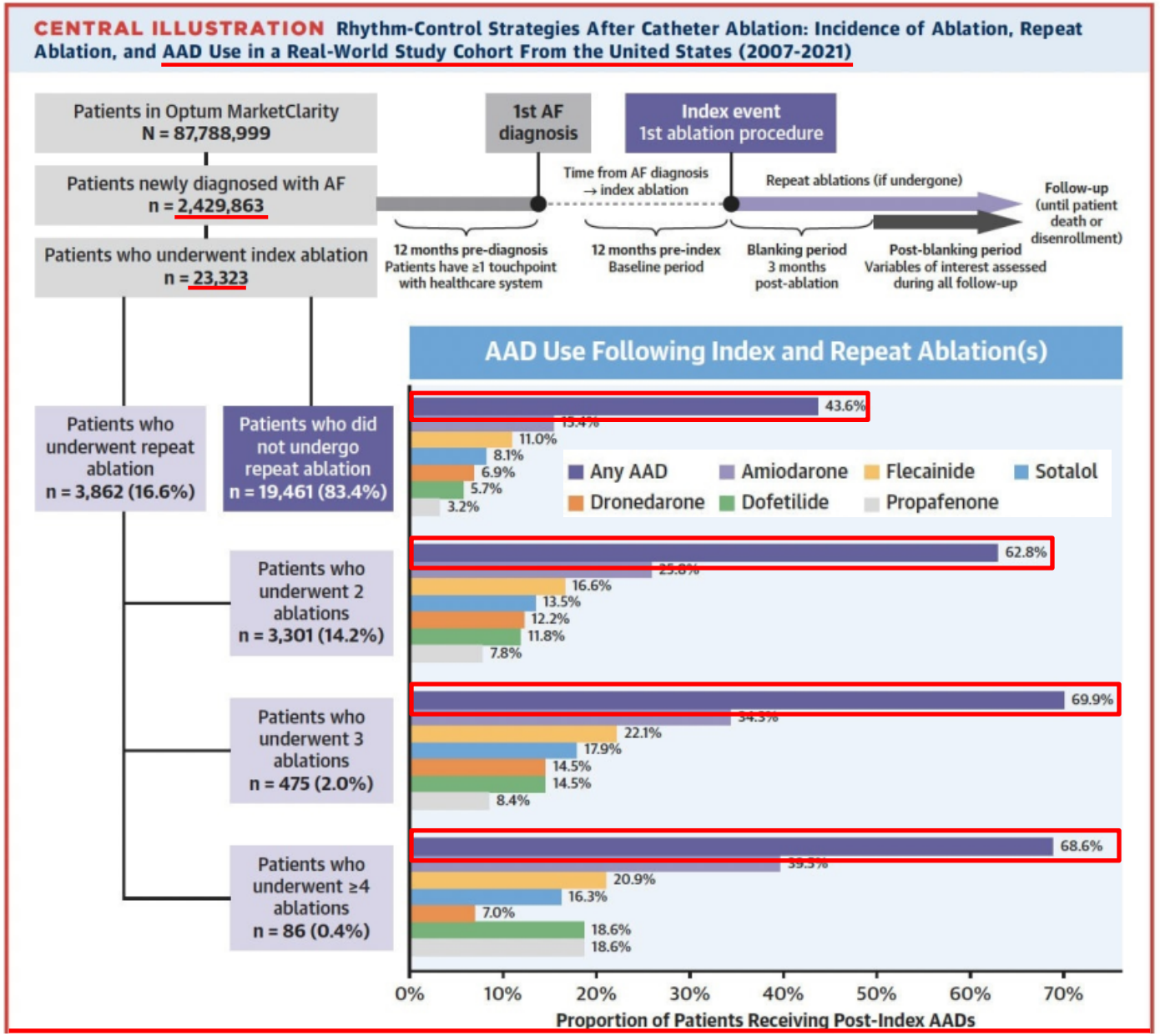
Complementary therapy: AADs serve as a valuable *complement* to other therapies, such as catheter ablation or CIEDs, by providing support during waiting periods, preparatory or postoperative phases, or by supplementing and enhancing their overall efficacy.

AADs, antiarrhythmic drug; CIED, cardiac implantable electronic device.

Merino et al., *Europace* 2025: epub on 30.03.2025, doi: 10.1093/europace/euaf076

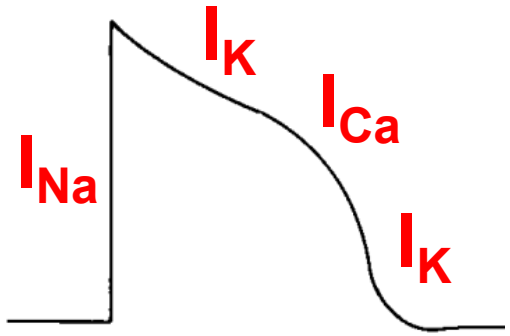
AADs are Appropriate, Backup, and Complementary Therapy

Only 0.9% undergone ablation!!!



Saksena et al., *JACC Clin Electrophysiol* 2025

Classes of Antiarrhythmic Drugs (AADs) according to Vaughan Williams in 1975

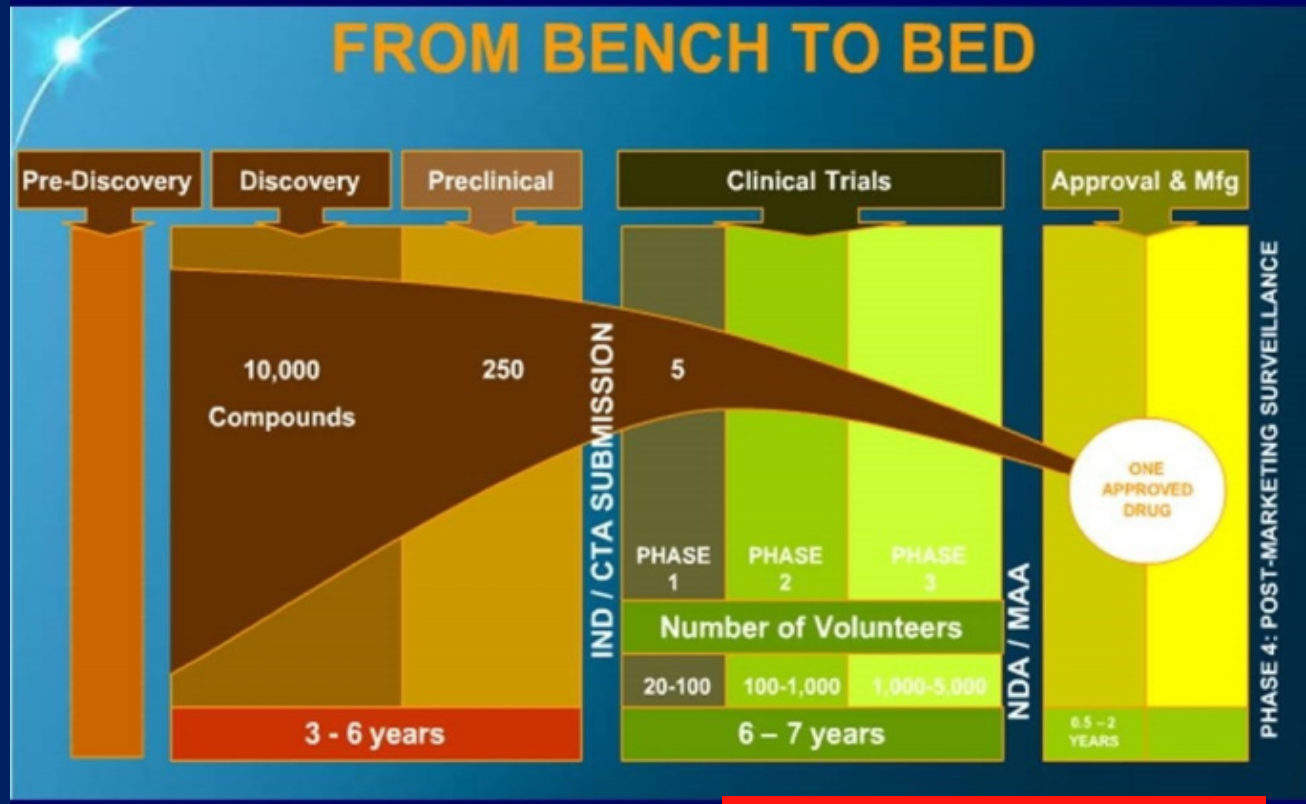


Class	Mechanism of action	Antiarrhythmic drug
Ia	Na^+-channels ↓, APD ↑	Quinidine, Procainamide
Ib	Na^+-channels ↓, APD ↓	Lidocaine, Mexiletine
Ic	Na^+-channels ↓, APD →	Flecainide, Propafenone
II	Beta receptors ↓	Metoprolol
III	K^+-channels ↓ (APD ↑)	Amiodarone, Sotalol
IV	Ca^{2+}-channels ↓	Verapamil, Diltiazem

Vaughan Williams, *Phar Ther* 1975;1:115-138.

Chronological overview of AA drugs

1749	Quinidine
1785	Digitalis
1936	Procainamide
1954	Disopyramide
1962	Beta-blocking agents
1972	Amiodarone
1978	Propafenone
1982	Flecainide
1984	Sotalol
1995	Ibutilide
1996	Dofetilide
1998	Azilimide
2010	Dronedarone



EHRA Classification of AADs in 2025: Part 1

Class	Subclass	Primary pharmacological target/action	Example of drugs
HCN channel blockers			
0		HCN channel-mediated pacemaker current (I_f)	Ivabradine
Voltage-gated Na^+ channel blockers			
I[a]	Ia	Nav1.5 (I_{Na}) open-state (intermediate dissociation)	Ajmaline, disopyramide[b], procainamide[b], quinidine/hydroquinidine[b,c,d]
	Ib	Nav1.5 (I_{Na}) inactivated-state (rapid dissociation)	Lidocaine, mexiletine[c], phenytoin
	Ic	Nav1.5 open/inactivated state (slow dissociation)	Antazoline[e], cibenzoline, flecainide[f], pilsicainide, propafenone[f]
	Id	Late Na^+ current	Ranolazine
Inhibitors and activators of the autonomic nervous system			
II	IIa	β-adrenoceptor antagonists	β1 blockers: atenolol, bisoprolol, esmolol, landiolol, metoprolol, nebivolol β1 & β2 blockers: nadolol, propranolol β1, β2 & α1 blockers: carvedilol, labetalol
	IIb	β-adrenoceptor agonists	Isoprenaline
	IIc	Muscarinic M2 receptor inhibitors	Atropine
	IId	Vagal nerve/ACh release activators	Digoxin, digitoxin
	IIe	Adenosine A1 receptor activators	Adenosine
K^+ channel blockers and openers			
III[f]	IIIa	Non-selective K^+ channel blockers	Amiodarone[h], dronedarone[h], sotalol[i], bretylium
		Kv11.1 (hERG) K^+ channel blockers	Dofetilide, ibutilide[j], nifekalant
		Kv1.5 (I_{Kur}) K^+ channel blockers	Vernakalant[k]
	IIIb	Kir6.2 (K_{ATP}) K^+ channel openers	Nicorandil
	IIIc	GIRK1 and GIRK4 (I_{KACh}) blockers	No approved medications

