Chapter 2
Class I Antiarrhythmic Drugs: Na^+ Channel Blockers

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Abbreviations

AAD	Antiarrhythmic drug
AF	Atrial fibrillation
AP	Action potential
APD	Action potential duration
ATP	Adenosine triphosphate
AVNRT	Atrioventricular nodal reentrant tachycardia
AVRT	Atrioventricular reentrant tachycardia
CAD	Coronary artery disease
CHF	Congestive heart failure
CPVT	Catecholaminergic polymorphic ventricular tachycardia

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DAD/EAD	Delayed/early afterdepolarization
ECG	Electrocardiogram
ERP	Effective refractory period
ICD	Implantable cardioverter-defibrillator
LQT3	Long QT 3 (syndrome)
LV	Left ventricular
LVH	Left ventricular hypertrophy
SCD	Sudden cardiac death
TdP	Torsades de Pointes
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Glossary of Abbreviations

I_{Na}	Sodium current
$I_{Na\text{-}early}$	Early sodium current
$I_{Na\text{-}late}$	Late sodium current
$I_{Na/K}$	Na/K pump current
$I_{Na/Ca}$	Na/Ca exchanger current
I_{to1}	Voltage-activated Ca^{2+} outward current
I_{to2}	Ca^{2+} activated transient outward current
I_{Kr}	Rapid component of delayed rectifier potassium current
I_{Kur}	Ultra-rapid component of delayed rectifier current
I_{Ks}	Slow component of delayed rectifier current
I_{K1}	Inward rectifier potassium current

Introduction

For several decades, sodium channel blockers, the so-called "class I antiarrhythmic drugs (AADs)", have been the frontline of antiarrhythmic therapy for the management of a variety of cardiac arrhythmias [1, 2]. Among many others, quinidine, procainamide, and lidocaine have been in use for several decades. Progress in understanding the mechanisms of arrhythmias on one hand, and understanding the mechanisms of action of AADs from the whole heart to the single ion channels on the other hand, has improved our management of arrhythmias.

In this chapter we review the old and new mechanisms of sodium channel blockers in their broad spectrum from basic to clinical, with focus on the novel indications of theses agents. We use "sodium current" and "I_{Na}" interchangeably.

There have been several classifications of AADs, based on their direct effect on normal and abnormal cardiac electrical systems as well as different arrhythmia mechanisms. Although each AAD has its own distinct characteristics, classifications are generally appealing for clinicians and teaching purposes.

Vaughan Williams

The Vaughan Williams classification has been used widely for several decades and is based on the effect(s) of AADs or groups of agents on action potential duration (APD) and respective ionic channels [3–5].

Class I AADs constitute agents that exclusively or predominantly block the fast sodium current, although many of them may exhibit other ion channel blocking effects such as quinidine's effect on K^+ channels. Table 2.1 illustrates the modified Vaughan Williams classification.

Sicilian Gambit

This classification is based on individual agents, which may have multiple effects.

The concept of AAD-specific arrhythmia mechanisms in relation to ion channels are well discussed in the Sicilian Gambit (Table 2.2) [6].

The electrophysiological effect of AADs may be investigated at several levels:

1. Cell membrane
2. Ion currents and ion channels
3. Gap junctions
4. Receptors
5. Pumps
6. The whole intact-heart

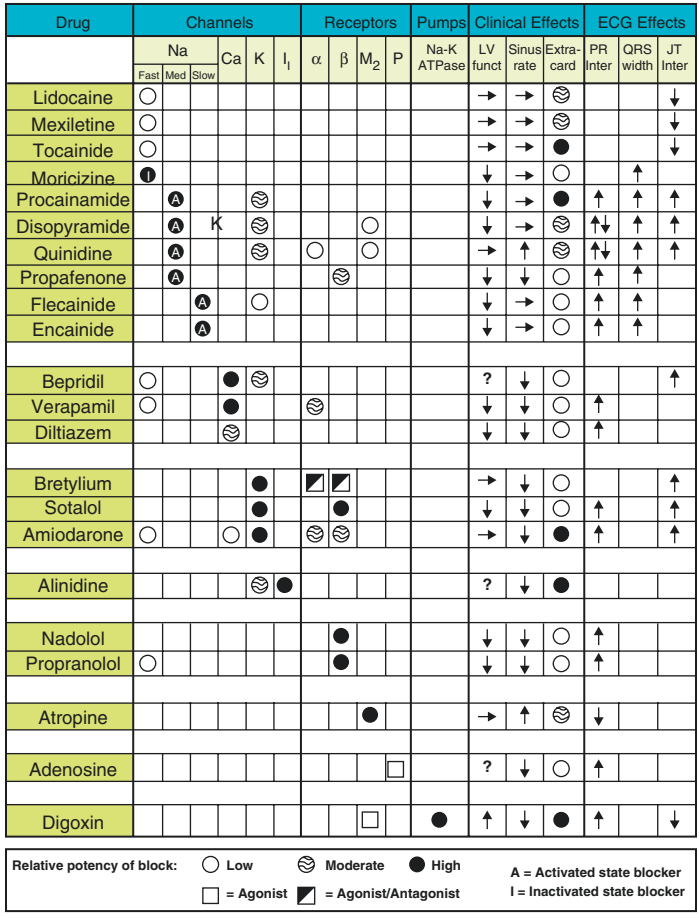
Table 2.1 Vaughan Williams classification of antiarrhythmic drugs [5]

	Class I	Class II	Class III	Class IV
	Drugs with direct membrane action (Na^+ channel blockade)	**Sympatholytic drugs**	**Drugs that prolong repolarization**	**Calcium channel-blocking effects**
Ia	Moderate depressant effect on phase 0 (Suppresses excitability) Slow conduction Prolong repolarization *Effect on phase 0 of APD*: Intermediate *Effect on APD*: Marked prolongation Eg: Quinidine, procainamide, dysopyramide	Eg: metoprolol, nadolol, and several other beta-blockers	Eg: amiodarone, sotalol, dronedarone, dofetilide (Predominantly blocks K^+ channels but may exert weak multichannel blocking effect)	Eg: verapmil, dilitazem

Ib	Little effect on phase 0 in normal tissue Depress phase 0 in abnormal fibers Shorten repolarization *Effect on phase 0 of APD*: Little effect *Effect on APD*: Little effect or may shorten Eg: Lidocaine, mexiletine, phenytoin
Ic	Markedly depress phase 0 Markedly slow conduction Slight effect on repolarization *Effect on phase 0 of APD*: Marked slowing *Effect on APD*: Little effect Eg: propafenone, flecainide

Abbreviations: *APD* action potential duration, *Eg* example

Table 2.2 Sicilian Gambit chart for AADs



This table is based on the mechanisms of antiarrhythmics on ion channels and arrhythmia mechanisms. Abbreviations: *card* cardiac, *funct* function, *inter* interval. With permission from Circulation 1991;84:1831–1851 [6]

Action Potential

The registration of a sudden movement of sodium ions from outside the cell membrane (depolarization), into it (inward current), and followed by the slow movement of K^+ ions from inside the cell membrane (repolarization) to the extracellular space (outward current) [7–9]. Fig. 2.1 shows the atrial and ventricular AP with its five phases and respective ion channels.

The Cardiac Action Potential: Role of I_{Na} Current

Figure 2.1 shows the typical atrial and ventricular action potential duration (APD) as well as the respective ion currents and genes that control the ion channels. The atrial and ventricular myocardial APD as well as Purkinje cells APD are somewhat similar and distinctive from those of the sino-atrial and A-V nodal cells.

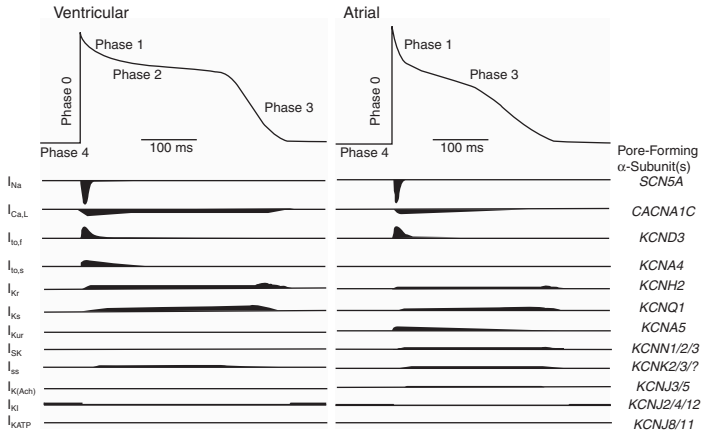


FIGURE 2.1 Illustrates atrial and ventricular AP and its respective ion channels involving different phases of APD and respective genes. With permission from Card Electrophysiol Clin 8 (2016) 257–273 [8]

The sinoatrial node has a fast phase 4 that produces spontaneous depolarization. The depolarizing current of the sinoatrial and A-V node is Ca^{2+} current and L-type Ca^{2+} (I_{Ca}) channel are discussed elsewhere in this book. Likewise, potassium ions and channels are discussed in another section.

Sodium channels are present in sinoatrial node, but for the most part, are inactivated under physiological (normal) conditions.

Ion Channels

Channels are segments of the cell membrane that allow movement of ions across the cell membrane whether active or passive.

Ion channels are from a group of complex glycoproteins that make pores and permit the transport of cardiac ions, i.e. sodium, potassium, calcium, and chloride across the cell membrane (either inward or outward the cell). This transport takes place when the channel changes from a "closed state" to an "open state". Opening and closing ion channels are governed by voltage and voltage-operated gates, simplified as "voltage-gated" [10]. Diffusion through these protein channels is called "gating" [11]. These channels have two important features:

1. Selective permeability to certain molecules and ions such as selective Na^+ channel and selective K^+ channels.
2. Many channels can be opened (open state) or closed (closed state) under certain conditions such as chemical or electrical charges, concentrations, etc. [12]

The anatomy and function of these ion channels determine the cardiac APD [13]. The ion transport therefore depends on several factors such as the electrical and concentration gradient of a specific ion across the membrane or other triggers.

These channels further operate at different states such as active transport, inactive transport, open state, and closed state [11, 14].

