

Global Spotlights

EHRA practical compendium of antiarrhythmic drugs: 10 key messages on contemporary use

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New therapies such as catheter ablation and device-based interventions have understandably shifted attention away from traditional antiarrhythmic drugs (AADs). However, AADs remain a cornerstone of rhythm management, especially when procedural therapies are unavailable, ineffective, incomplete, rejected by the patient, or not preferred upon shared decision-making. In fact, only around 1.5% of all patients with atrial fibrillation (AF) in Europe undergo ablation, and over 40% of US patients continue AAD therapy even after ablation.^{1,2} Recognizing this ongoing need, the *European Heart Rhythm Association* (EHRA) developed a comprehensive clinical consensus document on AADs—offering practical, scenario-based guidance for the modern clinician.³

The document spans 72 pages, with numerous tables, boxes, and figures, plus an extensive online supplement. In this brief editorial, we summarize 10 key messages that reflect the most relevant and clinically applicable themes of the compendium.

The ABC framework of AAD contemporary use

The compendium introduces a novel conceptual model: the ABC framework for AAD therapy (*Figure 1*, panel A). A—Appropriate: AADs as the primary or preferred therapy. B—Back-up: used when procedural options are unavailable, risky, or ineffective. C—Complementary: adjuncts to enhance efficacy of ablation, devices, or cardioversion. For example, in AF, AADs are often the first-line option for acute pharmacologic conversion or long-term control of non-paroxysmal AF and they are commonly used while waiting for

procedures or during or following ablation blanking periods in patients with recurrent arrhythmias.

Updated and practical AAD classification

The traditional Vaughan–Williams (VW) classification, while still useful, omits agents like digoxin, isoprenaline, ivabradine, and newer drugs such as vernakalant or ranolazine. EHRA adopts a simplified version of the 2018 modernized VW classification,⁴ incorporating modern and emerging agents while omitting theoretical classes without currently available drugs (*Figure 1*, panel B). This practical format helps guide real-world therapeutic decisions. Differences among drugs within a single class are also noted.

Electrophysiological dynamics and kinetics

Understanding concepts such as direct vs reverse use dependence and binding kinetics can be key to choosing the right AAD. Flecainide, for example, demonstrates stronger effect at higher heart rates, making it effective for tachycardia termination. In contrast, sotalol's effects are potentiated during bradycardia, increasing the risk of QT prolongation and *torsades de pointes*, especially when an arrhythmia terminates, and making it more effective for AF prevention than termination. First-pass metabolism and food interactions are important—dronedarone, amiodarone, calcium channels blockers (CCBs) and propranolol,