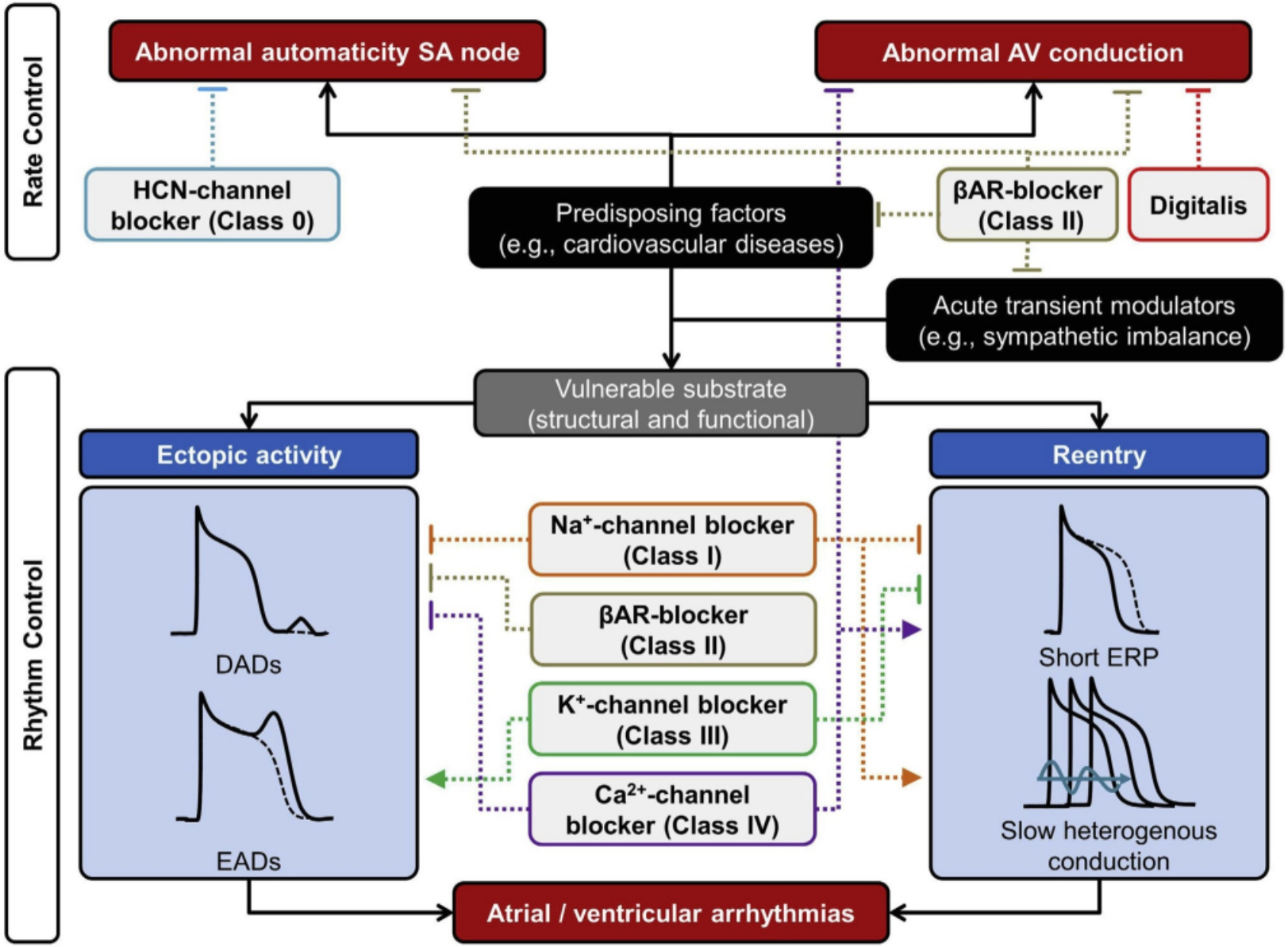
Merino et al., *Europace* 2025: epub on 30.03.2025, doi: 10.1093/europace/euaf076

EHRA Classification of AADs in 2025: Part 2

Class	Subclass	Primary pharmacological target/action	Example of drugs
Ca^{2+} channel modulators			
IV	IVa	Surface membrane non-selective & Cav1.2 and Cav1.3 channel mediated L-type Ca^{2+} current (I_{CaL}) blockers	Bepridil, diltiazem, etripamil, verapamil
	IVb	Intracellular sarcoplasmic reticulum RyR2-Ca^{2+} channel blockers	No approved medications
Mechanosensitive channel blockers			
V		Transient receptor potential channel (TRPC3/TRPC6) blockers	No approved medications
Gap junction channel blockers			
VI		Cx (Cx40, Cx43, Cx45) blockers	No approved medications
Upstream target modulators			
VII		ACEI, ARNI, Mineralocorticoid receptor antagonists, Omega-3 fatty acids, Sacubitril, Statins	Enalapril, lisinopril, losartan, candesartan, spironolactone, eicosapentaenoic acid, docosahexaenoic acid, statins, etc.

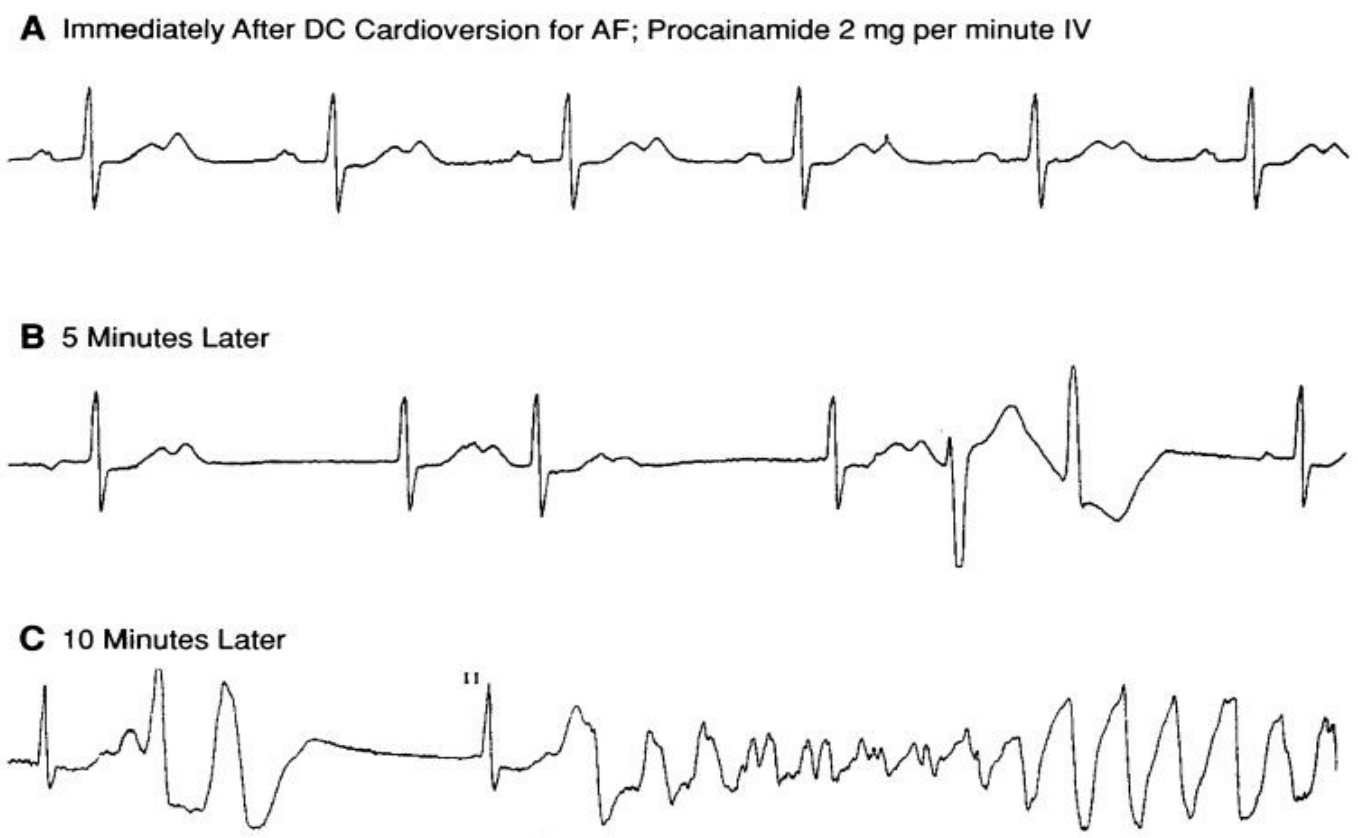
Merino et al., *Europace* 2025: epub on 30.03.2025, doi: 10.1093/europace/euaf076

Overview of Antiarrhythmic Effects of AADs



Heijman and Dobrev 2022. *Arrhythmias*. In: Kenakin, T. (Ed.), *Comprehensive Pharmacology*. Vol. 4, pp. 432-468. Elsevier.

How to avoid and manage proarrhythmia and toxicity?



THE AMERICAN JOURNAL OF CARDIOLOGY VOL. 82 (4A) AUGUST 20, 1998

Box 12 Risk factors associated with TdP

- Age >65 years[a]
- Female sex[a]
- Congenital long QT syndrome (clinical or subclinical due to incomplete penetrance, either mono- or polygenetic)
- Personal history
  - History of syncope
  - History of TdP or significant bradycardia
  - Current nausea, vomiting, diarrhoea, laxative use
- Structural heart disease
  - Myocardial ischaemia
  - Heart failure
  - Left ventricular hypertrophy
- Systemic disorders
  - Renal or liver failure
  - Hypo-thyroidism
  - Subarachnoid haemorrhage
  - Hypothermia
- Electrolyte disorders
  - Hypokalaemia (<3.5 mmol/L)
  - Hypocalcaemia (<8.5 mmol/L)
  - Hypomagnesaemia (≤0.7 mg/dL)
- Drugs
  - QT-prolonging medications
  - Diuretic therapy
  - Drug–drug interactions
- ECG signs (*Box 13*)

Abbreviations: ECG, electrocardiogram; TdP, torsades de pointes.

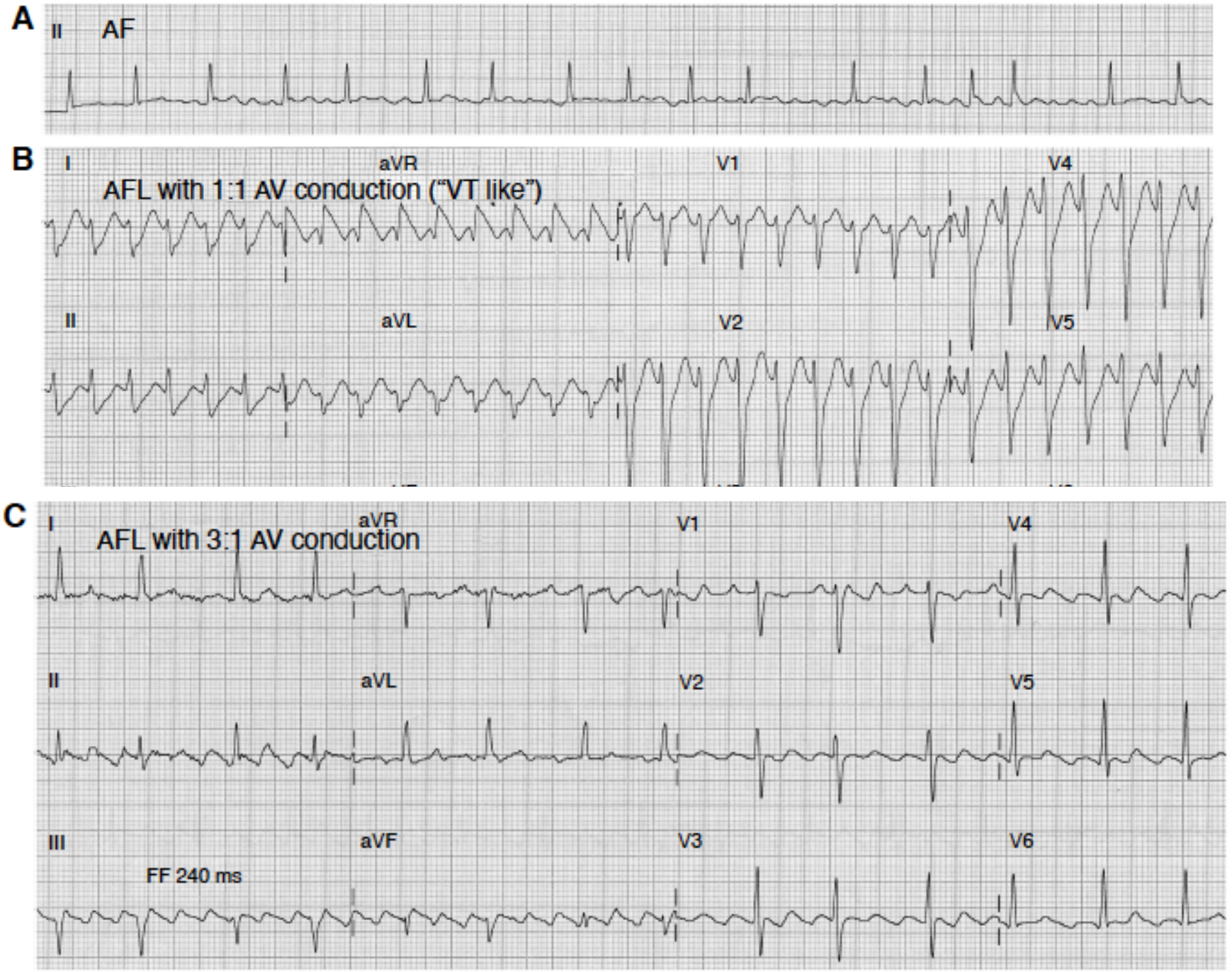
[a]Age and sex alone are not sufficient to contraindicate certain AADs, though they are advised for heightened monitoring and control of other risk factors

