Practical Compendium of Antiarrhythmic Drugs: A Clinical Consensus Statement of the European Heart Rhythm Association of the ESC

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Abstract

The EHRA Practical Compendium of Antiarrhythmic Drugs (AADs) offers advice on these drugs, focusing on their clinical use and the global impact of cardiac arrhythmias. This document aims to provide practical instructions to clinicians in arrhythmia management through pharmacological strategies.

The compendium highlights persistent challenges in arrhythmia treatment, including clinical constraints, procedural risks, and the complexity of certain arrhythmias. Notably, atrial fibrillation is highly prevalent, and the demand for invasive treatment often surpasses the capacity of existing healthcare systems. As a result, pharmacological management remains essential. This is particularly relevant for patients with cardiac implantable electronic devices or channelopathies, where ablation is often not a suitable option. AADs play a pivotal role in these scenarios.

The compendium introduces the ABC framework for AAD therapy: A (Appropriate therapy), for patients in whom AADs are the best therapeutic option, B (Backup therapy), as adjunctive treatment to invasive procedures, such as catheter ablation, and C (Complementary therapy), in combination with other therapies.

The document provides detailed insights into the mechanisms of action, efficacy, safety profiles, and drug interactions of each class of AADs.

Additionally, the compendium covers practical considerations, including initiation, combination strategies, monitoring, follow-up, special populations, and adverse effect management, with an emphasis on proarrhythmia risk mitigation. It also explores the integration of AADs with other therapeutic modalities, promoting a synergistic approach to optimize patient outcomes.

In summary, this compendium serves as an indispensable resource for clinicians, offering practical advice and evidence-based insights to navigate the complexities of arrhythmia management effectively.

Table of contents

Adenosine
Class IV
Verapamil and Diltiazem
Bepridil

Treatment by arrhythmias

General

Arrhythmia prevention

Atrial arrhythmias
Premature atrial contractions and focal atrial tachycardia
Inappropriate sinus tachycardia
Multifocal atrial tachycardia
Atrial flutter/macroreentrant atrial tachycardia
AF
AF after cardiac surgery
Autonomic AF
Aberrant conduction versus ventricular proarrhythmia
AADs for AF
Paroxysmal supraventricular tachycardias (PSVT)
Atrioventricular nodal re-entrant tachycardia (AVNRT)
Atrioventricular re-entrant tachycardia
Ventricular arrhythmias
Idiopathic PVCs and VT
PVCs and structural heart disease
VT and structural heart disease
Ventricular fibrillation

Tachycardia termination

AF (Oral – PITP)
AF (Intravenous)
Atrial flutter
Paroxysmal SVT
Focal atrial tachycardia
Junctional ectopic tachycardia
Ventricular tachycardia – Non-SHD
Ventricular tachycardia - SHD
Polymorphic VT and ventricular fibrillation

Practical aspects

Initiation of AAD

Follow-up and monitoring of patients on AADs

ECG antiarrhythmic drug effects

AAD tests for electrophysiological evaluation

Proarrhythmia

Sinus bradycardia and arrest
AV block
New onset, sustained, monomorphic VT
Increased frequency of sustained VT
Incessant VT
Torsades de pointes (TDP)
Atrial proarrhythmia
Brugada mechanism

Toxicity and adverse effects

Amiodarone-induced thyrotoxicosis
Amiodarone-induced pulmonary and other systemic toxicities
Quinidine systemic toxicities

Abbreviations and acronyms[a]

AADs	Antiarrhythmic drugs
ACC	American College of Cardiology
ACE	Angiotensin-converting-enzyme
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AFL	Atrial flutter
AHA	American Heart Association
AIH	Amiodarone-induced hypothyroidism
AIT	Amiodarone-induced thyrotoxicosis
AIT 1	Type 1 amiodarone-induced thyrotoxicosis
AIT 2	Type 2 amiodarone-induced thyrotoxicosis
cAMP	Cyclic adenosine monophosphate
AP	Action potential
APD	Action potential duration
APD90	Action potential duration at 90% repolarization
Arg	Arginine
ARVC	Arrhythmogenic right ventricular cardiomyopathy
AT	Atrial tachycardia
ATP	Adenosine triphosphate
AV	Atrioventricular
AVNRT	Atrioventricular nodal re-entrant tachycardia
AVRT	Atrioventricular re-entrant tachycardia
β-blocker	Betablocker
BBB	Bundle-branch block
BrS	Brugada syndrome
Ca^{2+}	Calcium
CA	Cardiac arrest
CAD	Coronary artery disease
Cav	Calcium channel
CCB	Calcium channel blocker
CI	Confidence interval
CNS	Central nervous system
CPVT	Catecholaminergic polymorphic ventricular tachycardia
CrCl	Creatinine clearance
CVD	Cardiovascular disease
CYP	Cytochrome P450
DADs	Delayed afterdepolarizations
DC	Direct current
DFT	Defibrillation threshold
DOAC	Direct oral anticoagulant
EADs	Early afterdepolarizations
ECG	Electrocardiogram
EMA	European Medicines Agency
EP	Electrophysiology
ERP	Effective refractory period
ERS	Early repolarization syndrome
ES	Electrical storm

ESC	European Society of Cardiology
FDA	Food and Drug Administration
GDMT	Goal directed medical therapies
Gly	Glycine
GMP	Guanosine monophosphate
GTP	Guanosine triphosphate
HCM	Hypertrophic cardiomyopathy
HCN	Hyperpolarization and cyclic nucleotide-gated
HDAC6	Histone deacetylase 6
hERG	Human ether-a-go-go-related gene
HF	Heart failure
HFpEF	Heart failure preserved ejection fraction
HFrEF	Heart failure reduced ejection fraction
HR	Hazard ratio
HRS	Heart Rhythm Society
IAST	Inappropriate sinus tachycardia
ICD	Implantable cardioverter defibrillator
$I_{Ca,L}$	L-type calcium current
I_f	Funny current
$I_{K,ACh}$	Acetylcholine-activated potassium current
I_{Kr}	Rapid delayed rectifier potassium current
I_{Ks}	Slow delayed rectifier potassium current
I_{Na}	Sodium current
$I_{Na,L}$	Late sodium current
$I_{Na,P}$	Peak sodium current
I_{to}	Transient outward potassium current
i.v.	Intravenous
IVF	Idiopathic ventricular fibrillation
JET	Junctional ectopic tachycardia
K^+	Potassium
K_{ATP}	ATP-dependent potassium
Kv	Potassium channel
LBBB	Left bundle-branch block
LQTS	Long QT syndrome
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
Na^+	Sodium
Nav	Sodium channel
NO	Nitric oxide
NSAT	Non-sustained atrial tachycardia
NYHA	New York Heart Association
P	P value
PFTs	Pulmonary function tests
P-gp	P-glycoprotein
PAC	Premature atrial contraction
PD	Pharmacodynamics
PITP	Pill-in-the-pocket
PK	Pharmacokinetics
PKA	Protein kinase A

PM	Pacemaker
PO	*Per os*, oral
PSVT	Paroxysmal supraventricular tachycardia
PV	Pulmonary veins
PVC	Premature ventricular contraction
PVT	Polymorphic ventricular tachycardia
QRS	QRS complex
QT	QT interval
QTc	Corrected QT interval
RMP	Resting membrane potential
RyR2	Ryanodine receptor 2
RVOT	Right ventricular outflow tract
SA	Sinoatrial
SERCA2a	Sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2a
SCD	Sudden cardiac death
SCN5A	Sodium channel protein type 5 subunit alpha
SGLT2i	Sodium-glucose co-transporter-2 inhibitors
SHD	Structural heart disease
SK or KCa2	Small-conductance calcium-activated potassium channel
SN	Sinus node
SND	Sinus node dysfunction
SQTS	Short QT syndrome
SR	Sinus rhythm
ST	ST segment
SVT	Supraventricular tachycardia
T2DM	Type 2 diabetes mellitus
T3	Triiodothyronine
T4	Thyroxine
TASK1 or K2P3.1	TWIK-related acid-sensitive potassium channel 1
TdP	Torsades de pointes
TSH	Thyroid stimulating hormone
VA	Ventricular arrhythmia
VF	Ventricular fibrillation
VT	Ventricular tachycardia
VW	Vaughan Williams
WPW	Wolff-Parkinson-White

[a]: *Table S1 provides a list of acronyms and summarized findings of the main trials on AADs.*

Introduction

Cardiac arrhythmias significantly impact global health. A definitive cure by invasive procedures has been pursued in the last decades. However, despite advances in invasive management by catheter ablation, challenges remain, such as anatomical limitations, procedural risks, and complex arrhythmias. In addition, the prevalence of some arrhythmic disorders limits the generalizability of invasive arrhythmia management. For example, atrial fibrillation (AF), the most common sustained arrhythmia, affects 1-2% of the population. Presently the demand for its invasive treatment commonly surpasses healthcare system capacity. In developed countries, only about 1% of AF patients currently receive ablation, with projections of it reaching only 10% in the foreseeable future due to limited resources and personnel.

Moreover, pharmacological management remains crucial for certain patients, either due to ablation failure or as part of periprocedural care. Antiarrhythmic drugs (AADs) are continued in approximately 50% of patients following index ablation, while one in six undergoes repeat ablation, with most receiving concomitant AAD therapy thereafter. These findings highlight that, in current clinical practice, rhythm control often relies on a combined approach integrating catheter ablation and AADs.[1] This is also especially relevant for patients with cardiac implantable electronic devices who experience recurrent arrhythmias, where AADs play a critical role in prevention. Conditions such as channelopathies, which are often unsuitable for ablative therapy, also necessitate the use of AADs. Additionally, the acute management of arrhythmias in emergency settings underscores the crucial role of these medications. The current indications for AADs can be summarized by the acronym ABC, as shown in **Box 1**.

Given these complexities, there is a clear need for appropriate, backup and complementary strategies, placing AADs at the forefront as essential components in managing arrhythmias. To address this, EHRA gathered international experts to create a practical compendium on AAD use, overseen by two chairs. The chairs planned the outline of the compendium, and each expert was tasked with reviewing the medical literature of a specific section. These reviews were later discussed by the entire group, and the final text underwent an external review by an independent group of experts.

This practical compendium systematically navigates the intricate landscape of AADs, elucidating their mechanisms of action, efficacy, and safety profiles within the general population of patients with arrhythmias. Special attention is directed towards subpopulations with specific arrhythmia mechanisms or characteristics that may influence AAD efficacy and safety. The compendium aims to provide clinicians with a comprehensive understanding of these mechanisms, empowering them to make informed decisions in the complex arena of cardiac arrhythmias. Furthermore, this compendium offers practical advice, providing insights into the judicious integration of these drugs into clinical practice. It highlights how AADs interact with other treatments like cardiovascular drugs, ablation, electrical cardioversion, and implantable devices. This unveils a synergistic approach that optimizes patient outcomes, ensuring a holistic and evidence-based strategy for rhythm management.

Box 1: ABC indications for the current use of AAD

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

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

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

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

Summary of advice

The EHRA Practical Compendium of AADs offers detailed advice on the usage, monitoring, and management of these medications in clinical practice. Key advice from the document include:

1. **Initiation of AADs**

In-hospital initiation is preferred for Class Ia AADs and some Class III drugs. Out-patient initiation with appropriate monitoring in patients without structural heart disease, is suitable for Class Ic agents, amiodarone, dronedarone, and ranolazine.

2. **Monitoring and follow-up**

Regular electrocardiography (ECG) monitoring is advised, especially in the first hours of AAD use, to detect rhythm disturbances, particularly with Class Ia and some Class III drugs.

Baseline and routine assessments, for example, visual, thyroid, liver, and pulmonary function tests are advised for amiodarone.

3. **Proarrhythmia risk management**

There is increasing awareness of proarrhythmic risks, particularly with Class I and III drugs. Monitoring for QT interval (QT) prolongation and avoiding concomitant use of QT-prolonging agents is essential.

It is important to educate patients about warning symptoms such as worsening palpitations, dizziness, or chest pain, and to provide guidance on lifestyle modifications to help avoid triggers, such as electrolyte imbalance.

4. **Special populations**

Specific advice is provided for the use of AADs in patients with structural heart disease (SHD), pregnant women, and paediatric patients. For instance, β-blockers are preferred during pregnancy, while it is advise to avoid some drugs like amiodarone and dronedarone due to potential foetal harm.

5. **Combination therapy**

Specific combinations, such as sotalol with flecainide or amiodarone with β-blockers, may be appropriate for resilient cases with careful monitoring of drug effects.

Combining AADs with other therapies such as ablation or CIEDs is advised to enhance efficacy and manage complex cases.

6. **Patient involvement and education**

Engaging patients in their treatment plan by educating them about the potential side effects and importance of adherence to therapy.

It is advised to integrate nurses and other healthcare professionals into the care team to support the safe administration and monitoring of AADs.

Overall, the compendium emphasises a tailored approach to AAD therapy, considering individual patient characteristics, underlying conditions, and potential risks to optimize outcomes in arrhythmia management.

Definition and principles of AAD mechanisms

AADs are pharmacological agents designed to prevent or correct cardiac arrhythmias by modulating the heart's electrical activity. This section explores their mechanisms of action, including their effects on ion channels, tissue specificity, and pharmacokinetics (PK), while also examining the role of genetics in influencing their efficacy and safety.

Mechanism of action of AADs

Arrhythmias primarily manifest through three key mechanisms: automatism, triggered focal activity due to early (EADs) or delayed afterdepolarizations (DADs), and re-entry. Among these, re-entry stands out as the most prevalent. This latter mechanism hinges on three main determinants crucial for its manifestation. Firstly, a trigger is essential to initiate the re-entrant electrical activity. This trigger could be an ectopic beat originating from a specific heart location not necessarily linked to the re-entrant circuit. Secondly, a re-entrant circuit is necessary, representing a pathway that allows the electrical impulse to circulate within the heart tissue, perpetuating the abnormal rhythm. Re-entry within the circuit is promoted by shorter refractoriness, slowed conduction (or a combination of the two) and unidirectional block. Lastly, the overall autonomic status plays a significant role in modulating the susceptibility to re-entry mechanisms. The interplay of sympathetic and parasympathetic influences on the heart's electrical properties can either enhance or mitigate the likelihood of arrhythmic events. Knowledge of these fundamental mechanisms and their interdependencies is paramount to understand the effect of AADs. It forms the basis for targeted interventions and tailored therapeutic strategies aimed at addressing the specific mechanisms underlying each patient's arrhythmic presentation. However, a comprehensive review of them[2–4] is beyond the scope of this practical compendium.

AADs exert their antiarrhythmic effect by modulating the electrophysiological determinants of automatism, triggered activity and re-entry. Class I AADs (see below “classification of AADs”) block cardiac Na^+ channels (Nav), reducing myocardial excitability and decreasing the likelihood of ectopic (triggered) activity.[5] They may also extend effective refractory period (ERP) by delaying cardiomyocyte recovery after repolarization, known as post-repolarization refractoriness. Some Class I AADs additionally prolong ERP through inhibition of rapid delayed rectifier potassium current (I_{Kr}) and other repolarization currents, causing action potential duration (APD) prolongation. Inhibition of I_{Kr} that leads to APD prolongation is also the primary mechanism of action of Class III AADs.[5] At the same time, the prolonged ERP will reduce the likelihood that triggering events encounter excitable tissue to initiate arrhythmias, decreasing the vulnerable substrate, thus explaining the role of these AADs in secondary prevention of both atrial and ventricular arrhythmias (VA). Class III AADs work mainly by inhibiting IKr, which prolongs APD. This extends ERP, making re-entry less stable and reducing the chance of persistent arrhythmias, justifying the use of Class I and III drugs for cardioversion.

Class II AADs have numerous indirect electrophysiological effects by reducing the β-adrenoceptor-dependent phosphorylation of numerous ion channels, Ca^{2+}-handling and myofilament proteins. The resulting reduction in ryanodine receptor 2 (RyR2) activity together with a smaller L-type calcium current ($I_{Ca,L}$) decreases the likelihood of DADs and EADs, and thus the likelihood of ectopic (triggered) activity.[6] Moreover, inhibition of β-adrenoceptor-

mediated regulation of hyperpolarization and cyclic nucleotide-gated (HCN) channels and L-type Ca^{2+} channels reduces automaticity in sinoatrial (SA) cells, providing a rationale for the use of Class II AADs for sinus tachycardia.[6] Similarly, inhibition of L-type Ca^{2+} channels, either indirectly by Class II AADs or directly by Class IV AADs, reduces the atrioventricular (AV) conduction rate, providing control of ventricular rate in atrial arrhythmias. Finally, the reduction in intracellular Ca^{2+} cycling due to $I_{Ca,L}$ inhibition, which underlies the negative inotropic effects of Class II and Class IV AADs, is also expected to reduce the likelihood of DADs. Thus, the primary mechanisms of action of AADs are inhibiting ectopic (triggered) activity (primarily Class I and II AADs), reducing the likelihood of re-entry (primarily Class I and III AADs), or modulating the regulation of impulse generation and conduction by the SA and AV nodes (primarily Class II and IV AADs).

Ion channel kinetics in cardiomyocyte membranes: fundamental states and use-dependence effects of AADs

Ion channels in cardiomyocyte membranes are essential for regulating cardiac action potentials and overall heart function. The kinetics of these ion channels and their fundamental states, along with the phenomena of use dependence and reverse use dependence, are key to understanding cardiac electrophysiology (EP) and the effects of AADs

Fundamental states of ion channels

Ion channels in cardiomyocytes typically exist in three primary states: resting (closed), activated (open), and inactivated closed (**Figure 1**).[7]

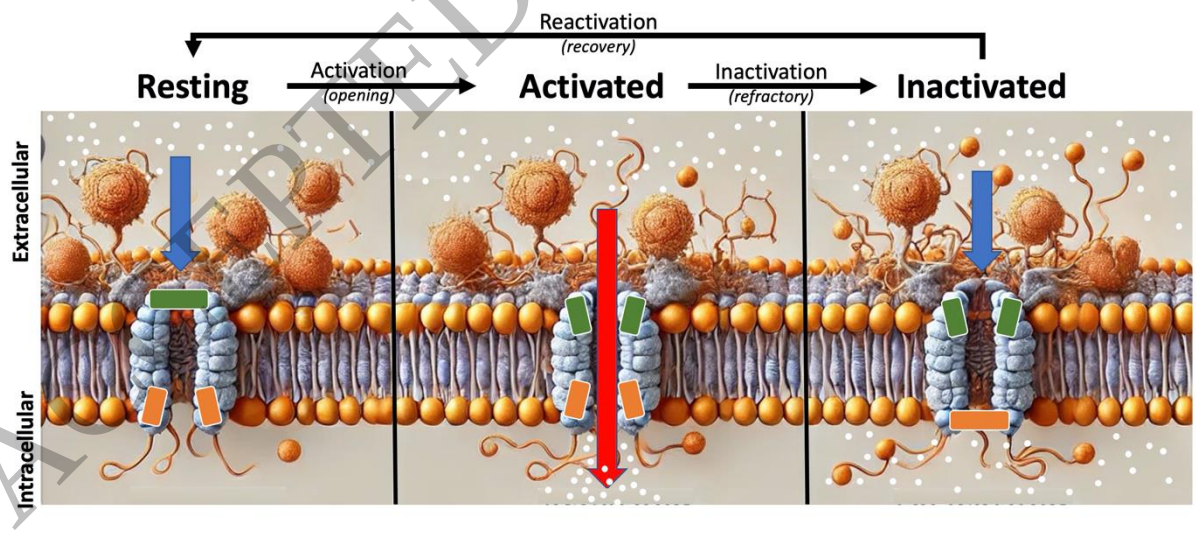

Figure 1: Schematic representation of the three main states (resting, activated and inactivated) of an ionic channel in the cellular surface membrane of a cardiomyocyte.

During the resting phase (left panel), the influx of ions into the cell is not possible (blue arrow) because the channel remains closed (green horizontal rectangles). Once the channel is activated (central panel), ions can enter the cell (red arrow) through the open channel (small oblique

rectangles). Following activation, the channel transitions to an inactivated state (right panel, orange horizontal rectangle), preventing further ion influx. Different antiarrhythmic drugs (e.g., flecainide) exhibit specific affinity and preferentially bind to particular states of the channel (e.g., the activated state).

1. **Resting state**: In the resting state, ion channels are closed, preventing ion flow across the membrane. This state is crucial for maintaining the resting membrane potential (RMP) of the cardiomyocyte.

2. **Activated state**: Upon depolarization, ion channels transition from the resting state to the activated state. In this state, the channels are open, allowing the influx or efflux of specific ions, which contributes to the rapid depolarization phase of the AP. For instance, the rapid influx of Na^+ through voltage-gated Na^+ channel is essential for the initial upstroke of the AP in atrial and ventricular cells, while the slow influx of Ca^{2+} through L-type voltage-gated channels is essential for the initial upstroke of the action potential in SA and AV nodal cells.

3. **Inactivated state**: Following activation, ion channels enter the inactivated state, during which they are closed but not capable of opening again immediately. This inactivation is vital for the refractory period, ensuring that the cell cannot be prematurely re-excited and facilitating a normal cardiac rhythm. After cellular repolarization, inactivated channels return to the resting state, making them ready for reactivation by a new stimulus. The movement from the inactivated to the resting state is termed channel reactivation.

Ion channel kinetics in cardiomyocyte membranes

Ion channel kinetics refer to the rates at which ion channels transition between their fundamental kinetic states: resting (closed), activated (open), and inactivated (closed but unresponsive to immediate reopening). These transitions can occur rapidly or slowly, depending on the type of ion channel and its physiological role.

1. **Fast kinetics:**

Sodium Channels (Nav): Voltage-gated Na^+ channel exhibit fast kinetics, with rapid transitions between states. Upon depolarization, these channels quickly move from the resting to the activated state, allowing a swift influx of Na^+ ions, which is crucial for the rapid upstroke of the cardiac AP. The inactivation of Na^+ channel also occurs quickly. Drugs with slow binding kinetics (e.g., Class Ic agents) accumulate within the channel during tachycardia, prolonging QRS complex (QRS) duration due to their persistent Na^+ blockade, whereas those with fast binding kinetics (e.g., Class Ib agents) dissociate quickly, limiting their effects at normal heart rates.

2**. Slow kinetics:**

Calcium Channels (Cav): Voltage-gated Ca^{2+} channels, particularly L-type Ca^{2+} channels, display slower kinetics. These channels open more gradually in response to depolarization, allowing a sustained influx of Ca^{2+} ions. This prolonged entry of Ca^{2+} is vital for the plateau phase of the cardiac AP and is instrumental in triggering Ca^{2+}-induced calcium release from the sarcoplasmic reticulum, leading to muscle contraction.

Potassium Channels (Kv): Some K^+ channels, like the delayed rectifier K^+ channel, also exhibit slow kinetics. They gradually activate and contribute to the repolarization phase of the AP, restoring the RMP.

Use dependence and reverse use dependence

AADs interact with ion channels in different states, depending on the frequency of cardiac action potentials, resulting in use dependence and reverse use dependence **(Figure 2).**[8]

1. **Use dependence**: Use dependence refers to the increased blocking effect of certain AADs on ion channels with increased frequency of APs. This is often observed with Class I AADs, such as flecainide, which block Na^+ more effectively at higher heart rates (**Figure 2B**). The mechanism involves the drug preferentially binding to the activated and/or inactivated states of the channel, which are more prevalent at higher rates of depolarization. Consequently, the therapeutic effect of the drug is enhanced during tachycardia, providing a targeted approach to suppressing tachyarrhythmias. Use-dependent effects are less pronounced for slow-kinetic channels since their activation is not significantly increased by higher heart rates.

2. **Reverse use dependence**: In contrast, reverse use dependence describes the phenomenon where the effectiveness of a drug is greater at lower heart rates **(Figure 2C)**. This is the case with some Class III AADs, such as sotalol, which block K^+ channels. The binding affinity of these drugs to the ion channel is enhanced during the resting state, particularly at slower heart rates. Consequently, the drug exerts a more pronounced effect on prolonging the AP duration and refractory period during bradycardia. While this mechanism can aid in maintaining sinus rhythm (SR) and preventing arrhythmias, it also raises the potential risk of proarrhythmia, especially at slower heart rates.

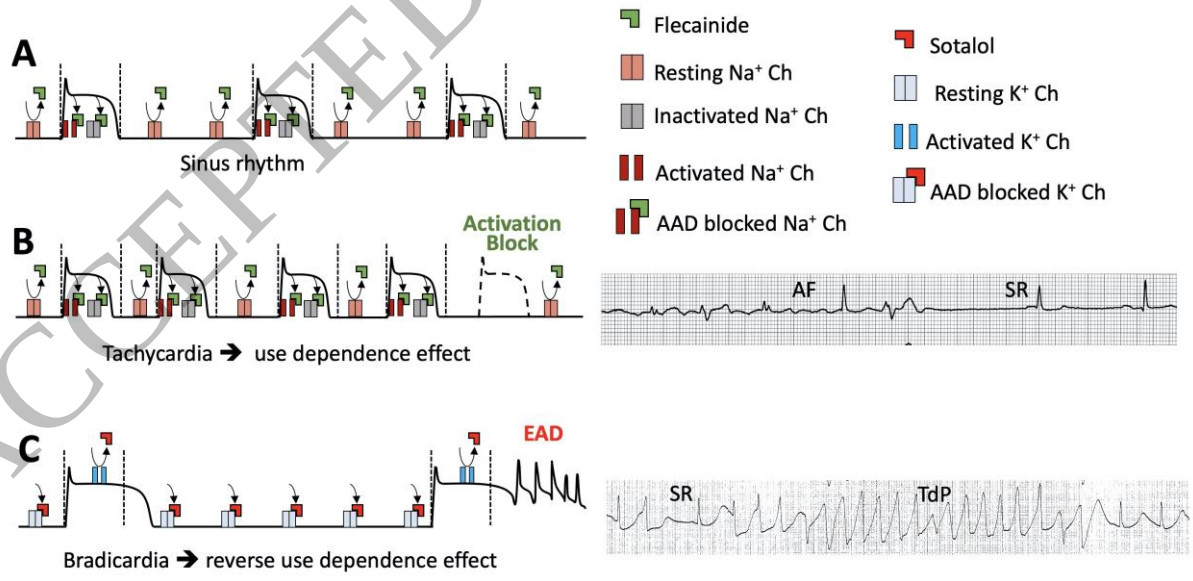

Figure 2: Schematic representation of the effects of flecainide (panels A and B) and sotalol (panel C) on the transmembrane action potential during sinus rhythm (SR) (panel A), atrial fibrillation (AF) (panel B), and sinus bradycardia (panel C). The figure also illustrates their

potential antiarrhythmic and proarrhythmic effects on AF (ECG in panel B) and sinus bradycardia (ECG in panel C), respectively.

Flecainide (green polygon) binds to the sodium channel (Na^+ Ch) primarily in its activated (slightly separated red rectangles) and inactivated (closely aligned grey rectangles) states. Its maximal effect is observed during tachycardia, as the shortened action potential duration keeps the sodium channel in these states more frequently. This use-dependent property enables flecainide to effectively block the activation front, contributing to the termination of atrial fibrillation (AF). Additionally, its very slow dissociation kinetics and strong binding to the inactivated state play a crucial role in prolonging post-repolarization refractoriness—a key mechanism underlying its antiarrhythmic efficacy but also a potential contributor to proarrhythmia.

In contrast, sotalol (red polygon) binds to several potassium channels (K^+Ch) mostly during its resting state (closely aligned blue rectangles). Its maximum effect occurs in bradycardia, where the channel remains in this state for a longer duration. This reverse use-dependent effect leads to prolonged action potential duration and QT interval prolongation, which can trigger early afterdepolarizations (EADs) and ventricular tachycardia, including torsades de pointes (TdP). Downward curved arrows represent antiarrhythmic drug (AAD) binding to the ion channel, while upward curved arrows indicate the absence of binding.

AAD binding kinetics

The effectiveness of AADs depends on their binding kinetics, which determine how quickly they attach to and dissociate from ion channels. Drugs like flecainide (Class Ic) have slow-on, slow-off kinetics, leading to cumulative Nav blockade at higher heart rates, prolonging QRS duration. In contrast, lidocaine (Class IB) binds and dissociates quickly (fast-on, fast-off), minimizing effects on conduction at normal heart rates.

For slow-kinetic K^+ channels, such as I_{Kr} (the rapid component of the delayed rectifier K^+ current), different Class III AADs exhibit distinct binding kinetics, which influence their clinical effects. Ibutilide, for instance, has very fast kinetics (rapid-on, moderate-off), making it effective for acute AF termination due to its use-dependent effect. In contrast, dofetilide and sotalol exhibit fast-on but slow-off kinetics, meaning their blocking effect is stronger at slower heart rates, leading to reverse use dependence, where QT prolongation becomes more pronounced with longer diastolic pauses.

Conversely, amiodarone and dronedarone display very slow binding kinetics (slow-on, very slow-off for amiodarone; slow-on, slow-off for dronedarone), resulting in weaker reverse use dependence. Additionally, their multichannel blocking effects (I_{Kr}, I_{Ks}, I_{Na}, I_{Ca}, and β-blockade) further reduce the risk of bradycardia-induced proarrhythmia, making them safer options for patients with low heart rates.

Ultimately, the interaction between AAD binding affinity, channel kinetics, and heart rate dependence influences drug efficacy and proarrhythmic risk, highlighting the need for tailored antiarrhythmic therapy.

Cardiac and systemic specificities of AADs

AADs exert distinct effects on different regions of cardiac tissue. Class II and IV agents primarily slow conduction and prolong refractoriness in the sinus and AV nodes, while Class I and III agents predominantly affect the working myocardium at both atrial and ventricular levels.

Another difference is the degree of ventricular myocardial contractility depression, which is most pronounced with Class Ic and Class IV agents but less significant with quinidine or oral amiodarone[9] (i.v. amiodarone can cause acute hypotension and myocardial depression, mainly due to its solvent polysorbate 80 and benzyl alcohol). Recognizing these region-specific effects is essential for selecting the appropriate drug for each patient.

Pharmacokinetics of AADs

AADs often exhibit a narrow therapeutic window, underscoring the critical role of PK in optimizing their efficacy and minimizing safety risks. A comprehensive understanding of their absorption, metabolism, distribution, and excretion processes enables clinicians to tailor therapies effectively and mitigate adverse effects (**Figure 3**).

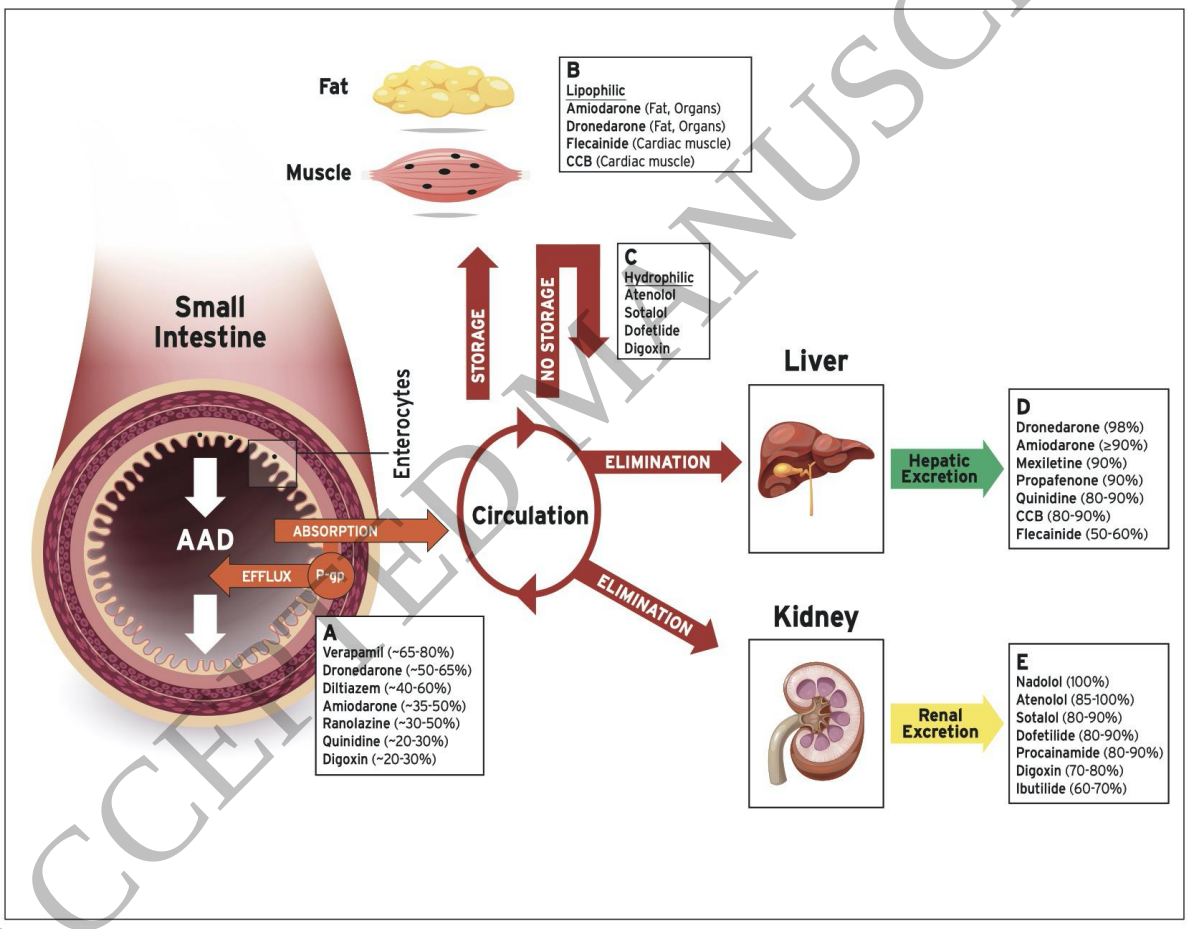

Figure 3: Schematic representation of intestinal absorption, tissue storage, and hepatic and renal excretion pathways for commonly affected antiarrhythmic drugs (AAD).
Box A: Intestinal absorption occurs through epithelial cells (enterocytes) of the small intestine. However, P-glycoprotein (P-gp) in enterocytes actively effluxes a portion of certain drugs back into the intestinal lumen, reducing systemic absorption. Box B: Lipophilic drugs tend to accumulate in fat-rich tissues and organs, such as the lungs, liver, thyroid, and adipose tissue (primary tissues of accumulation listed in brackets). Box C: Hydrophilic drugs exhibit minimal or no tissue accumulation and distribute predominantly in the extracellular fluid. Box D: Drugs are metabolized by the liver and excreted via bile into faeces. Box E: Renal clearance eliminates drugs or their metabolites through the kidneys.

Approximate percentages of drug efflux and elimination are indicated in the respective boxes. CCB, calcium channel blockers.

Intestinal absorption

Orally administered AADs rely on efficient intestinal absorption to achieve therapeutic plasma concentrations. Factors such as gastrointestinal pH, motility, and the presence of food can significantly influence drug absorption. For instance, the absorption of short-acting β-blockers like propranolol is enhanced when taken with food, attributed to delayed gastric emptying and prolonged intestinal transit time. Similarly, Class I agents, including flecainide and propafenone, depend on optimal gastrointestinal function to maintain steady plasma levels. Delayed gastric emptying or impaired intestinal absorption can reduce the amount of drug reaching the systemic circulation, leading to subtherapeutic levels. Diarrhoea can lead to variable absorption and fluctuating plasma levels. Other AADs, such as metoprolol, verapamil, and dronedarone, are advised to be taken with meals to improve absorption and reduce gastrointestinal side effects. Verapamil's absorption is slowed with food intake, decreasing the risk of adverse effects like dizziness or hypotension. Dronedarone's bioavailability is substantially increased when taken with food, leading to more consistent plasma concentrations. Conversely, certain extended-release formulations may exhibit reduced sensitivity to food timing, and in some cases, administering these medications on an empty stomach prevents unpredictable absorption variations caused by food presence.

First-pass hepatic metabolism

Many AADs undergo significant first-pass metabolism in the liver, which can markedly reduce their bioavailability. Propranolol, for example, may exhibit up to a tenfold variation in plasma levels for the same administered dose, primarily due to extensive hepatic metabolism before reaching the systemic circulation. Other AADs subject to notable first-pass metabolism include lidocaine—administered intravenously to bypass this effect—propafenone, and, to a lesser extent, flecainide. This variability underscores the necessity for meticulous dose titration and monitoring. The cytochrome P450 (CYP) enzyme system predominantly facilitates this metabolism, rendering AADs susceptible to drug-drug interactions. Individual differences in CYP enzyme activity can lead to significant interpatient variability in drug metabolism, influenced by genetic factors, environmental exposures, and concurrent disease states.

Distribution

After absorption and first-pass metabolism in the liver, AADs distribute throughout the body, with lipophilic agents like amiodarone achieving extensive tissue penetration. Amiodarone can accumulate in various tissues, including adipose tissue, liver, and lungs, resulting in a large volume of distribution and an extended half-life, sometimes exceeding 50 days. In contrast, hydrophilic agents such as sotalol have a more limited distribution, predominantly remaining within the extracellular fluid compartment.

Renal and hepatic excretion

The elimination pathways of AADs vary, with many Class I agents primarily undergoing hepatic clearance, while others like sotalol and nadolol are chiefly excreted renally (see below section

"Renal and liver failure"). Patients with impaired hepatic function may experience elevated plasma concentrations and heightened toxicity from hepatically metabolized drugs. Similarly, individuals with renal insufficiency may exhibit reduced clearance prolonging the half-lives of renally excreted medications. Consequently, dosage adjustments based on organ function are often necessary to maintain therapeutic efficacy and prevent adverse effects.

In summary, the PK of AADs—including aspects of intestinal absorption, first-pass hepatic metabolism, tissue distribution, and renal or hepatic excretion—is crucial for the therapeutic effectiveness and safety. Clinicians have to consider these factors, along with individual patient variability, to tailor antiarrhythmic therapy appropriately and reduce the potential for adverse outcomes.

Genetics and AADs

The influence of genetics on AADs is a critical aspect of pharmacogenetics, as genetic variations can significantly impact drug efficacy, metabolism, and the risk of adverse effects.[10,11] The effectiveness and safety of AADs vary significantly among individuals due to genetic differences affecting their metabolism, transport, and pharmacodynamics (PD). Drug metabolism genes, such as CYP2D6 and CYP3A4, influence how AADs like flecainide and propafenone are processed, impacting drug levels and toxicity risks. Ion channel genes (e.g., SCN5A, KCNH2) affect drug binding and can predispose individuals to arrhythmias, while drug transporter genes (e.g., ABCB1) modify AAD absorption and distribution. Variants in pharmacodynamic genes (e.g., ADRB1, CACNA1C) alter drug response, potentially affecting treatment success. Additionally, certain genetic mutations, such as those linked to Long QT Syndrome (KCNQ1, KCNH2, SCN5A), increase the risk of drug-induced arrhythmias like *torsades de pointes* (TdP). Disease-specific mutations in conditions like Brugada syndrome (BrS) or AF further influence drug selection. While pharmacogenetic testing is emerging in clinical practice, broader adoption requires further research and validation.

Classification of AADs

In the early 1970s, the AADs known at that moment were grouped into three classes based on their functional and electrophysiological effects by Vaughan Williams (VW) and Singh: Class I drugs reducing myocardial excitability; Class II drugs (β-blockers) having sympatholytic effects; and Class III drugs prolonging repolarization duration.[12,13] The electrophysiological effects of Class I and Class III drugs were later attributed to inhibition of I_{Na} and potassium (K^+) current, respectively. The discovery of the antiarrhythmic potential of verapamil, a calcium channel blocker (CCB), gave rise to Class IV. In addition, the distinct effects of different Class I AADs on repolarization duration, largely attributed to different binding and dissociation kinetics from the Na^+ channel, resulted into a further subdivision into Classes Ia, Ib and Ic. The strength of this classification lies in the clinical importance of the pharmacological properties on which it relies, resulting in electrophysiological actions, indications, and adverse side effects that are typical for each group of drugs.[14] However, subsequent research revealed that virtually all AADs affect multiple targets in cardiomyocytes, resulting in complex condition-specific electrophysiological effects that cannot be readily captured in the VW classification (**Table S2**).[14] Amiodarone and dronedarone are prime examples of AADs with pronounced multi-channel inhibitory effects. Although both are traditionally considered Class III AADs, they affect a range of cardiac

currents, e.g., Nav, Kv and Cav, along with α- and β-adrenoceptor blockade, thereby exhibiting effects of all four VW classes.[15,16] Moreover, other compounds with antiarrhythmic effects have been identified that did not fit into the VW classifications. These include, among others, magnesium sulphate for the treatment of TdP VA,[17] and ivabradine, an HCN-channel blocker primarily developed for lowering heart rates in patients with coronary artery disease (CAD), which has also been used to treat inappropriate sinus tachycardia (IAST) and may be effective against VA.[18]

The limitations of the traditional VW classification have fostered many attempts to improve the classification of AADs. The Sicilian Gambit was proposed in the early 1990s to integrate the multiple mechanistic actions of AADs with their clinical effects.[19] Although not intended as an AAD classification,[20] it accurately captures the complexity of AADs. However, the Sicilian Gambit has not been able to replace the VW classification in everyday clinical consideration of AADs. Subsequently, several extensions of the VW classification have been proposed to accommodate recent AADs as well as various compounds still under development. The most recent and most extensive of these is the 2018 Oxford AAD classification.[21] This classification maintains the four VW classes, but extends Class I with subclass Id for late Na^+ current ($I_{Na,L}$) blockers, further subdivides Classes II and III, and expands Class IV with other regulators of intracellular Ca^{2+} handling, including RyR2 inhibitors, sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2a (SERCA2a) activators and Na^+-Ca^{2+} exchanger inhibitors. Furthermore, this classification adds Classes 0 (HCN channel blockers), V (mechanosensitive channel blockers), VI (gap-junction channel blockers), and VII (upstream therapy). It has to be noted that for many of these new (sub)classes, there are no clinically approved AADs available. Conversely, most clinically available AADs belong in multiple subclasses due to their multi-channel blocking effects, including targeting of some elements of these new (sub)classes. **Table 1** shows the 2018 Oxford AAD classification and **Table 2** summarizes the most widely available market formulations and advised dosing regimens for commonly used AADs. The different agents are described below, with Class III following Class I and Class IV following Class II, reflecting a grouping based on their predominant targets and clinical applications—Class I and III are primarily used to modify atrial and ventricular myocardium activity, while Class II and IV are mainly chosen for their effects on the sinus and AV nodes.

Table 1: Classification of antiarrhythmic agents.

Class	Subclass	Primary pharmacological target/action	Example of drugs
HCN channel blockers			
0		HCN channel-mediated pacemaker current (I_f)	Ivabradine
Voltage-gated Na^+ channel blockers			
I[a]	Ia	Nav1.5 (I_{Na}) open-state (intermediate dissociation)	Ajmaline, disopyramide[b], procainamide[b], quinidine/hydroquinidine[b,c,d]
	Ib	Nav1.5 (I_{Na}) inactivated-state (rapid dissociation)	Lidocaine, mexiletine[c], phenytoin

	Ic	Nav1.5 open/inactivated state (slow dissociation)	Antazoline[e], cibenzoline, flecainide[f], pilsicainide, propafenone[f]
	Id	Late Na^+ current	Ranolazine
Inhibitors and activators of the autonomic nervous system			
II	IIa	β-adrenoceptor antagonists~	β1 blockers: atenolol, bisoprolol, esmolol, landiolol, metoprolol, nebivolol β1 & β2 blockers: nadolol, propranolol β1, β2 & α1 blockers: carvedilol, labetalol
	IIb	β-adrenoceptor agonists	Isoprenaline
	IIc	Muscarinic M2 receptor inhibitors	Atropine, scopolamine
	IId	Vagal nerve/ACh release activators	Digoxin, digitoxin
	IIe	Adenosine A1 receptor activators	Adenosine
K^+ channel blockers and openers			
III[f]	IIIa	Non-selective K^+ channel blockers	Amiodarone[h], dronedarone[h], sotalol[i], bretylium
		Kv11.1 (hERG) K^+ channel blockers	Dofetilide, ibutilide[j], nifekalant
		Kv1.5 (IKur) K^+ channel blockers	Vernakalant[k]
	IIIb	Kir6.2 (K_{ATP}) K^+ channel openers	Nicorandil, minoxidil
	IIIc	GIRK1 and GIRK4 (I_{KACh}) blockers	No approved medications
L-type Ca^{2+} channel modulators			
IV	IVa	Surface membrane non-selective & Cav1.2 and Cav1.3 channel mediated L-type Ca^{2+} current (I_{CaL}) blockers	Bepridil, diltiazem, etripamil, verapamil
	IVb	Intracellular sarcoplasmic reticulum RyR2-Ca^{2+} channel blockers	No approved medications
Mechanosensitive channel blockers			

V		Transient receptor potential channel (TRPC3/TRPC6) blockers	No approved medications
Gap junction channel blockers			
VI		Cx (Cx40, Cx43, Cx45) blockers	No approved medications
Upstream target modulators			
VII		ACEI, ARNI, Mineralocorticoid receptor antagonists, Omega-3 fatty acids, Sacubitril, Statins	Enalapril, lisinopril, losartan, candesartan, spironolactone, eicosapentaenoic acid, docosahexaenoic acid, statins, etc.

ACEI, Angiotensin converting enzyme inhibitors & receptor blockers; ACh, acetylcholine; ARNI, Angiotensin Receptor-Neprilysin Inhibitor; Cav, calcium channel, Nav, sodium channel; Kv, potassium channel.

[a]Nav1.5 Na^+ blockers differ based on their binding state and dissociation kinetics, which influence their therapeutic roles and effects on the cardiac action potential. Open/inactivated-state (slow dissociation kinetic) blockers, such as flecainide and propafenone, preferentially bind to open and inactivated Na^+ channels and dissociate slowly. They significantly reduce conduction velocity, particularly during tachycardia, making them effective for atrial and ventricular arrhythmias (Class Ic). Open-state (rapid dissociation) blockers, such as lidocaine and mexiletine, bind to open channels, but dissociate quickly, allowing selective targeting of ischaemic or depolarized tissues without affecting normal conduction (Class Ib). Inactivated-state (intermediate dissociation kinetic) blockers, such as quinidine and amiodarone, bind tightly to resting state of Na^+ channels, prolonging the refractory period and reducing re-entrant arrhythmias (Class Ia and multi-Class effects for amiodarone). Late Na^+ current inhibitors, such as ranolazine, target persistent Na^+ ion influx during the plateau phase, reducing Ca^{2+} overload and afterdepolarizations. This mechanism is particularly beneficial for ischaemic conditions and preventing arrhythmias like TdP.

[b]Class Ia AADs possess secondary anticholinergic activity (Class IIc), which is significant for disopyramide, moderate for quinidine, and mild for procainamide. This anticholinergic effect can lead to an accelerated sinus node rate by reducing parasympathetic influence on the heart.

[c]Quinidine and mexiletine also exhibit a secondary K^+ channel blockade effect (Class III), which contributes to their ability to prolong repolarization and modulate action potential duration, enhancing their antiarrhythmic efficacy in certain conditions.

[d]Quinidine and mexiletine also exhibit a secondary α-adrenergic blockade effect, which can potentially lead to hypotension, especially when used at higher doses or in sensitive patients.

[e]Antazoline also inhibits specific K^+ channels, particularly I_{Kr}, which may result in QT interval prolongation on the ECG, thereby increasing the risk TdP. Additionally, it exhibits a mild blocking effect on L-type Ca^{2+} channels.

[f]Flecainide and propafenone also exhibit a secondary intracellular sarcoplasmic reticulum RyR2-Ca^{2+} channel blocking effect (Class IVB), which is particularly relevant in specific arrhythmias like CPVT. This mechanism may be less relevant in their typical clinical use for common forms of arrhythmias such as AF or VT.

[g]Kv11.1 (hERG) K^+ channel blockers, such as dofetilide, act on the I_{Kr} in both atria and ventricles, prolonging repolarization and the QT interval. They are used broadly for arrhythmia management but carry a significant risk of TdP due to excessive QT prolongation. In contrast, Kv1.5 (I_{Kur}) blockers, such as vernakalant, target atrial-specific repolarization, making them highly effective for AF with minimal risk of ventricular proarrhythmia. Kir6.2 (K_{ATP}) channel openers, like nicorandil and minoxidil, regulate K^+ efflux in response to metabolic stress, shortening the action potential duration and providing protective effects during ischaemia.

While their primary use is in ischaemic protection and vasodilation, excessive opening can lead to hypotension or re-entrant arrhythmias

[h]*Amiodarone and dronedarone also exhibit secondary effects, including Na^+ channel blockade (Class I), Ca^{2+} channel blockade (Class IV), and non-selective β-adrenoceptor blockade (Class II). These additional mechanisms enhance their antiarrhythmic efficacy by slowing conduction, reducing automaticity, and mitigating sympathicus-driven arrhythmias.*

[i]*Sotalol also exhibits a secondary non-selective β-adrenergic receptor antagonist effect (Class IIA), which becomes more prominent at lower doses of the drug.*

[j]*Ibutilide also enhances late inward Na^+ current (INa), prolonging the action potential duration.*

[k]*Vernakalant is a potent open-state blocker of Na^+ channels, with rapid dissociation kinetics, with no major effects on K^+ currents in the human atrium.*

Class 0

Ivabradine

Ivabradine is a selective inhibitor of the SA node current or funny current (I_f). This current was originally identified in the SA node but it has been also found in the specialized conduction system, including the AV node and Purkinje fibres. The I_f is a mixed Na^+ and K^+ current that plays a pivotal role in the spontaneous depolarization of the SA node. By specifically targeting this current, ivabradine reduces the rate of spontaneous depolarization in the SA node, consequently slowing the heart rate without affecting significantly contractility or AV conduction. Unlike traditional β-blockers or CCBs, which exert their effects on the entire myocardium, ivabradine's selectivity for I_f allows for heart rate control with no side effects on other heart functions. This specificity is particularly advantageous in patients with conditions such as heart failure with reduced ejection fraction (HFrEF). Ivabradine may be used to reduce heart rate and symptoms in patients with IAST. More recently, it has been proposed to reduce heart rate in AF but with a milder effect than digoxin (11.6 vs 19.6 beats/min mean daytime heart rate decrease, $P<0.01$)[22] and for junctional ectopic tachycardia (JET).[23] However, ivabradine is not advised for patients with paroxysmal AF, as it may promote arrhythmic episodes.