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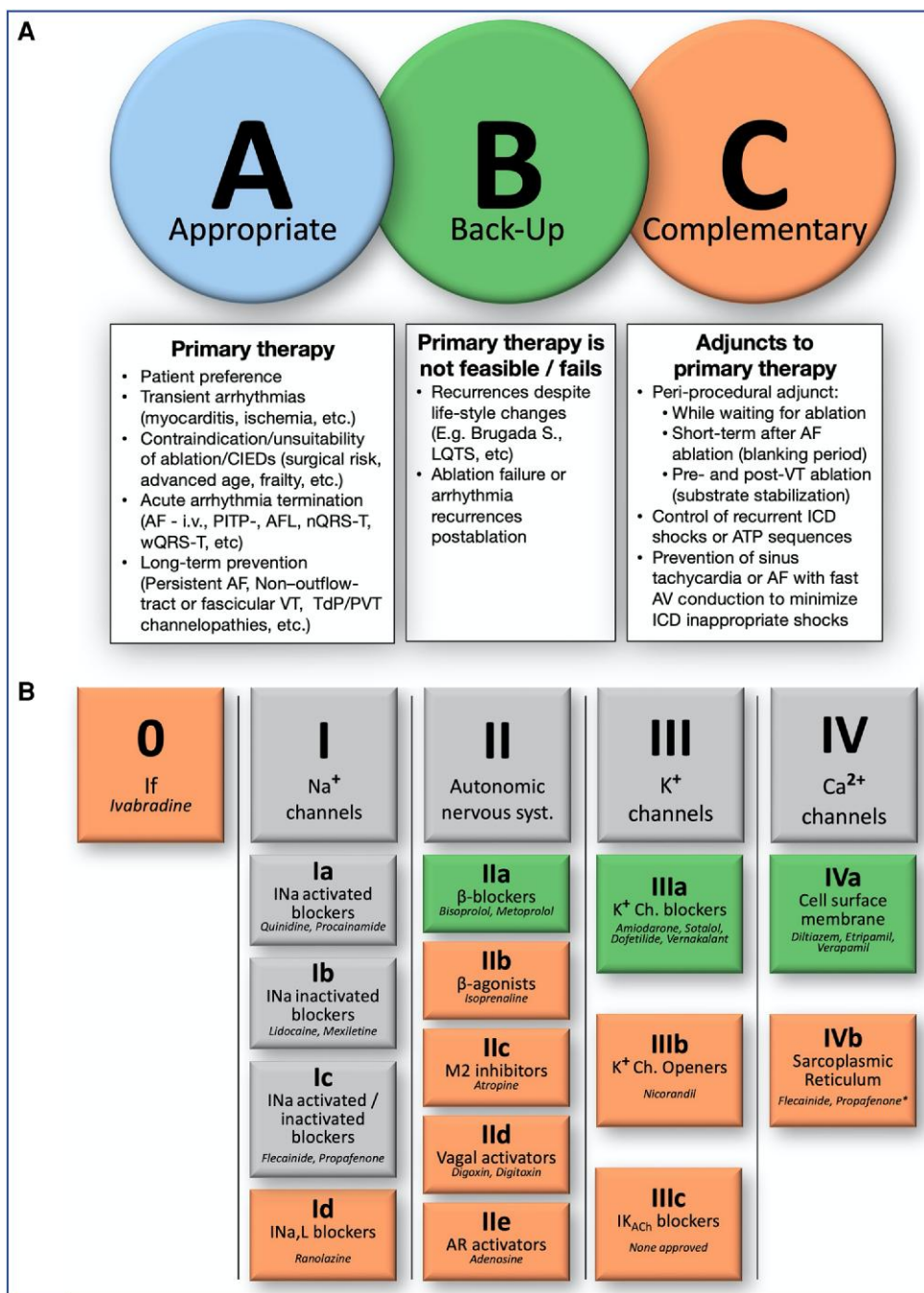


Figure 1 Panel A: Framework for the Clinical Use of Antiarrhythmic Drugs (AADs). The ‘ABC’ model from the EHRA Practical Compendium classifies antiarrhythmic drug use as A—Appropriate primary therapy, B—Back-up when primary therapy is not feasible or fails, and C—Complementary as an adjunct to procedures or devices. Examples of typical clinical scenarios for each category are provided within the panel. Panel B: Simplified update of the Vaughan–Williams classification of antiarrhythmic drugs (AADs). Classes 0–IV are shown with representative drug examples. Each class and subclass is highlighted in bold, accompanied by its principal ion-channel/receptor/body system target and sample agents presented in boxes. Classes appear across the top, their respective subclasses arranged below. Boxes are colour-coded as follows: grey—no significant change from the previous classification; green—relabelled compared with the classical VW scheme; light red—newly introduced classes. *Flecainide and propafenone are Class Ic AADs but also exhibit a secondary intra-cellular sarcoplasmic reticulum RyR2-Ca2+ channel-blocking effect (Class IVb), which is particularly relevant in specific arrhythmias such as catecholaminergic PVT. AF, atrial fibrillation; ACh, acetylcholine; AR, adenosine receptor; ATP, antitachycardia pacing; Ca²⁺, calcium; Ch, channel; CIED, cardiac implantable electronic device; ICD, implantable cardioverter-defibrillator; I_f, funny current; INa and IK, sodium and potassium currents; INa,L, late INa; K⁺, potassium; LQTS, long QT syndrome; M2, type-2 muscarinic receptor; Na⁺, sodium; nQRS-T, narrow QRS complex tachycardia; PITP, pill-in-the-pocket; PVT, polymorphic ventricular tachycardia; S, syndrome; Syst., system; TdP, torsades de pointes; VT, ventricular tachycardia; wQRS-T, wide QRS complex tachycardia.

for example, show enhanced absorption +/- first-pass metabolism with meals and should be administered with them.

Indications, contraindications, and selection flowcharts

The compendium provides a comprehensive table listing first-line indications, contraindications, and contra-use warnings based on ESC and AHA/ACC/HRS guidelines. Flowcharts help clinicians determine drug choice based on target (e.g. SA/AV nodes vs atrial/ventricular myocardium), presence of structural heart disease and heart failure class. For example, ivabradine, digoxin, CCBs, and β -blockers are the preferred agents when the sinus and AV are the main target while Class I and III agents are in general preferred for myocardial arrhythmias. However, avoid Class IC drugs and CCBs in ventricular scar or systolic dysfunction and sotalol and dronedarone in NYHA Class III–IV heart failure due to proarrhythmic and/or haemodynamic concerns.