Cardiac Sodium Current (I_{Na}) and Channel

Voltage-gated sodium channels made of transmembrane proteins that allow the sodium ion current to travel through these channels are responsible for the rapid upstroke (phase 0) of the cardiac AP (depolarization). Sodium current is an inward current and is the major current that is present in atria, myocardial, and Purkinje cells and is responsible for depolarization, i.e. phase zero of AP (Fig. 2.1). Therefore, the sodium current is responsible for the rapid impulse conduction through atrial, His-Purkinje system, and ventricular myocardium. The sodium channel and current is controlled with multiple genes; however, the most dominant one is SCN5A. Therefore, the sodium channels are the main molecular substrate that are involved in both inherited and acquired disorders of channelopathies. The sodium current in the atria, ventricular, myocardial, and Purkinje cells are voltage dependent activated channels at −75–90 mV [14]. The main voltage-gated sodium channel that is expressed in human cardiac myocytes is Na_v 1.5, which is encoded by the SCN5A gene [15–19]. Transport of I_{Na} through the channels is determined by α-subunits (i.e. proteins that make the channel). The α-subunits are comprised of four serially linked homologous domains, which make the ion channels pure (Fig. 2.2) [20, 21]. These proteins are encoded and regulated by several genes, the most dominant one being SCN5A. The cardiac sodium channel gene (SCN5A) resides on the short arm of chromosome 3 (3P21) [20]. The most common subunit that controls the sodium current is α-subunit that consists of four homogenous domains as shown in Fig. 2.2 [7, 20, 22]. At the same time, there exist pathways under regulation of ion channel expression, i.e. up or down regulation of certain genes [23, 24].

Most of the sodium current transport occurs early during phase zero (phase 0) of AP ($I_{Na\text{-}early}$ or I_{Na} fast). There remains a small amount of I_{Na} that causes the channel to remain open during phase 2 and 3 of AP called Late $I_{Na,}$ $I_{Na\text{-}late}$ or I_{Na} slow. Although $I_{Na\text{-}late}$ has little contribution under normal (healthy) conditions, it plays an important role under pathological (diseased) conditions (see section under $I_{Na\text{-}late}$ current) [25, 26].

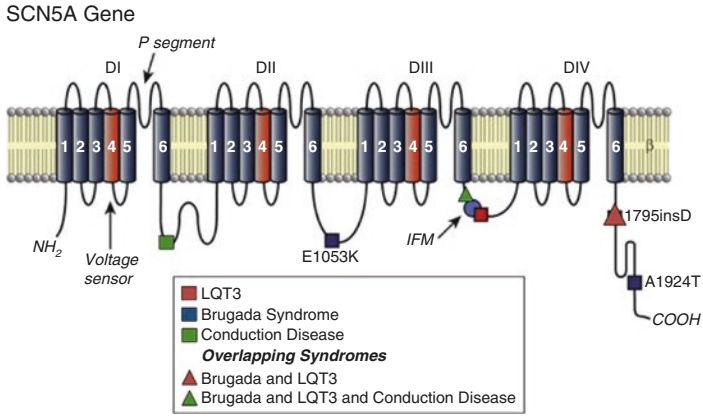


FIGURE 2.2 Illustrates the four domains of the sodium channel and SCN5A gene that are involved in various mutations and syndromes. Modified from: Hund T, Mohler PJ. Biophysics of Normal and Abnormal Cardiac Sodium Channel Function. In: Cardiac Electrophysiology: From Cell to Bedside (2014) Elsevier, Philadelphia, USA. With permission [20]

Sodium channels open fast in response to the onset of depolarization phase 0. When the voltage reaches −70 to −60 mV (the threshold of activation), the sodium ions move very rapidly into the cells. At the same time, depolarization triggers fast inactivation and sodium channels close.

The Biology of Cardiac Sodium Channels

1. Biophysical properties of the voltage-gated sodium currents [27].
2. *Biochemical (proteins that make the channel)*: The effects of different classes of AADs have been investigated using the patch clamp (single channel) technique over the past two decades or more on the Na^+ channels and its modulators [28]. Channel proteins and their genetic structures have diverse properties that are divided into two main subunits.

(a) *Alpha (α) subunits*: The α-subunit is a dominant one and determines the formation of ion pores and is sufficient to produce a normally functional sodium channel.

So far, nine sodium channel protein structures that make the α-subunits have been identified; Na V_1.1 to Na V_1.9 [29–31]. Relevant to cardiac sodium channels are Na_v I.5 and its gene SCN5A that is involved in some of the cardiac channelopathies and related syndromes such as Brugada syndrome, Long QT 3 (LQT3) syndrome, idiopathic VF, and J-wave syndrome that are discussed later in this chapter (Fig. 2.3).

Voltage-Gated Sodium Channels

- *Use-dependence Effect of Sodium Blocking Agents*: Most sodium channel blocking agents affect membrane excitability and conduction velocity in a use-dependent fashion.

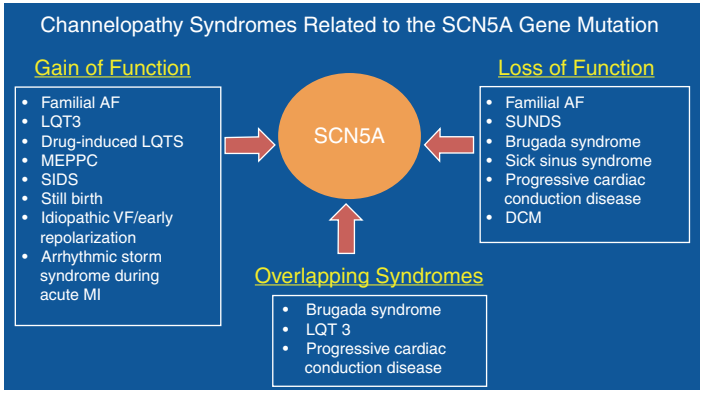


Figure 2.3 Shows the SCN5A mutations related to different channelopathy syndromes. Abbreviations: *AF* atrial fibrillation, *DCM* dilated cardiomyopathy, *LQTS* long QT syndrome, *MEPPC* multifocal ectopic Purkinje-related premature contractions, *MI* myocardial infarction, *SIDS* sudden infant death syndrome, *SUNDS* sudden unexplained nocturnal death syndrome

- *Frequency Dependence*: Most class I AADs demonstrate frequency-dependence, i.e. the effect is more pronounced at higher rates. However, there exists some differences between the three classes of sodium channel blockers in their frequency-response effect [32].
- *Effect of Sodium Blocking Agents*: Characterized by increase in refractoriness of the cardiac tissue at fast rates for sodium channel blockers (class I), whereas slower heart rates (lower frequency rates) are mostly observed in class III agents such as Sotalol [33].

Late Na^+ Current

The sodium current is composed of two components:

1. Peak or early sodium current ($I_{Na\text{-}early}$) occurs during the phase zero of AP and is a rapid inward current that takes approximately 1–2 msec.
2. The late sodium current ($I_{Na\text{-}late}$) takes place in phase 2 and early phase 3 of AP and lasts approximately 100–300 msec. An increase in the $I_{Na\text{-}late}$ prolongs APD, and blockade of the $I_{Na\text{-}late}$ shortens APD. Most I_{Na} blockers exhibit both early and late I_{Na} blocking effects, however, at different magnitudes. Ranolazine, a late sodium channel blocker, exhibits 5–9 times higher late than early Na^+ blocking effects. $I_{Na\text{-}late}$ channel blockers dissociate from the channel faster than $I_{Na\text{-}early}$, and is probably why they exhibit less proarrhythmic effect compared to $I_{Na\text{-}early}$ blockers [25, 34, 35].

General Electrophysiological and Electropharmacological Effects of Na^+ Channel Blockers

1. All class I agents have direct membrane effects and exhibit local anesthetic effects.
2. Slowing of rapid phase zero APD results in decrease in excitability.

3. Prolongation of conduction velocity (slowing conduction time).
4. Sodium channel blockers suppress both voltage-dependent and time-dependent recovery of excitability. Effects of these agents on voltage-dependent properties (kinetics) are more pronounced in ischemic tissue than normal tissue.
5. Suppression of time-dependent property by Na-channel blockers prolongs tissue refractoriness, and if such effect sustains longer than the repolarization phase it will cause post-repolarization refractoriness.
6. In cardiac fibers that demonstrate spontaneous automaticity, the sodium channel blockers exhibit increased slowing of the spontaneous diastolic depolarization [36, 37].
7. Sodium channel blockers can suppress excitability and prolong conduction and refractoriness. Therefore, may be effective on a variety of arrhythmias with diverse mechanisms and substrates.
8. Sodium ion channel blockers also eliminate the triggers, such as PAC and PVCs. It is also important to realize, as it was shown in the CAST trial, that elimination of triggers such as PVCs do not always translate to elimination of mechanisms of arrhythmias nor substrate modifications; risk predictors are not always the same as efficacy predictors. Thus, CAST showed failure of PVC elimination to improve outcome.

Effect of Na+ channel blockers on electrocardiographic and intracardiac intervals (Table 2.3).

Class Ia AAD: Quinidine, Procainamide, Disopyramide, and Ajmaline

As discussed earlier, according to the Vaughan Williams classification, Class I AADs are subdivided into three classes: Ia, Ib and Ic based on their effect on APD (Table 2.1). Class Ia agents mainly affect the phase 0 of APD and thus prolong

Table 2.3 The effect of sodium channel blocking agents on electrocardiogram and intracardiac intervals

Agent	Sinus rate	PR interval	QRS duration	QT interval	AH interval	HV interval
Class Ia						
Quinidine	↑ or —	↓ or variable	↑	↑	↓	↑
Procainamide	—	Variable	↑	↑	↑ or —	↑
Disopyramide	↑ or —	Variable	↑	↑	Variable	↑
Ajmaline	—	—	↑	↑	Variable	↑
Class Ib						
Lidocaine	—	—	No change	↓	↓ or variable	Prolongs
Mexiletine	—	—	No change	↓	Variable	↑ or variable
Class Ic						
Propafenone	↓ or variable	↑	↑	↑	↑	↑
Flecainide	↓ or variable	↑	↑	↑	↑	↑

Variable: May prolong or shorten, ↑ Prolongs, ↓ Shortens, "—" No change

conduction time, and also prolong repolarization to some degree. The prototypes of this class are quinidine, procainamide, and disopyramide.