Class Ia

Quinidine

Quinidine the d-isomer of the antimalarial drug quinine, is one of the oldest known AADs.[24] It is traditionally classified as a Class Ia AAD, inhibiting cardiac I_{Na} with high affinity for the open state and intermediate dissociation kinetics (time constants of 1-5 seconds) from the Na^+ channel, reducing both cardiac excitability and conduction velocity. The effects of quinidine are rate dependent, with more pronounced inhibition of I_{Na} at fast rates (use dependence). In addition to I_{Na}, quinidine inhibits a wide range of other currents, including repolarizing K^+ currents (notably I_{Kr}, I_{Ks} and I_{to}), as well as $I_{Ca,L}$ and $I_{Na,L}$.[25,26] Together, these effects result in significant quinidine-induced prolongation of repolarization duration, visible as QT-interval prolongation on the ECG, particularly at slow rates (i.e., exhibiting reverse use dependence) (**Figure 4**). Quinidine also decreases automaticity of SA node and Purkinje cells, but increases sinus rate *in vivo* due to a combination of its anticholinergic (due to inhibition of muscarinic receptors) and haemodynamic effects.[24] In particular, quinidine-mediated inhibition of α-adrenoceptors promotes peripheral vasodilation, hypotension and subsequent reflex sinus tachycardia. This

effect is most pronounced with intravenous (i.v.) quinidine administration or when combined with β-blockers or verapamil.

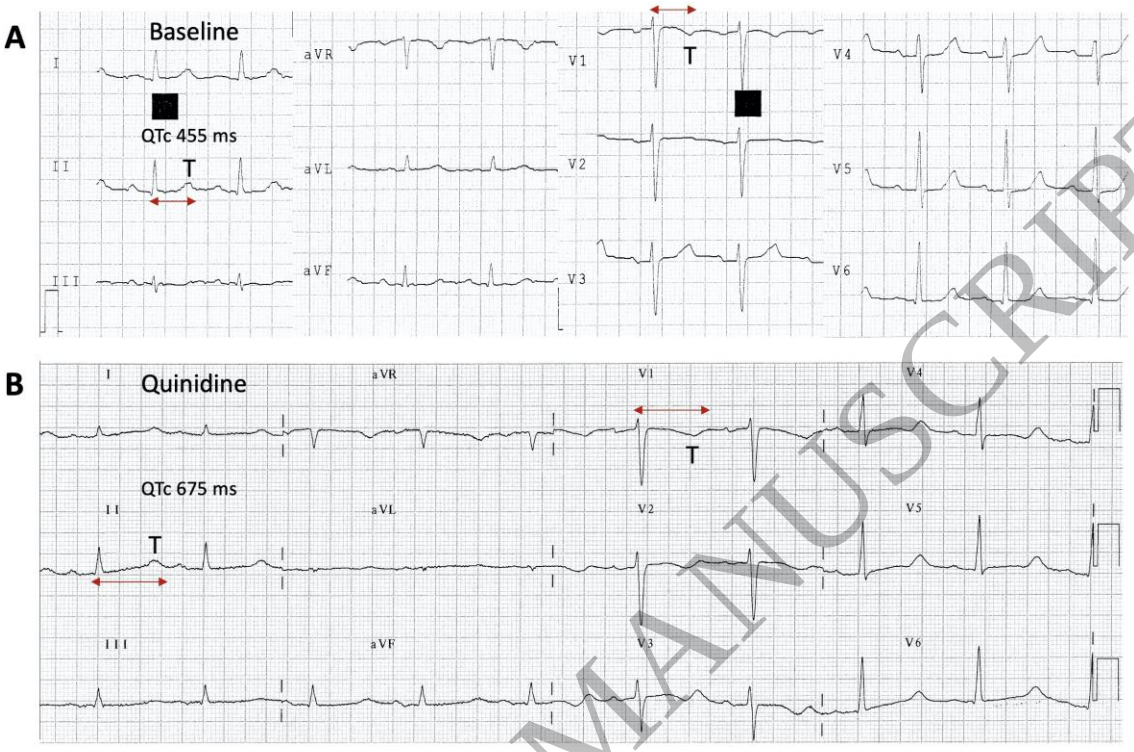

Figure 4: 12-lead ECGs illustrating the effect of quinidine on the QT interval in a female patient with no structural heart disease and a history of atrial fibrillation.

Panel A: Baseline ECG recorded prior to quinidine administration, showing a normal QTc interval duration (two-arrowhead red line). Panel B: ECG following quinidine administration, revealing marked QT interval prolongation, indicative of its effect on ventricular repolarization. This underscores the potential for proarrhythmic effects, even in the absence of structural heart disease.

The effects of quinidine after oral administration start 1–3 hours after intake and remain for 6–8 hours (**Table S3**).[24] Quinidine has a bioavailability of 60-80% and is 80-88% protein bound in serum. Its concentration is 4–10 times higher in the heart, than in the circulation. Quinidine is primarily eliminated by hepatic metabolism through the cytochrome P450 system (CYP) 3A4, resulting in hydroxylated metabolites, some of which have antiarrhythmic effects.[24] About 20% of quinidine is excreted unchanged via the kidneys. Quinidine is itself a potent inhibitor of CYP2D6 and P-glycoprotein (P-gp), potentially affecting effective concentrations of other drugs (**Tables S4 and S5**). For example, a potentially hazardous interaction between quinidine and digoxin may occur due to the quinidine-induced reduction in renal tubular secretion of digoxin, thereby increasing its toxicity and the risk of cardiac arrhythmias (see below section "AAD switch and combinations").[27]

Quinidine was initially used for SR maintenance in AF patients and prevention of recurrences of VA by reducing ectopic activity and prolonging repolarization duration, thereby reducing the likelihood of re-entry. However, its prominent adverse effects and the availability of new

antiarrhythmic therapies with higher efficacy and/or better safety profile have made quinidine obsolete for the treatment of AF.[24] Quinidine is currently used for the treatment of several inherited arrhythmogenic disorders. Brugada syndrome (BrS) is an inherited channelopathy resulting in a typical ECG pattern and increased risk of ventricular tachycardia (VT), with the epicardium of the right-ventricular outflow tract region as the primary source of electrophysiological abnormalities. BrS is often associated with decreased I_{Na}, potentially resulting in an imbalance between depolarizing I_{Na} and early repolarizing K^+ currents including transient outward K^+ current (I_{to}), which is highly expressed in the epicardium of the right-ventricular outflow tract. Inhibition of I_{to} normalizes the BrS ECG pattern and the clinical efficacy of quinidine in BrS patients[28] has been primarily attributed to its inhibition of I_{to}.[24] Similarly, data from small cohorts suggest that quinidine may represent a potential treatment option for short QT syndrome (SQTS) due to its repolarization-prolonging effects, as well as in patients with idiopathic ventricular fibrillation (IVF), particularly those with contraindications for implantable cardioverter defibrillator (ICD) treatment.[24,29] However, given the low prevalence of these rare arrhythmogenic conditions and the low price of quinidine, it has been considered economically unfavourable to widely distribute quinidine.[30] As a result, quinidine is currently no longer available in many countries.[30]

Syncopal events ("quinidine syncope"), first attributed to drug-induced TdP arrhythmias in 1964,[31] are the most serious adverse effects associated with quinidine (**Table S6** and see below section "Proarrhythmia, toxicity and other major adverse effects"). This proarrhythmia is typically the result of excessive, heterogeneous quinidine-induced repolarization prolongation, promoting the genesis of EADs initiating potentially life-threatening re-entrant VA. Quinidine has indeed also been associated with increased mortality.[32] In addition, quinidine has pronounced adverse gastrointestinal effects, typically diarrhoea, causing drug discontinuation in many patients.[24] The electrolyte disturbances promoted by quinidine-induced diarrhoea can further increase the risk of VA. Other dose-related and reversible side effects, usually defined as cinchonism, include tinnitus, headache, dizziness, visual disturbances, nausea and decreased hearing.[24]

Disopyramide and Ajmaline

Although classified as Class I AADs, ajmaline and disopyramide are not commonly used for antiarrhythmic therapy. Ajmaline was initially used to treat AF in patients with preexcitation, but it was later replaced by flecainide or propafenone for this purpose. Currently ajmaline is primarily used to unmask concealed arrhythmogenic phenotypes regulated by I_{Na} dysfunction (e.g., BrS) and in some countries for VT termination in patients without significant heart disease. Disopyramide is a Class Ia AAD with negative inotropic effects and can be used to suppress ventricular ectopy or in combination with β-adrenoceptor or Ca^{2+}-channel blockers in patients with hypertrophic obstructive cardiomyopathy.[33] In addition, disopyramide has significant anticholinergic effects, which are the primary cause of its adverse effects and have limited its use. However, these same properties make it particularly effective for certain patients with vagal AF, where a bedtime dose can be highly effective and reasonably well-tolerated, provided no daytime dosing is required.

Procainamide

Procainamide is a Class Ia AAD that inhibits cardiac I_{Na} with high affinity for the open state of the Na^+ channel and intermediate dissociation kinetics. It also blocks I_{Kr}. Combined, these effects reduce excitability, increase ERP and promote dispersion by prolonging APD and augmenting post-repolarization refractoriness.[34] In addition, procainamide slows conduction. Its major metabolite N-acetyl procainamide lacks I_{Na}-blocking effects but has similar APD-prolonging effects.[34]

Procainamide is almost completely absorbed after oral administration, with a bioavailability of 70-85% (**Table S3**). Its peak plasma concentrations are typically reached within 1 to 2 hours.[35,36] Its apparent volume of distribution is 2 L/kg body weight and about 15% is bound to plasma proteins.[35] Procainamide has a half-life of 3-4 hours and is eliminated 50% by hepatic metabolism and 50% via renal excretion of the unchanged drug. N-acetyl procainamide is renally excreted with a half-life of 6-10 hours. Because of these relatively rapid elimination rates, procainamide is usually administered as a slow-release formulation. Given the dependency on renal clearance, dose adjustments are needed in patients with renal failure.[34]

Procainamide is used for the acute cardioversion of haemodynamically stable VT (**Figure 5**). Procainamide is also used in patients with accessory pathways and pre-excited AF, slowing conduction across the accessory pathway and lowering ventricular rate and has recently been employed for the comparison of electrical versus pharmacological cardioversion of AF in emergency department settings. Finally, procainamide has been used for drug provocation testing in patients with suspected BrS, although it is less likely to provoke a type-1 Brugada electrocardiographic pattern compared with ajmaline.

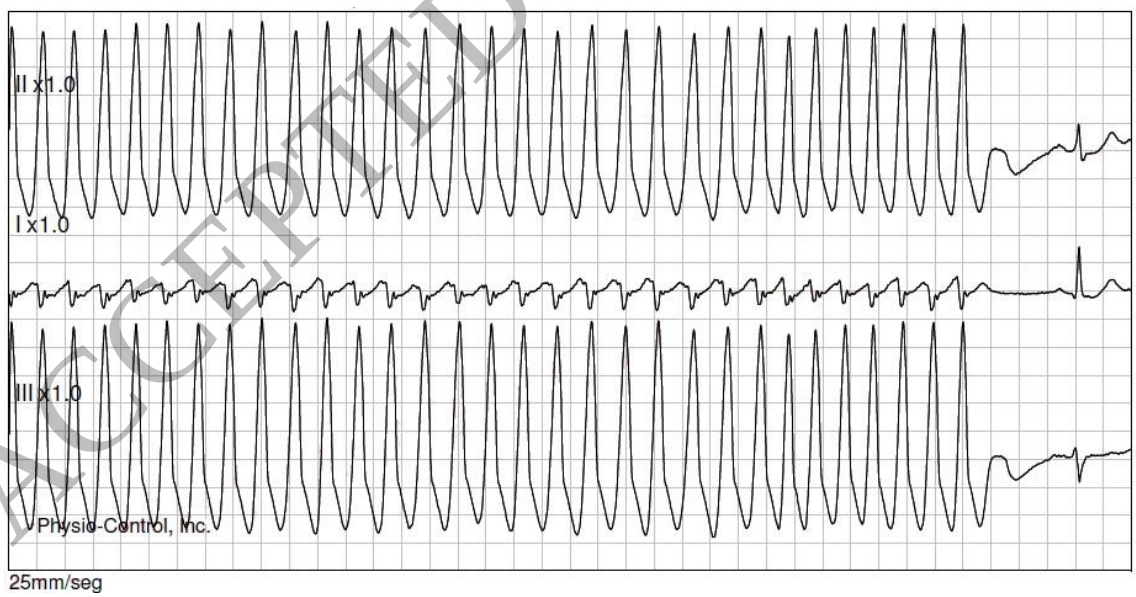

Figure 5: ECG tracings of leads II and III illustrating the termination of ventricular tachycardia (VT) after a 15-minute infusion of procainamide in a patient with structural heart disease (old myocardial infarction).

The tracings show VT transitioning to sinus rhythm after procainamide administration, demonstrating its antiarrhythmic efficacy in managing VT in the presence of underlying myocardial scarring. ECG recorded at a speed of 25 mm/s and a sensitivity of 10 mm/mV.

Drug-induced proarrhythmia is the most important adverse effect of procainamide and is directly related to the I_{Na} and I_{Kr}-blocking effects of procainamide and N-acetyl procainamide (**Table S6**). N-acetyl procainamide concentrations greater than 20 μg/mL carry a higher risk of TdP, whereas procainamide concentrations >10 μg/mL appear to carry a risk of marked QRS widening and potential arrhythmia exacerbation.[34]

Class Ib

Lidocaine

In addition to its local anaesthetic effects, lidocaine is a Class Ib AAD, inhibiting cardiac I_{Na}. Lidocaine blocks Na^+ channels preferentially in the inactivated state with rapid recovery from block (fast dissociation kinetics). As such, the effects of lidocaine are exacerbated in depolarized tissue (e.g., due to ischaemia) or in the presence of rapid electrical activation, when more Na^+-channels are already inactivated.[34] Conversely, lidocaine is less effective in the presence of hypokalaemia due to the associated RMP hyperpolarization (less Na^+ channels are inactivated). Lidocaine decreases automaticity and triggered activity by reducing the slope of phase 4 of the AP and reducing excitability. APD is either unaffected or shortened by lidocaine, with the latter due to inhibition of depolarizing $I_{Na,L}$.[34] Nonetheless, ERP could be prolonged due to an increased post-repolarization refractoriness resulting from the I_{Na} inhibition. Of note, lidocaine is the only clinically available AAD with no relevant inhibitory effects on cardiac K^+ channels.

Although lidocaine is well absorbed, it undergoes extensive first-pass hepatic metabolism, making it inappropriate for oral use (**Table S3**). Accordingly, it is primarily given i.v. for the treatment of cardiac arrhythmias.[34] Lidocaine is 60-80% protein bound. After i.v. administration of a bolus of lidocaine, plasma concentrations first decline rapidly (half-life of approximately 8 min), which is attributed to rapid distribution of the drug from the plasma to the periphery. Thereafter, the drug is eliminated by CYP3A4-mediated hepatic metabolism, with a half-life of approximately 2 hours.[36] Thus, steady-state plasma concentrations are reached in 8–10 hours after initiation of lidocaine maintenance infusion, but these values are significantly prolonged in patients with hepatic dysfunction, e.g., in elderly, or in the presence of HF or cardiogenic shock. Lidocaine metabolism is impaired by β-blockers, requiring dose adjustments when co-administered.

The potential use of lidocaine in the treatment of VT was already described in the 1950s and 1960s and likely results primarily from reduced myocardial excitability. Early studies in patients with acute myocardial infarction (MI) found that lidocaine suppressed premature ventricular contractions (PVCs) and non-sustained VT. However, later studies reported a higher mortality after acute MI in patients receiving lidocaine, possibly due to a higher incidence of asystole and bradyarrhythmias. As such, prophylactic lidocaine during acute MI was abandoned.[34] A systematic Cochrane analysis concludes that evidence of low quality suggests that prophylactic lidocaine has very little or no effect on mortality or ventricular fibrillation (VF) in people with acute MI and that its safety profile is unclear.

Mexiletine

This lidocaine analogue inhibits both the peak and late Na^+ currents ($I_{Na,P}$ and $I_{Na,L}$), shortens APD and refractoriness primarily in Purkinje fibres, and to a lesser extent in ventricular muscle. Additionally, it suppresses the automaticity of Purkinje fibres. However, it does not modify sinus rate, contractile force, AV nodal function, exert major haemodynamic effects or prolong the QT. Mexiletine is advised for the treatment of VA (sustained VT),[37] even in patients with recent MI, but had no favourable effect on mortality. Combined with sotalol it has been used in patients with frequent VT recurrences who have a defibrillator. It may be appropriate as off-label add-on-therapy to short the QT in long QT syndrome (LQTS) type 3 patients with a baseline corrected QT interval (QTc) >500 ms.[38]

Phenytoin

Phenytoin, an antiepileptic drug with membrane-stabilizing properties, has a limited but specific role as an AAD. Its primary action is through Na^+ channel blockade, which shortens the APD, particularly in ventricular myocardium. Historically, phenytoin has been used in digitalis-induced arrhythmias, especially when nodal or ventricular tachyarrhythmias occur, due to its ability to counteract the proarrhythmic effects of digitalis. However, its use as an AAD is rare in modern practice due to the availability of more effective and safer alternatives. Phenytoin requires careful monitoring for drug-drug interactions, as it is both a substrate and an inducer of CYP enzymes, which can complicate its PK in patients on multiple therapies.

Class Ic

Flecainide and propafenone

Flecainide and propafenone produce a potent frequency-dependent blockade of Na^+ channels, decrease cardiac excitability (increase pacing and defibrillating thresholds) and slow conduction in fast-response cardiac tissues, with the greatest effect in the His–Purkinje system. They suppress ectopic automaticity, shorten the APD in Purkinje fibres but prolong the APD in the ventricular muscle, and prolong ventricular refractoriness by lengthening the reactivation of Na^+ channels. Flecainide/propafenone prolong atrial APD, in a frequency-dependent manner, which may facilitate the conversion of AF to SR. During orthodromic and antidromic AV re-entrant tachycardia (AVRT), flecainide/propafenone slow conduction and increase anterograde and particularly retrograde refractoriness in accessory pathway in a frequency-dependent manner. Flecainide/propafenone have minimal haemodynamic effects in patients with normal left ventricular ejection fraction (LVEF), but reduce LVEF in patients with LV dysfunction and HF.

Flecainide also blocks the $I_{Na,L}$ mediated shortening the QT in patients with LQTS3, and is an open channel blocker of RyR2 Ca^{2+} release channels decreasing the arrhythmogenic Ca^{2+} release from the sarcoplasmic reticulum in CPVT patients with mutations in *RYR2* and *CASQ2* genes. Propafenone blocks $I_{Ca,L}$ and RyR2 channels, being an alternative to flecainide in CPVT, and exhibits mild β-blocking properties at doses >450 mg/day.

Flecainide/propafenone are advised for the cardioversion of symptomatic new-onset AF/AFL to SR and long-term maintenance of SR following cardioversion,[39–42] and to enhance success of

direct current (DC) cardioversion and reduce immediate/early recurrences of AF. In selected, highly symptomatic patients with rare paroxysmal AF episodes, a single self-administered oral dose of flecainide/propafenone ('pill-in-the-pocket' approach) could be used to restore SR, provided that anticoagulation advice is followed and once safety has been previously established in a medical environment.[43] Flecainide/propafenone can convert AF to AFL with 1:1 AV conduction and increase the ventricular rate; this can be prevented with AV nodal blocking agents (**Figure 6**).

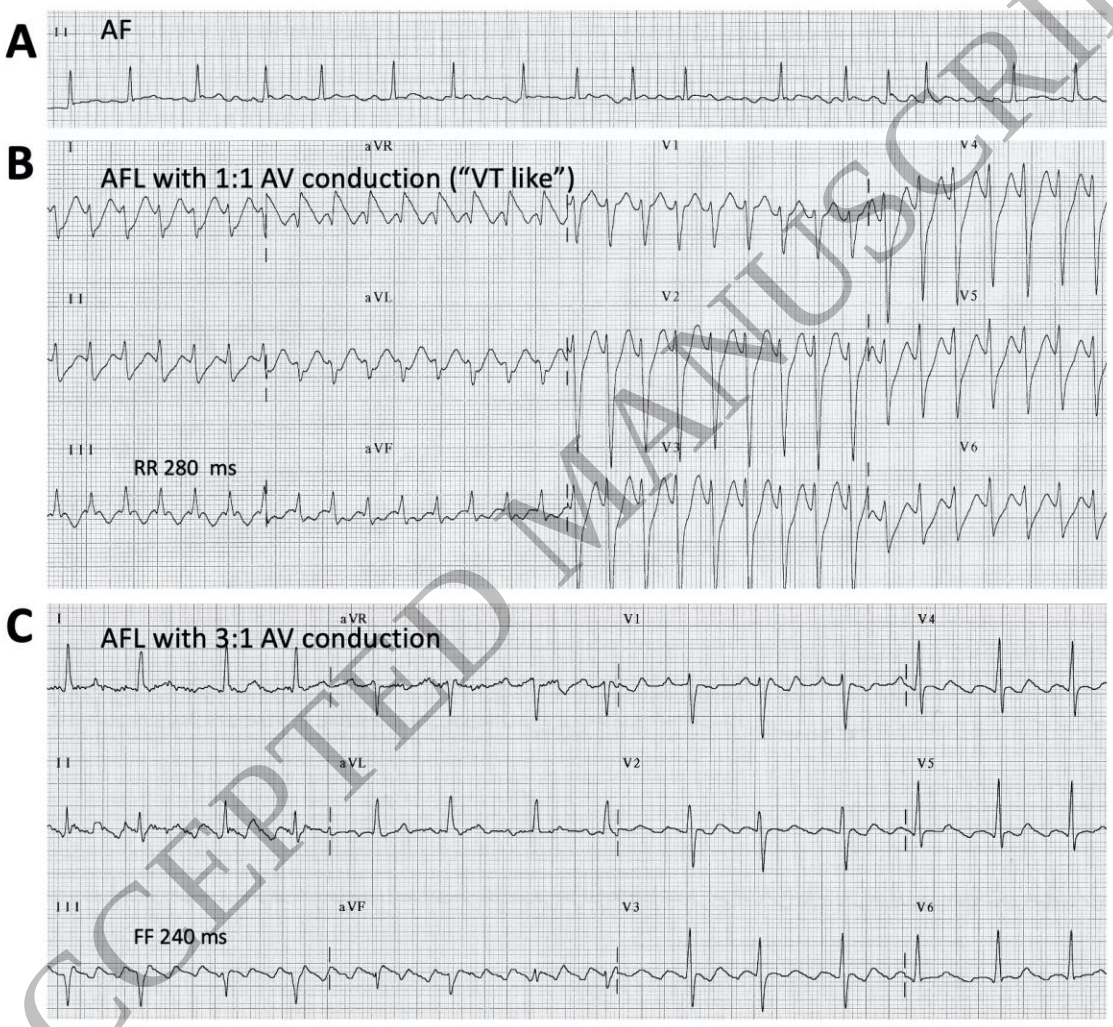

Figure 6: Single-lead (Panel A) and 12-lead ECG tracings (Panels B and C) demonstrating the progression of atrial arrhythmias in a 57-year-old hypertensive male patient taking 200 mg/day of flecainide for paroxysmal atrial fibrillation (AF).
Panel A: Baseline ECG showing AF at presentation. Panel B: After a few days of flecainide therapy, the patient developed atrial flutter (AFL) with 1:1 AV conduction, left bundle branch block (LBBB), and rapid ventricular response with RR intervals of 280 ms, mimicking ventricular tachycardia (VT). Panel C: Following the administration of 5 mg of intravenous atenolol, the AV conduction ratio changed to 3:1. This resulted in the resolution of LBBB and narrowing of the QRS complex, making the flutter waves apparent, with a cycle length of 240 ms (cycle length shortened by 40 ms after a partial washout effect of

flecainide). This case illustrates flecainide-induced proarrhythmia with AFL and the diagnostic clarity achieved through rate control and conduction ratio alteration.
ECG recorded at a speed of 25 mm/s and a sensitivity of 10 mm/mV.

Intravenous flecainide and propafenone may also be appropriate in the acute treatment of supraventricular tachycardia (SVT), including symptomatic focal atrial tachycardia (AT), pre-excited AF, AFL (when ibutilide fails or is not available) and AVNRT and orally, in the chronic treatment of focal AT and AVRT.[44]

It has been also used for the prophylaxis and treatment of life-threatening sustained haemodynamically tolerated VA, not controlled with other AADs or ablation or when they are not tolerated or possible. The combination of flecainide/propafenone with amiodarone is used in patients with frequent VT recurrences who have a ICD.[45] Flecainide may be appropriate as add-on therapy to shorten the QT in LQTS3 patients with a QTc >500 ms.[46,47] It is also advised in patients with CPVT who experience recurrent exercise syncope or polymorphic/bidirectional VT despite maximally tolerated β-blocker doses or when ICD implantation has risks/contraindications or is not available or accepted by the patient.[48–51]

Flecainide/propafenone can cause monomorphic VT and is associated with increased mortality, heart failure (HF) and cardiac arrest (CA) in patients with prior MI and impaired LV function.[32,52,53] Thus, it is advised to avoid them in patients with ischaemic or SHD.[54] Nevertheless, there is some controversy about the safety of use of flecainide for acute arrhythmia termination or chronic prevention in patients with SHD and no prior MI or ventricular dysfunction. Their prophylactic use is potentially harmful in patients with adult congenital heart disease and asymptomatic VA.[55] Flecainide and propafenone prolong the QRS duration, which can exacerbate existing conduction delays and increase the risk of complete heart block, especially in patients with pre-existing bundle branch block (BBB). In patients with BBB and no SHD, flecainide/propafenone can still be used for paroxysmal AF or SVT, but the QRS duration is advised to be closely monitored. If the QRS widens by >25% from baseline, it is advised to reduce the dose or to discontinue the drug. These drugs are not advised for patients with a baseline QRS >120 ms due to the risk of excessive conduction delay, especially in those with LBBB or bifascicular block. Flecainide and propafenone may also unmask the ECG of the BrS. Finally, flecainide may play a role in triggering Takotsubo syndrome or favour occurrence and severity of complications and it is advised to avoid it in patients with a history of this disorder.[56]

Other: Cibenzoline, pilsicainide, antazoline

Cibenzoline is a Class Ic drug (also found classified as Class Ia) that also blocks L-type Ca^{2+} and K^{+} channels and exhibits antimuscarinic activity.[57,58] It increases atrial and ventricular refractoriness and prolongs intracardiac conduction. Intravenous cibenzoline is advised for the cardioversion of recent-onset AF in patients with no clinically significant SHD. It is as effective as flecainide and disopyramide in haemodynamically stable patients with an accessory pathway who do not require electrical cardioversion.[57–59] Orally, it can be used as a "pill-in-the-pocket" (PITP) approach for paroxysmal AF.[60]

Pilsicainide is a Class Ic drug widely used in Japan for the cardioversion of recent-onset AF in patients with no clinically significant SHD.[58,61–63] This agent do not significantly affect the Ca^{2+},

delayed rectifier K^+, inward rectifying K^+, acetylcholine-induced K^+ or ATP-sensitive K^+ currents. From these results pilsicainide could be differentiated from other type Ic AAD as a pure Na^+ channel blocker. In patients with paroxysmal AF, pilsicainide prolongs refractoriness and slows conduction in the distal pulmonary veins (PV) and left atria (LA). PV-LA conduction block can be observed before AF termination.[62] Hybrid therapy with pilsicainide and PV isolation (by catheter ablation) appears to be an effective therapeutic approach for AF.[62] There are limited data on the use of pilsicainide in VA.[63] Pilsicainide can be taken as a PITP approach to terminate paroxysmal AF.[59,61]

Antazoline is a first-generation antihistaminic agent, which blocks Na^+ channel and several K^+ channels and has anticholinergic properties.[64,65] It slows intra-atrial conduction, prolongs atrial and ventricular ADP and refractoriness[66] and exerts a negative inotropic effect limiting its use in patients with SHD.[65] Intravenous antazoline is advised for the cardioversion of recent-onset AF in patients with preserved LV function (median time to conversion 16.0 min) being as efficacious as propafenone and amiodarone,[67–70] in patients undergoing pulmonary vein isolation[71] or during ablation of accessory pathways.[65] However, it fails to prevent AF recurrence while given orally.[72]

Class Id

Ranolazine

This antianginal drug selectively inhibits $I_{Na,L}$ and I_{Kr} and prolongs atrial and ventricular APD and refractoriness, but the effect is more pronounced in the atria.[73] Ranolazine does not slow intracardiac conduction velocity or modify heart rate, contractility or blood pressure. Off-label ranolazine reduces the incidence of AF post-cardiac surgery and post-electrical cardioversion, and high doses (2 g PO, *per os*)) may convert recent-onset AF (<48 h duration).[74,75] The combination of ranolazine and low doses of dronedarone, but not each drug in monotherapy, reduced AF burden vs placebo in patients with paroxysmal AF in one trial.[76] The combination of ranolazine and amiodarone can be effective in managing refractory arrhythmias, particularly AF and VT. However, it requires careful monitoring due to the risk of QT prolongation and potential drug interactions. Additionally, ranolazine and amiodarone can increase DOAC levels, heightening the risk of bleeding through P-gp and/or CYP3A4 inhibition. In patients with unstable angina and non-ST-segment elevation MI, ranolazine significantly reduces the incidence of non-sustained VT, SVT, AF and bradycardias as compared with placebo, but not sudden cardiac death (SCD).[77,78] Ranolazine may be appropriate as add-on therapy to shorten the QTc interval in LQTS3 patients with a QTc >500 ms.[45,47,79] Ranolazine is approved for this purpose in the USA but not elsewhere.

Class III

The prototypical Class III AAD effect is prolongation of APD and, thereby, ERP, reducing the likelihood of re-entry (**Table S2**).[80] For most AADs, this effect is achieved through inhibition of I_{Kr}. APD prolongation by Class III AADs is most pronounced at slow rates due to the previously mentioned reverse use dependence effect. Reverse use dependence of K^+ channel blockers has been attributed to the intrinsic relationship between total membrane current and APD, whereby a fixed reduction in membrane current (due to K^+ channel inhibition), will have a larger impact on APD when total membrane current is small (i.e., when baseline APD is already long).[81] This

mechanism partly explains the potential for excessive APD prolongation by Class III antiarrhythmic drugs in the setting of hypokalaemia or impaired repolarization reserve (e.g., due to a reduction in other repolarizing K^+ currents). The primary mechanisms of drug-induced proarrhythmia with Class III AADs include heterogeneous APD prolongation and early afterdepolarization (EAD)-mediated triggered activity.[82]

Class IIIa

Amiodarone

Amiodarone inhibits a wide range of ion channels and receptors, including I_{Kr}, I_{Na}, $I_{Ca,L}$ as well as α-adrenoceptors and β-adrenoceptors, thus exhibiting effects of all four original VW AAD classes (**Table S2**).[83] Consequently, amiodarone prolongs repolarization duration (primarily via I_{Kr} and I_{Ks} inhibition) and decreases conduction velocity by blocking I_{Na}. However, it has less pronounced reverse use-dependent effects than pure Class III AADs.[84] Amiodarone also produces non-competitive β-adrenoceptor blockade, which can promote sinus bradycardia, and reduces $I_{Ca,L}$ in a use-dependent manner. Of note, there are significant electrophysiological differences between i.v. amiodarone and chronically administered oral amiodarone.[83,84] Intravenous application produces predominantly slowing of ventricular conduction, a smaller repolarization prolongation, little effect on sinus rate, and more potent antiadrenergic activity.[85] These differences are likely in part due to additional effects of metabolites and due to amiodarone-induced electrical remodelling during chronic treatment.[83]

Amiodarone has a bioavailability of 35-65% (**Table S3**). The rate and extent of absorption of amiodarone increases when taken with food.[86] It also has a large volume of distribution (around 60 L/kg) and is highly lipophilic, being 96% protein bound and resulting in a delayed onset of action (with the antiarrhythmic effect plateauing after 10 weeks of therapy[86] and very long half-life (30-100 days).[34,36] Long and high oral loading doses are used to accelerate the onset of drug activity, although i.v. application has a rapid onset of action. Loading[87] may be done with 600 mg per day over four weeks. Afterward, the maintenance dose is established, typically ranging between 100 to 200 mg per day. Amiodarone undergoes extensive hepatic metabolism, primarily via CYP3A4, an enzyme that it also inhibits. Consequently, amiodarone can significantly alter the metabolism of numerous other drugs, necessitating careful consideration of potential drug interactions (**Table S5**).[86,88] For example, amiodarone can increase simvastatin and atorvastatin concentrations through its effect on CYP3A4 and similarly affects warfarin levels, necessitating warfarin dose reductions when amiodarone is initiated. Amiodarone also inhibits P-gp transporters, e.g., increasing digoxin levels.[89] The major metabolite of amiodarone is desethyl-amiodarone, which also has antiarrhythmic properties. The metabolism of amiodarone is inhibited by grapefruit juice, leading to elevated serum levels of amiodarone. Excretion is primarily hepatic and biliary with almost no elimination via the renal route.[34,36]

Although originally developed as an anti-anginal agent, amiodarone is generally considered the most effective AAD available. Its efficacy and relatively low proarrhythmic risk (discussed below) likely result from the complex interaction between numerous molecular targets, e.g., resulting in prolongation of repolarization duration without increasing dispersion of repolarization or an increased risk of EADs.[84,90] Amiodarone is approved by the Food and Drug Administration (FDA) for the treatment of VA, but is also commonly used for cardioversion and

rhythm control of AF. Amiodarone is first-line treatment in the setting of VF and CA.[86] A randomized controlled trial compared amiodarone, lidocaine and placebo in out-of-hospital CA refractory to shock therapy. Although there was no difference in outcomes in the overall population, amiodarone demonstrated a survival benefit compared with placebo in the witnessed arrest subgroup.[91] Likewise, amiodarone is commonly used in patients with recurrent VT receiving appropriate ICD shocks. In the OPTIC trial, amiodarone plus a β-blocker was associated with a significant 70% reduction in risk of appropriate ICD shocks.[92] In AF patients, amiodarone is less effective than Class Ic drugs and vernakalant for acute cardioversion, likely in part due to its relatively slow onset of action.[93] However, it is one of the few AADs available in HF patients. On the other hand, for long-term rhythm control in patients with AF, amiodarone is significantly more effective than dronedarone, sotalol, and propafenone, with a 1-year rate of maintaining SR of >65%.[88,93,94] Amiodarone is also used for the management of peri- and post-operative AF, which is common after cardiac surgery.[93] Finally, amiodarone's negative dromotropic effects can be employed for rate control when combination therapy with β-blockers and digoxin is insufficient in patients who do not qualify for non-pharmacological rate control, or in the acute setting in patients with haemodynamic instability.[93] Common side effects resulting from amiodarone use include nausea, vomiting, and taste disturbances (**Table S6**).[86]

Compared to other Class III AADs, amiodarone exhibits a relatively low proarrhythmic risk, with an incidence of drug-induced TdP <1%, despite its QT-prolonging effects.[34,88] Given its unique electrophysiological properties and lower propensity to induce TdP, amiodarone therapy may be safely maintained in patients with a QTc interval prolongation up to 550 ms, provided there are no additional risk factors such as bradycardia, electrolyte imbalances, or concomitant use of other QT-prolonging medications. It is advised to avoid the combination with other QT-prolonging drugs (notably Class Ia or Class III AADs) whenever possible and used with caution if deemed necessary (**Table S5**). Similarly, combination with Class II or Class IV AADs may promote sinus bradycardia or impair AV conductions. Importantly, the use of amiodarone is limited by potentially severe extra-cardiac toxicity (see below section "Proarrhythmia, toxicity and other major adverse effects"). Despite its pronounced toxicity, amiodarone remains the most commonly used AAD, accounting for 48% of prescriptions in 2016 in a United States insurance database,[95] 38% in the 'Get With the Guidelines – AF' registry[96] and 25% in a large international AF registry.[97] This predominance is likely due to the high prevalence of underlying cardiovascular disease (CVD), including ischaemic heart disease and HF, in patients at risk of atrial and VA. Under these conditions, many other AADs are contraindicated due to their increased proarrhythmic potential.

Dronedarone

Dronedarone is a non-iodine derivative of amiodarone, which was designed to retain antiarrhythmic efficacy while minimizing the potential for extracardiac adverse effects associated with amiodarone. Dronedarone exerts its antiarrhythmic effects through a multifaceted mechanism, involving inhibition of multiple ion channels (**Table S2**). It predominantly blocks Na^+ and K^+ channels, prolonging APD and refractory periods. Additionally, dronedarone possesses β-adrenoceptor blocking properties, further contributing to its antiarrhythmic action. Notably, it lacks the iodine moiety found in amiodarone, reducing the risk of thyroid dysfunction and other extracardiac adverse effects. Clinical trials, including EURIDIS/ADONIS (n=1237) and ATHENA (n=4628), have demonstrated the efficacy of

dronedarone in maintaining SR and reducing cardiovascular hospitalizations and mortality in patients with AF.[98–101] While not intended for use in patients with severe HF or those recently hospitalized for HF, dronedarone has shown promise in improving outcomes in those with milder HF.[99,102] Due to low bioavailability, dronedarone is advised to be taken with meals (oral absorption may increase 4-fold when taken with a fatty meal) (**Table S3 and S7)**. Dosing is non-complex: it is given in a fixed daily dose of 400 mg twice daily; dose adjustments do not apply. Dronedarone's safety profile, while generally favourable, warrants careful consideration. Gastrointestinal disturbances are among the more common adverse effects. Initially, there was apprehension regarding elevations in liver enzymes, but the overall incidence of mild to moderate liver injuries with dronedarone is only slightly increased when compared to other AADs.[103] The ANDROMEDA trial (n = 625) was conducted to evaluate the efficacy and safety of dronedarone in HF. Only 25% patients had AF.[104] Unfortunately, the trial was prematurely terminated due to safety concerns. The results indicated an increased mortality risk in patients with severe HF and a LVEF of less than 25%. As a consequence, dronedarone is not advised for use in this specific patient population. The PALLAS trial (n= 3236) investigated the use of dronedarone in patients with permanent AF (>6 months of continuous AF) and additional risk factors.[105] However, the trial was prematurely terminated due to safety concerns. The results indicated an increased risk of cardiovascular events, including stroke, HF and death, in patients receiving dronedarone compared to the placebo group and therefore is advised not to use dronedarone in this particular population and it should be discontinued in patients who develop persistent AF longer than 6 months during treatment. A subanalysis of this study found a strong effect of concurrent digoxin use on the adverse effect of dronedarone on cardiovascular death, but not on occurrence of HF.[106] The elevation of digoxin concentration induced by dronedarone is attributed to its interaction with P-gp. This interaction potentially may have contributed to the less favourable outcome observed in the dronedarone arm.

In summary, its effectiveness in rhythm control, coupled with its relatively favourable adverse effect profile, positions dronedarone as a valuable option for selected patients with AF. Its use is generally advised for patients with paroxysmal or persistent AF who do not have severe left ventricular dysfunction or advanced/recently decompensated heart failure (NYHA III or IV). It provides an alternative to amiodarone, especially when extracardiac adverse effects pose significant concerns. It is advised to avoid dronedarone in patients with permanent AF (> 6 months) and in those taking digoxin.

Sotalol

Sotalol is a racemic mixture of two isomers, D- and L-Sotalol. L-Sotalol is a non-selective β-adrenoceptor blocker with little Class III effects, while D-Sotalol primarily blocks the I_{Kr}. At low doses (e.g., ≤160 mg/day), racemic sotalol primarily exerts β-blocking (Class II) effects, while Class III effects remain minimal. At doses starting from 160 mg/day, with a linear increase thereafter, D-L-sotalol exhibits both β-blocking and Class III antiarrhythmic effects. Sotalol slows heart rate, prolongs cardiac action potential duration (QT interval), and increases refractoriness throughout the heart, particularly at slower heart rates due to its reverse use-dependence. In the AV node, it slows conduction and prolongs refractoriness, but it does not affect conduction velocity in fast-response tissues. In patients with reduced LVEF, sotalol can decrease the cardiac output and precipitate HF.[107–109]

Sotalol is less effective than amiodarone in maintaining SR after cardioversion of AF/AFL in patients with normal LV function, stable CAD, or valvular disease. However, it can enhance the success of direct current (DC) cardioversion.[32,110–113] To prevent AF, 80 mg twice daily may suffice, but a higher dosage may be prescribed if recurrences occur. Drug titration up to 160 mg twice daily (total 320 mg) may be performed based on arrhythmia complaints or results from ambulatory or remote rhythm monitoring. Sotalol also decrease heart rate even if AF persists,[92,114,115] but it is not effective for cardioversion of AF. In patients with haemodynamically stable VT, i.v. sotalol is more effective than lidocaine for the acute termination of the arrhythmia.[116] In addition, oral sotalol was significantly more effective than six Class I AADs (36% vs. 15% arrhythmia-free survival, $P < 0.001$) in preventing death and recurrences of VA at follow-up. This was demonstrated in 496 patients who were randomly assigned to undergo serial evaluation of drug efficacy using EP testing or Holter monitoring combined with exercise testing in the ESVEM trial.[117] In patients with an ICD and ischaemic or non-ischaemic recurrent VA despite a β-blocker, sotalol reduces the recurrences of sustained VT/VF and the frequency of discharges, but it does not improve survival.[32,118–120] Amiodarone plus β-blocker is more effective for preventing ICD shocks than sotalol but has an increased risk of drug-related adverse effect.[92] In survivors of acute MI, prophylactic D-sotalol therapy significantly reduces reinfarction, but not the incidence of SCD.[121] Sotalol can be used in idiopathic VT from the right ventricular outflow tract (RVOT) when associated with severe symptoms or haemodynamic compromise and in patients with a diagnosis of SQTS who present a contra-indication to the ICD or refuse it or in asymptomatic patients with diagnosis of SQTS a family history of SCD.[122,123] Defibrillation threshold (DFT) reassessment after sotalol is not required.[124]

Sotalol dose-dependently prolongs the QT and may cause TdP (0.3-2%), especially if renal impairment and HF are present.[32,108,122,125,126] Thus, sotalol is not advised in patients with less severe arrhythmias (PVCs, non-sustained VT), even if symptomatic, and may be appropriate for long-term treatment if close monitoring of QT, K^+ levels, creatinine clearance (CrCl), and other proarrhythmia risk factors is provided.[45,124,125,127]

Dofetilide

Dofetilide blocks the I_{Kr} and may increase the $I_{Na,L}$ via the inhibition of phosphoinositide-3-kinase leading to a prolongation of cardiac APD and refractoriness, without slowing intracardiac conduction.[109,128,129] The APD prolongation is more prominent in the atria and at slow heart rates but diminishes as the heart rate increases (reverse use-dependence).[128] Dofetilide has no significant haemodynamic effects.[128,130]

Oral (in-hospital) dofetilide is effective for the conversion of persistent AF/AFL of >1 week duration and the maintenance of SR after cardioversion, and to enhance the success of DC cardioversion in patients with SHD (HF, CAD, hypertrophic cardiomyopathy) or refractory to other AADs.[32,93,131–136] In patients with HFrEF or recent myocardial infarction, dofetilide restores and maintains the SR and reduces rehospitalizations for HF, and it does not increase all-cause or cardiac mortality.[133–137] It is also effective to cardiovert macro-re-entrant atrial arrhythmias to SR.[44]

Due to its QTc-prolonging effects and the associated risk of TdP (1–3.3% of patients), dofetilide is advised to be reserved for patients with symptomatic AF/AFL who are not candidates for catheter ablation and when other antiarrhythmic drugs are ineffective or contraindicated. It is advised to avoid it in patients with risk factors for QT prolongation.[133,136] Dofetilide is advised to be started in a setting that provides continuous ECG monitoring and patients hospitalized for at least 3 days. Dosage adjustments is advised to be based on CrCl and QT.

Ibutilide

Ibutilide is an I_{Kr} blocker that also activates $I_{Na,L}$, leading to the prolongation of cardiac APD and refractoriness. However, this prolongation is less pronounced at faster heart rates, demonstrating reverse use dependence.[109,138,139] Ibutilide has minor haemodynamic effects or negative inotropic effects and can be used safely in patients with SHD and prior MI.

Ibutilide is given intravenously and is advised for the rapid conversion of recent-onset AF/AFL to SR. It is more effective for the conversion of AFL[138–148] and to facilitate the success of electrical cardioversion in patients with AF refractory to prior electrical cardioversions.[141,143–147,149] It may also be appropriate for acute therapy of focal AT,[150] macro-re-entrant atrial arrhythmias,[44,141,143–147] AVRT due to manifest or concealed accessory pathways,[151] pre-excited AF,[151] and for the cardioversion of AFL and SVT during pregnancy in hemodynamically stable patients.[44,93,152,153] However, it is not useful for long-term prevention of AF/AFL. Ibutilide undergoes rapid hepatic metabolism, primarily via CYP enzymes, leading to significant degradation before it can reach systemic circulation. This results in poor bioavailability, making oral administration ineffective. The half-life of ibutilide is only about 6 hours, requiring frequent dosing if taken orally, which is impractical for maintaining therapeutic levels.

Ibutilide produces a dose-dependent QT prolongation and TdP can occur in up to 4% of patients during or within 1-4 hours after drug infusion.[139] Therefore, ibutilide is advised to be administered under continuous ECG monitoring, with resuscitation facilities readily available for at least 4 hours, or longer in patients with hepatic or renal impairment.[138,140,154]

Vernakalant

Vernakalant is a multichannel blocker with atrial specificity that prolongs atrial APD and refractoriness while slowing atrial conduction at depolarized potentials (~–70 mV) and high heart rates, particularly during AF. It has minimal effects on ventricular or AV nodal refractoriness, heart rate, or blood pressure.[155,156] Because of its fast dissociation kinetics from Na^+ channels, vernakalant is not expected to cause conduction abnormalities or proarrhythmia once the SR is recovered. Intravenous vernakalant is advised for rapid cardioversion (mean time 8-14 minutes, >50% conversion rate) of recent-onset AF (≤7 days for non-surgery patients; ≤3 days for post-cardiac surgery patients)[93,155,157–160] and also facilitates electrical cardioversion in cardioversion-resistant AF (**Figure 7**).[93,161] Although vernakalant produces a faster cardioversion of AF to SR and causes less proarrhythmic and extracardiac effects than Class Ic AADs and amiodarone, more comparative studies are needed.[158,159,162–164] Drug efficacy decreases with the duration of AF, being ineffective for the conversion of AF lasting >7 days, and in patients with AFL.[93,159,164]

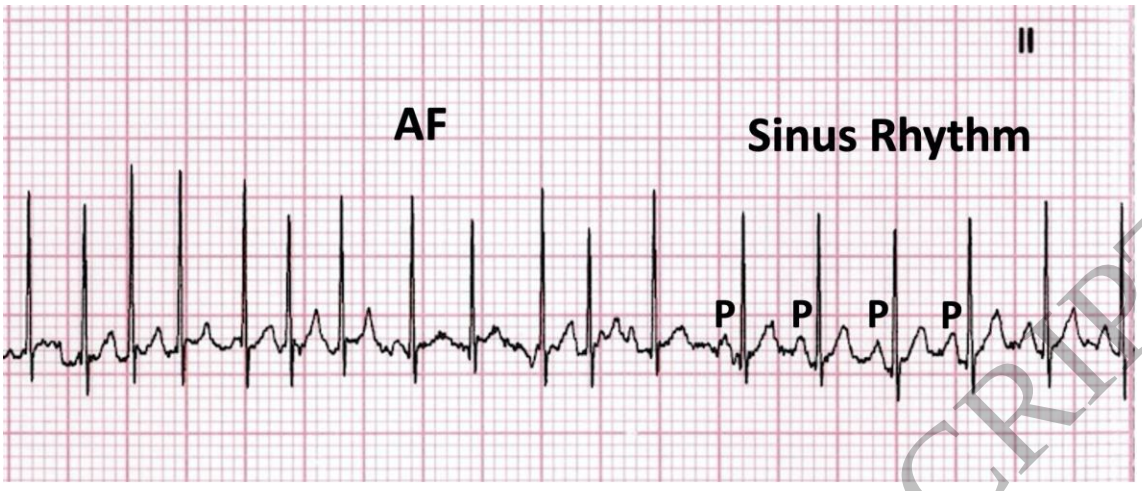

Figure 7: ECG tracing of lead II demonstrating the termination of atrial fibrillation (AF) after a 7-minute infusion of 350 mg of vernakalant in a patient with no structural heart disease.

The transition to sinus rhythm is marked by the appearance of normal P waves (P), indicating successful restoration of organized atrial activity. This highlights the efficacy of vernakalant in achieving cardioversion in patients with AF.
ECG recorded at a speed of 5 mm/s and a sensitivity of 10 mm/mV.

Class IIIb

Nicorandil

This antianginal drug is a nitric oxide (NO) donor and sarcolemmal and mitochondrial ATP-dependent K^+ (K_{ATP}) channel opener, producing vasodilation of coronary arteries and venous capacitance vessels.[165–167] During ischaemia/reperfusion, mitochondrial K_{ATP} channel opening exerts cardioprotective effects via hyperpolarization of the membrane potential that improves intracardiac conduction, shortens ventricular APD and refractoriness, prevents intracellular Ca^{2+} overload and suppresses triggered-induced arrhythmias.[165–167] Nicorandil decreases ischaemia-induced VA[167] and improve no-reflow phenomenon and VA in patients undergoing percutaneous coronary angioplasty.[165,168–170] In patients with LQTS1, nicorandil shortens the QT, improves repolarization abnormalities and abolishes EADs and recurrence of syncope.[171,172]

Class IIA

Bisoprolol, Metoprolol, Carvedilol, Nadolol, Propranolol

Chronic autonomic dysfunction promotes cardiac remodelling, including hypertrophy, apoptosis and fibrosis. It also contributes to the progression of multiple CVDs, indirectly promoting a vulnerable substrate for arrhythmias. Moreover, acute autonomic imbalance is a well-accepted trigger of cardiac arrhythmias.[6,173] Accordingly, β-blockers play a major role in the treatment of CVD. Here, the properties of β-blockers relevant for their antiarrhythmic effects are briefly summarized.

