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EHRA POSITION PAPER

Antiarrhythmic drugs–clinical use and clinical decision making: a consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Cardiovascular Pharmacology, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and International Society of Cardiovascular Pharmacotherapy (ISCP)

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Abbreviations

AAD	Antiarrhythmic drugs
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
AES	Atrial extrasystoles
AF	Atrial fibrillation
Afl	Atrial flutter
AIC	Arrhythmia-induced cardiomyopathy
AIHT	Amiodarone-induced hypothyroidism
APD	Action potential duration
APHRS	Asia-Pacific Heart Rhythm Society
ARVD	Arrhythmogenic right ventricular cardiomyopathy
AT	Atrial tachycardia
AV	Atrioventricular
AVNRT	Atrioventricular nodal reciprocating tachycardia
AVRT	AV-reciprocating tachyarrhytmias
BB	Beta-blockers
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CAMIAT	Canadian Amiodarone Myocardial Infarction Trial
CPVT	Catecholaminergic polymorphic ventricular tachycardia
CYP	Cytochrome P
DFT	Defibrillation threshold
DAD	Delayed after depolarization
EAD	Early after depolarization
ECG	Electrocardiogram
EHRA	European Heart Rhythm Association
EMIAT	European Amiodarone Myocardial Infarction Trial
ESC	European Society of Cardiology
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HRS	Heart Rhythm Society
ICD	Implantable devices
ICD	Implantable cardiodefibrillator
ISCP	International Society of Cardiovascular Pharmacotherapy
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
ND-CCA	Non-dihydropyridine calcium channel antagonists
NOAC	Non-antivitamin K oral anticoagulants
NSAT	Non-sustained atrial tachycardia
NSVT	Non-sustained ventricular tachycardia
PD	Pharmacodynamic
P-GP	P-glucoprotein
PK	Pharmacokinetic
PM	Pacemaker
PVT	Polymorphic ventricular tachycardia
SCD	Sudden cardiac death
SR	Sinus rhythm
SVT	Supraventricular tachyarrhythmias
TdP	Torsade de pointes
VA	Ventricular arrhythmias
VES	Ventricular extrasystoles
VF	Ventricular fibrillation
VPB	Ventricular premature beats
VT	Ventricular tachycardia
WPW	Wolff-Parkinson-White

Preamble

Despite extensive research on the topic of antiarrhythmic drugs (AAD) in the last years, there has been no significant improvement in clinical pharmacology for arrhythmias over the last decades. It seems that AAD were overlooked in favour of interventional therapy. However, new data on safety and efficacy of the 'classical' molecules lead to the necessity to develop a practical guide to improve the clinical decision-making. Despite the inclusion of AAD treatment recommendations in many guidelines, frequent under- or over-treatment errors may occur in clinical practice.[1,2] Moreover, regarding safety, AAD are not a neutral medication due to severe cardiac and extracardiac adverse effects and to narrow therapeutical index and complex drug–drug interactions. There are tremendous contemporary research efforts to discover target-specific AADs with better safety margins, but there is still a gap between the traditional AADs used currently in clinical practice and the 'future' AADs. Antiarrhythmic pharmacologic therapy in clinical practice is one of the clinical domains in which evidence based cardiology is less applied compared with other treatment modalities, and many physicians rely on the oversimplified Singh–Vaughan Williams classification which has minimal clinical relevance. After many years, a position document focused on AAD seems justified. Our intention is not to offer a new pharmacology textbook or a research perspectives review but a practical document intended for general cardiologists, internal medicine specialists, general practitioners, and cardiology fellows or residents based on the current knowledge and clear recommendations.

In recognizing this, the European Heart Rhythm Association (EHRA) and the European Society of Cardiology (ESC) Working Group on Cardiovascular Pharmacology convened a Task Force, with representation from the Heart Rhythm Society (HRS) and

Asia-Pacific Heart Rhythm Society (APHRS), with the remit to comprehensively review the available evidence to publish a joint practical guide on AAD therapy, and to provide up-to-date consensus recommendations for decision-making and its use in everyday clinical practice. The ultimate judgement regarding the care of a particular patient must be made by the health care provider, and the patient in light of all of the circumstances presented by that patient.

Literature search was conducted in the following databases: PubMed, MEDLINE, and the Cochrane Library (including the Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Registry). Focus was on the English-language sources and studies in human subjects. Articles related to animal experiments were only cited when information was important to understanding pathophysiological concepts pertinent to patient management and comparable data were not available from human studies. Additional information was requested from the authors where necessary.

Consensus statements are evidence based, and the scientific rationale is graded according to the strength of data (*Table 1*).

Table 1 Scientific rationale of recommendations

Definitions where related to a treatment or procedure	Consensus statement	Symbol
Scientific evidence that a treatment or procedure is beneficial and effective. Requires at least one randomized trial, or is supported by strong observational evidence and authors' consensus (as indicated by an*)	Recommended/ indicated	
General agreement and/or scientific evidence favour the usefulness/efficacy of a treatment or procedure. May be supported by randomized trials based on small number of patients or not widely applicable	May be used or recommended	
Scientific evidence or general agreement not to use or recommend a treatment or procedure	Should NOT be used or recommended	

This categorization for our consensus document should not be considered as being directly similar to that used for official society guideline recommendations which apply a classification (I–III) and level of evidence (A, B, and C) to recommendations.

Decisions to initiate antiarrhythmic drug therapy and follow-up

Decisions when starting therapy: the disease, the patient, the drug, the dose

Decision-making when starting AADs has evolved in recent years, after the Cardiac Arrhythmias Suppression Trial (CAST) trials. The importance of patient-centred decision-making was initially emphasized by the CAST study,[3] which demonstrated that powerful and effective AADs can be potentially dangerous, especially in the presence of structural heart disease. Thus, treating the arrhythmia when it represents a marker of the disease is very different than treating the disease itself.

The development of implantable cardioverter-defibrillators (ICD) to treat malignant ventricular arrhythmias and sudden cardiac death (SCD) has contributed to diminished interest for pharmacologic treatment in these settings. At present, AADs in malignant ventricular arrhythmias predominantly serve as adjunct therapy to ICD, to prevent electrical storm and frequent shocks rather than to suppress and cure the arrhythmias like in other clinical settings.

The high prevalence and health and cost consequences of atrial fibrillation (AF) have led to many developments in pharmacological therapies for this common arrhythmia, along with catheter ablation.[4] Focus is now directed towards the patient's clinical condition, the structural and functional substrate, and arrhythmia mechanisms at the cellular and molecular level. This approach is substantially different from the somewhat empirical one suggested by the simplified Singh–Vaughan Williams classification.[5]

Antiarrhythmic drugs preserve an important role as symptomatic therapy or to prevent the deterioration of cardiac function by tachycardia, irregular rhythm, or dyssynchrony (e.g. induced by frequent ventricular premature beats). Antiarrhythmic drugs are a valuable tool for preventing the transformation of well-tolerated arrhythmias into malignant arrhythmias.

Antiarrhythmic drugs are drugs with a narrow therapeutic window, and there is a small plasma concentration interval between the lowest effective dose and the first toxic dose, that is, between undertreatment and the toxic or proarrhythmic effect. Moreover, AADs are associated with a high degree of inter-subject variability in their drug actions. For practical reasons and because of many concurrent actions, when referring to AAD in this consensus document, we also include the rate-controlling drugs.

Indeed, multiple factors interfere with drug effects,[6] for example, race, gender, genetics, temperature, drug–drug interaction, triggering factors, neurohormonal changes, disease state and severity, disease-induced substrate remodelling, etc. The picture is further complicated by the fact that some AADs have multiple electrophysiological and pharmacologic effects with their action depending on the route of administration, plasma levels, and active metabolites. Such examples are propafenone, quinidine, and amiodarone.

Consensus statements

Recommendations	References

When balancing the efficacy, safety, and proven clinical benefit, the current available AAD have limited indications:
• To alleviate symptoms
• To improve cardiac performance if
  • deteriorated by tachycardia
  • deteriorated by dyssynchrony (i.e. frequent ventricular premature beats)
• To prevent degeneration to a malignant arrhythmia	

• To prevent frequent shocks or electrical storm in ICD patients	7
• AAD therapy should not be used to avoid oral anticoagulation	8

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

Follow-up of patients treated with antiarrhythmic drugs

For optimal management with AADs, careful follow-up is recommended. Until now, no AAD has demonstrated reduction in all-cause mortality.[9] Therefore the goals of therapy with the use of these drugs during follow-up include a reduction of the frequency and duration of episodes of arrhythmia, as well as the reduction in hospitalizations associated with arrhythmias. As almost all AADs may produce proarrhythmic effects, not only a careful pre-administration assessment, but follow-up for proarrhythmic effects is also indicated.[10]

However, it is often difficult to distinguish a proarrhythmic effect from the patient's underlying rhythm disorder. Thus, it is important to assess each patient taking AAD through the use of cardiac monitoring before therapy begins and also during the follow-up period to determine if the patient is experiencing a therapeutic response to the drug, developing another arrhythmia, or is experiencing worsening of the original arrhythmia.

Patient and family education are extremely important. The physician or a trained health professional should explain the adverse drug effects that may occur to the patient and family.[11] To ensure the adherence with the prescribed drug regimen, we emphasize the importance of taking these drugs exactly as prescribed. For example, it may be necessary to teach the patient or a family member how to check the pulse.

In addition, the attending physician or a nurse should order laboratory and diagnostic tests including electrocardiogram (ECG), renal and hepatic function tests, complete blood count, serum enzymes, and serum electrolytes during follow-up. Depending on the type of AAD used and the underlying heart disease, echocardiography could be performed to assess cardiac function, especially left ventricular systolic function.

Consensus statements

Recommendations	References
Adequate follow-up arrangements should be in place after initiation of AAD: • Education and counselling should be part of the initiation and reviewing process, pointing on targets of the therapy (symptoms, arrhythmia burden, etc.) and potential adverse effects • Shared decision making is essential to assure adherence to therapy • Appropriate laboratory and diagnostic tests should be part of the reviewing protocol; these tests should include scheduled ECGs and other tests according to the patient' s profile and AAD characteristics	10, 11

AAD, antiarrhythmic drugs; ECG, electrocardiogram.

Classification of antiarrhythmic drugs and overview of clinical pharmacology

Classification of antiarrhythmic drugs

Most of the currently available drugs act on the cardiac ion channels altering the channel structure, dynamics, or gating process. The desired effect is the alteration of excitability, effective refractory period, conduction, or abnormal automaticity. The substance of this concept is summarized in the Singh–Vaughan Williams classification.

Singh–Vaughan Williams[12] classified AADs in four classes: Na^+ channel blockers (Class I), beta-adrenoceptor antagonists (Class II), drugs that predominantly block K^+ channels and prolong the cardiac action potential duration (APD) without affecting intracardiac conduction (Class III), and non-dihydropyridine L-type Ca^{2+} channel blockers (Class IV). Later, Class I AADs were subclassified into drugs with intermediate (IA), fast (IB), and slow (IC) offset kinetics of the Na^+ channel blockade. This classification is widely used because it is easy to understand and it facilitates the discussion of potentially beneficial and adverse effects of AADs.

However, this approach also presents important limitations:

(1) It classifies antiarrhythmic 'actions', not 'drugs'. Most AADs can exert multiple effects on channels, receptors and pumps, and affect haemodynamics, autonomic nervous system or cardiac metabolism.

Thus, some drugs belong to several classes and AADs included in the same group show different electrophysiological effects and antiarrhythmic efficacy. Furthermore, some AADs are metabolized into active metabolites whose activity may differ from that of the parent drug.

(2) It is based on the electrophysiological effects of AAD on normal isolated cardiac tissues, but their effects differ in different cardiac tissues, following acute/chronic treatment and in the presence of structural heart disease.

(3) It is incomplete, as many AADs (Class V) were not originally included and the possibility that activation of channels or receptors might be antiarrhythmic was not considered.

(4) Action potential duration prolongation can be produced by multiple mechanisms, i.e. blockade of K^+ channels or activation of Na^+ and L-type Ca^{2+} channels.

(5) It provides an oversimplified view of a complex problem and an incomplete link between the mechanism of action and the clinical efficacy of AAD and the mechanisms that generate/maintain the arrhythmia.

However, all the 'classical' AADs have important efficacy and safety limitations. Better understanding of the complex arrhythmia mechanism created new perspectives for AAD development. In 1991, the Sicilian Gambit was proposed to provide a more realistic view of AADs[13–15] (*Table 2*). It presents a two-dimensional framework that considers each drug as a unit, describing its effects on different molecular targets (ion channels, receptors, pumps) as well as their clinical effects. This framework is more flexible as new molecular targets and AAD can be added as new columns/rows.

The Sicilian Gambit takes into consideration not only the basic arrhythmia mechanism but also importance of electrophysiological remodelling since during the disease state, the ion channel properties are modified, limiting the effect of 'classical' AADs. It is a holistic approach, which holds a special clinical relevance, involving estimation of the global AAD effect (electrophysiological, clinical, and electrocardiographic).

In the Sicilian Gambit, the process of AAD selection starts with the diagnosis of the arrhythmia and the identification of known or suspected arrhythmogenic mechanisms to determine the 'vulnerable parameter(s)', whether functional or structural, that might be particularly amenable to a therapeutic approach, while manifesting a minimum of undesirable effects on the heart. Intervening on this parameter, there is the highest chance to terminate arrhythmia or to prevent its initiation. Therefore, the focus of interest is moved from AAD mechanism to arrhythmia mechanism[16] (*Figure 1*).

Finally, an AAD and a specific property are selected to target the particular vulnerable parameter. Thus, an atrioventricular (AV) nodal re-entrant tachycardia implicates a re-entry involving the AV node (the 'vulnerable parameter'), and because it generates L-type Ca^{2+} channel-dependent action potentials, the arrhythmia can be targeted by Ca^{2+} channel blockers, adenosine, or beta-blockers.

However, in many patients the underlying mechanisms of arrhythmia remain incompletely understood, and the choice of a given AAD is empiric and based on the characteristics of arrhythmia, the pharmacological properties of the AAD and above all, its safety profile.

Structural cardiac disease produces electrophysiological and structural remodelling that increases susceptibility to arrhythmias and makes arrhythmias resistant to AAD. Of note, neither classification considered antiarrhythmic upstream therapies (renin–angiotensin–aldosterone inhibitors, statins, omega-3 polyunsaturated fatty acids, antifibrotic agents) that can prevent or delay myocardial structural or electrical remodelling caused by structural heart disease.[17,18]

Of note, almost all current AADs can reduce cardiac performance through direct effects on contractility, or indirectly through alterations of vascular properties or neurohormonal signalling. Usually, the effect cannot be explained by a single specific mechanism. One contributor to the haemodynamic effect is linked to use-dependence (rate dependence) properties of AAD. Class I AADs block sodium channels in a rate-dependent manner, making them active during tachycardia. However, because of the same mechanism, they depress contractility at higher rate as a consequence of altered sodium/calcium interdependence and decrease in intracellular calcium. Under these circumstances, the positive effects on contractility of the APD prolongation and of the increased frequency (Bowditch effect) are importantly diminished. This is why AAD considered haemodynamically neutral (lidocaine) may have important negative inotropic effects especially in heart failure patients when the Bowditch effect is reduced. On the other hand, reverse use-dependence (i.e. APD prolongation increases at slower rate), as seen with sotalol or quinidine, could predispose to proarrhythmia during sinus rhythm (SR).

New approaches to antiarrhythmic drug development

Novel targets for AAD therapy are developing in parallel with better understanding of complex mechanisms involved in the arrhythmia[19] (*Table 3*). The keystone of the new paradigm resides in looking for and targeting the 'vulnerable electrophysiological parameter' of the arrhythmia (*Figure 1*).

One approach is to identify 'atrial specific' drugs for rhythm control in AF to increase the efficacy and decrease the ventricular proarrhythmic risk. Vernakalant has such properties[20] because INa block increases at faster rates (use dependence) and at more positive membrane potential, and the atrial membrane potential is more positive than the ventricular membrane potential; this difference increases during AF. Moreover, the rapid onset/offset channel kinetics of this drug implies a lower risk of conduction disturbances or proarrhythmia once the heart rate slows (when INa block is no longer required). Ranolazine shares some of these characteristics. Another attractive target is the ultra-rapid component of the potassium current (IK_{ur}) responsible for shortening of APD during AF and arrhythmia perpetuation. Several investigational blockers of IK_{ur} which prolong APD without proarrhythmic risk[21] have been developed and are currently investigated. However, the down-regulation of IK_{ur} during AF could limit the efficacy of these new molecules. TASK-1 channel, a member of the two-pore-domain potassium channels (K2P) family is specifically expressed in atria. This channel contributes to the background potassium current and inhibition of this channel will have a Vaughan Williams Class III effect, prolonging APD and destabilizing re-entrant arrhythmia.[22] Atrial selective AADs acting on IK_{ur} have also affinity for TASK-1, explaining some of the antiarrhythmic effect.[23] TASK-1 is also inhibited by amiodarone. Other members of the family are inhibited by existing AADs (vernakalant inhibits TREK-1) emphasizing the important electrophysiological role or these channels.

The late component of the sodium current (INa_L) is increased when normal sodium current is inactivated under genetic or acquired

Table 2 **Classification and pharmacological properties of antiarrhythmic drugs**

Class	Drugs	Channel blockade			Receptor blockade			Other MOA	APD	ECG
		Na^+	Ca^{2+}	K^+	α	β	M2			
IA: Intermediate offset kinetics	Ajmaline	● A							↑	0/↑ PR, ↑ QRS, QT and JT
	Cibenzoline	● A	○	⊘			○		↑	↑ PR, QRS andQT
	Disopyramide[a]	● A		⊘			○		↑	↓/↑ PR, ↑ QRS, QT and JT
	Pilsicainide	● A							↑	↑ PR, QRS and QT
	Procainamide[a]	● I		⊘					↑	0/↑ PR, ↑ QRS, QT and JT
	Quinidine[a]	● A		⊘	○		⊘		↑	↓/↑ PR, ↑ QRS, QT and JT
IB: Fast offset kinetics	Lidocaine[a]	○ I							↓	0/↓ QT, ↓ JT
	Mexiletine	○ I							↓	0/↓ QT, ↓ JT
	Phenytoin	○ I							↓	0
IC: slow offset kinetics	Flecainide	● A							0/↑	↑ PR, QRS and QT
	Propafenone[a]	● A	⊘			⊘			0/↑	↑ PR, QRS and QT
II	Atenolol, Carvedilol								0/↓	↑ PR, 0/↓ QT
	Esmolol, Metoprolol									
	Nadolol, Propranolol					●				
III	Amiodarone[a]	○	⊘	⊘	⊘	⊘			↑	↑ PR, QRS, QT and JT
	Dronedarone	○	⊘	⊘	⊘	⊘			↑	↑ PR, QRS, QT and JT
	Dofetilide			● IK_{ur}					↑	0 PR, ↑ QT and JT
	Ibutilide	INa_L		○ IK_{ur}					↑	0/↓ PR, ↑ QT and JT
	Sotalol			● IK_{ur}		●			↑	↑ PR, QT and JT
IV	Diltiazem		⊘						↓	↑ PR
	Verapamil[a]		●						↓	↑ PR
V	Adenosine							IK_{Ado}	↑	↑ PR
	Atropine						●			
	Digoxin							● Na^+/K^+-ATPase		↑ PR, ↓ JT
	Ivabradine							● I_f		
								Antianginal drug		
	Ranolazine	○		○ IK_{ur}				Antianginal drug	↑	↑ QT and JT
		● INa_L								
	Vernakalant	○ I		⊘		⊘				

[†]Antiarrhythmic drugs are subdivided using the Singh–Vaughan Williams system and their effects on targets (channels, receptors, or pumps), and clinical effects are presented following the Sicilian Gambit classification system. Class I AADs are subdivided in three groups [fast (IB), intermediate (IA) and slow (IC)] according to the time constants for recovery from block (offset kinetics) and the affinity for the open (O) or inactivated (I) states of the Na^+ channels is shown. The relative potency of blockade of ion channels and receptors and their extracardiac side effects observed at therapeutic plasma levels are classified as low (open circles), moderate (stripped circles), or high (black circles).