Quinidine

- *Effects of quinidine on the ECG* (Table 2.3).
- *Electrophysiologic and antiarrhythmic properties of quinidine (*Table 2.4*). Pharmacokinetic properties of quinidine (*Table 2.5*)* [38].
- *Drug interactions* (Table 2.6).
- *Novel indications of sodium channel blockers of quinidine*: Recent reports suggest that low dose quinidine (<600 mg/day) was effective in preventing ventricular arrhythmia recurrences and storm in patients with Brugada syndrome [39–43]. Mizusawa, et al. reported on the effects of low-dose quinidine in VT in patient with Brugada syndrome [44]. High dose quinidine (≥ 1 g/day; needed to block the transient rapid outward potassium current (I_{to})) was also found to be effective in ventricular tachyarrhythmias and VT storm in patients with Brugada syndrome [39, 45–47]. This effect is only tested in a limited number of patients with Brugada syndrome who have implantable cardioverter-defibrillators (ICDs) [39, 45, 48–50].

  Belhassen, et al. reported that quinidine was effective in preventing induction of VF in 22/25 (88%) patients with Brugada syndrome [48].

  The mechanisms of quinidine's efficacy in patients with Brugada syndrome and ventricular tachyarrhythmias are believed (in part) to be due to blockade of rapid inward I_{Na}. Quinidine, besides its direct effect on I_{Na} channel blocker, also exhibits I_{to} inhibition [44].

  Interestingly, quinidine selectively blocks I_{to} current more in the epicardial than endocardial region of the right ventricle. This may explain, in part, its efficacy against ventricular arrhythmias in Brugada syndrome [40, 51, 52].

Table 2.4 Effects of sodium channel blockers on electrophysiological variables

Agent	APD	Vmax	CT	Rate dependence		Atrial ERP	Ant ERP-AVN	Ant ERP-HPS	ERP-VM	Ret ERP-AVN	Ret ERP-HPS	Ant ERP-AP	Ret ERP-AP
				All rates	Fast rates								
Class Ia													
Quinidine	↑	↓	↓	++		↑	Variable	↑	↑	↑	↑	↑	↑
Procainamide	↑	↓	↓	++		↑	Variable	↑	↑	↑	↑	↑	↑
Disopyramide	↑	↓	↓	++		↑	Variable	↑	↑	↑	↑	↑	↑
Ajmaline	↑	↓	↑	—	—	↑	Variable	↑	↑	↑	↑	↑	↑
Class Ib													
Lidocaine	↓	↓	↓		++	—	Varible	↑	Variable	—	—	—	—
Mexiletine	↓	↓	↓		++	—	Variable	Variable	—	—	—	—	—
Class Ic													
Propafenone	↑	↓	↑	++		↑	↑	↑	↑	↑	↑	↑	↑
Flecainide	↑	↓	↑	++		↑	↑	↑	↑	↑	↑	↑	↑

Abbreviations: *APD* action potential duration, *CT* conduction time, *ERP* early refractory period

TABLE 2.5 Dosage and pharmacokinetic properties of sodium channel blockers

	Class Ia			Class Ib		Class Ic	
	Quinidine	**Procainamide**	**Disopyramide**	**Lidocaine**	**Mexiletine**	**Propafenone**	**Flecainide**
Daily dose	600–1600 mg	Oral: 1000–4000 mg IV: 0.5–1 mg/kg/min	250–750 mg	IV: 3–5 mg/kg (25–50 mg/min)	450–900 mg	450–900 mg	200–400 mg
Absorption	>90%	>90%	80–90%	—	>90%	80–90%	90%
Bioavailability	70–80%	75–90%	70–90%	—	>80%	13–55%	90–95%
Peak blood level (hours)	1–3 h	1–2 h	0.5–2 h	—	2–4 h	2–5 h	3–4 h
Protein binding	85–95%	15%	20–60%	70%	60–70%	90–95%	40–60%
Mean half-life	7–18 h	3–5 h	7–9 h	1–2 h[a]	10 h[b]	10–32 h	20 h
Metabloism and elimination	Hepatic: 50–90% renal: 10–30%	Hepatic: 40–70% renal: 30–60%	Hepatic: 11–37% renal: 36–77%	Hepatic: 90%	Hepatic: 80–90% renal: <20%	Hepatic: 99%	Renal: 85%
Volume of distribution (L/kg)	2–3	1.5–2.5	0.5–1.5	1	6–9	3	10

(continued)

TABLE 2.5 (continued)

	Class Ia			Class Ib		Class Ic	
	Quinidine	**Procainamide**	**Disopyramide**	**Lidocaine**	**Mexiletine**	**Propafenone**	**Flecainide**
Plasma concentration (μg/mL)	2–6	4–10	2–5	1.5–5	1–2	<1	0.2–1
Active metabolites	4-OH-Quinidine	NAPA	Mono-N-dealkyl disopyramide	MEGX, GX[b]	—	5-OH-propafenone	Meta-O-Dealkylated flecainide
Safety in pregnancy (class)	C	C	C	B	C	C	C

Abbreviations: *h* hours, *NAPA* N-Acetyl procainamide, *MEGX* monoethylglycylxylidide

[a]In patients with HF, half-life may increase to 10–12

[b]15–17 h in patients with acute myocardial infarction

TABLE 2.6 Sodium channel blocker drug interactions

	Cardiac drugs					Non-cardiac drugs	
	Digoxin	**β blockers**	**Ca^{2+} blockers**	**Warfarin**	**Amiodarone**	**Cimetidine**	**Phenytoin**
Class Ia							
Quinidine	↑	↑[b]	↑[b]	↑[a]	↑	↑	↓
Procainamide	—	↑[b]	↑[b]	—	↑	↑	—
Disopyramide	—	↑[b]	↑[b]	↓	—	—	↓
Class Ib							
Lidocaine	—	↑	—	—	—	↑	—
Mexiletine	—	—	—	—	—	↓	↑
Class Ic							
Propafenone	↑	↑	↓	↑	—	↑	—
Flecainide	↑	↓	↓	—	↑	↑	—

↑ increase, ↓ Decrease, "—" no change
[a]By decreasing clotting factors
[b]Cardiodepressent effect

Quinidine is also effective in patients with short QT (SQT) syndrome by prolonging the QT interval and preventing ventricular arrhythmias [53–55]. The SQT interval is due to the gain of function in I_{Kr} and is related to the mutation in the HERG gene. The SQT syndrome is often seen in combination with familial AF; therefore, quinidine is effective for both conditions. In these cases, quinidine normalizes the QT interval and renders VF as non-inducible [54]. Similarly, quinidine has been shown to be effective in patients with J-wave/early repolarization syndrome [56–59]. Procainamide, propafenone, flecainide, and disopyramide may induce or unmask ST segment elevation in patients with concealed J-wave syndrome [60–62].

- *Adverse effects of quinidine*:
  - *Cardiac*: Quinidine has long been known to prolong QT interval and thus induces TdP known as quinidine syncope (1–3%). The mechanism of quinidine-induced TdP is assumed to be due to EAD [63, 64]. The QT prolongation effect of quinidine is more effective at slower heart rates (bradycardia-dependent).

Procainamide

- *Effects of procainamide on the ECG* (Table 2.3).
- *Electrophysiogical properties of procainamide* (Table 2.4).
- *Phamacokinetic properties of procainamide* (Table 2.5).
- *Oral dosing* (Table 2.5): Due to the short half-life of procainamide, multiple dosages per 24 h are required. Thus, a total dose of 1000–4000 mg per day may be administered. Long acting (slow release of procainamide) is also available and may be administered at twice a day intervals.
- *Novel indications of procainamide to unmask "concealed" Brugada ECG patterns in patients suspected of Brugada Syndrome*: In Europe, IV ajmaline is used to unmasked concealed or suspected Brugada syndrome (1 mg/kg) [65], whereas in the United States, IV procainamide is used for this purpose [61, 66–68].

Disopyramide

- *Effects of disopyramide on the ECG* (Table 2.3).
- *Electrophysiogical properties of disopyramide* (Table 2.4).
- *Phamacokinetic properties and dosage of Disopyramide* (Table 2.5).
- *Drug interactions* (Table 2.6).
- *Indication*: Disopyramide is effective against atrial and ventricular arrhythmias as well as effective in patients with paroxysmal and persistent AF. It is also effective against sinus node reentry tachycardia, atrial flutter, atrial tachycardia, AVNRT, and AVRT. Intravenous disopyramide is effective in controlling AF in patients with Wolff-Parkinson-White Syndrome [69]. Disopyramide has been used in the past to control a variety of ventricular arrhythmias such as PVCs, couplets, non-sustained and sustained VT; however, it has been less frequently used in recent years. Effects of disopyramide in post-infarction phase have been investigated and showed that although disopyramide reduced ventricular extrasystoles, it did not show a significant decrease in VT and VF or a reduction in cardiac mortality [70]
- *Use of disopyramide in patients with HCM and AF*: Disopyramide, due to its negative inotropic effect as well as ventricular relaxation property, is effective in reducing the LV outflow tract gradually. As AF is the most common arrhythmia in patients with HCM, disopyramide is also effective in controlling AF in these patients (300–600 mg daily; others have used 250–750 mg daily [71]) [72]. However, due to its significant cardiac and non-cardiac side effects, long-term use is limited. Sherrid et al., reported on a multicenter study of efficacy and safety of disopyramide in obstructive HCM and reported in this large cohort (118 patients) that disopyramide appeared effective in reducing the symptoms in 78 (66%) of the patients. In the remaining 40 (34%) patients, disopyramide did not adequately reduce their symptoms [73]. Several reports suggest the use of disopyramide for controlling AF in patients with HCM. However, due to its vagolytic effect, disopyramide

may increase the ventricular rate in these patients. Therefore, it should be used concomitantly with A-V nodal slowing agents such as beta-blockers or calcium antagonists. Interestingly, disopyramide did not increase the risk of proarrhythmia in these patients [73]. Needless to say, the QT/QTc interval should be monitored during disopyramide therapy in these patients [74]. In summary, disopyramide is effective in selected patients with HCM; however, due to its potential proarrhythmic and torsadogenic effect, careful monitoring is recommended and should generally be used after a beta-blocker trial before considering surgical or alcohol septal ablation [73, 75].