Typically, β-blockers are subdivided into three generations: first generation β-blockers (e.g., propranolol) have similar affinity for β_1- and β_2-adrenoceptor subtypes, second-generation β-blockers (e.g., metoprolol, atenolol or bisoprolol) have a higher affinity for β_1-adrenoceptors, and third-generation β-blockers (e.g., carvedilol) have additional α-blocking properties.[6] Most of the proarrhythmic effects of sympathetic stimulation have been attributed to β_1-adrenoceptors and may involve Ca^{2+} overload due to elevated heart rates (themselves promoted by sympathetic stimulation of HCN channels) and hyperphosphorylation of Ca^{2+}-handling proteins, thereby promoting triggered activity. In addition, sympathetic stimulation can facilitate re-entry-promoting repolarization instability when slow delayed rectifier K^+ current (I_{Ks}) is downregulated or dysfunctional due to genetic mutations (in the case of long-QT syndrome types 1 and 5)[174] or in the presence of abnormal autonomic innervation.[175]

All β-blockers inhibit automaticity and have negative chronotropic effects. Their inhibition of L-type Ca^{2+} channel phosphorylation, decreasing $I_{Ca,L}$, contribute to the β-blocker-induced inhibition of AV conduction (negative dromotropy). The reduction in phosphorylation of L-type Ca^{2+} channels and other Ca^{2+}-handling proteins also reduces intracellular Ca^{2+} levels, explaining the potential negative inotropic effects of β-blockers in the acute setting. This reduction in Ca^{2+} levels also decreases the likelihood of ectopic (triggered) activity.[45,174] Finally, β-blockers reduce electrophysiological heterogeneity caused by inhomogeneous autonomic innervation. With long-term use, they may help prevent proarrhythmic remodelling by lowering myocardial energy consumption and oxidative stress, partly due to their negative inotropic and chronotropic effects.

Due to their negative dromotropic effects and rapid onset of action, β-blockers are the first-line treatment for rate-control in AF.[93] In addition, β-blockers suppress PVCs, reduce the likelihood of VT, (in)appropriate ICD interventions, and SCD. Overall, they improve morbidity and mortality in a wide range of patients, including in the setting of acute coronary syndrome (ACS), MI, HF, long-QT syndrome and CPVT.[45] Interestingly, the prognostic benefit of β-blocker seen in HF patients with SR has not been consistently detected in patients with AF.[176] Perioperative β-blocker therapy is commonly used for the prevention of postoperative AF after cardiac surgery, but must not be used in patients undergoing non-cardiac surgery.[93]

Although all β-blockers have antiarrhythmic properties and detailed comparisons between different β-blockers are rare, a number of relevant clinical distinctions have to be noted.[177] Non-selective β-blockers (propranolol and particularly nadolol) appear more effective than β_1-adrenoceptor selective blockers in patients with long-QT syndrome or CPVT,[178] possibly due to a sensitization of β_2-adrenoceptors with β_1-adrenoceptor selective blockers.[174] In agreement, the combination of i.v. amiodarone and oral propranolol is safe, effective, and superior to amiodarone and metoprolol in the management of electrical storm (ES) in ICD patients.[179] The better efficacy of nadolol compared to propranolol has been partially attributed to better compliance due to more favourable pharmacokinetic properties. In particular, propranolol is highly lipophilic, allowing it to cross the blood-brain barrier and is therefore associated with more central nervous system (CNS) side effects than nadolol.[174] In addition, as mentioned earlier, short-acting β-blockers like propranolol are advised to be taken with food to improve absorption, as they are primarily metabolized in the liver and undergo significant first-pass metabolism. This hepatic processing can lead to substantial interindividual variability in plasma drug concentrations, necessitating careful dosing and monitoring. If a short-acting, hepatically metabolized β-blockers appears ineffective, switching to a renally excreted β-blockers such as

nadolol, may be a more effective alternative. Finally, propranolol appears to have a higher affinity for Na^+ channels than other β-blockers, which may have pro- or antiarrhythmic consequences.[174] As such, nadolol is among the most commonly used β-blocker in patients with channelopathies.[178] On the other hand, carvedilol stabilizes RyR2 gating, and has anti-inflammatory and anti-oxidant effects. Experimental work using carvedilol analogues without β-blocking properties has suggested that direct RyR2-stabilizing effects of carvedilol may contribute to its antiarrhythmic effects.[5] Carvedilol also possesses α-blocking properties, which can promote vasodilation and potentially lead to hypotension. Finally, pharmacokinetic considerations as well as indications for specific comorbidities may direct the choice of individual β-blockers (**Table S3**).[177,180]

Other (Nebivolol, Esmolol, Landiolol)

Nebivolol is a selective β_1-adrenoceptor blocker with a NO-potentiating vasodilatory effect, which makes it suitable for the prevention of arrhythmias particularly in patients with CAD.[181] Esmolol is selective β_1-adrenoceptor blocker with rapid onset of action but a very short duration of action (~10 mins), which is used intravenously to terminate supraventricular arrhythmias.[182] Landiolol, an another selective β_1-adrenoceptor blocker with rapid onset of action and very short half-life, was subsequently developed by modifying the chemical structure of esmolol to produce a compound with a higher β_1-adrenoceptor selectivity and potency without increasing its duration of action.[183]

Class IIB

Isoprenaline (Isoproterenol)

Isoprenaline, also known as isoproterenol in some countries, such as the United States, is a non-selective β-adrenoceptor agonist. Activation of both β_1- and β_2-adrenoceptors causes the α-subunit of G-protein coupled receptors to exchange GMP for GTP, activating them, and allowing the α-subunit to dissociate from the β and γ-subunits.

Dissociation of the α-subunit activates adenylate cyclase, converting ATP to cyclic AMP. Cyclic AMP activates protein kinase A (PKA), which phosphorylates cardiac L-type Ca^{2+} channels. These channels depolarize sinoatrial and AV nodal cells by inward active transport of Ca^{2+} ions. Activation of β_1-adrenoceptors increases contractility, enhances conduction velocity, accelerates relaxation, raises heart rate, and shortens the QT. Activation of β2-adrenoceptors leads to glycogenolysis in the liver, glucagon release from the pancreas, and activation of the renin-angiotensin-aldosterone system. Isoprenaline is metabolized by catechol O-methyltransferase and its elimination half-life following i.v. administration is 2.5-5 minutes.

Patients experiencing an overdose may present with tachycardia, arrhythmias, palpitations, angina, hypotension, or hypertension. In case of overdose, treatment involves stopping the administration of isoprenaline and monitoring blood pressure, pulse, respiration, and ECG.

Isoprenaline infusion is advised for ES related to bradycardia related acquired LQTS, BrS, early repolarization syndrome (ERS) and SQTS.[184] It is highly effective in acute suppression of recurrent ICD shocks in these latter settings. It may also be useful in the acute management of unstable third-degree AV block while awaiting definitive pacemaker implantation. Isoprenaline

infusion is contraindicated in ACS, hypertrophic cardiomyopathy (HCM) and uncontrolled hypertension. The main side effects are sinus tachycardia, vasodilatation, tremor, sweating and nausea.

Class IIC

Atropine

Atropine is a competitive antagonist of muscarinic-M2 receptors located in SA and AV nodes. It reverts sinus bradycardia to normal SR, shortens AV nodal refractoriness and enhances AV node conduction, but has little effect on infranodal conduction tissues.[185] It is advised for patients with symptomatic or hemodynamically unstable sinus bradycardia and second- or third-degree AV block.[186–189] Additionally, it is used for symptomatic or unstable bradyarrhythmias caused by increased vagal activity in the setting of acute inferior MI and for CA associated with brady-asystole.[186–191] However, atropine may worsen AV conduction block in the presence of intra-His or distal conduction disease[192] and may be ineffective in heart transplant recipients due to vagal denervation.[193]

Class IID

Digoxin

Digoxin increases cardiac vagal tone via activation of I_{KACh} in the atria, which inhibits I_f in the SA node and $I_{Ca,L}$ in the AV node, and activates acetylcholine-activated potassium current ($I_{K,Ach}$) in the atria. As a result, digoxin decreases SA automaticity, prolongs AV conduction and refractoriness and produces a non-uniform shortening of atrial APD and refractoriness, respectively.[93,131,194] Digoxin is advised to slow the ventricular rate in patients with permanent and persistent AF. However, digoxin slows ventricular rate at rest, when vagal tone predominates, but is less effective when sympathetic activity increases (i.e., during exercise, fever, hyperthyroidism, postoperative AF).[93,131] Thus, digoxin has been replaced by β-blockers and diltiazem/verapamil that control heart rate both at rest and/or during exercise. Digoxin can be combined with these drugs when ventricular rate remains uncontrolled or these drugs are not tolerated or contraindicated.[93,114,131,195–197] Because of its positive inotropic effect, digoxin and/or β-blockers are appropriate for rate control in patients with HFrEF.[93,131] Digoxin may be used to slow the ventricular rate in patients with AF and ACS or with acute HF when β-blockers and diltiazem/verapamil are contraindicated. In HF patients who cannot tolerate higher doses of β-blockers, low doses of digoxin can be added to reach the desired heart rate and symptom control. It is important to note, as mentioned before, that both dronedarone and amiodarone increase digoxin levels which potentially may cause drug toxicity. Digoxin abbreviates atrial refractoriness and is ineffective in the cardioversion of AF/AFL to SR or the maintenance of SR and is advised to be avoided in pre-excited AF.[93,131,197,198]

Class IIE

Adenosine

Adenosine is an purine nucleoside that interacts with adenosine G_i-protein coupled A1 receptors in atrial muscle, SA and AV nodal cells.[199,200] It activates $I_{K,ACh}$ that hyperpolarizes the membrane potential, slows SA pacemaker activity and shortens atrial APD and refractoriness. It

also inhibits the I_f and reduces adenyl cyclase activity and intracellular cAMP levels, which indirectly inhibits the $I_{Ca,L}$ during sympathetic stimulation. As a consequence, adenosine slows sinus rate and AV conduction (**Figure 8A and 8B**) and prolongs AV refractoriness leading to a transient AV block responsible for AV nodal dependent tachycardia termination and abolishes EADs/DADs induced by catecholamines.[156,199,200] Stimulation of cardiac Gs-protein coupled A2 receptors in endothelium and vascular smooth muscle results in coronary vasodilation.

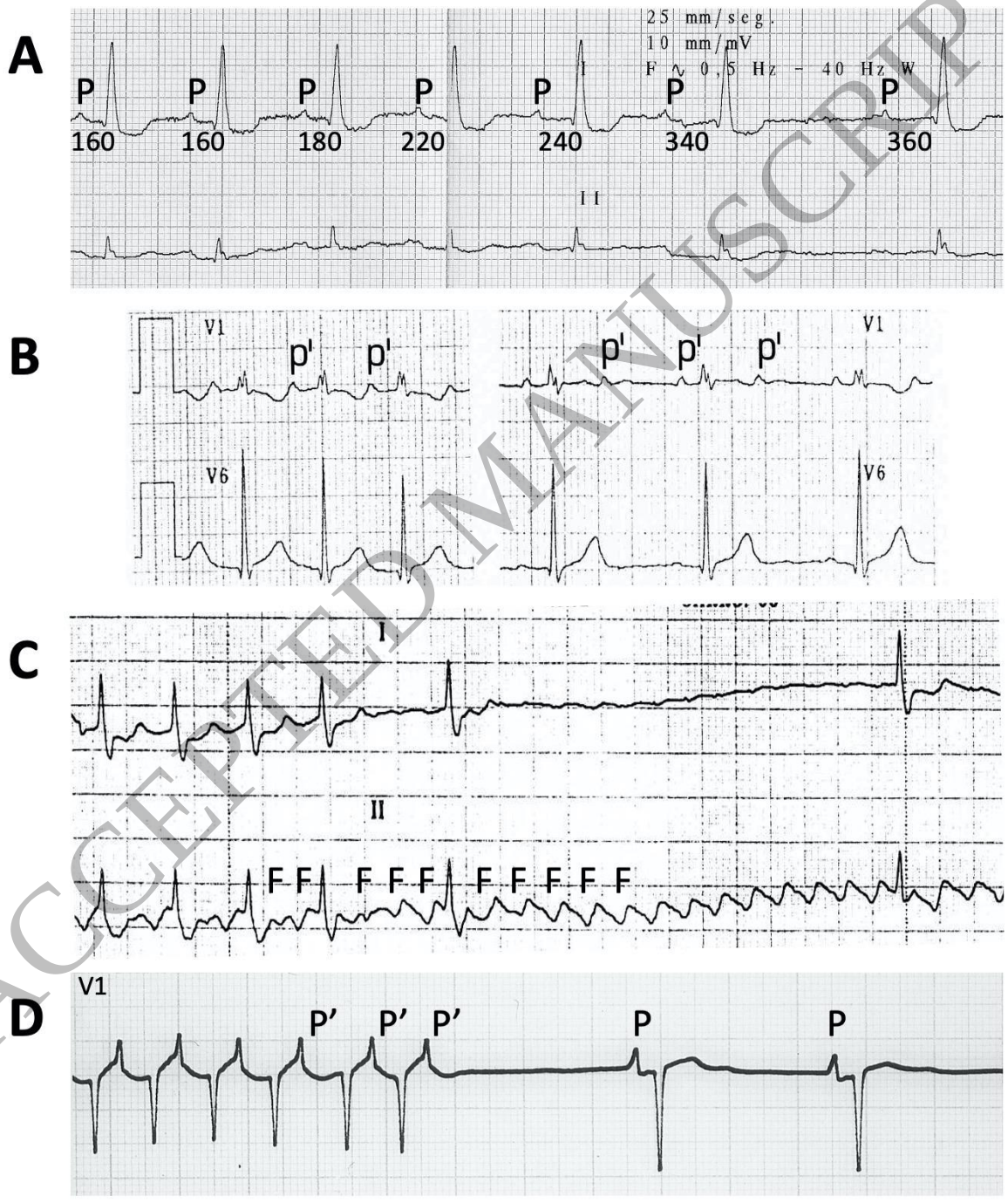

Figure 8: ECG tracings illustrating the effects of adenosine on different atrial rhythms: sinus rhythm (Panel A), atrial tachycardia (Panel B), atrial flutter (Panel C), and paroxysmal supraventricular tachycardia (PSVT) (Panel D).
Panel A: Sinus rhythm at a rate of 88 bpm slows significantly with PR interval prolongation following adenosine infusion. Panel B: Atrial tachycardia at 125 bpm, characterized by a non-sinus P wave morphology (P'). Initially, conduction is 1:1 AV (left). After adenosine administration, conduction changes to 2:1 AV (right) without a significant change in atrial rate. Panel C: Common atrial flutter with 2:1 AV conduction. Adenosine-induced AV block reveals prominent F waves, enhancing visualization of the flutter waves. Panel D: Termination of atrioventricular reentrant tachycardia (AVRT) mediated by a left-sided concealed accessory pathway. Termination occurs after AV node conduction block, interrupting conduction of the final retrograde P' wave and restoring sinus rhythm. All ECGs were recorded at a speed of 25 mm/s and a sensitivity of 10 mm/mV.

Due to its rapid onset and short duration of action (10–30 seconds), intravenous adenosine is the drug of choice for the rapid termination of SVT when vagal manoeuvres are ineffective. It is effective in treating sinus node (SN) re-entry tachycardia, triggered focal AT, AV nodal re-entrant tachycardia (AVNRT), and atrioventricular re-entrant tachycardia (AVRT) due to accessory pathways (**Figure 8D**). Additionally, it may be useful for certain VTs and SVTs in congenital heart disease.[44,199–203]. Adenosine is preferable to verapamil or diltiazem, particularly in patients treated with i.v. β-blockers or with history of HF or severe hypotension, and in children. Adenosine also slows sinus rate, may cause sinus exit block and can terminate SAN re-entry.[44,204] Like digoxin, adenosine is unlikely to terminate AF or AFL, because it shortens atrial refractoriness which promotes re-entry (**Figure 8C**).[93,131] For the same reason, it does not interrupt macro-re-entrant ATs unless the circuit involves the AV node,[93,205] and does not affect conduction velocity through the His-Purkinje or normal accessory pathways (**Figure 9**). However, conduction may be blocked in pathways with long conduction times or decremental conduction properties.[44,204–206] In general, VT does not respond to adenosine, but adenosine can terminate idiopathic right outflow tract VT caused by cAMP-mediated triggered DADs, and less commonly, left fascicular idiopathic VT.

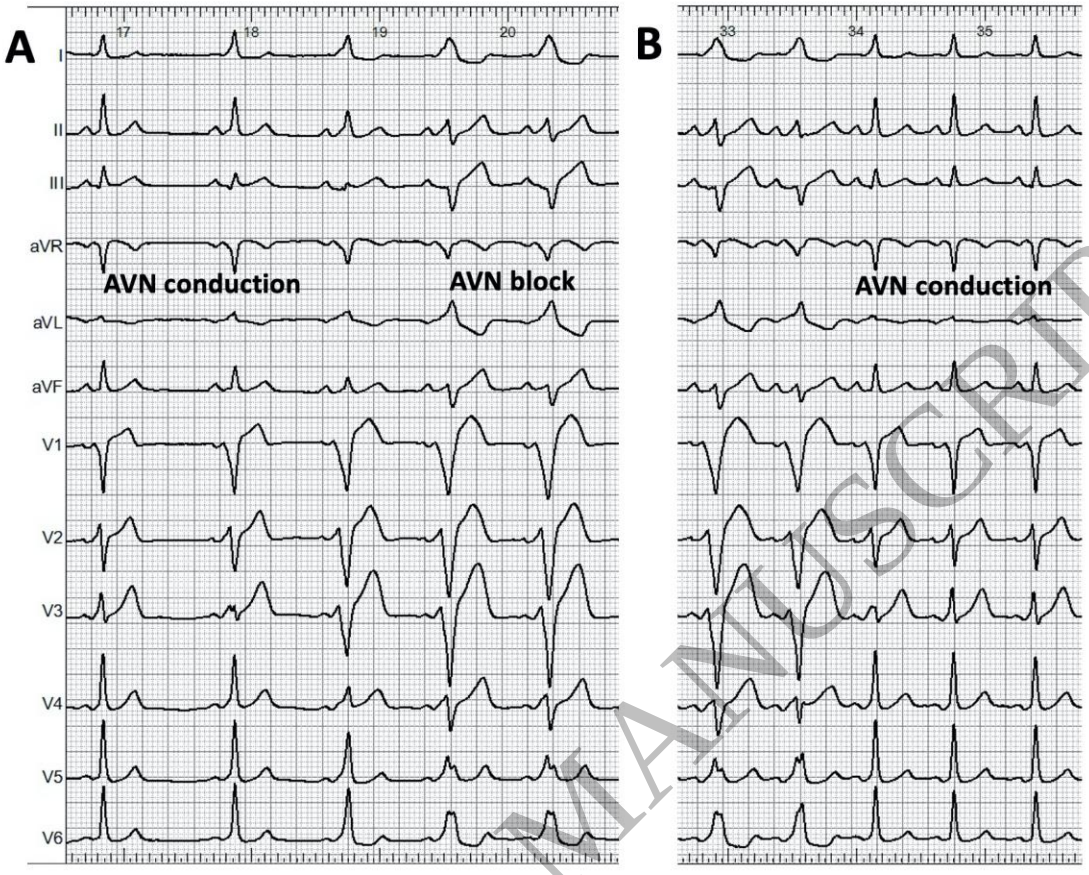

Figure 9: 12-lead ECGs of a patient with Wolff-Parkinson-White (WPW) syndrome caused by a right posteroseptal accessory pathway which becomes more prominent following adenosine infusion**.**
Panel A: Preexcitation becomes more apparent following the infusion of 12 mg of adenosine, which blocks conduction through the AV node. This is evidenced by a pronounced delta wave, indicative of increased conduction via the accessory pathway. Panel B: Preexcitation diminishes as AV nodal conduction resumes after the effects of adenosine dissipate, reducing the contribution of the accessory pathway to ventricular depolarization. These findings demonstrate the dynamic interplay between AV nodal conduction and accessory pathway activation in WPW syndrome, highlighting the diagnostic utility of adenosine in unmasking preexcitation.
The recordings were obtained at a speed of 25 mm/s and a sensitivity of 10 mm/mV.

Adenosine may cause transient new arrhythmias at the time of cardioversion because it heterogeneously shortens atrial APD and refractoriness and produces transient sympathetic stimulation through baroreflex activation in response to hypotension. Adenosine may lead to hyperpolarization of dormant pulmonary vein myocytes increasing their excitability and automaticity[207,208] and could accelerate pre-excited atrial arrhythmias.[200,209]

Class IV

Verapamil and Diltiazem

These agents block cardiac $I_{Ca,L}$, decrease heart rate and cardiac contractility, slow conduction, and prolong refractoriness at the AV node. They also suppress abnormal automaticity in depolarized cells and inhibit triggered activity induced by EADs.[210,211] However, they do not alter excitability, conduction velocity, or refractoriness in atrial or ventricular muscle or His-Purkinje fibres that generate Na^+-driven APs. Since sinus node rate and cardiac contractility may be suppressed, these agents are advised to be used with caution in patients with impaired left ventricular function or those receiving β-blockers. However, the impact on sinus rate depression may be less pronounced, as their vasodilatory effect induces a sympathetic reflex activation that counteracts their direct cardiac effects.

Because of their depressant effect on the AV node, diltiazem and verapamil are advised to control the ventricular rate at rest and during exercise in patients with AF/AFL. They may be used alone or in combination with β-blockers or digoxin.[114,196,212–219] Intravenous verapamil and diltiazem are often used to slow ventricular heart rate in the acute setting in patients without pre-excitation.[217,220–222]

Verapamil and diltiazem are advised for acute ventricular rate control in hemodynamically stable patients with SVT, including focal or multifocal AT,[223–225] narrow QRS tachycardia, IAST, AFL, macro re-entrant atrial arrhythmias,[220,224,226] AVNRT[221,227] and AVRT if no signs of pre-excitation are present.[221,228–232] They are appropriate when vagal manoeuvres and adenosine fail. Verapamil and diltiazem are not advised for cardioversion of AF or AFL or for maintaining SR after cardioversion, as they shorten atrial refractoriness, potentially promoting re-entry.

Verapamil is advised in idiopathic left VT related to interfascicular re-entry or in LV fascicular VT, symptomatic patients with papillary muscle tachycardia and mitral and tricuspid annular VT.[45,233–235] Occasionally, diltiazem and verapamil can suppress VA associated with myocardial ischaemia. In short-coupled TdP, i.v. verapamil can suppress and prevent ES or recurrent ICD interventions.[236,237]

Verapamil and diltiazem are contraindicated in patients with hypotension or HFrEF,[201,203,238–240] haemodynamic instability or pre-excited AF as they may increase the ventricular response.[241,242] They can also cause severe hemodynamic deterioration in patients with wide QRS tachycardia of unknown aetiology.[234,243,244]

Finally, there are differences between verapamil and diltiazem. Verapamil has stronger negative inotropic and chronotropic effects, making it more effective for arrhythmias like AF and SVT, but it is more likely to cause bradycardia, worsen HF, and lead to constipation due to its impact on gastrointestinal smooth muscle. It also has sympatholytic properties and can relieve bronchospasm. Diltiazem has a balanced action on both vascular smooth muscle and the heart, making it more suitable for hypertension and angina without significantly reducing cardiac output. It is generally better tolerated, with fewer side effects such as constipation, but it is more likely than verapamil to cause leg oedema. It is preferred for patients who require a gentler approach to rate control or blood pressure management.

Bepridil

This antianginal drug is a multichannel blocker and acts intracellularly as a calmodulin antagonist which reduces sarcoplasmic reticulum Ca^{2+} release and inhibits ischaemia-induced catecholamine release.[245] Bepridil prolongs atrial and AV nodal refractoriness, but has minor effects on ventricular refractoriness and reduces heart rate, peripheral vascular resistances and blood pressure.[245,246] Bepridil is effective for the conversion of persistent AF in patients without SHD and normal QT and for blocking AV nodal conduction. It may decrease heart rate even if AF persists.[59,245,247,248] The efficacy of bepridil in preventing AF recurrence is considered limited.[59,249–251]

Table 2: Typical market formulations and dosing of commonly used AADs and antiarrhythmic agents (for detailed information, please refer to Table S7 in the supplement).[a]

Modified VW Class	AAD	Intravenous Bolus	Intravenous Infusion	Oral Loading	Oral Maintenance
0	**Ivabradine** (5 & 7.5 mg tablets)	No i.v. formulation available	No i.v. formulation available	No oral loading dose is specified.	5-7.5 mg/12 hrs
IA	**Ajmaline** (50 mg vials)	1 mg/kg in 10 min (max 100 mg)	-	No oral formulation available	No oral formulation available
	Quinidine (Sulphate: 200 & 300 mg tablets. Gluconate: 324 mg tablets)	Gluconate: <5 mg/kg at 0.25 mg/kg/min (max 10 mg/kg)	-	200 mg/3 hrs (max 3 g in 1 d)	• Sulphate: 200-400 mg/6-8 hrs or 600 mg ER/8-12 hrs (max dose 3-4 g/day • Gluconate: 648 mg/12 hrs or 324-660 mg/8 hrs
	Procainamide (1 g vials. 250 mg capsules)	100 mg; can be repeated every 5 min (max 500–750 mg, 50 mg/min)	2-6 mg/min (max 1 g/d)	500-1000 mg	250 mg/6 hrs
	Disopyramide (50 mg vials. 100 & 150 mg ER capsules)	2 mg/kg in 10 min	400 mcg/Kg/h	No loading dose specified	100-150 mg IR/6 hrs or 200-300 mg ER/12 hrs (max 750 mg/d)
IB	**Lidocaine** (50 & 100 mg vials)	100 mg (1-1.5 mg/kg); can repeat 50 mg (0.5-0.75 mg/kg) in 5-10 min (max 3 mg/kg)	1-4 mg/min (max 3 mg/kg)	No oral formulation available	No oral formulation available
	Mexiletine (50, 100, 150, 167, 200 &	No i.v. formulation available	No i.v. formulation available	400 mg followed by 300 mg 2-3 times (max 1.2 g in 1 d)	167 mg/d (max 500 mg)

	250 mg capsules)				
	Phenytoin (100 mg vials. 30, 100, 200 & 300 mg ER capsules)	50-100 mg every 10-15 minutes (max 1 g)	-	-	300-400 mg/day orally in divided doses 1 to 4 times/d (max 600 mg/d)
IC	**Flecainide** (150 mg vial. 50, 100 & 150 mg IR tablets. 100, 150 & 200 mg ER capsules)	1-2 mg/Kg in 10 min	50 mg/h (max 1 g/d)	300 mg[b]	100 mg/12 hrs or 200 mg ER/d (max 300 mg/d[c])
	Propafenone (70 mg vial. 150, 225 & 300 mg IR tablets. 225, 325 & 425 mg ER tablets)	2 mg/Kg in 10 min	7 mg/Kg in 1 d	600 mg[b]	150-300 mg IR/8 hrs or 225-425 mg ER/12 hrs (max 900 mg/d)
	Antazoline (100 mg vial)	100 mg in 1 min; 50 mg can be repeated every 5 min (max 300 mg)	100 mg over 60 min (30–50 mg/min)	-	-
	Pilsicainide (50 mg vial. 25 & 50 mg capsules)	0.75 mg/kg	-	150 mg	50 mg/8 hrs (max 225 mg/d)
	Cibenzoline (75 mg vial. 50 & 100 mg tablets)	1 mg/kg	-	No oral loading dose is specified	100 mg/8 hrs
ID	**Ranolazine** (375, 500, 750 & 1000 mg ER tablets)	No i.v. formulation available	No i.v. formulation available	2 g[b]	500-750 mg /12 hrs (with food) (max 1 g/12 hrs)
IIA	**Atenolol** (5 mg vials. 25, 50 & 100 mg tablets)	2.5 mg in 2.5 min (1 mg/min) repeated at 5 min intervals (max 10 mg)	0.15 mg/kg bodyweight may be administered over a 20 min period and repeated every 12 hrs	No oral loading dose is specified.	25-50 mg/d (max 100 mg/d)
	Bisoprolol (1.25, 2.5, 5 & 10 mg tablets)	No i.v. formulation available	No i.v. formulation available	No loading dose is specified	1.25-5 mg/d (max 20 mg/d)
	Carvedilol (3.125, 6.25, 12.5 & 25 mg tablets)	No i.v. formulation available	No i.v. formulation available	Initially 3.125 mg/12 hrs	25 mg/12 hrs (max 100 mg/d)
	Metoprolol (5 mg vial. 25, 37.5, 50, 75 &	5 mg in 2 min (max 15 mg)	No dose is specified for prolonged infusion	No loading dose specified	25-100 mg 12 hrs (metoprolol tartrate) or 50-200 mg/d (metoprolol XL succinate)

	100 mg tablets)				
	Nebivolol (2.5, 5, 10 & 20 mg tablets)	No i.v. formulation available	No i.v. formulation available	No loading dose specified	2.5-10 mg/d (max 20 mg/d)
	Propranolol (10, 20, 40, 60 & 80 mg tablets. 60, 80, 120 mg & 160 mg ER tablets)	1-3 mg in 1 min; repeat every 2-5 min if needed up to 5 mg (max 0.2 mg/Kg)	-	No loading dose specified	20–40 mg IR/6 hrs, 80–160 mg ER/d (max 240 mg/d) (with food)
	Nadolol (20, 40 & 80 mg tablets)	-	-	No loading dose specified	40-80 mg/d (max 320 mg/d)
	Esmolol (100 mg vial)	0.5 mg/Kg in 1 min	0.05-0.2 mg/kg/min (max 0.3 mg/kg/min)	No oral formulation available	No oral formulation available
	Landiolol (288 mg vial)	0.1 mg/kg in 1 min	10-40 mcg/kg/min (max 57.6 mg/kg /d)	No oral formulation available	No oral formulation available
IIB	**Isoprenaline** (0.2 mg ampoules)	10 mcg	2-20 mcg/min		
IIC	**Atropine** (0.4, 0.8 & 1 mg ampoules)	1 mg followed by additional doses up to 3 mg (0.04 mg/kg)	No prolonged infusion advised	No oral formulation available	No oral formulation available
IID	**Digoxin** (0.25 mg ampoules. 0.125 & 0.25 tablets. 0.1-0.25 mg/ml solution	0.25-0.5 mg followed by additional doses (max 1.5 mg/d)	0.25 mg/d No prolonged infusion advised	0.5-0.75 mg in 2 doses 6 hours apart (max 1.5 mg/d)	0.25 mg/d (adjust to blood levels and CrCl)
	Digitoxin (0.07 mg ampoules. 0.0625, 0.125 & 0.25 mg tablets)	0.5 mg followed by additional doses (max 1.5 mg/d)	0.1 mg/d No prolonged infusion advised	0.6-1.2 mg given in divided doses over 1 d	0.05-0.1 mg/d (adjust to blood levels and CrCl)
IIE	**Adenosine** (6, 12, 30, 60, 90 & 100 mg vials)	6, 12 & 18 mg boluses	No prolonged infusion advised	No oral formulation available	No oral formulation available
III	**Amiodarone** (150 & 300 mg vials. 100, 200 & 400 mg tablets)	150 mg in 10 min or 300 mg over 30 min followed by 900–1200 mg i.v. over 24 hrs[d] (max 2200 mg/d)	600-1200 mg/d for 8-10 ds[e]	Standard: 600 mg/d in 2-4 weeks Accelerated: 1200 mg/d in 3 doses for 2 weeks[e] (total ≈10 g)	200 mg/d (max 600 mg/d)
	Dronedarone (400 mg tablets)	No i.v. formulation available	No i.v. formulation available	-	400 mg/12 hrs (with food)

	Dofetilide (125, 250 & 500 mg capsules)	No i.v. formulation available	No i.v. formulation available	No loading dose specified	125-500 mcg/12 hrs (specific algorithm followed based on QT and CrCl)
	Ibutilide (1 mg vial)	1 mg over 10 min if ≥60 kg (0.01 mg/kg if <60 kg); can repeat 1 mg once if needed	-	No oral formulation available	No oral formulation available
	Sotalol (150 mg vials. 80, 120, 160 & 240 mg tablets & capsules)	1 mg/kg in 10 min; can be repeated after 6 hrs (Adjust dose based on CrCl) (max 450 mg/d)	75 mg/12 hrs	No oral loading dose specified	80-160 mg/12 hrs (max 480 mg/d)
	Vernakalant (500 mg vials)	3 mg/Kg in 10 min followed in 15 min by 2 mg/Kg in 10 min if needed	No prolonged infusion advised	No oral formulation available	No oral formulation available
IV	**Verapamil** (5 mg ampoule. 40, 80, 120 mg IR tablets. 100, 120, 180, 240, 300 & 360 mg ER tablets)	2.5-5 mg in 2 min followed in 15 min by 5-10 mg if needed	2-4 mg/h (max 100 mg/d)	No loading dose specified	80-120 mg IR/8 hrs or 180-240 mg ER/d (max 480 mg/d)
	Diltiazem (30, 60, 90 & 120 mg IR tablets & capsules. 120, 180, 200, 240 & 300 mg ER tablets & capsules)	0.25 mg/kg in 2 min followed by 0.35 mg/Kg if needed	5-15 mg/h	No loading dose specified	60 mg/8 hrs or 120-360 mg ER/24 hrs (max 480 mg/d)
	Bepidril (100 & 200 mg tablets	-	-	No loading dose specified	200 mg/d (max 400 mg/d)
Other agents	**Magnesium** (1.5 g ampoules)	1-2 g in 5 min	0.5-1 g/h	No loading dose specified	350 mg/d

AAD, antiarrhythmic drug; CrCl, creatinine clearance, ER, extended release; IR, immediate release.

[a]*Some of the drugs listed have varying availabilities and approval statuses for the treatment of arrhythmias. Ranolazine is approved by both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) for the treatment of chronic angina, but not specifically for arrhythmias. Vernakalant is approved by the EMA for the rapid conversion of recent-onset AF to sinus rhythm in adults, but it has not received FDA approval. Conversely, dofetilide is approved by both the FDA and EMA for maintaining sinus rhythm in patients with AF or flutter; however, it is marketed only in the United States and not in Europe. Additionally, certain dosage formulations may not be available in all countries.*

[b]*See **Box 6**.*

[c]*The maximum advised dose in the U.S. for the treatment of VT is 400 mg/day.*

[d]*It is advised to dilute the drug in 5% dextrose (glucose) to a concentration not exceeding 2 mg/mL. This dilution is advised to be administered via a central venous catheter (CVC) to minimize the risk of thrombophlebitis.*

[e]*Goal to achieve cumulative doses of 5-10 grams by i.v. loading and 10–15 g by oral loading.*

Treatment by arrhythmias

General

Several considerations come into play when choosing an AAD, with a key determinant being whether the drug is intended for arrhythmia termination or prevention. While it is generally true that drugs effective in terminating a specific arrhythmia often exhibit preventive properties, exceptions abound. For instance, amiodarone is highly effective in preventing AF but has a weaker efficacy in terminating acute episodes. Beyond these dynamics, factors such as the route of administration and the drug's use-dependent or reverse use-dependent effects can significantly impact its effectiveness for prevention versus termination of arrhythmias.

Additionally, AADs exert distinct effects on different regions of cardiac tissue. Class II and IV agents primarily slow conduction and prolong refractoriness in the sinus and AV nodes, while Class I and III agents predominantly affect the working myocardium at both atrial and ventricular levels **(Figure 10)**. The presence of ventricular structural changes or scarring generally discourages the use of Class I AADs, particularly Class Ic, due to their potential to slow conduction and promote ventricular reentry and proarrhythmia. Another key consideration is the degree of ventricular myocardial contractility depression and the risk of HF aggravation, which are most pronounced with Class Ic and Class IV agents but less significant with quinidine or amiodarone. Both proarrhythmic risks and extracardiac specificities and toxicities—discussed in a separate section—are critical factors in the selection of an AAD. Recognizing these region-specific effects is essential for selecting the appropriate drug for each patient.

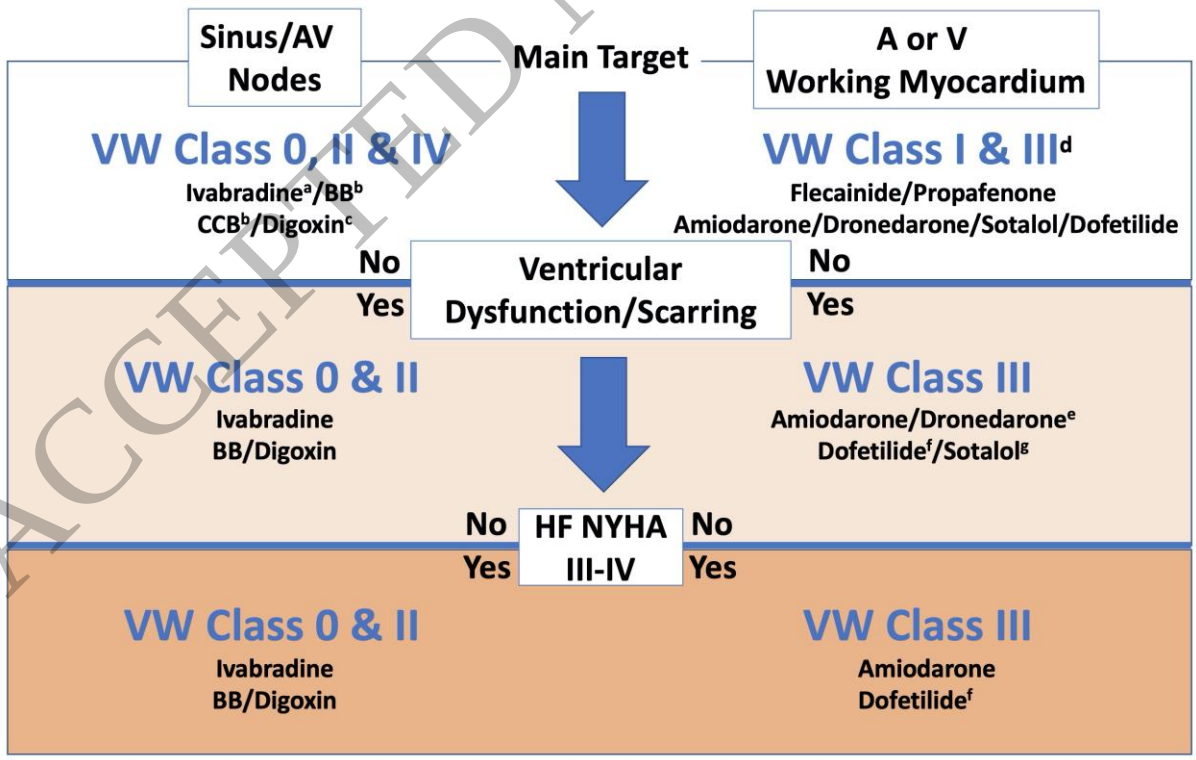

Figure 10. Antiarrhythmic drug (AAD) selection based on cardiac substrate and main target of action.
This figure advises on the selection of AADs based on their primary target (sinus/AV nodes vs. working atrial [A] and ventricular [V] myocardium) and the presence of ventricular dysfunction, scarring, or heart failure. Class 0, II, and IV agents (e.g., ivabradine, BB, CCB, and digoxin) are preferred for rate control by acting on the sinus and AV nodes. Class I and III agents (e.g., flecainide, propafenone, amiodarone, dronedarone, sotalol, and dofetilide) are used for rhythm control, but their choice depends on the structural integrity of the ventricles. Structural heart disease discourages Class I use, favouring Class III instead. In HF, amiodarone is the preferred option, while other AADs are generally avoided to prevent worsening of the condition. BB, β-blockers; CCB, Ca^{2+} channel blockers; HF, heart failure, VW, Vaughan Williams AAD classification.
[a]: Ivabradine is primarily advised for slowing the sinus rate, with some evidence suggesting it may also influence AV nodal conduction.
[b]: BBs and CCBs also affect cardiac tissues beyond the sinus and AV nodes and may be the AADs of choice for certain disorders, such as ectopic AT or idiopathic fascicular VT, respectively.
[c]: Digoxin is less effective in sinus tachycardia compared to ß-blockers or calcium channel blockers. However, digoxin toxicity can lead to severe bradycardia, sinus arrest, or junctional escape rhythms due to excessive vagal stimulation.
[d]: Class I and III agents also influence the sinus node and AV conduction but are not the preferred choices for this purpose.
[e]: Dronedarone is not advised in patients with symptomatic heart failure or LVEF <40%.
[f]: Dofetilide does not worsen survival in HFrEF but can prolong the QT interval and cause torsades de pointes.
[g]: Sotalol is not advised in patients with advanced heart failure or severe left ventricular dysfunction (LVEF <35%) due to the risk of worsening HF.

Finally, it is important to keep in mind some key considerations for optimizing the safe and effective use of AADs, emphasizing patient education, risk management, and integrated care strategies (**Box 2**)

The following sections review the published literature on the use of specific AADs in the management of various arrhythmia disorders, both for prevention and termination. The key recommendations from the European Society of Cardiology (ESC) guidelines for selecting AADs to treat or prevent these conditions are summarized in **Table 3**, while **Table 4** outlines the typical indications and contraindications of major AADs.

Table 3: Advised AADs and Agents for Various Heart Rhythm Disorders Based on Clinical Practice Guidelines

Tachycardia prevention					
	1st choice AAD	Strength of Advice	2nd choice AAD	Strength of Advice	ESC guideline (year/topic)
Sinus tachycardia[a]	Ivabradine β-blockers	Medium	Alternative or Combined	Medium	2019 SVT

AT focal	β-blockers, CCB, or Ic	Medium	Alternative		2019 SVT
AFL	β-blockers or CCB[b]	Medium	Amiodarone[c]	Low	2019 SVT
AF – No SHD or HF	Ic or Dronedarone	High	Alternative		2024 AF
AF - SHD or HFpEF/HFmrEF	Dronedarone	High	Alternative		2024 AF
AF - HFrEF	Amiodarone	High			2024 AF
PSVT - non preexcited	β-blockers or CCB	Medium[e]	Alternative	Medium	2019 SVT
PVT/VF SHD or ischaemia	β-blockers & K^+/Mg^{2+} repletion	High	Amiodarone	Medium	2022 VA
PVCs/VT idiopathic from outflow tract or fascicular	β-blockers or CCB or Ic	Medium[e]	Alternative		2022 VA
PVCs/VT idiopathic from other origin	β-blockers or CCB	High	Alternative or ablation		2022 VA
VT SHD	β-blockers	High[j]	Amiodarone or Sotalol	Medium	2022 VA
TdP/VF non-SHD	Nadolol/propranolol (LQTS 1 & 2, CPVT). Mexiletine (LQTS 3). Quinidine (SQTS, idiopathic VF, ERS, Brugada)	High & Medium	Flecainide (CPVT)	Medium	2022 VA

Tachycardia termination/control

	1st choice AAD	Strength of Advice	2nd choice AAD	Strength of Advice	ESC guideline
AT focal	Adenosine i.v.	Medium	CCB i.v. β-blockers i.v.	Medium	2019 SVT
AFL	Ibutilide/dofetilide i.v.	High	Amiodarone	Low	2019 SVT
AFL	β-blockers or CCB[b]	Medium	Amiodarone[c]	Low	2019 SVT

AF – No SHD/HF	Vernakalant i.v.[f] Flecainide / propafenone i.v. or PITP	High	Alternative Ibutilide[k]		2024 AF
AF – SHD/HF	Vernakalant i.v.[f] Amiodarone i.v.	High	Alternative		2024 AF
AF – No SHD or HF (HR control)	β-blockers, CCB or Digoxin[d]	High	Alternative		2024 AF
AF – SHD or HF (HR control)	β-blockers or Digoxin	High	Alternative		2024 AF
Narrow QRS T	Adenosine i.v.	High	CCB i.v. β-blockers i.v.	Medium	2019 SVT
Wide QRS T	Adenosine i.v.	High	Procainamide i.v.	Medium	2019 SVT
SVT – Pre-excited	Ic or Ibutilide or procainamide i.v.	Medium[g]	Alternative		2019 SVT
AF – Pre-excited	Ibutilide or Procainamide i.v.	Medium	Ic	Low	2019 SVT
PVCs/VT idiopathic from outflow tract or fascicular	β-blockers (outflow tract) or CCB (fascicular) i.v.	High	Alternative		2022 VA
VT SHD or unknown[h]	Procainamide i.v.	Medium[i]	Amiodarone	Low	2022 VA
TdP/VF non-SHD	Mg^{2+}, K^+, β-blockers (congenital LQTS). Isoprenaline (acquired LQTS, idiopathic VF, ERS, Brugada). Verapamil, Quinidine (idiopathic VF)	High Medium			2022 VA
PVT/VF SHD or ischaemia	β-blockers & K^+/Mg^{2+} repletion	High	Amiodarone	Medium	2022 VA

Alternative, the second alternative AAD is advised to be used when two options are offered. *AADs, antiarrhythmic drugs; AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; CCB, calcium channel blockers; CPVT, catecholaminergic PVT; ERS, early repolarization syndrome; HF, heart failure; HFpEF/HFmrEF/HFrEF, HF with preserved/mildly reduced/reduced left ventricle ejection fraction; HR, heart rate; LQTS, long QT syndrome; PITP,* pill-in-the-pocket; PVC, premature ventricular contraction; PVT, polymorphic VT; SHD, structural heart disease; SVT, supraventricular tachycardia; TdP, torsades de pointes; VA, ventricular arrhythmias; VF, ventricular fibrillation; VT, ventricular tachycardia.

[a]The treatment of reversible causes is the first-line option.

[b]Used for HR control with little effect on AFL prevention.

[c]Sotalol and dofetilide are also recommended in the 2023 AHA/ACC/HRS AF guidelines, with dronedarone identified as another reasonable alternative to amiodarone in this consensus.

[d]May have limited efficacy if high adrenergic tone.

[e]Catheter ablation is advised is the first-line option.

[f]Vernakalant can be given to patients with SHD but no severe aortic stenosis, recent ACS or moderate to severe HF

[g]Vagal manoeuvres are the first-line option.

[h]ICD is advised is the first-line option.

[i]Electrical cardioversion is the first-line option.

[j]β-blockers are advised as a first-line option to treat HF but have low efficacy to prevent sustained episodes of VT in this setting.

[k]In geographies with no access to Vernakalant or to i.v. type Ic drugs advised by the 2023 AHA/ACC/HRS AF guidelines.

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

Modified VW Class	AAD	Main indications	Not to be used/Main contraindication
0	**Ivabradine**	Inappropriate sinus tachycardia	AF termination

Box 2: Practical tips on using AAD

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

IA	**Ajmaline**	AF (preexcitation) termination MVT (no significant SHD) termination	BrS HFrEF
	Quinidine	PVT (channelopathies) prevention	Long QT
	Procainamide	MVT (SHD) termination	HFrEF
	Disopyramide	AF (vagotonic) prevention	HFrEF
IB	**Lidocaine**	PVT/VF (ischaemia) termination	Bradycardia
	Mexiletine	TdP (LQTS 3) prevention	Bradycardia
	Phenytoin	JET (digitalis toxicity) termination	Bradycardia
IC	**Flecainide** **Propafenone**	AF (idiopathic) prevention/termination WPW syndrome	BrS SHD
	Antazoline	AF (idiopathic) termination	Bradycardia SHD
	Pilsicainide	AF (Idiopathic) termination	SHD
ID	**Ranolazine**	AF prevention/termination	Long QT
IIA	**β1 blockers (e.g. Bisoprolol, metoprolol)**	AF/AFL rate control VT/PVCs (idiopathic)	Bradycardia
	β1+β2 blockers (e.g. Nadolol, propranolol)	TdP (LQTS 1 & 2) prevention CPVT	Bradycardia
IIB	**Isoprenaline**	TdP (acquired LQTS) PVT (BrS)	CPVT
IIC	**Atropine**	Sinus bradycardia	Inappropriate sinus tachycardia
IID	**Digoxin**	AF/AFL rate control	Amyloidosis
IIE	**Adenosine**	PSVT termination	Asthma/COPD
III	**Amiodarone**	AF/AFL (HFrEF) prevention/termination MVT (SHD) prevention/termination	Bradycardia
	Dronedarone	AF/AFL (SHD) prevention	Permanent AF HFrEF
	Dofetilide	AF/AFL (HFrEF) prevention	Long QT
	Ibutilide	AFL termination	Long QT
	Sotalol	MVT (SHD) prevention	CKD
	Vernakalant	AF (≤7 d) termination	Aortic Stenosis NYHA III/IV
IV	**Verapamil**	AF/AFL rate control	MVT (SHD)

	Diltiazem	VT (fascicular) prevention/termination	HFrEF

Conditions for indications and contraindications are stated in brackets.
AADs: antiarrhythmic drugs; AF: atrial fibrillation; AFL: atrial flutter; BrS: Brugada syndrome; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CPVT: catecholaminergic polymorphic ventricular tachycardia; HFrEF: heart failure with reduced ejection fraction; JET: junctional ectopic tachycardia; LQTS: long QT syndrome; LVEF: left ventricular ejection fraction; MVT: monomorphic VT; PVC: premature ventricular contraction; PVT: polymorphic ventricular tachycardia; RVOT: right ventricular outflow tract; SHD: structural heart disease; TdP: torsades de pointes; VF: ventricular fibrillation; VT: ventricular tachycardia; WPW: Wolff-Parkinson-White.

Arrhythmia prevention

Atrial arrhythmias

Atrial arrhythmias, including AF and AFL, are the most common sustained cardiac rhythm disorders and associated with an increased risk of stroke and heart failure. AADs play a key role in their management. The preferred AADs for treating and preventing AF and AFL are shown in **Figure 11**.

Premature atrial contractions and focal atrial tachycardia

Independent of underlying heart disease, β-blockers are a particularly good choice for adrenergic premature atrial contractions (PACs) or focal non-sustained ATs (**Box 3**). If no or minimal heart disease is present, flecainide[252] and propafenone[253] may be used when β-blockers are ineffective. Flecainide is especially effective in vagal or (relative) bradycardia-dependent PACs or non-sustained atrial tachycardia (NSAT). If β-blockers or Class Ic drugs are ineffective then sotalol may be used.[204,254,255] Propranolol, verapamil and procainamide have been reported to specifically suppress PACs from the PVs.[256] Note that ß-blockers may be proarrhythmic by inducing bradycardia-dependent ectopy. Rate slowing with β-blockers, digoxin and verapamil/diltiazem may help suppress symptoms in NSATs. Amiodarone is advised to be used only exceptionally in patients with significant SHD.[204,254,255] Flecainide and verapamil were shown effective in unspecified recurrent SVT including ATs.[257] Case reports suggest ivabradine may be useful[258,259] and amiodarone must only be used as last resort drug therapy.[260,261] Combination of sotalol with flecainide – producing an amiodarone-like Ic plus III effect - may be tried in resilient cases. Focal PACs and ATs with tachycardiomyopathy are best managed with catheter ablation.[254]

Inappropriate sinus tachycardia

General measures, such as ruling out any cause for sinus tachycardia or treating aggravating factors, are advised to be taken before initiating any AAD therapy for inappropriate sinustachycardia.[44] β-blockers and ivabradine, up-titrated to a dosage may bring relief of symptoms, and both drugs may be combined[44,262] to enhance efficacy. Non-dihydropyridine CCBs may be proarrhythmic by causing rebound sinus tachycardia.[44,263]

Multifocal atrial tachycardia

Management of the underlying condition, in particular lung diseases and HF, is of utmost importance for chronic prevention. Digoxin is ineffective for the treatment and may contribute to its cause. Verapamil or diltiazem (in the absence of HFrEF),[223,225] or β-blockade may be helpful aiming at rate control. Class I or Class III drug therapy usually fails and sometimes the combination of the looking for amiodarone-like 'Class Ic plus III effect', is a rational option in resilient cases with no contraindications (**Box 3**).