Box 13 ECG signs indicative of risk for TdP

- Bradycardia (<60 bpm), including recent conversion from AF
- QTc >500 ms
- QT increase >60 ms from baseline
- T-wave alternans
- T- or U-wave distortion
- Ventricular ectopy and non-sustained VT triggered after a pause

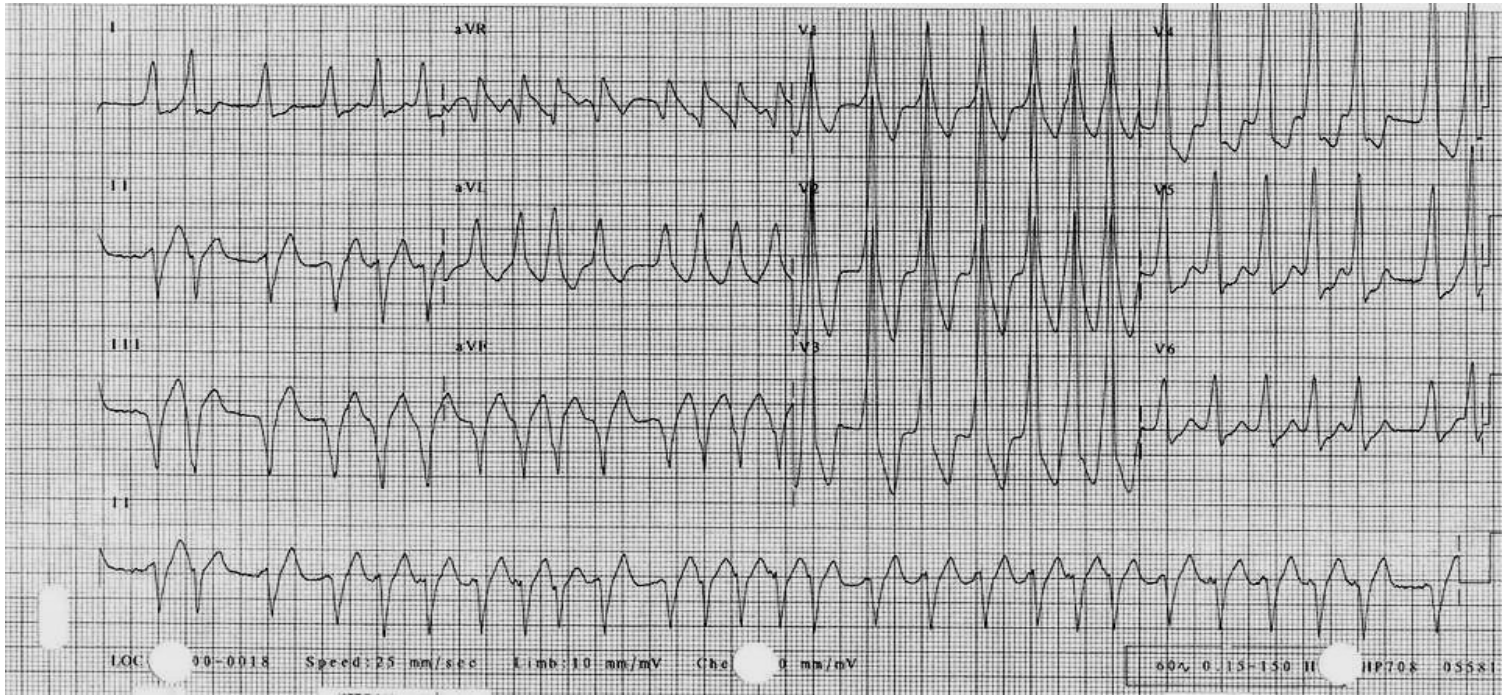
Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram; TdP, torsades de pointes; VT, ventricular tachycardia.

Merino J, et al. EHRA compendium on AAD. *Europace* 2025

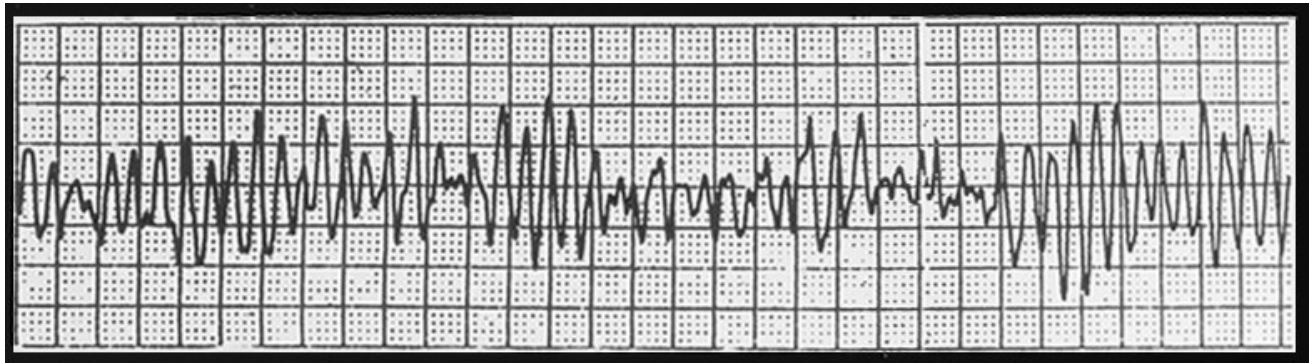

A
II
AF
B
I
aVR
V1
V4
AFL with 1:1 AV conduction ("VT like")
II
aVL
V2
V5
C
I
aVR
V1
V4
AFL with 3:1 AV conduction
II
aVL
V2
V5
III
aVF
V3
V6
FF 240 ms

THE IMPORTANCE OF DRUG PHARMACOKINETICS – PHARMACODYNAMIC KNOWLEDGE

AF with ventricular preexcitation



VF few minutes after amiodarone i.v. …



G BORIANI ET AL. Am Heart J 1996

1: G Ital Cardiol. 1986 Nov;16(11):969-74.

[Possible danger of rapid intravenous amiodarone in re-entry tachycardia in subjects with Wolff-Parkinson-White syndrome]

[Article in Italian]

Vitale P, De Stefano R, Auricchio A.

1: Int J Cardiol. 1987 Jul;16(1):93-5.

Enhanced accessory pathway conduction following intravenous amiodarone in atrial fibrillation. A case report.

Schützenberger W, Leisch F, Gmeiner R.

Acceleration of ventricular rate by amiodarone in atrial fibrillation associated with the Wolff-Parkinson-White syndrome

BRYAN D SHEINMAN, TOM EVANS

BRITISH MEDICAL JOURNAL VOLUME 285 9 OCTOBER 1982

10. Perticone F, Cuda G, Spadea F, Pintaudi C, Tropea R. Malignant ventricular arrhythmia in the Wolff-Parkinson-White syndrome during amiodarone treatment. *Clin Cardiol*. 1987;10(8):477-480.

BRIEF COMMUNICATIONS

Ventricular fibrillation after intravenous amiodarone in Wolff-Parkinson-White syndrome with atrial fibrillation

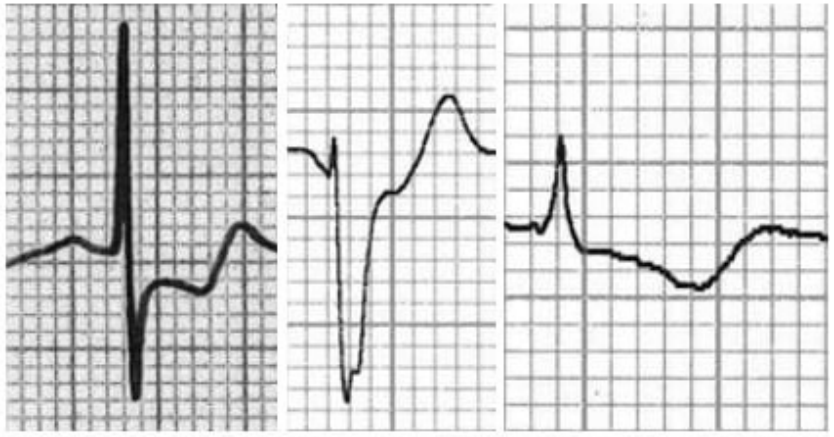
Giuseppe Boriani, MD, Mauro Biffi, MD, Lorenzo Frabetti, MD, Umberto Azzolini, MD, Paolo Sabbatani, MD, Gabriele Bronzetti, MD, Alessandro Capucci, MD, and Bruno Magnani, MD
Bologna, Italy

Volume 131, Number 6
American Heart Journal 1996

… a verapamil-like effect with i.v. amiodarone !

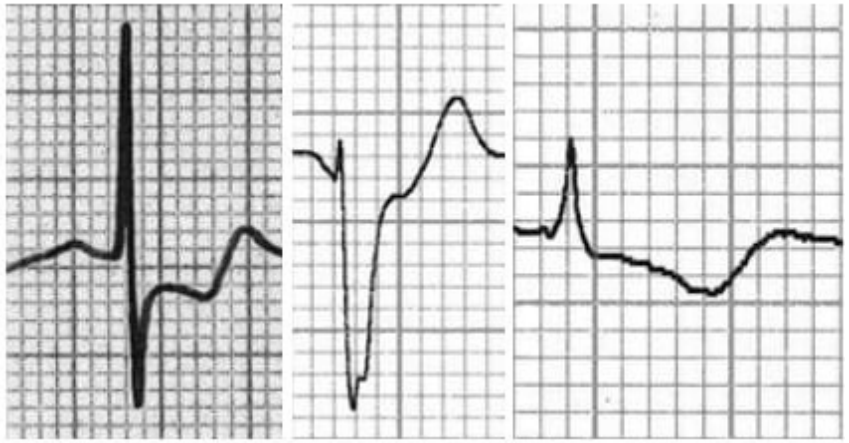
662 **Table 4: Typical indications and contraindications of major AADs.**

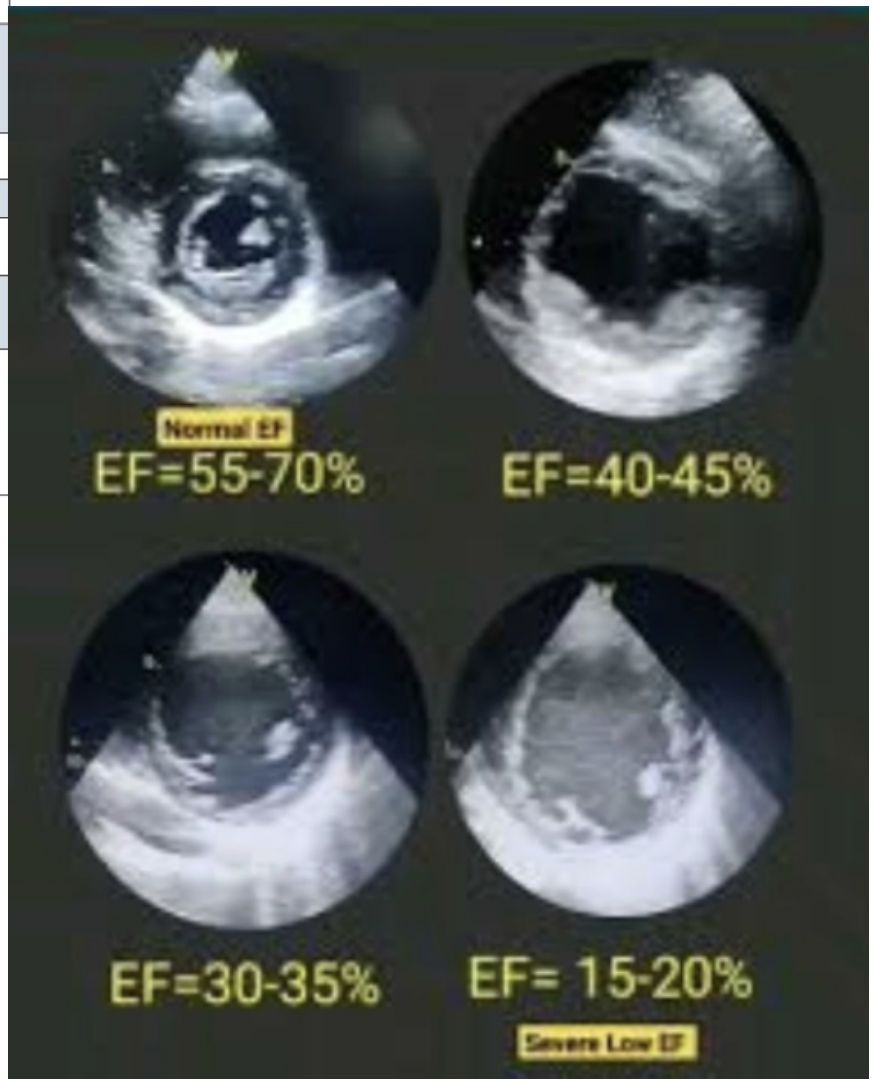
Modified VW Class	AAD	Main indications	Not to be used/Main contraindication
0	**Ivabradine**	Inappropriate sinus tachycardia	AF termination
IA	**Ajmaline**	AF (preexcitation) termination MVT (no significant SHD) termination	BrS HFrEF
	Quinidine	PVT (channelopathies) prevention	Long QT
	Procainamide	MVT (SHD) termination	HFrEF
	Disopyramide	AF (vagotonic) prevention	HFrEF
IB	**Lidocaine**	PVT/VF (ischaemia) termination	Bradycardia
	Mexiletine	TdP (LQTS 3) prevention	Bradycardia
	Phenytoin	JET (digitalis toxicity) termination	Bradycardi
IC	**Flecainide** **Propafenone**	AF (idiopathic) prevention/termination WPW syndrome	BrS SHD
	Antazoline	AF (idiopathic) termination	Bradycardia SHD
	Pilsicainide	AF (Idiopathic) termination	SHD
ID	**Ranolazine**	AF prevention/termination	Long QT
IIA	**β1 blockers (e.g. Bisoprolol, metoprolol)**	AF/AFL rate control VT/PVCs (idiopathic)	Bradycardia
	β1+β2 blockers (e.g. Nadolol, propranolol)	TdP (LQTS 1 & 2) prevention CPVT	Bradycardia
IIB	**Isoprenaline**	TdP (acquired LQTS) PVT (BrS)	CPVT
IIC	**Atropine**	Sinus bradycardia	Inappropriate sinus tachycardia
IID	**Digoxin**	AF/AFL rate control	Amyloidosis
IIE	**Adenosine**	PSVT termination	Asthma/COPD