According to the most recently published guidelines, due to disopyramides vagolytic property, should be used in combination with an A-V nodal blocking agent to avoid rapid ventricular response [74].

Ajmaline

Ajmaline is a derivative of the Rauwolfia plant and is not approved in the United States

- *Electrophysiogical properties of ajmaline* (Table 2.4).
- *Phamacokinetic properties and dosage of ajmaline* (Table 2.5).
- *Novel Indications of Ajmaline*: Aside from its usual indication for acute termination of supraventricular or ventricular arrhythmias, ajmaline is used for diagnostic purposes of:

  1. Blocking the accessory pathway in patients with Wolff-Parkinson-White syndrome [76–78]
  2. Unmasking the Brugada ECG signs in individuals suspected of this syndrome [79].
  3. Unmasking the latent His-Purkinje system disease.

- Life-threatening ventricular arrhythmias have been reported during ajmaline tests in patients with Brugada syndrome. The incidence is about 1.8% of patients in a large cohort [80, 81]

Class Ib AAD: Lidocaine, Mexiletine

Lidocaine

- *Effects of lidocaine on the ECG* (Table 2.3).
- *Electrophysiologic and antiarrhythmic properties of lidocaine* (Table 2.4).
- *Pharmacokinetic properties of lidocaine* (Table 2.5).
- *Drug interactions* (Table 2.6).

Mexiletine

- *Effects of mexiletine on the ECG* (Table 2.3).
- *Electrophysiologic and antiarrhythmic properties of mexiletine (*Table 2.4*). Pharmacokinetic properties of mexiletine* (Table 2.5).
- *Drug interactions* (Table 2.6).
- *Novel indication of mexiletine*: Since mexiletine does not prolong repolarization, it has been used safely in patients with LQT syndrome; specifically LQT3 in which the SCN5A gene involved that controls the I_{Na+} current [82–84]. Indeed, mexiletine shortens the QT and QTc interval and therefore reduces indices of malignant arrhythmic events in patients with LQT syndrome. Torsadogenic effects of mexiletine are rare. Another interesting finding is the blockade of mexiletine of the $I_{Na\text{-}late}$ and its potential use in patients with Timothy syndrome [85].

Class Ic AAD: Propafenone and Flecainide

Propafenone (Table 2.1)

- *Effects of propafenone on the ECG* (Table 2.3).
- *Electrophysiologic and antiarrhythmic properties of propafenone* (Table 2.4) [43].

- *Pharmacokinetic properties of propafenone* (Table 2.5).
- *Drug interactions* (Table 2.6).
- *Efficacy of propafenone in patients with AF*: Propafenone's use-dependent property makes it effective against AF and atrial flutter [86, 87]. The recommended dose of propafenone for AF is 150–300 mg three times daily. The average efficacy at 1 year is 40–75% [88]. Propafenone is currently approved for use in patients with paroxysmal and persistent AF [63].

  Propafenone prolongs anterograde and retrograde A-V nodal conduction. Thus, this makes it effective in the prevention and termination of arrhythmias that are A-V node-dependent, i.e. AVNRT and AVRT. Propafenone also reduces excitability, spontaneous automaticity, and triggered activity. It also has mild I_{Kr} blocking effect as well as a weak beta-blocker effect; however, it is higher than flecainide. Propafenone also prolongs and blocks both anterograde and retrograde conduction of the accessory pathways; thus it is effective against patients with recurrent AVRT [89, 90].
- *Efficacy of propafenone in patients with ventricular arrhythmias*: Propafenone prolongs ventricular conduction time at a greater degree than refractoriness. This imbalance may be the mechanism of propafenones proarrhythmia that facilitates (promotes) ventricular tachyarrhythmias [89, 90]. Propafenone is effective in reducing PVCs, couplets, and non-sustained VT. Efficacy for sustained VT in chronic phase of MI is based on electrophysiological testing and is moderate, i.e. 40%.
- *Proarrhythmic effects of propafenone*: Like flecainide and other class Ic agents, propafenone poses significant ventricular proarrhythmias, especially in patients with CAD, ischemia, presence of myocardial scar, reduced LV systolic function, as well as LVH. Propafenone may increase ventricular response in patients with atrial flutter. This effect is due to propafenone slowing atrial flutter rate and thus allowing more flutter wave conduction to the ventricle [91, 92].

Flecainide

- Effects of flecainide on the ECG (Table 2.3).
- *Electrophysiologic and antiarrhythmic properties of flecainide* (Table 2.4) [43].
- *Pharmacokinetic properties of flecainide* (Table 2.5).
- *Drug interactions* (Table 2.6) [93, 94].
- *Dosage* (Table 2.7).
- *Indication*: Flecainide is effective in reducing PVCs, ventricular couples, and non-sustained VT. Initial experience found flecainide effective against sustained monomorphic VT based on Holter and electrophysiological testing; however, due to its proarrhythmic effect, it is less used (see guidelines) [95]. No data supports the reduction of sudden cardiac death (SCD) with flecainide or propafenone. Flecainide for sustained monomorphic VT in patients with CAD based on electrophysiological studies and program stimulation is not very effective: the VT often remains inducible (Fig. 2.4).
- *Ventricular arrhythmias*: Flecainide is effective in reducing PVCs, non-sustained, and sustained VT; however, it carries the risk of proarrhythmias. Conceptually, any agent that prolongs conduction time changes the balance between conduction time and refractoriness and hence may cause increased likelihood of facilitating reentry. This was well documented in the case of propafenone, and is similar to flecainide [89, 90]. Fig. 2.4 shows exercise induced VT in a patient with CAD (see Fig. 2.4 legend for explanation). Indication for the use of flecainide in patients with VT is summarized in Table 2.7 from the 2015 ESC Guidelines.

  Almost all class I AADs effects are reversible with isoproterenol [96].
- *Novel indication of flecainide*: Interesting data is emerging on the use and effectiveness of flecainide in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) [97–104]. Although the treatment of choice for patients with CPVT is beta-blockers and ICDs, only one study has reported flecainide-inhibited ryanodine receptor-mediated calcium release in two

Table 2.7 Available AADs for the treatment of ventricular arrhythmias [95]

AADs (Vaughan Williams class)	Dose (mg/day)	Common or important adverse effects	Indication	Cardiac contra-indications and warnings
Quinidine	600–1600	Nausea, diarrhea, auditory and visual disturbance, confusion, hypotension, thrombocytopenia, hemolytic anemia, anaphylaxis, QRS and QT prolongation, TdP	VT, VF, SQTS, Brugada syndrome	Severe sinus node disease (unless a pacemaker is present); severe AV conduction disturbances (unless a pacemaker is present); severe intraventricular conduction disturbances; previous myocardial infarction; CAD; HF; reduced LVEF; hypotension; inherited Long QT Syndrome; concomitant treatments associated with QT interval prolongation
Procainamide	1000–4000	Rash, myalgia, vasculitis, hypotension, lupus, agranulocytosis, bradycardia, QT prolongation, TdP	VT	Severe sinus node disease (unless a pacemaker is present); severe AV conduction disturbances (unless a pacemaker is present); severe intraventricular conduction disturbances: previous myocardial infarction; CAD; HF; reduced LVEF; hypotension; reduced LVEF, Brugada syndrome

Disopyramide	250–750	Negative inotrope, QRS prolongation, AV block, pro-arrhythmia (atrial monomorphic VT, occasional TdP), anticholinergic effects	VT, PVC	Severe sinus node disease (unless a pacemaker is present); severe AV conduction disturbances (unless a pacemaker is present); severe intraventricular conduction disturbances; previous myocardial infarction; CAD; HF; reduced LVEF; hypotension
Mexiletine	450–900	Tremor, dysarthria, dizziness, gastrointestinal disturbance, hypotension, sinus bradycardia	VT, LQT3	Sinus node dysfunction (unless a pacemaker is present); severe AV conduction disturbances (unless a pacemaker is present); severe HF; reduced LVEF; inherited LQTS (other than LQTS3); concomitant treatments associated with QT-interval prolongation

(continued)

Table 2.7 (continued)

AADs (Vaughan Williams class)	Dose (mg/day)	Common or important adverse effects	Indication	Cardiac contra-indications and warnings
Propafenone	450–900	Negative inotrope, gastrointestinal disturbance, QRS prolongation, AV block, sinus bradycardia, pro-arrhythmia (atrial monomorphic VT, occasional TdP)	VT, PVC	Severe sinus bradycardia and sinus node dysfunction (unless a pacemaker is present); (without the concomitant use of AV-blocking agents); severe AV-conduction disturbances (unless a pacemaker is present); severe intraventricular conduction disturbances; previous myocardial infarction; CAD; HF; reduced LVEF; haemodynamically valvular heart disease; Brugada syndrome; inherited LQTS (other than LQTS3); concomitant treatments associated with QT interval prolongation

Flecainide	200–400	Negative inotrope, QRS widening, AV block, sinus bradycardia, pro-arrhythmia (atrial flutter, monomorphic VT, occasional TdP), increased incidence of death after myocardial infarction	VT, PVC	Sinus node dysfunction (unless a pacemaker is present); AF/flutter (without the concomitant use of AV-blocking agents); severe AV conduction disturbances (unless a pacemaker is present); severe intraventricular conduction disturbances; previous myocardial infarction; CAD; HF; reduced LVEF; haemodynamically valvular heart disease; Brugada syndrome; inherited LQTS (other than LQTS3); concomitant treatments associated with QT-interval prolongation