□ indicates agonist, indicates increase or prolong; ↓indicates decrease or shorten.

0, minimal effect; α/β, α- and β-adrenoceptors; A, activated state Na^+ channel blocker; APD, action potential duration; ECE, extracardiac effects; HR, heart rate; I, inactivated state Na^+ channel blocker; Kr, rapid component of the delayed rectifier outward K^+ current; LVF, left ventricular function/contractility; M2, muscarinic receptor subtype 2; MOA, mechanism of action.

[a]Active metabolites.

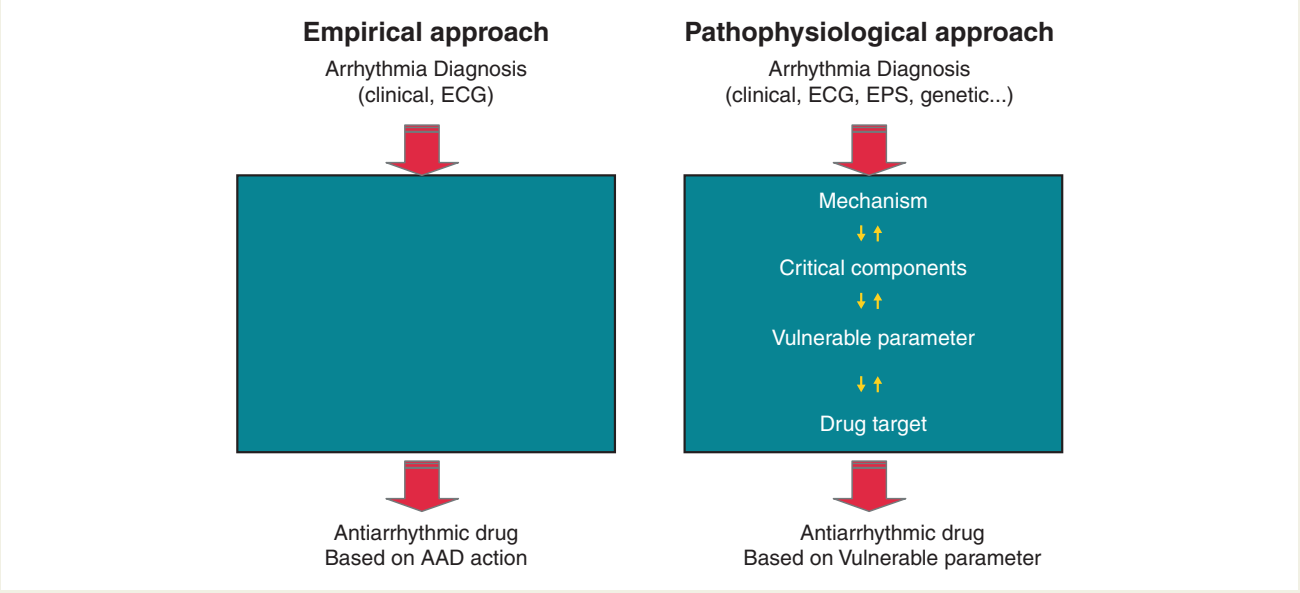

Figure 1 The concept of the 'vulnerable parameter'. In the 'empirical approach', AAD therapy is based on arrhythmia diagnostic and Singh–Vaughan Williams classification irrespective of the specific mechanism of arrhythmia, while in the pathophysiological approach, a specific vulnerable parameter of the arrhythmia is the target of AAD. While classic approach is based on the AAD properties (Singh–Vaughan Williams classification) with final aim to alter excitability, conduction or automaticity irrespective of the arrhythmia type, the modern AAD therapy is based on discovering the critical components of the arrhythmia and identifying the vulnerable parameter. AAD, antiarrhythmic drug; ECG, electrocardiogram; EPS, electrophysiological study.

Table 3 New targets for antiarrhythmic drugs in atrial fibrillation

Mechanism	Vulnerable parameter/drug target
Excitability and effective refractory period	Gap junctions; atrial-specific ion-channel modulation (IK_{ur}, IK, I_{KACh}, SK channels, K2P/TASK channels)
Excitability and ectopic activity	Atrial-selective INa inhibition; INa_L inhibition, abnormal Ca^{2+} handling inhibition (CaMKII, RyR2); NCX
Remodelling	Ca^{2+} signalling (calpains, calcineurin); kinases and phosphatases; TRP channels; miRNAs

CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; miRNA, micro-ribonucleic acid; NCX, sodium–calcium exchanger; RyR, ryanodine receptor; SK, small conductance Ca^{2+}-dependent K^+ channel; TRP, transient receptor potential channel.

situations (e.g. ischaemia). It prolongs APD, favouring triggered activity of the early after depolarization (EAD) type, and alters the sodium–calcium intracellular homeostasis causing proarrhythmic effects. Blockers of INa_L have antiarrhythmic properties and ranolazine, a drug with antianginal properties, has a high affinity for INa_L[24] also blocking the IK_{ur}. The Ranolazine Implantable Cardioverter-Defibrillator (RAID) study (NCT01215253) demonstrated a significant reduction in ventricular tachycardia (VT) with ranolazine. The combination of low doses of ranolazine and dronedarone (which has an amiodarone-like profile) increases the frequency-dependent block of INa_L and IKs with minimized effect on ICa_L, decreasing the negative effect of dronedarone on cardiac contractility.[25]

Abnormal calcium handling has an important contribution to arrhythmogenesis. Triggered activity of the delayed after depolarization (DAD) type results from spontaneous sarcoplasmic reticulum calcium release and is involved in AF and ventricular arrhythmias. Consequently, the ryanodine receptor (RyR) becomes an important target for AADs. Drugs like dantrolene (a muscle relaxant) and other new molecules have direct RyR stabilizing properties and other molecules (e.g. ivabradine) enhance FKBP12.6 expression (an enzyme, previously named calstabin, which regulates the RYR function).[26] Other drugs such as flecainide, propafenone (open state blocker), tetracaine (closed state blocker), and carvedilol analogues are direct RyR blockers.[21,26] Other potential future AADs will target re-entry and refractoriness through the small conductance Ca^{2+}-activated K^+-current (I_{SK}) and atrial remodelling through Ca^{2+} signalling molecules (calpains, calcineurin) and transient receptor potential (TRP) channels.[19]

Pharmacokinetics, pharmacodynamics, and drug interactions data of most commonly available antiarrhythmic drugs

Toxicity of AAD or any drug it interacts with, depend on both pharmacokinetic (PK) properties of the drugs, i.e. how the human body affects drug metabolism by renal, hepatic, and other mechanisms and

on pharmacodynamic (PD) properties of AAD, i.e. how the drug affects the human body. Changes in PK are often predictable and measurable by differences in plasma concentration of the drug, whereas changes in PD are often unpredictable, individual, and reflected by augmented effect and/or side effects. These complex properties are often the reason for drug dosing errors and drug toxicity when prescribing AAD. Important principles for PK interactions are impaired absorption, e.g. formation of complexes between drugs and salts in the gastric tract, changed absorption, e.g. induction or inhibition of P-glycoprotein (P-GP) and metabolism, e.g. inhibition or induction of the cytochrome P (CYP) enzymes. When drugs are metabolized by several CYP-enzymes, the clinical effect depends on the capacity of all enzymes involved.[27,28]

Pharmacokinetic characteristics

Pharmacokinetics encompasses the processes of absorption, distribution, biotransformation, and elimination.[29] Supplementary material online, *Table S1* summarizes the main PK parameters of AAD. For many AAD, paediatric specific PKs data are unavailable.

Absorption

Orally, AADs are rapidly absorbed but some present low bioavailability due to an extensive first pass effect, reaching peak plasma levels within 1–3 h (3–6 h for digoxin and dronedarone, 6–8 h for amiodarone). Oral bioavailability increases in the elderly and in patients with hepatic impairment. Intestinal microflora converts digoxin to inactive metabolites; tetracycline and erythromycin destroy the microflora and increase digoxin plasma levels. Following intravenous administration, onset of antiarrhythmic action occurs after 2–5 min. Gastrointestinal absorption may be critical to drug bioavailability. Meals may facilitate as well as hinder this process. For example, the oral absorption of dronedarone is four times greater with a high-fat meal. The manufacturer recommends one tablet of 400 mg b.i.d. with morning and evening meals.

Distribution

Except sotalol, AADs bind to some extent to plasma proteins. Amiodarone, digoxin, flecainide, and propafenone reach cardiac levels higher than in plasma and are not dialyzable. Disopyramide, mexiletine, sotalol, and verapamil cross the placenta and are excreted in breast milk. Procainamide concentrates in breast milk and is slowly eliminates from neonates.

Oral amiodarone reaches steady-state plasma levels after several weeks unless large loading doses are used; even when given intravenously its full effect is delayed. This reflects a multi-compartmental distribution including the intravascular compartment which is easily saturated by a standard loading dose, a peripheral compartment constituted by many tissues, and a deep compartment formed by the adipose tissue acting as drug reservoir.

Biotransformation

Most AADs are metabolized in the liver by CYP450 isoenzymes into active metabolites that block Na^+ channels (mexiletine, propafenone), prolong APD [*N*-acetylprocainamide (NAPA)] or mediate central nervous system toxicity (lidocaine). CYP2D6 metabolism is under genetic control; plasma levels of metoprolol and propafenone are higher and half-life ($t_{1/2}$) is longer in poor metabolizers (~7% of Caucasians) than in rapid metabolizers. Procainamide is metabolized (15–20% in 'slow-acetylators', 25–33% in 'fast-acetylators') in NAPA. These phenotypes are genetically determined and, unfortunately, there is no routine test to identify the phenotype before treatment (except the determination of procainamide/NAPA concentration ratio[30]). Doses should be reduced in poor/slow metabolizers (≤2/3 of maintenance dose).

Lipophilic beta-blockers (bisoprolol, carvedilol, metoprolol, propranolol) are metabolized mainly by CYP2D6 and their bioavailability and $t_{1/2}$ increases with liver impairment. Hydrophilic beta-blockers (atenolol, sotalol) are mainly excreted unchanged in urine.

After an intravenous loading dose, lidocaine is metabolized rapidly ($t_{1/2}$ 1.5–2 h), so plasma levels and $t_{1/2}$ are significantly prolonged in patients with hepatic dysfunction or reduced hepatic blood flow (elderly, cardiogenic shock, heart failure, myocardial infarction, cimetidine, beta-blockers). Under these circumstances, both loading and maintenance doses should be reduced. Because of its short $t_{1/2}$, the initial loading dose must be followed by a continuous infusion or repeated doses to maintain stable plasma levels.

Intravenous esmolol is rapidly hydrolyzed in red blood cells ($t_{1/2}$ ~9 min) and full recovery of beta-blockade occurs 20–30 min after drug discontinuation. The effect of intravenous adenosine occurs within 15–30 s. It is rapidly cleared by cellular uptake into erythrocytes and vascular endothelial cells where it is metabolized by adenosine deaminase ($t_{1/2}$ <10 s).

Elimination

Antiarrhythmic drugs are excreted to a different extent in urine and faeces. The $t_{1/2}$ increases in elderly and patients with renal (digoxin, disopyramide, dofetilide, flecainide, procainamide, and mainly sotalol) or hepatic impairment (amiodarone, diltiazem, flecainide, lidocaine, metoprolol, mexiletine, propafenone, propranolol, quinidine, and verapamil), congestive heart failure (amiodarone, flecainide, lidocaine, mexiletine, procainamide, and quinidine), or myocardial infarction (disopyramide, lidocaine, and mexiletine). In these patients, doses should be reduced, and periodic ECG monitoring is recommended. Amiodarone undergoes extensive hepatic metabolism, is excreted mainly by biliary excretion and presents a long $t_{1/2}$ (25–110 days), which explains why its effects persist weeks or months after drug discontinuation.

Because of the short $t_{1/2}$, some AADs are administered in modified-release preparations (beta-blockers, diltiazem, propafenone, and verapamil).

Elderly patients are susceptible to physiological PK changes which can interfere with AAD dosing (Supplementary material online, *Table S2*).

Interactions

Pharmacokinetic

Supplementary material online, *Table S2* summarizes the substrates, inhibitors, and inducers of CYP 3A4, 2D6, and 1A2 and P-Gp.[31] According to the CYP, isoform involved in their biotransformation, plasma levels, and $t_{1/2}$ of AAD increase/decrease when co-administered with CYP3A4/2D6 inhibitors/inducers, respectively. Patients receiving these drugs should be monitored closely and doses adjusted; potent inhibitors/inducers should be avoided.

Amiodarone, cimetidine, diltiazem, ketoconazole, procainamide, propranolol, and verapamil increase quinidine plasma levels. Quinidine is a potent CYP2D6 and P-gp inhibitor increasing plasma levels of substrates of this isoform; it decreases digoxin clearance (reduce the dose by 50%). Beta-blockers, cimetidine, and halothane increase lidocaine plasma levels; so, lidocaine doses should be reduced. Mexiletine increases plasma levels of theophylline; amiodarone increases mexiletine levels.

Flecainide and propafenone increase digoxin and propranolol plasma levels. Propafenone increases the plasma levels of digoxin, metoprolol, propranolol, and warfarin. Mexiletine and quinidine also enhance the effects of warfarin; reduce the dose and monitor the prothrombin time/international normalized ratio (INR) closely.

Amiodarone inhibits P-gp, CYP1A2, CYP2C9, CYP2D6, and CYP3A4, and therefore, it has the potential to increase plasma levels of drugs metabolized by these isoenzymes or substrates of P-gp (Supplementary material online, *Table S2*). Dose adjustments are required for digoxin, flecainide, and warfarin; monitor digoxin levels and the INR. Cholestyramine decreases the absorption of amiodarone. Diltiazem and verapamil are moderate inhibitors of CYP3A4 and P-gp; thus, doses of CYP3A4 and P-gp substrates should be adjusted as appropriate. Verapamil inhibits hepatic metabolism of lipophilic beta-blockers increasing their plasma levels.

There is an important PK interaction between some AAD/rate controlling drugs (amiodarone, quinidine, dronedarone, verapamil, digoxin, and diltiazem) and non-antivitamin K oral anticoagulants (NOAC) because of competition for P-gp or CYP3A4 inhibition (by diltiazem, dronedarone, and verapamil).[32] Because of this interactions and the consecutive increase in NOAC plasma level, the association between dronedarone and dabigatran is not recommended and for edoxaban a 50% reduction dose is recommended. Also, NOAC dose reduction should be considered for all NOAC when amiodarone is a concomitant medication (when other P-gp competitors are, also, associated). Dabigatran dose reduction is recommended when taken simultaneously with verapamil. For the association of verapamil with edoxaban a dose reduction should be considered for edoxaban (when other P-gp competitors are, also, associated).

Drugs that acidify or alkalinize urine increase or decrease, respectively, the renal excretion of flecainide, mexiletine, and quinidine.

Pharmacodynamics

Class I antiarrhythmic drugs. Combinations of these drugs reduce cardiac contractility and increase the risk of bradycardia, intracardiac conduction disturbances, and proarrhythmia. Co-administration of Class I AAD with beta-blockers, diltiazem, verapamil, or digoxin increases the risk of bradycardia, AV block and hypotension. Quinidine potentiates and procainamide inhibits the effects neuromuscular blocking agents. Lidocaine is less effective in the presence of hypokalaemia; therefore, it should be corrected. Propafenone increases the effects of cyclosporin, desipramine, and theophylline.

Beta-blockers. Their combination with Class I AAD, digoxin or amiodarone increases the risk of bradycardia, AV block and myocardial depression. The combination with diltiazem and verapamil should be avoided because increases the risk of hypotension, bradycardia, AV block, and heart failure. The risk of hypotension increases when beta-blockers are co-administered with nitrates, general anaesthetics, tricyclic antidepressants, or anti-psychotics. Beta-blockers can increase the hyperkalaemia produced by renin–angiotensin–aldosterone inhibitors.

Amiodarone. Co-administration with digoxin, beta-blockers, verapamil, or diltiazem increases the risk of bradycardia and AV block and hypotension; thus, ECG and blood pressure should be monitored. Severe bradycardia has been reported, when amiodarone is co-administered with hepatitis C antiviral drugs (daclatasvir, ledipasvir, and sofosbuvir). Combination of amiodarone with fentanyl may cause hypotension, bradycardia, and decreases cardiac output. Higher IV doses of dopamine and dobutamine are needed in patient on amiodarone, possibly because of its β-blocker activity. Rarely, amiodarone may decrease the effectiveness of clopidogrel.

Class I and III AAD (particularly dofetilide, ibutilide, and sotalol) prolong the QT interval and should be used with caution (or avoided) in patients with congenital/acquired long-QT syndrome (LQTS), treated with QT-prolonging drugs (https://www.crediblemeds.org/pdftemp/pdf/CompositeList.pdf) or with risk factors for torsades de pointes. Hypokalaemia increases the risk of torsades de pointes and potentiates digoxin-induced arrhythmias.

Diltiazem and verapamil. They exert additive depressant effects on sino-atrial and AV nodes when co-administered with amiodarone, beta-blockers and digoxin, and additive vasodilator effects when combined with antihypertensive agents, vasodilators (nitrates), phenothiazines, or alcohol. Co-administration of diltiazem or verapamil with disopyramide or inhaled anaesthetics decreases cardiac contractility and increases the risk of bradycardia, AV block, and hypotension; therefore, it should be avoided.

Adenosine. Its coadministration with beta-blockers, digoxin, diltiazem, or verapamil increases the risk of bradycardia and AV block. Dipyridamole inhibits the uptake of adenosine potentiating its effects; theophylline blocks adenosine receptors and decreases the effects of adenosine.

Consensus statements

Recommendation	References
Evaluate the possible interactions of any antiarrhythmic drug with any concomitant therapy using web-based tools e.g. www.drugs.com (also mobile application) www.crediblemeds.org	

Monitoring of antiarrhythmic drugs

The initiation and maintenance of arrhythmias need the presence of an arrhythmogenic substrate (chronic or acute) (e.g. the spatial coexistence of necrotic and normal myocardium at the borders of myocardial infarction, atrial fibrosis) and usually triggers (e.g. ventricular or atrial premature complexes, triggered activity from pulmonary veins) and modulators (e.g. superimposed ischaemia, autonomic imbalance, electrolyte abnormalities, or drugs) (*Figure 2*).

Thus, patients with arrhythmias might develop new clinical circumstances changing this substrate or the triggers and modulators. Therefore, it could be necessary to periodically evaluate the clinical status of the patients for early detection of relevant changes that could provoke the new or re-development of arrhythmias, or the elimination of transitory dangerous situations. The appropriate timing for re-evaluation depends on the illness and overall clinical status of the person.

In addition, lethal (ventricular) arrhythmias can be facilitated by drugs (cardiovascular, non-cardiovascular, and also non-prescription agents) causing proarrhythmia (new or aggravated arrhythmia develops during drug therapy at clinically usually non-toxic concentration levels). Antiarrhythmic drugs, antibiotics, antipsychotic, and antidepressant drugs are the most well-known groups that might generate proarrhythmia. However, the presence of structural heart disease, age, and the genetics of the patient are crucial for the development of arrhythmia and proarrhythmia.[33] In addition, it is well recognized that evaluation of the QTc interval, although very important, is not enough to assess proarrhythmic risk.[33] Thus, it is necessary to consider the spatial or temporal dispersion of repolarization as well as PR and QRS intervals,[34] PKs, PDs, comorbidities, concomitant drugs, and side effects.[35] Furthermore, monitoring of therapeutic drug concentrations in serum is required for some drugs with a narrow therapeutic range.[36,37]

However, it is mandatory to take into account symptoms and the risk profile of the patient since they may determine the indication for treatment or the decision to follow the patient without specific therapy. Hence, it is necessary to balance the arrhythmic risk of the patient and the risk caused by therapy.[33,35,38–40]

Supplementary material online, *Table S3*summarizes the role of different diagnostic tools for the evaluation of the patient with arrhythmia and the indications for PK monitoring of drugs, respectively. *Figure 3* summarizes the simplified strategy for the management of patients with arrhythmias.