J Merino et al AAD Compendium EP Europace March 30 2025

III	**Amiodarone**	AF/AFL (HFrEF) prevention/termination MVT (SHD) prevention/termination	Bradycardia
	Dronedarone	AF/AFL (SHD) prevention	Permanent AF HFrEF
	Dofetilide	AF/AFL (HFrEF) prevention	Long QT
	Ibutilide	AFL termination	Long QT
	Sotalol	MVT (SHD) prevention	CKD
	Vernakalant	AF (≤7 d) termination	Aortic Stenosis NYHA III/IV
IV	**Verapamil** **Diltiazem**	AF/AFL rate control VT (fascicular) prevention/termination	MVT (SHD) HFrEF





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AAD in pts with ICDs

Box 18 ICD–AAD interactions

- AADs may increase ICD pacing thresholds (see *Table 21*)
- AADs may alter DFT (see *Table 21*)
- AADs may aggravate bradycardia/AV block requiring more antibradycardia pacing
- AADs may slow AFL leading to 1:1 conduction or pacing
- AADs may slow VT rate and increase cycle length above the ICD tachycardia detection interval
- AADs may alter VT sensing by slowing the dV/dT and increasing the QRS duration
- AADs may cause pro-arrhythmia or incessant VT, potentially increasing the need for ICD interventions or rendering ICD therapy ineffective

Abbreviations: AAD, anti-arrhythmic drug; AFL, atrial flutter; AV, atrioventricular; DFT, defibrillation treshold; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia.

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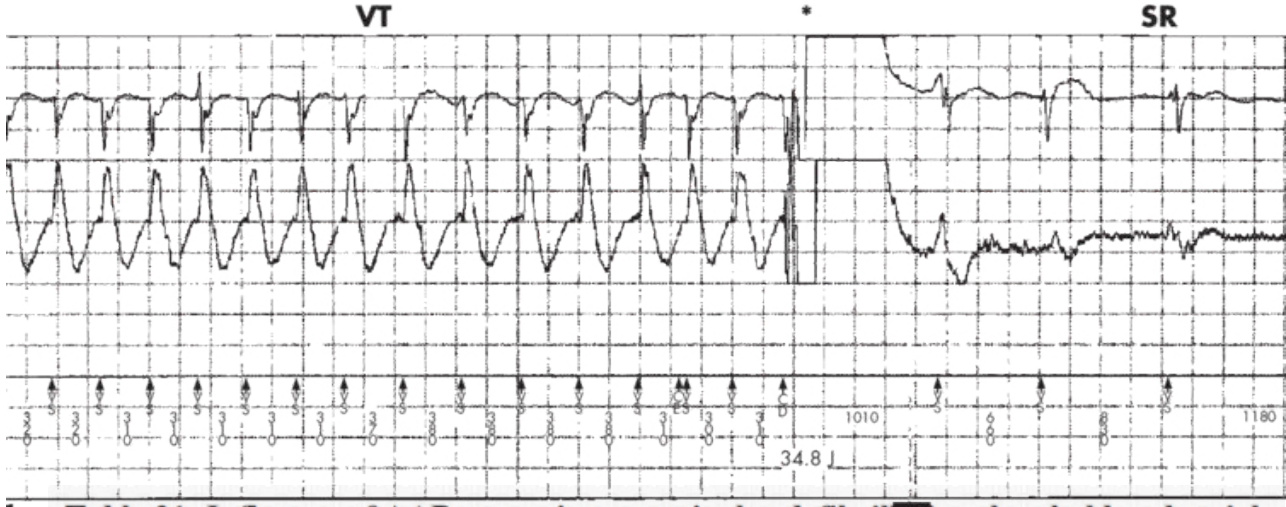

Table 21: Influence of AAD on pacing, ventricular defibrillation threshold and atrial cardioversion failure

AAD Class	AAD	Pacing Threshold	Ventricular Defibrillation Threshold	Atrial Defibrillation Threshold[a]
Ia	Procainamide Disopyramide	+	0	-
Ib	Lidocaine Mexiletine	0	+	
Ic	Flecainide	+	+	
IIa	β-blockers	0	0/-	
IIb	Isoprenaline	-	?	
III	Amiodarone	0	+	-
	Sotalol	0	-	
	Ibutilide			-
IV	Verapamil Diltiazem	0	+	

Table 8 Advisable tests at baseline and during follow-up for patients taking AADs

Evaluation	Test/parameter	Frequency	Toxicity/interaction evaluation
AADs other than amiodarone			
ECG	Rhythm, PR, QRS, QTc	Baseline, shortly after initiation or dose adjustments (1–2 days for Class Ia, sotalol, dofetilide) and periodically (e.g. every 6 months)	QT interval prolongation (for Class Ia and III drugs) QRS duration prolongation (for Class Ic drugs) Pro-arrhythmic tachycardia (e.g. type Ic AFL), bradycardia or BBB/atrioventricular block
Echocardiography	Ventricular function	Baseline and updated if change suspected/risk	Systolic dysfunction (contraindication for Class Ic and IV AADs)
Blood test and serum electrolytes	GFR, K^+, Mg^{2+}	Baseline, periodically (e.g. every 6 months)	Reduced drug elimination, Pro-arrhythmia risk
Liver function	ALT, AST, and total bilirubin	Baseline, periodically (e.g. every 6 months)	Reduced drug elimination
Exercise test	QRS at peak exercise, myocardial ischaemia	To consider for Class Ic at follow-up	QRS widening at exercise
Amiodarone			
ECG	Rhythm, PR, QRS, QTc	Baseline, steady state (1–3 months), annually	QT interval prolongation, pro-arrhythmic tachycardia (e.g. AFL), bradycardia, or atrioventricular block
Echocardiography	Ventricular function	Baseline, update if potential changes suspected	Systolic dysfunction
Serum electrolytes	K^+, Mg^{2+}	Baseline, every 6 months	Pro-arrhythmia risk
Liver function	ALT, AST, and total bilirubin	Baseline, every 6 months	Hepatotoxicity
Thyroid function	TSH, free T4, and free T3	Baseline, every 6 months	Hypo-thyroidism or hyper-thyroidism
Pulmonary function	Chest X-ray and pulmonary function tests (diffusion capacity)	Baseline, annually	Interstitial lung disease
Visual function	Corneal slit-lamp exam and fundoscopic evaluation	Baseline, annually	Corneal microdeposits and, rarely, optic neuropathy

Abbreviations: AAD, anti-arrhythmic drug; AFL, atrial flutter; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BBB, bundle branch block; ECG, electrocardiogram; GFR, glomerular filtration rate; TSH, thyroid-stimulating hormone.

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Table 10 Pro-arrhythmia risk and typical pro-arrhythmia forms of different AADs

Class	Drug	Risk	Type of pro-arrhythmia
0	Ivabradine	Low	Bradycardia, AV block, AF
Ia	Quinidine	High	TdP
	Procainamide	Moderate	AV block, monomorphic VT[a], TdP
	Disopyramide	Low	Bradycardia
Ib	Mexiletine/ lidocaine	Low	Bradycardia, AV block
Ic	Flecainide	Moderate	AFL[b], monomorphic VT[a], bradycardia[c]
	Propafenone	Moderate	AFL[b], monomorphic VT[a], Bradycardia[c]
Id	Ranolazine	Low	QT prolongation
IIa	β-Blockers	Low	Bradycardia, AV block
IIb	Isoprenaline	Low	Sinus tachycardia, PACs, PVCs, VT
IIc	Atropine	Low	Sinus tachycardia, paradoxical AV block[d]
IId	Digoxin/ digitoxin	Moderate	AV block, junctional tachycardia, polymorphic VT, AT with AV block
IIe	Adenosine	Moderate	Transient sinus bradycardia and AV block, AF, PACs, PVCs
III	Amiodarone	Low	Bradycardia, AFL[b]
	Dronedarone	Low[e]	Bradycardia
	Dofetilide	High	TdP
	Ibutilide	High	TdP
	Sotalol	High	TdP, bradycardia
	Vernakalant	Low	Sinus bradycardia, NSVT
IV	Verapamil	Low	Bradycardia, AV block
	Diltiazem	Low	Bradycardia, AV block

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; AV, atrioventricular; NSVT, non-sustained VT; PAC, premature atrial contraction; PVC, premature ventricular contraction; TdP, torsades de pointes; VT, ventricular tachycardia.

[a]In patients with structural heart disease.

[b]In patients with AF.

[c]In patients with sinus node dysfunction or AV conduction disorders.

[d]Worsening of AV block on the ECG, such as a progression from second-degree AV block to AV block as atropine increases the sinus rate.

[e]High when combined with digitalis, as dronedarone reduces the renal excretion of digitalis, amplifying its associated risks. The combination may also increase the likelihood of AV block and other pro-arrhythmic effects.