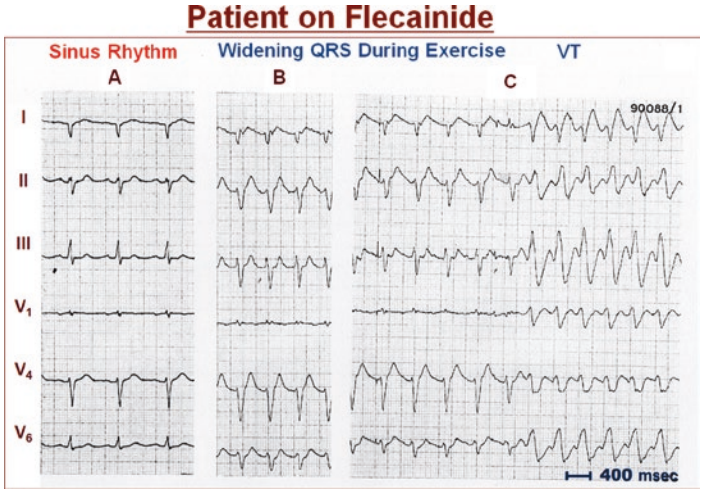


FIGURE 2.4 Exercise-induced VT in a patient with CAD on 300 mg of flecainide. (**a**) Baseline sinus rhythm with a narrow QRS morphology. (**b**) Sinus rhythm with a wider QRS duration under flecainide. (**c**) Progressive prolongation of the QRS duration and initiation of sustained monomorphic VT during exercise testing

patients with CPVT [105]. Van der Werf, et al. reported that flecainide, with a median dose of 150 mg daily, prevented exercise-induced ventricular arrhythmias in 2/3 (76%) of the patients with CPVT [100].

Flecainide may be used to unmask SCN5A related Brugada syndrome [106]. In a cohort of 22 patients, Wolpert, et al. reported on the intravenous use of flecainide and ajmaline on unmasking Brugada syndrome [107]. Flecainide unmasked 15 of the 22 patients and ajmaline unmasked 100%. Some reports suggest that flecainide may be useful in LQT-related SCN5A mutations. Interestingly, it was found that flecainide normalized the ventricular repolarization [108]. Recent reports suggested that flecainide alone or in combination with digoxin, was highly effective in converting fetal SVT to sinus rhythm [109–113]. The dosage administered was 100 mg 4 times daily for the first 2–3 days and then changed to 300 mg/d. The median time to conversion was 3 days (1–7 days).

- *Proarrhythmic effect of flecainide*:

  As flecainide exhibits negligible effect on anterograde A-V nodal conduction, when used in patients with atrial flutter, the drugs prolong atrial flutter cycle length [114] and allow a faster conduction via A-V node with 1:1 and 2:1 A-V conduction causing rapid ventricular response; therefore, flecainide should be used concomitantly with slow A-V nodal conduction agents like calcium antagonists or beta blockers [115]. Ventricular proarrhythmic effects of flecainide include sustained monomorphic VT, TdP, and incessant VT. Also, flecainide induces QRS prolongation during exercise and exercise-induced VT as shown in Fig. 2.4. An increase in the QRS duration by 15–20% is a recognized pharmacologic effect of flecainide; however, several cases have reported that as the QRS duration gets longer during exercise, sustained VT emerges, i.e. exercise-induced VT during flecainide therapy [116]. There is an exception that flecainide is effective in patients with CPVT and exercise-induced arrhythmias. Overall, the use of flecainide worldwide is still low. The Euro-Heart survey on AF shows that 17% and 13% of patients with paroxysmal and persistent AF respectively have been treated with class Ic AAD (flecainide and propafenone) [117].

  Contraindications of both propafenone and flecainide include CAD with and without myocardial ischemia, LV systolic dysfunction, and significant evidence of A-V conduction system disease.

Other Drug and Substance Interactions

Grapefruit interacts with many cardiovascular and AADs namely quinidine, disopyramide, and propafenone. Since grapefruit decreases the activity of CYP3A4, any pharmacological agent that metabolizes through this enzyme may cause the blood levels of the drug to rise, resulting in the risk of adverse events [118–121]. For further detail of other substances, see Table 2.6 [122].

Selective Sodium Channel Blockers

The concept of ion-channel selective agents has emerged as an interesting and appealing notion in avoiding global cardiac effect, potential arrhythmogenesis, and proarrhythmic effects [123, 124]. There exists evidence that atrial channel selectivity is expressed in the atria [125]. Among the selective I_{Na} channel blockers are vernakalant and ranolazine. Both have significant atrial-selective blocking properties, which are effective against atrial arrhythmias, specifically AF and atrial flutter. Both agents also demonstrate sodium channel blocking effects in experimental models of pulmonary veins [126, 127].

Sodium channels are highly selective for sodium ions to travel across the cell membrane in a voltage-dependent manner [128]. The sodium channel selectivity is significantly higher than the potassium channel selectivity [129]. There are several factors that influence their selectivity such as voltage, pH, and other modulators and modifiers.

In general, sodium channel blockers have high binding affinity to the early ($I_{Na\text{-}early}$) phase than late ($I_{Na\text{-}late)}$ phase. Ranolazine predominantly blocks the $I_{Na\text{-}late}$ phase and thus has less proarrhythmic effect. Also, late sodium currents exhibit a rapid unbinding to the sodium channel as compared to early sodium current [130]. Interestingly, recent data demonstrates that permanent AF increases the number of late Na^+ currents in the atria; thus, it is conceivable that ranolazine, a late sodium current blocker, is effective in patients with AF [125, 131–134].

Sodium channel blocking agents have a direct frequency-dependent effect; therefore, their efficacy will be increased during high-rate arrhythmias such as AF. Furthermore, sodium channels demonstrate higher affinity to AADs in their activated/inactivated states compared to their closed state. Late sodium channel blockers ($I_{Na\text{-}late}$) dissociate faster from ion channels than early sodium channel blockers ($I_{Na\text{-}early}$). This may, in part, explain lower proarrhythmic effect of these agents [128].

The limitations of selective ion-channel blockers are as follows:

1. At higher concentrations, they lose selectivity properties. This selectivity may work in normal tissue; however, remodeled tissue may be different.
2. Some agents like ranolazine exhibit differential effect on the I_{Na} channels of the atria as compared to the ventricle.
3. They still carry the risk of proarrhythmias
4. Studies on selective ion-channel blockers are done on healthy tissue preparations in the absence of autonomic, hemodynamic, and structural changes.

Interestingly, both amiodarone and ranolazine are multi-channel blockers; however, they exert an atrial selective sodium channel blocking effect [125, 135–137].

Genetics of Sodium Channel Dysfunction and Blockers

Molecular Genetics of Arrhythmias and Channelopathies Related to Sodium Channel Blockers and their Mutations

It is quite important to briefly discuss this topic, as more evidence is emerging on the relation of sodium channels and channelopathies to many genetic syndromes related to sodium channels. These concepts are well discussed in the following references [92, 138–143].

As discussed earlier, it is now well established that ion channels operate under genetic control and that certain genes encode proteins for healthy sodium channel function. The site of each gene on chromosomes is called the *locus,* and when genetic information on the DNA sequence is translated to the respective protein(s) via a transcript code with mRNA, it is then passed through the next generation (from the parent). Many of these genes are gender specific and may be dominant

or recessive (Mendelian pattern). Several factors affect and determine these mutations including environmental (i.e. radiation, drugs, and chemicals) or other unknown factors. Any errors or modification in their process may cause abnormal mutations, which may lead to the development of specific diseases. Some mutations in the sodium channels are related to Brugada Syndrome, LQT3 Syndrome, dilated cardiomyopathy, AF, and sick sinus syndrome [21, 91, 144].

Sodium Channel Mutations and Related Channelopathies

The term channelopathies refers to a group of genetic abnormalities and mutations of ion channels that produce cardiac arrhythmias [145–147]. The most common is the SCN5A mutation related to sodium channels that produce the arrhythmia syndromes listed below and are listed in Table 2.8 and Fig. 2.3 [149, 153].

These genetic mutations may cause either loss [154] or gain of function or both [17] (Fig. 2.3).

Loss of Function

1. Brugada syndrome [154–156]
2. Sudden unexplained nocturnal death syndrome [157]
3. Familial AF.
4. Atrial standstill.
5. Sick sinus syndrome [158]
6. Cardiac conduction disease.
7. Progressive cardiac conduction disease [154, 159–162]
8. Congenital A-V block.
9. Dilated cardiomyopathy [163–166]: 16 mutations have been reported.

Gain of Function

1. LQT3 syndrome.
2. Drug-induced LQTs.
3. Familial AF.

TABLE 2.8 Genetic-related sodium channel arrhythmias [140, 148, 149]

Arrhythmia syndrome	Affected ion channel	Protein	Gene	Chromosomal locus	Gain/ loss of function	Gender dominance	Inheritance
Brugada syndrome	Sodium Na_V 1.5	B1–3: α-subunit B4–B7: β-subunit	SCN5A	3p21–p24	Loss	Male	Autosomal dominant
LQT3 syndrome	Sodium Na_V 1.5	α-subunit	SCN5A	3p21–p24	Gain	Female	Autosomal dominant or recessive (rarely), sporadic, acquired
Idiopathic VF [150]	Sodium Na_V 1.5	α-subunit	SCN5A	3p21–p24	Gain	Male	Autosomal dominant
Familial AF	Sodium Na_V 1.5	α-subunit	SCN5A	10q22–24 4q25 Others [151]	Gain and loss	Male	Autosomal dominant
Sick sinus syndrome	Sodium Na_V 1.5	α-subunit	SCN5A	3p21–p24	Loss	—	Autosomal dominant or recessive

(continued)

Table 2.8 (continued)

Arrhythmia syndrome	Affected ion channel	Protein	Gene	Chromosomal locus	Gain/ loss of function	Gender dominance	Inheritance
PCCD syndrome	Sodium Na_V 1.5	α-subunit	SCN5A	3p21–p24	Loss	—	Autosomal dominant
Dilated Cardiomyopathy [152]	Sodium Na_V 1.5	α-subunit	SCN5A	3p22–p25	Loss	Male	Autosomal dominant (adult) Autosomal recessive (pediatric)
Sudden infant death syndrome	Sodium Na_V 1.5	α-subunit	SCN5A	—	Gain	Male	Autosomal recessive, sporadic

Early repolarization syndrome, several genes may be operational

Since J-wave and early repolarization is a syndrome, there will be overlap of J-wave syndrome with other channelopathies; thus, more than one ion channel may be involved. In some of the mutations in early repolarization syndrome (type 6), SCN5A is involved

Abbreviations: *AF* atrial fibrillation, *LQT3* long QT 3 syndrome, *PCCD* progressive cardiac conduction defect, *VF* ventricular fibrillation

4. Multifocal ectopic Purkinje-related premature contractions [167]
5. Sudden infant death syndrome [24]
6. Stillbirth.
7. Idiopathic VF/early repolarization [150, 168]
8. Arrhythmic storm syndrome during acute myocardial infarction [169]

Sodium Ion Channelopathies and Related Syndromes (Table 2.8 and Fig. 2.3)

Most of these syndromes are related to the SCN5A gene mutation. These are divided into two categories, loss of function, and gain of function [170]. Furthermore, there are a few syndromes that have common genetic mutations such as LQT3 syndrome, Brugada syndrome, and progressive cardiac conduction defect [141, 160, 171–174]. Laurent G, et al. recently reported a new SCN5A-related cardiac channelopathy that presents as multifocal ectopic Purkinje-related premature contractions [167].