Determination of drug level concentration is appropriate if the drug has a narrow therapeutic evidence-based range, marked inter- or intra-individual PK variability exists, there is no appropriate direct measure of desired therapeutic effect but a suitable and accessible laboratory assay. It may be useful in the following situations (*Table 4*):

Table 4 Indications for pharmacokinetic monitoring of antiarrhythmic drugs

- After initiation of treatment or dose adjustment of the drug
- If treatment is failing
- If non-compliance or toxicity is suspected
- After clinically relevant physiological changes (e.g. development of hepatic or renal failure)
- If concomitant potentially interacting drugs are initiated or stopped
- To confirm or exclude abstinence of the drug

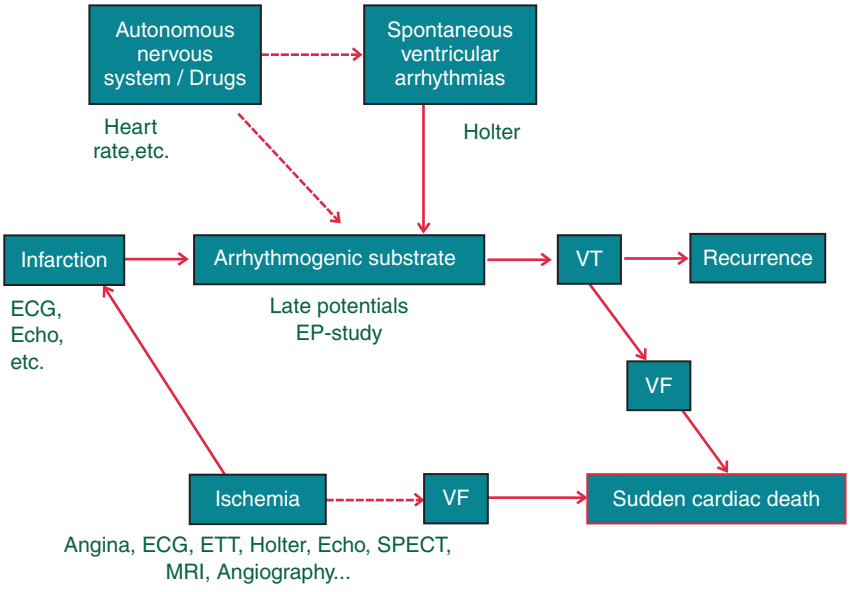

Figure 2 Potential mechanism leading to lethal ventricular tachyarrhythmias and some tests aimed to identify different components of the arrhythmogenic mechanism. The text under boxes are examples of different diagnostic tools that could be used for risk stratification of the arrhythmia mechanism. ECG, electrocardiogram; Echo, echocardiogram; EP, electrophysiological; ETT, exercise treadmill test; MRI, magnetic resonance imaging; SPECT, single photon emission tomography; VF, ventricular fibrillation; VT, ventricular tachycardia.

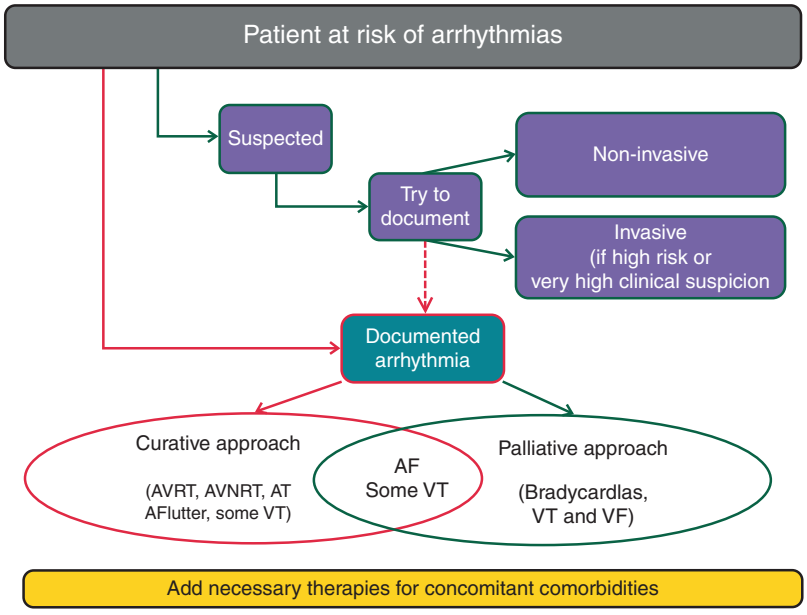

Figure 3 Simplified strategy for the management of patients with arrhythmias. AF, atrial fibrillation; AFlutter, atrial flutter; AT, atrial tachycardia; AVNRT, atrioventricular nodal re-entrant tachycardia; AVRT, atrioventricular re-entrant tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

Consensus statements

Recommendation	References
Evaluate separately the acute and chronic arrhythmic risk profile of patients and the effect on symptoms and outcome	33, 35, 38–40
Be aware of possible proarrhythmic effects of antiarrhythmic and non-anti-arrhythmic drugs. Perform pharmaco-kinetic tests in special situations (as listed in *Table 4*)	36, 37

Individualization of recommendations for pharmacological therapy of arrhythmias based on patient's characteristics

Gender and age

While the efficacy of AAD therapy appears to be similar in men and women,[41,42] risk of proarrhythmias appears to be greater in women compared with men. Female sex has been associated with an increased risk of torsade de pointes (TdP) in those treated with Class I and III AADs.[43–47] There are several potential reasons for the increased risk in women, including longer resting corrected QT intervals, greater QT hysteresis, and the lack of protective antiarrhythmic influence from androgens.[48,49] To minimize the risk of TdP in women, it is advisable to use the lowest effective doses[44,49] and to avoid the concomitant use of any QT prolonging agent. Importantly, given the increased risk of proarrhythmia with Class III AADs in women, these drugs should be avoided if they present additional risk factors for torsades, including the presence of heart failure.[44] When there is suspicion for proarrhythmia, 24 h of Holter monitoring can be helpful due to the reverse-use dependence of Class III drugs and propensity for proarrhythmia during periods of nocturnal bradycardia. Finally, patients should be instructed to contact providers when they suffer from dizziness or palpitations.

Arrhythmias are much more frequent with advanced age and age-related physiologic changes significantly alter AAD PKs[50] (*Table 5*).

Underlying heart disease

While the exact definition of structural heart disease varies across studies, in general, congenital heart disease, ischaemic, valvular, or significant myocardial heart disease [including significant left ventricular hypertrophy (LVH)] are all included in this broad term.

Patients with structural heart disease have higher risks of ventricular arrhythmia as well as higher risks of proarrhythmia with antiarrhythmic medications. In general, these patients (e.g. heart failure or cardiomyopathy) are not candidates for Class IC,[3] or Class III AADs other than amiodarone or sotalol.[7,51] Sotalol can be use in patients with coronary artery disease preferably with implanted ICD[52] as sotalol is associated with increased mortality due to proarrhythmia.[53]

A more difficult and challenging question is what antiarrhythmic agents are permissible in patients with LVH.[54] Patients with LVH have been shown to have greater transmural dispersion of

Table 5 Pharmacokinetics alterations in elderly

PK component	Physiological change	Effect
Absorption	Reduced gastric acid Reduced gastric emptying rate Reduced GI motility Reduced GI blood flow Reduced absorptive surface	Reduced tablet dissolution Reduced solubility for basic drugs Decreased absorption of acid drugs Less drug absorption
Distribution	Decreased body mass Increased body fat Decreased proportion of body water Decreased plasma albumin	Increased Vd of lipid soluble drugs Decrease Vd of water-soluble drugs Changed proportion of free drug
Metabolism	Reduced liver mass Reduced liver blood flow Reduced liver metabolism rate/capacity	Accumulation of metabolized drugs
Excretion	Reduced glomerular filtration Reduced renal tubular function Reduced renal blood flow	Accumulation of renal cleared drugs

GI, gastrointestinal; PK, pharmacokinetics; Vd, distribution volume.

repolarization and higher risks of polymorphic VT (PVT).[55] Due to concern over proarrhythmia, prior guideline recommendations have cautioned against use of Class IC or Class III agents in patients with significant LVH. In the 2016 ESC guidelines for the management of AF, dronedarone, sotalol, and amiodarone are accepted alternatives for patient with AF and LVH. However, only amiodarone is accepted for patients with heart failure.[8] Amiodarone is also an alternative in the case of failure of other AADs.

There are few data demonstrating increased mortality or adverse cardiovascular events in patients with substantial LVH who are treated with AADs other than amiodarone. Recent observational data have suggested that patients with persistent AF and LVH (defined as ventricular wall thickness greater than or equal to 1.4 cm) treated with Class IC and Class III agents did not have higher mortality compared with patients treated with amiodarone.[56] Until more data available, the 2016 ESC guidelines for the management of AF[8] recommend avoiding Class IC AADs in patients with substantial LVH based upon the recognition of LVH as a marker of arrhythmic risk.

In patients with congenital heart disease, especially those with complex congenital heart disease and paediatrics, AAD (other than beta-blockers or verapamil[7]) should be reserved to selected cases, because AAD are frequently poorly tolerated in these patients due to their negative inotropic actions and other side effects, and because there is few evidence regarding efficacy and safety.[7,57]

Consensus statements

Recommendations	References
Avoid the use of Class IA, IC, and Class III membrane active antiarrhythmic drugs in patients with significant structural heart disease (including cardiomyopathy, left ventricular dysfunction, myocardial infarction, and myocardial ischaemia) other than amiodarone or sotalol.	7, 8
Except for amiodarone, dronedarone, or sotalol and disopyramide, avoid the use of Class IA, IC, and Class III membrane active AAD in patients with substantial LVH (≥1.4 cm)	7, 8
Disopyramide is recommended in patients with obstructive hypertrophic cardiomyopathy (in conjunction with beta-blockers) to improve symptoms (taking caution in patients with AF where it can increase ventricular rate)	58
Indication of AAD in congenital heart disease (especially complex congenital heart disease) should be reserved to selected cases, because AAD are frequently poorly tolerated due to negative inotropic actions and other side effects and because of paucity of efficacy and safety evidence	7, 57

AAD, antiarrhythmic drugs; LVH, left ventricular hypertrophy.

Renal disease

A reduction in kidney function may have important implications for drug PKs, with alterations that may involve bioavailability, volume of distribution, protein binding, drug metabolism, and elimination.[59] This may result in reduced ability to excrete drugs and/or their metabolites, increased sensitivity to medications (e.g. those bound to albumin in hypoalbuminaemic states such as nephrotic syndrome), diminished tolerance of side effects, particularly in the elderly, and even in loss of efficacy. A recent position paper regarding management in patients with concomitant arrhythmias or implantable electrical devices and chronic kidney disease (CKD) was published by EHRA.[59]

For AADs eliminated by the kidney the most dangerous consequences of drug accumulation include toxic and proarrhythmic effects, with potentially life-threatening complications. The main PK characteristics and suggestions for appropriate prescription in CKD patients for most used AAD are shown in the *Table 6*.

When deciding to use AAD in a haemodialysis patient the key point is related to drug dialysability, which depends on molecular size, protein binding, volume of distribution, water solubility, and plasma clearance. Some technical aspects of the dialysis procedure could have an impact on the extent of removal. The usual approach requires us to know the 'sieving coefficient' representing the ratio of

drug concentration in the ultra-filtrate to the pre-filter plasma water concentration of the drug. The closer this coefficient is to 1, the more complete removal of the drug is obtained by dialysis.

Procainamide and sotalol should be avoided in patients treated with haemodialysis.[59,60] The dose of flecainide should be at least 50% of the usual recommended dose. Conversely, dialysis has little impact on amiodarone clearance, and no dosage adjustment is necessary.[60]

Consensus statements

Recommendation	References
Renal function should be assessed in all patients treated with AAD.	59

Continued

Recommendation	References
Glomerular filtration rate (GFR) need to be estimated through the Cockcroft–Gault formula, the Modification of Diet in Renal Disease (MDRD) equation, or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and AAD dosage adapted to specific AAD pharmacokinetics	

AAD, antiarrhythmic drugs.

Table 6 Pharmacokinetic characteristics and suggestions for appropriate prescription of antiarrhythmic drugs or rate-controlling drugs in chronic kidney disease patients

Drug	PK and elimination	Indications for CKD
Sotalol	Not protein bound; $t_{1/2}$ ~ 7–18 h; not metabolized; excreted unchanged in urine (~85%)	Dose to be reduced to one half in CKD and one quarter in severe renal failure (GFR < 30 mL/min) where there is relative contraindication in view of the risk of proarrhythmic effects.
Procainamide	15% protein bound; bounds to different tissues; active hepatic metabolite; variable hepatic and renal elimination (60% unchanged); longer elimination in renal failure	Reduction of dose recommended
Quinidine	80–90% protein bound; 50–90% metabolized by the liver to active metabolites; $t_{1/2}$ ~ 6–8 h; 20% excreted in urine	Proarrhythmia; could interfere with renal clearance of other drugs
Lidocaine	70% protein bound; 80% rapidly metabolized by the liver to active metabolites; $t_{1/2}$ < 2 h; <10% excreted unchanged in urine	No special requirements
Mexiletine	50–70% protein bound; $t_{1/2}$ ~ 10–12 h; ~10% excreted unchanged in urine	No special requirements
Flecainide	$t_{1/2}$ ~ 20 h; metabolized by the liver and excreted unchanged in urine (35%)	Dose reduction if GFR < 35 mL/min/1.73 m^2
Propafenone	95% protein bound; metabolized by the liver to active metabolites, excreted in urine (50%); two genetically determined pathways of metabolism (>90% people are rapid metabolizers with $t_{1/2}$ ~ 2–10 h); <1% excreted unchanged in urine	Careful monitoring recommended (in hospital initiation may be preferable if advanced CKD)
Vernakalant	40–55% protein bound, extensively and rapidly distributed in the body after intravenous administration, not extensively bound to plasma proteins. Mainly eliminated by the liver with $t_{1/2}$ ~ 3–5.5 h	Available for intravenous administration at the dose of 3.0 mg/kg followed by 2.0 mg/kg if required.
Amiodarone	99% protein bound; widely distributed to different tissues; metabolized by the liver to two active metabolites; no renal elimination	No dosage adjustment required; not dialyzable; many drug to drug interactions
Dronedarone	~98% protein bound; metabolized by the liver to active and inactive metabolites; $t_{1/2}$ ~ 13–19 h; 6% excreted in urine. Early increase in creatinine ≥10%	No dosage adaptation required in mild and severe renal failure
Diltiazem	80% protein bound; extensive first-pass effect, metabolized in the liver to active metabolites; bioavailability of about 40%; $t_{1/2}$ ~ 3.5–5 h; only 2% to 4% unchanged drug excreted in the urine	Use with caution
Verapamil	~90% protein bound; high first-pass metabolism, metabolized in the liver to at least 12 inactive metabolites; bioavailability 10–35%; 80% is excreted in the urine and 15% in faeces; $t_{1/2}$ ~ 5–12 h.	Dose reduction by 25–50% if CrCl <10 mL/min. Not cleared by haemodialysis.

Colour code: red indicates proarrhythmia risk; orange indicates dose reduction; white indicates no special recommendations; yellow indicates monitoring.
CKD, chronic kidney disease; PK, pharmacokinetics.

Pre-existent bradycardia and/or conduction disturbances

The pathophysiological basis for tachy- and bradyarrhythmias is often similar, i.e. scar formation or ischaemia. Patients therefore may require AAD therapy to suppress atrial or ventricular arrhythmias, while also having underlying sinoatrial node dysfunction, AV conduction disturbances, or intraventricular conduction problem. This scenario is most commonly encountered in the tachycardia–bradycardia variant of sick sinus syndrome—paroxysmal AF with underlying sinus bradycardia, chronotropic incompetence, and conversion pauses.

The rationale to institute AAD in order to prevent arrhythmias such as AF is to improve symptoms, not to improve survival. Overall, AAD are only moderate effective to maintain SR. Any AAD should always be carefully prescribed in patients with pre-existent bradycardia or conduction disturbances because they might be worsened (*Table 7*). This precaution is even more important when prescribing rate-controlling agents alone or in combinations, as they can induce severe bradycardia in SR.

Class IA drugs (disopyramide, blocking both K^+ channels, and Na^+ channels) are rarely instituted for prevention of AF and other arrhythmias nowadays. Class IC drugs flecainide and propafenone (strong Na^+ channel blockers, propafenone also having beta-blocker properties) are moderately effective. These drugs can be safely instituted in patients without ischaemic heart disease or heart failure with a reduced ejection fraction (HFrEF). Propafenone also has a beta-blocking effect, which may worsen baseline bradycardia and conduction disturbances. Sotalol is a beta-blocker with additional Class III K^+ channels blocking effects when ≥160 mg daily is prescribed. Attention is justified in patients with pre-existent bradycardia, even more because proarrhythmia (torsades de pointes) especially occurs at lower heart rates (reverse use dependency).

Dronedarone and amiodarone are multichannel blockers. Therefore, in patients with pre-existent bradycardia and/or AV conduction disturbances initiation of these drugs should be carefully monitored both clinically (symptoms) and with ECG. Bradycardia, sinus node dysfunction, and AV node conductions disturbances are relatively frequent adverse effects of AAD. Sotalol, dronedarone, and amiodarone may also reduce heart rate during AF due to AV nodal effects.

Table 7 Effect of antiarrhythmic drugs on heart rate, conduction, and repolarization

Drug	Main contraindication	Caution	ECG features prompting discontinuation
Disopyramide	HFrEF Long QT	SAN, AV, or conduction disease Concomitant QT prolonging drugs	Symptomatic bradycardia QTc > 500 ms
Flecainide	IHD HFrEF Severe LVH QRS > 130 ms Creatinine clearance <50 mL/min Liver disease	SAN, AV, or conduction disease	Symptomatic bradycardia QRS duration increase > 25%, QRS > 150 ms
Propafenone	IHD HFrEF Severe LVH QRS > 130 ms	SAN, AV, or conduction disease. Renal disease Liver disease Asthma	Symptomatic bradycardia QRS duration increase > 25%, QRS > 150 ms
D,L-Sotalol	LVH HFrEF Long QT Concomitant QT prolonging drug Hypokalaemia Creatinine clearance <30 mL/min	SAN, AV node, or conduction disease. Moderate renal disease Asthma	Symptomatic bradycardia, QTc > 500 ms
Amiodarone	Long QT	SAN, AV node, or conduction disease. Concomitant QT prolonging drugs Pre-existing liver disease	Symptomatic bradycardia QTc > 500 ms
Dronedarone	NYHA III–IV Unstable HF Long QT Concomitant QT prolonging drug Creatinine clearance <30 mL/min	SAN, AV node or conduction disease. Pre-existing liver disease Early increase in serum creatinine ≥10% (inhibition of tubular secretion)	Symptomatic bradycardia QTc > 500 ms

AV, atrioventricular; HFrEF, heart failure with reduced ejection fraction; IHD, ischaemic heart disease; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; SAN, sinoatrial node.

Consensus statements

Recommendation	References
All AAD may induce bradycardia or worsen bradycardia due to sinus node dysfunction or abnormal AV conduction. In patients with a history of syncope, sinus bradycardia or PR prolongation/AV conduction disturbances the start of AAD therapy may cause significant bradyarrhythmia. Caution is warranted in patients with pre-existent conduction disturbances	27
If patients have symptomatic bradyarrhythmias before starting an AAD, implantation of a pacemaker is required beforehand. Sodium channel blockers (Class IA and IC) may raise the pacing threshold, but this is rarely clinically relevant*	61, 62
In patients with a pre-existent QRS duration >130 ms, Class IC drugs should be prescribed with caution	27

AAD, antiarrhythmic drugs; AV, atrioventricular.