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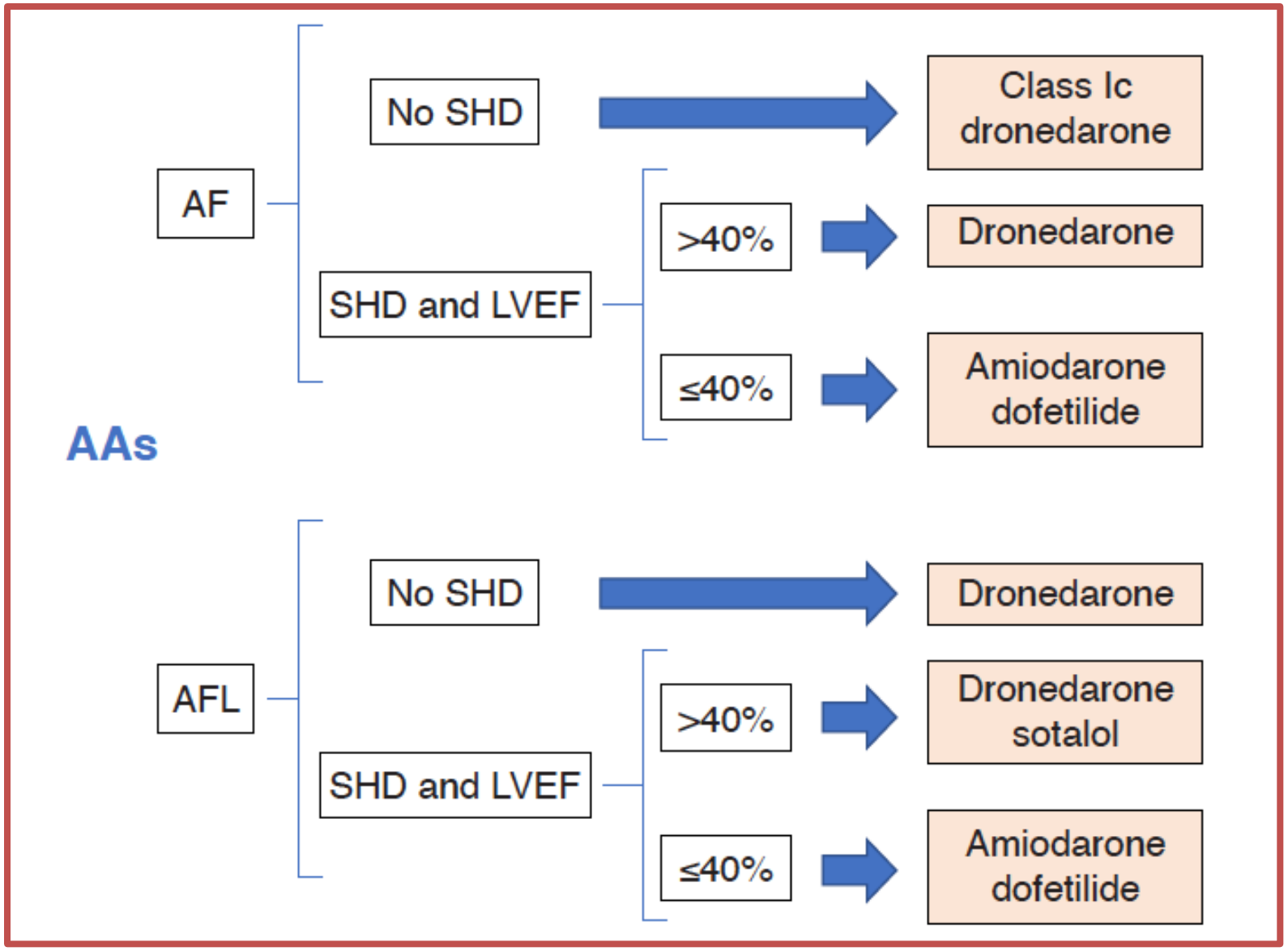

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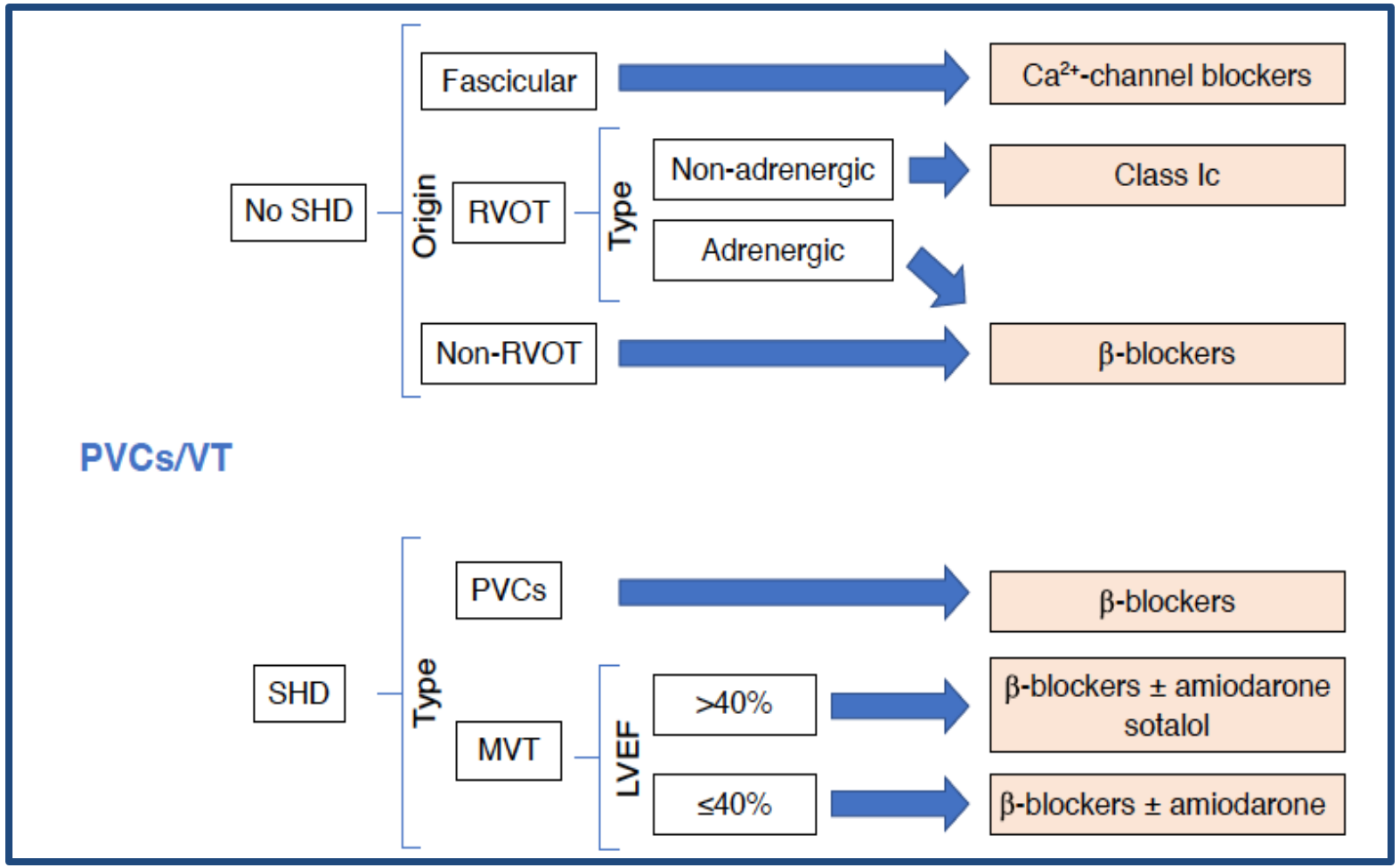

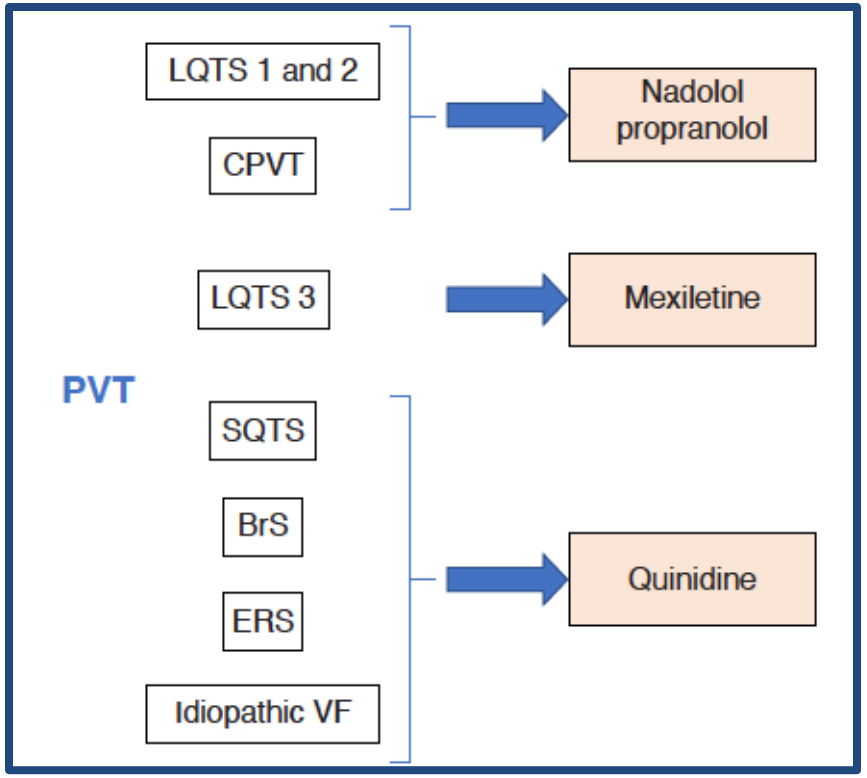

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ESC European Society of Cardiology
Europace (2023) 25, 1–8
https://doi.org/10.1093/europace/euad162

CLINICAL RESEARCH

Real-world utilization of the pill-in-the-pocket method for terminating episodes of atrial fibrillation: data from the multinational Antiarrhythmic Interventions for Managing Atrial Fibrillation (AIM-AF) survey

James A. Reiffel [1]*, Carina Blomström-Lundqvist [2,3], Giuseppe Boriani [4], Andreas Goette [5], Peter R. Kowey [6,7], Jose L. Merino [8,9], Jonathan P. Piccini [10], Sanjeev Saksena [11,12], and A. John Camm [13]

Multinational survey of over 600 cardiologists, stratified from USA and Europe (cardiologists and electrophysiologists):

the APPROPRIATENESS of Pill in the Pocket use of AAD should improve!

Need for physician education !

Pill-in-the-Pocket (PITP) Therapy for Termination of Acute/Recent-Onset AF is a Guideline-Included, Literature-Supported, Established Treatment Strategy. However, its Real-World Usage is Uncertain.

The AIM-AF Survey [1] included questions about the use of PITP by European (UK, Germany, Italy, Sweden) and American cardiologists (CDs) and electrophysiologists (EPs) in their AF patients. Over 600 respondents provided data for analysis.

- 42% indicated PITP for PAF patients with no or minimal SHD.
- 18% indicated PITP for persistent AF patients with no or minimal SHD.
- 16% indicated PITP for PAF patients with SHD.
- 12% indicated PITP for persistent AF patients with SHD.

Antiarrhythmic Drug Selection for PITP

Patients with No/Minimal SHD	Patients with SHD
Overall:	Overall:
Flecainide 77%	Amiodarone 32%
Propafenone 32%	Sotalol 21%
Amiodarone 13%	Propafenone 15%
Sotalol 13%	Dronedarone 13%
Dronedarone 7%	Flecainide 12%
Dofetilide 2%	Dofetilide 4%

- Amiodarone is considered an inappropriate agent for PITP therapy owing to its long onset of action.
- Sotalol is not an appropriate choice for PITP therapy due to its relatively ineffective cardioversion properties.
- Use of class IC agents for PITP was appropriate and highest in patients with no or minimal heart disease.
- However, the IC agents were also inappropriately used in some patients with SHD.

Conclusions:

- PITP is used by many cardiologists and electrophysiologists in both Europe and America.
- Most PITP usage is for PAF in the absence of SHD where class IC AADs are the most frequent drugs used (per guidelines).
- However, PITP use was also reported for patients with persistent AF (where inefficacy is highly likely).
- Guideline-inappropriate AAD selection for PITP was not uncommon.
- Regional differences were present among the European countries.
- Our data suggest additional physician education is needed.

AF = atrial fibrillation; PAF = paroxysmal AF; PITP = pill-in-the-pocket; SHD = structural heart disease

1. Camm AJ, et al. AIM-AF: a physician survey in the United States and Europe. J Am Heart Assoc. 2022; 11:e023838. DOI: 10.1161/JAHA.121.02.3838

Conclusion Our findings highlight the frequent use of PITP and the need for further physician education about appropriate and optimal use of this strategy.

	During Atrial Fibrillation		During Sinus Rhythm	
	In-patient	Out patient	In-patient	Out patient
Class Ia				
Class Ib				
Class Ic				
Sotalol				
Dofetilide				
Dronedarone				
Ranolazine				
Amiodarone				

¶: *for type III long QT syndrome or PVCs*

*: *If uncertain sinus node function or risk for AFL conversion with 1:1 AV conduction*

**: *If known absence potential risk of sinus node dysfunction or AV conduction disorders*

***: *If no TdP risk markers and in sinus rhythm.*

For women and patients over 65, sotalol should only be initiated in an outpatient setting with close monitoring, in the absence of other risk factors. Patients should be educated to recognise warning symptoms, avoid certain medications, and adhere to follow-up appointments. US FDA recommends hospitalizing all patients being initiated or re-initiated on sotalol for at least 3 days or until steady-state drug levels are achieved in a facility that can provide cardiac resuscitation and continuous ECG monitoring.