Atrial flutter/macroreentrant atrial tachycardia

Patients refusing catheter ablation of AFL and infrequent recurrences may opt for season-ticket cardioversion (**Box 3**).[264] Alternatively, rate control using β-blockers, verapamil or diltiazem may be applied if recurrences are relatively well tolerated. Rate control may be difficult to achieve and frequently a combination of rate control drugs is needed.[93,204] Therefore, it is important to emphasise that catheter ablation is advised to be the first-line therapy for AFL, particularly when it is cavotricuspid isthmus-dependent. For acute termination, cardioversion may be supported by chronic AAD therapy. If no significant SHD is present, flecainide or propafenone can be used.[265–267] However, dronedarone,[99] sotalol[268] or amiodarone[269–271] may be more effective in broader clinical scenarios.

AFL may occur in patients treated to prevent recurrences of AF or drug termination of AF with Class Ic drugs or amiodarone with the classical saw-tooth flutter pattern potentially changed (hampering recognition of the classical flutter pattern) and the flutter revolution time being prolonged, typically to 240-360 ms (**Figure 6B**).[132] This lengthened cycle maybe associated with 1:1 AV conduction. The wide QRS tachycardias associated with aberrant conduction during 1:1 AV conduction may show a bizarre QRS mistaken for VT.[272] To prevent 1:1 AV conduction, it is commonly to prescribe one of the negative dromotropic drugs like β-blockers, verapamil or diltiazem along with the prophylactic Class Ic drug (not amiodarone which itself may provide sufficient AV block) but it is particularly useful to advise patients to avoid exercise or stress during breakthrough AF or flutter.[93] Deterioration of aberrancy with pseudo-VT to true VT or VF is highly unlikely to occur if the indication for Class Ic agents was correct (absence of underlying heart disease). If AFL occurs during flecainide treatment cavotricuspid isthmus ablation is treatment of choice[273,274] and, in any event, the Class Ic agent is advised to be discontinued.

Box 3. Practical tips for use of AADs for atrial arrhythmias

Focal atrial tachycardia

- Diurnal pattern may reveal **adrenergic PACs or NSATs** suggesting beta-blocker as preferred rhythm control therapy; if a **vagal pattern** prevails try flecainide first and avoid beta-blocker. Alternatively, disopyramide may be particularly effective for vagally mediated AF when the former fails or cannot be used
- Rate control drugs are a rational option in NSATs.

Multifocal atrial tachycardia

- Combining **sotalol with flecainide**, aiming to achieve an amiodarone-like effect through the synergy of Class Ic and Class III properties, could be a potential option in refractory cases for patients without significant heart disease. However, this approach have to be undertaken with extreme caution, as it requires careful and regular monitoring due to the risks of proarrhythmia, myocardial contractility depression, and the limited clinical evidence supporting its use.

Atrial flutter

- Rhythm control o AFL is rarely achieved with antiarrhythmic drugs; **catheter ablation is generally preferred**, especially for cavotricuspid isthmus-dependent cases (see **Figure 6**).
- Nevertheless, using **cardioversion as needed** for infrequent AFL is an excellent, patient-specific treatment option.
- **Rate control is difficult** to achieve in AFL but if effective this allows long term treatment with ß-blocker, verapamil or diltiazem, or combinations of these in patients with AFL not suitable for catheter ablation.
- Beware of inadvertent flutter elicited by Class Ic drugs during termination or prevention of AF and know how to recognise **pseudo-ventricular tachycardias** due to aberrant conduction.

General

- [illegible]

Spontaneous termination of a breakthrough flutter while on a Class Ic drug is very unlikely.[132] If concomitant HF occurs in flutter which is not amenable to cardioversion and ablation, β-blockers are the most preferred rate control therapy.

Flutter or macro-re-entrant tachycardia during the blanking period after AF ablation (about 8 weeks) may be managed by cardioversion and AADs since they often resolve spontaneously.

AF

Rhythm control in AF including the application of AAD therapy is increasing[275] and can be applied safely (**Box 4**).[276,277] Flecainide, propafenone, sotalol, dofetilide,[275] dronedarone and amiodarone are among the most frequently used drugs to maintain SR and prevent recurrences. In the past decades flecainide use has increased while sotalol use has declined.[278] Quinidine and disopyramide are advised to be avoided for risk of proarrhythmia,[122] and procainamide is hardly used to prevent AF due to complex drug application, need for sampling plasma concentrations and potentially severe side effects. Current ESC guidelines recommend dronedarone, flecainide or propafenone for AF prevention in patients with no or minimal SHD, amiodarone and dronedarone in patients with coronary artery disease, valvular disease or heart failure with preserved ventricular ejection fraction (HFpEF), and amiodarone in patients with HFrEF. In the USA, where dofetilide is available, it is also advised for patients with AF and HF. Sotalol is considered a second-line option for the first two patient groups.[93]
At follow-up a breakthrough episode does not mean that therapy failed. Patients may report breakthrough episodes but still be perfectly content with continuing the AAD in use because of overall effectiveness and improved quality of life. To terminate breakthrough episodes many patients apply one or more extra doses of their prescribed AAD, i.e. add-on therapy (see also section 'pill-in-the-pocket'), but this approach may be hazardous unless carefully reviewed and controlled. In case of troublesome recurrences, Thyroid-stimulating hormone (TSH) (especially if on amiodarone) and change in medical condition (heart failure, angina, infection) are advised to be checked and treated. Also it is important to check whether the AAD dose is still right and increase or even decrease the dose depending on clinical judgment: QRS or QT duration on therapy, drug side effects, and drug efficacy parameters (see also section 'follow-up').

AF after cardiac surgery

Post-operative AF is common (20-50%) in the 3 days after cardiac surgery. Most patients present with AF although AFL is also common. Several mechanisms such ischaemia and inflammation may be causative but a hyperadrenergic state is believed to be the main one. For this reason, β-blockers are the first line therapy in this situation and are advised to be started 24 hours before the operation and continue during the postoperative period. Amiodarone is appropriate in combination with them in resistant cases and vernakalant may be appropriate for AF termination.

Autonomic AF

Like with PACs and NSATs, β-blockers may prevent AF recurrences especially if adrenergic factors play a role, e.g. after cardiac surgery, exercise-induced AF or AF occurring exclusively during daytime, stress or anxiety, or in patients with systolic HF.[279] β-blockers (including sotalol) and digoxin may however worsen vagally-mediated AF[280] with increasing attacks and progression to permanent AF.[281] Sotalol and amiodarone are effective in the suppression of adrenergic AF but sotalol is advised to be avoided if AF-promoting conditions like HF are present. AADs to treat vagal AF include disopyramide, flecainide and amiodarone.
Disopyramide is no longer a mainstream AAD but patients with vagal AF may benefit from its marked anticholinergic effects which may also cause typical side effects of dry mouth, urinary hesitancy and constipation. Disopyramide may induce HF, AV-block in susceptible patients, and TdP.

Aberrant conduction versus ventricular proarrhythmia

Differentiating aberrant conduction from VT when using Class I and Class III AADs is very important. Monomorphic VT hardly ever happens, even with exercise, if flecainide or propafenone are used appropriately.[282] If a wide QRS rhythm occurs during exercise on class Ic drugs, it mostly is due to aberrant conduction. Aberrantly conducted QRS are bizarrely shaped due to a normal initial but very broad last part of the QRS (class Ic drugs). Hallmark features of aberrancy with Class III AADs include (a) atypical types of aberrancy including left bundle-branch block (LBBB) with extreme left axis, (b) aberrancy onset with atypically long coupling intervals (due to prolonged refractory period in the Purkinje system), and (c) sequential bilateral BBB.[283] ECG criteria differentiating aberrant conduction from VT do not apply due to AAD effects on QRS morphology. Aberrant conduction may be a reason to reduce the dose or stop the drug.

AADs for AF

Flecainide is used to prevent AF recurrences in patients with paroxysmal or persistent AF without SHD.[276,278] Also in lone, focal, vagal AF[280,284,285] flecainide may be very effective whilst in adrenergic AF – frequently associated with underlying heart disease – flecainide is not advised for use. Pre-treatment before cardioversion of persistent AF may help reduce immediate and subacute recurrences.[264] When AV conduction is controlled, flecainide does not exert negative dromotropic effects during ongoing AF, pre-treatment during uncontrolled heart rates may be proarrhythmic and reduce quality of life. Therefore, pre-treatment with flecainide is advised to be done in hospital with ECG monitoring and patients have to be advised to refrain from exercise until after the cardioversion. Similarly, patients progressing from paroxysmal to persistent AF while on flecainide may suffer from uncontrolled high heart rates and reduced quality of life. The use of propafenone is largely the same as for flecainide.

Dronedarone has been approved to maintain normal heart rhythm in adults whose rhythm has been restored after a period of paroxysmal or persistent AF but is not advised for use in patients with permanent AF and those with left ventricular systolic dysfunction and LVEF <35% or previous episodes of HF.[104,105,286] It does not convert persistent AF to SR. The drug is very safe in patients without SHD and in stable patients with heart disease, including CAD.[287] It has a very low risk for proarrhythmia.[98,99,277] It is a reasonable first line alternative before sotalol[288] or when Class Ic drugs are contra-indicated. It has been shown to reduce progression of self-terminating AF to more persistent forms.[100,289]

Dronedarone has vastly underappreciated pleiotropic effects in part explaining its success in the ATHENA trial.[99] It reduces vasoconstriction and blood pressure. Through vascular effects, lowering heart rate and cellular protective effects it ameliorates (ACS). Dronedarone is also associated with reduced stroke rate in AF.[290]

Ranolazine shows promise in AF prevention, particularly as an adjunct therapy in combination with other AADs like dronedarone.[76] While some trials suggest benefit, larger studies are needed to confirm its role. Due to off-label status and potential QT prolongation, its use is advised to be carefully individualized based on patient risk factors.

Box 4: Practical tips to use AAD for AF prevention

- **Safety** must take precedence over efficacy when selecting AADs for AF prevention.
- Recognition of the **autonomic pattern** of paroxysms may guide specific AAD treatment decisions in vagal or adrenergic AF.
- Despite add-on ß-blocker or verapamil/diltiazem, advise patients on Class Ic drugs to **avoid exercise during breakthrough episodes** until AF has stopped or cardioversion has been performed. This may help avoiding side effects of these add-on drugs.
- **Oral amiodarone** may convert 25% of persistent AF patients, thus avoiding cardioversion.
- Dependent on the dose of rate control medication, the **decrease of the dose of rate control medication may be needed** shortly after starting amiodarone to prevent bradycardia.
- In cases of **proarrhythmia or breakthrough AF**, evaluate for potential triggers, including ischaemia, heart failure, electrolyte imbalances, thyroid dysfunction, infections, drug interactions, and abnormal plasma AAD concentrations (e.g., due to non-adherence or dosing errors).

The effectiveness of amiodarone to prevent recurrent AF exceeds that of other antiarrhythmic agents. Amiodarone is advised to be reserved for second line treatment of AF but may be given safely as first line agent in patients with AF and mild HF in whom other AADs are discouraged.

Amiodarone is the most effective AAD for AF but frequently causes significant adverse effects),[197,291] and it may negatively affect time in INR target range[292] in patients using vitamin K antagonists. Amiodarone is also a P-gp inhibitor and may increase the anticoagulant effect of direct oral anticoagulants.

During the loading phase in patients with persistent AF conversion to normal SR may occur in up to a quarter of patients.[112] Conversion is usually not associated with bradycardia but negative chronotropic and dromotropic drugs is advised to be reduced during the loading phase (see below).

Amiodarone slows AV nodal conduction and heart rate during AF and prolongs the PR interval in SR, both of which are advised to be monitored during initiation of therapy. The use of rate control drugs is advised to be adapted according to the heart rate. As a rule, ß-blockers, verapamil or diltiazem may be stopped around 6 weeks after initiation of amiodarone loading.

Sotalol is a β-blocker with reverse use-dependency with stronger AP prolongation during bradycardia or after pauses. Conversely, the antiarrhythmic effect may be reduced during tachycardias. At the atrial level, the latter means that during the fast atrial rates of AF, atrial effects are considered minimal. Nevertheless, during chronic oral treatment, sotalol may, similarly to amiodarone, convert persistent AF to SR in up to 25% of cases.[112]

Pre-treatment with sotalol before cardioversion of persistent AF may be applied but immediately after electrical cardioversion of persistent AF it is important to measure reverse use-dependent QT prolongation which may be excessive when a relatively high ventricular rate during AF changes to relatively low sinus rate. For Class III drugs, safety is best ensured by measuring at the time the risk is maximal, i.e., during relative bradycardia.

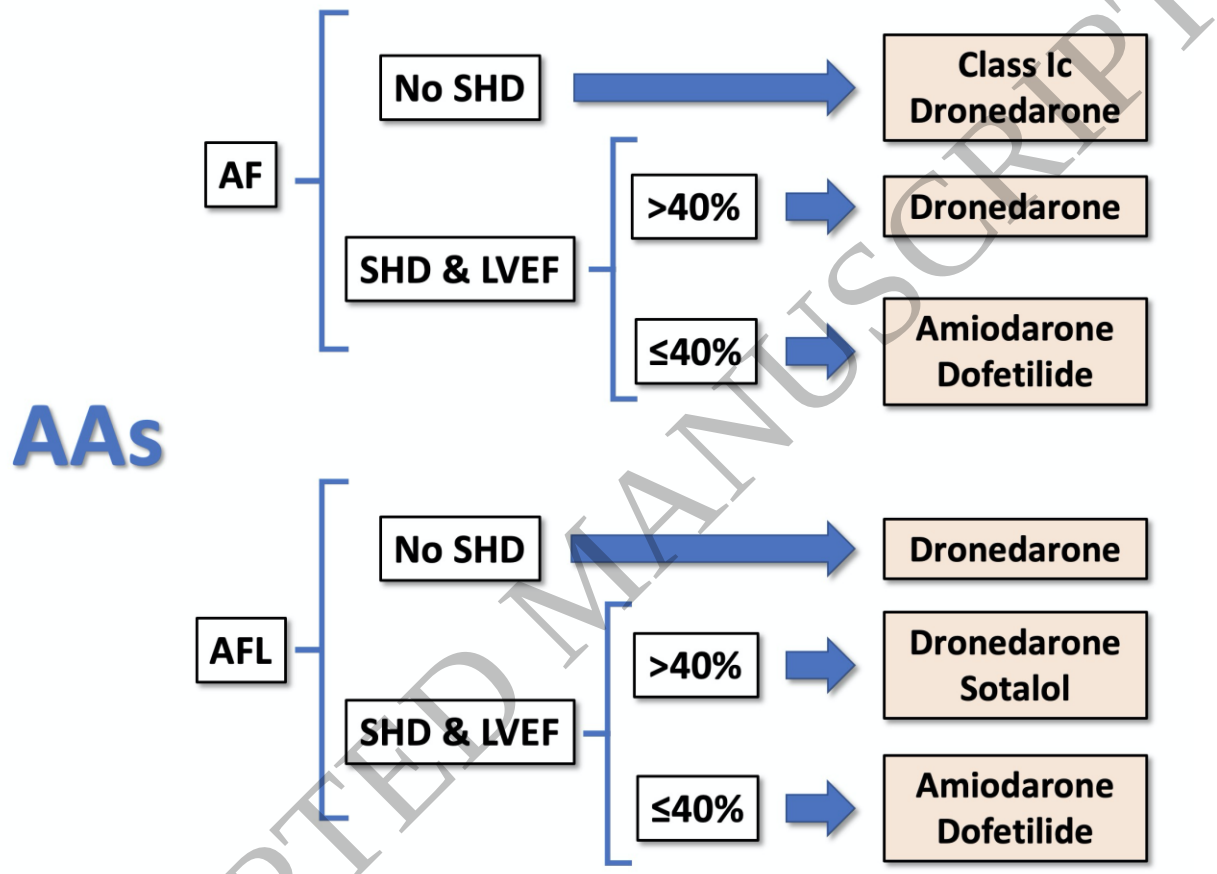

Figure 11: Schematic representation of the preferred AADs for prevention of atrial arrhythmias. *The figure serves as a general reference for selecting the most appropriate drug; however, the final choice—or consideration of alternative therapeutic options (e.g., catheter ablation for cavotricuspid isthmus-dependent atrial flutter)—is advised to be based on the general patient characteristics and conditions, as outlined in the relevant sections of this document. Additionally, not all AADs are available in all regions. For secondary or alternative drug options, refer to* ***Table 3****. AADs, antiarrhythmic drugs; AAs, atrial arrhythmias; AF, atrial fibrillation; AFL, atrial flutter; LVEF, left ventricular ejection fraction; SHD, structural heart disease.*

Paroxysmal supraventricular tachycardias (PSVT)

PSVT may be the result of different arrhythmia mechanisms including, AVNRT and AVRT. Catheter ablation, due to its high efficacy, is advised for almost all patients with recurrent AVNRT and AVRT.[44,293]

Atrioventricular nodal re-entrant tachycardia (AVNRT)

AVNRT may occur as an isolated or, quite frequently, as a recurrent arrhythmia. In a series of patients presenting with AVNRT (mean age=33.5±18.1 years) arrhythmia recurrence during long term follow up was found in a substantial proportion of patients presenting with non-severe symptoms and this should be taken into consideration when evaluating therapeutic strategies for individual patients.[294] However, for patients with important symptoms and recurrent AVNRT, ablation is the definitive treatment. In AVNRT catheter ablation has a success rate of 97% with a recurrence of 1.3-4% % and a risk of AV block < 1%.[44] A randomized controlled trial was performed in patients with at least one symptomatic episode of tachycardia per month and an electrophysiological diagnosis of AVNRT, randomly assigned to catheter ablation or chronic AAD therapy (bisoprolol and/or diltiazem).[255] Hospital admissions for persistent tachycardia cardioversion were significantly lower in patients treated with ablation and AAD were not well tolerated over the long term.[255]

In appropriately selected patients with infrequent well-tolerated episodes of AVNRT episodic treatment with an antiarrhythmic agent ("pill in the pocket") could be used, but acute testing is advised in order to exclude adverse effects.[295] Single oral doses of flecainide (3 mg/kg), or diltiazem (120 mg) plus propranolol (80 mg) have been used, resulting in a high conversion rate to SR within 2 hours.[295]

The efficacy of diltiazem and verapamil has been validated for prevention of recurrences of AVNRT,[254] although adherence over the long term may be problematic and overall efficacy may be in the rage of 30-50%.[296] Also β-blockers have been used for prevention of recurrences of AVNRT but the indication is based on expert opinion.[254]

In case of documented AVNRT resistant to β-blockers or CCBs, or in case of PSVT of uncertain mechanism prevention of recurrences can be achieved effectively by the use of flecainide or propafenone at adequate dosages in patients without contraindications to Class Ic agents (such as left ventricular dysfunction, ischaemic heart disease, severe left ventricular hypertrophy or conduction system disturbances).[296–299] Amiodarone and sotalol must generally be avoided for the prevention of AVNRT recurrences, as safer alternatives are usually available.

Atrioventricular re-entrant tachycardia

Atrioventricular re-entry tachycardias occur in the presence of an accessory pathway that constitute a by-pass between the atria and the ventricles, with the possibility to conduct the impulses retrogradely or anterogradely, leading to orthodromic and antidromic AVRT, respectively. According to patient's age, there is a progressive decline in the proportion of SVT that correspond to AVRT, moving from 60% in the first decade of age to 9% after 70 years.[300] Antidromic AVRT constitute 5 to 10% of all AVRTs.[301] Wolff-Parkinson-White syndrome (WPW) is the combination of an accessory pathway activation seen on an ECG as a delta wave,

expression of anterograde conduction through the accessory pathway and episodes of SVT.[302] The simple presence of a delta wave (called "WPW pattern") can be detected in 0.2% of the general population, but many patients with the WPW pattern do not have the tachycardia needed to fulfil the definition of WPW syndrome. The risk of WPW is related to the possibility that an episode of AF will develop with rapid conduction down an accessory pathway leading to VF and sudden death, an event reported in less than 0.1% of the patients with WPW pattern.[302,303] In the 2019 ESC Guidelines the risk of CA/VF was estimated to be 2.4 per 1000 person/years.[44]

For the prevention of supraventricular tachyarrhythmias and WPW-related adverse events, the treatment of choice is ablation of the accessory pathway, advised for symptomatic patients and selected asymptomatic individuals, particularly athletes and younger patients at risk.[304]

Therapy with AADs could be used in symptomatic patients while waiting for ablation or in patients who are not suitable candidates for ablation or refuse the procedure. In these cases Class Ic antiarrhythmic agents, i.e. flecainide or propafenone can be used to prevent AVRTs. Drugs that act mainly on AV conduction, such as diltiazem, verapamil and β-blockers are discouraged in patients with ventricular preexcitation because of the risk of blocking AV conduction through the AV node and favouring conduction through the accessory pathway if AF occurs. In addition, calcium channels blockers are associated with vasodilation and a secondary adrenergic response, which may further promote conduction though the accessory pathway.[254] Digoxin is contraindicated as it may shorten refractoriness of accessory pathways.[198]

Ventricular arrhythmias

AADs play a crucial role in preventing VA, which can lead to SCD. By modulating ion channels and stabilizing cardiac electrophysiology, AADs help reduce arrhythmia recurrence and improve patient outcomes. The preferred AADs for preventing monomorphic VAs are shown in **Figure 12**.

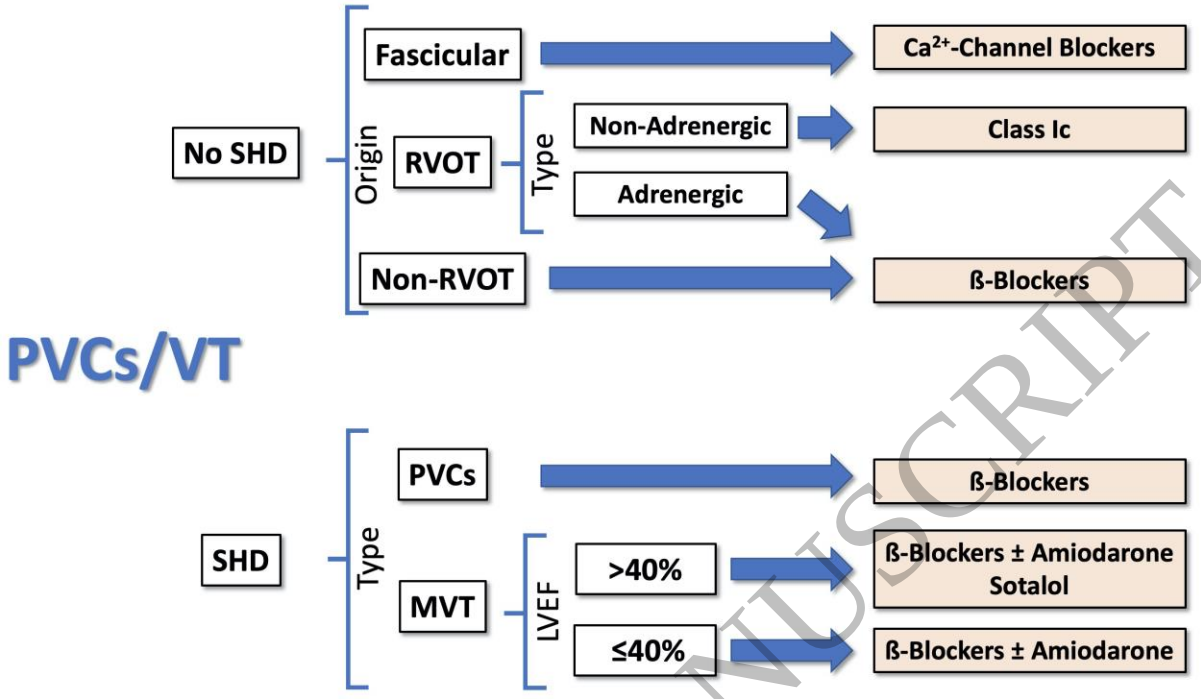

Figure 12: Schematic representation of the advised AADs for prevention of monomorphic ventricular arrhythmias.
The figure serves as a general reference for selecting the most appropriate drug; however, the final choice—or consideration of alternative therapeutic options (e.g., catheter ablation for idiopathic RVOT PVCs)—is advised to be based on the general patient characteristics and conditions, as outlined in the relevant sections of this document. Additionally, not all AADs are available in all regions. For secondary or alternative drug options, refer to ***Table 3.*** *Adrenergic PVCs/VT are characterized by an increased burden and/or severity in response to exercise or mental stress. AADs, antiarrhythmic drugs; Ca^{2}, calcium; LVEF, left ventricular ejection fraction; MVT, monomorphic VT; PVC, premature ventricular contraction; RVOT, right ventricular outflow tract; SHD, structural heart disease; VT, ventricular tachycardia.*

Idiopathic PVCs and VT

PVCs may produce symptoms, haemodynamic deterioration and ventricular dysfunction. However, their treatment is not clearly associated with prognostic benefits in patients either with or without SHD especially if the latter are not present. Responses to different pharmacological agents are considered essentially the same for PVCs and VT in patients without SHD and they will be treated as a single entity in this practical compendium.

Pharmacological preventive therapies for PVCs and VTs in patients without SHD have been mostly studied in non-randomized or small series of patients with monomorphic PVCs. Most of these studies made no distinction about the arrhythmic origin or mechanism and their results are extrapolated for the different types of idiopathic of PVCs/VTs in the ESC guidelines and this practical compendium (**Table 5**.[305,306] Some few studies specifically included just patients with PVCs/VTs originating from the RVOT or the left fascicles of the His bundle providing more

specific evidence.[307,308] The information available for other forms or sources of idiopathic VT/PVCs is more limited. β-blockers and non-dihydropyridine CCBs are among the most studied drugs and both were shown to effectively suppress the arrhythmia in this clinical setting.[305,307] There are also studies demonstrating the efficacy of Class Ic drugs to suppress PVCs in patients with no or minimal SHD.[305,306] In addition, one study demonstrated that they were effective for PVC suppression and tachycardiomyopathy recovery in patients with idiopathic PVCs.[309] Mexiletine has been also demonstrated to suppress PVCs in some old studies.[310] However, its relative efficacy is inferior to other drugs and it is not available in many countries. Sotalol has been demonstrated effective for both PVC patients with and without SHD and some studies have even shown better efficacy than other β-blockers.[107,305] However, the risk of TdP makes its use more complex and less preferable than other drugs, especially in patients with otherwise little arrhythmic risk. Preference is advised to be given to β-blockers when there is a correlation between the number of PVCs and heart rate or they are more frequent during exercise.[311] If there is no such correlation, the use of Class Ic or CCB drugs has been associated with better PVC suppression.[305,311] It is also advise to select β-blockers when a focal triggered activity mechanism is suspected, the origin is not apparently in the RVOT or the patient shows signs of ventricular function deterioration. CCBs are advised to be the drugs of choice for fascicular PVC/VTs although his advice is primarily based on the common termination of fascicular VT by i.v. verapamil.[308]

Some forms of SHD may present with PVCs or VT as their initial manifestation mimicking an idiopathic mechanism. In this case β-blockers and CCBs are more appropriate than Class I drugs for non-RVOT or fascicular idiopathic PVCs/VT because of the proarrhythmia risk in a less defined clinical setting. In addition, a recent report found short-coupled PVCs induced during Na^+ blocker infusion in some patients with structurally normal hearts and suspected or documented ventricular polymorphic arrhythmias and therefore they are discouraged in this setting.[312] CCBs must also be avoided in patients with ventricular dysfunction because they may depress myocardial contractility, similarly to Class Ic drugs. In this situation, β-blockers and amiodarone are the preferred drugs. However, amiodarone is associated with severe systemic toxicity and is advised to be only used if other drugs fail or cannot be used.[313] Dronedarone, which was developed only as an antiarrhythmic agent for treatment of AF, is devoid of most of the amiodarone toxicity but there are no reports of its use to treat PVCs or VTs in patients without SHD. Some reports found a significant decrease of PVC burden using ranolazine in patients with ischemic heart disease and this drug may be appropriate in this population.[77] However, in general, β-blockers are advised to be the drugs of choice to reduce the burden of PVCs in patients with SHD.

Table 5: AADs reported with positive and negative effects for the treatment of PVCs and idiopathic VT[373]

	β-blockers	CCB	Ic	Sotalol	Amiodarone	Ranolazine
Idiopathic RVOT PVCs/VT	++	++	++	+	-	?

No SHD						
Idiopathic Fascicular PVCs/VT No SHD	+	++	+	?	-	?
Idiopathic Non-RVOT/Fascicular PVCs/VT No SHD	++	++	+[a]	+	-	?
PVCs/VT PVC/VT induced cardiomyopathy	++	-	+[b]	?	+	?
PVCs SHD	++	-	-	+	+	+[c]

White background/$^{++}$, preferred positive AAD effects; light blue background/$^{+}$, conditional use and/or less established positive effect; black/-, to be avoided; grey, not enough data. *AAD, antiarrhythmic drug; CCB, calcium channel blockers;* PVC, premature ventricular contraction; RVOT, right ventricular outflow tract; SHD, structural heart disease; VT, ventricular tachycardia.

[a]Not to be used if an unmasked SHD or malignant short, coupled PVCs are suspected

[b]Only if no heart failure or severe ventricular dysfunction present (risk of myocardial contractility depression)

[c]If ischaemic heart disease present.

Children need to be treated like adults. A recent registry found that only flecainide reduced the burden of PVCs compared to no treatment, β-blockers or verapamil.[314] Verapamil is not advised as the first line therapy in children less than 1 year old because it has been associated with hypotension in some case reports, although all of them had HF, overdosing of verapamil and/or other concurrent AADs at the time this drug was given.[315]

PVCs and structural heart disease

SHD generally refers to the presence of any morphological, functional or recognised histological abnormality in the ventricles, encompassing cardiomyopathies, HFrEF, HFpEF, significant left ventricular hypertrophy (LVH), congenital heart disease, ischaemic, valvular, or other myocardial disorders. However, preventive therapies for PVCs and VTs in patients with SHD may differ, as some drugs used to treat the underlying condition can reduce the PVC burden but are not specifically targeted or sufficiently potent to suppress VT. This section of the practical compendium only addresses those aspects of pharmacological therapy for PVCs in patients with SHD that may differ from those for VT prevention, which is considered in the following section.

A high burden of PVC may be associated with left ventricular dysfunction and in recent years this has led to the concepts of both a form of cardiomyopathy induced by PVCs (PVC-induced cardiomyopathy) or to the concept of a worsening of systolic function in patients with pre-existing cardiomyopathy (PVC-worsened cardiomyopathy).[316] The baseline PVC burden plays a central role in the development of PVC-induced cardiomyopathy and a PVC burden higher than 24% was found to best to distinguish the patients with impaired as compared to patients with preserved LV function among consecutive patients referred for ablation.[317] In patients with a suspected cardiomyopathy induced or aggravated by PVCs, ablation is a valuable option since improvement in left ventricular function was demonstrated in patients with a tachycardia-

mediated mechanism, also in subjects with prior infarction.[316,318] Alternatively, in patients without a prior infarction, an observational study[309] showed that flecainide and propafenone effectively suppressed PVCs in patients with a mean LVEF of 37% who were suspected of having PVC-induced cardiomyopathy. This suppression led to LVEF recovery in most of these patients. In patients with PVCs in the setting of known CAD treatment with β-blockers is advised, while suppression of PVCs with antiarrhythmics other than β-blockers has not demonstrated any survival benefit and was harmful, since associated with worsening of survival in the case of Class Ic AADs, as shown in the CAST trial.[319] This advice has been extrapolated to other forms of SHD, especially when myocardial scarring is present.

VT and structural heart disease

Currently, AADs for malignant ventricular tachyarrhythmias in the setting of SHD predominantly serve as adjunctive therapy to the ICD to prevent VT, frequent shocks, avoid transformation of well-tolerated arrhythmias into malignant arrhythmias or to prevent deterioration of cardiac function because of tachycardia, irregular rhythm, or desynchrony, rather than to cure the arrhythmia itself (**Box 5**). Shared decision-making is important when initiating AADs balancing the risk for proarrhythmia and efficacy, particularly if the indication is

Box 5: Current AAD aims in patents with structural heart disease and ventricular tachycardia

- Improve quality of life and symptoms
- Improve cardiac function[a] if:
  - deteriorated because of the VT
  - deteriorated by dyssynchrony (frequent PVCs & NSVT)
- Prevent aggravation to malignant or intolerable VT
- Prevent recurrent shocks in ICD patients

Note: No AAD, except for β-blockers, has demonstrated reduction in all-cause mortality in patients with ventricular tachycardia (VT). ICD; implantable cardioverter-defibrillator; NSVT, non-sustained VT; PVC, premature ventricular contraction.
[a]*Catheter ablation is the first-line therapy for tachycardia-induced cardiomyopathy and isis advised to be the preferred treatment approach.*

symptomatic therapy. It is advised to instruct patients to contact physicians when they suffer from syncope, dizziness or palpitations.

β-blockers are considered the basic medication in SHD and can be very effective in polymorphic VT but has low efficacy in preventing monomorphic sustained VT. Recurrent polymorphic VT (QRS morphology changing from beat to beat) are often signs of acute ischaemia or incomplete reperfusion and mandates a search for and correction of reversible causes (hypokalaemia, hypomagnesaemia, exacerbation of HF, and proarrhythmic drugs). Patients with SHD have higher risks of ventricular tachyarrhythmias and are at higher risk of proarrhythmia when using

AADs.[320] In principle, patients with HF or cardiomyopathy are not candidates for VW Class Ic or Class III AADs other than amiodarone or sotalol (see ESVEM and OPTIC trials above).[320] Although Sotalol can be used in patients with CAD, the drug is advised to be used with caution related to its increased risk for HF, proarrhythmia and mortality.[92,122] Catheter ablation is increasingly being used for the management of recurrent VT and outperforms drug escalation in patients with VTs despite baseline AAD therapy.[321] Patients with LVH have increased dispersion of repolarization and higher risks of polymorphic ventricular tachycardia (PVT),[322] which may support the concern over proarrhythmia and the caution against using Class Ic or Class III AAD. Observational studies, however, reported comparable mortality rates in patients with LVH and AF treated with Class Ic and Class III agents as in those treated with amiodarone.[323]

Given this background it is important to evaluate the risk for proarrhythmia before starting AADs and to optimize treatment of comorbidities already at baseline. It is further crucial to assess clinical status, symptoms, concomitant drugs (www.crediblemeds.org), ECG changes, left ventricular function and objective signs of relevant changes that could provoke proarrhythmia on a regular basis during follow-up.[324] The appropriate timing of such follow-ups depends on the disease state of the patient. Given the increased risk of proarrhythmia with Class III AADs in females it is advisable to use the lowest effective doses, avoid concomitant use of any other QT prolonging agent or proarrhythmia promoting factors e.g., hypokalaemia (**Figure 13**).

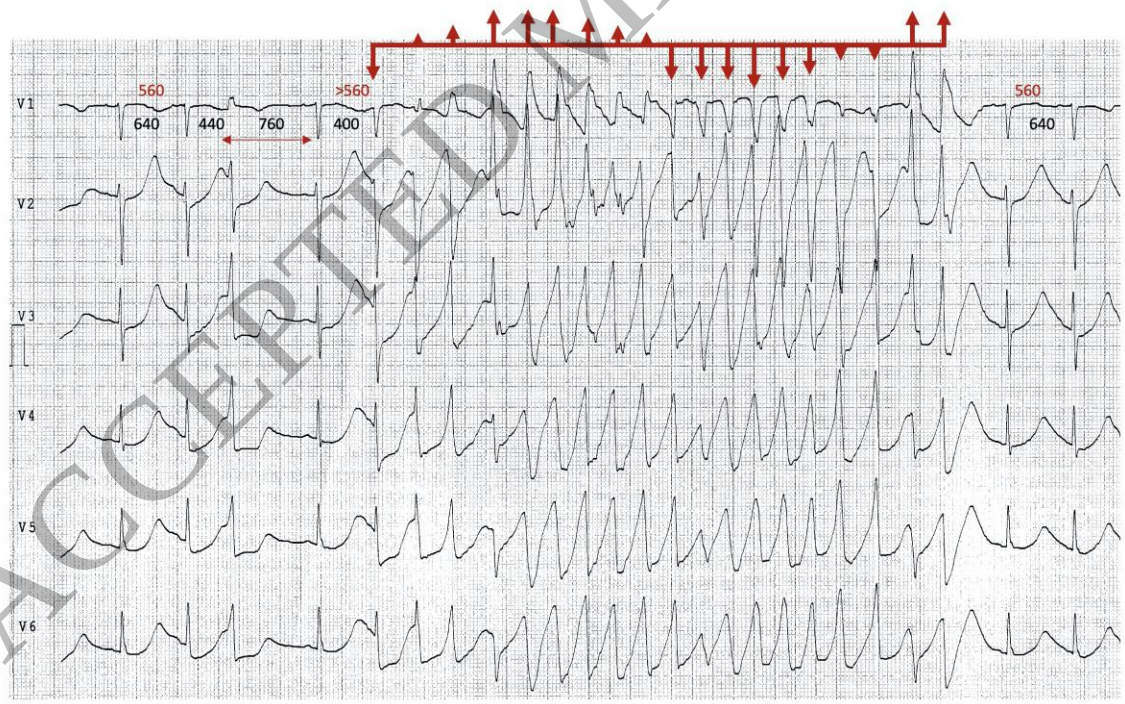

Figure 13: 12-lead ECG demonstrating QT interval prolongation and a 5.5-second run of non-sustained polymorphic ventricular tachycardia (*torsade de pointes*, TdP) following a postextrasystolic pause in a patient with hypomagnesemia. This highlights the association between electrolyte imbalances, prolonged repolarization, and proarrhythmic events such as TdP.

The typical TdP twisting pattern of QRS complexes around the isoelectric line (red line) is marked with red arrows of varying amplitude above lead V1. Cycle lengths and QT intervals are annotated with black and red numbers, respectively. TdP is triggered by a pause (two-arrowhead red line) that further prolongs the QT interval.
The ECG was recorded at a speed of 25 mm/s and a sensitivity of 10 mm/mV.

Ventricular fibrillation

Polymorphic VT (VT) and VF are life-threatening ventricular tachyarrhythmias. Polymorphic VT occurring in a setting without prolongation of the QT has a different management as compared to TdP which is polymorphic VT occurring in congenital or acquired long QT.[254] Prevention of VF and polymorphic VT is often required in patients implanted with an ICD, in order to avoid recurrent shocks, that may occur in the form of "storms". Correction of myocardial ischaemia, with revascularization and avoidance of electrolyte abnormalities, as well as of drugs with a proarrhythmic potential are important preventive measures. With regard to drugs, the combination of amiodarone and a β-blocker (metoprolol, carvedilol or bisoprolol) was more effective than a β-blocker alone in reducing ICD activation for ventricular tachyarrhythmias, while sotalol (240 mg/day) had a trend towards higher efficacy when compared to a β-blocker without Class III antiarrhythmic activity.[92]

Tachycardia termination

In the termination of tachycardia, the choice between oral and i.v. administration of AAD hinges on the urgency of intervention and the patient's clinical stability. Oral administration is often considered in stable patients with well-tolerated tachycardia, allowing for gradual onset and sustained effect. Conversely, i.v. administration is preferred in acute and unstable situations, aiming for a rapid onset of action. The decision to utilize electrical cardioversion arises when prompt restoration of normal rhythm is imperative, especially in cases of haemodynamic compromise or severely symptomatic tachycardia. This intervention may ensure a swift and effective reset of the cardiac rhythm, offering an immediate resolution in critical scenarios.

The selection among these strategies is directed by a comprehensive assessment of the patient's clinical status, the nature of tachycardia, and the urgency of intervention. A tailored approach that factors in these considerations allows for a more effective and patient-centred management of tachycardia (**Figure 14**).

AF (Oral – PITP)

PITP therapy[325] refers to use of an orally administered AAD for the termination of a recent-onset arrhythmia – most commonly occasional[326] AF with well-tolerated episodes.[325] Agents and conditions required to use of a PITP strategy are shown in **Box 6** and **Box 7** respectively.

Because conversion to AFL may occur (with or without subsequent reversion to SR), an AV node blocker must precede administration of flecainide or propafenone (e.g., β-blockers or CCB given 2 hrs prior to PITP initiation, unless taken chronically). Dofetilide can convert AF, but its time course is too slow (days) to use as PITP. Amiodarone is much too slow; sotalol is not effective as PITP and dronedarone has not been tested. Typical conversion rates with the Ic AADs and ranolazine are 70-80% by 8 hrs (about twice that of placebo) with a mean time of 3-4 hrs for Ic drugs and 3-6 hrs for Ic drugs and 3-6 hrs for ranolazine.

Box 6: Antiarrhythmic agents and dosing for "pill in the pocket" treatment of AF

- Flecainide (immediate release formulation): 300 mg (single dose and consider 200 mg for weight <70 kg).
- Propafenone (immediate release formulation): 600 mg (single dose and consider 450 mg for weight < 70 Kg).
- Ranolazine[a]: 2000 mg single dose (or 1000 mg x 2 given 4 hrs or less apart).

AF, Atrial fibrillation.

[a]*Consider further reducing the dose (100 mg of flecainide or 300 mg of propafenone) in elderly patients or those with suspected sinus node dysfunction.*

[b]*Ranolazine has not been approved as an antiarrhythmic drug by the European Medicines Agency or the United States Food and Drug Administration except for the long QT syndrome.*

Box 7: Conditions required to use PITP strategy for AF termination

- Recent onset of AF (<7 days)
- Properly anticoagulated if advised
- No underlying sinus node, AV node dysfunction (in the absence of a pacemaker), Brugada syndrome or other contraindications to AADs, ischaemia or haemodynamic intolerance
- Established or acutely administered rate-control therapy to prevent 1:1 AV conduction in case of transient conversion to AFL prior to return to sinus rhythm
- Acceptance of the need to stay at rest for at least 3 hours after drug administration to minimize the risk of proarrhythmia
- Prior demonstration of tolerance to the AAD or initial PITP usage are advised to be conducted under observation to verify effectiveness and ensure no adverse effects.

AF (Intravenous)

The primary mechanisms underlying the termination of AF (AF) with i.v. drugs are diverse, reflecting the complex and still incompletely understood nature of this arrhythmia. The effectiveness of i.v. drugs in terminating AF is influenced by various factors, including patient characteristics, AF duration, underlying SHD, and the presence and functional Class of HF (see **Table 6**).

In cases of recent-onset AF, particularly within the first 48 hours, Class I and III agents have demonstrated high efficacy rates, often exceeding 70%. However, it is important to note that, in most instances, these drugs may not achieve higher conversion rates compared to placebo but may lead to earlier conversion.[327] The efficacy of ibutilide and dofetilide is lower for converting AF compared to AFL. Vernakalant stands out with a favourable efficacy and safety profile, making it a valuable option for AF termination, especially in patients with recent-onset AF (within 7 days). A recent meta-analysis evaluating the efficacy of different antiarrhythmic agents in restoring SR in paroxysmal AF identified vernakalant, amiodarone-ranolazine, flecainide, and ibutilide as the most effective medications.[328]

While efficacy is a critical consideration, safety holds paramount importance in the selection of i.v. drugs for AF termination. The proarrhythmic and ventricular contractility depression potential, particularly with Class I antiarrhythmics, necessitates meticulous patient selection, precluding their use in individuals with SHD or significant ventricular dysfunction. Class III

agents, while generally safe, require vigilant monitoring of renal function and the QT interval to mitigate potential risks.

Another important factor in AAD selection is the timing of AF termination. Vernakalant has a median time to termination of 11 minutes in patients with AF lasting less than 48 hours, which is significantly shorter compared to i.v. flecainide or amiodarone (**Figure 7**). The rapid onset of action of vernakalant enhances the likelihood of restoring SR within 48 hours, resulting in cost savings compared to alternative treatment approaches.[329] With i.v. amiodarone, only 5.2% of patients converted to SR within 90 minutes.[158]

Finally, it is worth noting that ß-blocker infusion is not advised for AF termination, although it may still be advised for heart rate control.

Table 6: AADs currently advised for AF termination.[a]

AAD	No SHD & AF ≤7 days[b]	No SHD & AF >7 days[c]	SHD with HF NYHA I-II & AF ≤7 days	HF NYHA III-IV[d]
Vernakalant i.v.	**1**	-	**1**[e]	**No**
Procainamide i.v.	-	**3**		**No**
Flecainide/Propafenone i.v./p.o. PITP	**2**	**1**	**No**	**No**
Sotalol[f,g] i.v.	-	-	-	**No**
Ibutilide[g] i.v.	**3**	**2**	**2**	**2**
Amiodarone[h] i.v.	**3**	**2**	**2**	**1**

"1" on white background, 1st choice; "2" on blue background, 2nd choice; "3" on light brown background, 3rd choice; "-"on grey, minimal effect/not advised; "No" on black background, contraindicated. *AAD, antiarrhythmic drug; AF, atrial fibrillation; HF, heart failure; i.v., intravenous; NYHA, New York Heart Association functional class; PITP,* pill-in-the-pocket; *p.o., per os;* PVC, premature ventricular contraction; SHD, structural heart disease.

[a]Anticoagulation and/or exclusion of left atrial thrombi must always be ensured before attempting AF termination, in accordance with the recommendations outlined in ESC AF guidelines.

[b] Antazoline, cibenzoline, and pilsicainide are also used in some countries, such as Japan, Korea and Poland, for the treatment of short-lasting AF, provided that patients do not have significant SHD, HF, or bradycardia.

[c]The efficacy of conversion with each drug decreases as the duration AF increases, with a significant decline in success for episodes lasting more than 7 days, making electrical cardioversion a more effective option in such cases.

[d]Consider electrical cardioversion first if haemodynamic instability

[e]Contraindicated if severe aortic stenosis or acute myocardial ischaemia

[f]Sotalol is not advised in patients with moderate-to-severe heart failure but still may be appropriate if AF last >7 days

[g]Not to be given if renal insufficiency, hypokalaemia, QT prolongation risk or LVEF≤40%

[h]Amiodarone has a slow and delayed effect on AF termination, with most of its benefits stemming from heart rate control rather than immediate rhythm conversion.

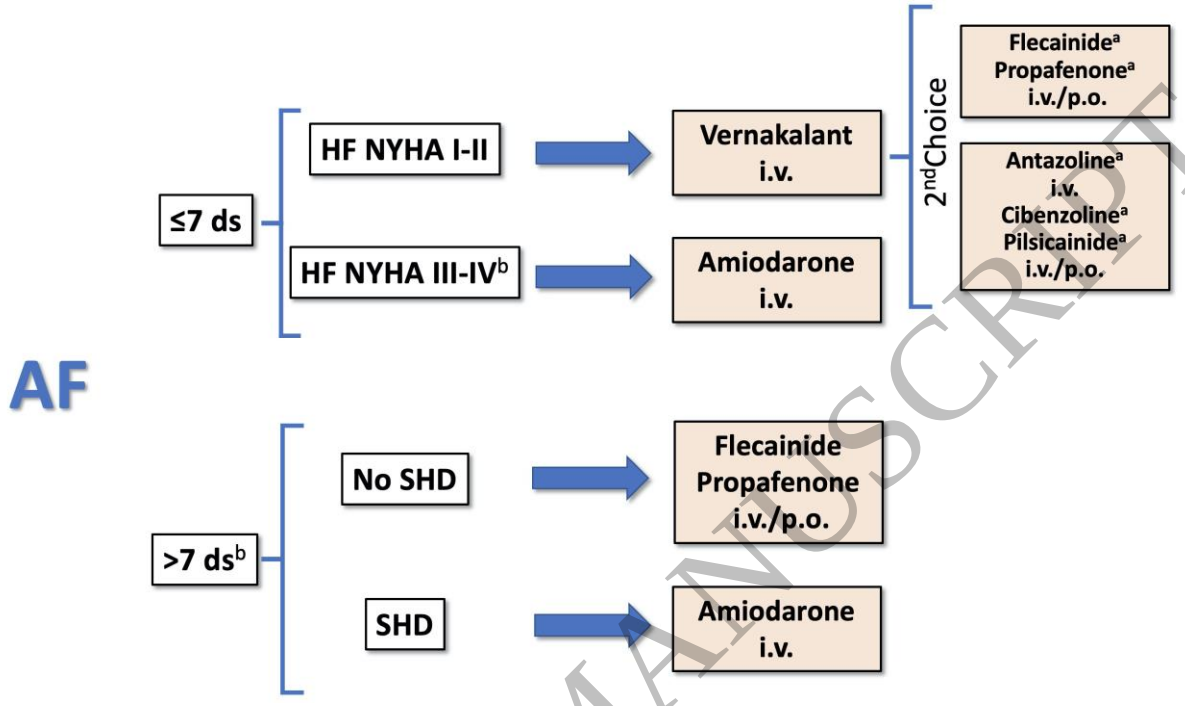

Figure 14: Schematic representation of the advised AADs for termination of atrial fibrillation (AF).
The figure serves as a general reference for selecting the most appropriate drug; however, the final choice is advised to be done by patient-specific characteristics and conditions, as detailed in the various sections of this document. Additionally, drug availability plays a crucial role in decision-making. For example, vernakalant is available in many European countries but not in the U.S. Flecainide and propafenone i.v. are not available in many American countries. Antazoline is primarily produced and marketed in Poland, where it is registered for antiarrhythmic use, though its availability in other European countries remains limited. Pilsicainide is primarily approved and used in Japan and Korea, but its presence in Europe is scarce. Cibenzoline is also used in Japan and has been available in certain European countries. ds, days; HF, heart failure; NYHA, New York Heart Association functional class; i.v., intravenous; p.o., per os; SHD, structural heart disease.
[a]: Class Ic AADs are contraindicated in patients with SHD, HF, or significant conduction disturbances due to the risk of proarrhythmia and conduction block.
[b]: Oral ranolazine has been used off-label for AF conversion in patients with ischemic heart disease. However, it is advised to be used with caution in NYHA class III-IV heart failure and avoided in patients with QT prolongation due to the risk of proarrhythmia.