Pregnancy

There are few data to guide AAD treatment during pregnancy. Most antiarrhythmic medications are Food and Drug Administration (FDA) Category C, which means that animal reproduction studies have shown an adverse effect on the foetus, and there are no adequate and well-controlled studies in pregnant women. Category C drugs can be helpful when the benefits of therapy outweigh the presumably small, but poorly defined risks.

In pregnant patients who require acute termination of supraventricular tachycardia, vagal manoeuvres should be the first line therapy, followed by adenosine administration, and then beta-blocker therapy with metoprolol (in the absence of pre-excited tachycardia). Metoprolol can also be used to prevent recurrence with a dose as low as possible except pregnancy and post-partum period in LQTS patients in whom usual beta-blockade is advisable.[7] Some advocate avoidance of beta-blockers in the first trimester (except LQTS) if possible to minimize the risk of intrauterine growth retardation.[7] When beta-blocker therapy fails, AAD therapy with sotalol or flecainide can be considered.[63] Sotalol has recently been observed to be of use in the treatment of foetal supraventricular tachycardia as well.[64] Propafenone has been insufficiently studied in pregnancy, but there are no reports suggestive of an increased drug-related prenatal risk.

Haemodynamically significant VT should be treated with emergent cardioversion while haemodynamically stable VT can be pace-terminated (if ICD is present) or treated with intravenous lidocaine. Procainamide or quinidine can also be used if lidocaine fails. However, amiodarone (FDA Category D) should be avoided due to significant risks to the foetus including foetal hypothyroidism, growth retardation, and prematurity.[63,65]

Consensus statements

Recommendation	References
Due to potential risks to the foetus, treatment of arrhythmia in pregnancy should be limited to recurrent, haemodynamically significant arrhythmias.	65
When drugs fail, catheter ablation with minimal fluoroscopy can be considered as a second-line treatment. • In this instance, maternal–foetal medicine specialists should be part of the heart team, to help determine the optimal timing of the procedure to minimize risk to the mother and foetus.	66

Perioperative antiarrhythmic drug therapy in cardiac and non-cardiac surgery

Perioperative antiarrhythmic drug for cardiac surgery

Atrial fibrillation and atrial tachyarrhythmias

Post-operative AF occurs predominantly during the first 48–96 h after cardiac surgery, with the majority of patients presenting with a paroxysmal form. The incidence of AF ranges from 20–25% after isolated coronary artery bypass grafting (CABG) to 50% after combined CABG and valvular surgery, but it may complicate other thoracic interventions (e.g. pulmonary surgery) in about 15% of patients.[67,68] Atrial flutter and atrial tachycardias, including multifocal atrial tachycardia, are also common. The pathophysiology relates to sterile pericarditis, electrolyte changes, and ischaemia and oxidative stress that accompany surgery and are correctable which explains the transient (reversible) nature of post-operative AF.

If AF is well tolerated, rate control may be sufficient as AF is often self-limiting. Only the minority of patients with new-onset early post-operative AF proceed to develop persistent AF requiring intervention. It is reasonable to defer electrical cardioversion for at least 24 h after AF onset because of the high rates of spontaneous conversion, reduced immediate success of electrical cardioversion (70%), and the high likelihood of early AF recurrence in the post-surgical setting.[69] Rate control and rhythm control strategies have been associated with equal numbers of days of hospitalization, similar complication rates, and similarly low rates of persistent AF within 2 months after surgery.[68]

Beta-blockers should be considered the first-line choice because of their beneficial effects in the hyper-adrenergic post-operative state. *While beta-blockers are usually not considered anti-arrhythmic drugs, they have proven anti-arrhythmic potential to prevent post-operative AF.* Short-acting beta-blockers (esmolol 500 mcg/kg of IV bolus over 1 min) are particularly useful when haemodynamic instability is a

concern or selective beta-blockers without intrinsic sympathomimetic activity (metoprolol tartrate 2.5–5.0 mg of IV bolus over 2 min which could be repeated 2–3 times if necessary).

The rate-controlling effect of digoxin (0.25–0.5 mg of IV bolus which can be repeated up to maximum dose of 1.0 mg over 24 h) is delayed,[70] and the drug efficacy is reduced in the presence of a high adrenergic tone, but digoxin in combination with either beta-blockers or a non-dihydropyridine calcium antagonist will often provide effective therapy in otherwise difficult cases.

Prevention of post-operative atrial fibrillation

The best evidence of the efficacy in prevention of post-operative AF has been accumulated for beta-blockers, sotalol, and amiodarone which have been shown to reduce the risk of AF by 50–65%,[67,71] with the preference given to beta-blockers. The downside of beta-blockers is bradycardia (5–10%) and risk of longer ventilation (1–2%). Cardiac pacing using temporary epicardial wire electrodes placed at the time of surgery in most patients should permit the use of beta-blockers in the presence of bradycardia. Treatment should be started at least 24 h before surgery, preferably with a selective beta-blocker without intrinsic sympathomimetic activity (bisoprolol, metoprolol) and resumed early in the post-operative period in the absence of contraindications. Patients already on beta-blockers should continue therapy as withdrawal is associated with a greater risk of AF following the surgery.

The second-line treatment is amiodarone which prevents AF and offers an additional protection against ventricular tachyarrhythmias.[72–75] The adverse events such as hypotension and bradycardia necessitating inotropic and chronotropic support or pacing may limit the routine use of amiodarone to patients at high risk of post-operative AF (e.g. those with a history of AF).

In contrast with other therapies, treatment with amiodarone was associated with a statistically significant shorter length of hospital stay (due to its superior antiarrhythmic efficacy). Sotalol has the potential incremental benefit due to its Class III antiarrhythmic property compared with beta-blockers, but its efficacy is inferior to that of amiodarone[76,77] and its use risks bradycardia and TdP, especially in patients with electrolyte disturbances.

The effect of magnesium sulfate on the incidence and number of episodes of AF was comparable to those of beta-blockers, sotalol, and amiodarone, and no adverse events were reported.[71,78] Its favourable effects may relate to restoration of electrolyte balance, in addition to potassium supplementation, after surgery. The stimulating effect of magnesium on the sodium/potassium pump may act beneficially by inducing a calcium-channel blocking effect. However, magnesium is not commonly employed as a primary agent for prevention or treatment of AF and usually adjunctive to beta-blockers or AAD.

For conversion of post-operative AF amiodarone or vernakalant are the preferred choice.[8] Vernakalant given as a 3 mg/kg bolus followed, if necessary by the second bolus of 2 mg/kg at a 10 min of interval, can be used for rapid conversion of post-operative AF. The advantage of the drug is a rapid antifibrillatory effect which occurs within 90 min after the start of infusion in the majority of patients, with a median time to conversion of 12 min.[79] Vernakalant is recommended for termination of AF ≤ 3 days after surgery and is contraindicated in patients with severe hypotension, acute coronary syndrome (ACS), and significantly impaired left ventricular systolic function.[80] The use of other AAD is not well supported, although there is limited experience with ibutilide 1 mg/kg followed, if necessary, by a second bolus of 1 mg/kg (for conversion of atrial flutter)[81] and propafenone and flecainide[82] (may be considered in non-CABG patients). Magnesium infusion may potentiate the antiarrhythmic effect of beta-blockers or AAD.

Ventricular tachyarrhythmias

VPBs and non-sustained ventricular tachycardia (NSVT) are common in the early post-operative period and are transient in the majority of patients. Adequate electrolyte balance including magnesium supplementation maintenance usually is sufficient. Membrane-stabilizing effects of beta-blockers also provide protection against these arrhythmias. No specific antiarrhythmic drug therapy is indicated.

Electrical cardioversion/defibrillation should be performed in the case of haemodynamically unstable VT or VF. Intravenous amiodarone, lidocaine, and mexiletine can be effective in suppression and prevention of haemodynamically stable VT as well as for prevention of recurrent ventricular fibrillation.

Perioperative antiarrhythmic drugs in non-cardiac surgery

Arrhythmias have an important impact on perioperative outcome and when VT or AF are present, they indicate the presence of abnormal structural substrate.[83] If present before surgery, an extensive evaluation of the cause and correction of risk factors is recommended. The prognostic impact of VPBs, non-sustained VT, and the benefit of suppression by AAD have not been demonstrated. Polymorphic VT is usually a marker of acute myocardial ischaemia. Intravenous amiodarone is the most suitable AAD in haemodynamically stable patients with sustained monomorphic VT and for prevention of VT recurrence, given the broad range of indications and the lower risk of proarrhythmias in patients with structural heart disease. The effect is already manifest in the first hour post-administration because of early beta-adrenergic and calcium channel blockade effect[84] and is enhanced by pre-treatment with magnesium sulfate. Adverse effects may include hypotension, bradycardia, and, very rarely, acute lung injury (especially after thoracotomy).[85] Intravenous amiodarone is reasonable for recurrent stable PVT in the absence of inherited or acquired LQTS. Beta-blockade is efficient in recurrent PVT of ischaemic aetiology. For supraventricular arrhythmias the same principles apply for non-cardiac surgery, as for cardiac surgery.

Consensus statements

Recommendations	References
In post-operative AF, rate control may be sufficient as the arrhythmia is often self-limiting. Beta-blockers are the first-line therapy in presence of a fast ventricular response rate during AF	8, 83

Continued

Continued

Recommendations		References
A rhythm control strategy, including electrical or pharmacological restoration of sinus rhythm with subsequent prophylactic AAD therapy if necessary should be considered in haemodynamically unstable or highly symptomatic patients with post-operative AF		83
For the prevention of post-operative AF, beta-blockers (first-line therapy), amiodarone (second option) and sotalol (third option) may be used.		8, 83
Magnesium sulphate is useful as adjunctive treatment to beta-blockers or AADs for the prevention of post-operative AF		83
For conversion of post-operative AF in stable patients amiodarone and vernakalant are the preferred choice		8
In post-operative patient, no specific AAD therapy is indicated to suppress ventricular extrasystoles and non-sustained VT. Adequate electrolyte balance including magnesium supplementation and beta-blockers provide sufficient protection*		83
Intravenous amiodarone, lidocaine, and mexiletine can be effective in suppression and prevention of stable ventricular tachycardia as well and amiodarone for prevention of recurrent ventricular fibrillation.		83, 84

AAD, antiarrhythmic drugs; AF, atrial fibrillation.

Table 8 Proarrhythmic effects with antiarrhythmic drugs

Effect	Drug	Incidence
Marked sinus bradycardia, sino-atrial blocks	Class IA, Class IC	Rare, except when latent sinus node disease is present
High-grade AV block	Class IA, Class IC	Rare
Conversion of AF to atrial flutter with higher ventricular rate	Quinidine and other Class IA	Rare with current dosages
Conversion of AF to atrial flutter with 1:1 AV conduction and wide QRS	Flecainide and propafenone	3.5–5%
Torsade de pointe	Quinidine and Class IA	1–8%
	Ibutilide, dofetilide, sotalol	Up to 8%
	Amiodarone	0.7%
Ventricular tachycardia or ventricular fibrillation	Potentially all AADs	Rare, except when LV dysfunction or heart failure are present

AAD, antiarrhythmic drugs; AF, atrial fibrillation; AV, atrioventricular; LV, left ventricular.

In-hospital vs. out-of-hospital drug initiation

Initiation of any AAD implies some risk of adverse event, including proarrhythmic effects, as shown in the *Table 8*. With regard to the most serious risk of proarrhythmia, specific risk factors are well known[7] (see 'Safety issues for patients treated with antiarrhythmic drugs' section). Patients at higher risk for proarrhythmias should be closely monitored in the hospital.

For Class IC AADs the following clinical features are predictors of increased risk of ventricular proarrhythmia at initiation or during treatment: bundle branch block or wide QRS duration at baseline (>120 ms), structural heart disease, left ventricular dysfunction (LVEF < 0.40), tachyarrhythmia with a rapid ventricular response, high drug dose or rapid dose increase, history of ventricular tachyarrhythmias, concurrent treatment with drugs with negative inotropic effect.

For both Class IA and Class III AADs the following clinical features are predictors of an increased risk of ventricular proarrhythmia at initiation or during treatment: long-QT interval (QTc > 460 ms), female gender, bradycardia or long-RR intervals, excessive QT/QTc lengthening during treatment (>550 ms or >25% over baseline), structural heart disease, LVH, LV dysfunction or heart failure, hypokalaemia or hypomagnesaemia, reduced renal function, high drug dosage or rapid dose increase, pharmacological interactions, and the history of proarrhythmias.

Proarrhythmic events tend to cluster shortly after drug initiation, especially if a loading dose or a change in dosage is prescribed. For this reason when the risk of proarrhythmia is particularly high (i.e. structural heart disease with some degree of left ventricular dysfunction), in-hospital drug initiation with continuous telemetry monitoring and resuscitation facilities can be recommended and arguably constitutes the gold standard for proarrhythmia detection.[86,87] However, for financial and practical reasons this approach is limited to selected cases at high risk and is not indicated for amiodarone because of its slow onset of action and long half-life.

Patient education on the potential symptoms associated with proarrhythmia (severe palpitations, pre-syncope, and syncope) accompanied by a 12-lead ECG for several days after drug initiation is a strategy that can be applied to the majority of patients in order to safely monitor the effects of AADs.[88] These safety rules apply even more strictly in patients with risk factors for TdP or with concomitant non-antiarrhythmic torsadogenic medication with close QTc monitoring. Usually, as demonstrated for sotalol, the proarrhythmia occurs in the first few days after the initiation of therapy; some advocate for in-hospital monitoring of patients at risk because of the availability of

monitoring and resuscitation facilities.[87] In patients taking Class IC AAD for rhythm control in AF or atrial flutter, including the patients in whom the 'pill in the pocket' strategy is applied, slowing of arrhythmia can induce a paradoxical brisk increase in ventricular rate. As the action of IC AAD is use-dependent (see 'Classification of antiarrhythmic drugs and overview of clinical pharmacology' section), the concomitant prolongation of QRS makes difficult the differentiation from VT.

In selected patients, administration of an oral loading dose of flecainide or propafenone may be effective for converting AF to SR in the ambulatory setting, with a faster effect than other regimens[89–92]; however, this approach is less effective than the hospital-based regimen.[8] Previous in-hospital testing with intravenous, and not oral, administration of flecainide or propafenone does not predict the safety of the 'pill-in-the-pocket' approach[93] and is not recommended.

Consensus statements

Recommendations		References
Before initiation of antiarrhythmic drugs therapy, an individual evaluation of the proarrhythmic risk of the patient with a specific is mandatory		88
In appropriately selected patients with recurrent AF, out-of-hospital self-administration of oral flecainide or propafenone, according to the 'pill-in-the-pocket' approach can be used following adequate patient education and a previous in-hospital testing of the oral preparation, demonstrating safe conversion of AF to sinus rhythm, without any proarrhythmia. Adding a beta-blocker is recommended to avoid conversion of AF into atrial flutter with 1:1 conduction		90, 94

Pharmacogenomics and antiarrhythmic drug therapy

Pharmacogenetics studies the genetic variations underlying variable response to drugs. Two main classes of genetic variants influence interindividual variability in AAD drug response[95–97] (Supplementary material online, *Table S4*).

Pharmacokinetic variability depends on the processes of absorption, distribution, metabolism, and elimination that determine the drug (and active metabolites) concentration reaching its target site. Variants in the genes encoding specific transporters and metabolizing enzymes, mainly the CYP450 superfamily, can explain the PK variability in AAD effects. This variability is important for AAD with a single predominant route of metabolism or elimination (digoxin, dofetilide, propafenone, and sotalol), but has minor consequences for AAD metabolized/eliminated by multiple pathways. CYP2D6, CYP2C9, and CYP3A4/5 are main drug-metabolizing enzymes for AADs. Poor metabolizers present higher drug plasma levels and sometimes a higher risk of adverse effects, but there are insufficient data regarding antiarrhythmic efficacy. Similarly, CYP450 inhibitors and inducers significantly increase or decrease AAD plasma levels, respectively.[98,99] For example, procainamide is metabolized to NAPA, a Class III AAD which prolongs the QT interval. Slow acetylators present higher procainamide plasma levels and higher risk to develop drug-induced lupus erythematosus.[100] P-glycoprotein acts as an efflux pump, and Pgp inhibitors increase digoxin plasma concentrations and toxicity.

Pharmacodynamic variability arises from variants in target molecules (channels, receptors, and transporters) with which AAD interact to produce beneficial/adverse effects or in the complex biological context within which the drug–target interaction takes place.[95,97] Variants in genes encoding beta-adrenoceptors modify heart rate and blood pressure responses to β-blockers/agonists.[95,97,99] The main concern with AAD therapy is proarrhythmia appearing even in the absence of clear risk factors. Many AADs block cardiac ion channels and the risk of torsades de pointes during QT-prolonging AAD therapy is associated with variants in genes encoding components of cardiac ion channels.[95,97,98] Indeed, rare variants in genes responsible for congenital arrhythmia syndromes are frequent in patients with drug-induced LQTS.[101,102] The risk of proarrhythmia usually increases with drug exposure, so both genetic and pharmacological modifications in CYP450 activity are also risk factors for drug-induced proarrhythmia.

Even when the existing genetic data identify a clear opportunity to improve the management of cardiac arrhythmias, at the present time the extent to which PK/PD genetic variations are associated with clinical outcomes is uncertain and their predictive value to determine AAD efficacy and safety is not well established.

Consensus statements

Recommendations		References
Routine pharmacogenetic testing in the clinical use of antiarrhythmic drugs cannot be recommended at present.		96

Individualizing recommendations for pharmacological therapy of arrhythmias

Ventricular premature beats and non-sustained ventricular tachycardia

The majority of monomorphic VPBs, most commonly of the right or left ventricular outflow tract origin which occur in the absence of structural heart disease, are not associated with an adverse prognosis and usually do not require any specific antiarrhythmic therapy, probably apart from a beta-blocker or a non-dihydropyridine calcium antagonist (verapamil) in the presence of symptoms.[103]

In patients without structural heart disease, Class IC AADs (propafenone and flecainide) and Class IA agent disopyramide may be used in symptomatic patients with a high burden of ventricular ectopics, but their efficacy is lower than non-pharmacological therapy such as

ablation.[104] There is no established clear cut-off point for the initiation of treatment with regard to the number of VPBs. Patients with extremely frequent VPBs (>10% of the total beats during 24 h of monitoring) are more likely to experience some degree of left ventricular dysfunction or to develop arrhythmia-induced cardiomyopathy.[105,106] A VPB burden of >24% or >20 000 VPBs during the 24 h period has shown a strong association with the development of cardiomyopathy.[107,108] However, the threshold varies greatly, with arrhythmia-induced cardiomyopathy being reported in association with VPB frequency as little as 4%, whereas patients with VPBs > 20% did not demonstrate left ventricular function impairment. Other VPB features such as QRS duration as a measure of ventricular dyssynchrony, prematurity index, multiform VPBs, and duration of exposure to frequent VPBs may be associated with the development of cardiomyopathy. Beta-blockers and amiodarone are indicated for medical suppression of VPBs in the presence of left ventricular systolic dysfunction.

The same principles apply to management of patients with NSVT. Patients with frequent idiopathic runs of NSVT should be evaluated for the inherited cardiac conditions predisposing to sudden death. In those without significant heart disease, NSVT may respond to beta-blockers or calcium antagonists; however, if AAD therapy is required the choice of the drugs is limited to amiodarone and (less preferable) sotalol. The latter is suitable for symptomatic patients with moderate structural heart disease[51] including coronary artery disease, preferably in patients with ICD[7] because of the proarrhythmic risk of sotalol. Class IC agents may be used in patients without myocardial infarction or evidence of ischaemia[109] and without other significant myocardial structural diseases.