Merino J, et al. EHRA compendium on AAD. *Europace* 2025

Box 10 Advantages, disadvantages, and advice for inpatient and outpatient initiation of AADs

In-hospital initiation

Advantages

- Direct monitoring of drug effects on arrhythmia
- Faster drug loading (e.g. sotalol)
- Use of parenteral AADs if needed
- Immediate response to acute adverse effects:
  - Sinus node/AV conduction disturbances
  - Conversion to AFL with 1:1 conduction
  - QT prolongation, TdP
  - Heart failure, early drug intolerance, interactions
- Addresses medical–legal concerns for specific AADs

Disadvantages

- Requires hospitalization (inconvenient, disruptive)
- Higher costs and logistical challenges
- Long half-life drugs (e.g. amiodarone, digoxin) will not reach steady state
- Pro-arrhythmia risk may still occur later due to evolving conditions (e.g. electrolyte changes, new drug interactions, heart rate change)

Outpatient initiation

Advantages

- Patient preference and practicality
- Lower cost; avoids hospitalization for most low-risk cases
- Safe for low-risk groups:
  - Class Ic AADs, dronedarone, amiodarone in non-SHD patients
  - Sotalol in males in sinus rhythm with normal renal function, electrolytes, and no LV hypertrophy
- Predictable drug interactions can be managed
- AFL with 1:1 conduction preventable with AV nodal blockers

Disadvantages

- Rare but serious pro-arrhythmic events may go undetected and untreated

Abbreviations: AAD, anti-arrhythmic drug; AFL, atrial flutter; AV, atrioventricular; LV, left ventricle; TdP, torsades de pointes.

Box 11 Advice/requirements for in-hospital/outpatient initiation of AADs

In-hospital initiation

- Class Ia: required for most drugs (some exceptions).
- Class III (dofetilide): must always be initiated and dose-adjusted in-hospital.
- Class III (Sotalol): in-hospital if QTc ≥450 ms (500 ms if intraventricular conduction delay), HR ≤60 b.p.m., or specific risk factors (e.g. SHD and renal dysfunction). See *Box 12*

- QT prolongation or unconfirmed sinus rhythm (risk of sick sinus syndrome or bradycardic pauses): require in-hospital initiation
- Pro-arrhythmic risk: high ventricular pro-arrhythmia risk (TdP, syncope, cardiac arrest) necessitates in-hospital monitoring

Outpatient initiation

- Class Ib (mexiletine): Allowed for non-tachycardic ventricular ectopy or type III long QT syndrome.
- Class Ic (fleainide/propafenone): Permitted in patients without SHD with ECG checks unless normal sinus rhythm has not been previously documented.
- Class Id (ranolazine): Safe for patients with or without SHD.
- Class III (dronedarone and amiodarone): permitted with ECG checks in low-risk patients.
- Patients with ICDs: ICDs provide protection against pro-arrhythmia, enabling outpatient initiation

Abbreviations: AADs, anti-arrhythmic drugs; ECG, electrocardiogram; HR, heart rate; ICD, implantable cardioverter defibrillator; QTc, corrected QT interval; SHD, structural heart disease.

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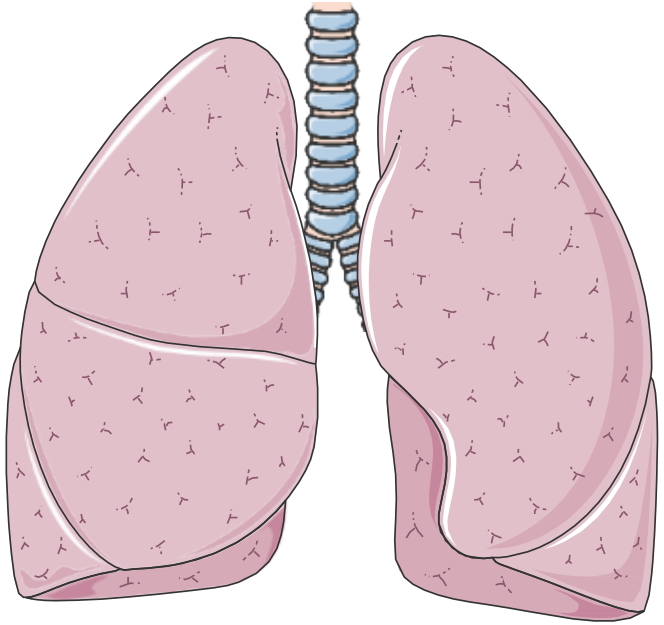
Box 2 Practical tips on using AADs

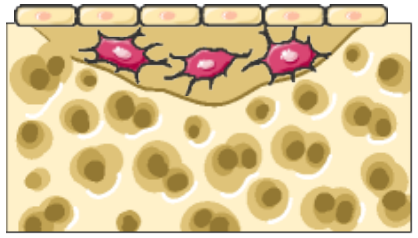
- To enhance safety of AAD use, it is advised to involve patients in AAD treatment:
  - Patients have to be taught about *warning symptoms* (progressive palpitations, unexpected dizzy spells or syncope, development of chest pain, dyspnoea, and recent-onset exercise intolerance)
  - Patients have to be taught about *critical circumstances* (to avoid concomitant QT-prolonging drugs, to report when a new drug is prescribed, the risk of developing hypokalaemia with diarrhoea and/or vomiting, excessive sweating during fever, dietary deficiencies, or the addition of diuretics)
  - Patients have to be taught about *over-the-counter agents*, including supplements and herbal remedies, and which may interact with AADs, potentially affecting their efficacy or increasing the risk of adverse effects. Patients have to promptly report any additions or discontinuations of such agents
  - These have to be repeated during *regular follow-up visits*
- *Integrated nurse-driven* care with experienced nurses supervised by the physician can substantially improve AAD management
- It is advisable to perform an *exercise test on Class Ic* drugs to rule out exercise-induced excessive QRS widening or ventricular tachycardia, if in doubt
- *Flecainide or propafenone are not contraindicated* in patients with a high cardiovascular risk profile (e.g. incidental Agatston score <400) in the absence of angina pectoris or with uncomplicated mild left ventricular hypertrophy (both in the absence of left ventricular scar tissue and dysfunction)
- *CNS side effects of Class Ic drugs* may be tackled by changing to an extended-release formulation
- If *dronedarone* is prescribed correctly, patients may greatly benefit from its often-overlooked *pleiotropic effects*, including amelioration of acute coronary syndrome, reduction of stroke rate and improving of survival. Dronedarone must always be *taken with food* to increase its oral bioavailability
- *Class Ic drugs* exert excess anti-arrhythmic effects *during tachycardia* (atrial or ventricular) and *sotalol and amiodarone during bradycardia*: therefore, observe ventricular Class Ic effects during infusion for tachycardia conversion or with exercise and ventricular Class III effects after cardioversion. Use dependency of dronedarone is unknown. Direct clinical manifestations of use dependency of AADs at the atrial level are not well known

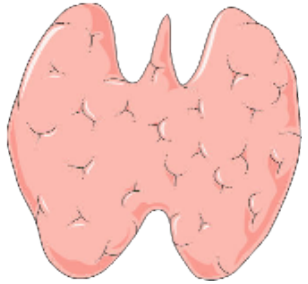
Abbreviations: AAD, anti-arrhythmic drug; CNS, central nervous system.

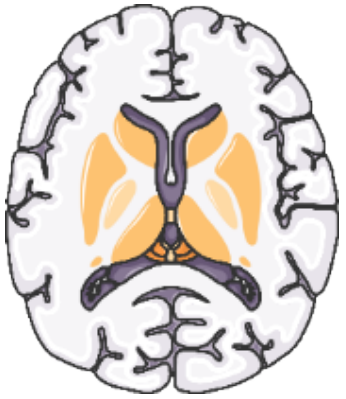
Merino J, et al. EHRA compendium on AAD. *Europace* 2025

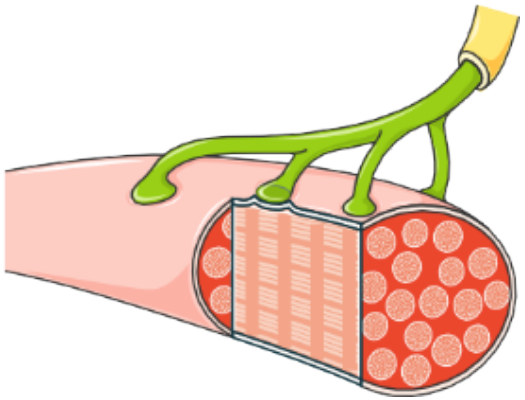
Amiodarone: side effects

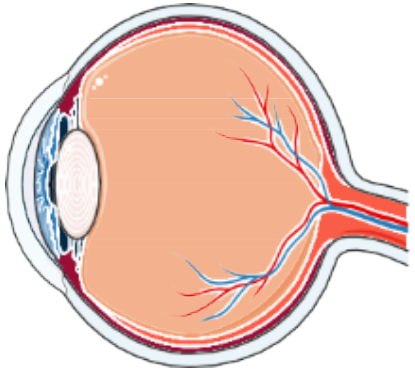


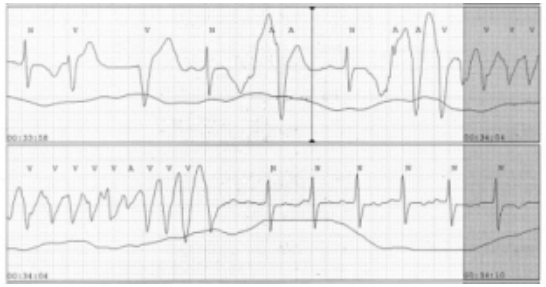












Adverse effect	Prevalence and/or annual incidence
Corneal microdeposits	> 90%
Optic neuropathy/neuritis	< 1%–2%
Hypothyroidism	5%–10%
Hyperthyroidism	0.9%–10%
Photosensitivity	25%–75%
Blue-gray skin discoloration	4%–9%
Pulmonary toxicity	1%–17%
Elevated liver enzyme levels	15%–30%
Hepatitis and cirrhosis	< 3%; 0.6%/yr.
Tremor and ataxia	3%–35%
Peripheral neuropathy	0.3%/yr.
Bradycardia and AV block	3%–5%
Torsades de Pointes	< 1%
Hypotension (IV formulation)	15–26%

Insomnia, memory disturbances and delirium have also been reported.

Trends Cardiovasc Med. 2019;29(5): 285–295. doi:10.1016/j.tcm.2018.09.005.

Amiodarone: side effects

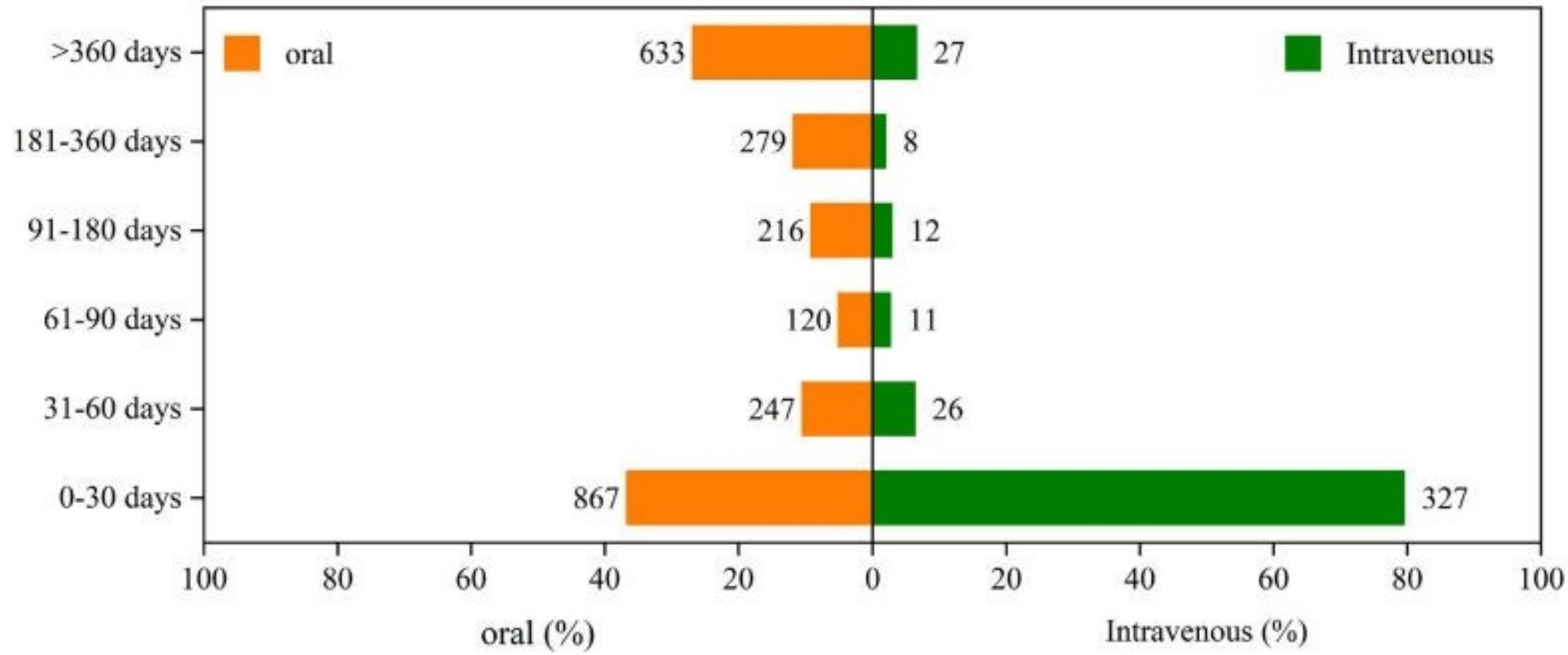


FIGURE 3
The induction time of adverse reactions associated with different routes of administration.