Atrial flutter

The AFL cycle length is determined by atrial conduction velocity and re-entrant circuit size, typically slightly longer than the APD. Modest APD prolongation, achievable with Class III agents like IV dofetilide and ibutilide, is ideal for terminating AFL. A randomized multicentre trial showed IV dofetilide terminated AFL more frequently (75%) than IV amiodarone (0%) or placebo (10%) ($P < 0.001$).[330] While these agents might not be available in many countries,

sotalol (1.5mg/Kg body weight over 5-10 minutes) can also be applied with careful dosing since too low drug blood levels may result in failure.

Class Ia and Ic drugs (flecainide, propafenone, cibenzoline) and vernakalant are ineffective in terminating AFL, as they fail to sufficiently suppress conduction within the atrial re-entrant circuit. Instead, they typically prolong the atrial cycle length by ~100 ms without interrupting tachycardia. This slower atrial rate increases the risk of 1:1 AV conduction, given the weak negative dromotropic effect of Class I AADs at the AV node. AFL with 1:1 AV conduction is often associated with aberrant conduction, producing wide, bizarre QRS complexes that mimic VT and can lead to hemodynamic instability. Due to these risks, Class I AADs are generally discouraged, and AFL termination is advised to be pursued with selective Class III AADs or electrical cardioversion.

Paroxysmal SVT

Patients with SVT, either corresponding to AVNRT and AVRT, may respond to vagal manoeuvres, carotid massage, or adenosine i.v.[254,331,332] Assessment of the exact diagnosis of the PSVT, and specifically of AVNRT vs AVRT is important but in some cases the exact diagnosis may remain uncertain.[331] The first and very important step in the approach to patients with PSVT as with other re-entrant arrhythmias, is to assess haemodynamically stability. If the situation is unstable synchronized cardioversion is recommended by the ESC guidelines of SVT.[44]

Adenosine is widely used in patients with tolerated PSVT because the resulting transient AV blockade is helpful both for arrhythmia termination and for differential diagnosis of other supraventricular tachyarrhythmias (e.g., AFL or AT). Adenosine is advised to be used with caution and always under ECG monitoring, since it may induce the onset of AF with a rapid ventricular response in the presence of an accessory pathway with antegrade conduction capabilities, even when previously unknown.[202]

Assessment of the exact diagnosis of the PSVT, and specifically of AVNRT vs AVRT is important but in some cases the exact diagnosis may remain uncertain.[331]

Intravenous diltiazem, verapamil, metoprolol, esmolol or other β-blockers can be useful in terminating haemodynamically stable regular SVT of uncertain type or when a diagnosis of with AVNRT or AVRT is suspected. However, drugs that mainly act by slowing the conduction through the AV node (e.g. diltiazem, verapamil, β-blockers) are discouraged in patients with known pre-excitation with antegrade conduction capabilities, in consideration of the risk of AV nodal blockade and acceleration of the ventricular rate if AF occurs.[254] Also i.v. amiodarone may precipitate a VF in case of AF with anterograde conduction over an accessory pathway.[333] Assessment of the underlying mechanism of PSVT is important but in some cases ruling out participation of an accessory pathway remain uncertain.[331]

Procainamide, flecainide or propafenone are advised for interrupting antidromic AVRT without haemodynamic instability, but Class Ic AADs (flecainide, propafenone) are contraindicated in the presence of left ventricular dysfunction, ischaemic heart disease, severe LVH or conduction system disturbances.[254]

Focal atrial tachycardia

Focal AT is characterized as a tachyarrhythmia arising from a focal atrial area and may occurs in many clinical conditions, including catecholamine excess, digoxin toxicity, congenital heart disease, chronic obstructive pulmonary disease and different types of cardiomyopathy[334] For the differential diagnosis between a focal AT and other supraventricular tachyarrhythmias i.v. adenosine can be useful. Adenosine is also useful for therapeutic purposes, as an alternative to vagal manoeuvres. However, it has to be noted that focal AT is frequently terminated by adenosine, and this is not usually the case with vagal manoeuvres.

There is limited evidence on the acute treatment of focal AT. In cases of haemodynamic instability, DC cardioversion may be required, although AT is typically resistant to this. Intravenous β-blockers, diltiazem, or verapamil can be used initially. If these treatments fail, i.v. flecainide, propafenone, or amiodarone may be appropriate after an appropriate wash-out period to avoid the mixing of different agents in a short time frame.[44]

Junctional ectopic tachycardia

This is a tachyarrhythmia arising from the region of the AV node or AV junction, including the bundle of His, due to enhanced automaticity. It is usually observed in the postoperative settings of surgery for congenital heart disease or in children as a congenital disorder. Usually the QRS is narrow, but aberrant conduction can occur. For treating this arrhythmia i.v. amiodarone has been successfully used, but also flecainide, procainamide, propafenone, landiolol and sotalol have also

Box 8: Factors associated with concealed structural heart disease in patients presenting with apparent idiopathic ventricular tachycardia.

- Poor haemodynamic tolerance
- ECG:
  a. Sustained VT[a]
  b. Tachycardia cycle length <250 ms
  c. Tachycardia QRS complex duration >140 ms
  d. Atypical QRS complex morphology for an RVOT or fascicular-type VT
  e. Several VT morphologies or pleomorphic VT[a]
  f. Abnormal sinus rhythm ECG (Q waves, ventricular hypertrophy or low voltage QRS complex in frontal plane leads, inverted T waves beyond V2, etc.)
- Abnormal cardiac findings on chest X-ray or echocardiogram
- No response to adenosine

[a]*Fascicular idiopathic VT typically presents with sustained monomorphic VT though, RVOT typically presents with multiple bursts of non-sustained monomorphic VT and frequent same morphology PVCs*. RVOT, right ventricular outflow tract; VT, ventricular tachycardia.

been used with some success.[335,336] Also digoxin, and anti-inflammatory agents such as steroids or even colchicine have been proposed.[335,336] In an open-label randomized controlled trial, oral ivabradine was not inferior to i.v. amiodarone in converting postoperative JET to SR, and no difference was found in the time taken to SR conversion between the groups, although the rate control was earlier in patients who received amiodarone.[337] Therefore, according to this study and other contributions monotherapy with ivabradine may be appropriate as an alternative to amiodarone in the management of postoperative JET, as well as an adjunct to amiodarone for refractory JETs after surgery for congenital heart disease.[338]

Ventricular tachycardia – Non-SHD

Patients without SHD may present with premature ventricular contractions (PVC) and occasional non-sustained bursts of VT. However, caution is advised when dealing with sustained VT in this population, as it could be the first manifestation of an underlying SHD. This consideration is crucial, especially when selecting an AAD for termination (see **Box 8**).
Clinical studies have predominantly focused on VT originating from the RVOT or the left fascicles of the His bundle. Adenosine and verapamil are often advised for acute termination of outflow tract and fascicular idiopathic VT, respectively. It is worth noting that there are reports and small series supporting the use of both drugs in both VT mechanisms.
However, the use of verapamil requires caution due to its association with myocardial contractility depression and hypotension. This caution is particularly relevant when considering VT termination in patients with less established absence of SHD.

Ventricular tachycardia - SHD

For acute termination of haemodynamically stable monomorphic VT of unknown aetiology, procainamide or amiodarone may be used[339,340] with preference for procainamide[341] for safer and shorter time to conversion (**Figures 5 and 15**). The ESC and the AHA/ACC/HRS guidelines[45] recommend procainamide over amiodarone, largely based on the randomized controlled PROCAMIO trial,[341] which showed that procainamide was associated with fewer major cardiac adverse events and a higher proportion of tachycardia termination within 40 min.[342] However, if the patient suffers from severe HF, acute MI or end-stage kidney disease amiodarone is the acute treatment of choice.

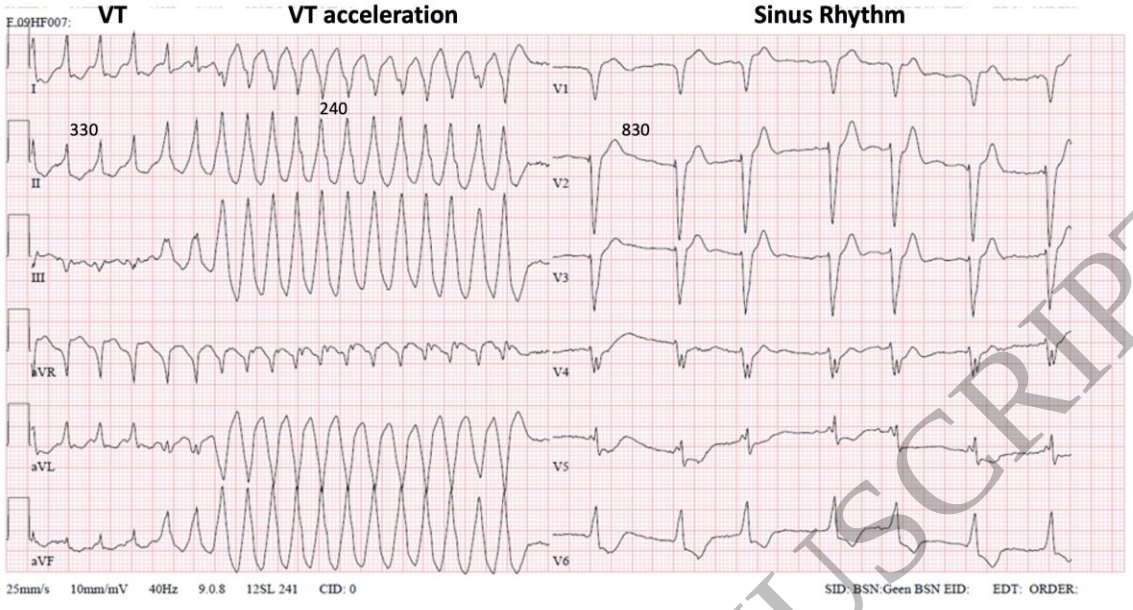

Figure 15: 12-lead ECG illustrating the termination of hemodynamically tolerated monomorphic ventricular tachycardia (VT) following the infusion of amiodarone in an 81-year-old female patient with a history of anterior wall myocardial infarction. *Panel A: Initial VT with a cycle length of 330 ms during intravenous amiodarone infusion, showing no significant change in cycle length. Panel B: Subsequent change in VT morphology and acceleration to a cycle length of 240 ms, followed by VT termination and resumption of sinus rhythm. The ECG was recorded at a speed of 25 mm/s and a sensitivity of 10 mm/mV. This case highlights the dynamic response of VT to antiarrhythmic therapy. ECG recorded at a speed of 25 mm/s and a sensitivity of 10 mm/mV.*

Amiodarone is also preferred in ES with frequent VT episodes.[45,343] When underlying disease is suspected, ajmaline, sotalol, and flecainide are not advised.[305,344] If the underlying diagnosis is not clear, amiodarone may be preferred acknowledging that initial effects occur only within hours and include mainly early β-adrenergic and calcium channel blockade.[345] Initial treatment with β-blockers, preferably non-selective β-blockers like propranolol, is advised.

Intravenous lidocaine is only moderately effective, but may be appropriate for the treatment of recurrent, haemodynamically stable sustained VT not responding to β-blockers or amiodarone or in the presence of contraindications to amiodarone.[45] Lidocaine has been advised as an alternative to amiodarone also for acute treatment of shock-refractory VF/pulseless VT.[346] Although there is no evidence for improvement in survival to hospital discharge associated with lidocaine, return of spontaneous circulation was higher in patients receiving lidocaine compared with placebo after CA, and survival to hospital admission was higher compared with placebo.[346]

If incessant slow monomorphic VT ensues from AAD treatment, catheter ablation may be needed with AAD mostly continued after the intervention.[45]

Besides AAD selection, other aspects are also important. In all cases of haemodynamically stable monomorphic VT documentation on 12-lead ECG is important key. Also, it is advised to monitor

and documented by 12-lead ECG VT cycle length and morphology as well as QRS width and QT of the QRST complex during VT during AAD infusion (**Table 7**).

Table 7: Potential ECG changes after AAD administration for monomorphic VT termination

ECG parameter	Electrophysiologic mechanism	VM Class of AAD
VT cycle length prolongation	- AAD-induced slowing of conduction due to reduced Na^+ channel activation or - Prolongation of refractoriness impinging on the excitable gap and widening the re-entrant VT circuit	- More marked with Class Ic than with Class III AADs - Also seen with Class Ia procainamide - More marked with higher dosed and the higher the VT rate (use-dependency)
QRS complex morphology change	Multiple exits which result from stopping one circuit and initiating another	May occur especially with Class Ic AAD
QRS complex widening during VT	Reduction of conduction velocity of the ventricular activation through the myocardium independent from the AAD effect in the re-entrant circuit; comes with risk of acute heart failure, AV-block and sinusoidal VT	Mainly with Class Ic AADs and more marked with faster VTs (use-dependency)
QT interval lengthening during VT	Prolongation of the action potential; may associate with TdP due to combination of relative bradycardia and bradycardia-dependent AAD-induced long QT after tachycardia termination	Mainly with Class III drugs. Not expected with Class Ia drugs. Post termination long QT may relate to reverse use-dependency of Class III AAD

AAD, antiarrhythmic drug; VM, Vaughan Williams; VT, ventricular tachycardia.

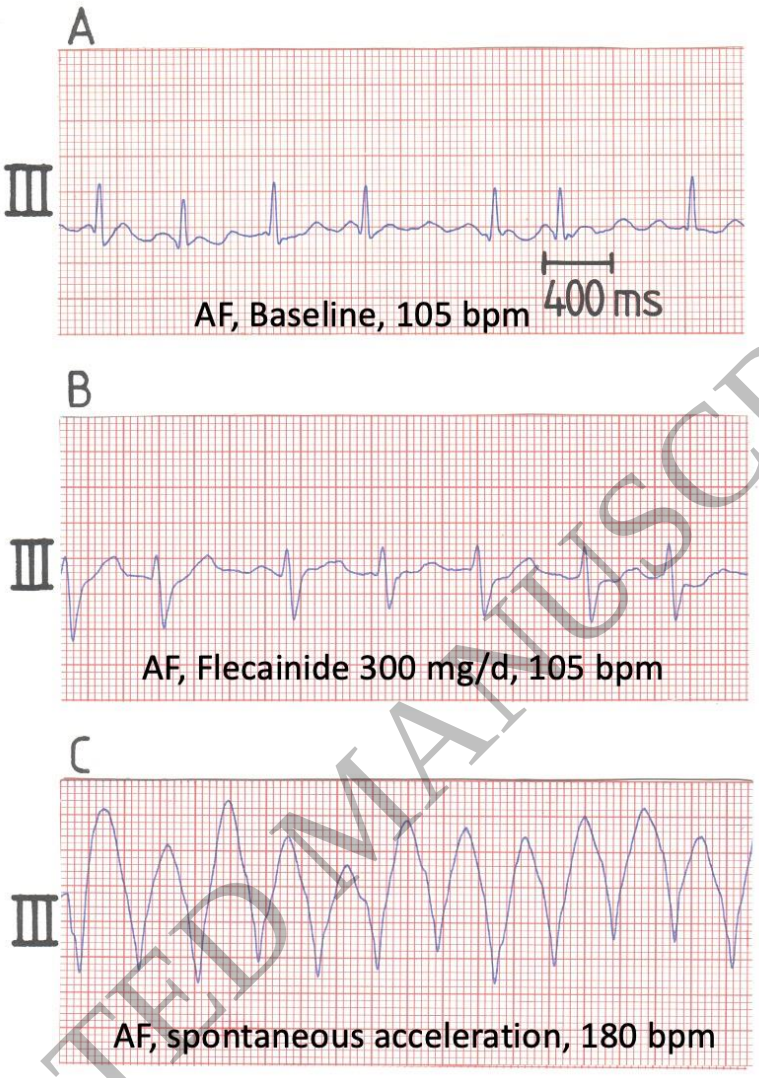

Figure 16: ECG tracings (lead III and monitor lead) illustrating the progression of atrial fibrillation (AF) and its response to 300 mg/day flecainide, culminating in ventricular tachycardia (VT) in a 66 year old female with no underlying heart disease.
Panel A: Baseline AF at a heart rate of 105 bpm with a QRS duration of 90 ms. Panel B: After administration of 300 mg of flecainide, QRS duration prolongs to 120 ms, while the heart rate remains unchanged at 105 bpm. Panel C: Spontaneous acceleration of AF to 180 bpm leads to further QRS widening to 210 ms, attributed to the use-dependent effect of flecainide. This sequence underscores the potential proarrhythmic effects of flecainide in AF management, if high dosage is used. ECG recorded at a speed of 25 mm/s and a sensitivity of 10 mm/mV.

Polymorphic VT and ventricular fibrillation

VF and PVT are life-threatening cardiac arrhythmias. Prompt and appropriate treatment is crucial in managing these conditions. Treatment involves immediate initiation of cardiopulmonary resuscitation and early defibrillation. In patients without SHD, the management of PVT involves addressing underlying causes, such as electrolyte imbalances, medication side effects, bradycardia or a channelopathy. Magnesium sulphate and potassium are often

administered intravenously to stabilize the myocardium. It is advised to manage patients with bradycardia, acquired or LQTS3 by elevating heart rate by isoprenaline infusion or pacing with supra-normal rates. BrS patients are advised to be managed by isoprenaline or quinidine. Patients with CPVT are advised to be treated by β-blockers and flecainide.

Polymorphic VT in SHD frequently is a marker of myocardial ischaemia and apart from resolving ischaemia with a standard coronary intervention i.v. β-blockers and amiodarone are considered the most suitable AAD treatments in haemodynamically stable cases. Lidocaine[347] and mexiletine may also be effective, and the latter AADs may be used as add-on therapy. Sometimes polymorphic VT/FV occurs in post-infarct patients without any evidence of myocardial ischaemia, and which is due to triggering from surviving Purkinje fibres. They are initiated with a relatively short-coupled PVC (350ms) and may occur with normal QT (polymorphic VT with normal QT) or a long QT (pseudo-TdP). Storms due to these Purkinje triggered polymorphic VTs respond well to quinidine but are refractory to β-blockers, lidocaine, mexiletine, Class Ic drugs, and amiodarone.[348–350]

Practical aspects

Initiation of AAD

The initiation of AADs requires a comprehensive and safety-driven approach to optimize outcomes while minimizing risks. This involves careful management of concomitant conditions, vigilant monitoring, and patient education. Underlying conditions such as ischaemic heart disease are advised to be addressed with revascularization and statin therapy, adequate β-blockade, and elimination of triggers like electrolyte imbalances. For patients with HF, therapy is advised to be tailored to the subtype: in HFrEF, optimization involves β-blockers, aldosterone antagonists (e.g., spironolactone or eplerenone), ACE inhibitors, sacubitril/valsartan, and sodium-glucose co-transporter-2 inhibitors (SGLT2i), while in HFpEF, SGLT2i play a central role. Baseline ECG, echocardiography, renal and hepatic function, along with a haematology and biochemical profile, including lipid, glucose, and electrolyte parameters, are advised to be established for future reference **(Table 8)**. For amiodarone, baseline assessments must also include thyroid function tests, a chest X-ray and pulmonary function tests (PFTs), including diffusion capacity, and, ideally, visual assessment by a corneal slit-lamp exam and a fundoscopic evaluation. An exercise test to assess QRS widening during exercise or detect subclinical myocardial ischaemia may be also considered for patients after initiating Class Ic AADs.

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

AADs other than amiodarone			
Evaluation	**Test/Parameter**	**Frequency**	**Toxicity/Interaction evaluation**

ECG	Rhythm, PR, QRS, QTc	Baseline, shortly after initiation or dose adjustments (1-2 days for Class Ia, Sotalol, Dofetilide), and periodically (E.g. every 6 months)	QT interval prolongation (for Class Ia and III drugs) QRS duration prolongation (for Class Ic drugs) Proarrhythmic tachycardia (e.g., type Ic AFL), bradycardia or BBB/atrioventricular block
Echocardiography	Ventricular function	Baseline and updated if change suspected/risk	Systolic dysfunction (contraindication for Class Ic & IV AADs)
Blood test & Serum Electrolytes	GFR, K^+, Mg^{2+}	Baseline, periodically (e.g., every 6 months)	Reduced drug elimination, Proarrhythmia risk
Liver Function	ALT, AST, and total bilirubin	Baseline, periodically (e.g., every 6 months)	Reduced drug elimination
Exercise test	QRS at peak exercise, myocardial ischaemia	To consider for Class Ic at follow-up	QRS widening at exercise
Amiodarone			
Evaluation	**Test/Parameter**	**Frequency**	**Toxicity/interaction evaluation**
ECG	Rhythm, PR, QRS, QTc	Baseline, steady state (1-3 months), annually	QT interval prolongation, proarrhythmic tachycardia (e.g., AFL), bradycardia or atrioventricular block.
Echocardiography	Ventricular function	Baseline, update if potential changes suspected.	Systolic dysfunction
Serum Electrolytes	K^+, Mg^{2+}	Baseline, every 6 months	Proarrhythmia risk

Liver Function	ALT, AST, and total bilirubin	Baseline, every 6 months	Hepatotoxicity
Thyroid Function	TSH, Free T4, and Free T3	Baseline, every 6 months	Hypothyroidism or hyperthyroidism
Pulmonary Function	Chest X-ray and pulmonary function tests (diffusion capacity)	Baseline, annually	Interstitial lung disease
Visual function	Corneal slit-lamp exam and fundoscopic evaluation	Baseline, annually	Corneal microdeposits and, rarely, optic neuropathy

AAD, antiarrhythmic drug; AFL, atrial flutter; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BBB, bundle-branch block; GFR, glomerular filtration rate; TSH: Thyroid-stimulating hormone.

Regular blood pressure measurements are critical when initiating AADs, especially via i.v. infusion, as these drugs can cause vasodilation and hypotension. It is advise to carefully control infusion rates to ensure appropriate peak plasma concentration and to avoid hypotension, and a physician has to remain close to the patient during administration (**Box 9**).

Controversy (**Box 10**) exists regarding the safety of initiating AADs in outpatient settings, with advice varying depending on the drug and patient profile (**Box 11 and Table 9**). The choice between in-patient and out-patient initiation is primarily driven by safety considerations.[351] Importantly in-patient initiation is advised for high-risk patients, such as those with SHD or significant arrhythmias, as it allows for close monitoring and timely intervention. Out-patient initiation, while more convenient, requires adequate monitoring using tools like smartwatches, trans-telephonic devices, or other patient-activated ECG methods. For example, sotalol is advised for inpatient initiation in AF patients, but some trials suggest that outpatient initiation with daily and symptomatic ECG transmissions via event recorders, smartphone apps, or smartwatches for 10 days could be a safe alternative.[352] However, these were small and non-controlled and have to be taken with caution. Any abnormal findings recorded on digital devices must prompt a confirmatory 12-lead ECG.

Since urgency is less critical in the out-patient setting, dosing must start low and progress gradually, with adjustments based on the longest known half-life of the drug to ensure a steady state before dose increases.

Patient education and counselling are essential for safety and adherence. This includes defining the goals of therapy, such as symptom relief or arrhythmia prevention, and educating patients on recognizing potential adverse effects, including rapid palpitations or (pre-)syncope during exercise or at rest which might suggest proarrhythmia. Patients must also be informed of potential food-drug and drug-drug interactions, particularly with QT-prolonging medications.

Box 9: ECG parameters to monitor/ observe during AAD infusion

- Atrial rate, atrial cycle length (in AFL)
- Bradycardia
- Enhanced AV conduction, 1:1 AV conduction
- Unexpected AV block (Class Ic and Class III AAD)
- Termination of AF or AFL
- Signs of sinus node dysfunction upon AF/AFL termination
- QRS prolongation and aberrant conduction (Class Ic AAD)
- QT prolongation (Class Ia and III AAD)
- Signs of Brugada ECG in right precordial leads (Class I AAD)
- TdP and other ventricular arrhythmias

AAD, antiarrhythmic drug; AF, atrial fibrillation; AFL, atrial flutter; AV, atrioventricular; TdP, torsades de pointes.

Box 10: Advantages, disadvantages, and advice for in-patient and out-patient initiation of AADs

IN-HOSPITAL INITIATION

Advantages:

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

Disadvantages:

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

OUT-PATIENT INITIATION

Advantages:

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

Disadvantages:

- Rare but serious proarrhythmic events may go undetected and untreated.

AAD, antiarrhythmic drug; AFL, atrial flutter; AV, atrioventricular; LV, left ventricle; TdP, torsades de pointes.

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Box 11: Advice/requirements for in-hospital/out-patient initiation of AADs

IN-HOSPITAL INITIATION

- **Class Ia**: Required for most drugs (some exceptions).
- **Class III (Dofetilide)**: Must always be initiated and dose-adjusted in-hospital.
- **Class III (Sotalol)**: In-hospital if QTc ≥450 ms (500 ms if intraventricular conduction delay), HR ≤60 bpm, or specific risk factors (e.g., SHD, renal dysfunction). See **Box 12**.
- **QT Prolongation or unconfirmed sinus rhythm** (risk of sick sinus syndrome or bradycardic pauses): Require in-hospital initiation.
- **Proarrhythmic Risk**: High ventricular proarrhythmia risk (*torsades de pointes*, syncope, cardiac arrest) necessitates in-hospital monitoring.

OUT-PATIENT INITIATION

- **Class Ib (Mexiletine)**: Allowed for non-tachycardic ventricular ectopy or type III long QT syndrome.
- **Class Ic (Fleainide/propafenone)**: Permitted in patients without SHD with ECG checks unless normal sinus rhythm has not been previously documented.
- **Class Id (Ranolazine)**: Safe for patients with or without SHD.
- **Class III (Dronedarone, Amiodarone)**: Permitted with ECG checks in low-risk patients.
- **Patients with ICDs**: ICDs provide protection against proarrhythmia, enabling out-patient initiation.

AADs, antiarrhythmic drugs; HR, heart rate; ICD, implantable cardioverter-

2

Table 9: Advisable agents for in-hospital/out-patient initiation of AADs.

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

¶:
for type III long QT syndrome or PVCs
**: If uncertain sinus node function or risk for AFL conversion with 1:1 AV conduction*
***: If known absence potential risk of sinus node dysfunction or AV conduction disorders*
****: If no TdP risk markers and in sinus rhythm (see **Box 12**). For women and patients over 65, sotalol must only be initiated in an outpatient setting with close monitoring, in the absence of other risk factors. Patients have to be educated to recognise warning symptoms, avoid certain medications, and adhere to follow-up appointments. US FDA advises hospitalizing all patients being initiated or re-initiated on sotalol for at least 3 days or until steady-state drug levels are achieved in a facility that can provide cardiac resuscitation and continuous ECG monitoring.*

Follow-up and monitoring of patients on AADs

The follow-up and monitoring of AADs necessitate a structured approach to ensure both safety and efficacy, while minimizing the risks of proarrhythmic effects and other adverse events **(Table 8)**. For patients in SR, obtaining a follow-up ECG shortly after initiation—typically within one week—is practical. For drugs with a prolonged loading phase, such as amiodarone, an ECG after achieving steady-state is advisable. Specifically, for Class Ia and III AADs (excluding amiodarone), a follow-up ECG is advised to be performed within two days of initiation to monitor for excessive QT prolongation and the associated risk of TdP.

Subsequent regular ECGs are advised every 6 to 12 months, tailored to the specific AAD and the patient's clinical profile. These ECGs must monitor for QTc prolongation, QRS widening, new bundle branch blocks, bradycardia, or tachycardia.

Beyond ECG assessments, regular monitoring must include liver function tests (ALT, AST, total bilirubin), creatinine, and serum electrolytes—particularly K^+ and Mg^{2+}—within 3 to 6 months of initiation to identify potential hepatic or renal impairment. If transaminase levels exceed three times the normal value, or double in a patient with elevated baseline levels, the AAD dose is advised to be reduced or discontinued. Patients on flecainide or propafenone must undergo routine checks of QRS duration and renal and hepatic function at yearly or half-yearly intervals.

Amiodarone requires additional and specific monitoring. ECG assessments of rhythm, PR, QRS, and QTc intervals must occur at steady-state (1–3 months) and annually. Given amiodarone's low TdP risk, it may be continued despite QT prolongation, but QTc must not exceed 550 ms to prevent proarrhythmic complications. Biannual assessments of K^+ and Mg^{2+} levels are necessary to mitigate proarrhythmia risks. Liver function tests are advised to be performed every 6 months to detect hepatotoxicity. Pulmonary evaluations, including chest X-rays and pulmonary function tests with diffusion capacity, are advised to be conducted at baseline and annually to monitor for interstitial lung disease. Visual function, including corneal slit-lamp exams and fundoscopic evaluations, must also be assessed annually to identify potential ocular complications. Thyroid function (TSH; free thyroxine, T4; free triiodothyronine, T3) is advised to be evaluated every 6 months to screen for hypo- or hyperthyroidism.[353]

For dronedarone, a moderate, asymptomatic increase in creatinine (approximately 0.1 mg/dL) is commonly observed due to reduced tubular secretion, without altering glomerular filtration rate (GFR). This elevation stabilizes after 7 days and should be taken as the patient's new baseline, rather than prompting discontinuation of renin-angiotensin system inhibitors or dronedarone. Monitoring must include electrolytes, QT (ensuring QTc does not exceed 500 ms), and hepatic function. Repeat hepatic tests are advised within the first six months and yearly thereafter; the drug is advised to be discontinued if permanent AF develops.[354–356]

For patients on sotalol or dofetilide, regular monitoring of serum creatinine, potassium, and magnesium levels is essential, with dose adjustments as necessary to minimize the risk of proarrhythmia. The QTc interval is advised to be maintained below 500 ms, with monitoring conducted annually or semi-annually, as well as promptly following any changes in clinical conditions or the addition of medications that could interact with the drug or prolong the QT.

In addition to ECG and laboratory evaluations, echocardiography is advised to be scheduled periodically to assess LVEF, particularly in patients with SHD or HF. For intermittent arrhythmia detection, Holter monitoring, event recorders, or implantable cardiac monitors may be employed. Exercise testing can assess myocardial ischaemia, a potential contributor to arrhythmic events in patients taking Class Ic AADs.

Beyond drug-specific advice, adherence to treatment is advised to be evaluated at every visit, with risk factors for proarrhythmia carefully assessed. This systematic approach ensures that AAD therapy is managed effectively, balancing therapeutic goals with patient safety.

During follow-up, the clinical condition of patients may change, leading to drug accumulation or development of an arrhythmogenic substrate, including electrolyte disturbances, ischaemia, and heart failure. Therefore, it is important to ensure at each visit that patients can recognize warning symptoms, including worsening palpitations, unexpected dizzy spells or syncope, development of chest pain, dyspnoea, and recent-onset exercise intolerance. It is essential to reiterate these warning symptoms during regular follow-up visits. For all drugs, it is important that patients themselves know that renal function must remain constant. For Class III drugs, patients have to be instructed to avoid QT-prolonging drugs and, with new prescriptions, refer to the treating cardiologist or arrhythmologist. Additionally, the risk of developing hypokalaemia has to be emphasized, which may occur in cases of diarrhoea, excessive sweating during fever, dietary deficiencies, or the addition of thiazides or loop diuretics, especially when unprotected by angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers. Integrated nurse-driven care with experienced nurses supervised by a cardiologist can be extremely helpful in safely applying AAD therapy AF.[357]

ECG antiarrhythmic drug effects

Initiation of AADs may induce within days alterations of the surface ECG encompassing slowing of the sinus rate, SA block, AV prolongation, higher degree AV block, QRS- and QT prolongation **(Table S8**). The electrophysiological effects of AADs are different, and therefore, the impact on the surface ECG may differ between Class I and Class III AADs. Occurrence of PVC and non-sustained VT might be first signs for the occurrence of proarrhythmic fatal events due to VT or VF. Occurrence of symptomatic electrophysiological changes (bradycardia, SN arrest, AV block or repetitive PVCs etc.) must lead to dose reduction of the AAD or even termination of therapy. Prolongation of the QRS width greater than 25% or prolongation of the QTc above 125% from baseline (or QTc above 500ms) must trigger termination of the AAD therapy.

After initiation of flecainide an increase up to 25% of baseline QRS duration on steady state therapy (after approximately 5 plasma half-lives, after 3-4 days) is a sign of drug action and underlies effective treatment (**Figure 16A & 16B**). An increase in QRS duration of > 25-50% (depending on baseline QRS duration) compared to baseline represents a potential risk for proarrhythmia or induction of HF (**Figure 16C**). In that case the dose is advised to be reduced, or flecainide be discontinued. Exercise enhances use-dependent effects. Therefore, exercise testing to exclude excessive use-dependent QRS widening and show the potential for causing VA may be used after reaching steady state.[358] Recently it has been proposed to apply a test dose of 250 mg of fast-acting oral flecainide (or 200 mg if body weight below 70 Kg) to find the flecainide starting dose and exclude treatment in potentially high risk patients.[359] The scheme includes check of blood pressure and change in QRS duration at the predicted peak plasma concentration at 2 hours. After initiation of sotalol and amiodarone, an excessive increase in QT beyond 60 ms may be associated with TdP proarrhythmia, and discontinuation, drug reduction or avoidance of concomitant drugs with a known potential to prolong the QT are warranted.

AAD tests for electrophysiological evaluation

AADs are essential tools in the pharmacological assessment of patients' electrophysiological properties, enabling clinicians to identify and evaluate various cardiac conduction abnormalities.

Class I AADs

Class I are utilized to assess His-Purkinje system conduction. By inhibiting sodium channels, these agents can unmask latent conduction defects within the His-Purkinje network, facilitating the diagnosis of conditions such as bundle branch blocks or intraventricular conduction delays. In addition, ajmaline or flecainide are employed to unmask conditions such as Brugada syndrome by revealing characteristic electrocardiographic patterns.

Adenosine

Adenosine maybe used for evaluation of AV nodal conduction.

Adrenaline

Adrenaline infusion is employed in the evaluation of congenital long QT syndrome by provoking characteristic ECG changes, thereby aiding in the diagnosis of this condition. It is also use in the diagnosis of catecholaminergic polymorphic VT.

Isoprenaline, atropine and autonomic blockade

Isoprenaline increases heart rate and enhances conduction through the AV node and His-Purkinje system, making it useful in identifying latent conduction abnormalities and assessing susceptibility to tachyarrhythmias under sympathetic stimulation. Atropine, by inhibiting parasympathetic influences, accelerates SN activity and improves AV nodal conduction, helping differentiate between intrinsic conduction system disease and vagally mediated conduction delays in the AV node and in the SN function. The combined administration of a β-blocker and atropine achieves autonomic blockade, minimizing autonomic influences on the heart. This approach allows for the assessment of intrinsic SN function and AV conduction properties without autonomic interference.

These pharmacological interventions are instrumental in evaluating the electrophysiological characteristics of the His-Purkinje system and AV nodal conduction, particularly in diagnosing conduction disorders and susceptibility to arrhythmias. A more comprehensive review of these interventions has been published recently.[360]

Proarrhythmia

AADs share a narrow therapeutic window due to their association with multiple adverse effects, particularly with proarrhythmic effects and organ toxicity **(Table S6)**. Therefore, the pharmacological management of AF and other arrhythmias requires a strategy of "First, do no harm" perspective.[361] The full profile of potential adverse effects is advised to be taken in consideration in every patient. Knowledge of potentially dangerous proarrhythmia and toxic effects (see below) is therefore of paramount importance on a patient-by-patient basis.

Paradoxical worsening or new onset of arrhythmias caused by an AAD or other medications that affect cardiac electrophysiology is termed proarrhythmia. The proarrhythmic effects of AADs

have been noted as early as in the 1960s (description of quinidine syncope).[361] In the 1990s, two landmark trials of AAD, the CAST and the SWORD trials, demonstrated increased mortality in post infarction patients presumably due to proarrhythmic effects of the AAD studied.[362,363] Such drug-induced ventricular proarrhythmic effects have also been described in studies evaluating AAD in subjects with AF. Since this arrhythmia constitutes the major field of AAD use nowadays, risk stratification for and avoidance of proarrhythmia is critical.

The potential for proarrhythmic effects is shared in common by all AAD[122] and may manifest itself as a pathological bradyarrhythmia (i.e. sinus bradycardia, AV conduction disturbances) or as tachyarrhythmias (i.e. polymorphic VT of the TdP type, or incessant monomorphic VT) (**Table 10**). Systematic studies have revealed distinct risk factors for the occurrence of proarrhythmia, such as female gender, age, presence of structural heart disease, reduced left ventricular function, impaired renal function (i.e., in case of sotalol), or concomitant polypharmacy. In addition, genetic variants may influence the metabolism of a particular AAD, particularly important in drugs primarily eliminated by a single affected pathway. This is the case for digoxin, propafenone, sotalol and dofetilide which show higher plasma levels in poor metabolizers. Finally, combination of AADs may substantially increase the proarrhythmic effects. Although ranolazine mitigates the proarrhythmic risks of Class III AADs by blocking early EADs and TdP through $I_{Na,L}$ current inhibition, making it a potentially safer adjunct in AAD combination therapy, it is also a moderately P-gp inhibitor which may impair elimination of DOACs. The risk of proarrhythmia also has implications in terms of where to initiate therapy with AAD (i.e., in- or out of hospital) since proarrhythmic events have the tendency to occur shortly after drug initiation (i.e., pharmacological cardioversion of AF) as discussed before. Details of proarrhythmic effects associated with the use of specific AAD are provided in the following sections.

Table 10: Proarrhythmia risk and typical proarrhythmia forms of different AADs.

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

The background colour is displayed as black, light brown, and blue to indicate high, moderate, and low proarrhythmic risk, respectively. AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; AV, atrioventricular; NSVT, non-sustained VT; PAC, premature atrial contraction; PVC, premature ventricular contraction; TdP, torsades de pointes; VT, ventricular tachycardia.

[a] *In patients with AF*

[b] *In patients with structural heart disease*

[c]*In patients with sinus node dysfunction or AV conduction disorders*
[d]*Worsening of AV block on the ECG, such as a progression from second-degree AV block to AV block as* atropine increases the sinus rate
[e]*High when combined with digitalis, as dronedarone reduces the renal excretion of digitalis, amplifying its associated risks. The combination may also increase the likelihood of AV block and other proarrhythmic effects.*

Sinus bradycardia and arrest

All AADs can cause sinus bradyarrhythmias.[364] AADs can influence SN function by exacerbating both intrinsic and extrinsic factors that contribute to sinus node dysfunction (SND).[365] Intrinsic factors include pre-existing, either manifest or subclinical, SND, which makes the SN more susceptible to dysfunction. Extrinsic factors include metabolic or autonomic system disturbances that affect SN activity. AADs can exert direct effects by depressing pacemaker currents or impairing SA conduction, leading to bradycardia or sinus arrest **(Table 11**). Indirectly, AADs may modulate autonomic influences on the SN, either by inhibiting sympathetic stimulation or potentiating parasympathetic tone, further suppressing SN activity. These effects underscore the need for careful assessment of baseline SN function and close monitoring of patients receiving AAD therapy.

Table 11: Effects of AADs on sinus node function

Modified VW Class	Drug	Potential for SN depression
0	Ivabradine	Moderate
Ia	Quinidine	Mild[a]
	Procainamide	Mild
	Disopyramide	Mild[a]
Ib	Mexiletine/Lidocaine	~None
Ic	Flecainide	Mild to Moderate[b]
	Propafenone	Mild to Moderate[b]
Id	Ranolazine	~None
IIa	β-blockers	Potent
IIb	Isoprenaline	~None (reverse depression)
IIc	Atropine	~None (reverse depression)
IId	Digitalis	Variable (depends upon autonomic balance; mild direct effect)
IIe	Adenosine	Potent
III	Amiodarone	Potent
	Dronedarone	Mild
	Dofetilide	~None
	Ibutilide	~None
	Sotalol	Potent
	Vernakalant	Mild to Moderate
IV	Verapamil	Mild[a]
	Diltiazem	Mild[a]

The background colour is displayed as black, light brown, and blue to indicate potent, moderate, and mild effects on the sinus node (SN), respectively. AAD, antiarrhythmic drug.
[a]Associated mild vasodilation partially offsets SN depression.
[b]*Moderate in patients with SN dysfunction.*

AV block

High-grade AV block is a rare proarrhythmic effect of Class Ic and Class Ia antiarrhythmic agents[254] and may be also observed during treatment with β-blockers, verapamil, diltiazem, digoxin and even with amiodarone or dronedarone. When seen the clinical question is if AV block is mainly caused by the pharmacological agent or is the result of pharmacological effects acting on an already altered substrate that will eventually lead to AV block in the absence of the drug. It is important to distinguish between cases of drug overdosing or interactions leading to supra-therapeutic drug levels and cases with appearance of AV block at normal levels of antiarrhythmic agents, frequently after a long period of treatment. Beyond overdosing and drug interactions, the traditional view that antiarrhythmic agents are the sole cause of AV block—and that pacemaker (PM) implantation is unnecessary after drug discontinuation—has recently been challenged. Emerging data indicate that these patients often do not follow a benign course after stopping the suspected proarrhythmic medication, with more than 50% experiencing recurrence of AV block during follow-up despite the absence of ongoing therapy.[366,367] In these series, AV block "truly caused by drugs" was found in only 15% of patients who had 2nd or 3rd degree AV block during therapy with β-blockers, verapamil, or diltiazem, suggesting that AV block is more commonly "unmasked by drugs", while is rarely "caused by drugs" and that in daily practice permanent pacing may be appropriate.[366,367]

New onset, sustained, monomorphic VT

The first occurrence of spontaneous monomorphic, sustained VT, soon after initiating antiarrhythmic therapy in a patient without previous sustained VT, is considered a proarrhythmic response.[368,369] This type of proarrhythmia is most likely to occur in the presence of organic heart disease, left ventricular dysfunction and with Class Ic agents.[370,371] Increasing the drug dose further may lead to a slower but more frequent sustained VT and the offending drug is advised to be discontinued as soon as this proarrhythmic response is recognised.

Increased frequency of sustained VT

The occurrence of an increased frequency of sustained VT in a patient with a clinical history of ventricular tachyarrhythmias is also a proarrhythmic response.[368,369] However, this condition may often be secondary to a spontaneous recurrence and inefficacy of the AAD. Increasing[372] the drug dose further in this situation may lead to worsening of the arrhythmia or may cure the arrhythmia if this represented inefficacy secondary to inadequate antiarrhythmic blood levels. Stopping the drug that caused this arrhythmic response will improve this situation and may prevent incessant VT from developing.

Incessant VT

Incessant VT is a proarrhythmic response that can occur during AAD therapy.[368–371] Class Ic agents have been associated with the highest occurrence of this type of proarrhythmia.[370,371] These drugs profoundly slow conduction with minimal effects of refractoriness; therefore, these drugs may alter the balance between refractoriness and conduction in an arrhythmogenic zone. Incessant VT can occur with other antiarrhythmic agents. The occurrence of incessant VT is most common in patients with a history of sustained VT associated with left ventricular dysfunction[373–375] and characterized by a wide complex, “sine wave” tachycardia that has broad, undulating complexes. The rate of the tachycardia is usually slower than that of a spontaneous

tachycardia. Incessant VT often cannot be terminated by pacing or even cardioversion. Incessant VT may be sustained or have long runs of non-sustained VT with periodic sinus beats and quick resumption of paroxysms of VT. Adding other AADs is usually not helpful. Discontinuing the provoking AAD and cardioverting the patient after the drug's effects have passed is the best treatment. In case of haemodynamic compromise, mechanical left ventricular support devices can transiently maintain the patient's haemodynamic status.

Torsades de pointes (TDP)

Desertenne[376] described TDP as "twisting around the points" VT. However, TDP is more than a QRS changing pattern and is classically described as a pause-dependent, polymorphic VT associated with QT prolongation and U waves. Many polymorphic VTs are miss-classified as TDP that do not meet these classic criteria.[377] The mechanism of this arrhythmia is secondary to prolongation of repolarization that results in activation of EADs, which may promote triggered activity.[377] Re-entry, due to a dispersion of refractory periods of the different layers of the ventricle is another mechanism of TDP.[378–381] QT prolongation is due to blockade of one of the cardiac K^+ channel expressed by the human ether-a-go-go-related gene (hERG).[378–382] This results in inhibition of a major repolarizing potassium current, I_{Kr}. TDP may result from proarrhythmia which occurs secondary to QT prolonging agents. Although TDP is usually secondary to an AAD overdose with marked prolongation of the QT, some episodes are idiosyncratic and may occur after only a few doses of AAD. The Class Ia AADs, quinidine, procainamide and disopyramide, and the Class III antiarrhythmic agents, sotalol, dofetilide, ibutilide and other psychotropic drugs, that block the delayed rectifier potassium current have the highest frequency of causing this arrhythmia.[154,382,383] In particular, the heart rate slowing effect of sotalol may enhance its proarrhythmic effect due to reversed use-dependency with stronger AP prolongation during bradycardia or after pauses. These drugs cause TDP in up to 5% and are advised to be initiated under telemetry conditions since most TDP occurs early during drug initiation, as mentioned before. A list of drugs that can provoke TDP and are discouraged in patients with LQTS or previous TDP have been published (**Table S9**, www.crediblemeds.org).[384] Amiodarone and dronedarone, multichannel blockers including Class III effects that also prolongs the QT, are rarely, associated with this form of proarrhythmia.[385,386] The low incidence of amiodarone-induced TDP may be related to its lack of reverse-use dependence (see above) and less effect on prolonging APD in the "M" cell region than other Class Ia and IIIa agents.[386] Most amiodarone-induced episodes of TDP occur when the drug is combined with a type Ia antiarrhythmic agent. Class lb AADs and β-blocking agents, which shorten the QT, are useful treatment for this syndrome. Class Ic agents have little effect on repolarization and are only rarely associated with this form of proarrhythmia.

A close relationship between QT prolongation and the development TDP has not been well established[377,382] for Class Ia agents. With d,l-sotalol and dofetilide, QT prolongation and higher doses increase the risk of TDP. For d,l-sotalol, avoiding QTc more than 525 msec. and doses more than 320 mg will decrease the incidence of TDP from 5% to less than 2%. In general, patients with baseline QT prolongation must avoid drugs that prolong the APD. Many other factors (**Box 12 and Box 13**)[387–389] are related to the development of QT prolongation including concomitant therapy with other drugs that prolong APD, the presence of congenital prolonged QT syndrome, hypokalaemia, hypocalcaemia, hypomagnesaemia, diuretic use, female gender, renal dysfunction, and severe bradycardia. Certain drugs resulting in drug interactions are

common contributors to TDP risk. QT-prolonging medications such as clarithromycin, levofloxacin, or haloperidol, when taken concurrently with CYP inhibitors, such as fluoxetine, cimetidine, or particular foods including grapefruit, can result in higher-than-normal levels of medications that prolong the QT and the development of TDP.[384]

Box 12: Risk Factors for *torsades de pointes (TdP)*

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

TdP, torsades de pointes.
[a]*Age and sex alone are not sufficient to contraindicate certain antiarrhythmic drugs, though they are advised for heightened monitoring and control of other risk factors*

Atrial proarrhythmia

Box 14 lists potential criteria for atrial proarrhythmia.[390] The development of AT with digitalis and the increased frequency of incessant AFL exemplify atrial proarrhythmia. This phenomenon has been observed with all class Ia agents, amiodarone, and most notably with class Ic agents. Class Ic antiarrhythmic drugs slow atrial conduction, which can stabilize macro re-entry circuits in predisposed anatomical regions, leading to more frequent and incessant AFL.[391–393]

Box 13: ECG signs indicative for *torsades de pointes* risk

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

AF, atrial fibrillation; VT, ventricular tachycardia.

Occasionally, AFL with 1:1 atrioventricular (AV) conduction may occur due to a combination of slowed atrial rates and enhanced AV nodal conduction, potentially resulting from vagolytic effects or incidental sympathetic stimulation. Adrenergic events, such as stress testing, may unmask 1:1 AV conduction.[282] Due to rapid rates and wide QRS morphology secondary to rate dependence, these tachycardias may be misclassified as ventricular in origin.

Re-entrant arrhythmias may occur more frequently, although slower after antiarrhythmic therapy.[391] A classic example of this is with Na^+ channel blockers used to treat patients with orthodromic SVT in the Wolff-Parkinson-White syndrome. Typically, AADs will slow conduction and prolong refractoriness more in the antegrade than the retrograde direction of the pathway. Thus, a PAC is more likely to develop unidirectional block and initiate SVT, although at a slower rate. The occurrence of more frequent but slower SVTs can be noted with drugs such as digitalis or verapamil or β-blockers that slow conduction in the AV node.

Brugada mechanism

Class Ic antiarrhythmic agents are largely used in the treatment of AF and other supraventricular tachyarrhythmias.[93,254,394] In clinical practice unselected patients treated with propafenone or flecainide, at therapeutic doses, exhibit a typical type 1 Brugada pattern, with a right bundle branch block and ST-segment (ST) elevations in the right precordial leads, in the absence of symptoms due to unexplained syncope, or a family history of sudden death or CA. In a series of 176 patients serial ECGs before and after achieving steady-state (>5 half-lives) concentrations of

propafenone and flecainide were done and a Brugada ECG pattern was found in only 2.3% of the patients, in some cases several months after therapy initiation.[395] Of note, drug therapy was continued in all patients regardless of drug effects on ST or the development of BBB and no VA events occurred in any of the patients during follow-up.[395] These and other data suggest the opportunity to reconsider the specificity of a Brugada pattern induced by Class Ic drugs in asymptomatic patients. Indeed, the recent ESC Guidelines on VA and SCD clearly report that BrS is diagnosed in patients without other heart disease and a spontaneous type 1 pattern, regardless of symptoms.[45] The guidelines emphasize that a type 1 ECG pattern induced by a Nav-blocking drug, either as part of diagnostic testing or resulting from antiarrhythmic treatment, should be considered less specific than previously thought, as it can be seen in 2–4% of healthy individuals without a spontaneous type 1 pattern. In the opinion of the ESC Guidelines panel of experts, an induced type 1 Brugada pattern therefore requires other clinical features, such as documented ventricular tachyarrhythmias, arrhythmic syncope, or relevant family history to make a diagnosis of BrS.[45] Other data confirm the good prognosis of patients who do not have symptoms typical of BrS, but who develop a Brugada pattern during treatment with Class Ic drugs or other agents.[396] Regardless, of their good prognosis in these cases drug discontinuation is advised[396] and therefore it appears important in daily practice to plan a ECG check few days after initiation of propafenone or flecainide, as suggested by Guidelines.[93]

Toxicity and adverse effects

All AADs have the potential for significant toxic effects encompassing different organs **(Table 12)**. Direct organ toxicity may be encountered with specific AADs. Furthermore, some AADs like quinidine and amiodarone have substantial vasodilatory effects, and thereby, profound hypotension can be induced by combination with other vasodilators or rapid i.v. injections. An example, for a substance with significant organ toxicity is amiodarone, one of the most popular AAD. This drug may affect several organ systems including the thyroid, the lungs, the skin, the liver, the eyes and others.[397] This extra-cardiac toxicity has in large part been attributed to the iodine moieties of amiodarone in combination with its high lipophilicity, together with its direct effects on thyroid function.[83]

Table 12: Key side effects and toxicities of AADs aside from proarrhythmia.