Consensus statements

Recommendations	References
In presence of, or if development of arrhythmia induced cardiomyopathy is suspected, ablation of very frequent ventricular premature beats or non-sustained VT is recommended as first-line therapy	7, 104
Beta-blockers and non-dihydropyridine calcium channel blockers might be used in symptomatic patients with ventricular premature beats	7, 103
In the absence of structural heart disease, Class IC AAD (propafenone and flecainide) and Class IA agent disopyramide may be used in symptomatic patients with a high burden of ventricular premature beats, but ablation is the first-line recommended therapy	110
Antiarrhythmic drugs should not be used to treat asymptomatic ventricular premature beats, in the absence of arrhythmia-induced cardiomyopathy	7

AAD, antiarrhythmic drugs; VT, ventricular tachycardia.

Atrial premature beats and non-sustained atrial tachycardia

Atrial premature beats (APBs) and non-sustained atrial tachycardia (NSAT) are a common finding in older individuals and frequent APBs are considered a marker of atrial electrical vulnerability and predictors of incident AF.[111] In addition, AES are markers of increased risk of stroke and cardiovascular death in older individuals.[112–114] There is no consensus whether pharmacological suppression of APBs and runs of NSAT reduces the risk of AF and cardiovascular morbidity and mortality, and what is the threshold for intervention. The efficacy of sotalol, flecainide, and propafenone has been demonstrated for suppression of sustained atrial tachycardia and can be extrapolated to frequent APBs and NSAT. Amiodarone and beta-blockers are the preferred option in the presence of left ventricular systolic dysfunction if AAD treatment is indicated. When frequent APBs and NSAT occur in the presence of structural heart disease, optimization of medical therapy for the underlying condition may reduce the arrhythmia burden and deter the development of arrhythmia-induced cardiomyopathy.[110]

Consensus statements

Recommendations	References
Symptomatic patients without structural heart disease with frequent atrial premature beats and non-sustained atrial tachycardia might be treated with beta-blockers, sotalol, flecainide, or propafenone	115, 116
Patients with structural heart disease presenting symptoms and/or high atrial premature beats burden and/or non-sustained atrial tachycardia might be treated with amiodarone or beta-blocker. Optimization of therapy of the underlying condition is recommended	115, 116

Sustained supraventricular arrhythmias

Supraventricular tachyarrhythmias (SVT) represent a spectrum of tachycardias with a mechanism that involves tissue from the His bundle or above. Thus, the term SVT includes atrioventricular nodal re-entrant tachycardia (AVNRT), atrial tachycardia (AT), and atrioventricular re-entrant tachycardia (AVRT). Although formally AF and atrial flutter are also from supraventricular origin, they are presented separately.

Echocardiographic or other image explorations (e.g. magnetic resonance tomography) should be performed to exclude significant structural heart disease, if the echocardiographic window is limited. Exercise testing might be useful for detection of arrhythmias related to exertion. Ambulatory Holter, wearable event monitoring and hand-held ECG event-recorders are advisable for patients

complaining of frequent transient not documented tachyarrhythmias. Implantable loop recorders are helpful for those patients with rare and severe symptoms (e.g. with haemodynamic instability) whom had no inducible arrhythmias after an invasive electrophysiological testing.[117] Thus the first step for correct treatment is to have the correct diagnosis. Thereafter, the best strategy for the person can be decided based on the confirmed individual characteristics.

Figure 4 shows the algorithm for evaluation of patients presenting with palpitations. The correct diagnostic of arrhythmia, including differential diagnostic of narrow and wide QRS tachycardia, is crucial for appropriate treatment and is presented elsewhere.[115–117] The drugs recommended for acute management of haemodynamically stable and regular tachycardias with the levels of evidence are presented in *Table 9* and *Figure 5*.

The sinus node may be involved in several arrhythmias. The sinus node re-entry tachycardia may respond to vagal manoeuvres, adenosine, beta-blockers, non-dihydropyridine calcium-channel blockers, amiodarone, and digoxin. In very rare cases, catheter ablation may be required. Supplementary material online, *Table S5* strategies for management of patients with inappropriate sinus tachycardia and postural orthostatic tachycardia syndrome.

Catheter ablation, due to it high efficacy, is recommended for the majority of patients with AVNRT and AVRT. However, until this treatment is available, patients with AVNRT and AVRT may respond to vagal manoeuvres, carotid massage, or adenosine which is helpful for arrhythmia termination and/or for differential diagnosis with other arrhythmias (Supplementary material online, *Figure S1*). Adenosine should be used with caution because it may provoke AF with a rapid ventricular response in the presence of pre-excitation, and it can also induce or worsen myocardial ischaemia due to the vasodilator-induced coronary steal phenomenon in the presence of severe coronary stenosis. Alternative options for patients with AVNRT and AVRT are presented in *Tables 10* and *11*. Importantly, drugs that mainly slow the conduction through the AV node (e.g. digoxin, verapamil, beta-blockers, adenosine, diltiazem) are discouraged in patients with pre-excitation because of the risk of AV nodal blockade and acceleration of the ventricular rate if AF occurs. Class IC AADs (flecainide, propafenone) are contraindicated in the presence of structural heart disease (especially after myocardial infarction). Furthermore, Class III drugs are discouraged for the treatment of SVT (although they might be effective) because of their toxicity and the potential of proarrhythmias (e.g. TdP).[117]

Supplementary material online, *Table S6* presents the therapeutic options for focal and non-paroxysmal junctional tachycardia, and *Table 12* shows recommendations for the treatment of patients with focal AT. Focal AT may be induced by digitalis excess (usually with AV

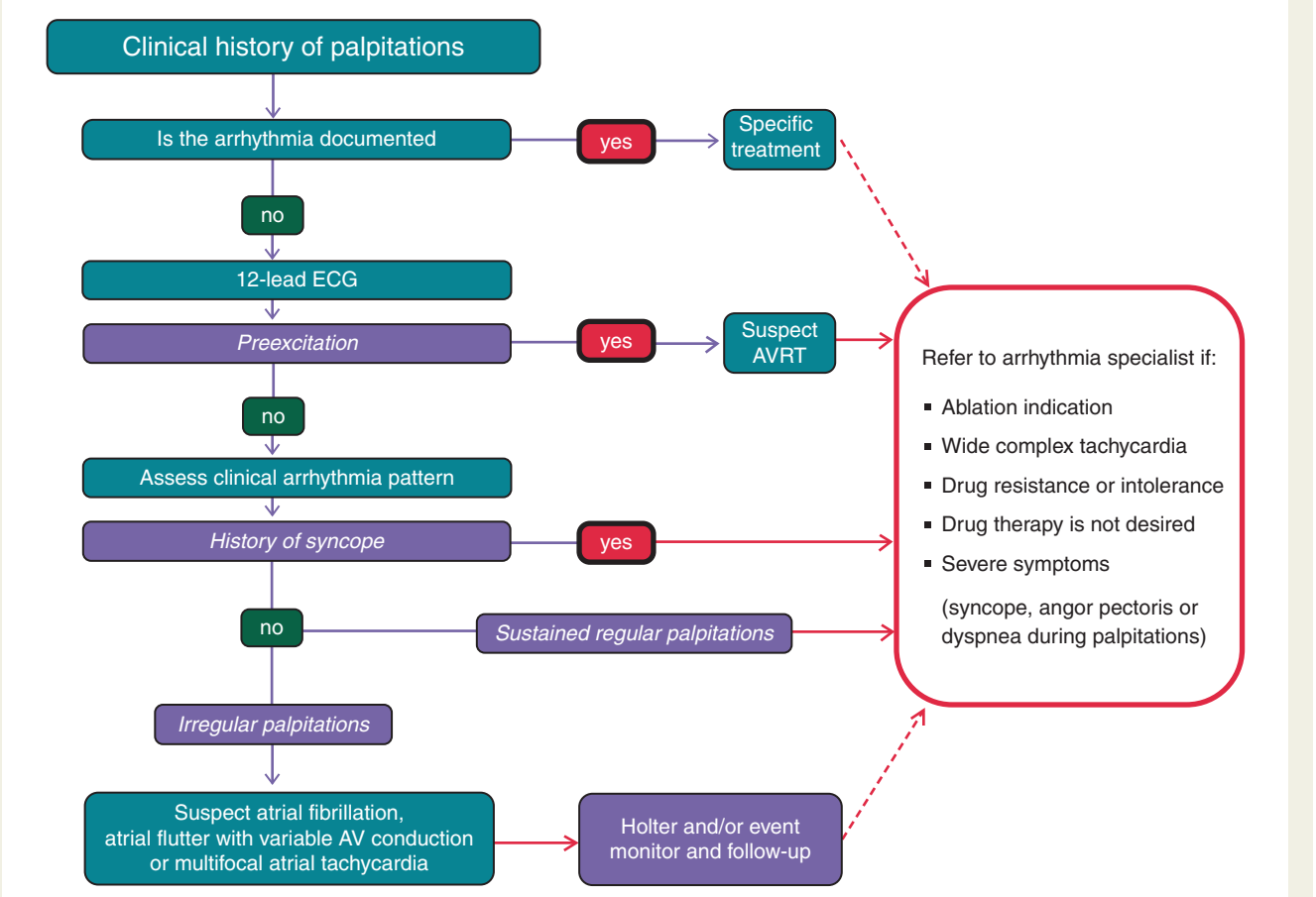

Figure 4 Evaluation of patients presenting with palpitations. AV, atrioventricular; AVRT, atrioventricular re-entrant tachycardia; ECG, electrocardiogram.

Table 9 Drugs recommended for acute management of haemodynamically stable and regular tachycardia

ECG	Recommendation	Class of recommendation	Level of evidence
Narrow QRS-complex tachycardia	Vagal manoeuvres	I	B
	Adenosine	I	A
	Verapamil/diltiazem	I	A
	Beta-blockers	IIb	C
	Amiodarone	IIb	C
	Digoxin	IIb	C
Wide QRS-complex tachycardia			
SVT and BBB	See above		
Pre-excited SVT	Flecainide[a]	I	B
	Ibutilide[a]	I	B
	Procainamide[a]	I	B
	DC cardioversion	I	C
Of unknown origin and preserved LV function	Procainamide[a]	I	B
	Sotalol[a]	I	B
	Amiodarone	I	B
	DC cardioversion	I	B
	Lidocaine	IIb	B
	Adenosine[b]	IIb	C
	Beta-blockers[c]	I	C
	Verapamil[d]	I	B
Of unknown origin and poor LV function	Amiodarone	I	B
	DC cardioversion	I	B
	Lidocaine		

All drugs should be administered intravenously. Based on the ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias[117] and 2017 EHRA consensus document.[115]
BBB, bundle branch block; DC, direct current; ECG, electrocardiogram; LV, left ventricular; QRS, ventricular activation on ECG; SVT, supraventricular tachycardia.
[a]Should not be used in patients with impaired left ventricular function.
[b]Adenosine should be used with caution in patients with severe coronary artery disease because it may cause vasodilatation of normal coronary arteries causing ischaemia in stenotic territories. It should only be used with full CPR equipment available.
[c]Beta-blockers may be used as first-line therapy for catecholamine-sensitive tachycardia (e.g. right ventricular outflow tract tachycardia).
[d]Verapamil may be used as first-line therapy for left ventricular fascicular tachycardia.

block) and exacerbated by hypokalaemia. It may rarely be terminated by vagal manoeuvres but is adenosine-sensitive. In patients with automatic AT, pacing, adenosine, and electrical cardioversion seldom terminate the arrhythmia, unless the mechanism is micro-re-entry or triggered automaticity. Multifocal atrial tachycardia is usually associated to severe pulmonary disease and often requires treatment with calcium-channel blockers without any definitive role for other antiarrhythmic drugs, DC cardioversion or ablation.

Atrial fibrillation and flutter

Rhythm control

Current evidence suggests that rhythm control has no morbidity or mortality benefit compared with ventricular rate control in elderly AF patients with established cardiac co-morbidity and moderately symptomatic AF.[128] Whether early aggressive rhythm control using catheter ablation alone or in combination with AAD improves long-term outcomes in younger AF patients or those with different risk profiles remains to be established, and several ongoing trials are addressing these aspects [EAST[129] and CABANA (NCT00911508)].

Severely haemodynamically compromised AF patients (i.e. those with severe acute left ventricular failure, ongoing myocardial ischaemia or symptomatic arterial hypotension) should undergo *emergency* external electrical cardioversion, since rapid restoration of SR may improve the short-term outcome. In haemodynamically stable AF patients, *elective* cardioversion (either electrical or pharmacological) is performed to improve symptoms, and the choice of cardioversion mode should be based on the clinical setting.[8,80,126,127,130]

Electrical cardioversion is generally associated with greater immediate success rate (particularly in persistent AF) and shorter hospitalization, whereas pharmacological cardioversion does not require general anaesthesia/deep sedation and prior fasting and may prevent early AF recurrence.[80] In the EURObservational Research Programme (EORP) Pilot AF General Registry, pharmacological cardioversion was used in >50% of patients with paroxysmal (52.1%) or persistent AF (65.2%).[131]

In controlled trials, spontaneous restoration of SR within 48 h of hospitalization occurred in 76–83% of patients with recent-onset AF (in 10–18% within 3 h, and in 55–66% within 24 h),[92,132] but more rapid symptom relief is often warranted. Acute pharmacological cardioversion success rate ranges from 10% to 80%, depending on AF duration (AADs are generally more effective in cardioversion of recent-onset AF) and the agent used (see *Table 13*).[21] Importantly, the choice of specific drug should be based on the presence, type and severity of underlying structural (or functional) cardiac disease (*Figure 6*).[8] Intravenous vernakalant allows the rapid restoration of SR in patients with AF (but not in atrial flutter) and may be administered in mild to moderate heart failure and stable ischaemic heart disease. Intravenous flecainide and propafenone are restricted to patients without altered cardiac substrate. Ibutilide is an alternative to intravenous flecainide and propafenone; however, it is torsadogenic and should be avoided in patients with long QT and the QTc interval should be carefully monitored during and immediately after the infusion. Intravenous amiodarone was not shown to convert AF acutely in placebo controlled studies[133]; however, it can be administered in heart failure patients and it slows significantly the heart rate in less than 12 h[8] and is superior to intravenous sotalol concerning overall conversions.

Acute pharmacological AF cardioversion is generally performed in the hospital setting and requires continuous medical supervision and ECG monitoring during the drug infusion and afterwards for at least half of the drug half-life. Most AADs are given intravenously, with the exception of flecainide and propafenone which could be administered orally with similar efficacy (*Table 13*).

Oral bolus of flecainide or propafenone can also be self-administered by selected outpatients with infrequent symptomatic paroxysmal AF, provided that their safety has been previously established in the hospital setting.[94] This 'pill-in-the-pocket' strategy is marginally less effective than in-hospital cardioversion or continuous AAD therapy but may be preferred by eligible patients.[134] Pre-treatment with oral AAD such as amiodarone,[135] sotalol,[136] or ibutilide[137] may improve the efficacy of electrical cardioversion of AF and/or prevent early AF recurrences post-cardioversion, or sometimes SR may be restored (e.g. during a 3–4 weeks of pre-treatment with

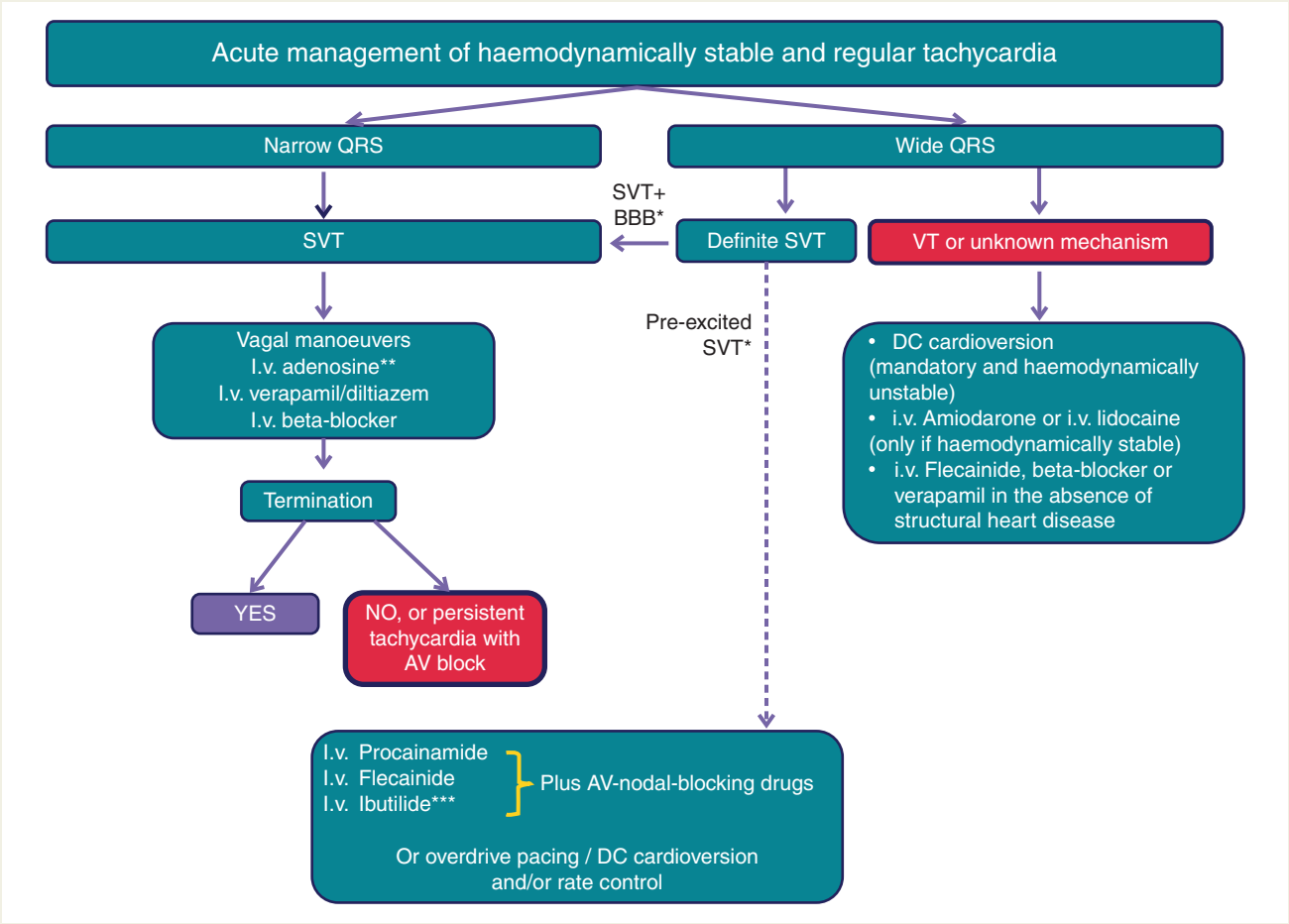

Figure 5 Acute management of haemodynamically stable and regular tachycardia. *12-lead ECG during sinus rhythm must be available for diagnosis. **Adenosine should be used with caution in patients with severe coronary artery disease and may facilitate atrial fibrillation. ***Ibutilide is especially effective for atrial flutter but should not be used in patients with left ventricular ejection fraction <30% due to increased risk of polymorphic VT. AV, atrioventricular; BBB, bundle branch block; DC, direct current; ms, milliseconds; QRS, ventricular activation on electrocardiogram; SVT, supraventricular tachycardia; VT, ventricular tachycardia. Reproduced from reference.[117]

oral amiodarone SR was restored in 27% of patients with persistent AF).[138]

Typical atrial flutter is best treated by catheter ablation, which is comparably safe and more effective than AAD.[139] Flecainide, propafenone, or ibutilide may be used for cardioversion of atrial flutter. Flecainide and propafenone may slow the flutter cycle thus facilitating 1:1 AV conduction with increased ventricular rates.[140] Adding a beta-blocker is recommended to avoid conversion of AF into atrial flutter with 1:1 conduction. Ibutilide is more effective in conversion of flutter than AF,[141] whereas vernakalant is ineffective for typical atrial flutter.[142] Prior to pharmacological cardioversion of AF or flutter any electrolyte imbalance should be corrected, and anticoagulant therapy should be administered according to the guidelines.[8]