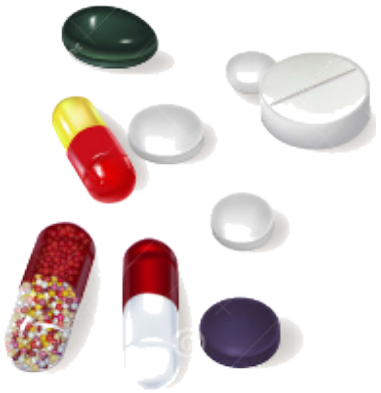
Yang J, et al. (2025) Front. Pharmacol. 16:1517616. doi: 10.3389/fphar.2025.1517616

Drug interactions: avoiding pitfalls

- AADs are often subject to significant drug–drug interactions, (see practical tables).
- One common pitfall is combining amiodarone with CYP3A4-metabolized statins (e.g. atorvastatin and simvastatin), increasing risk of myopathy ; favor other statins (e.g. rosuvastatin, pravastatin) instead.
- Interactions with digoxin, anticoagulants, and QT-prolonging drugs among others are also crucial to consider.

Merino J, et al. *Europace* 2025

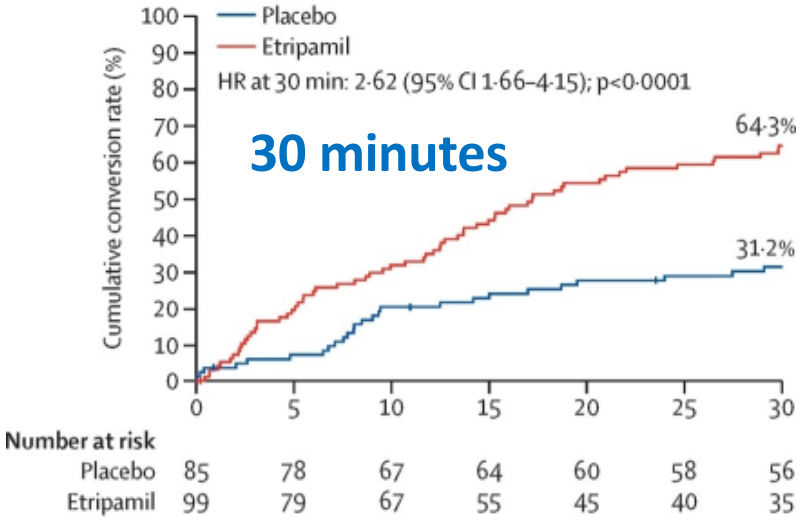
New Antiarrhythmic Drugs and Formulations

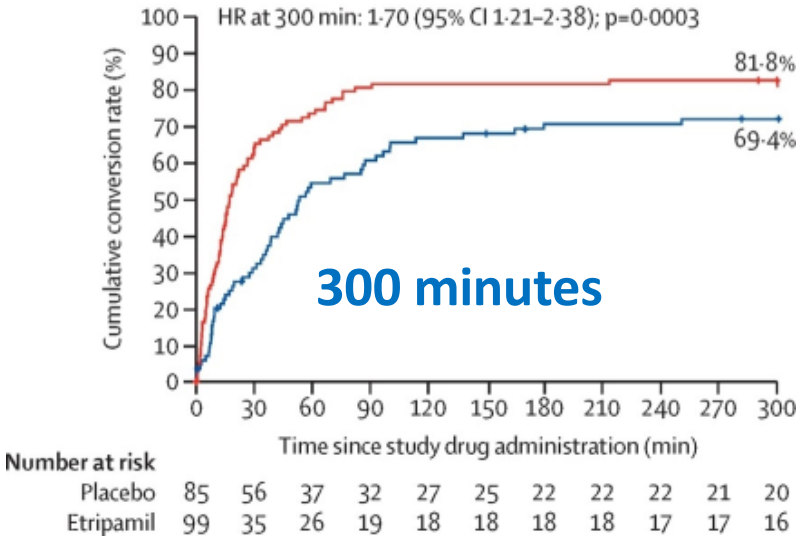


- **Etripamil** – intranasal administration
- **Budiodarone** – short T½ multichannel blocker
- **Inhaled flecainide** – a new formulation
- **SK channel inhibitors** – several molecules
- **Sulcardine** – a multichannel blocker
- **Bucindolol** – for the prevention of AF in heart failure
- **Doxapram** – a TASK 1 (K2P 3.1) inhibitor
- **HDAC inhibitors**, e.g., CKD-501/PKN-605
- **Botulinum toxin** – for epicardial fat pad injection
- **Fixed dose oral combinations**:- dronedarone and ranolazine, dofetilide and mexiletine
- **Antisense oligo-nucleotides and monoclonal antibodies**

Etripamil: RAPID Trial
Self-administered, Out-of-Hospital

- Nasal spray, short-acting drug, blood half- life <5’
- Multicentre, randomised, placebo-controlled, event-driven trial
- Symptomatic ECG documented PSVT episodes (≥20’)
- Random assignment to etripamil or placebo
- 70 mg etripamil or placebo and, if symptoms persisted beyond 10 min, a repeat dose
- 1^0 endpoint of time to conversion of PSVT to sinus rhythm for at least 30 s within 30 min of 1^{st} dose
- 692 patients randomly assigned, 184 (99 from the etripamil group and 85 from the placebo group) self-administered study drug





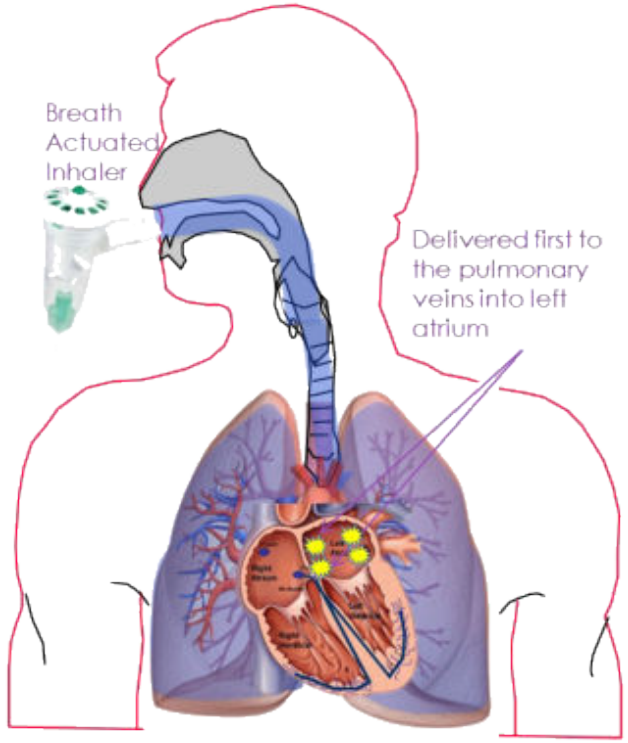
Stambler BS, et al. Lancet. 2023;402:118-128

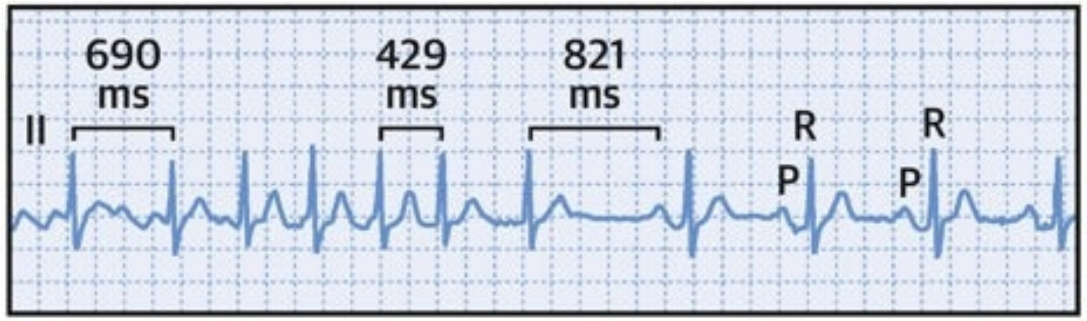
NCT03464019

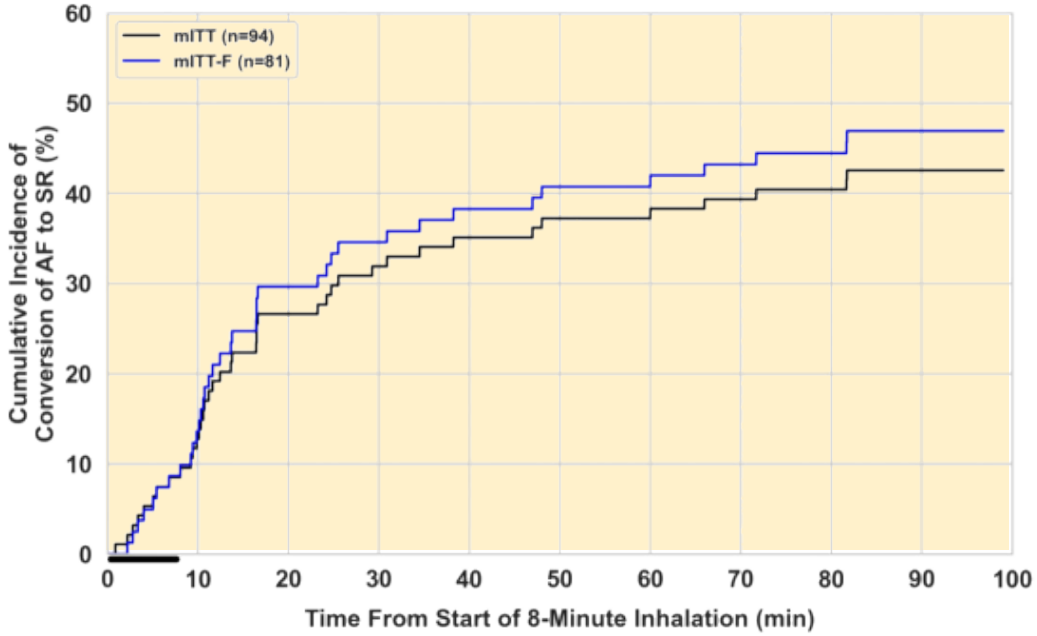
Inhaled Flecainide: INSTANT Study

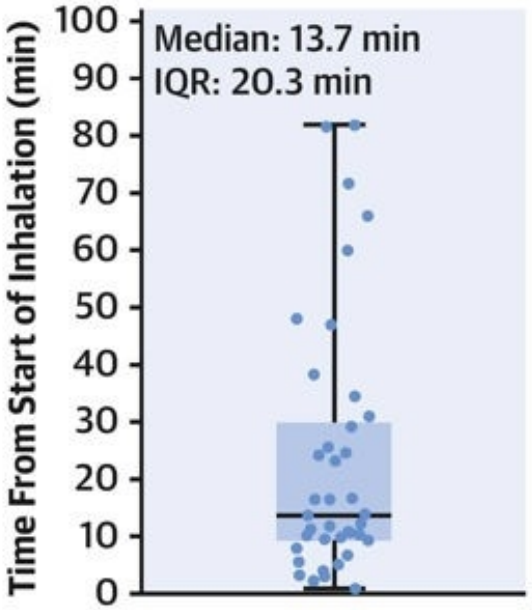
INhalation of Flecainide to Convert Recent Onset SympTomatic Atrial Fibrillation to siNus rhyThm