Progressive Cardiac Conduction Disease Syndrome: This syndrome is due to the mutation of SCN5A gene of the Na_V 1.5 channel. It is an inherited arrhythmia disorder and is due to loss of function [175]. Recent studies suggest that autoimmune response may express the sodium channel Na_v 1.5 and produce AV block [176, 177]. So far, 11 forms of mutations have been described. This syndrome overlaps with other sodium channelopathies such as Brugada syndrome, LQT3, and DCM (Fig. 2.3) [160, 178, 179].

Genetic Forms of AF: There is now compelling evidence that a genetic form of AF exists, [180] either as a standalone or part of a broader spectrum of other genetic arrhythmia syndromes such as Brugada syndrome, LQT syndrome, and SQT syndrome [181–185]. Several genes and their mutations are associated with genetic forms of AF such as mutations in sodium channels related to SCN5A, SCN1B-2B and many others [149, 186–188].

Aside from ventricular tachyarrhythmias and SCD, AF is the most common arrhythmia associated with Brugada syndrome [189]. The incidence varies from 20–50% according to different geographical regions [190]. Besides Brugada syndromes, AF may also exist in other cardiac channelopathies such as LQT, SQT and CPVT [191].

LQT3 syndrome: LQT3 syndrome is due to an increased function in the late sodium current that prolongs APD [192]. The gene responsible in LQT3 syndrome is related to SCN5A mutation and is either autosomal dominant or a recessive inheritance pattern [179, 193]. Therefore, LQT3-related arrhythmia blockade of the late sodium current by ranolazine is effective against arrhythmias related to LQT3 [194]. Ranolazine, by decreasing $I_{Na\text{-}late}$, shortens APD and abolishes arrhythmias related to LQT3 [194].

Other genetic-related sodium channel arrhythmias are summarized in Table 2.8.

Management of cardiac sodium channelopathies includes [195]:

1. Risk stratification of patients and their relatives. This depends on the severity of the symptoms, phenotypes (ECG findings), and genotypes, i.e. identifying genetic profile and mutations.
2. Pharmacological therapy such as beta-blockers, quinidine, ranolazine, and flecainide (see section on novel indication of class I agents).
3. ICDs in high-risk patients.
4. Surgical left cardiac sympathetic denervation [196, 197].

AAD Drug-Induced Arrhythmias: Proarrhythmia, Arrhythmogenesis, or Arrhythmia Aggravation

Proarrhythmia (Latin) or arrhythmogenesis (Greek) is defined as aggravation of an existing arrhythmia or development of new arrhythmias that were not present before therapy due to a pharmacological agent (cardiac or non-cardiac)

or a non-pharmacological intervention [198]. Proarrhythmia has been far recognized [199]; however, this effect has become more obvious since the CAST and other respective trials [200]. In general, cardiac tissue is anisotropic (non-uniform), particularly in myocardial disease, ischemia, and infarction, which increases anisotropic conduction. The most common form and serious proarrhythmia is TdP due to QT prolongation [201]. In general, TdP is usually initiated with a long-short RR interval sequence [202]. AADs exacerbate the occurrence of serious VT in this setting [203]. An important complication of pharmacological agents, whether cardiac or non-cardiac, is their torsadogenic effect. The mechanisms of drug-induced TdP remain controversial. Most studies suggest that ventricular arrhythmias due to TdP are related to EAD-triggered activity, and it may change to reentrant mechanisms. Multiple factors play a role including genetics, gender, and other mechanisms. Focal or reentry mechanisms are contemplated. It is most likely that both are operational [204, 205].

Virtually all class I agents have the risk of proarrhythmia and TdP. The incidence varies significantly depending on the method that is used for evaluation of proarrhythmia, i.e. invasive vs non-invasive methods and interplay of AADs with arrhythmia substrate (Figs. 2.5 and 2.6).

Class Ia and Ic AADs are among the pharmacological agents that have a high risk of drug-induced TdP (disopyramide, procainamide, quinidine, propafenone, flecainide). Drug-induced LQT Syndrome is also considered an acquired form of LQT Syndrome [206]. Genetic predisposition is an important factor that promotes drug-induced QT prolongation [207, 208]. A comprehensive review of this subject is published by Camm, et al. [209]

Ventricular proarrhythmic effect of class I agents includes increasing the ventricular response in patients with AF and flutter as well as sustained monomorphic VT, incessant VT, polymorphic VT, VF, TdP, and others.

A recent report has been published by Riad et al. on drug-induced QT prolongation. Patients were divided into four risk profiles: no risk, conditional risk, possible risk and known risk [210].

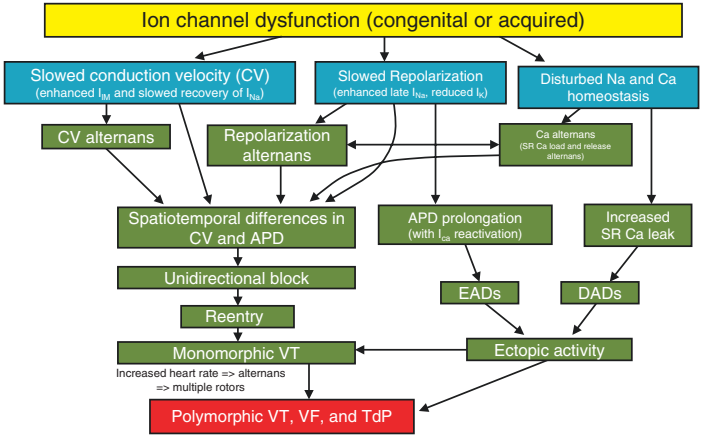


FIGURE 2.5 Interplay of different ion channel dysfunctions related to channelopathies, ventricular arrhythmias and SCD. With permission from Wagner S, et al. Circ Res 2015;116:1956–1970 [15]. Abbreviations: *APD* action potential duration, *Ca alternans* Calcium alternans, *DADs* delayed afterdepolaizations, *EADs* early afterdepolarizations, *SR* sinus rhythm, *TdP* torsades de pointes, *VF* ventricular fibrillation, *VT* ventricular tachycradia

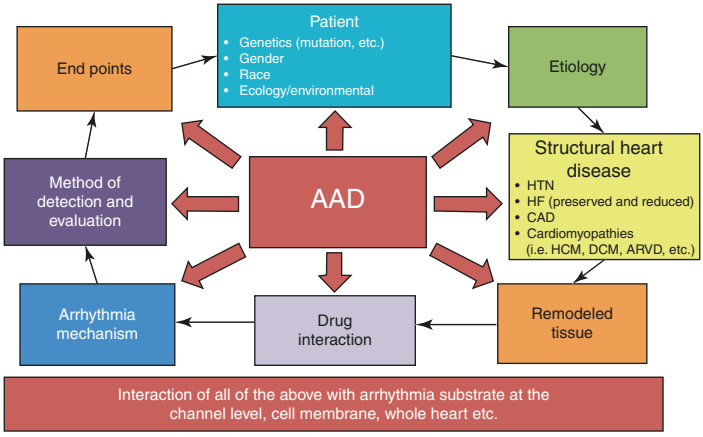


FIGURE 2.6 Relationship of AADs to Clinical Pathophysiology. Abbreviations: *AAD* antiarrhythmic drug, *ARVD* arrhythmogenic right ventricular dysplasia, *CAD* coronary artery disease, *DCM* dilated cardiomyopathy, *etc.* etcetera, *HCM* hypertrophic cardiomyopathy, *HF* heart failure, *HTN* hypertension

There are several risk factors for drug-induced proarrhythmias that are determined elsewhere [201, 208, 211–219].

Prevention of Sodium Channel Blocker Proarrhythmia [220]:

1. Elimination of the predisposing factors such as bradycardia, electrolyte imbalance, cardiac, and non-cardiac agents that promote TdP.
2. Modification of underlying heart disease such as HF, impaired renal function, hepatic disease, etc.
3. Appropriate monitoring in patients at risk of proarrhythmia and TdP such as ECG monitoring for QT prolongation, etc. [221, 222]
4. Appropriate patient teaching and use of digital devices to obtain urgent rhythms.

Sodium Ion Channel Remodeling

There is some evidence, although controversial, about sodium channel remodeling. This mostly occurs in patients with HF, ischemia and infarction, and AF. However, in the remodeled tissue, more than one ion channel is often involved, particularly in patients with persistent and permanent AF [223]. Sodium channel remodeling creates abnormalities that favor occurrence of reentry and EADs. Reverse remodeling hopefully will correct arrhythmias related to sodium channel remodeling [224]. Amiodarone, a multichannel blocker which also blocks the sodium current, has been reported to be effective against AF-induced remodeling [225]. Sodium channels are reduced in remodeled atria during atrial tachycardia in experimental models and in patients with long-standing AF. Under these conditions the sodium channels are down-regulated [226–229].