Maintenance of sinus rhythm post-cardioversion

In general, AAD are moderately effective in maintenance of SR after conversion of AF (*Table 14*). In the meta-analysis of 59 AF studies, AF recurrences were significantly reduced with Class IA (disopyramide and quinidine), IC (flecainide and propafenone), and III (amiodarone, dofetilide, dronedarone, and sotalol), drugs [odds ratio (OR) 0.19–0.70, number needed to treat to benefit (NNTB) 3–16], and beta-blockers (metoprolol, OR 0.62, 95% CI 0.44–0.88, NNTB 9). However, quinidine and disopyramide [OR 2.39, 95% CI 1.03–5.59, number needed to treat to harm (NNTH) 109, 95% CI 34–4985] and sotalol (OR 2.23, 95% CI 1.1–4.50, NNTH 169, 95% CI 60–2068) were associated with increased all-cause mortality compared to controls, whereas other AAD had a neutral effect on mortality.[53]

Amiodarone is more effective in rhythm control than other AADs, but extracardiac adverse effects may limit its long-term use.[180,181] Dronedarone is less effective than amiodarone, but reduces cardiovascular hospitalizations and death in paroxysmal or persistent AF or Afl.[166,182,183] However, dronedarone has been associated with increased mortality and cardiovascular events in patients with recently decompensated heart failure[167] or permanent AF.[184]

In a recent European survey, beta-blockers, flecainide, propafenone, and amiodarone were most frequently used first-line AAD for rhythm control.[185] Overall, amiodarone was the most commonly used AAD for rhythm control in the EORP Pilot AF general Registry.[131]

Table 10 Therapies recommended for long-term treatment of patients with atrioventricular nodal re-entrant tachycardia

AVNRT	Recommendation	Class of recommendation	Level of evidence
Poorly tolerated with haemodynamic intolerance	Catheter ablation	I	A
	Verapamil, diltiazem	IIa	C
	Beta-blockers	IIa	C
	Sotalol, amiodarone	IIa	C
	Flecainide[a]	IIa	C
	Propafenone[a]	IIa	C
Recurrent symptomatic	Catheter ablation	I	A
	Verapamil	I	B
	Diltiazem	I	C
	Beta-blockers	I	C
	Digoxin[b]	IIb	C
Recurrent, unresponsive to beta-blockers or calcium channel blockers and patients refusing catheter ablation	Flecainide[a]	IIa	B
	Propafenone[a]	IIa	B
	Sotalol	IIa	B
	Amiodarone	IIb	C
Infrequent or single episode in patients not desiring long-term drug therapy	Catheter ablation	I	B
Documented SVT with only AV nodal dual pathways or single echo beats demonstrated during electrophysiological study and no other identified cause of arrhythmia	Verapamil Diltiazem Beta-blockers Flecainide[a] Propafenone[a]	I	C
	Catheter ablation	I	B
	No therapy	I	C
Infrequent, well tolerated	Vagal manoeuvres	I	B
	'Pill-in-the-pocket'	I	B
	Verapamil, diltiazem	I	B
	Beta-blockers Catheter ablation	I	B

Modified from the ESC/AHA/ACC guidelines for the management of patients with supraventricular arrhythmias[117] and 2017 EHRA consensus document.[115] The 2017 EHRA consensus document recommends no therapy for infrequent well-tolerated SVT.
AVNRT, AV nodal re-entrant tachycardia; SVT, supraventricular tachycardia.
[a]Contraindicated for patients with coronary artery disease, left ventricular dysfunction, or other significant heart disease.
[b]Often ineffective because of enhanced sympathetic tone.

Consensus statements

Recommendations	References
The choice of AAD for rhythm control should be guided by the presence and severity of underlying cardiac disease, potential for adverse effects, symptom burden, and patient preferences.	8
In selected patients, AADS may be used in combination with AF ablation. Such hybrid therapy may result in a small decrease in post-procedural AF recurrences and total AF burden, particularly in the first months after AF ablation.	186, 187

Rate control

In patients with AF/flutter, a rapid and irregular ventricular rate may be associated with symptoms, impaired haemodynamics and an increased risk of developing heart failure.[188] Based on the results of the rate vs. rhythm control trials in AF, a rate control strategy can be the first choice therapy, especially in elderly patients without severe symptoms.

Limited data are available on the best type of rate control therapy and optimal heart rate during AF. There is only one randomized trial, the Rate Control Efficacy in Permanent Atrial Fibrillation (RACE II) trial. This study randomized 614 patients with permanent AF to either a target heart rate <80 b.p.m. at rest and <110 b.p.m. during moderate exercise, or to a lenient heart rate target <110 b.p.m. After more than 2 years of follow-up, there was no difference in a composite of clinical events, NYHA class, or hospitalizations.[189] Comparable results were found in a pooled analysis of the Atrial

Table 11 Therapies recommended for long-term treatment of patients with atrioventricular re-entrant tachycardia

AVRT	Recommendation	Class of recommendation	Level of evidence	EHRA consensus
WPW syndrome (pre-excitation and symptomatic arrhythmias) well tolerated	Catheter ablation	I	B	Sotalol not included
	Flecainide, propafenone	IIa	C	
	Sotalol, amiodarone	IIa	C	
	Beta-blockers	IIa	C	
	Verapamil, diltiazem	IIa	C	
	Digoxin	III	C	
WPW syndrome with AF and rapid conduction or poorly tolerated AVRT	Catheter ablation	I	B	
AVRT poorly tolerated (without pre-excitation)	Catheter ablation	I	B	Sotalol not included
	Flecainide, propafenone	IIa	C	Amiodarone if
	Sotalol, amiodarone	IIa	C	other AAD
	Beta-blockers	IIb	C	ineffective
	Verapamil, diltiazem	III	C	
	Digoxin	III	C	
Single or infrequent AVRT (without pre-excitation)	Vagal manoeuvres	I	B	
	'Pill in the pocket'	I	B	
	Verapamil, diltiazem	IIa	B	
	Beta-blockers	IIb	B	
	Catheter ablation	IIb	C	
	Sotalol, amiodarone	III	C	
	Flecainide, propafenone	I	C	
	Digoxin	IIa	B	
Pre-excitation without symptoms	None catheter ablation			

Modified from the ESC/AHA/ACC guidelines for the management of patients with supraventricular arrhythmias[117] and 2017 EHRA consensus document.[115] In the 2017 EHRA consensus document, sotalol is not included among drugs recommended for treatment of WPW syndrome with pre-excitation and well-tolerated symptomatic arrhythmias or poorly tolerated AVRT without pre-excitation. However, for the latter, amiodarone may be used if other AADs are ineffective.
AF, atrial fibrillation; AVRT, atrioventricular re-entrant tachycardia; WPW, Wolff–Parkinson–White.

Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) and RACE trials.[190] Since then, lenient rate control is a reasonable initial approach, with more aggressive rate control recommended in the case of persistence of symptoms or deterioration of left ventricular function.

Pharmacological rate control strategies rely on agents prolonging AV node refractoriness including beta-blockers, non-dihydropyridine calcium channel antagonists, digitalis, and amiodarone alone or in combination.[188] Acute rate control can be achieved by intravenous drugs administration, shifting towards oral formulations for long-term management.

Depending on patients' comorbidities, BB or non-dihydropyridine calcium channel antagonists monotherapy should be used as first choice (*Figure 7*). Non-dihydropyridine calcium channel antagonists are not recommended in patients with significant left ventricular systolic dysfunction because of their negative inotropic effect.[192] Digitalis alone is ineffective in controlling ventricular rate during exertion and its use should be considered in combination with beta-blockers or calcium channel antagonists in patients failing to achieve rate control with monotherapy. Amiodarone may slow the ventricular rate in haemodynamically unstable patients, especially in the acute setting. It may be also used for chronic treatment, but its side effects limit long-term tolerability. Dronedarone should not be used for rate control in patients with permanent AF because of safety concerns.[184]

In patients with pre-excited AF, agents acting primarily on the AV node (e.g. or calcium channel antagonists, digitalis) may paradoxically increase the ventricular rate increasing the risk of haemodynamic compromise and ventricular fibrillation.[193] In this specific scenario, agents prolonging the anterograde refractory period of the accessory pathway, such as Class I AADs (e.g. flecainide, propafenone, procainamide) should be used for rate control and may achieve cardioversion. Class III AADs (e.g. amiodarone) may be used as second-line treatment, especially in patients with left ventricular systolic dysfunction, given the potential for proarrhythmia.[194]

Ventricular arrhythmias

The acute management of VT includes the use of beta-blocker therapy and typically the use of AADs such as amiodarone, lidocaine and procainamide intravenously. The amiodarone i.v. protocol for acute suppression of VT includes 150 mg over 10 min, followed by 1 mg/min for 6 h, then 0.5 mg/min for 18 h; the maintenance dose is 0.5 mg/min.

Antiarrhythmic drugs therapy for the prevention of SCD due to ventricular tachyarrhythmias has not been shown to be effective in randomized controlled clinical trials, and therefore should be considered as adjunct therapy to ICD or catheter ablation. Most patients with ventricular arrhythmias have structural heart disease, and therefore pharmacologic treatment is limited to amiodarone, sotalol, or

Table 12 Recommendations for treatment of focal atrial tachycardias

Clinical situation	Recommendation	Classification	Level of evidence	EHRA consensus
Acute treatment				
* *Conversion*				
haemodynamically unstable	DC cardioversion	I	B	
haemodynamically stable	Adenosine	IIa	C	
	Beta-blockers	IIa	C	
	Verapamil, diltiazem	IIa	C	Not included
	Procainamide	IIa	C	
	Flecainide, propafenone	IIa	C	
	Amiodarone, sotalol	IIa	C	Ibutilide
* *Rate regulation*				
	Beta-blockers	I	C	
	Verapamil, diltiazem	I	C	Not included
	Digoxin	IIb	C	
Long term treatment				
Recurrent symptomatic AT	Catheter ablation	I	B	
	Beta-blockers,	I	C	
	Ca^{++}-channel blockers	I	C	
	Disopyramide*	IIa	C	Not included
	Flecainide *	IIa	C	
	propafenone *	IIa	C	
	Sotalol, amiodarone	IIa	C	
Any incessant AT	Catheter ablation	I	B	Not included
Nonsustained and asymptomatic	No therapy	I	C	
	Catheter ablation	III	C	

Based and modified from ESC/AHA/ACC guidelines for the management of patients with supraventricular arrhythmias[114] and 2017 EHRA consensus document[112]. All drugs for acute treatment are to be given intravenously. Excluded are patients with multifocal atrial tachycardia in whom beta-blockers and sotalol are often contraindicated due to severe pulmonary disease.
AT, atrial tachycardia; DC, direct current; *, should not be used unless they are combined with an AV-nodal blocking agent.

other AAD in conjunction with ICD.[195] Side effects, interactions, and proarrhythmic risk have to be taken into account. In patients with an ejection fraction ≤35–40%, ICD therapy has been shown to reduce mortality when compared to AADs. In patients with monomorphic VT, catheter ablation has evolved as alternative treatment and results in a significant reduction of VT recurrences.[196]

Idiopathic ventricular tachycardia

Patients suffering from VT arising from the right ventricular outflow tract, the left ventricular fascicular system or the mitral annulus, may respond to beta-blockade and or non-dihydropyridine-calcium channel blockers (i.e. verapamil or adenosine sensitive tachycardias). In patients not responding to conventional beta-blocker therapy, sotalol, flecainide, mexiletine, propafenone, or amiodarone may be used as alternative treatments. As idiopathic VT can be successfully treated by catheter ablation in the majority of cases, usually patients will undergo the procedure having failed beta-blockade.

Ventricular tachycardia in structural heart disease

Although beta-blockers are considered the mainstay of AAD therapy, their efficacy is low in preventing monomorphic sustained VT. Combined amiodarone and beta-blocker therapy, and sotalol monotherapy, were both superior to beta-blockade in the Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) trial in reducing ICD shocks.[52] Sotalol was more effective than other antiarrhythmics in suppressing VT in patients with arrhythmogenic cardiomyopathy. Amiodarone has been shown to reduce ICD interventions when used for secondary prevention.

Polymorphic ventricular tachycardia and ventricular fibrillation in patients with structural heart disease without QT prolongation

In PVT QRS morphology changes from beat to beat because of the different sequence of the ventricular activation. The PVT which occurs in the setting of normal QT interval is distinct from that which occurs in the setting of QT prolongation; the last, called TdP, is characterized by QRS morphology which is twisting around the isoelectric line. Not only the ECG appearance but also the management is different between the two forms. The PVT often degenerates into VF in which the ventricular activation is chaotic, and QRS morphology is identified with difficulty. Recurrent PVT or VF (called 'electrical storm' when occurring within a short period of time) are often indicators of acute ischaemia or incomplete reperfusion. Pharmacological suppression with beta-blockers, amiodarone (150–300 mg i.v. bolus), or lidocaine is

Table 13 Antiarrhythmic drugs currently used for cardioversion of atrial fibrillation

Drug	Administration route	Initial dose for cardioversion	Further dosing for cardioversion	Acute success rate and expected time to sinus rhythm	Contraindications/Precautions
Flecainide[a]	Oral[b] i.v.	200–300 mg 1.5–2 mg/kg over 10 min	—	Overall: 59–78% (51% at 3 h, 72% at 8 h[118])	Should not be used in ischaemic heart disease and/or significant structural heart disease May induce arterial hypotension, atrial flutter with 1:1 conduction (in 3.5–5.0% of patients), QT prolongation
Propafenone[a]	Oral[b] i.v.	450–600 mg 1.5–2 mg/kg over 10 min	—	Oral: 45–55% at 3 h, 69–78% at 8 h[119]; i.v.: 43–89% Up to 6 h	Should not be used in ischaemic heart disease and/or significant structural heart disease May induce arterial hypotension, atrial flutter with 1:1 conduction (in 3.5–5.0% of patients), mild QRS widening
Amiodarone[a]	i.v.	5–7 mg/kg over 1–2 h	50 mg/h (maximum 1.2 g for 24 h)	44% 8–12 h to several days[120–122]	May cause phlebitis (use a large peripheral vein, avoid i.v. administration >24 h and use preferably volumetric pump) May cause arterial hypotension, bradycardia/AV block
Ibutilide[c]	i.v.	1 mg over 10 min 0.01 mg/kg for a body weight of < 60 kg	1 mg over 10 min (10–20 min after the initial dose)	31–51% (AF) 63–73% (Afl) ≈1 h[123]	Should not be used in patients with prolonged QT, severe LVH or low LVEF Should be used in the setting of a cardiac care unit as it may cause QT prolongation, polymorphic VT/TdP ECG monitoring for at least 4 h after ibutilide administration to detect a proarrhythmic event[92]
Vernakalant[b]	i.v.	3 mg/kg over 10 min	2 mg/kg over 10 min (10–15 min after the initial dose)	<1 h (50% conversion within 10 min)	Should not be used in patients with arterial hypotension (SBP < 100 mmHg), recent ACS (within 1 month), NYHA III–IV HF, prolonged QT, or severe aortic stenosis May cause arterial hypotension, QT prolongation, QRS widening or non-sustained VT
Sotalol[d]	i.v.	1.5 mg/kg over 10 min	—	11–13%[124,125]	Should not be used in uncontrolled asthma, congenital or acquired long QT, cardiogenic shock, or uncontrolled HF Should be used with caution in reduced renal function (decreased clearance can result in drug accumulation and proarrhythmia)

The use of dofetilide for AF cardioversion is recommended by the US guidelines,[126] but not by the Canadian AF guidelines,[127] and the drug is not available in Europe.
AV, atrioventricular; HF, heart failure; i.v., intravenous; LVH, left ventricular hypertrophy; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; TdP, torsades de pointes; VT, ventricular tachycardia.
[a]Most frequently used for cardioversion of AF, available in most countries.
[b]May be self-administered by selected outpatients as a 'pill-in-the-pocket' treatment strategy.
[c]Not available in some countries.
[d]Rarely used for cardioversion of AF (not indicated in reference 8).

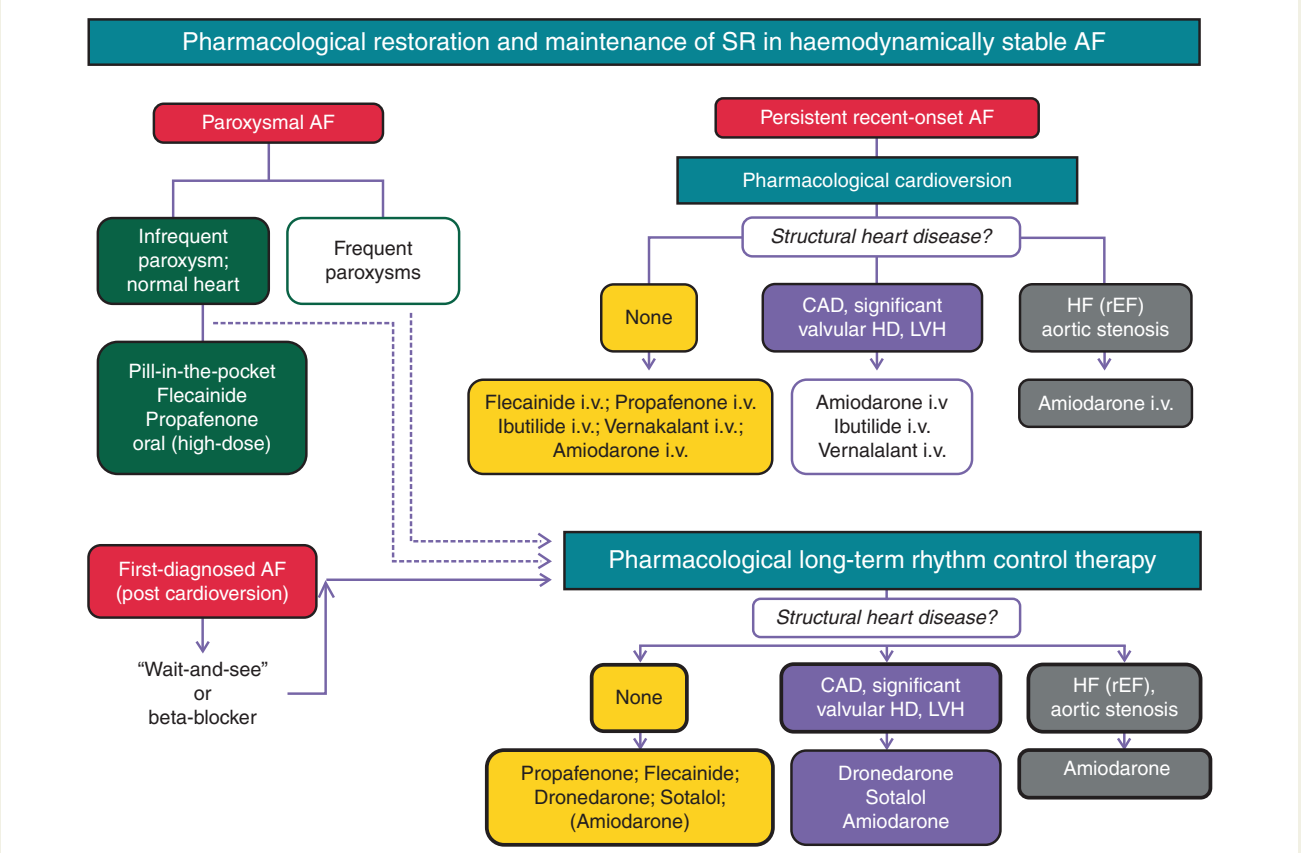

Figure 6 Pharmacological restoration and maintenance of sinus rhythm in AF patients. Colour code: yellow indicates minimal structural heart disease; violet indicates significant structural heart disease (including moderate HFrEF and HFpEF); grey indicates significant heart failure rEF (and significant aortic stenosis). AF, atrial fibrillation; CAD, coronary artery disease; HD, heart disease; LVH, left ventricular hypertrophy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; SR, sinus rhythm.

indicated for acute treatment.[7,51] Other AADs (e.g. flecainide, propafenone) are not recommended in this setting. Deep sedation, neuraxial modulation, mechanical ventilation, and catheter ablation are recommended in unstable patients non-responding to pharmacological therapy. Immediate coronary angiography is indicated when ischaemia is the cause.[197]

In all patients, the search for and correction of reversible causes (hypokalaemia, hypomagnesaemia, acute decompensated heart failure, and proarrhythmic drugs) are indicated. Hypomagnesaemia is typically associated with PVT and responds to intravenous magnesium. Short-coupled TdP is a rare variant of PVT affecting young patients with syncope of unclear origin and a positive family history for SCD.[198,199] Intravenous verapamil can suppress the arrhythmia. Catecholaminergic PVT is accompanied by PVT/bidirectional tachycardia responding to beta-blockers in addition to ICD. The addition of flecainide should be considered in patients who experience recurrent PVT or syncope while on beta-blocker, or in patients non-suitable for ICD implantation.[7] Brugada syndrome is also associated with PVT responding to quinidine (see 'Antiarrhythmic drug therapy in inherited arrhythmopathies and channelopathies' section).