InRhythm









Ruskin JN, et al. J Am Coll Cardiol EP. 2024;10(6):1021-33

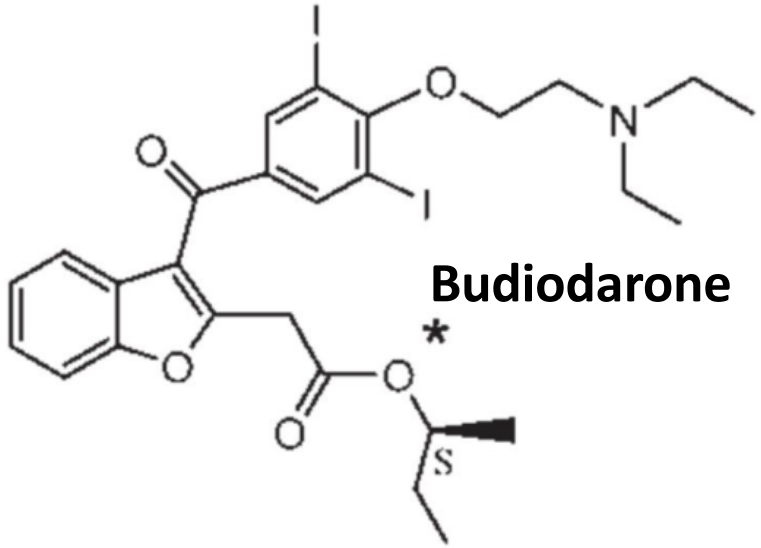
NCT03539302

Budiodarone : an Effective Antiarrhythmic Drug

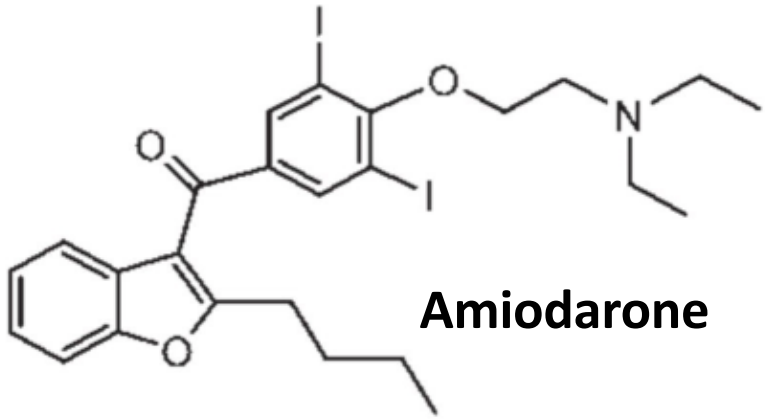
Budiodarone has a similar structure

and electrophysiological effects to amiodarone

- **Mixed ion channel with additional late sodium channel inhibition**
- **Ester group insertion reduces half life of budiodarone to 7 hours**
- **Phase 2 clinical trials show relief of AF symptoms, a reduction of AF burden and elimination of long episodes of uninterrupted atrial fibrillation**
- **Clinical trials show no change in ECG parameters, respiratory symptoms, hyperthyroidism or deaths on drug**



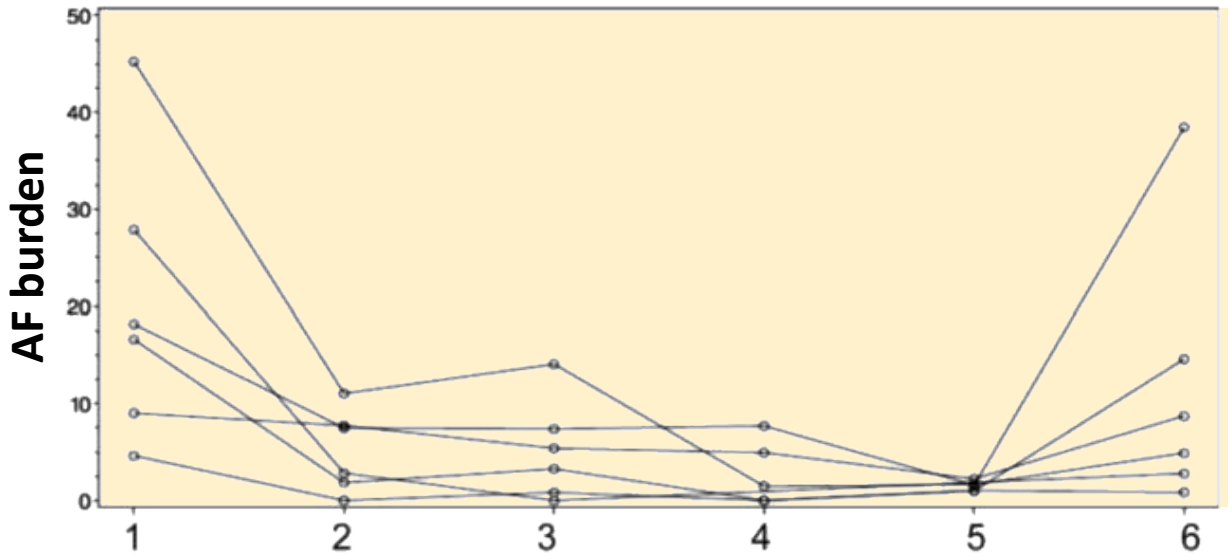
Budiodarone



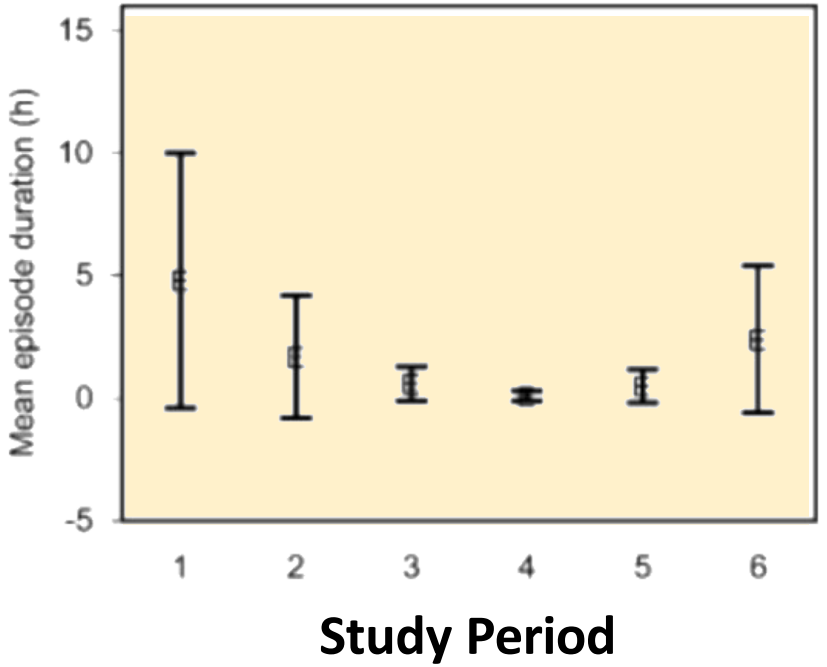
Amiodarone

Budiodarone reduces AF Burden in Phase 2a study

- **Relative Risk Reduction of AF Burden: 86.8% vs. 22-44% with other antiarrhythmic drugs or 25% AF ablation**
- **Dose-related reduction of AF burden from 4.8 hours to 6 minutes**



- **AF episode duration fell from 4.8+/-5.2 hrs to 0.5+/-0.7 hrs**



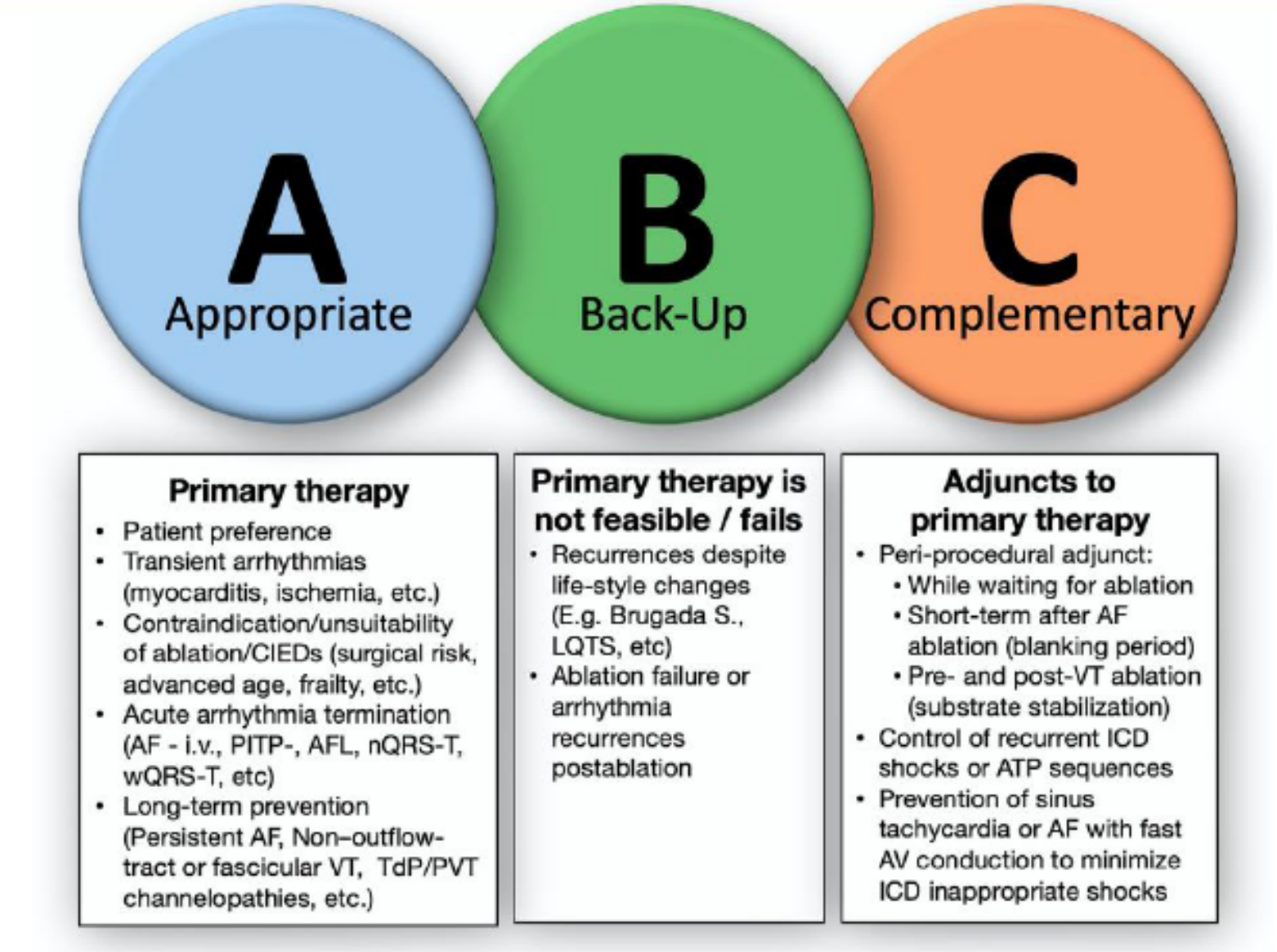
Mean (95% CI) (SD) AF episode duration

Arya A, et al. EP Europace. 2009;11(4):458-64

Summary: Development of New Antiarrhythmic Drugs

- **Selective Ion Channel Blockers**: developed to selectively target atrial-specific ion channels, to avoid ventricular proarrhythmia or negative inotropic effects, e.g., SK channel inhibitors such as **AP31969**
- **New Formulations:** Improving the safety, speed or convenience of traditional antiarrhythmic drugs or similar new drugs to enhance their safety and reduce adverse effects, as with **inhaled flecainide** or **intranasal etripamil**
- **Repurposing Existing Drugs:** Using drugs targeting specific ion channels which are already developed (and approved) for another disease such as **doxapram** (respiratory stimulant) or **botulinum toxin** (cosmetic effects)
- **Drugs with Indirect Antiarrhythmic Effects:** agents which improve underlying disorders (upstream therapy), often with both direct (electro-physiological) and indirect (improved co-morbidity) effects e.g., **empagliflozin**
- **Innovative Mechanisms:** Novel approaches, such as **HDAC6 inhibitors** which prevent myofilament damage and prevent atrial remodelling
- **New Multichannel Blockers:** with different combination of ion channel blockade e.g., **sulcardine**
- **Chemically Similar Molecules:** to avoid unwanted effects whilst retaining antiarrhythmic effect e.g., **budiodarone** is a short half-life drug like amiodarone
- **Fixed-Dose Combinations:** Combining drugs with specific effects e.g., **mexiletine plus dofetilide**
- **Genotype specific drugs:** Such agent have antiarrhythmic effects only in patients with a specific genotype e.g., **bucindolol**

Antiarrhythmic drugs



Merino J, et al.
EHJ 2025