Drug interactions: avoiding pitfalls

AADs are often subject to significant drug–drug interactions,⁵ many of which are detailed in 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.

Combining AADs: when and how?

While combinations of AADs should generally be avoided due to summative toxicity and proarrhythmia, some combinations are strategically beneficial.⁶ Class IC agents + β -blockers or CCBs are recommended to prevent rapid AV conduction in case of AF transforming into flutter. In ventricular arrhythmias, particularly with right ventricular dysplasia, sotalol combined with flecainide or mexiletine may be effective. On the other hand, avoid combinations like sotalol + quinidine, which may lead to excessive QT prolongation, or dronedarone + digoxin, which may reduce digoxin excretion and enhance toxicity.

Toxicities and proarrhythmia: still a concern

Though rare with proper selection, toxicity and proarrhythmia remain critical concerns. Amiodarone can cause corneal deposits (>90%), thyroid disorders, hepatic pathology, and pulmonary fibrosis (1%–2%). The two types of amiodarone-induced thyrotoxicosis (AIT-1 and AIT-2) differ in pathogenesis and treatment. Ventricular proarrhythmia is now rare with flecainide when patients with structural heart disease are excluded.

Drug initiation and monitoring: in-patient vs out-patient vs pill-in-the-pocket

Initiation of some AADs (e.g. Class Ia and dofetilide) still requires in-hospital monitoring. However, pill-in-the-pocket regimens (out-patient

after first shown effective and safe when given in a medical facility) are encouraged for selected patients using flecainide, propafenone, or ranolazine.⁷ The compendium also outlines ECG monitoring schedules, laboratory follow-up, and baseline testing (e.g. thyroid, liver, and pulmonary), particularly for amiodarone.

Use in special populations

Detailed guidance is given for pregnancy (avoid amiodarone, dronedarone and atenolol; prefer other β -blockers or digoxin), elderly (start at reduced and 50% dose in older than 65 and 75 years, respectively, and titrate slowly due to anticipated hepatic/renal decline), heart failure, channelopathies, congenital disease, and athletes.

Formulations, dosing, and future drugs

A dedicated table summarizes the most common world-wide formulations, dosages, and routes of administration. Some agents are available only in some countries. Looking ahead, Etripamil, a short-acting intranasal calcium channel blocker, is close to approval for self-administration at home for supraventricular tachycardia termination.⁸ Inhaled flecainide may offer rapid onset for AF termination.⁹ Others in development include budiodarone, HDAC6 inhibitors, and small-conductance K⁺ channel blockers.

Conclusion

AADs are far from obsolete. They remain critical in managing arrhythmias across a range of patients and clinical scenarios—and this need will only grow as populations age and healthcare capacity remains constrained. The EHRA Practical Compendium provides not only updated pharmacological knowledge but a toolbox for real-world decision-making. When chosen appropriately, AADs are here to stay—smarter, safer, and more essential than ever.

Declarations

Disclosure of Interest

A.J.C. has received personal consulting fees from Acesion, InCarda, Menarini, Milestone, Sanofi, Anthos, Bayer, Daiichi Sankyo, Pfizer, Abbott, Biosense Webster, Biotronik, Boston Scientific, Medtronic, GlaxoSmithKline, and Johnson & Johnson. J.A.R. reports being an investigator for Sanofi, InCarda Therapeutics, Johnson & Johnson, and Amarin and as a consultant for Sanofi and Acesion. J.L.M. has received fees and honoraria for lectures, education, and scientific advice from Abbott, Biosense Webster, Biotronik, iRhythm Technologies, MicroPort, and Zoll. He is also a member of the steering committee in the EHRA-PATHS (Addressing Multimorbidity in Elderly Atrial Fibrillation Patients Through Interdisciplinary, Tailored, Patient-Centered Care Pathways, GA 945260) and PROFID (Implementation of Personalized Risk Prediction and Prevention of Sudden Cardiac Death After Myocardial Infarction, GA 847999) projects, both funded by the European Union under the Horizon 2020 Research and Innovation Programme.

Funding

J.L.M. acknowledges support from the Instituto de Salud Carlos III (ISCIII) (grant no. PI22/00278).

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