Polymorphic ventricular tachycardia in patients with QT prolongation

Polymorphic VT in the presence of a QTc interval longer than 500 ms (or 480 ms[7]) is classified as TdP (after description of Dessertene, 1966) and is distinct from other PVT by the ECG appearance, mechanism, and therapy.[200] Torsade de pointes is triggered by the reduction in repolarization reserve, or by the increase in dispersion of repolarization,[201] as in genetic LQTS or in drug-induced TdP. Torsadogenic drugs differ significantly in their arrhythmic risk profile. Also, the patient's risk profile is important in deciding the risk–benefit ratio when indicating a drug with potential torsadogenic properties (see 'Safety issues for patients treated with antiarrhythmic drugs' section). Magnesium sulfate 2 g i.v. is the first-line therapy for patients with prolonged QTc and TdP, irrespective of the serum magnesium level.[200] A second dose can be necessary if TdP persists. The anti-torsadogenic mechanism of magnesium is poorly understood. As TdP is initiated after long pauses, prevention of pauses by increasing the heart rate above 70 b.p.m. may be attempted using temporary pacing. Increasing heart rate with isoproterenol or repletion of potassium to serotherapeutic levels (4.5–5 mmol/L)[200] can be considered, with less evidence for their recommendation.

Table 14 Antiarrhythmic drugs currently used for rhythm control in atrial fibrillation

Drug	Dose	Efficacy[a]	Precautions[b]	Comments	References
Amiodarone	3 × 200 mg daily over 4 weeks, 2 × 200 mg another 4 weeks, then 200 mg daily	>65%	Concomitant use with other QT prolonging drugs Concomitant use with VKAs or digitalis (their dose should be reduced), Increased risk of myopathy when used with statins Should be discontinued in case of excessive QT prolongation (>500 ms).	Requires regular surveillance for liver, lung and thyroid toxicity Has AV nodal slowing properties, but should not be used as monotherapy for rate control QT prolongation is common, but very rarely associated with TdP (<0.5%)[143]	135, 138, 144–150
Flecainide Flecainide Slow Release	100–200 mg b.i.d., or 200 mg once daily (Flecainide SR)	70–80%	Should not be used in patients with CrCl < 50 mL/min, significant liver disease, ischaemic heart disease or reduced LV systolic function, LVH > 14 mm Should be discontinued in case of QRS widening >25% above baseline	May increase atrial flutter cycle length, thus promoting 1:1 AV conduction and increasing ventricular rate	150–158
Propafenone Propafenone SR	150–300 mg three times daily, or 225–425 mg b.i.d. (Propafenone SR)	65–75%	Should not be used in patients with significant renal or liver disease, ischaemic heart disease, reduced LV systolic function, or asthma Should be discontinued in case of QRS widening >25% above baseline	May increase atrial flutter cycle length, thus promoting 1:1 AV conduction and increasing ventricular rate	42, 148, 150, 154, 155, 159–164
Dronedarone	400 mg b.i.d.	36%	Should not be used in NYHA Class III–IV or unstable HF, in combination with QT prolonging drugs or with strong CYP3A4 inhibitors (e.g. verapamil, diltiazem) and in patients with CrCl < 30 mL/min When used with digitalis or beta-blockers their dose should be reduced Should be discontinued in case of excessive QT prolongation (>500 ms)	A modest increase in serum creatinine is common and reflects drug-induced reduction in CrCl rather than a decline in renal function[165]	41, 166–169
Sotalol (D,L-racemic mixture)	80–160 mg b.i.d.	37–74%	Should not be used in patients with systolic HF, significant LVH, prolonged QT, asthma, hypokalaemia, CrCl < 30 mL/min Should be discontinued in case of excessive QT prolongation (>500 ms).	In patients with CrCl 30–60 mL/min should be dosed once daily[143] The potassium channel blocking effect increases with increasing dose and, consequently, the risk of ventricular proarrhythmia (TdP) increases	138, 144–147, 149, 160, 161, 163, 170–175
Disopyramide	100–400 mg two or three times daily (maximum 800 mg/24 h)	54%	Associated with increased 1 year of mortality[53] Should not be used in patients with a structural heart disease Rarely used for rhythm control in AF patients, due to increased mortality and frequent intolerance to side effects	May be useful in 'vagal' AF occurring in athletes or during sleep[143] Reduces LV outflow obstruction and symptoms in patients with HCM[176]	177–179

AV, atrioventricular; b.i.d., twice daily; CrCl, creatinine clearance; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; TdP, torsades de pointes; VKA, vitamin K antagonists.

[a]One year of rate of maintaining sinus rhythm.

[b]Caution is needed when using any AAD in patients with conduction system disease (e.g. sinoatrial or atrioventricular node disease).

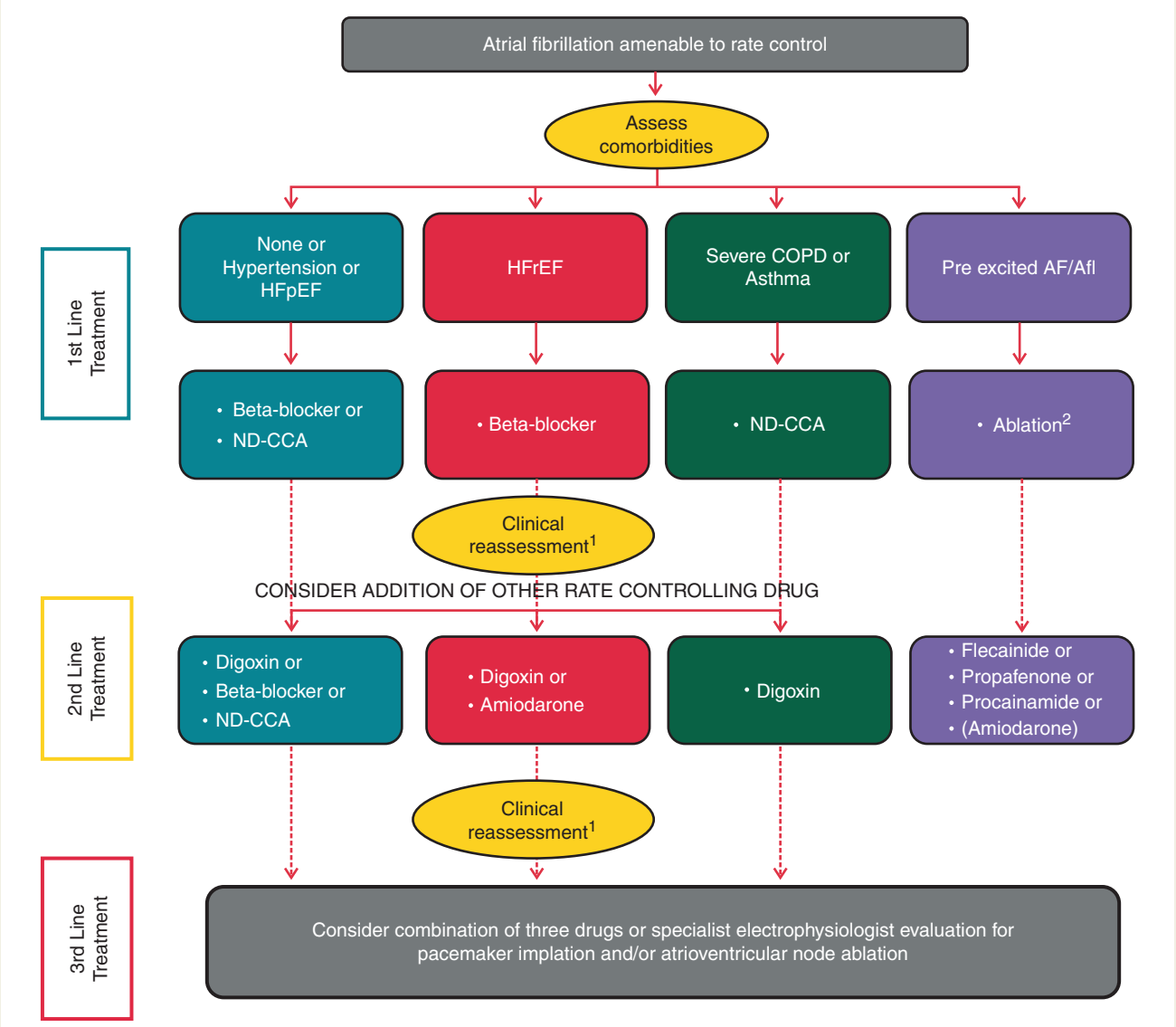

Figure 7 Medication for rate control inf atrial fibrillation (adapted from[191]). [1]Clinical reassessment should be focused on evaluation of resting heart rate, AF/flutter-related symptoms and quality of life. In the presence of suboptimal rate control (resting heart rate >100 b.p.m.), worsening of symptoms or quality of life consider second-line and, if necessary, third-line treatment options. [2]Ablation of the accessory pathway is the first-line therapy in patients with pre-excited AF/flutter; AAD should be reserved for acutely slowing of the heart rate (i.v. amiodarone should be used with caution because of the risk of increasing ventricular rate)[8] or in patients in whom ablation is not possible or are not willing to accept ablation therapy. AAD, antiarrhythmic drugs; AF, atrial fibrillation; Afl, atrial flutter; COPD, chronic obstructive pulmonary disease; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ND-CCA, non-dihydropyridine calcium channel antagonists.

Antiarrhythmic drug therapy to prevent sudden cardiac death in high-risk patients

Acute myocardial infarction and acute coronary syndrome

Prevention of SCD in patients with ACS is based on revascularization and beta-blockade. In patients with ACS without ventricular arrhythmias, prophylactic AAD treatment should not be administered.[202–204]

One unique situation in which prophylactic treatment with lidocaine might have a role is its use after cardiac arrest and successful resuscitation, where it has led to suppression of recurrent ventricular arrhythmias and improved survival.[205]

Early use of beta-blockers in the setting of ACS reduces mortality, and the incidence of ventricular arrhythmias and is therefore recommended.[203,206] Beta-blocker treatment is recommended particularly for

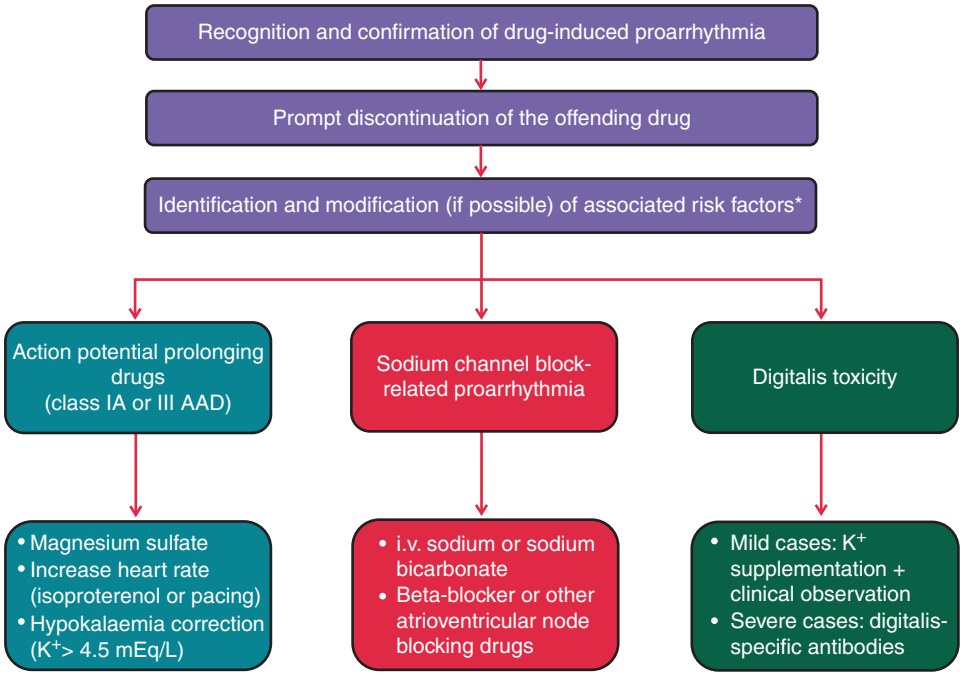

Figure 8 Algorithm for management of the proarrhythmic risk. *Associated risk factors include 'non-modifiable' risk factors (e.g. female gender, advanced age, renal or liver dysfunction, underlying structural/ischaemic heart disease, pre-existing channelopathies) and 'modifiable' risk factors (e.g. hypokalaemia, hypomagnesaemia, high drug doses/concentrations, rapid intravenous administration, bradycardia, QT prolongation, QT dispersion). AAD, antiarrhythmic drugs.

recurrent PVT. Correction of hypomagnesaemia and hypokalaemia may help in selected patients.[7]

Amiodarone may have the most balanced efficacy-to-risk profile, and should be considered only if episodes of VT or VF are frequent, and can no longer be controlled by successive electrical cardioversion or defibrillation.[7,207] A recent meta-analysis[208] confirmed that amiodarone decreases the SCD risk and represent a viable alternative in patients who are not eligible for, or who do not have access to ICD therapy. However, the effect on global mortality is neutral. The combined analysis of European Myocardial Infarct Amiodarone Trial (EMIAT) and Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT)[209] confirmed the positive antiarrhythmic interaction between amiodarone and beta-blockers in preventing SCD. Lidocaine may reduce the incidence of ventricular arrhythmias related to myocardial ischaemia, although no beneficial effect on early mortality has been demonstrated.[210] When compared to amiodarone for the treatment of ventricular arrhythmias complicating ACS, lidocaine may have a more favourable safety profile.[211]

Statin therapy reduces mortality in patients with coronary artery disease, mostly through prevention of recurrent coronary events, and is therefore part of the recommended routine medication.[212] Statin therapy also appears to be associated with a reduction in ICD shocks.[213]

Stable coronary artery disease after myocardial infarction with preserved ejection fraction

Evidence does not support the use of AADs for overall mortality reduction in patients with ventricular arrhythmias post-myocardial infarction and neither as prophylactic treatment in patients without demonstrable ventricular arrhythmias. The following statements apply for patients with stable coronary artery disease after myocardial infarction and with preserved ejection fraction:

- At present, only beta-blockers are recommended for the primary prevention of SCD in patients with stable coronary artery disease after myocardial infarction and with preserved ejection fraction. Beta-blockers improve survival in patients who have had myocardial infarction in part by reducing the incidence of SCD.[7]
- Amiodarone may be considered for relief of symptoms from ventricular arrhythmias in survivors of a myocardial infarction but it has no effect on mortality.[7,202]
- Therapy with sodium channel blockers (Class IC) should not be given to prevent sudden death in patients with coronary artery disease or who survived myocardial infarction.[7]

Left ventricular dysfunction, with or without heart failure

A substantial part of the survival benefit seen with beta-blockers in patients with heart failure is due to a significant reduction in SCD. Amiodarone may be considered for prevention of SCD, particularly in patients who cannot receive or do not have access to ICD therapy.[208] Amiodarone treatment should be considered to prevent recurrent VT. Ranolazine may have a role in the prevention and/or treatment of VT in patients with left ventricular dysfunction.[214,215] Optimization of heart failure therapy is

recommended in patients with left ventricular dysfunction and sustained VT.[202]

Angiotensin-converting enzyme (ACE) inhibitors improve survival in all stages of heart failure. However, there are conflicting data as to whether ACE inhibitors reduce SCD. Early clinical trials, before the advent of more modern therapies, including the ICD demonstrated significant reduction in SCD with ACE inhibitor therapy.[216] The aldosterone antagonists spironolactone and eplerenone significantly reduce overall mortality and SCD in patients with advanced heart failure.[217] They also reduce the frequency of ventricular premature beats and non-sustained VT.[218]

Consensus statements

Recommendations		References
Routine prophylaxis AAD treatment should not be recommended in patients with acute or chronic coronary artery disease except for beta-blockers after recent myocardial infarction		7
Revascularization, beta-blockade, statin therapy, and elimination of triggers (e.g. electrolyte imbalance) are the keystones of prevention of SCD in coronary artery disease. In addition, beta-blocker therapy is recommended particularly for recurrent polymorphic VT.		7
Lidocaine may reduce the incidence of ventricular arrhythmias related to myocardial ischaemia, although no beneficial effect on early mortality has been demonstrated. It should not be routinely used as for SCD prophylaxis		7
Amiodarone should be considered if episodes of VT or VF are frequent. It may be considered for prevention of SCD, particularly in patients who cannot receive or do not have access to ICD therapy		7, 208
Optimization of heart failure therapy is essential in patients with left ventricular dysfunction for prevention of SCD. Aldosterone antagonists (spironolactone and eplerenone) and possibly ACE inhibitors significantly reduce overall mortality and SCD in patients with advanced heart failure		7, 216, 217

AAD, antiarrhythmic drugs; ACE, angiotensin-converting enzyme; ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

Antiarrhythmic drug therapy in inherited arrhythmopathies and channelopathies

Antiarrhythmic drugs play a major role in the treatment of both arrhythmogenic diseases such as arrhythmogenic right ventricular cardiomyopathy (ARVC), hypertrophic cardiomyopathy as well as in ion channel diseases, since catheter ablation is associated with little or no success, and because electrical storm in these patients can only be controlled by AADs.[7,219]

Patients with ARVC are often well controlled with amiodarone or sotalol, since they suffer most frequently from recurrent monomorphic VT.

In patients with hypertrophic cardiomyopathy, the main problem is recurrent AF and/or flutter or recurrent VF, and amiodarone is the therapy of choice.[7,220,221]

In LQTS, there are reports on many different beta-blockers. The most frequently used drugs are propranolol, metoprolol, and bisoprolol. Nadolol, which is very efficient, is used infrequently because of its limited availability in many countries.[222,223] Mexiletine, flecainide, and ranolazine are effective for shortening QTc interval in LQT3 syndrome.[7,224]

In Brugada syndrome, quinidine is the therapy of choice as adjunct to an ICD or if a patient refuses an ICD, with reported favourable outcome. There is a large series of patients reported from Belhassen *et al.*, in whom Brugada syndrome patients had a very favourable outcome on quinidine without an ICD.[7,220,221]

In catecholaminergic PVT, beta-blockade is first line therapy and flecainide can be added with considerable success if beta-blockade does not suppress arrhythmias effectively.[7,225] There is evidence that nadolol is more effective in suppressing CPVT as compared to metoprolol.[226]

In the setting of an electrical storm accompanying early repolarization syndrome, short-QT syndrome, and Brugada syndrome, quinidine can be used. Additionally, isoproterenol infusion is recommended in Brugada syndrome.[7] The largest reported series of patients with Andersen-Tawil syndrome (LQT17 syndrome associating facial dysmorphism and hypo- or hyperpotassemic palsy), a rare entity, were treated with beta-blockers; a few patients were added flecainide.[227] *The reader is referred to 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death for detailed information.*[7]

Antiarrhythmic drugs as adjuvant to devices and arrhythmia interventions

Pacemakers and antiarrhythmic drugs

Pacemakers (PM) are usually indicated for patients with symptomatic or high-risk bradyarrhythmia. They may also be indicated when a mandatory antiarrhythmic or other medication causes significant chronotropic or dromotropic side effects.[61] Antiarrhythmic medications may be indicated in patients with PM when tachyarrhythmia is also present: tachy–brady variant of sick sinus syndrome, AF, other SVT (when ablation is not pursued), ventricular tachyarrhythmia

Table 15 Effect of antiarrhythmic medications on the pacing threshold

Effect	Antiarrhythmic drugs	Comments
Increase	Class IA	
	Class IC	Most commonly noted in clinical practice Neural and metabolic factors modulate the effect
No significant effect	Class IB	
	Class II	Except propranolol: i.v. administration may increase
	Class III	
	Class IV	

i.v., intravenous.