Modified VW Class	AAD	#1	#2	#3	Other less frequent or significant effects
0	**Ivabradine**	**Phosphenes** (2-14%)	Hypertension (8%)	Fatigue (5%),	CNS effects (5%)
Ia	**Quinidine**	Gastrointestinal (Nausea, vomiting, diarrhoea, - 30-50%)	Light headedness/headache (15%)	Hypotension (5-10%),	**Cinchonism**[a], Allergic reaction (5-10%), Thrombocytopenia (1-2%), CNS effects (5%)
	Procainamide	**Lupus erythematosus-like syndrome** (20-30%)	Hypotension (5%)	Gastrointestinal (Nausea, vomiting, diarrhoea, -- 5-10%)	Allergic reaction (5%), Blood dyscrasias (**agranulocytosis**, thrombocytopenia - 1%) CNS effects (5%)
	Disopyramide	**Anticholinergic** (urinary retention, constipation, dry mouth - 30-40%)	Hypotension (5-10%)	Gastrointestinal (Nausea, vomiting, - 5-10%)	Heart Failure (5%) Hypoglycaemia (2%) CNS effects (5%)
Ib	**Lidocaine**	**CNS effects** (Dizziness, tremors, tinnitus - 1-10%)	Hypotension (1-5%)	Gastrointestinal (Nausea, vomiting, constipation - 1-5%)	Skin rash (1%)
	Mexiletine	Gastrointestinal (Nausea, vomiting, diarrhoea, - 5-40%)	**CNS effects** (dizziness, ataxia, tremor, 5-20%)	Hypotension/Fatigue/Weakness (5-10%)	Sin rash, Limb swelling (3%)
	Phenytoin	CNS effects (nystagmus, ataxia, other, 5-50%)	**Gingival hyperplasia** (20-40%),	Gastrointestinal (Nausea, vomiting, constipation -, 13%)	Hypotension (<10%), Thrombocytopenia (<1%)

Box 14: Criteria for supraventricular proarrhythmia

- Conversion of AF to incessant AFL
- Atrial flutter with slower atrial rate and new onset 1:1 AV conduction
- New onset supraventricular tachyarrhythmia
- More frequent with slower rate paroxysmal supraventricular tachycardia
- Incessant accessory pathway mediated tachycardia following drug induced bundle-branch block
- Digitalis-induced atrial tachycardia with AV block

AFL, atrial flutter; AT, atrial tachycardia; AV, atrioventricular.

Ic	**Flecainide**	CNS effects (Dizziness, **blurred vision**, 15-50%)	Fatigue/Weakness (5-10%)	Gastrointestinal (Nausea, vomiting, - 5-10%)	Dyspnoea/Heart failure (5%)
	Propafenone	CNS effects (Dizziness, blurred vision, 10-30%)	**Metallic taste** (5-10%)	Gastrointestinal (Nausea, vomiting - 10-15%)	Fatigue/Dyspnoea/Heart failure (5%)
Id	**Ranolazine**	Dizziness (6-15%)	Gastrointestinal (Nausea, vomiting, constipation - 10%)	Headache (5%)	Asthenia (<5%)
IIa	**β-blockers**	Fatigue/Asthenia (10-30%)	Dizziness/Hypotension (10%)	Cold extremities (10%)	**Sexual dysfunction** (1-%), insomnia (1-5%), **depression** (1-5%), bronchospasm (1-5%)
IId	**Digitalis**	Nausea/Vomiting (>10%%)	CNS effects (confusion, dizziness, 5-10%)	**Visual disturbances** (yellow vision, halos around light, 5%)	Fatigue (5%), Gynecomastia (<1%)
III	**Amiodarone**[d]	Corneal microdeposits (>90%), optic neuritis with risk of blindness (1%)	Photosensitivity (25-75%) & blue-grey skin discoloration (10%)	**Hypo** (5-20%) & **Hyperthyroidism** (1-5%)	CNS effects (30%), Nausea/Vomiting (10-25%), Liver toxicity (15-30% elevated enzymes) Lung toxicity (1-10%),)
	Dronedarone	**Increased serum creatinine**[b] (10-20%)	Gastrointestinal (Nausea, vomiting, Diarrhoea, 5-15%)	Fatigue & Asthenia (5-10%)	Skin reactions (5%), Mild elevation of liver enzymes (1-5%, hepatotoxicity <1%))
	Dofetilide	**Headache & Dizziness** (10%)	Chest pain (10%)	Gastrointestinal (Nausea, vomiting, diarrhoea - 5%)	Insomnia (<5%)
	Ibutilide	Headache & Dizziness (5%)	**Hypo/hypertension** (2%)	Gastrointestinal (Nausea - 5%)	Flushing (<5%)
	Sotalol	**Fatigue** (10-20%)	Dizziness (5-15%)	Hypotension (5-10%)	Gastrointestinal (Nausea, vomiting, diarrhoea - 5%) Worsening heart failure (1-3%)
	Vernakalant	**Dysgeusia** (25%)	**Sneezing** (15%)	Hypotension & Dizziness (5-10%)	Cough, Nausea (5%)
IV	**Verapamil**	**Constipation** (10%)	Hypotension & Dizziness (5-10%)	Headache (2%)	Gingival hyperplasia, nausea, peripheral oedema, worsening heart failure (<5%)
	Diltiazem	**Peripheral oedema** (10%)	Hypotension & Dizziness (5-10%)	Headache (2-5%)	Gingival hyperplasia, gastrointestinal (Nausea, vomiting, diarrhoea, constipation, worsening heart failure (<5%)

Side effects and toxicities are listed in columns: #1 represents the most frequent, followed by #2 and #3 as the second most frequent. Additionally, the most characteristic side effects are highlighted in bold. A more comprehensive list of all effects can be found in the supplement. AAD, antiarrhythmic drug; CNS: central nervous system effects, including dizziness, ataxia, tremor, blurred vision, confusion, headache; VM, Vaughan Williams.

[a]*Tinnitus, reversible hearing loss, flushing, confusion, diarrhoea, and visual disturbances, including permanent blindness in some cases*
[b]*Due to inhibition of tubular secretion of creatinine without affecting kidney function*
[c]*Dizziness, headache, ataxia*
[d]*Up to 70% incidence of adverse effects (15% during first year, 50% during long-term use) with 18-37% rate of adverse effect driven drug discontinuation at 5 years follow-up. 15% during first year of amiodarone use increasing to up to 50% during long-term use*

Amiodarone-induced thyrotoxicosis

Amiodarone may influence thyroid function tests (transient elevation of TSH and decrease of T3 is commonly seen), and in addition, induce thyroid dysfunction (amiodarone-induced hypothyroidism, AIH, and amiodarone-induced thyrotoxicosis, AIT) (**Table 13)**. AIH as well as AIT might occur in apparently normal thyroid glands. There are two types of AIT: type 1 AIT (AIT 1), a form of iodine-induced hyperthyroidism occurring in nodular goitres or latent Graves' disease, and type 2 AIT (AIT 2), due to destructive thyroiditis.

Table 13: Main features of the two types of amiodarone-induced thyrotoxicosis[a]

	AIT1	AIT2
Geographical areas of incidence	Iodine-depleted	No relation
Pre-existing thyroid abnormalities	Present (*latent or overt Graves' disease or nodular goitre*)	Absent (*normal thyroid*)
Main mechanism	Iodine overload from amiodarone	Destructive thyroiditis (*cytolysis with release of stored thyroid hormones*)
Onset	Gradual Shortly after amiodarone start (*3 months*)	Sudden Long after amiodarone start (*30 months*)
Laboratory findings	TSH antibodies may be present	Elevated inflammatory markers (PCR)
Colour flow Doppler	Increased vascularity	Decreased vascularity
Radioiodine uptake	Normal/increased	Suppressed
Treatment	Antithyroid drugs Potassium perchlorate (*in iodine-depleted areas*) Thyroidectomy or radioactive iodine ablation may be appropriate.	Oral glucocorticoids (*Antithyroid drugs are ineffective*)
Amiodarone discontinuation	Advised	May not be needed since often resolves with glucocorticoids
Outcome	No spontaneous remission High risk of recurrence	Spontaneous remission possible

AIT, amiodarone-induced thyrotoxicosis; PCR, Protein C-Reactive; TSH: Thyroid-stimulating hormone
[a]Both conditions require careful differentiation for optimal management but sometimes they may coexist and may necessitate combined therapeutic approaches.
NB: During amiodarone treatment it is expected that TSH serum levels may increase up to 2.7 times by 2 weeks with a fall of TSH to the upper end of the normal range after 3 months.

Amiodarone-induced pulmonary and other systemic toxicities

Amiodarone toxicity affects multiple organs other than the thyroid, including the lungs, liver, skin, and eyes. Pulmonary toxicity results in interstitial pneumonitis and fibrosis in 1-2% of patients (**Figure 17**).[86,398] Pulmonary toxicity is often not recognised in patients who commonly have other reasons for respiratory failure. Symptoms include cough, dyspnoea fever, and pleuritic chest pain. Patients may also present with fatigue, weight loss, and hypoxia. Blood Tests usually show elevated markers of inflammation such as C-reactive protein and erythrocyte sedimentation rate. Chest X-ray may show diffuse interstitial or alveolar infiltrates and computed tomography scan ground-glass opacities, interstitial thickening, and consolidation in both lungs. PFTs often show a restrictive pattern with reduced diffusion capacity. Definitive diagnosis of amiodarone-induced pulmonary toxicity is achieved through bronchoalveolar lavage, which typically reveals the presence of lipid-laden (foamy) macrophages, and biopsy can confirm the diagnosis if other tests are inconclusive. Treatment includes prompt amiodarone interruption although due to its long half-life does not result in quick improvement and patients often need complementary treatment with

high-dose corticosteroids (e.g., prednisone 40-60 mg/day). In addition, amiodarone can produce hepatotoxicity in 0.5-1.0% of cases and involves elevated liver enzymes, with potential for acute hepatitis or cirrhosis. Skin toxicity typically presents as photosensitivity and blue-grey discoloration, particularly in sun-exposed areas (25-75% of patients). Ocular toxicity includes corneal microdeposits in most treated patients, which are usually asymptomatic, but can also cause optic neuropathy (1-2%), leading to vision loss. All these toxicities result in discontinuation in up to 20% of patients during long-term therapy.[83]

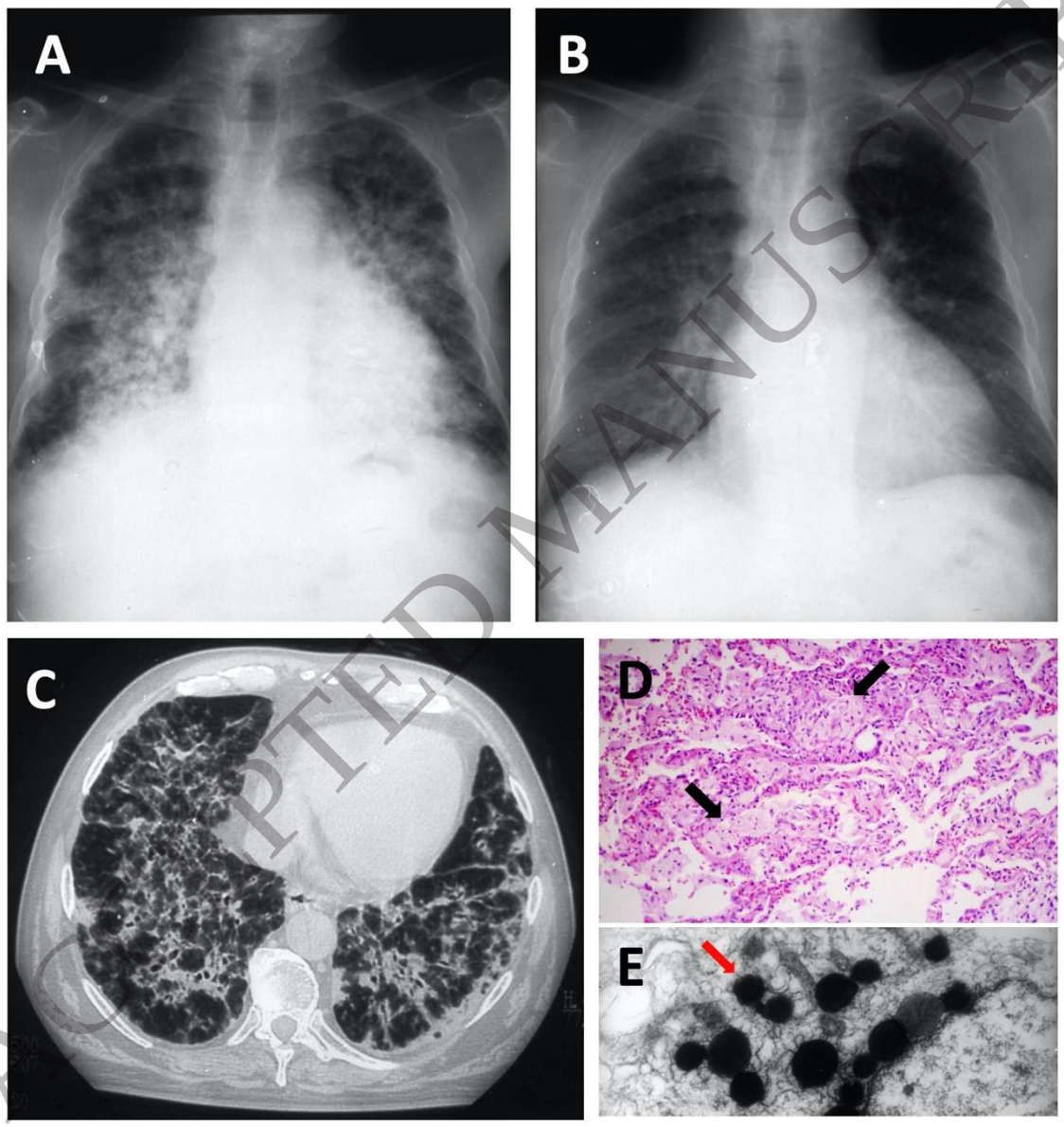


Figure 17: Chest X-ray (Panels A and B), computed tomography (CT) scan (Panel C), and microscopic views of a lung biopsy (Panels D and E) from a 77-year-old former smoker with a history of old myocardial infarction and preserved left ventricular ejection fraction, taking 200 mg/day of amiodarone for paroxysmal atrial fibrillation. The patient presented with cough, dyspnoea, and weight loss. Findings were suggestive of amiodarone-induced lung toxicity.

Panel A: Chest X-ray at presentation showing a diffuse alveolar-interstitial pattern indicative of pulmonary involvement. Panel B: Follow-up chest X-ray after three months of amiodarone withdrawal and steroid therapy showing resolution of lung abnormalities. Panel C: CT scan confirming the diffuse alveolar-interstitial pattern at the initial presentation. Panel D: Optical microscopy (haematoxylin-eosin stain) of lung parenchyma showing clusters of alveolar macrophages (black arrows) with foam-like cytoplasmic changes, characteristic of amiodarone toxicity. Panel E: Electron microscopy of the biopsy sample revealing phospholipid inclusions (red arrow) in macrophages, further confirming the diagnosis of amiodarone-induced pulmonary toxicity. This case underscores the potential for severe pulmonary adverse effects associated with amiodarone therapy and the potential reversibility of findings following drug discontinuation and appropriate treatment.

Quinidine systemic toxicities

The most frequent secondary effects of quinidine are nausea, vomiting, and diarrhoea, which may appear in up of one third of patients. It may also be associated with anaemia, thrombocytopenia, urticaria and, more infrequently, lupus-like reactions. It may also provoke orthostatic hypotension due to α-adrenergic block, which is potentiated by the concurrent use of vasodilators, such as ACE inhibitors. Quinidine toxicity can lead to a condition known as cinchonism, characterized by symptoms such as tinnitus, hearing loss, and blurred vision.[399,400]

Other AAD systemic toxicities

Phenytoin has been associated with gingival hyperplasia in rare patients. **Disopyramide** may be responsible of glaucoma, urinary retention and hypoglycaemia. Systemic serositis has been rarely reported with AADs such as flecainide. A systemic lupus erythematosus like syndrome, agranulocytosis and hypersensitivity reactions may develop with procainamide treatment. **Flecainide** toxicity is frequently seen patients when renal function deterioration occurs due to the high renal elimination of this drug, and propafenone is advised to be selected instead in patients with impaired renal function. **Propafenone** overdosage may result in hypotension, bradycardia, intra-atrial and intraventricular conduction disturbances, and VA. As with flecainide, CNS adverse effects dizziness, nausea, unusual taste, blurred vision and convulsions) occur most frequently with higher dose or plasma concentrations. **Sotalol** intoxication (2-16 grams) may cause death due to proarrhythmia (asystole, TdP, polymorphic VT) and congestive HF. Other extracardiac toxicities include hypotension, bronchospasm and hypoglycaemia, which may be also seen with other β-blockers. **Digitalis** toxicity can manifest through various non-arrhythmic symptoms, including gastrointestinal disturbances such as nausea, vomiting, and abdominal pain. Neurological symptoms may also occur, presenting as confusion, dizziness, and visual disturbances like blurred-yellow vision or seeing halos. **Verapamil** effects include hypotension, bradycardia, cardiac conduction defects, arrhythmias, hyperglycaemia, and decreased mental status. In addition, there have been reports of non-cardiogenic pulmonary oedema in patients taking large overdoses of verapamil (up to approximately 9g).

Proarrhythmia and AAD toxicity management

General aspects

In addition to general supportive measures, the cardiac rhythm and blood pressure have to be monitored, and if bradycardia ensues, a β-adrenergic agonist or a PM may be used. Hypotension

with inadequate tissue perfusion is advised to be treated with positive inotropic and/or vasopressor agents. Acute bradycardia and bradycardia-induced polymorphic VT can be treated with temporary ventricular pacing at a fast rate (90 bpm). In some cases, with predominant β-blocking effects, the use of isoprenaline might be useful. For severe hypotension the use of i.v. catecholamines (adrenalin, noradrenalin) may be appropriate. Haemodialysis for drug removal is effective for procainamide, disopyramide and sotalol. All other AADs cannot be removed by haemodialysis (e.g., flecainide / propafenone, verapamil, dronedarone and amiodarone).

TDP management

The first step in managing TDP is preventing its onset by targeting modifiable risk factors and preventing TDP from occurring.[387] Treatment of TDP aims to restore a normal rhythm and to prevent the arrhythmia recurring. TDP is usually non-sustained and spontaneously reverts to a normal SR. Sustained TDP requires emergency treatment, including electrical cardioversion if needed.[45,401] Treatment to prevent recurrent TDP includes withdrawal of all QT prolonging drugs, IV magnesium sulphate and correction of hypokalaemia, hypomagnesaemia, and hypocalcaemia. Isoprenaline and pacing may help prevent pause-dependent TDP as other measures are undertaken. Treatments used to prevent TDP in specific circumstances include β-blockers or mexiletine in long QT syndromes 1-2 and 3 respectively.[369]

Drug specific aspects

When appropriately prescribed and monitored, **flecainide** and **propafenone** presents a low risk of proarrhythmia or other significant side effects.[276,277] However, in rare instances, patients may develop bradyarrhythmias, sinus pauses, or AV block, necessitating dose reduction or discontinuation of the drug. A notable concern is the potential conversion of AF to AFL with 1:1 AV conduction, which can be mistaken for VT due to aberrant conduction patterns (**Figure 6B**). In such cases, catheter ablation of the AFL circuit is advised.[273,274]Additionally, if HF symptoms emerge, immediate cessation of these drugs is imperative. To mitigate side effects associated with high peak plasma concentrations—such as dizziness, tremor, visual disturbances, or nausea—transitioning to a slow-release formulation may be beneficial. Monitoring plasma concentrations can also aid in optimizing dosing. Overdosage of flecainide or propafenone is potentially life-threatening; treatment is primarily supportive, by infusion of agents like dopamine and isoprenaline to stabilize rhythm and blood pressure, as no specific antidote exists (**Figure 18**). Interventions may include gastrointestinal decontamination and administration of hypertonic sodium bicarbonate to counteract sodium channel blockade. Due to their high protein binding and large volume of distribution, haemodialysis is ineffective in removing these drugs. Convulsions associated with propafenone toxicity have been treated with intravenous diazepam.

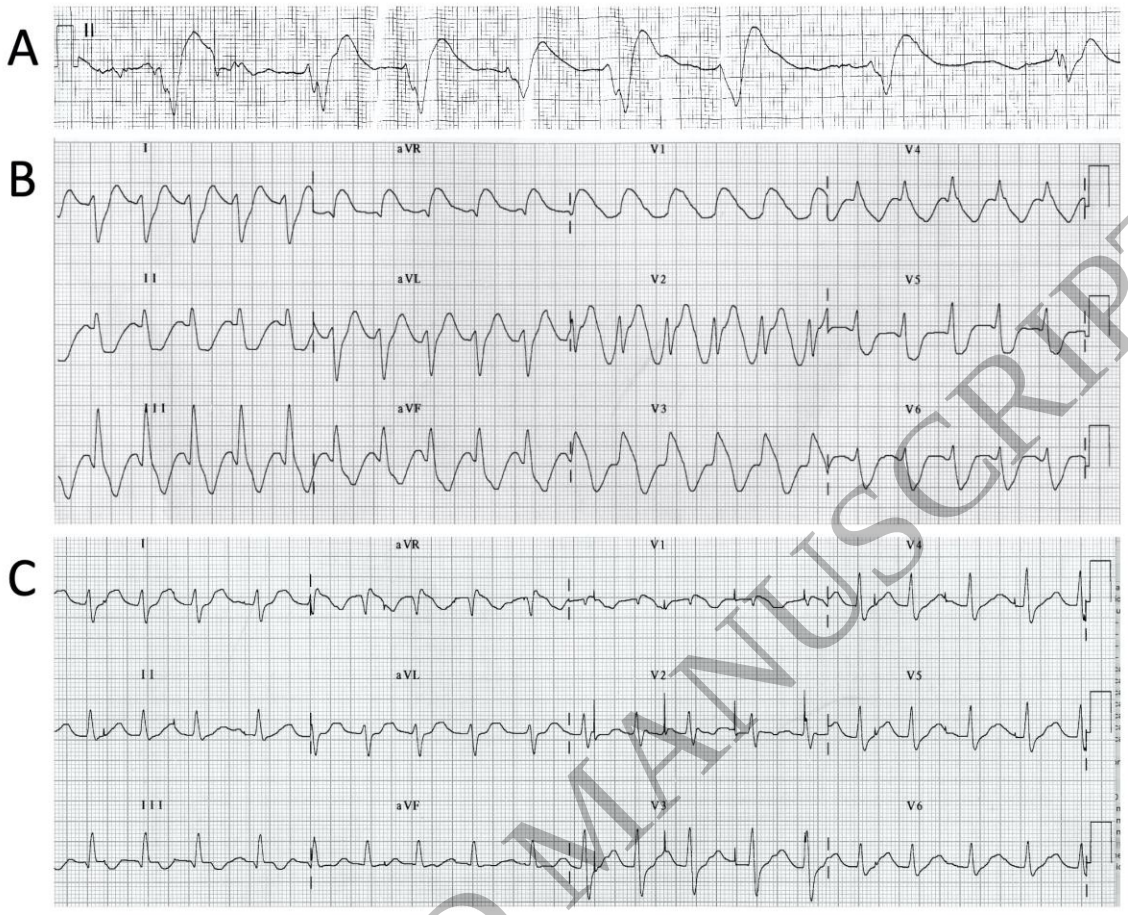


Figure 18: Single-lead and 12-lead ECGs of a 14-year-old girl with no prior heart disease shortly after ingesting 24 flecainide tablets (2400 mg) in a suicide attempt. *Panel A: ECG recorded shortly after ingestion shows severe sinus bradycardia with low-amplitude P waves and an extremely wide QRS complex, indicative of significant sodium channel blockade caused by flecainide toxicity. Panel B: Following resuscitation efforts with sodium chloride, bicarbonate, isoproterenol, and dopamine/dobutamine, the ECG shows sinus tachycardia with less pronounced QRS broadening and repolarization changes. Panel C: After 9 hours of treatment, the ECG demonstrates decrease of QRS duration and resolution of repolarization abnormalities. Non-captured ventricular temporary pacemaker spikes are also visible. These findings illustrate the severe cardiotoxic effects of flecainide overdose, the dynamic ECG changes during treatment, and the efficacy of intensive medical intervention in reversing these abnormalities.*
The ECGs were recorded at a speed of 25 mm/s and a sensitivity of 10 mm/mV.

Both medications are metabolized by the cytochrome P450 2D6 enzyme; thus, genetic variations or interactions with other drugs metabolized by this pathway can influence plasma levels and toxicity risk. Regular monitoring and appropriate dose adjustments are essential to minimize adverse effects.

Amiodarone overdose might be fatal. In addition to general supportive measures, the patient's cardiac rhythm and blood pressure are advised to be monitored, and if bradycardia ensues, a β-adrenergic agonist or a PM may be used. Neither amiodarone nor its metabolite is dialyzable.

Induced AIH does not necessarily require termination of amiodarone therapy and requires hormone replacement therapy in most cases. AIT 1 is advised to be treated with thionamides combined with Na^+ perchlorate if necessary. AIT 2 is advised to be managed with oral glucocorticoids. Once euthyroid status is established, patients with AIT 2 are followed without further specific treatment. Patients AIT 1 are advised to be treated with thyroidectomy or radioiodine after euthyroid status is reached. Oral glucocorticoids might be added from the very beginning of therapy if type of AIT is uncertain, or if response to thionamides is poor. Termination of amiodarone therapy in AIT is advised to be individualized and balanced with the antiarrhythmic benefits of the drug. Rapidly deteriorating cardiac conditions may require emergency thyroidectomy for all forms of AIT.

Sotalol shows lack of protein binding and haemodialysis is useful for reducing its plasma concentrations. Patients are advised to be monitored until QT is normalised and the heart rate returns to levels >50 bpm. Sotalol-induced hypotension may be associated with an initial slow drug elimination phase (half-life of 30 hours) thought to be due to a temporary reduction of renal function caused by the hypotension. In case of severe bronchospasm, the use of aminophylline or aerosol β-2-receptor stimulant may be appropriate.

Dronedarone overdose requires supportive therapy based on clinical symptoms. It is not known whether dronedarone and/or its metabolites can be removed by dialysis (haemodialysis, peritoneal dialysis, or haemofiltration). As with other antiarrhythmic drugs except digoxin, there is no specific antidote available for dronedarone.

Verapamil has no specific antidote for overdosage; thus, treatment is advised to be supportive. Delayed pharmacodynamic consequences may occur with sustained-release formulations, and patients have to be observed for at least 48 hours, preferably under continuous hospital care. In acute overdosage, gastrointestinal decontamination with cathartics and whole bowel irrigation may be appropriate. Calcium, inotropes (i.e., isoprenaline, dopamine, and glucagon), atropine, vasopressors (i.e., noradrenaline, and adrenaline), and cardiac pacing have been used with variable results to reverse hypotension and myocardial depression. Overdose with CCBs that was initially refractory to atropine may became responsive when large doses (close to 1g/hour for more than 24 hours) of calcium chloride were administered. Calcium chloride is preferred to calcium gluconate since it provides 3 times more calcium per volume. Verapamil cannot be removed by haemodialysis.

Digoxin toxicity when mild can often be managed by simply discontinuing digoxin and monitoring the patient, as symptoms may resolve with time. In cases where hypokalaemia is present, potassium supplements may be administered to restore normal levels, as low potassium can exacerbate digoxin's effects. For arrhythmias such as ectopic junctional and VTs resulting from digitalis toxicity, antiarrhythmic agents like phenytoin or lidocaine may be effective. In severe cases, characterized by life-threatening arrhythmias or significant hyperkalaemia, the administration of digoxin-specific antibody fragments (digoxin immune Fab) is advised to neutralize the drug.

Contraindications and precautions

Flecainide

As a rule, flecainide is not advised for patients with a baseline QRS >120 ms, particularly those with LBBB or bifascicular block. It is not advised in patients with CAD (including an Agatston score >400), heart failure, cardiogenic shock, or reduced LVEF. An incidental finding of an Agatston score < 400 in the absence of angina pectoris and uncomplicated LVH, both in the absence of left ventricular scar tissue, are not a contraindication for flecainide. Also, in patients with a glomerular filtration rate <35 ml/min flecainide is discouraged or reduced due to the significant elimination of the drug by the kidneys. It is not allowed in patients with BrS. Unless pacing rescue is available, flecainide is not advised in patients with SND, atrial conduction defects, second degree or greater AV block or BBB. Flecainide may be combined with β-blockers, verapamil or diltiazem in patients with AF to prevent fast rates during arrhythmia recurrences or if conversion to type Ic AFL occurs. Renal function is advised to be carefully considered when combining flecainide with β-blockers like atenolol, as both drugs have significant elimination through the kidneys. Impaired renal clearance may result in drug toxicity and severe bradycardia. It is also important to advise patients to avoid exercise during breakthrough episodes until AF has stopped or active cardioversion is performed. Flecainide is contraindicated in case of hypersensitivity to the drug.

Propafenone

Contraindications of propafenone are like flecainide. However, due to its mild β blocking effect combination with AV negative dromotropic agents may not be needed to prevent high ventricular rates during AF or type Ic AFL conversion. On the other hand, bronchospastic disorders or severe obstructive pulmonary disease are relative contraindications for the use of propafenone. Dose adjustments may be needed with hepatic disease but not with renal dysfunction.

Amiodarone

Contraindications include cardiogenic shock, sick sinus syndrome, second- or third-degree atrioventricular block, bradycardia leading to syncope without a functioning PM. Known hypersensitivity to the drug or to any of its components, including iodine. Hyperthyroidism, and long-QT syndrome are also considered as contraindications.

Dronedarone

Contraindications include New York Heart Association (NYHA) Class IV HF or NYHA Class II - III HF with a recent decompensation requiring hospitalization or referral to a specialized HF clinic. Furthermore, second- or third-degree atrioventricular (AV) block or sick sinus syndrome (except when used in conjunction with a functioning PM), significant bradycardia, and severe hepatic impairment are considered contraindications.

Sotalol and dofetilide

Sotalol and dofetilide are discouraged in LQTS, bradyarrhythmias/AV block (<50 bpm during walking), uncontrolled HF, hypokalaemia (<4,0 mmol/l), and CrCl below 50 ml/min. Caution is

advised to be exercised in low weight females with LVH. As previously mentioned, careful monitoring of the QTc interval is advised during both the initiation and follow-up.

Verapamil and diltiazem

Contraindications to verapamil include severe left ventricular dysfunction, hypotension (systolic pressure < 90 mmHg), and cardiogenic shock. It is also contraindicated in patients with severe sick sinus syndrome or second- or third-degree AV block, except in those with a functioning ventricular PM. Additionally, CCBs are discouraged in patients with atrial arrhythmias and an accessory bypass tract (e.g., Wolff-Parkinson-White syndrome) due to the risk of ventricular fibrillation. Lastly, their use is contraindicated in individuals with a known hypersensitivity to the drug. Intravenous verapamil is discouraged after doses of intravenous β-blocker.

A more comprehensive review of contraindications and cautions associated with AADs is provided in **Table S10**.

AAD plasma concentration

The PK of antiarrhythmics exhibit significant variability among patients, influenced by factors such as age, renal or hepatic function, and drug interactions. In addition, therapeutic ranges for most AADs remain poorly defined. Appropriate drug plasma concentrations have not been carefully derived and are often extrapolated from limited patient samples, hindering precision. Finally, the lack of standardized therapeutic ranges and the limited integration of plasma concentration data into clinical studies contribute to the challenge of tailoring antiarrhythmic therapy effectively for individual patients. Consequently, the current application of optimizing individual antiarrhythmic therapy is highly limited and is mostly reserved for suspected cases of drug toxicity. Flecainide plasma levels are usually measured as trough levels, e.g., in the morning prior to intake of the morning tablet. Normal values are between 200 and 400 ng/mL. Propafenone, unlike flecainide, differences in speed of metabolism and saturable oxidative elimination between patients make plasma concentrations even less predictable. The normal therapeutic range for propafenone is between 400 and 1100 ng/mL. The main electrophysiological effects of amiodarone are mediated through intracellular metabolites such as desethyl-amiodarone. When using plasma concentration monitoring, N-monodesethylamiodarone is advised to be followed together with amiodarone. Finally, levels of digoxin (therapeutic range 0.8 to 2 ng/dl, though levels >1.2 ng/mL may increase toxicity risk without additional benefit) are nowadays rarely determined and mostly reserved for intoxication suspicion.

Drug-drug interactions

Antiarrhythmic drug-drug interactions

Drug-drug interactions represent 3% of preventable in-hospital adverse drug events and contribute to hospital admissions and emergency room visits.[402,403] Patients with arrhythmias are vulnerable to these interactions due to the narrow therapeutic index of antiarrhythmic agents and the frequent use of multiple cardiovascular drugs in patients with arrhythmias.[404] Pharmacodynamic interactions, such as the added AV nodal blockade of digoxin used in combination with a β-blockers or calcium blocking agent can be a desirable effect or an

unintentional adverse effect.[404] Pharmacokinetic interactions relate to changes in the absorption, distribution, metabolism, and elimination of either the substrate or precipitant drug (**Figure 3**).

The most common pharmacokinetic drug-drug interactions involve the CYP monooxygenation system and the P-gp (permeability glycoprotein).[405–407] Several AADs undergo biotransformation by hepatic oxidative metabolism through the CYP system. Co-administered drugs that inhibit these pathways will result in a lower metabolism of the AAD and thus a higher plasma concentration that can cause adverse drug reactions. A precipitant drug that induces these enzymes can decrease the plasma level of antiarrhythmic agent which can lead to an ineffective antiarrhythmic effect. Some drugs, like ritonavir are strong CYP3A4 and P-gp inhibitors and significantly increase the blood concentration of multiple antiarrhythmic agents and direct oral anticoagulants (DOAC). Because of these interactions, potent inhibitors and inducers are best avoided in combination with antiarrhythmics. Predisposing factors that can aggravate these drug-drug interactions include: advanced age, gender, HF, renal and liver dysfunction, polypharmacy, female sex, weight, inherited enzyme systems and racial differences.[408–410] The frequency of CYP genetic polymorphisms varies across ethnicities with 5% to 10% of whites (≈1% of Asians; up to 19% in Blacks) being poor metabolizers of CYP2D6.[410,411]

CYP2D6 is the major enzyme for biotransformation of metoprolol, propranolol, flecainide, and propafenone. “Poor metabolizers” (5-10% of Caucasian and Black population) have reduced amounts of CYP2D6.[406] Low doses of quinidine can inhibit CYP2D6 thus increasing the peak and steady-state plasma concentrations and prolonging the half-life of parent compounds such as propafenone. CYP3A4 is responsible for the metabolism of amiodarone, bisoprolol, diltiazem, disopyramide, dronedarone, ivabradine, quinidine, ranolazine or verapamil CYP3A4 is inhibited by clarithromycin, erythromycin, itraconazole or ritonavir.

Amiodarone, cimetidine, diltiazem, ketoconazole, procainamide, propranolol, and verapamil increase quinidine plasma levels.[407] Quinidine is a potent CYP2D6 and P-gp inhibitor resulting in increased plasma levels of substrates of these enzyme systems. Because quinidine decreases digoxin clearance, one must reduce digoxin doses by 50% when used in combination. Class I and III antiarrhythmics prolong the QT and are best avoided in patients treated with other QT-prolonging drugs.

β-blockers, cimetidine, and halothane increase lidocaine plasma levels.[407] Mexiletine increases plasma levels of theophylline and amiodarone increases mexiletine levels.

Fluoxetine, duloxetine, and paroxetine are potent CYP2D6 inhibitors and co-administration increases plasma flecainide levels.[411,412] Concomitant administration of flecainide with amiodarone has also been shown to increase plasma flecainide concentrations by 50%. Co-administration of flecainide with digoxin increased digoxin trough serum concentrations by an average of 24% but usually this is not enough to make a dose adjustment.

Propafenone undergoes extensive first-pass metabolism, mainly by CYP2D6, with 2 active metabolites (5-hydroxypropafenone and N-depropylpropafenone), which are renally excreted.[407] Because of active metabolites, poor or extensive metabolizer status does not affect the dosing of the drug. Propafenone can increase the plasma levels of digoxin, metoprolol, propranolol, and

warfarin but these interactions are minimal and usually does not require any dose adjustments.[407,413]

Sotalol is not hepatically metabolized and excreted renally and is not subject to drug interactions involving the hepatic CYP enzyme system.

Dofetilide is also mainly excreted renally with no significant CYP interactions.[128] However, plasma dofetilide concentrations are significantly elevated when co-administered with verapamil, cimetidine, trimethoprim, ketoconazole, prochlorperazine, megestrol, dolutegravir, and hydrochlorothiazide, which compete with the active tubular secretion (via the cation transport system), and their concomitant use is an absolute contraindication.

Amiodarone inhibits P-gp, CYP1A2, CYP2C9, CYP2D6, and CYP3A4, and has the potential to increase plasma levels of drugs metabolized by these isoenzymes or substrates of P-gp When used in combination with amiodarone, lower doses for digoxin, flecainide, and warfarin are often required and one must monitor digoxin levels and the INR. [414–416] Cholestyramine decreases the absorption of amiodarone. Co-administration of amiodarone with digoxin, β-blockers, verapamil, or diltiazem increases the risk of bradycardia and AV block. Severe bradycardia has been reported, when amiodarone is co-administered with hepatitis C antiviral drugs (daclatasvir, ledipasvir, and sofosbuvir).[417] Amiodarone can also inhibit cyclosporin metabolism and cause higher blood levels requiring a dose reduction of cyclosporin.[418] Statins, especially simvastatin levels can increase when used concomitantly with amiodarone.[419]

Dronedarone is highly metabolized by CYP3A4 and is a moderate inhibitor of CYP3A4 and a weak inhibitor of CYP2D6.[420] Dronedarone is discouraged to be administered at the same time with potent CYP3A4 inhibitors. Dronedarone can be co-administered with moderate CYP3A4 inhibitors such as verapamil and diltiazem. Dronedarone is a P-gp inhibitor and can increase the level of digoxin and dabigatran if co-administered together.[420–422] It is discouraged to be co-administered with digoxin.

Diltiazem and verapamil are moderate inhibitors of CYP3A4 and P-gp; thus, doses of CYP3A4 and P-gp substrates are advised to be adjusted as appropriate. Concomitant QT prolonging drugs (https://crediblemeds.org) and strong CYP3A inhibitors (discontinue before initiation) are best avoided.

As mentioned above, multiple drugs interact with concomitant use of digoxin but the most significant are quinidine, amiodarone and dronedarone.[413,415,421,423,424]

The co-administration of adenosine with β-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.[407] These latter two drugs need to be avoided with adenosine stress testing.

Table 14 summarizes the substrates, inhibitors, and inducers of CYP3A4, 2D6, and 1A2 and P-gp and **Table 15** key drugs with potential interactions involving AADs, excluding AAD combinations (see **Table 16**) and anticoagulants (see Table **21**). More comprehensive reviews of substrates, inducers, and inhibitors of CYP and P-gp transporter, as well as drug-drug interactions of AADs, are provided in **Tables S4** and **S5**, respectively.

Drug-herb and drug-food interactions involving AADs

St. John's wort (Hypericum perforatum) is a potent inducer of CYP2C9, CYP2C19, and CYP3A4 and can decrease verapamil and dronedarone plasma concentrations.[425,426] St. John's wort has no effect on CYP1A2 or CYP2D6. St. John's wort can induce P-gp transport and lower plasma levels of digoxin.

Concomitant consumption of green tea (catechins) with nadolol and digoxin can significantly reduce plasma concentrations.[427]

Grapefruit juice is a moderate inhibitor of CYP3A4 and its effects may last from 4 to 24 hours.[428,429] Coadministration of grapefruit juice with amiodarone and dronedarone can cause major increases in peak plasma concentrations of these antiarrhythmic agents.[430] In addition, grapefruit juice inhibits the metabolic breakdown of amiodarone to its active metabolite n-desethyl-amiodarone. Grapefruit juice can increase plasma concentrations of other AADs such as quinidine and verapamil that undergo CYP3A4 metabolism listed in **Table 14**.

Food may affect the bioavailability of AADs.[431] Both amiodarone and dronedarone have a food effect and absorption, peak plasma concentrations and area under the curve will be increased if these drugs are taken with a meal.[420,432] Taking amiodarone with a meal can increase plasma levels and be used instead of increasing the dose when needed in patient staking the drug on an empty stomach. The oral bioavailability of dronedarone increases when administered with a high-fat meal. Dronedarone has low absolute bioavailability (~4%) when taken in a fasted state, but co-administration with food, particularly high-fat meals, increases its absorption significantly (by up to 2- to 4-fold).[432] For this reason, it is advised to be taken with meals to enhance its bioavailability and therapeutic effect.[432] All clinical studies with dronedarone were performed with patients taking their medication with meals and this is how the drug is encouraged to be used in clinical practice.[420]

Table 14: Cytochrome P450 complex enzymes and P-glycoprotein involved in the metabolism or affected by antiarrhythmic drugs (AADs) and other substances (a more comprehensive table is provided in Table S4).

CYP or P-gp	Inhibition, Induction or substrate	AADs	Other drugs or substances
CYP 3A4	**Inhibitors**	• Strong: **Class IV:** Verapamil • Moderate: **Class III:** Amiodarone, Dronedarone **Class IV:** Diltiazem	• Strong: grapefruit juice, azole antifungals (itraconazole, etc.), macrolides: (clarithromycin, erythromycin, etc.), nefazodone, HIV protease inhibitors. • Moderate: cimetidine, ciprofloxacin
	Inducers	Phenytoin	Alcohol chronic exposure, carbamazepine, glucocorticoids, rifampicin, St. John's wort

CYP or P-gp	Inhibition, Induction or substrate	AADs	Other drugs or substances
	Substrates	Ivabradine **Class I** (Quinidine, Lidocaine, Ranolazine) **Class II** (Carvedilol, Metoprolol, Nebivolol, Propranolol) **Class III** (Amiodarone, Dronedarone) **Class IV** (Diltiazem, Verapamil)	Benzodiazepines, bosentan, clopidogrel, colchicine, AntiXa DOACs, eplerenone, HCV protease inhibitors, HIV protease inhibitors, immunosuppressants (cyclosporine, tacrolimus), macrolides (clarithromycin, erythromycin, etc), omeprazole, ondansetron, PDE5 inhibitors, statins[a], ticagrelor. Many anticancer drugs
CYP 2D6	**Inhibitors**	**Class I** (Quinidine, Propafenone) **Class III** (Amiodarone, Dronedarone) **Class IV** (Diltiazem, Verapamil)	• Strong: bupropion, SSRI (fluoxetine, fluvoxamine, paroxetine), ritonavir, terbinafine • Moderate/mild: amiodarone, cimetidine, duloxetine, mirtazapine, SSRI (citalopram, escitalopram, fluvoxamine, sertraline)
	Inducers	Phenytoin	Carbamazepine, dexamethasone, phenobarbital, rifampicin
	Substrates	**Class I** (Mexiletine, Flecainide, Propafenone Ranolazine) **Class II** (Bisoprolol, Carvedilol, Metoprolol, Nebivolol, Propranolol) **Class III (**Vernakalant)	**Most antidepressants, antipsychotics, ondansetron, opioids, tamsulosin, trazodone, tropisetron**
CYP 1A2	**Inhibitors**	Propranolol Amiodarone Verapamil	Alopurinol, cimetidine, ciprofloxacin, famotidine, fluoxetine, fluvoxamine
	Inducers	**Phenytoin**	Tobacco, carbamazepine, rifampicin, ritonavir
	Substrates	**Class I** (Lidocaine, Mexiletine, Propafenone) **Verapamil**	Clopidogrel, clozapine, olanzapine, tamoxifen, theophylline, tizanidine, warfarin
P-gp	**Inhibitors**	**Class I** (Quinidine, Propafenone) **Class II** (Bisoprolol, Carvedilol, Propranolol) **Class III** (Amiodarone, Dronedarone) **Class IV** (Diltiazem, Verapamil)	Azole antifungals (itraconazole, etc.), conivaptan, HCV/HIV protease inhibitors, cyclosporine, proton pump inhibitors, macrolides (clarithromycin, erythromycin, etc.), tamoxifen, ticagrelor, tolvaptan

CYP or P-gp	Inhibition, Induction or substrate	AADs	Other drugs or substances
	Inducers	None significant	Carbamazepine, phenytoin, rifampicin, St. John's wort
	Substrate	**Class I** (Quinidine, Ranolazine) **Class IIa** (Carvedilol, Metoprolol, Nadolol, Nebivolol, Propranolol) **Class IIb** (Digoxin, Digitoxin) **Class III** (Amiodarone, Dronedarone) **Class IV** (Diltiazem, Verapamil)	Ambrisentan, cimetidine, clopidogrel, colchicine, dipyridamole, DOACs, erythromycin, fexofenadine, immunosuppressants (cyclosporine, tacrolimus), ondansetron, opioids, riociguat, statins

Cytochrome P450 Enzymes (CYP) are responsible for the metabolism of many drugs. Inhibition or induction of these enzymes can lead to significant drug interactions with agents which are substrates of these enzymes. P-glycoprotein (P-gp) is a transporter protein expressed in various tissues (intestine, liver, kidneys) that affects the absorption and elimination of various drugs. Inhibitors can increase drug levels, while inducers can decrease them. Antiarrhythmic Drugs often interact with these enzymes and transporters, affecting the metabolism of other drugs and vice versa. Non-Antiarrhythmic Drugs/Substances can also inhibit or induce these enzymes and transporters, leading to potential interactions when combined with AADs. DOACs, direct oral anticoagulants; HCV, hepatitis C virus; HIV human immunodeficiency virus; PDE, phosphodiesterase; SSRI, Selective serotonin reuptake inhibitor.

[a]*Atorvastatin, simvastatin, and lovastatin are metabolized by CYP3A4, while rosuvastatin, pravastatin, pitavastatin, and fluvastatin are not significantly metabolized by it.*

Table 15: Key drugs with potential interactions involving AADs, excluding anticoagulants (covered in Table 21) and AAD combinations (discussed in Table 16). Table S5 gives a more comprehensive description.[a]

Modified VW Class	AAD	Drug #1	Advice for concurrent use with drug #1	Drug #2	Advice for concurrent use with drug #2
0	**Ivabradine**	Strong CYP3A4 inhibitors[b] (+ivabradine)	Avoid combination	CYP3A4 inducers[c] (-ivabradine)	Avoid combination
IA	**Quinidine**	Strong CYP3A4 inhibitors[b] (+quinidine)	Caution, monitor levels	Other QT prolonging drugs	Avoid combination
	Procainamide	Cimetidine, propranolol, verapamil (+procainamide)	Replace (e.g. cimetidine by PPIs), monitor procainamide levels	Amiodarone (+procainamide, summative effect)	Monitor ECG

	Disopyramide	Anticholinergic (H1-antihistaminics, antispasmodics, tricyclic antidepressants) (summative)	Avoid combination	β-blockers, CCB (additive negative inotropic effect)	Monitor cardiac function
IB	**Lidocaine**	Amiodarone, β-blockers, Cimetidine (+lidocaine)	Replace (e.g. PPIs, renal excreted β-blockers), reduce lidocaine dose or monitor levels	β-blockers (+lidocaine)	Reduce lidocaine dose
	Mexiletine	Theophylline (+theophylline)	Reduce and monitor theophylline levels	Phenytoin (mutual reduction)	Adjust dose, monitor levels
	Phenytoin	CYP3A4 inhibitors[b] (+phenytoin)	Reduce phenytoin dose, monitor phenytoin levels	Oral contraceptives (reduces contraceptive efficacy) & corticosteroid (reduces efficacy)	Avoid or increase corticosteroid dose
IC	**Flecainide**	Digoxin (+digoxin)	Reduce digoxin dose (25%), monitor digoxin levels	Amiodarone, Fluoxetine/Paroxetine (+flecainide)	Replace (e.g. escitalopram or sertraline), reduce (30%) flecainide dose, monitor levels & ECG
	Propafenone	Digoxin (+digoxin)	Reduce digoxin dose (25%), monitor digoxin levels	Fluoxetine/Paroxetine (+propafenone)	Replace (e.g. escitalopram or sertraline), reduce (30%) flecainide dose, monitor levels & ECG
ID	**Ranolazine**	Strong CYP3A4 inhibitors[b] (+ranolazine)	Avoid combination	Statins (potentiates myopathy)	Limit statin dose or use non-CYP3A4 statins (pitavastatin, pravastatin, rosuvastatin)
IIA	**β-blockers**	Antidiabetic drugs (mask hypoglycaemic symptoms)	Counsel patient, avoid non-selective β-blockers (use carvedilol or nebivolol)	Clonidine (hypertension if abrupt discontinuation)	Avoid abrupt clonidine discontinuation
IID	**Digitalis**	Amiodarone/dronedarone/Flecainide/Propafenone/Quinidine/Ranolazine/Verapamil (+digoxin)	Reduce (50%) or avoid digoxin, monitor digoxin levels	Macrolides (+digoxin)	Monitor digoxin levels

IIE	**Adenosine**	Dipyridamole (potentiates adenosine)	Reduce adenosine dose	Theophylline/caffeine (antagonizes adenosine)	Increase adenosine dose
III	**Amiodarone**	Simvastatin, lovastatin, atorvastatin (potentiates myopathy)	Reduce statin dose or use non-CYP3A4 statins (pravastatin, rosuvastatin)	β-blockers (summative)	Adjust dose, Monitor the ECG
		Clopidogrel (decreases the active metabolite	Replace by prasugrel or ticagrelor	Hepatitis C antiviral drugs (potentiate bradycardia)	Monitor heart rate during the first 48 hrs
	Dronedarone	Simvastatin, lovastatin, atorvastatin (potentiates myopathy)	Reduce statin dose or use non-CYP3A4 statins (pravastatin, rosuvastatin)	Potent CYP3A4 inhibitors (increase Dronedarone)	Avoid combination
	Dofetilide	Cimetidine, trimethoprim, dolutegravir (reduce dofetilide OCT2 renal elimination)	Avoid combination	CYP3A4 Inhibitors (+dofetilide)	Avoid combination
	Ibutilide / Dofetilide / Sotalol	Drugs producing hypokalaemia/hypomagnesaemia	Increase the risk of QT prolongation and TdP. Monitor ionic levels	Other QT prolonging drugs	Avoid combination
	Vernakalant	CYP3A4 inhibitors[b] (+vernakalant)	Caution	Strong CYP2D6 inhibitors[d] (+vernakalant)	Caution
IV	**Verapamil / Diltiazem**	CYP3A4 substrates (+substrate)	Replace or adjust substrate dose	P-gp substrates (+substrate)	Replace or adjust substrate dose

+: increases levels of the AAD; -: decreases levels of the AAD; OCT2: organic cation transporter 2; AAD, antiarrhythmic drug; CCB, calcium channel blockers; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitors; TdP, torsades de pointes.