The Ideal Antiarrhythmic Agent

A “wish list” of an ideal AAD includes:

1. Being effective in prevention of arrhythmias.
2. Induce reverse-remodeling.

3. Prevent and reverse inflammation and fibrosis.
4. Exhibit both ion-channel as well as systemic effect (system pharmacology).
5. Minimal to no adverse effect including cardiac and systemic, i.e. no proarrhythmic consequences.
6. No drug interaction
7. Affordable

At present, such expectations are far from reality.

Nontraditional Sodium Channel Blockers

1. Vanoxerine is an oral multichannel blocker that also affects the sodium current and has been reported in a randomized trial that it is effective in converting patients with recent onset of AF and atrial flutter to sinus rhythm. Piccini, et al. reported on using a single oral dose of Vanoxerine (400 mg). In 18 out of 26 patients (69%) who received Vanoxerine for atrial arrhythmias converted to sinus rhythm; however, the trial was prematurely terminated due to increased risk of TdP [230]
2. Another agent is Relaxin, which has been tested as an antifibrosis agent and was found to improve the sodium current in a rat model of AF [231]
3. WenXin KeLi is a traditional Chinese medicine which has significant multichannel blocking effects, including late and early sodium current [232]
4. There is evidence that suggest that fish oil and n-3 PUFA blocks the sodium channels [233, 234]. Furthermore, limited evidence suggests that fatal arrhythmias may be prevented in high-risk subjects by fish oil n-3 fatty acid intake [235, 236]
5. Conflicting results exist on the efficacy of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients with AF. This is in part due to the complexity on the mechanisms of AF as well as the relation to structural heart disease. For example, it may be effective in patients with hypertension-related AF due to HF and probably not to other etiologies.

Previous trials have failed to show significant improvement on the efficacy of these agents in patients with AF. The hypothesis is that these agents may have an antifibrotic effect [237, 238]. Two large trials did not show any beneficial effects on reducing AF by valsartan and Irbesartan [239, 240]. Similarly, ACEs and ARBs did not prevent recurrence of AF after catheter ablation [241]. In summary, there is conflicting data regarding the use of ACEs and ARBs. They only work to prevent angiotensin-mediated fibrotic remodeling. Treatment, which has to be given before remodeling, is so advanced that nothing can be done. At the same time, patients have to be at high enough risk for fibrosis that an effect is detectable over the time frame of observation.

Guidelines on the Use of Sodium Channel Blockers (EHRA/ESC; AHA/ACC/HRS; CCS)

Guidelines for the use of sodium channel blockers by EHRA/ESC are summarized in Table 2.7 [242–244]. Fig. 2.7 shows the algorithms for using AADs in patients with AF.

Summary

1. The cardiac sodium channels are voltage-dependent channels that consist of four homologous domains, which are regulated mostly by SCN5A genes.
2. AADs that block or modulate the sodium current have a diverse effect on atrial, ventricular, and specialized conduction system. They also exhibit different effects, normal (healthy) and abnormal (pathological substrate) hearts.
3. Abnormalities in cardiac sodium channels, respective genes, and their mutations are responsible for a variety of "channelopathies" and related syndromes such as Brugada Syndrome, LQT3, progressive cardiac conduction defect, and many others.

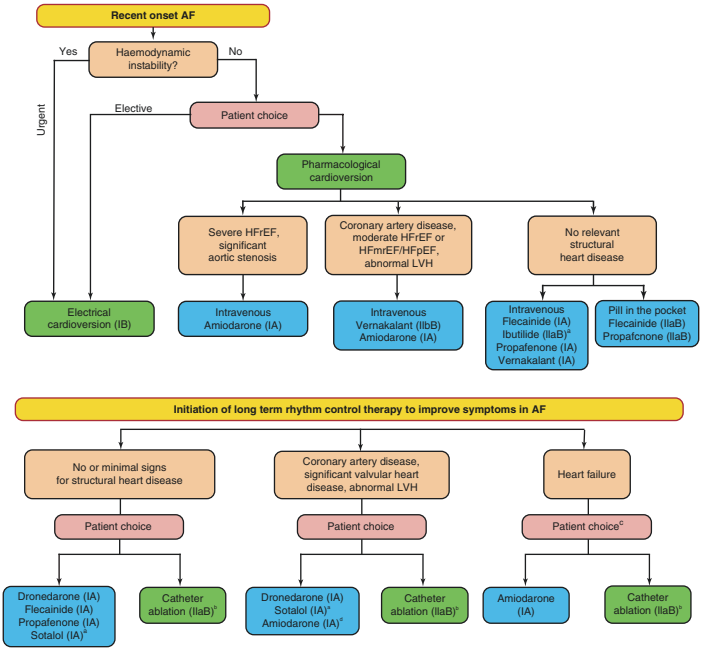


FIGURE 2.7 Algorithm for using AADs in patients with AF. (**a**) Recent onset AF, (**b**) Initiation

4. Precaution should be exercised in patients with systemic disease such as HF, renal, and hepatic failure.
5. The concept of AF is constantly evolving; therefore, response to chronic therapy may change over time [245].
6. Sodium channel blockers or class I AADs, especially class Ic agents, remain the most common AAD used for the control of a variety of arrhythmias; however, caution must be used to exercise the potential proarrhythmic events, i.e. TdP.
7. Recent observations suggest that there are novel indications for several class I agents including quinidine for Brugada syndrome and mexiletine for LQT3 and the like.
8. Class I AADs are among the first class of drugs that came into clinical practice and remain among the major indications for cardiac arrhythmias per the current guidelines,

and more novel indications related to the sodium current and channels will emerge.

Future Directions

1. Development of novel channel selective agents (sodium channel specific targets) [246]. Due to negative impact of large randomized trials on AADs on VAs and sudden death, the pharmaceutical companies were not interested to invest in developing new AADs; however, with the new frontiers in drugs, devices, and pharmacogenetics, new agents may be developed and expedited by the FDA [247, 248]
2. Development of screening methods to identify responders, non-responders, and proarrhythmic effects with respect to the channels, substrates, and pharmacological agents [249]
3. Gene therapy for channelopathy-related arrhythmias [250]
4. Identification of genetic modifiers.
5. Correlation with genotype-phenotype and detection of high-risk carriers.
6. More detailed insight into the gender/racial, geographic, socioeconomic, circadian variations, and response to medications should be implemented in drug therapy guidelines [251]
7. Identification of the level of penetrance of all related genes and mutations and the role of genetics [252]
8. Identification of factors that precipitate upregulation or down-regulation of genetic function [24]
9. Genomic medicine, pharmacogenomics, and proteomics [253–255]
10. Role of Receptors.
11. Role of MicroRNA [256, 257]
12. Development of substrate-based pharmacological agents such as anti-fibrosis and anti-inflammation.
13. Pharmacological agents that modulate the gap junction (normalize gap junction conduction) [258].

14. Identification of genetic factors related to the risk of drug-induced arrhythmias (the most common one is TdP) [259–261].
15. Stem cell therapy and regenerative medicine relative to arrhythmias and antiarrhythmics.
16. Spinal cord stimulation in the management of drug refractory arrhythmias and storms [262]
17. Personalized and precision medicine [263]
18. Most importantly, considering the effect of AADs on patients, specifically system biology and pharmacology.
19. A gene-specific approach should be implemented more for both risk stratification and selection of AADs [144]

For further information the readers are referred to the following references [176, 264–266]

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Disclosures

The authors do not report any disclosures.

Conflict of Interest

None.

References

1. Roden DM. Anti-arrhythmic drugs. In: Brunton L, Chabner B, Knollman B, editors. Goodman & Gilman's: the pharmacological basis of therapeutics. New York: McGraw Hill; 2011.
2. Fuster V, Harrington RA, Narula J, Eapen ZJ. Hurst's the heart. 13th ed. New York: McGraw Hill; 2011.
3. Williams EMV. A classification of antiarrhythmic actions reassessed after a decade of new drugs. J Clin Pharmacol. 1984;24(4):129–47. https://doi.org/10.1002/j.1552-4604.1984.tb01822.x.

4. Williams V. Significance of classifying antiarrhythmic action since the cardiac arrhythmia suppression trial. J Clin Pharmacol. 1991;31:123–35.
5. Williams V. Subgroups of class 1 antiarrhythmic drugs. Eur Heart J. 1984;5(2):96–8.
6. The Sicilian Gambit. A new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. Circ. 1991;84:1831–51.
7. Grant AO. Cardiac ion channels. Circ Arrhythm Electrophysiol. 2009;2(2):185–94. https://doi.org/10.1161/CIRCEP.108.789081.
8. Nerbonne JM. Molecular basis of functional myocardial potassium channel diversity. Card Electrophysiol Clin. 2016;8(2):257–73. https://doi.org/10.1016/j.ccep.2016.01.001.
9. Marban E. Cardiac channelopathies. Nature. 2002;415(6868):213–8.
10. Lehmann-Horn F, Jurkat-Rott K. Voltage-gated ion channels and hereditary disease. Physiol Rev. 1999;79:1317–72.
11. Hall J. Transport of substances through cell membranes. In: Hall J, editor. Guyton and Hall textbook of medical physiology. 13th ed. Amsterdam: Elsevier; 2015.
12. Sheets M, Hanck D. Voltage-dependent open-state inactivation of cardiac sodium channels: gating current studies with anthopleurin-A toxin. J Gen Physiol. 1995;106:617–40.
13. Shih H. Anatomy of the action potential in the heart. Tex Heart Inst J. 1994;21:30–41.
14. Jalife J, Delmar M, Anumonwo J, Berenfeld O, Kalifa J. Basic cardiac electrophysiology for the clinician. Hoboken: Wiley-Blackwell; 2009.
15. Wagner S, Maier LS, Bers DM. Role of sodium and calcium dysregulation in tachyarrhythmias in sudden cardiac death. Circ Res. 2015;116(12):1956–70. https://doi.org/10.1161/CIRCRESAHA.116.304678.
16. Abriel H, Rougier JS, Jalife J. Ion channel macromolecular complexes in cardiomyocytes: roles in sudden cardiac death. Circ Res. 2015;116(12):1971–88. https://doi.org/10.1161/CIRCRESAHA.116.305017.
17. Abriel H. Cardiac sodium channel Na(v)1.5 and interacting proteins: physiology and pathophysiology. J Mol Cell Cardiol. 2010;48(1):2–11. https://doi.org/10.1016/j.yjmcc.2009.08.025.
18. Rook MB, Evers MM, Vos MA, Bierhuizen MF. Biology of cardiac sodium channel Nav1.5 expression. Cardiovasc Res. 2012;93(1):12–23. https://doi.org/10.1093/cvr/cvr252.