(frequent VPBs or VT/VF, when ICD implantation or ablation is not pursued).

Antiarrhythmic drugs blocking sodium channel currents may increase pacing thresholds and lead to loss of capture. Specifically, some type IA agents (quinidine, procainamide) and most type IC agents (encainide, flecainide, propafenone) increase the pacing threshold, especially at higher doses.[62,228] The change in QRS duration correlates with the amount of an increase in the stimulation threshold. Caution is advised in PM-dependent patients, when using these drugs, either a higher safety margin or automatic output regulation is recommended. These drugs may also slow down atrial tachyarrhythmia below the mode switch rate and may lead to inadvertent rapid ventricular pacing or affect device statistics.

Propranolol, a Class II agent, also has some sodium channel-blocking effect and can increase the stimulation threshold when administered intravenously.[229] Class IB (lidocaine, mexiletine), Class III (amiodarone), Class IV drugs (verapamil, diltiazem), and digoxin have negligible effect on the pacing threshold (*Table 15*).

Antiarrhythmic drugs in patients with implantable cardioverter-defibrillators

Among AAD therapies, amiodarone plus beta-blocker is effective for reducing ICD therapy,[52] though amiodarone adverse effects need to be appreciated. Sotalol is also effective,[230] but less than amiodarone plus a beta-blocker. Most AADs influence the defibrillation threshold (DFT). Since defibrillation failure due to drug-induced high DFT may result in SCD in ICD patients, it is important to consider if a prophylactic AAD therapy is needed, and when necessary, which drug should be selected.[231] However, as long as the interactions are appreciated and the modern ICD system and implantation techniques are applied, most AAD can be used safely (*Table 16*).

Table 16 Antiarrhythmic drugs for implantable cardioverter-defibrillator patients

Effect	Antiarrhythmic drugs	Comments
Prevention of ICD shock	Amiodarone plus beta-blocker	Reduced any ICD shock compared with β-blocker alone (HR 0.27; $P < 0.001$) and sotalol (HR 0.43; $P = 0.02$)[52] Reduced appropriate shock or arrhythmic death compared with a beta-blocker alone (HR 0.34; $P = 0.006$) and sotalol (HR 0.69; $P = 0.24$)[52]
	Sotalol	Tended to reduce any ICD shocks compared with β-blocker alone (HR 0.61; $P = 0.055$)[52] Reduced any-cause death or any-reason ICD shock compared with placebo (RR 0.52; $P < 0.001$)[230]
Influence on DFT	Class Ia AAD	Procainamide and disopyramide had no effect on DFT[231]
	Class Ib and Ic AAD	Lidocaine, flecainide, mexilitene, and moricizine increased DFT[231]
	β-blockers	Minimal effect on DFT[52]Decreased DFT ($P = 0.027$)[232]
	Amiodarone	Increased DFT ($P = 0.004$)[233]
	Amiodarone plus beta-blocker	Slightly increased DFT ($P = 0.091$), but the effect size with modern ICD systems is small[232]
	Sotalol	Decreased DFT ($P = 0.21$)[232]
	CCB	Diltiazem and verapamil increased DFT[231]

AAD, antiarrhythmic drugs; CCB, calcium channel blocker; DFT, defibrillation threshold; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; RR, relative risk.

Antiarrhythmic drugs following ablation therapy

Few randomized studies have investigated the impact of empirical AAD therapy after AF ablation on the occurrence of AF (*Table 17*). In the first randomized study which evaluated the effects of AAD after radiofrequency catheter ablation of AF, after 12-month follow-up, no significant difference was observed in the rates of AF recurrences, either in patients with paroxysmal or persistent AF, but AAD increased the proportion of patients with asymptomatic AF episodes.[234] The 5A study demonstrated that paroxysmal AF patients treated with AAD for 6 weeks after ablation were less likely to have AF recurrence than those treated

Table 17 Randomized trials of empirical antiarrhythmic drug therapy after ablation of atrial fibrillation on the recurrence rate

Study (year)	AF patients	Patients on AAD (*n*)	Follow-up	Early recurrences	Late recurrences	Key findings
Turco *et al.*[234]	64 PAF; 43 PersAF	Amiodarone: 38 Flecainide: 10 Propafenone: 3 Sotalol: 2	12 months	1 month 19/54 (35%) vs. 9/53 (17%); $P = 0.02$	1 year 18/53 (34%) vs. 16/54 (30%); $P = 0.63$	AAD only reduced AF recurrences during the run-in period
5A[236,237]	110 PAF	Sotalol: 19 Flecainide: 18 Propafenone: 14 Dofetilide: 2	6 months	6 weeks 13% vs. 28%; $P = 0.05$	6 months 15/53 (28%) vs. 16/57 (32%); $P = 0.84$	While short-term use of AAD decreased early recurrence of atrial arrhythmias, early use of AAD did not prevent arrhythmia recurrence at 6 months
Gu *et al.*[235]	123 PersAF	Propafenone + amiodarone: 62 Amiodarone: 35 Propafenone: 26	12 months	2 months 17/62 (27%) vs. 29/61 (48%); $P = 0.02$	1 year 21/62 (34%) vs. 22/61 (36%); $P = 0.8$	Extensive AAD use decreased early AT within the initial 2 months only
Darkner *et al.*[187]	212 PAF or PersAF	Amiodarone 8 weeks vs. placebo	6 months	3 months blanking	No significant difference vs. placebo at 6 months	Amiodarone reduced hospitalizations for arrhythmias and cardioversion

AT, atrial tachycardia; PAF, paroxysmal AF; PersAF, persistent AF.

with AV nodal blocking agents.[236] This demonstrated about a 50% reduction in the rate of recurrent AF in the first weeks after ablation.[236,237] Gu *et al.* investigated whether an early rhythm suppression strategy with extensive AAD in persistent AF after catheter ablation decreases arrhythmia recurrence at the 12-month follow-up.[235] There was no difference with regard to atrial tachyarrhythmias at 12 months between the groups. Initiation of AAD at discharge after catheter ablation has been shown to be associated with a significant reduction in readmission within 90 days (11.6% vs. 16.2%).[238] In unadjusted time to event analysis, amiodarone was associated with the greatest reduction in readmission whereas dronedarone, Class II agents, and Class IC agents had no statistically significant effect on readmission. Antiarrhythmic drugs were discontinued in 44.5% of patients at 3 months.

However, not all studies demonstrated a benefit of AAD therapy in patients who underwent catheter ablation. For instance, a retrospective, non-randomized, single-centre study of 274 ablation patients demonstrated no difference in the rates of early AF recurrence among those treated with an AAD or an AV nodal blocking agent alone.[239] Furthermore, 9 of the 185 patients treated with an AAD discontinued the medication due to side effects, suggesting the possibility of harm with an empiric AAD use strategy. According to the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of AF, the usefulness of initiation or discontinuation of AAD therapy following ablation for AF in order to improve long-term outcome is unclear.[240]

Consensus statements

Recommendations	References
Antiarrhythmic drugs may reduce arrhythmia recurrence and/or symptoms related to arrhythmia recurrence after catheter ablation	235–238

Safety issues for patients treated with antiarrhythmic drugs

Proarrhythmias: risk stratification and management

With the exception of beta-blockers, AADs have not been demonstrated to prevent life-threatening ventricular arrhythmias and SCD.[7,203] Controversial results have been presented with amiodarone. However, most AAD might cause proarrhythmia.[241,242] Flecainide, propafenone, and quinidine are contraindicated in patients with previous myocardial infarction because they increase mortality mostly because of proarrhythmias. Mexiletine and disopyramide should also be avoided in post-myocardial infarction patients. Dofetilide may provoke TdP in patients with severe heart failure. Amiodarone may also cause TdP although this is a very rare effect of the drug. Digitalis may

Table 18 Mechanisms promoting proarrhythmia

Drug–substrate interaction associated with proarrhythmia
- Left ventricular hypertrophy: sotalol, flecainide, and propafenone
- Myocardial infarction: sodium channel blocking agents (antiarrhythmic drugs but also tricyclic antidepressants)
- Other structural heart disease: sodium channel blockers
- Heart failure: dronedarone, dofetilide

Drug–drug interaction favouring proarrhythmia
- Inhibitors of potassium channels (e.g. some antibiotics [quinolones, azithromycin, erythromycin, clarithromycin]); inhibitors of renin-angiotensin system combined with antibiotics (e.g. cotrimoxazole), and hyperkalaemia
- Inhibitors of sodium-channels (e.g. tricyclic antidepressants)
- Cardiotoxics drugs (e.g. anthracycline)
- Toad venom
- Herbal products (e.g. foxglove tea)

Factors facilitating proarrhythmia
- Female gender (women to men: 2:1–3:1; testosterone mainly regulates repolarization)
- Hypokalaemia (especially when potassium serum concentration <3.5 mmol/L)
- Rapid rise in extracellular potassium
- Hypomagnesaemia (magnesium <1.5 mg/dL)
- Bradycardia (<60/min)
- Recent conversion from AF with QT prolonging drugs
- Pacing
- Myocardial ischaemia
- Congestive heart failure
- Left ventricular hypertrophy
- Digitalis therapy (rare)
- Rapid intravenous administration of QT prolonging drugs
- Acquired or congenital QT prolongation
- Subclinical congenital LQTS (<10% of LQTS; incomplete penetrance)
- Ion channel polymorphisms (compound with QT prolonging drugs)

cause diverse arrhythmias [e.g. enhanced atrial and ventricular automaticity (including sustained ventricular arrhythmias), AV block]. In addition, several drugs (e.g. verapamil, diltiazem, beta-blockers, and digoxin) cause bradycardia and this situation may predispose to severe ventricular arrhythmias in some situations (e.g. hypokalaemia).[7,203,243]

Since polypharmacy is very often necessary, drug-drug interactions and their pharmacological consequences (especially QT interval modification) might become crucial (*Table 18*).[243] Therefore, careful ECG evaluation prior to and after the administration of the drug is mandatory.[244] Acquired LQTS and the resulting potentially lethal PVT in form of TdP is the most important drug-induced proarrhythmia because hERG K channel block (an important mediator of repolarization) is determined by many drugs at a clinical plasma concentration. However, other forms of drug induced rhythm disturbances, as bradycardia, may occur.[245] The reader is referred to several web-based tools for the list of the torsadogenic drugs (www.torsades.org; https://crediblemeds.org; www.longqt.org; www.sads.org). The list is very long, including almost all classes of drugs other than AAD: antianginal (e.g. bepridil), gastrointestinal (e.g. cisapride), anticancer agents, antimicrobial drugs (e.g. clarithromycin and erythromycin), neurologic, narcotics (e.g. methadone), and psychiatric (e.g. haloperidol and thioridazine). There is an individual (genetic) predisposition to proarrhythmia to a specific drug, the PD sensitivity, and vulnerability due to abnormal high plasma concentration of a drug given in therapeutic dosage. The PK sensitivity, is explained by the interference of a single metabolizing pathway (e.g. CYP 2D6 or CYP 3A4) with genetic factors or other drugs.[33] Administration of a drug can unmask a subclinical genetic abnormality; mutations of LQTS type were described in patients with acquired QTc prolongation and TdP presenting with a normal QTc before administration of the culprit drug.

In patients at risk for TdP (see PD and PK sensitivity above and risk factors below) the QTc monitoring is recommended using the same ECG recording device and the same QTc formula before and after drug administration. This monitoring is appropriate in hospital settings.[200] The ECG signs indicative for TdP risk include QT prolongation with more than 60 ms from baseline, QTc prolongation >500 ms, T–U wave distortion exaggerated after a pause, macroscopic T wave alternans, new-onset ventricular ectopy and non-sustained TdP initiated by the beat after a pause.

Treating proarrhythmias

Effective treatment requires the accurate recognition/confirmation of drug-induced proarrhythmia and prompt discontinuation of the implicated agent (*Figure 8*). Important are also the identification and modification (whenever possible) of risk factors potentially associated with arrhythmia onset or worsening (e.g. female gender, advanced age, renal or liver dysfunction, underlying structural/ischaemic heart disease, hypokalaemia, hypomagnesaemia, high drug doses/concentrations, rapid intravenous administration, bradycardia, QT prolongation, QT dispersion, and pre-existing channelopathies).

In the case of drug-related proarrhythmia, the first-line of management is to stop the offending drug; however, in selected cases, the implantation of ICD needs to be considered based on the individual characteristics of the patient and the future risk of life-threatening ventricular tachyarrhythmias.[7,203]

Treatment of drug-induced TdP, commonly seen in association with Class IA or Class III AAD, involves the following:

- intravenous administration of magnesium sulfate[246] irrespective of serum magnesium levels (i.e. 2 g bolus followed by another 2 g bolus and by continuous infusion in case of arrhythmia persistence);
- increasing heart rate (to reverse bradycardia and to prevent pauses that may prolong repolarization and promote TdP) by means of isoproterenol or overdrive pacing at rates >70 beats per minute[247,248];
- correction of hypokalaemia, replenishing serum potassium to the high-normal range (i.e. 4.5–5.0 mEq/L) although the evidence to support this practice is limited.[203]

Sodium channel blocker-related proarrhythmia, generally secondary to slowing of conduction, include atrial flutter with 1:1 AV conduction and incessant slow VT. Besides discontinuation of the

Table 19 Cardiac effects, extracardiac toxicities, and contraindications for antiarrhythmic drugs

Agent	Cardiac effects	Extracardiac toxicities	Cardiac cautions and contraindications
Class IA			
Procainamide	Torsade de pointes	Lupus-like syndrome; agranulocytosis; hypersensitivity reactions	Prolonged QT interval; LVH
Disopyramide	Torsade de pointes; congestive heart failure; negative inotropic effects	Glaucoma; urinary retention; hypoglycaemia	LVH, HF
Quinidine	Torsade de pointes; increased AV node conduction; syncope	Hypersensitivity reactions	LVH, HF
Class IC			
Flecainide Propafenone	Ventricular tachycardia; Conversion of AF to wide complex flutter with 1:1 AV conduction in structurally normal heart; congestive heart failure; negative inotropic effects		Ischaemic or structural heart disease
Class III			
Dofetilide	Torsade de pointes		Prolonged QT interval; LVH
Amiodarone	Torsade de pointes (infrequent)	Pulmonary toxicity; hypothyroidism; hepatic toxicity; corneal deposits; optic neuropathy; skin discoloration	
Sotalol	Torsade de pointes; congestive heart failure; bradycardia; hypotension; mild negative inotropic effects	Exacerbation of chronic obstructive lung disease; bronchospasm; fatigue	LVH
Dronedarone	Possible exacerbation of advanced heart failure		Advanced heart failure

AV, atrioventricular; HF, heart failure; LVH, left ventricular hypertrophy.

offending drug, management is based on control of the ventricular response by intravenous beta-blocker or calcium antagonist whereas incessant slow VT can be reversed by intravenous administration of sodium or sodium bicarbonate.[249]

Beta-blockers have been reported to be effective in treating ventricular arrhythmias related to flecainide.[250]

In milder cases, arrhythmias due to digitalis toxicity can be managed by discontinuation of the drug, potassium supplementation, and observation. For digitalis-induced life threatening arrhythmias, several AAD have been proposed in the past (e.g. phenytoin,[251] lidocaine, and beta-blockade). More recently, digitalis-specific antibodies have proven effective in reversing digitalis toxicity by rapidly binding to and acutely lowering serum digitalis.[252] Isoproterenol infusion or cardiac pacing is usually effective when symptomatic bradyarrhythmias secondary to conduction abnormalities occur.

Organ toxicity and other safety aspects

The pharmacological management of AF and other arrhythmias requires careful consideration from a safety perspective (*Table 19*). The full profile of potential cardiac effects should therefore be considered for each AAD and carefully tailored to the individual patient history before treatment is initiated.[253] Amiodarone is widely used, and it interferes with thyroid function (because of iodine content). Amiodarone treatment may result in elevation of TSH and, subsequently, a serum T4 and free T4 concentration increase (by >50%), while T3 concentration decreases; therefore, an increase in T4 alone does not constitute an evidence of hyperthyroidism. After 3 months of amiodarone therapy, T4 and free T4 may return to the upper normal limit, T3 returns to lower normal limit and TSH returns to normal.[254] The thyroid tests normalize after more than 2 months following drug discontinuation. Thyroid function tests should be evaluated at baseline and every 6 months during amiodarone therapy.[133,181] Positive antithyroid peroxidase antibodies are markers of risk for the development of amiodarone-induced hypothyroidism (AIHT).

Not only thyroid tests can be modified, but, also, hyopthyroidism or hyperthyroidism can be induced. Amiodarone-induced hypothyroidism usually develop in patients with underlying thyroid abnormalities.[254] The diagnosis of AIHT is confirmed by elevated TSH in combination with normal or low free T4 and the clinical manifestations are not different from other forms of hypothyroidism. Stopping amiodarone or adding hormone replacement, are acceptable strategies in AIHT. Amiodarone-induced thyrotoxicosis is encountered mainly in the regions with insufficient iodine intake and it is more prevalent in men. Type 1 amiodarone-induced thyrotoxicosis occurs in patients with abnormal thyroid function, whereas Type 2 is a direct consequence of amiodarone. Inflammatory markers (IL-6) are markedly elevated in Type 2 amiodarone-induced thyrotoxicosis and thyroid autoantibodies are typically present in Type 1. Amiodarone should be stopped in amiodarone-induced thyrotoxicosis. In Type 1 amiodarone-induced thyrotoxicosis, prophylactic thyroid ablation (thyroidectomy or radioactive iodine) following the restoration of

the normal thyroid function is recommended.[254] Dronedarone (as a non-iodinated derivative) can replace amiodarone with fewer thyroid adverse reactions. However, Dronedarone is less effective than amiodarone and has itself adverse effects discussed in previous sections. Pulmonary fibrosis occurs in ~1–4% of patients and can be potentially life-threatening in severe cases. Periodic monitoring of lung function is required, and amiodarone should be avoided in patients with impaired pulmonary function.

Consensus statements

Recommendations		References
Proarrhythmias are life-threatening side effects of AADs. When initiating AAD therapy, the individual risk–benefit should be assessed, especially in patients with structural heart disease and taking other potential torsadogenic drugs*		241–243
Before initiating AAD therapy, individual risk for torsade de pointes tachycardia can and should be assessed (*Table 18*)		243, 244
Monitoring of ECG signs indicative for torsade de pointes tachycardia is appropriate when AAD therapy is initiated in patients at risk in hospital settings		200, 244
Discontinuation of the offending drug, prompt administration of magnesium sulfate, increase in heart rate, and close ECG monitoring in hospital settings with available defibrillators are the recommended actions in the case when TdP is imminent		7, 203, 246
Thyroid function should be assessed before initiation of amiodarone therapy and reassessed after 6 months during amiodarone therapy		254
Amiodarone should be stopped in amiodarone induced thyrotoxicosis*		254

Supplementary material

Supplementary material is available at *Europace* online.

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