[a] *For other potential interactions see Table 15.*

[b] *Verapamil, grapefruit juice, azole antifungals, macrolides and others (see Table 15).*

[c] *Phenytoin, rifampicin and others (see Table 15).*

[d] *Bupropion, SSRI (fluoxetine, fluvoxamine, paroxetine), ritonavir, others (see Table 15).*

AAD switch and combinations

When an AAD is ineffective or not tolerated, changing it (drug switch) or adding another (drug combination)[433] can be tried. Reasons for switching or combining are inefficacy (initial or lost over time), adverse effect and development of a contraindication (e.g., new disorder, new potential drug interaction) (**Box 15)**. The combination of flecainide or propafenone with sotalol[434–436] may create a pseudo-amiodarone effect but there is limited clinical experience in

AF.[437,438] Flecainide has been combined with amiodarone in children.[439,440] but more guideline-relevant AAD studies are needed.

The main potential AAD combinations, those with uncertain safety, and those to be avoided are summarized in **Table 16.**

Table 16: Main potential antiarrhythmic drug (AAD) combinations.

Potential AAD combinations[441] *(Supported by some evidence[a])*						
Class #1	**AAD #1**	**Class #2**	**AAD #2**	**Rationale**	**Objective**	**Study, reference**
0	Ivabradine	II	β-blockers	Summative complementary effects	Inappropriate sinus tachycardia	442
Ia	Quinidine	Ia	Disopyramide	Combined reduced doses to minimize side effects	Decrease gastrointestinal intolerance	437,443

Box 15: Considerations when switching or combining antiarrhythmic drugs (AADs)

SWITCHING AADs

- **Pharmacokinetics:**
  - For AADs with similar half-lives, start the new AAD at its usual dose/interval when the next dose of the prior AAD is due.
  - For AADs with long washout periods (e.g., amiodarone), up-titrate the new AAD gradually.
- **Monitoring:** Use **serum drug levels** and/or **ECG markers** to direct washout and initiation.

COMBINING AADs

Reasons:

- **Additive efficacy:**
  - Combining drugs (e.g., Class Ic + III or Ia + Ib) may enhance effectiveness under close monitoring. β-blockers: Usually enhance efficacy of AADs when added.
  - One AAD may enhance the binding of another (e.g., Ia or III lengthens plateau phase allowing increased time for Ib binding)
- **Improved tolerance:**
- Lower combined doses may reduce side effects.
  - Mechanism of one AAD may decrease proarrhythmic profile of another (e.g., ranolazine can block Class III early after depolarizations.)

Considerations:

- **Experience with prior AADs:** Tailor combinations based on previous response.
- **Do not combine full doses** of Class Ia and III (increased risk of *torsades de pointes*).

					(constipation for disopyramide, diarrhoea for quinidine)[b]	
		Ib	Mexiletine	- Complementary actions on refractory period (Ia prolongs; Ib shortens). - Quinidine favours mexiletine biding to the inactivated state of the Na^+ Channel	VAs	444–446
		IV	Verapamil	Verapamil may prevent: - AAD Class I induce EAD. - Fast AV conduction during AF due to the vagolytic effect of quinidine	AAs[b] & VAs	447, PAFAC[448], SOPAT[449]
Ic	Flecainide	Ib	Mexiletine	Summative effects	VAs	450
	Flecainide, Propafenone	II IV	β-blockers CCB	Complementary effects on myocardium and AV node[c]	Rate control of AF/AFL/ type Ic AFL & SVT prevention/termination[c]	93
III	Amiodarone	Ia Ib	Quinidine Mexiletine	Complementary effects on ventricular conduction and refractoriness	VAs	451–453
		Ic Id	Flecainide/propafenone Ranolazine	Complementary effects on conduction and refractoriness	AAs & VAS	454–456
		II	β-blockers	Complementary effects on myocardium and adrenergic tone	SHD VAs	OPTIC[92]
	Dronedarone	Id	Ranolazine	Combined reduced doses to potentiate efficacy and minimize side effects (constipation for ranolazine, diarrhoea for dronedarone)	AF	HARMONY[76]
	Sotalol	Ib Ic	Mexiletine Flecainide[d]	Complementary effects on conduction and refractoriness	VAs in ARVC	436,457, 20B
IIa	β-blockers	0, I, IIb, IId, III		Blocks sympathetic stimulation enhancing the efficacy and/or safety of other AADs	AAs & VAs	458
IV	CCB	IId	Digoxin[f]	Summative effects	Rate control of AF	459
Uncertain AAD combinations *(limited data on efficacy and safety)*						

Class #1	AAD #1	Class #2	AAD #2	Rationale	Objective	
III	Dronedarone	IV	Verapamil, Diltiazem[e]	Additional rate control to that of dronedarone	AAs	Limited data
III	Sotalol Dofetilide	Id	Ranolazine	Ranolazine may mitigate EADs caused by Class III drugs, reducing TdP risk.	AAs & VAs	Limited data[460,461]
Potentially hazardous AAD combinations *(To avoid or to be used at reduced doses)*						
Class #1	**AAD #1**	**Class #2**	**AAD #2**	**Rationale**	**Risk**	
Ia	Disopyramide	IV	CCB[g]	Both reduce cardiac contractility.	Heart failure and shock	462
Id	Ranolazine	Ia	Quinidine	Both are metabolized primarily by CYP3A4	TdP	
			Disopyramide	Both may produce constipation	Constipation	
		Ib Ic	Mexiletine Flecainide	Both have CNS effects	Tremor	
II	β-blockers	IV	CCB	Both depress the SN, AV conduction and cardiac contractility	AV block	
III	Sotalol	II IV	β-blockers CCB	Both depress the SN, AV conduction and cardiac contractility	Bradycardia	
	Sotalol/Dofetilide	Ia	Quinidine	Both prolong the QT interval	TdP	463,464
	Dronedarone	Id	Digoxin	Dronedarone decreases renal clearance of digoxin	Digitalis toxicity	106
	Dofetilide	IV	CCB	CCB increase dofetilide levels	TdP	

Column #1 lists AADs commonly used as the first-choice drug, while Column #2 includes AADs typically added as complementary therapy when the primary drug fails to control the arrhythmia or may result in proarrhythmia or other adverse effects. This order may be reversed depending on specific circumstances. AA, atrial arrhythmias; ARVC, arrhythmogenic right ventricular dysplasia; AF, atrial fibrillation; AFL, atrial flutter; AV, atrioventricular; CCB, calcium channel blockers; EAD, early after depolarizations; SN, sinus node; SHD, structural heart disease; SVT, supraventricular tachycardia; VA, ventricular arrhythmias; TdP, torsades de pointes; VA, ventricular arrhythmias; VF, ventricular fibrillation; VM, Vaughan Williams; VT, ventricular tachycardia.

[a]*Combining AADs increases risks and necessitates careful evaluation of alternatives and patient conditions, along with close dose adjustments and ECG monitoring to mitigate myocardial depression and proarrhythmia. Most evidence come from small non-controlled studies.*

[b]*In general ablation is advised before quinidine for AF treatment*

[c]*Contraindicated in patients with structural heart disease due to the risk of myocardial contraction depression and heart failure*

[d]*Flecainide may potentiate the myocardial contraction depression effect of sotalol*

[e]*Diltiazem, verapamil, and dronedarone are substrates and inhibitors of CYP3A4, and their concurrent use can increase plasma concentrations of each drug, potentially amplifying their pharmacological effects and side effects. When rate control is required, combining dronedarone with a β-blocker is generally preferred over CCBs. Additionally, both dronedarone and CCBs can depress AV conduction,*

increasing the risk of bradycardia or heart block. Therefore, the combination of dronedarone with CCBs must only be used with caution and under close clinical and ECG monitoring.
[f]*Consider reducing the dose of digoxin and monitoring serum levels closely due to the risk of toxicity. CCB can increase digoxin levels by 50-75% through inhibition of P-glycoprotein activity, which decreases renal tubular elimination of digoxin.*
[g]*With caution to improve symptoms in hypertrophic cardiomyopathy.*

AAD in special situations

Pregnancy

AADs are best avoided, if possible, during the first trimester because of the risk of teratogenic effects. Then, they may cause adverse effects on foetal growth and development and on uterine contractility, or produce pro-arrhythmic events.[465,466] The main characteristics of AADs during pregnancy and lactation are summarized in **Table 17**.

During pregnancy symptomatic PAC and PVC rarely require treatment, although β-blockers may be used. Treatment of SVT, the most common sustained arrhythmia in pregnancy, is advised when symptomatic or causing haemodynamic compromise. In the absence of pre-excitation, vagal manoeuvres, followed by adenosine, β1-selective blockers (except atenolol) and verapamil (diltiazem is teratogenic in animals), or a combination of β-blockers[465–469] and verapamil are advised.[465,467–470] Adenosine is the drug of choice for acute conversion of SVT, AT, and orthodromic AVRT.[44,199,200,204,465,471] β-Blockers are considered safe in pregnancy for the treatment of cardiac arrhythmias and other CVD[465,468–470,472,473] although they are associated with lower birth weights. Flecainide and propafenone are advised as second-line agents in patients without ischaemic or SHD and in maternal and foetal SVT with pre-excitation.[465,474,475] Amiodarone and dronedarone produce foetal harm and are encouraged to only be used when other measures fail.[465,467]

Rhythm control is the preferred strategy of AF during pregnancy. i.v. ibutilide or flecainide may be appropriate for termination of AF/AFL in haemodynamically stable patients without SHD.[93,152] Electrical cardioversion preceded by anticoagulation is advised if there is haemodynamic instability or considerable risk for mother or foetus;[44,204,465] foetal heart rate is encouraged to routinely be controlled post-cardioversion.[476] Intravenous β1-selective blockers (metoprolol, bisoprolol, not atenolol) are advised for acute rate control; if they fail, digoxin and verapamil are appropriate in the absence of pre-excited AF.[465,467] Oral flecainide, propafenone, or sotalol are appropriate to prevent AF if AV nodal-blocking drugs fail.[93]

VA in the absence of SHD are usually sensitive to β-blockers;[45,465,477] sotalol or Class Ic drugs may be appropriate if β-blockers are ineffective, and catheter ablation if drug treatment fails.[45,465,478,479] Sotalol or procainamide IV are appropriate for acute conversion of haemodynamically stable monomorphic sustained VT, while oral metoprolol, propranolol or verapamil are advised for long-term management of idiopathic sustained VT.[45] β-blockers are advised during pregnancy and the post-partum in patients with LQTS or CPVT.[45,480] Finally, verapamil and diltiazem are discouraged during the late pregnancy, breast feeding and in children less than 1 year old because they have been associated with hypotension in some case

reports. However, all of them had HF, overdosing and/or other concurrent AADs at the time the drug was given and therefore some controversy exists.

Table 17: AADs during pregnancy and breastfeeding.[465]

Drug	Former FDA category	Placental transfer	Present in human milk	Safety in lactation (5)	Adverse effects	Used for foetal arrhythmias
Adenosine	C	No	No	LD	No foetal adverse effects reported (limited human data)	Yes
Amiodarone	D	Yes	Yes	Contraindicated	Goitre, hypo- (9%), hyper-thyroidism, neurodevelopmental abnormalities, premature birth, growth retardation; bradycardia and QT prolongation in new-borns	(Yes, Last choice)
Atenolol	D	Yes	Yes	Produces IUGR Avoid its use	Significant IUGR.	
Atropine	C	LD	Yes	Yes	LD	
Bepridil	C	LD	Yes	Avoid its use	LD	
Bisoprolol, carvedilol, metoprolol, propranolol	C	Yes	Yes	LD	Foetal bradycardia and hypoglycaemia, IUGR and immature and preterm birth	Yes (metoprolol)
Cibenzoline	C	LD	In animals	LD	LD	
Digoxin	C	Yes	Yes	Considered safe	Serum levels unreliable, safe	Yes
Diltiazem	C	Yes	Yes	Avoid its use	Diltiazem is teratogenic in animals	
Disopyramide	C	Yes	Yes	Avoid its use	Uterine contractions, placental abruption, prolonged QT	
Dofetilide	C	In animals	LD	Avoid its use	Adverse effects in animals	
Dronedarone	X		Unknown	Contraindicated	It may cause foetal harm when administered to a pregnant woman. Dronedarone is teratogenic in rats	
Esmolol	C/D[a]	LD	Unknown	Avoid its use	See β-blockers	
Flecainide	C	Yes	Yes	Plasma levels in nursing infants are 5-10 times	LD	Yes

				lower than therapeutic plasma levels		
Ibutilide	---	Unknown	Yes	Contraindicated	Teratogenic (abnormalities included adactyly, interventricular septal defects, and scoliosis) in rats	
Ivabradine[b]	LD	Yes (in rats)	Yes	Avoid its use	Animal reproduction studies have shown adverse effects	
Lidocaine	B	Yes	Yes	Considered safe	Foetal bradycardia/tachycardia, neonatal bradycardia, hypotonia or respiratory depression	Yes
Mexiletine	C	Yes	Yes	Caution	Limited data, but probably safe	
Nicorandil	B	LD	Yes in animals	LD	No harmful effects in animals	
Pilsicainide	C	LD	Yes in animals	LD		
Procainamide	C	Yes	Yes	Avoid its use	Lupus-like syndrome, prolonged QT	
Propafenone	C	Yes	Unknown	LD	Limited data. Probably safe	Yes
Quinidine	C	Yes	Yes	Yes	Foetal/neonatal thrombocytopenia, uterine contraction, prolonged QT.	Yes
Ranolazine	LD	LD	Unknown	Avoid its use	Foetal bradycardia, hypoglycaemia, reduced birth-weight, QT prolongation	
Sotalol	B	Yes	Yes	Avoid its use	Maternal QTc prolongation	Yes
Verapamil	C	Yes	Yes	LD	Pre-maturity, IUGR, foetal bradycardia, impaired uterine contraction	
Vernakalant	Unknown	LD	Unknown	Unknown	LD	

AADs are shaded black to indicate contraindications, light brown where avoidance is advised when possible.
IUGR: intrauterine growth retardation. LD: limited human data
Cells are shaded black to denote contraindications, while light brown shading highlights situations where dose reduction or caution in use is advised.
[a]*D in 2nd and 3rd trimesters.*
[b]*Women of child-bearing potential must use appropriate contraceptive measures during treatment. In red: contraindicated.*
Pregnancy categories formerly advised by the US FDA:

- *A: Controlled studies show no risk to the foetus.*
- *B: May be acceptable. Either animal studies show no risk but human studies not available or animal studies showed minor risks and human studies showed no risk.*

- *C: Use with caution if benefits outweigh risks. Animal studies show risk and human studies not available or neither animal nor human studies done.*
- *D: Use in life-threatening emergencies when no safer drug available. Positive evidence of human foetal risk.*
- *X: Do not use in pregnancy. Risks involved outweigh potential benefits. Safer alternatives exist.*

Children

As a general rule, prescription of AADs in children requires a clear diagnosis with ECG documentation of the arrhythmia.[136] Paediatric population present specific characteristics, including few or poorly described symptoms, differences in drug PK, lack of specific drug formulations and immaturity of the specialized cardiac conduction tissue.[481] In newborns milk can substantially modify the absorption of some drugs (i.e., flecainide) and erratic feeding schedules and vomiting can affect AAD availability. Additionally, certain arrhythmic substrates are more common in this age group—such as permanent junctional re-entrant tachycardia (PJRT, or Coumel's tachycardia) and both congenital and postoperative junctional ectopic tachycardia—and may require combination AAD therapy for adequate control. Although catheter ablation is possible for children of almost any size, recent European registries show that AAD therapy is generally preferred in those weighing less than 15 kg.[482]

AADs commonly used for arrhythmias in infants and children are summarized in **Table 18**[483] and **Table S11**. For patients without SHD, adenosine, β-blockers (metoprolol, propranolol), digoxin, flecainide, propafenone and sotalol, can be safely used. Class I AADs are discouraged to be given in the presence of SHD and/or systolic ventricular dysfunction because of their negative inotropic effect and the risk for proarrhythmia. Careful dose adjustment based on renal dysfunction is needed for digoxin, flecainide, propafenone and sotalol. As discussed before, i.v. verapamil is discouraged when possible in VA in infants <1 year of age. Nonetheless, verapamil remains the treatment of choice for some arrhythmias (e.g., posterior fascicular VT, even at this age) and can be used safely in acute settings.[484] Ivabradine is emerging as an option for the prevention and treatment of junctional ectopic tachycardia (JET) in both postoperative and congenital presentations.[337,485] Amiodarone is encouraged to be used when other AADs fail or are contraindicated.[45,315,483]

Very few studies, all of limited scope, have compared different AADs for the prophylactic treatment of SVTs.[486,487] No evidence demonstrates clear superiority of one agent over another,[487,488] and combination therapy may be necessary in some cases.[489] Factors influencing drug choice include local availability and safety profiles.[488] The optimal duration of treatment is also under debate, with some clinicians endorsing shorter treatment courses (four to six months instead of extending up to the first year of life).[490]

Table 18: Pharmacological therapy for arrhythmias in infants and children[483]

Drug	Dose	Arrhythmia	Comments
Intravenous			
Lidocaine	1 mg/kg (up to 3 doses in 10 min); then 20–50 mg/kg/min		
Flecainide[a]	1.5–2 mg/kg over 5 min 2–4 mg/kg/day		Avoid in patients with structural heart disease[c]. Milk reduces flecainide absorption.
Propafenone[a]	Loading: 2 mg/kg over 2 hrs. Maintenance: 4–7 mg/kg/min		
Amiodarone	Loading: 5–10 mg/kg over 60 min. Maintenance dose: 5–15 mg/kg/min		It may take hours until successful conversion to SR occurs. The safety and efficacy of amiodarone in children has not been established
Adenosine	Rapid i.v. bolus: a) for infants: 0.15 mg/kg. For >1 year of age: 0.1 mg/kg Increasing dosage up to 0.3 mg/kg.		
Esmolol	Bolus 100-500 μg/kg; then 25–100 μg/kg/min		
Propranolol	1 mg/kg/day		
Verapamil[a]	0.1 mg/kg slowly over 2 min		Avoid in infants <1 year of age.
Oral			
Digoxin		SVT/VT SNRT	Bradycardia[b]. Children require proportionally larger doses than adults based on body weight/surface area. Avoid in WPW patients[c]
Propranolol	1–3 mg/kg three times daily	SVT/VT	Bradycardia[b], asthma[c]
Atenolol	0.3–1.3 mg/kg three times daily	SVT/VT	Bradycardia[b], asthma[c]
Verapamil	4–8 mg/kg three times daily	SVT/VT	Bradycardia[b], reduced LV function[c] Avoid in infants <1 year of age[c] Avoid in WPW patients
Flecainide	2–7 mg/kg twice daily 'Pill-in-the-Pocket': 3 mg/kg	WPW & SVT	QRS duration 25% above baseline[b], CrCl <50 mg/mL[c], reduced LVEF[c]. Caution if conduction system disease[c] Flecainide is not approved for use in children below the age of 12 years
Propafenone	200–600 mg/m^2 or 10–15 mg/kg in 3× daily	WPW & SVT	QT interval >500 ms[b], conduction system disease[c] and renal impairment[c] Contraindicated if reduced LVEF[c].
Sotalol	1–2 mg/kg/day twice daily for neonates and children <6 years; 1.5–3 mg/kg/day twice daily for infants and children >6 years	WPW & SVT	Contraindicated[c]: significant LVH, systolic HF, pre-existing QT prolongation, hypokalaemia, CrCl <50 mg/mL and asthma. QT interval >500 ms. Dose adjustment based on renal function[b]
Amiodarone	Loading: 10 mg/kg for 10 days. Maintenance: 5 mg/kg/day	WPW & SVT, JET, PJRT	QT interval >500 ms[b]. Caution with QT-prolonging drugs[c]. Reduce the dose of vitamin K & digoxin[c]

CrCL, creatinine clearance; HF, heart failure; JET, junctional ectopic tachycardia; LV, left ventricle; LVEF, LV ejection fraction; LVH, LV hypertrophy; PJRT, permanent junctional ectopic tachycardia; SN, sinus node; SNRT, sinus node reentrant tachycardia; SVT, supraventricular tachycardia; VT, ventricular tachycardia, WPW, Wolf Parkinson White syndrome.

[a]*Myocardial depressant effect.*
[b]*Features prompting lower dose or discontinuation.*
[c]*Main contraindications and precautions.*

Foetal arrhythmias.

Sustained foetal tachyarrhythmias (>180 beats/minute) develops in up to 2% of pregnancies[491–493] and they lead to foetal nonimmune hydrops, cardiac dysfunction, preterm delivery, and higher perinatal morbidity and mortality.[493–495] However, data are limited regarding optimal treatment, route of treatment, and drug dosages. Thus, AAD selection is encouraged to be based on the severity (presence of maternal haemodynamic instability or hydrops foetalis), associated congenital abnormalities, and maternal desires.[496] Digoxin, flecainide or sotalol, alone or in combination, depending on the type of tachycardia, are useful in terminating foetal tachyarrhythmias,[483,491,497] but flecainide is more effective than digoxin in terminating foetal SVT in patients with and without hydrops foetalis.[497,498] During treatment, adverse effects of these AADs can appear both in foetus and mother and maternal intolerance can be a limiting factor to appropriate treatment of foetal arrhythmias; thus, a close follow-up of mother and foetus is needed.[435,474,483,492]

Elderly

Normal ageing is associated changes in body composition, cardiac electrophysiological and structural changes and homeostatic mechanisms that increase the susceptibility to develop CVDs (**Table S12**).[499–502] Additionally, patients ≥80 years present several comorbidities that markedly affect the PD (effects of the drugs on the body) and PK (absorption, distribution, metabolism and excretion) of AADs and are treated with polypharmacy, increasing the risk of adverse events and drug-drug and drug-disease interactions (**Tables 12 and 15**).[502–506] However, very old people with arrhythmias and comorbidities are under-represented/excluded in clinical trials and, therefore, the benefit-risk balance of AADs to direct effective and safe treatment of arrhythmias in this population is unknown and is extrapolated from the results obtained in younger populations.[507–509]

Age-related cardiac changes include the loss of SA and AV nodal cells that decrease in heart rate and slow AV conduction, changes in the expression/function of cardiac ion channels leading to a prolongation of the APD (QT interval) and the presence of CVD leading to ventricular hypertrophy, amyloidosis, cardiac valvular degenerative changes and annular calcification, and fibrous infiltration of the conduction system. These structural changes render the aging heart more susceptible to the development of cardiac arrhythmias (proarrhythmia).[499–502]

Pharmacodynamic changes. β-blockers are probably the most used and safe AADs in older people, being of choice drugs administered once daily. Hydrophilic drugs (atenolol and nadolol) produce fewer CNS side effects, but they are best avoided in patients with renal dysfunction. The coadministration of β-blockers with verapamil/diltiazem and/or digoxin increases the risk of severe bradycardia or different degrees of AV block in the elderly. In older sedentary people and

HF patients who cannot tolerate higher doses of β-blockers low doses of digoxin (to maintain serum digoxin levels <1 ng/mL) can be added to reach the desired heart rate and symptom control. Therefore, it is particularly important in elderly patients to obtain 24-h Holter monitors to ensure that there is not excessive bradycardia or pauses during the night when vagal tone is highest.[507] It is advised to carefully manage Class I AADs in the elderly because they often have SND, or SHD; if advised the ECG is encouraged to be closely monitored. Class Ia, dofetilide and sotalol are AADs particularly prone to inducing QT-related ventricular proarrhythmia in this population with frequent SHD, comorbidities, renal function impairment and frequent ionic imbalance.[370] Amiodarone is often given in the very elderly, because it is more effective that other AADs, it can be administered in patients with ischaemic or SHD and doses do not need to be adjusted for renal or hepatic function.[45,93] The risk of cardiovascular events and mortality with dronedarone appears to be reduced in elderly patients with non-permanent AF.[99] Although the incidence of SCD increases with age, the proportion of deaths that are sudden compared with total mortality declines markedly in the elderly.[510] In a meta-analysis of randomized trials, AADs significantly reduced recurrent VT without improving mortality,[511] but the benefit of was mainly driven by amiodarone.

Older patients may have different responses to AADs and are more susceptible to some adverse effects than younger patients.[502,512–515] Furthermore, several drugs with non-cardiovascular indications prolong the QTc interval and increase the risk of developing TdP and are advised to be avoided. The Beers criteria advise to avoid:[516] a) amiodarone as first-line therapy for AF unless the patient has HF or LVH if rhythm control is preferred over rate control, because safer drugs are available; b) disopyramide, because of its potent negative inotropic effects and anticholinergic properties; c) dronedarone in patients with permanent AF or severe (Class IV) or recently decompensated HF, because of increased risk of death; d) digoxin as first-line therapy for AF or HF in daily doses greater than 0.125 mg/day for any indication, because more-effective and safer alternatives exist.

Pharmacokinetic changes. Oral drug absorption may be delayed in the older individuals, but full drug absorption can be achieved because most drugs are absorbed by passive diffusion.[513,517–519] The most important changes refer to drug distribution, biotransformation and excretion of AADs (**Table S12**). In older people body fat mass increases, while total body water and peripheral (hepatic and renal) blood flow and lean body mass decrease.[512,513,518,519] Thus, the volume of distribution (Vd) and half-life of lipophilic drugs may increase, while the Vd of hydrophilic drugs decreases, leading to a more rapid increase in plasma concentrations. Hepatic biotransformation of some AADs depends on plasma protein binding, hepatic blood flow (which decreases with age, hepatic impairment, HF, shock or β-blockers) and expression/activity of drug metabolizing enzymes.[520] Hepatic metabolism via CYP-mediated phase I reactions (oxidization, reduction, hydrolysis) leading to active metabolites decreases, while phase II conjugation reactions leading to inactive metabolites remained unaltered.[517,518,521,522] Thus, hepatic impairment may reduce the clearance and increase the half-lives of AADs metabolized by the liver and, therefore, dose adjustments according to age may be required to minimize the risk of adverse effects.[518] Furthermore, older people are especially prone to drug interactions, which frequently occur at the level of drug metabolism.[502,513,522]

Older people present a reduction in renal blood flow, estimated glomerular filtration rate and tubular secretion/reabsorption and an increase in renal diseases that impair renal function. These

changes reduce the clearance and increase the exposure, the half-lives and risk of adverse events of renally-cleared drugs.[502,512,513,518,520]

As a rule, lower starting doses (for patients ≥65 years) or a 50% dose reduction (for those ≥75 years) of AADs are advised in elderly patients. Doses are advised to be gradually up-titrated based on regular monitoring of symptoms, ECG findings, plasma drug levels, relevant laboratory parameters, and overall patient tolerance to ensure safety and efficacy. The selection of AADs in the elderly is mainly determined by the treatment target, patient's tolerance, possible drug interactions, comorbidities, and renal and liver function[514] (see **Table 19** of renal and hepatic failure excretion and **Box 16**).

Box 16: • Key Advice for AAD Use in the Elderly

- β-blockers are first-line; **atenolol/nadolol** have fewer CNS effects but require caution in renal dysfunction.
- **Avoid combining β-blockers with verapamil, diltiazem, or digoxin** to prevent severe bradycardia and AV block. **Low-dose digoxin** (<1 ng/mL) may be used in HF or sedentary patients.
- **Avoid Class Ia** AADs, dofetilide, and sotalol due to high proarrhythmic risk. Use **Class Ic cautiously** due to potential sinus node depression.
- **Amiodarone is often preferred** for elderly patients with structural heart disease due to efficacy and tolerance.
- **Dronedarone may reduce cardiovascular events** but is not advised for use in permanent AF or severe HF due to increased mortality risk.
- **Lipophilic drugs** (e.g., amiodarone, propranolol) have prolonged half-lives, increasing accumulation risk, while **hydrophilic drugs** (e.g., sotalol, atenolol) reach higher plasma concentrations due to age-related changes.
- **Declining renal and hepatic functions** increase toxicity risk; frequent renal function and plasma drug level monitoring is essential.
- **Reduce doses** in older adults:
  - Start with lower doses ≥65 years.
  - Reduce by 50% for patients ≥75 years and titrate gradually with ECG and lab monitoring.

Athletes

AAD therapy in athletes presents unique challenges due to their young age, hypervagotonic state, and reluctance to take medications that may impact physical performance, such as β-blockers. β-blockers and CCBs can exacerbate bradycardia, increasing the risk of fatigue, dizziness, and syncope. Class Ic drugs are advised to be used with caution due to their use-dependent effects, which can increase the risk of exercise-induced proarrhythmia. Conversely, drugs with reverse use dependence, such as sotalol, may heighten the risk of TdP in athletes, particularly in those with frequent bradycardia. Additionally, some drugs, including metoprolol and sotalol, are classified as prohibited substances by the World Anti-Doping Agency in precision-based sports such as archery, automobile racing, billiards, darts, golf, shooting, ski jumping, snowboarding (with jumping), and underwater apnoea sports.[523] However, other AADs, including amiodarone, Class Ic agents, and CCBs, are not subject to these restrictions. Given these complexities, AAD selection must carefully balance efficacy, safety, and regulatory compliance, ensuring optimal arrhythmia control while preserving athletic performance and minimizing drug-related impairments.

Heart failure

Reduced ejection fraction

In patients with HFrEF, both AF (AF) and VA are more likely to occur. AADs are used for symptomatic atrial and ventricular tachyarrhythmias, after the use of goal directed medical therapies (GDMT), all of which have a role in improving LVEF, overall survival and reducing arrhythmias.[524] β-blockers and aldosterone receptor blockers also reduce SCD.[524] In HFrEF patients, avoiding hypokalaemia, hypomagnesaemia, and digitalis toxicity is required to minimize proarrhythmic events.

Rate and rhythm control strategies in AF patients with HFrEF are important to minimize the development of tachycardia-induced cardiomyopathy.[93,131,524] In addition, HF adds to thromboembolic risk and therapeutic anticoagulation is a necessary part of the treatment strategy based on risk/benefit ratio. Worldwide, amiodarone is the main antiarrhythmic used as a rhythm control strategy for AF in HFrEF patients based on safety from the GESICA and CHF-STAT studies,[525,526] higher efficacy rates than other drugs[527] and guideline recommendations.[93,131,397] However, a caution is that amiodarone increased mortality in Class III HF patients in SCD-HeFT (HR 1.44; CI 1.05-1.97, p=0.01 compared to control).[528] In North America, dofetilide is recommended by the AHA/ACC/HRS guidelines based on the drug's safety in the DIAMOND-HF study.[529] The use of dofetilide in HFrEF patients can be restricted due to its high renal excretion rate, risk of TdP and poor renal function in these patients.[530] If a rhythm control strategy is chosen and amiodarone is ineffective, rhythm control with catheter ablation has to be considered based on the CASTLE AF and CABANA AF HF substudy[531,532] and ESC and other societies guideline recommendations.[93,131] In these studies, LV function and quality of life improved although overall efficacy rates of catheter ablations were less than in patients without HFrEF.[533]

In patients with HFrEF who develop recurrent symptomatic AF a rhythm-control strategy with AADs is not superior to a rate-control strategy.[534] However, a recent study in end-stage HF

patients AF ablation improved survival vs optimal medical therapy.[535] Also ablation are encouraged to be preferred as first line therapy whenever a component of tachycardia mediated cardiomyopathy is involved (e.g., lack of late gadolinium enhancement at cardiac magnetic resonance).[536] For acute and chronic rate control of AF, β-blockers are first line therapy followed by digoxin.[93,131,524] The Dig-trial, which predated current GDMT, primarily enrolled patients with NYHA Class II to III HF and showed that treatment with digoxin for 2 to 5 years had no effect on mortality but modestly reduced the combined risk of death and hospitalization.[537] For chronic rate control non-dihydropyridine CCBs are advised to be used with caution and dronedarone is discouraged to be administered to patients with decompensated HF.[104] Oral amiodarone can be used as added rate control prior to considering AV junction ablation for uncontrolled ventricular rates.[93,131,524]

For acute termination of AF in HFrEF, DC cardioversion is the safest and most effective besides rate control and spontaneous conversion.[538] i.v. amiodarone is safe but conversion rates are acutely limited and delayed.[158,538,539] i.v. ibutilide can be used with caution for conversion and is more effective in converting AFL than AF.[138,538] i.v. vernakalant is discouraged in Class III/IV HF patients and in patient with hypotension.[164] Class Ic agents are best avoided for conversion AF in this subset of patients.[52,93,131]

For acute rate control of AF with a rapid ventricular response, i.v. β-blockers and digoxin are appropriate front-line agents and i.v. non-dihydropyridine CCBs are advised to be used with caution.[93,131,524] i.v. amiodarone is an effective rate control agent short-term in the acute management.[93,131,539] Ivabradine in combination with ranolazine is being studied to determine efficacy in controlling the ventricular response in HFrEF patients[540]

Because of the safety profile and effectiveness in treating VA and reducing the risk of sudden death, β-blockers are often first-line antiarrhythmic therapy.[478] Amiodarone is the next AAD of choice for patients with VT or VF who are not otherwise candidates for an ICD.[397,478,528] This is based on the efficacy, minimal negative inotropic effects, and low proarrhythmic potential. Amiodarone, combined with a β-blocker, reduced frequent implantable cardioverter-defibrillator shocks in the OPTIC trial.[92] Sotalol has some efficacy in suppressing VA but it has significant proarrhythmic effects and has not been shown to improve survival. Sotalol appears to reduce the DFT and decreases ICD therapies.[120] Sotalol can lead to HF decompensation, and is discouraged in patients with an LVEF <20%.[478]

Preserved ejection fraction

HFpEF and AF often coexist and facilitate the occurrence and aggravate the prognosis of each other.[176,541,542] In symptomatic patients, it seems reasonable to start with rate control to optimize ventricular filling time and improve symptoms. The ESC guidelines recommend β-blockers, diltiazem, verapamil, and digoxin for rate control (<100-110 bpm) in patients with HFpEF; amiodarone may be appropriate only in the acute setting.[93] Digoxin is associated with a neutral effect on mortality and a lower rate of hospital admissions and although the benefit of β-blockers therapy in reducing mortality in AF patients with HFrEF has been questioned,[176] some real-world studies supporting an improved prognosis.[541] Pharmacological cardioversion using i.v. amiodarone may be attempted if haemodynamic instability or worsening of HF.

A rhythm control strategy is challenging in patients with HFpEF, often with advanced age and other comorbidities that may influence the success and risk of adverse events. Drugs of choice are amiodarone, dofetilide, dronedarone and sotalol.[93] In a post-hoc analysis of RACE 3 trial, recruiting patients with early persistent AF and mild-to-moderate stable HFpEF and HFrEF, AAD treatment was effective in nearly half of the patients at 1 year.[542] Maintenance of SR was significantly better with amiodarone (58%) compared with flecainide (32%) and sotalol/dronedarone (23%). In an observational study, rhythm control (mainly amiodarone) showed a lower 1-year all-cause death over rate control in older patients (≥65 years) with HFpEF[543] and in a retrospective study, maintenance of SR was associated with a lower risk of composite of cardiovascular death or hospitalization for HF in patients with HFpEF and AF.[544] Furthermore, in a recent systematic review comparing rhythm and rate control treatment strategies in patients with HFpEF and AF, rhythm control was associated with a 15% lower mortality, as compared to rate control, but no differences were found between rhythm and rate controls for HF admission rates, stroke/transient ischaemic attack, and cardiovascular mortality.[545] Additionally, in a pooled analysis of AFFIRM and AF-CHF trials, amiodarone's efficacy in maintaining SR and reducing the burden of AF was similar in the presence or absence of severe LV dysfunction.[546] In the 2024 ESC AF guidelines, dronedarone is recommended for long-term rhythm control in AF patients with HFpEF or mildly reduced but stable LV function.[93] Therefore, when carefully instituted, rhythm control a viable and relatively safe option in patients with HFpEF and AF.[542] Although mineralocorticoid receptor antagonists are advised for patients with HFpEF,[524] spironolactone does not reduce the risk of new-onset AF or AF recurrence in patients with HFpEF.[547]

Amiodarone is effective in suppressing VA and improving LV function but does not reduce the incidence of sudden death or prolong survival among patients with HFrEF, except for a trend toward reduced mortality among those with non-ischaemic cardiomyopathy. However, its effects in patients with HFpEF remain uncertain.[526]

Recently, the EMPEROR-Preserved trial, where empagliflozin reduced the combined risk of cardiovascular death or hospitalization for HF in patients with HFpEF regardless of the presence or absence of type 2 diabetes (T2DM). In a meta-analysis, SGLT2i are associated with significantly reduced risks of incident atrial arrhythmias and SCD in patients with T2DM with or without HF,[548] but was not with an overall lower risk of SCD or VAs in patients with T2DM and/or HF and/or chronic kidney disease.[549] Prospective trials are warranted to confirm the antiarrhythmic effect of SGLT2i is and whether this is a Class or drug-specific effect.

Although it seems clear that weight loss is associated with less risk of AF recurrence and that the pleotropic effects such as anti-inflammatory effects) of the metabolic weight loss reducing agents, for example the GLP receptor agonists, are potentially advantageous, their value for AF rhythm control has yet to be established, but seem likely.

Cardiomyopathies

Limited data exist regarding the use of AADs in cardiomyopathies other than HCM and arrhythmogenic right ventricular cardiomyopathy (ARVC). Therefore, the principles for AAD use in these cases must align with those for other forms of SHD. Class I AADs are generally to be avoided, and the preferred choices are typically β-blockers, sotalol, and amiodarone.[45]

Hypertrophic cardiomyopathy

β-blockers are commonly used as first-line therapy in HCM, providing dual benefits of symptom reduction and decreased risk of VA.[462]

Disopyramide (Class I AAD) may be appropriate in specific situations due to its potential to reduce left ventricular outflow tract obstruction and alleviate symptoms. However, no demonstrated prognostic benefits exist, and its use requires close monitoring.

Amiodarone is reserved for refractory cases or when other medications are not well-tolerated. Long-term use is not convincingly associated with sudden death reduction and is carefully weighed against potential side effects.

Arrhythmogenic right ventricular cardiomyopathy

β-blockers are the first-line therapy for VA in ARVC.[45] Other AADs, such as flecainide, sotalol, amiodarone), demonstrated VT suppression in small observational studies, but their ability to prevent VT recurrences at follow-up is either minimal or not established.[550,551] A small study showed some benefit in combining flecainide with β-blockers or sotalol.[436]

Renal and liver failure

Most AADs are bio-transformed in the liver via CYP enzymes, mainly CYP3A4 and CYP2D6 and their exposure and half-life increase/decrease when co-administered with CYP inhibitors/inducers, respectively, leading to important drug-drug interactions as discussed above[154,552,553] (**Tables 14 and 15**). Additionally, some AADs (**Table S3**) are bio transformed in the liver into active metabolites with similar or different electrophysiological effects from those of the parent compound (N-acetyl-procainamide is a Class III drug; 5-hydroxypropafenone lacks β-adrenergic blocking effects).

Hepatic drug clearance depends on the expression/activity of drug metabolizing enzymes, hepatic blood flow and drug protein binding.[520,521,554] Drugs with high hepatic clearance (diltiazem, lidocaine, metoprolol, propranolol, verapamil) are rapidly metabolized and the rate of drug loss is determined by the hepatic blood flow. In patients with hepatic impairment or decreased hepatic blood flow (elderly, cirrhosis, HF, shock, MI or treated with β-blockers) drug biotransformation is inhibited, so that exposure and half-life of the parent compound significantly increase, while the formation of active metabolites decreases.

Patients vary in their responses to drug therapy, and some of that variability is genetically determined.[254,521,555] CYP2D6 metabolism is under genetic control and plasma levels, half-life and the risk of adverse effects of CYP2C6 substrates increase in poor metabolizers (~7% of Caucasians), while a decrease in drug efficacy can be observed in ultra-rapid metabolizers. Slow acetylators of procainamide develop more often and earlier drug-induced lupus syndrome than rapid acetylators. Thus, doses are advised to be reduced in carriers of poor/slow phenotypes.

Renal failure decreases the clearance and increases the exposure and the risks of adverse effects of renally-cleared drugs (digoxin, disopyramide, N-acetyl procainamide, dofetilide, flecainide, ibutilide, procainamide, and mainly sotalol). Thus, doses, clinical response and plasma levels of these drugs are advised to be carefully titrated in patients with kidney impairment. Some AADs

(amiodarone, dronedarone, quinidine) inhibit the P-gp required for renal excretion of digoxin, thereby increasing its plasma levels.[553] Therefore, in patients with impaired hepatic and/or renal function, both loading and maintenance doses of AADs are advised to be reduced, and ECG monitoring is advised to minimize the risk of adverse events, mainly proarrhythmia **(Table 18)**.

Table 19: Main pharmacokinetic characteristics of AADs with advice for their use in patients with renal or liver impairment (a more comprehensive review is provided in Table S3).

AAD Class	AAD	T max (h)	$t_{1/2}$ (h)	Excretion Renal / Hepatic (%)	Advice in Renal impairment	Advice in Hepatic impairment
0	Ivabradine	1	2 (11[a])	4/90	Avoid	Avoid
Ia	Quinidine	2-4	4-10	20/80[d]	DR (75%)	DR
	Procainamide	3	3.5-5	60/40	DR	DR
	Disopyramide	1-2.5 4-7[b]	6.5 (4-10)	55/45	DR	DR
Ib	Lidocaine	45-90 s	1.5-2	5/95		Close monitoring
	Mexiletine	2-4	10-14	10/90[d]	DR	DR
Ic	Flecainide	2-4	20 (7-22)	20/80[d]	DR	
	Propafenone	2-3.5	2-10 10-32[e]	1/99		DR
Id	Ranolazine	2-6	7	70/-	Avoid	Avoid
III	Amiodarone	3-8	25-100 days	<5/95		DR
	Dronedarone	3-6	25-30	16/84		Avoid
	Sotalol	2.5-4	10-20	90/10	Avoid	
	Dofetilide	2-4	7-13	80/20	Avoid	
	Ibutilide	1.5	6 (2-12)	7/82	Caution	Caution
	Vernakalant	1-5 min	1.5-3.5	7/93		
IIa	Acebutolol	1.3-3	3-4	40/60	DR if CrCl <50 mL/min	
	Bisoprolol	2-4	9-12	50/50	DR if CrCl <50 mL/min	
	Nadolol	2-4	20-24	75/25	DR if CrCl <50 mL/min	
	Atenolol	2-4	6-9	90/10	DR	
	Propranolol	2 (p.o.) 2-10 min (i.v.)	4-6.5 8-10[b]	10/90[c]		DR
	Metoprolol	1-2; 3-3.5[b]	3-5 (2.8 IR, 7.5	5/95		DR

			ER); 24[b]			
	Carvedilol	1-3	7-10	2/98		Avoid
	Esmolol	2-10 min	9 min	---		
IIb	Isoprenaline			80/20		
IIc	Atropine	2-4 min	2-4	60/40		
IId	Digoxin	3-6 (1-3 min i.v.)	35 (30-48)	75/25	DR done by CrCl and serum levels	
IIe	Adenosine	10-30 sec	< 20 seg	---		
IV	Diltiazem	30-60 min p.o. 3 min i.v.	iv: 2-5 IR: 4.5-12 ER: 12	10/90	Caution	DR
	Verapamil	1-2,5-11[b]	4-7	15/85	Caution	DR

In the table, light blue and ochre highlight AADs predominantly cleared (>70%) by hepatic and renal pathways, respectively. Advice with black and light brown backgrounds indicate AADs that are discouraged or require dose reduction in cases of hepatic or renal impairment. AAD, antiarrhythmic drug; CrCl, creatinine clearance; DR, dose reduction; H, hepatic; h, hours; i.v.; intravenous; Min: minutes; p.o., oral administration; R, renal; s, seconds, Tmax, time to peak plasma levels; $T_{1/2}$, drug half-life.

[a]*Effective half-life.*

[b]*Slow/extended release.*

[c]*Short-acting β-blockers can undergo significant first-pass liver metabolism. As a result, their serum levels may vary substantially for the same dose. These β-blockers are advised to be taken with food to improve absorption*

[d]*Drugs that alkalinize urine decrease renal excretion of the AAD*

[e]*<10% people are poor metabolizers of the AAD.*

Congenital heart disease

Arrhythmias are common and poorly tolerated in patients with congenital heart disease. Various factors (**Box 17**), including elevated single ventricle or systemic morphologic right ventricle, cyanosis, residual postsurgical obstructive lesions and scars, ventricular dysfunction, and pulmonary hypertension, contribute to the complexity of managing arrhythmias in this population.[556,557] Despite advancements in invasive therapies, AADs remain crucial for their management. However, there is limited evidence supporting AAD selection for this specific population, and advice is largely extrapolated from those for the general arrhythmia population. Nevertheless, there are specific considerations to be mindful of when dealing with individuals having congenital heart disease.

Channelopathies

LQTS and SQTS

LQTS is characterized by a prolonged QT, T wave changes and syncope, polymorphic VT, SCA and SCD mainly triggered by adrenergic activation in a structural normal heart. The annual rate

of SCD in asymptomatic patients with untreated LQTS has been estimated to be less than 0.5%, while it may increase to at around 5% in high-risk patients depending on ECG, symptoms and specific mutation. β-blockers are advised in all LQTS patients but may be omitted in asymptomatic low risk patients with side effects of the drugs. Non-selective β-blockers nadolol (oral dose per day 40–120 mg) and propranolol (oral dose per day 80–320 mg, slow release preferred) have been shown in observation studies to have higher efficacy in preventing VA.[558] Mexiletine (oral dose per day 5-10 mg/kg) may be used in addition to β-blockers in LQTS3 and LQTS2 highlighting the importance of genetic testing to direct pharmacological treatment. In LQTS2 and 3 mexiletine reduces the length of QT and the number of arrhythmic events. Not all mutations in sodium channel protein type 5 subunit alpha (SCN5A) or hERG, the genes responsible for LQTS3 and LQTS2, responds to mexiletine, therefore it is advised to perform oral testing to document that the QTc shortens 40ms or more in the outpatient clinic or at the department before prescribing chronic treatment.[559] Lifestyle advice includes avoidance of drugs (**Figure 19**) that prolongs QT (**Tables S8** and **S9**, also see www.crediblemeds.org/).

Box 17: Specific Factors for antiarrhythmic (AAD) selection in Patients with Congenital Heart Disease

1. Frequent sinus node dysfunction and AV conduction abnormalities:
   - → Examples: Post atriotomy, D-transposition of the great arteries

2. Accelerated AV conduction potentially leading to sudden death:
   - → Patients with atrial arrhythmias, especially in D-transposition of the great arteries.[536]

3. Frequent postsurgical or spontaneous myocardial scars and ventricular dysfunction:
   - → Risk of proarrhythmia or heart failure
   - → Particularly in Fallot or univentricular patients

4. Higher systemic venous pressures:
   - → May alter hepatic metabolism, potentially leading to AAD toxicity (e.g., amiodarone)[537]
   - → Relevant for Fontan patients and those with cyanotic conditions

5. Young age factors:
   - → Low body mass
   - → Child-bearing potential
   - → Need for long-duration AAD treatment

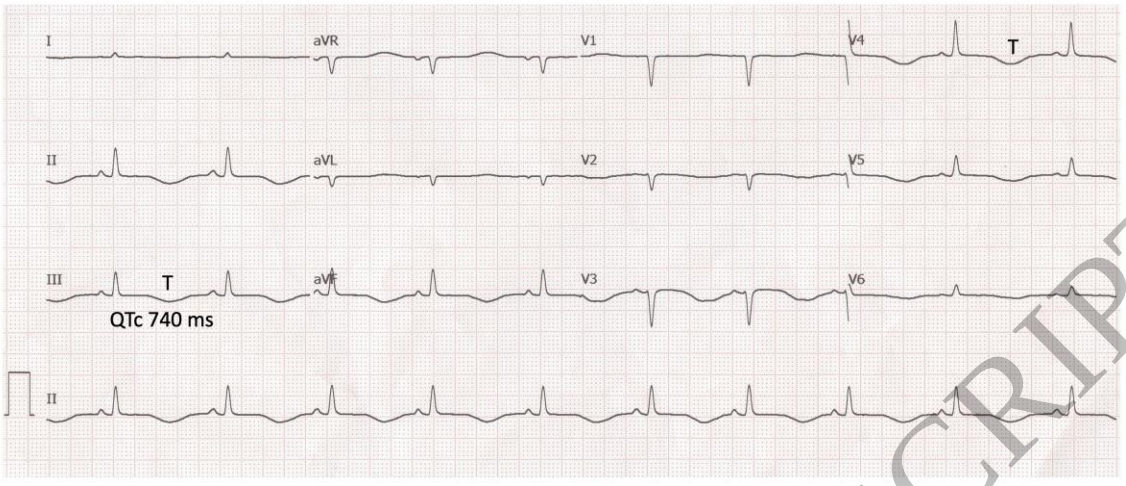


Figure 19: 12-lead ECGs of a 22-year-old woman with no prior heart disease presenting with ventricular fibrillation and pleomorphic ventricular arrhythmias. The patient was initially treated with oral quinidine and was later diagnosed with type II long QT syndrome.
The ECG demonstrates inverted T waves (T) across several leads and an extremely prolonged QT interval. This case underscores the proarrhythmic potential of quinidine in patients with underlying repolarization disorders.
The recordings were obtained at a speed of 25 mm/s and a sensitivity of 10 mm/mV.

SQTS is characterized by a very short QT, AF, and SCA in a structurally normal heart. Quinidine (oral dose per day 600–1600mg. Loading dose: 200 mg every 3 hours until effect) is the advised AAD, but is advised to be monitored for excessive QT prolongation and other side effects, and isoprenaline infusion (0.5–10 μg/min) is the drug of choice in ES.[560] Lifestyle advice includes avoidance of drugs that shorten QT (e.g. Nicorandil).

Brugada syndrome

The type 1 Brugada ECG pattern is characterized by ST elevation and T wave inversion in one right precordial ECG lead. The ECG changes may be spontaneous or induced by exposure to fever or Nav-blocking agents (**Figure 20**).[45,561] AAD strategy depends on whether the BrS patient is asymptomatic or symptomatic. To lower the risk of SCA lifestyle advice includes the avoidance of drugs that are known to block the Na^+ current (**Table S13**, also see www.Brugadadrugs.org). Quinidine (Oral dose per day 600–1600mg. Loading dose: 200 mg every 3 hours until effect) is the drug of choice in the prevention of VA and in treatment of ICD shocks, and ES.[562] In a Canadian report of IVF, BrS and ERS cases ICD shocks were reduced from 7.47 in 34 months to 0.86 in 44 months after quinidine initiation. In case of ES isoprenaline infusion (0.5–10 μg/min) is recommended by ESC guidelines.[563]

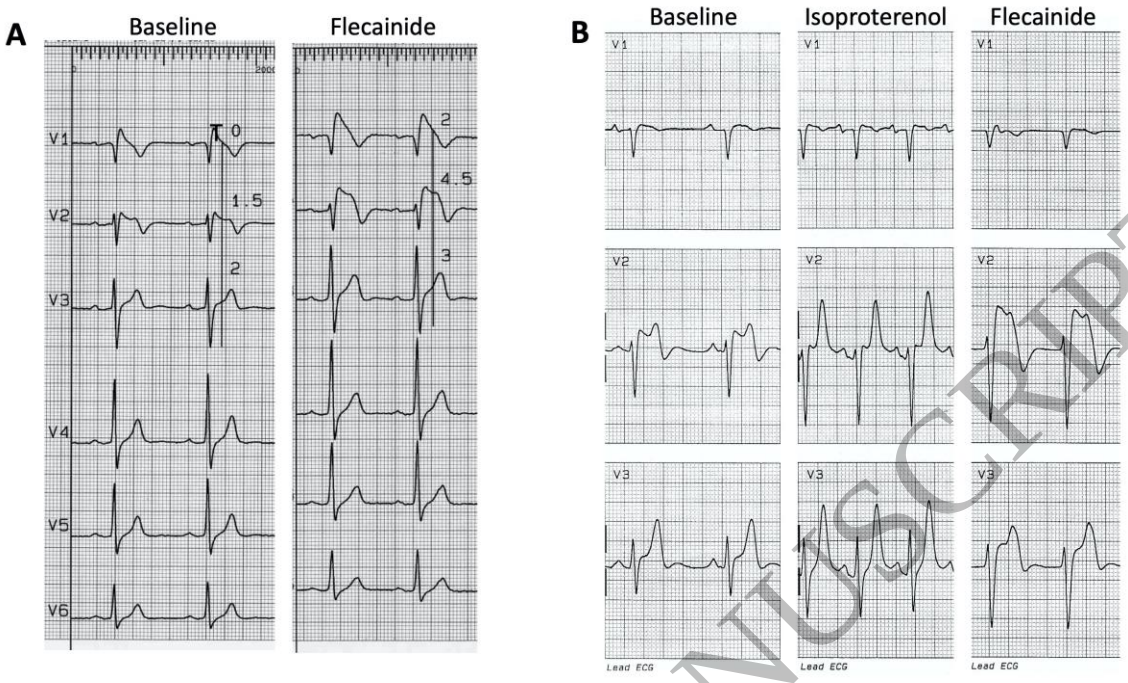


Figure 20: ECG tracings of leads V1 to V6 (Panel A) and V1 to V3 (Panel B) illustrating the dynamic changes in two patients with Brugada syndrome at baseline, during isoproterenol infusion, and following intravenous administration of flecainide (2 mg/kg).
Panel A: Baseline ECG shows mild ST-segment elevation (1.5 mm) in V2, measured at 80 ms from the J point. Following flecainide infusion, ST-segment elevation increases significantly to 4.5 mm. Panel B: In another patient, baseline ECG reveals ST elevation and T-wave inversion in V2. These abnormalities normalize during isoproterenol infusion but are markedly exaggerated following flecainide administration.
ECG recorded at a speed of 25 mm/s and a sensitivity of 10 mm/mV.

Catecholaminergic polymorphic VT

CPVT is a rare inherited heart disease characterized by catecholamine-induced bidirectional VT or PVT in a structural normal heart and absence of ischaemia or digitalis. CPVT patients often have normal resting ECG but the exercise stress test reveals the VA. Pharmacologic treatment is always initiated with β-blockers and nonselective β-blockers such as nadolol (Oral dose per day 40–120 mg) and propranolol (oral dose per day 80–320 mg, slow release preferred) are preferred. As noted in the individual AAD descriptions, short-acting β-blockers like propranolol, which are metabolized by the liver, can exhibit significant variability in serum levels due to first-pass metabolism, with up to a tenfold variation reported. If propranolol proves ineffective, switching to nadolol—a renally excreted β-blockers—may provide more consistent therapeutic effects. The effect of β-blockers is advised to be evaluated by a repeated exercise stress test on number of PVC, VA and max heart rate. Data convincingly suggests that flecainide (Oral dose per day 50-200 mg) significantly reduces the VA burden in CPVT patients and often desirable in addition to β-blockers when control of arrhythmias is incomplete.[50] In a multicentre study 22 patients out 29 patients treated with β-blockers and flecainide had either partial (n = 8) or complete (n = 14)

suppression of exercise-induced VA with flecainide. In selected patients who show intolerance to β-blockers therapy, pharmacological therapy with flecainide alone is an option.[564]

Early repolarisation syndrome

ERS is diagnosed in SCA patients with documented PVT or VF with structural normal heart, and the early repolarization pattern, J-point elevation ≥1 mm in 2 or more adjacent lateral and/or inferior ECG leads. Isoprenaline infusion (0.5–10μg/min) is effective in treatment of ES or recurrent ICD discharges, which also attenuated the J-wave amplitude.[565] AAD that block the I_{to} seems to prevent VA. A multicentre study found a decline in recurrent VF after initiation of quinidine (oral dose per day 600–1600 mg. Loading dose: 200 mg every 3 hours until effect) but not by other AAD.[566] Cilostazol and milrinone have in an experimental model been shown to reduce the recurrence of VF.[184]

The advised AADs for prevention of polymorphic ventricular arrhythmias in patients with channelopathies is summarized in **Figure 21**.

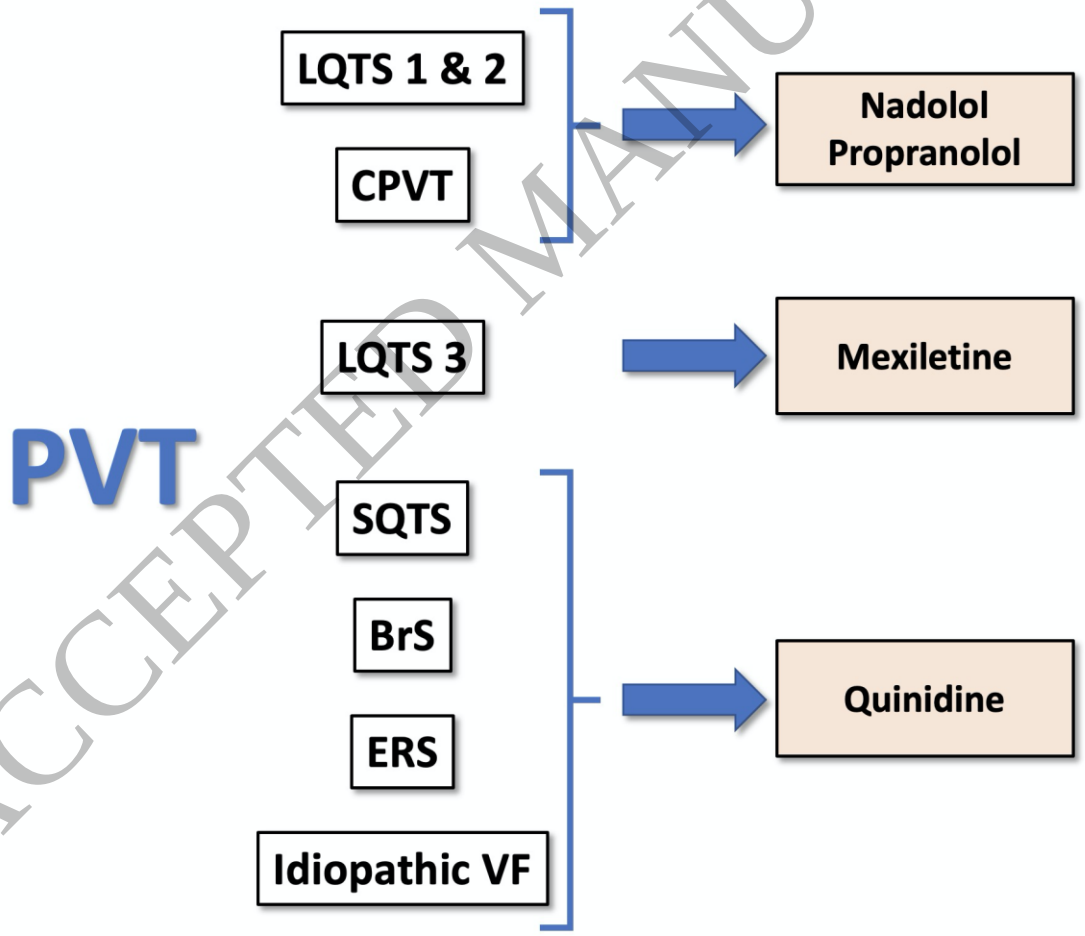


Figure 21: Schematic representation of the advised AADs for prevention of polymorphic ventricular arrhythmias.

The figure provides a general reference for selecting the most appropriate drug; however, the final choice is advised to be based on additional patient characteristics and conditions, as detailed in the various sections of this document. AADs, antiarrhythmic drugs; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; ERS, early repolarization syndrome; LQTS, long QT syndrome; PVT, polymorphic ventricular tachycardia; SQTS, short QT syndrome.

Anticoagulation

Anticoagulants and AADs are commonly prescribed concurrently for the same patient. Potential interactions within these medication classes involve both pharmacokinetic and pharmacodynamic aspects, potentially resulting in an intensified anticoagulation effect **(Table 20)**.[567]

Certain AADs hinder the degradation of warfarin through the CYP pathway, while specific DOACs experience reduced elimination via P-gp due to direct competition with some AADs (amiodarone, dronedarone, quinidine, verapamil, diltiazem and digoxin).[568,569] However, dronedarone plays a role in influencing both the degradation of warfarin and DOACs via the CYP pathway and the elimination of these anticoagulants via P-gp. In addition, verapamil and diltiazem contribute to decreased clearance of DOACs through competitive interactions with P-gp elimination but also exert a mild inhibitory effect on the CYP pathway, impacting the degradation of these drugs. Apixaban and rivaroxaban are most affected due to CYP3A4 metabolism, while dabigatran and edoxaban are primarily affected via P-gp inhibition.

It is noteworthy that CYP-mediated drug interactions are minimally affected by the timing of drug administration, while P-gp-mediated interactions can be mitigated by spacing the intake of the two drugs by at least 2 hours. Careful consideration of these factors is crucial for optimizing therapeutic outcomes and minimizing potential complications in patients receiving both anticoagulants and AADs.

Table 20: Main interactions of AADs with anticoagulants[a]

Class	AAD	Dabigatran	Apixaban	Edoxaban[570]	Rivaroxaban	Warfarin
I	**Quinidine** *(Inhibits CYP2D6 and P-gp)*	Caution. Avoid coadministration if CrCl <50 mL/min	Caution	Caution	Caution	Reduce the warfarin dose by 10–20%. Monitor INR
	Propafenone *(Inhibits CYP2C9 and CYP3A4)*	Safe	Safe	Safe	Safe	Reduce warfarin dose. Monitor INR
III	**Amiodarone** *(Inhibits CYP3A4 and P-gp)*	Caution if CrCl 30-50 mL/min	Safe	Caution if CrCl 15-50 mL/min	Caution if CrCl 15-50 mL/min	Reduce the warfarin dose by 40%, 35%, 30% and 25% if the amiodarone dose is 400, 300, 200 or 100 mg/d, respectively
	Dronedarone *(Inhibits CYP2C9, CYP3A4, and P-gp)*	Avoid	Caution	Reduce the edoxaban dose by 50% (to 30 mg/12 hrs)	Avoid	Monitor INR
IIB	**Digoxin** (*Potential displacement of warfarin from plasma protein binding sites)*	Safe	Safe	Safe	Safe	Monitor INR
IV	**Verapamil** *(Inhibits P-gp)*	Reduction the dabigatran dose (110 mg/12 hs)	Caution	Caution	Caution	Safe

Cells are shaded black to show contraindications (according to drug official label), light brown where dose reduction is advised, and blue where caution is advised, with potential dose reduction if additional risk factors are present. Agents with some interaction with anticoagulants are shown in bold. AAD, antiarrhythmic drug; CrCL, creatinine clearance; P-gp, P-glycoprotein.

[a]DOACs are substrates of P-glycoprotein (P-gp) and P-gp inhibitors can increase their plasma concentrations, leading to a heightened bleeding risk. Warfarin is metabolized primarily by CYP2C9, along with other cytochrome P450 enzymes. Inhibitors of these enzymes can significantly increase INR and the risk of bleeding. Unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs) are not metabolized by CYP enzymes or P-gp. As a result, they exhibit minimal pharmacokinetic interactions with AADs.

AAD and non-pharmacological antiarrhythmic therapies

AADs and pacemakers

PM are usually used in patients with symptomatic bradyarrhythmias, including sick sinus syndrome and AV block. PM are often implanted when an effective AAD causes significant negative chronotropic or dromotropic side effects. Antiarrhythmic medications may be advised in patients with PM when atrial or ventricular tachyarrhythmia need to be treated in patients who are not ablation candidates. AADs blocking Na^+ channels may increase pacing thresholds, especially at higher doses and lead to loss of capture (**Table 21**).[571–573] The increase in pacing thresholds is usually minimized by added safety margins programmed into atrial and ventricular PM. Drugs that slow sinus heart rate may cause a PM to pace more frequently and provocation of AV block may increase the frequency of ventricular pacing.

AADs in patients with ICDs

AADs are commonly used in ICD patients and to decrease delivered therapies, such as antitachycardia pacing, cardioversion and defibrillation.[92,572–575] Amiodarone plus β-blockers is effective for reducing ICD therapy, though amiodarone adverse effects need to be appreciated.[92] Sotalol is also effective, but less than amiodarone plus a β-blockers.[575] However, in one placebo-controlled trial sotalol reduced ICD therapies and is effective in reducing DFT similar other Class III agents.[120] In a small series, dofetilide reduced ICD therapies.[576] In placebo-controlled trials, azimilide (not commercially available) demonstrated an ability to decrease total all cause shocks and VT terminated by antitachycardia pacing[577] and ranolazine did not reduce the incidence of first VT or VF or death but had a 30% reduction (p=0,028) of ICD therapies, for recurrent VT or VF.[578] Although no ICD interactions studies exist with dronedarone, a sister compound, celivarone, had no benefit, at doses tested, to reduce ICD therapies compared to placebo.[579] Most AADs influence the DFT (**Table 20**) and since ICD defibrillation failure due to drug-induced high DFTs may result in SCD, it is important to check DFTs on AADs when an ICD is in place. **Table 21** and **Box 18** list the main influences of AADs on pacing threshold, ventricular DFT, and atrial cardioversion failure.[580]

Box 18: ICD – Antiarrhythmic Drug Interactions

- → Increase in pacing thresholds (see Table 21).
- → Alteration of DFT (see Table 21).
- → Drug-induced aggravation of bradycardia/AV block requiring more antibradycardia pacing.
- → May slow AFL leading to 1:1 conduction or pacing.
- → May slow VT rate and increase cycle length to above the tachycardia detection interval.
- → Alter VT sensing by slowing the dV/dT and increasing the QRS duration.
- → Development of drug-induced proarrhythmia and/or incessant VT requiring increased and/or rendering ICD therapy ineffective.

AFL, atrial flutter; AV, atrioventricular; ICD; implantable cardioverter-defibrillator; VT, ventricular tachycardia.

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

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

IV	Verapamil Diltiazem	0	+	

+: increases threshold, -: decreases threshold or risk of cardioversion failure. Light brown: clinical negative effect. Blue: clinical positive effect. AAD, antiarrhythmic drug.
[a]Inferred from atrial arrhythmia cardioversion failure.

AADs following ablation therapy

The number of randomized trials evaluating AADs after AF ablation is limited. One study, after 12-month follow-up, showed no significant difference 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.[581] The 5A study demonstrated that paroxysmal AF patients treated with AAD for 6 weeks after ablation had about a 50% reduction in AF recurrences than those treated with AV nodal blocking agents.[582,583] Further reports from 5A reported no benefit of an early rhythm suppression strategy with AADs in persistent AF after catheter ablation to decrease arrhythmia recurrence after the blanking period.[584] 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%).[585] 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. The POWDER-AF study suggested that a longer-lasting treatment with AAD might be a strategy to less AF recurrences during long-term follow-up.[586]

Not all studies demonstrated a benefit of AAD therapy in patients who underwent catheter ablation. A retrospective, non-randomized 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.[587] In a recent large retrospective German study,[588] the rates of AF recurrences, cardiovascular events and mortality did not differ between patients discharged with or without AAD after AF catheter ablation. Therefore, expert consensus statements on catheter and surgical ablation of AF,[589] gives a moderate level of advice and states that administration of AADs following AF catheter ablation is reasonable in selected patients to prevent early post-ablation AF recurrence.[1] Studies of specific antiarrhythmics post- ablation of AF are lacking and drug choice is based on AF guidelines and com-morbidities and prior efficacy and safety in each patient.[590]

Finally, a recent study examined rhythm-control strategies following index catheter ablation for AF in a large patient cohort (n=23,323).[1] Over a median follow-up of 1,165 days, AAD use post-ablation was prevalent (46.9%), with a notable increase among patients requiring repeat ablations (62.8%-92.3%). These findings underscore the widespread clinical practice of combining catheter ablation and AAD therapy to enhance rhythm control in AF patients.[590]

AADs: effects on DC cardioversion and defibrillation

AADs may alter the energy for cardioversion of atrial and ventricular tachyarrhythmias cardioversion energy requirement and the DFT **(Table 21)**. A study involving 57 patients with persistent AF assessed the energy levels required for successful electrical cardioversion among those receiving different classes of antiarrhythmic drugs. The findings show that patients on Class Ia or Class III antiarrhythmic drugs had a median cardioversion energy requirement of 100 joules, whereas those on Class Ic drugs required a median of 200 joules (P = 0.03).[591]

Importantly, the frequency of unsuccessful cardioversions did not differ significantly between these groups.

AF cannot always be converted to SR by transthoracic electrical cardioversion although this is less likely with biphasic shock waveforms.[538] Ibutilide, which lowers CER, has been used in refractory DC cardioversions of AF. One study showed an increased cardioversion success rate go from 72% to 100% after i.v. ibutilide (p<0.001). However, ibutilide caused sustained polymorphic VT in 2 of 64 patients in this trial, both of whom had an LVEF of 20% or less.[149] Ibutilide decreased the CER from 228±93 to 166±80 J, p<0.001. AADs have the benefit after AF cardioversion of reducing immediate and early recurrence of AF.[538]

AAD under development

After a hiatus for the last few years several new AADs have reached the stage of phase II or Phase III pre-approval studies and it is possible that one or more may become available within the next few years. This constitutes only a minority of the novel molecules with antiarrhythmic potential.[592] More of these may emerge from pre-clinical development in the near future.[593] Only the histone deacetylase 6 (HDAC6) inhibitor (see below) has a fundamentally new mechanism of action has emerged recently.

Seven new drugs/formulations deserve mention. Two exploit new methods of drug delivery to facilitate patient self-administration in the out-of-hospital setting. Two of these drugs predominantly inhibit ion channels which have not previously been considered AAD targets. Several of these drugs are multiple ion channel blockers although the balance of ion channel inhibition or the PK/PD properties of the formulations are sufficiently different to offer new therapeutic opportunities.

Etripamil

Etripamil is a novel, L-type CCB which has a rapid onset of action ($T_{max} \leq 7$ min) and is short-lasting being inactivated by blood esterases. Etripamil is administered using a nasal spray. It has been developed for patient self-administration for the termination of PSVT where the AV node is a critical component of the re-entry circuit, i.e., AVRT and AVNRT. It prolongs AV nodal conduction and increases the Wenckebach rate. The drug has been studied when given by medical staff in the EP laboratory for the termination of induced PSVT. It was shown that etripamil 70 mg was the most appropriate dose, terminating 90% of tachycardias without inducing significant hypotension.[594] Subsequently, several large studies, with substantial extensions were undertaken with patient self-administrations outside the medical setting.[595–597] The etripamil 30-minute conversion rates from the latest of these studies (RAPID – so named because of the rapidity of action of intranasal etripamil) was 64% (63/99) compared with and 31% (26/85) with placebo (HR: 2.62 CI:1.66-4.15; p<0.001. There were few adverse events other than local nasal irritation, etc.

Etripamil has also been evaluated for the treatment of AF presenting with a rapid ventricular rate > 110 beats per minute. In the ReVeRa study where the drug was given by medical staff to patients presenting at the emergency department with fast heart rates, the ventricular rate fell on

average by 30 beats per minute (placebo-adjusted). Overall, the effect lasted as long as 150 minutes and was associated with patient satisfaction and relief of symptoms.[598] This suggests that etripamil may be useful as a therapy to provide symptomatic relief quickly allowing transport to medical facilities for cardioversion or giving time for other patient self-administered therapies such as PITP oral antiarrhythmic or AV-nodal blockade to be effective.

Inhaled flecainide

Flecainide is an effective antiarrhythmic agent used orally to prevent recurrences of AF or to terminate the arrhythmia (PITP). AF termination following oral flecainide administration takes between 2 to 4 hours on average whereas with the highest dose of inhaled flecainide, 48% of AF episodes were terminated with a median time to conversion of 8 minutes. A small number of patients had post-conversion pauses, bradycardia or AFL with 1:1 AV conduction.[599] The conversion rate of recent-onset produced by orally inhaled flecainide acetate was 42.6% with a median time to conversion of 14.6 minutes in some studies.[600] A recent randomized clinical trial (RESTORE-1)[601] demonstrated that inhaled flecainide was significantly more effective than placebo in converting AF to sinus rhythm (30.8% vs. 0.0%; p = 0.04). The median time to conversion was 12.8 minutes. Safety data revealed no serious adverse events. Further studies are needed to optimize drug formulation and inhalation delivery to achieve higher plasma concentrations and improved AF conversion rates while maintaining a favourable safety profile.

SK channel inhibitors

AP30663 is a Small-conductance calcium-activated potassium channel (KCa2) inhibitor with mild off-target inhibition of I_{Kr}. KCa2 channels are upregulated in patients with AF and show increased Ca^{2+}-sensitivity which increases their open probability. AP30663 decreases the Ca^{2+}-sensitivity of KCa2 channels and markedly prolongs atrial refractoriness with only a mild increase of the QT. It seems unlikely to provoke VA since even in severely hypokalaemic guinea pig hearts, unlike dofetilide, it failed to induce VA.[602] In experimental models, it terminates vernakalant-resistant pacing-induced AF.[603] However, in healthy human volunteers placebo corrected dose-dependent QTc interval prolongation of up to 18 msec was found.[604] A phase 2 trial of AP30663 involved 63 patients with an episode of ongoing AF who were randomised to AP30663 or placebo. Conversion to SR at 90 minutes occurred much more frequently in those treated with the[605] active agent rather than placebo. There were no adverse safety signals except for QT prolongation. For this reason, plans are underway to commence a placebo-controlled randomised study with a second-generation molecule with greater specificity for the KCa2 channel and no off-target I_{Kr} inhibition.

Sulcardine (HBI-3000)

The multiple ion channel blocker ($I_{Na,P}$, $I_{Na,L}$, $I_{Ca,L}$, and I_{Kr}), like ranolazine, is being developed for the treatment of ventricular tachyarrhythmias and AF. Sulcardine induces dose-dependent increases in all cardiac ECG intervals except the J-point to T-wave peak which it shortens.[606] The drug suppresses dofetilide-induced after-depolarisations and is not expected to cause torsade.[607] Sulcardine is being evaluated in a dose-finding study for the termination of AF by i.v. infusion.

Doxapram

Doxapram is a TASK1 (TWIK-related acid-sensitive potassium channel 1) inhibitor which is already approved as a ventilatory stimulant. TASK-1 expression is increased in AF and contributes to the shortening of the atrial AP.[608,608] TASK-1 inhibitors increase the atrial refractory period and reduce AF burden in experimental animal models.[609] Since TASK-1 channels are found in atrial but not ventricular tissue, ventricular proarrhythmia is not expected. The DOCTOS (Doxapram Conversion TO Sinus rhythm trial is currently underway, testing the value of i.v. doxapram for cardioversion of AF.[610]

Bucindolol

Bucindolol is a nonspecific β-adrenoceptor blocker which also inhibits α1-adrenoceptors potentially causing vasodilation. In a substudy of the BEST trial new-onset AF was reduced by 75% in patients with the β1 389 arginine homozygotes (Arg/Arg), but there was no reduction in patients with the β1 389 Arg/Gly genotype who constituted approximately 50% of the substudy population.[611]

In the GENETIC AF (Genotype-Directed Comparative Effectiveness Trial of Bucindolol and Toprol-XL for the Prevention of Symptomatic AF/AFL in Patients With Heart Failure) trial, HFrEF patients with the ADR β1 Arg/Arg genotype were randomised to bucindolol or metoprolol. Bucindolol did increase the time to AF/AFL or all-cause mortality but trends were seen in subgroups with AF and HF diagnoses occurring <12 years previously and AF onset that did not precede HF by >2 years.[612] In a subgroup of patients implanted with a loop recorder AF burden was significantly reduced by 33% in those assigned to bucindolol, as were AF interventions, plasma levels of nor-adrenaline and N-terminal pro B-type natriuretic peptide.[613] Bradycardia occurred less often in in bucindolol than metoprolol-treated patients.[614]

Budiodarone

Budiodarone is a multichannel multiple ion channel blocker, like amiodarone but with a short elimination half-life. It was shown to be effective at reducing AF in patients with implanted PM who suffered from paroxysmal AF (PASCAL trial).[615] Recently, further interest has been shown in this molecule and more clinical studies are planned.

Histone deacetylase 6 (HDAC6) inhibitors

PKN605 is a potent and selective HDAC6 inhibitor being developed as an oral therapy for AF. In AF, cardiomyocyte refractoriness, measured by action potential duration at 90% repolarization (APD90), is shortened, promoting reentry circuits and facilitating AF initiation and maintenance. HDAC6 inhibition is expected to normalize APD90, reducing reentry substrates and restoring SR. As a cytosolic enzyme, HDAC6 regulates protein acetylation, affecting key cellular functions such as microtubule stability, intracellular transport, and protein degradation. One of its primary targets, α-tubulin, plays a crucial role in maintaining stable microtubules. Studies have shown that Tubastatin A, a selective HDAC6 inhibitor, increased acetylated α-tubulin levels in atrial cardiomyocytes and reduced AF in a beagle dog model. Preclinical studies of PKN605 demonstrated its ability to restore shortened APD90 in rabbit and human atrial tissue and reduce AF duration in a canine model.[616] In healthy volunteers, PKN605 was well-tolerated and led to increased circulating acetylated α-tubulin, confirming its pharmacodynamic activity.

These findings suggest that PKN605 has strong potential as an antiarrhythmic agent, offering a novel mechanism-based approach for maintaining SR in AF patients by targeting electrophysiological and structural remodelling processes.

Areas of uncertainty & gaps of knowledge

1. After the unanticipated adverse results of the CAST, SWORD and ANDROMEDA physicians became more reliant on interventional therapies such as catheter ablation and ICDs and pharmaceutical companies lost interest in AAD development. Paradoxically AAD use increased, but the hybrid value of an intervention plus AAD therapy has not been sufficiently researched.
2. There has almost been no recent development in AAD therapy for VA. This is urgently needed because interventional therapy such as anti-tachycardia pacing or cardioverter shock is uncomfortable and often highly symptomatic. This therapy repeatedly reminds the patients of their dependence on the treatment and the fragility of their health.
3. AAD targets have been single or multiple transmembrane ion channels and/or autonomic nervous system receptors. Novel drug targets are emerging (inflammatory, antifibrotic, electrophysiological, genetic) but progress has been slow in evaluating the antiarrhythmic effect of modulating these targets.
4. Many arrhythmia mechanisms have a genetic element. Genotyping is often employed clinically in monogenetic diseases and may facilitate effective antiarrhythmic therapy. However, this is far from being well-developed for polygenic disease. Such advances are needed.
5. There are many theoretical “drug-based” genetic approaches, such as gene delivery, micro ribonucleic acid regulation, modulation of noncoding RNA, etc. that are increasingly well understood at a preclinical level and meanwhile applied to small patient populations with genetic forms of diseases.
6. Precision medical approaches to match appropriate AAD therapy to match their underlying cause have not been well developed at an experimental or clinical level. The development of machine learning and augmented intelligence may support progress in this area.
7. In the coming years, precision medicine will become an indispensable component of clinical practice, and this will extend to AAD therapy. For example, combining clinical, genetic, imaging, and electrocardiographic analysis with the cellular response of tissue derived from the patient to specific therapies may allow the most effective and safe therapy to be prescribed. Research into this so-called tailored therapy is ongoing.
8. Most arrhythmias occur because of substrates and/or triggers resulting from “underlying comorbidities. Effective treatment of the comorbidities may prevent or reduce the likelihood of arrhythmias. This has often been studied, but accurate phenotyping of the underlying condition and adequate documentation of any resulting arrhythmia has usually been poor.
9. When an arrhythmia first presents in the clinical domain the pathophysiological substrate that supports the arrhythmia is usually already well-developed. However, the use of lay ECG devices, artificial intelligence analysis of ECGs during SR, genetic profiles, biomarkers, etc. are now available such that potential arrhythmias may be detected at a much earlier stage. Patients with atrial cardiomyopathy and early onset arrhythmias may

respond differently and better to AAD therapy. This is a new opportunity to manage arrhythmia effectively.

10. AAD choices are often made based on the underlying cardiac pathology. These choices have often been based on safety rather than efficacy. Concerns stemming from the CAST study have been widely extrapolated to restrict the use of Class Ic drugs when any form of SHD is present. Other drugs are advised against based on purely theoretical considerations, for example, Class III drugs for patients with LVH. These restrictions have limited research on AAD therapy for many forms of heart disease, such as valvular heart disease and HFpEF. New research have to address these underdeveloped areas.
11. Some arrhythmias are clinically "silent" and may not have serious clinical consequences until many years after their onset. Conventional clinical trials, lasting only several months or years, do not capture late adverse outcomes. Alternative designs, for example, based on clinical registries, are needed to properly address this unmet need.
12. AAD therapy is advised to be compared with alternative interventional strategies. The EP community has not found these trials easy to perform because of the reluctance of patients to be randomised away from "popular" interventional therapy or concern about possible hazards related to an interventional approach. For similar reasons, crossovers between assigned groups are also frequent. Physician bias towards a particular therapy may also play a negative role. One solution is to perform such comparisons earlier in the life cycle of the interventional therapy, but this is countered by the ongoing improvement of the intervention and the learning curve required to implement such therapy A needed solution is to improve the trial discipline to ensure this information to be more easily and quickly acquired.
13. Few studies have evaluated AAD combinations, though some, like amiodarone or dronedarone with ranolazine, show promise. Further research is needed on other potential combinations.
14. A poly-modular approach may be needed for effective management of arrhythmia. Examples include autonomic modulation, AAD therapy and ablation. Systematic studies are needed to ascertain the value of combinations of these therapies.
15. Initially, conversion of cardiac arrhythmias and suppression or delay of arrhythmia recurrence were accepted as suitable clinical and regulatory outcomes by which to evaluate AAD therapy. Now regulators regard such outcomes as "surrogates" for more serious outcomes such as mortality, stroke, MI, hospitalisation and impaired quality of life. Adequate assessment of these outcomes requires large and generally expensive clinical trials based on appropriate clinical models, in many instances not yet developed and difficult to fund.
16. Guidelines provide recommendations on antiarrhythmic therapy, which have changed little over the past decades. Nevertheless, AAD therapy which is prescribed is often not adherent to guideline recommendations. Future AAD use is likely to become more complicated and major educational efforts, or the implementation of automated prescription aids will be essential.
17. AADs have been classified for many years by various iterations of a scheme introduced by VW. The alternative classification known as the Sicilian Gambit was too complicated and was never used. As we begin to practice in the era of precision medicine many elements of the Sicilian Gambit will be valuable for prescribing better and safer therapy.

The use of the traditional VW classification will decline because of its simplicity and relative imprecision.

18. Surprisingly, despite their proven efficacy, not all AADs are available in every country, even within the European Union, due to national and international regulatory constraints and corporate marketing strategies. For example, vernakalant, cibenzoline and dofetilide have EMA approval, but the pharmaceutical companies choose not to supply the drug to all countries. Moricizine/ethmozine was widely approved but the drug company chose to discontinue its production. Ibutilide is a nationally approved therapy and is not widely used. Some drugs, such as antazoline and ranolazine are not generally approved as antiarrhythmic agents but have been re-purposed as antiarrhythmics. Some drugs such as bepridil, pilsicainide and cibenzoline are infrequently used but do have approval in some areas. Low sales volumes led to the withdrawal of some drugs such as quinidine, which is valuable for BrS in adult and paediatric patients, and mexiletine which can be used for the management of LQTS3, but professional complaints led to limited supplies being made available. This is a rather chaotic situation adding to the complexity of choosing and gaining access to antiarrhythmic therapy, which needs resolution.

Conclusions

In the face of waning attention on AADs due to the emergence of alternative therapies, the persistently high prevalence of cardiac arrhythmias, the synergistic benefits of AADs alongside other treatments, and their indispensability in addressing acute episodes underscore their continued importance. In this regard, AADs still fulfil an ABC Approach—serving as Appropriate therapy, Backup therapy, and Complementary therapy—in the management of cardiac arrhythmias.

This significance is further underscored by the ongoing development of new and promising AADs, despite the rigorous regulatory requirements that contribute to a protracted, intricate, and costly development process. These developments may, in turn, drive new or marginally used therapeutic approaches, such as individual self-administration for arrhythmia termination. Understanding how these drugs work is essential for proper selection, but potential hazardous interactions with other medications or patient conditions have to be taken into consideration.

This practical compendium offers a comprehensive review of the knowledge necessary for prescribing these agents—tools that are not only useful and potent but also carry the potential for severe adverse effects. Navigating this balance is paramount for healthcare professionals aiming to optimize the management of cardiac arrhythmias.

Tables of advice

Table of Advice 1: Definitions of supporting and strength of evidence

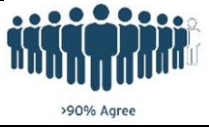
Type of supporting evidence	Strength of evidence	Icons
Published data[$]	>1 high quality RCT Meta-analysis or high quality RCT	
	High quality RCT >1 moderate quality RCT Meta-analysis or moderate quality RCT	
	High quality, large observational studies	
Expert opinion*#	Strong consensus > 90% of WG supports advice	>90% Agree
	Consensus >70% of WG supports advice	>70% Agree

[$]: The reference and trials for the published data that fulfil the criteria are indicated in the table of advice, if applicable

[*]: Expert opinion also considers: Randomized, nonrandomized, observational or registry studies with limitations of design or execution, case series, meta-analyses of such studies, physiological or mechanistic studies in human subjects.

[#]: For areas of uncertainty strong consensus/consensus that the topic is relevant and important to be addressed by future trials.

1 **Table of Advice 2: Main advice on AAD treatment.**

AAD SELECTION	Strength	Trials & references
Advice TO DO		
For rhythm control of AFL, selective flutter ablation is generally preferred, particularly for cavotricuspid isthmus dependent flutter, but if not possible or contraindicated, amiodarone or dronedarone have to be attempted.		ATHENA trial[99]
Vernakalant is the AAD of choice for AF termination lasting less than 7 days, provided the patient has no NYHA Class III/IV heart failure or other contraindications.		ACT &AVRO trials[617–620,158]
Type Ic are the AADs of choice for AF termination lasting more than 7 days, provided the patient has no SHD, heart failure or other contraindications.		621
May be appropriate TO DO		
Flecainide could be used as the first-line treatment, while ß-blockers are advised to be avoided in AT with a vagal pattern.		
Disopyramide may be particularly effective for vagally mediated AF and could be used as an alternative when other treatments fail or are contraindicated.		
Flecainide or propafenone are not contraindicated in patients with a high cardiovascular risk profile (e.g. accidental Agatston score < 400) in the absence of angina pectoris or with uncomplicated mild left ventricular hypertrophy (both in the absence of left ventricular scar tissue).		
Dronedarone can provide significant benefits beyond rhythm control, including pleiotropic effects such as mitigating acute coronary syndrome and reducing stroke risk.		
Flecainide, propafenone, or ranolazine can be used for AF termination with a PITP strategy in patients without underlying SND or other contraindications to AADs, provided there is prior demonstration of tolerance to the AAD or that the initial PITP usage is conducted under observation to verify effectiveness and ensure no adverse effects.		622
Sotalol is an alternative when ß-blockers fail for controlling PVCs in patients with SHD, while ranolazine serves as another viable option specifically for patients with ischemic heart disease.		
Advice NOT TO DO		
Dronedarone is advised to be avoided in patients taking dabigatran		

Ivabradine, ranolazine, sotalol, and dofetilide are advised to be avoided in patients with severe renal impairment		
Ivabradine, ranolazine, dronedarone, and carvedilol are advised to be avoided in patients with severe hepatic impairment		
Amiodarone and dronedarone are advised to be avoided during the pregnancy to avoid foetal harm		
AAD INITIATION AND FOLLOW-UP	**Strength**	**Trials & references**
Advice TO DO		
Patient education and counselling during the initiation and follow-up of AAD therapy is advised to cover the goals of treatment, recognition of symptoms and signs of potential adverse effects, and awareness of possible drug interactions.		
When initiating an AAD, it is crucial to optimize the management of concomitant diseases and assess baseline parameters, including ECG, echocardiography, haematology, renal and hepatic function, and electrolyte status		
When initiating amiodarone therapy, it is essential to assess baseline thyroid, pulmonary, and visual function, in addition to the standard tests required for AADs.		
All intravenous AADs are advised to be monitored with continuous ECG.		
Patients prescribed Class Ia AADs or the Class III agents dofetilide and sotalol, as well as those at high risk for proarrhythmia, are advised to be closely monitored in the hospital during the initiation of therapy.		
After initiating an oral Class IA, sotalol, or dofetilide AAD, it is advised to perform an ECG within 2 days of initiation to evaluate its effects on heart rhythm and the RR, PR, QRS, and QTc intervals.		88,623
After initiating an oral AAD, excluding Class Ia agents and the Class III agents dofetilide and sotalol, it is advised to perform an ECG shortly after initiation or dose adjustments (e.g., within 7 days) or at steady state (e.g., 1–3 months for amiodarone) to evaluate its effects on heart rhythm and the RR, PR, QRS, and QTc intervals.		
Adequate and regular follow-up, typically every 6 to 12 months, is advised to be scheduled in patients taking AADs to assess adherence to AAD therapy, to monitor for potential risk factors for		

proarrhythmia and to evaluate ECG, haematology, renal and hepatic function, and electrolyte status.		
Adequate and regular follow-up is advised to be scheduled to evaluate thyroid (6 months), hepatic (12 months), pulmonary (12 months), and visual function (12 months), in patients taking amiodarone addition to the standard tests required for AADs.		
May be appropriate TO DO		
Integrated nurse-driven care with experienced nurses supervised by the physician may substantially improve AAD management.		
An exercise test may be performed to rule out exercise-induced excessive QRS widening or VT in selected patients on Class Ic drugs.		
AADs, excluding Class Ia agents and the Class III agents dofetilide and sotalol, may generally be initiated in the outpatient setting with appropriate ECG monitoring, unless the patient has not previously been documented in SR, in which case underlying or associated sick sinus syndrome cannot be ruled out.		352
Class III sotalol may be initiated out-hospital unless specific conditions are present and if titration is slow with frequent ECG checks looking for QTc prolongation (≥500 ms) or HR (≤50 bpm) depression.		624
Patients with an ICD may be protected from the proarrhythmic effects of AADs, allowing for the initiation of AAD therapy in an outpatient setting.		
PROARRHYTHMIA/TOXICITY	**Strength**	**Trials & references**
Advice TO DO		
To enhance the safety of AAD use, patients are advised to be educated about warning symptoms and critical circumstances related to their treatment.		
AADs such as acebutolol, atenolol, nadolol, flecainide, quinidine, and digoxin are advised to be carefully monitored in patients with severe renal impairment to avoid toxicity and dose reductions may be appropriate.		
AADs such as metoprolol, propranolol, CCBs, propafenone, amiodarone, and lidocaine are advised to be carefully monitored in patients with severe hepatic impairment to avoid toxicity, and dose reductions may be appropriate.		
When proarrhythmia occurs, potential triggers such as ischaemia, heart failure, electrolyte disturbances, thyroid dysfunction, infection, drug interactions, and high or low plasma AAD concentrations are advised to be evaluated.		

AAD with significant effect on the SN are advised to be avoided when the latter is suspected.		
May be appropriate TO DO		
Patients on Class Ic drugs, despite add-on ß-blocker or verapamil/diltiazem, may avoid exercise during breakthrough episodes until AF has resolved or cardioversion has been performed.		625
Ventricular use-dependent effects may be observed during the infusion of Class Ic for tachycardia conversion or during exercise, while reverse use dependence is characteristic of Class III AADs, particularly after cardioversion.		
Regular rate control drugs may be discontinued shortly after initiating sotalol or amiodarone to prevent bradycardia in the event of conversion to SR.		
Greater caution is advised in women regarding use of sotalol, as women are at increased risk of developing TdP during-administration of this drug.		626
CNS side effects of Class Ic drugs may be tackled by changing to a slow release preparation.		
AAD COMBINATION OR SWICTHING	**Strength**	**Trials & references**
Advice TO DO		
Class Ic AADs are advised to be combined with ß-blockers or calcium channel blockers (CCBs) to enhance efficacy and complement their effects on the AV node, providing a treatment option for resistant cases of atrial arrhythmias and SVT that do not respond to monotherapy or other therapies.		
May be appropriate TO DO		
Serum drug concentrations and/or ECG markers are advised to be used to decide the washout process and initiation of a new AAD.		
AADs with similar half-life may be switched by starting the new AAD at usual dose/dosing intervals when a dose of the prior AAD was due		
The long lasting washout of some AADs (e.g., amiodarone) is so slow that the new AAD may have dosing up-titrated over time		
Ivabradine and ß-blockers may be combined to manage resistant cases of inappropriate sinus tachycardia that do not respond to monotherapy or other treatments.		

Quinidine maybe combined with Class IA, IB or IV AADs to increase efficacy and tolerance to manage resistant cases of atrial and VA that do not respond to monotherapy or other treatments.		
Flecainide and mexiletine maybe combined to enhance efficacy, providing a treatment option for resistant cases of VA that do not respond to monotherapy or other therapies.		
Combining sotalol with flecainide to achieve an amiodarone-like "Class Ic plus Class III effect" can be a rational approach in refractory cases with MAT or VA and right ventricular arrhythmogenic cardiomyopathy, provided there are no other significant SHDs.		627
Amiodarone maybe combined with Class I AADs or ß-blockers to enhance efficacy and complement their effects, providing a treatment option for resistant cases of atrial or VA that do not respond to monotherapy or other therapies.		
Dronedarone and ranolazine maybe combined to enhance efficacy and minimize side effects in patients with AF that do not respond to monotherapy or other therapies.		HARMONY trial[76]
Beta-blockers may be combined with AADs other than sotalol to enhance their efficacy.		
CCB and digoxin maybe combined to complement their effects on the AV node and achieve rate control in patients with arial arrhythmias that do not respond to monotherapy or other therapies.		
Advice NOT TO DO		
Combination of Class Ia and III AADs are advised to be avoided at their conventional doses due to the increased TdP risk.		
Combination of dofetilide and CCBs are advised to be avoided due to the increased risk of TdP		
CCBs are advised to not be combined at their usual dose with ß-blockers or disopyramide due to potential depression of the SN, AV conduction and cardiac contractility		
Ranolazine is advised to not be combined with other Class I AADs due to the potential for central nervous system effects, constipation, or an increased risk of TdP		
Combination of dronedarone and digoxin is advised to be avoided due to the increased risk of digitalis toxicity and death.		PALLAS trial[105]
AREAS OF UNCERTAINTY		

The extent to which the findings of the CAST study is advised to be applied to restrict the use of Class Ic drugs in patients with mild or non-ischemic SHD remains uncertain, posing a challenge in clinical decision-making.		
The advice against using Class III drugs such as sotalol and dofetilide in patients with LVH is based on theoretical considerations rather than robust clinical evidence, leaving some uncertainty in decision-making for this population.		
The clinical significance of drug-induced QT prolongation in the absence of TdP remains unclear, complicating decisions about whether to discontinue or adjust therapy.		
The safety and efficacy of amiodarone for long-term rhythm control in younger patients are advised to be weighed against its potential for cumulative toxicity, with no clear consensus on the best alternative.		
While dronedarone is contraindicated in patients with HFrEF, its safety in those with mildly reduced LVEF remains uncertain due to limited data.		
The effectiveness of upstream therapies, such as renin-angiotensin system inhibitors, in reducing the need for AADs in AF management remains an area of ongoing investigation.		

AAD, antiarrhythmic drug; AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; AV, atrioventricular; CCB, calcium channel blockers; HF, heart failure; HFpEF/HFmrEF/HFrEF, HF with preserved/mildly reduced/reduced left ventricle ejection fraction; ICD; implantable cardioverter-defibrillator; LV, left ventricle; LVEF, LV ejection fraction; LVH, LV hypertrophy; NYHA, New York Heart Association functional class; PITP, pill-in-the-pocket; SHD, structural heart disease; SN, sinus node; SND, SN dysfunction; SNRT, sinus node reentrant tachycardia; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

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CBL has received fees and honoraria for lectures, education, and scientific advice from Abbott, Biosense-Webster, Bayer, Sanofi, Organon, Philips, Medtronic, Boston Sci, Cathprint.

DD has received fees and honoraria for lectures and education from Daiichi Sankyo.

GB reports small speaker fees from Bayer, Boehringer Ingelheim, Boston, Daiichi Sankyo, Janssen and Sanofi outside of the submitted work. He is also the Principal Investigator of the ARISTOTELES project (Applying ARtificial Intelligence to define clinical trajectorieS for personalized predicTiOn and early deTEction of comorbidity and muLtimorbidity pattErnS) that received funding from the European Union within the Horizon 2020 research and innovation programme (Grant N. 101080189).

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JAR reports being an investigator for Sanofi, InCarda Therapeutics, Johnson & Johnson, and Amarin; and as a consultant for Sanofi and Acesion.

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MMC: no declared conflict of interest.

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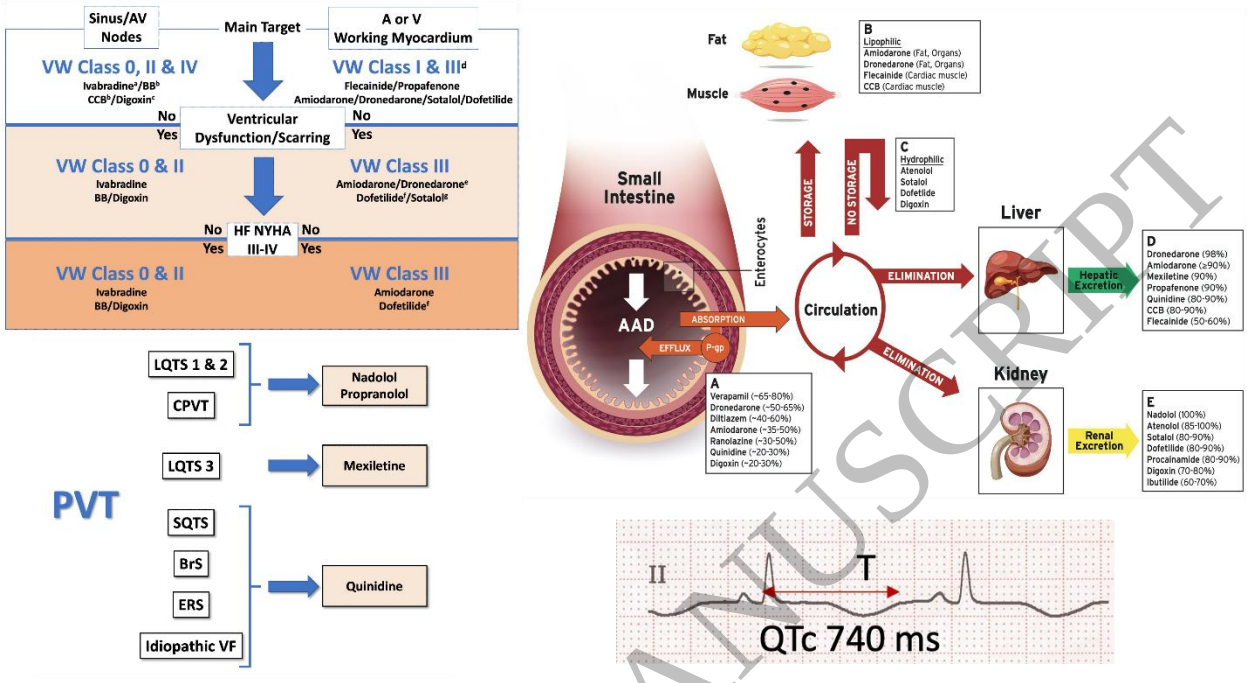

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3 Graphical Abstract