19. Perez-Riera AR, Daminello Raimundo R, Akira Watanabe R, Luiz de Figueiredo J, Carlos de Abreu L. Cardiac sodium channel, its mutations and their spectrum of arrhythmia phenotypes. J Hum Growth Dev. 2016;26(3):281–96. https://doi.org/10.7322/jhgd.119236.
20. Hund T, Mohler PJ. Biophysics of normal and abnormal cardiac sodium channel function. In: Cardiac electrophysiology: from cell to bedside. Philadelphia: Elsevier; 2014.
21. Wilde AA, Brugada R. Phenotypical manifestations of mutations in the genes encoding subunits of the cardiac sodium channel. Circ Res. 2011;108(7):884–97. https://doi.org/10.1161/CIRCRESAHA.110.238469.
22. Amin AS, Tan HL, Wilde AA. Cardiac ion channels in health and disease. Heart Rhythm. 2010;7(1):117–26. https://doi.org/10.1016/j.hrthm.2009.08.005.
23. Rosati B, McKinnon D. Regulation of ion channel expression. Circ Res. 2004;94(7):874–83. https://doi.org/10.1161/01.RES.0000124921.81025.1F.
24. Van Norstrand DW, Tester DJ, Ackerman MJ. Overrepresentation of the proarrhythmic, sudden death predisposing sodium channel polymorphism S1103Y in a population-based cohort of African-American sudden infant death syndrome. Heart Rhythm. 2008;5(5):712–5. https://doi.org/10.1016/j.hrthm.2008.02.012.
25. Noble D, Noble PJ. Late sodium current in the pathophysiology of cardiovascular disease: consequences of sodium-calcium overload. Heart. 2006;92(Suppl 4):iv1–5. https://doi.org/10.1136/hrt.2005.078782.
26. Antzelevitch C, Nesterenko V, Shryock JC, Rajamani S, Song Y, Belardinelli L. The role of late I_{Na} in development of cardiac arrhythmias. Handb Exp Pharmacol. 2014;221:137–68. https://doi.org/10.1007/978-3-642-41588-3_7.
27. Fozzard H, Hanck D. Structure and function of voltage dependent sodium channels: comparison of brain II and cardiac isoforms. Physiol Rev. 1996;76:887–926.
28. Balser JR. Structure and function of the cardiac sodium channels. Cardiovasc Res. 1999;42:327–38.
29. Catterall WA. Voltage-gated sodium channels and electrical excitability of the heart. In: Cardiac electrophysiology: from cell to bedside. Amsterdam: Elsevier; 2014.

30. Catterall WA. From ionic currents to molecular review mechanisms- the structure and function of voltage-gated sodium channels. Neuron. 2000;26:13–25.
31. Goldin A, Barchi R, Caldwell J, Hofmann F, Howe J, Hunter J, Kallen R, Mandel G, Meisler M, Netter Y, Noda M, Tamkun M, Waxman S, Wood J, Catterall WA. Nomenclature of voltage-gated sodium channels. Neuron. 2000;28:365–8.
32. Weirich J, Antoni H. Differential analysis of the frequency dependent effects of class I-J Cardiovasc Pharma-1990-Weirich & Antoni. J Cardiovasc Pharmacol. 1990;15:998–1009.
33. Hondeghem L, Snyders D. Class III antiarrhythmic agents have a lot of potential but a long way to go: reduced effectiveness and dangers of reverse use dependence. Circ. 1990;81(2):686–90.
34. Shryock JC, Song Y, Rajamani S, Antzelevitch C, Belardinelli L. The arrhythmogenic consequences of increasing late INa in the cardiomyocyte. Cardiovasc Res. 2013;99(4):600–11. https://doi.org/10.1093/cvr/cvt145.
35. Belardinelli L, Giles WR, Rajamani S, Karagueuzian HS, Shryock JC. Cardiac late Na(+) current: proarrhythmic effects, roles in long QT syndromes, and pathological relationship to CaMKII and oxidative stress. Heart Rhythm. 2015;12(2):440–8. https://doi.org/10.1016/j.hrthm.2014.11.009.
36. Campbell T. Differing electrophysiological effects of class IA, IB and IC antiarrhythmic drugs on guinea-pig sinoatrial node. Br J Pharmacol. 1987;91:395–401.
37. Williams V. Disopyramide. Ann N Y Acad Sci. 1984; 432:189–200.
38. Podrid PJ, Kowey P. Specific Antiarrhythmic Drugs. In: Cardiac arrhythmia: mechanisms, diagnosis, and management. Philadelphia: Williams & Wilkins; 1995. p. 369.
39. Marquez MF, Bonny A, Hernandez-Castillo E, De Sisti A, Gomez-Flores J, Nava S, Hidden-Lucet F, Iturralde P, Cardenas M, Tonet J. Long-term efficacy of low doses of quinidine on malignant arrhythmias in Brugada syndrome with an implantable cardioverter-defibrillator: a case series and literature review. Heart Rhythm. 2012;9(12):1995–2000. https://doi.org/10.1016/j.hrthm.2012.08.027.
40. Antzelevitch C, Fish JM. Therapy for the Brugada syndrome. Handb Exp Pharmacol. 2006;171:305–30.

41. Belhassen B. Is quinidine the ideal drug for Brugada syndrome? Heart Rhythm. 2012;9(12):2001–2. https://doi.org/10.1016/j.hrthm.2012.08.037.
42. Marquez MF, Salica G, Hermosillo AG, Pastelin G, Gomez-Flores J, Nava S, Cardenas M. Ionic basis of pharmacological therapy in Brugada syndrome. J Cardiovasc Electrophysiol. 2007;18(2):234–40. https://doi.org/10.1111/j.1540-8167.2006.00681.x.
43. Hermida JS, Denjoy I, Clerc J, Extramiana F, Jarry G, Milliez P, Guicheney P, Di Fusco S, Rey JL, Cauchemez B, Leenhardt A. Hydroquinidine therapy in Brugada syndrome. J Am Coll Cardiol. 2004;43(10):1853–60. https://doi.org/10.1016/j.jacc.2003.12.046.
44. Mizusawa Y, Sakurada H, Nishizaki M, Hiraoka M. Effects of low-dose quinidine on ventricular tachyarrhythmias in patients with Brugada syndrome low-dose quinidine therapy as an adjunctive treatment. J Cardiovasc Pharmacol. 2006;47:359–64.
45. Adler A, Viskin S. Clinical features of genetic cardiac diseases related to potassium channelopathies. Card Electrophysiol Clin. 2016;8(2):361–72. https://doi.org/10.1016/j.ccep.2016.02.001.
46. Al-Ahmad A, Shenasa M, Shenasa H, Soleimanieh M. Incessant ventricular tachycardia and fibrillation. Card Electrophysiol Clin. 2014;6(3):613–21. https://doi.org/10.1016/j.ccep.2014.05.010.
47. Belhassen B, Glick A, Viskin S. Excellent long-term reproducibility of the electrophysiologic efficacy of quinidine in patients with idiopathic ventricular fibrillation and Brugada syndrome. Pacing Clin Electrophysiol. 2009;32(3):294–301.
48. Belhassen B, Glick A, Viskin S. Efficacy of quinidine in high-risk patients with Brugada syndrome. Circ. 2004;110(13):1731–7. https://doi.org/10.1161/01.CIR.0000143159.30585.90.
49. Viskin S, Wilde AA, Guevara-Valdivia ME, Daoulah A, Krahn AD, Zipes DP, Halkin A, Shivkumar K, Boyle NG, Adler A, Belhassen B, Schapachnik E, Asrar F, Rosso R, Fadreguilan EC, Veltman C, Veerakul G, Marquez M, Juneja R, Daoulah AN, Caorsi WR, Cuesta A, Jensen HK, Hamad AK, Spears D, Lozano IF, Urda VC, Peinado R, Panduranga P, Emkanjoo Z, Bergfeldt L, Janousek J. Quinidine, a life-saving medication for Brugada syndrome, is inaccessible in many countries. J Am Coll Cardiol. 2013;61(23):2383–7. https://doi.org/10.1016/j.jacc.2013.02.077.

50. Shen T, Yuan B, Geng J, Chen C, Zhou X, Shan Q. Low-dose quinidine effectively reduced shocks in Brugada syndrome patients with an implantable cardioverter defibrillator: a Chinese case series report. Ann Noninvasive Electrocardiol. 2017;22(1):e12375. https://doi.org/10.1111/anec.12375.
51. Marquez M, Salica G, Hermosillo AG, Pastelin G, Cardenas M. Drug therapy in Brugada syndrome. Curr Drug Targets Cardiovasc Haematol Disord. 2005;5(5):409–17.
52. Wilde AA, Postema PG, Di Diego JM, Viskin S, Morita H, Fish JM, Antzelevitch C. The pathophysiological mechanism underlying Brugada syndrome: depolarization versus repolarization. J Mol Cell Cardiol. 2010;49(4):543–53. https://doi.org/10.1016/j.yjmcc.2010.07.012.
53. Giustetto C, Schimpf R, Mazzanti A, Scrocco C, Maury P, Anttonen O, Probst V, Blanc JJ, Sbragia P, Dalmasso P, Borggrefe M, Gaita F. Long-term follow-up of patients with short QT syndrome. J Am Coll Cardiol. 2011;58(6):587–95. https://doi.org/10.1016/j.jacc.2011.03.038.
54. Wolpert C, Schimpf R, Giustetto C, Antzelevitch C, Cordeiro J, Dumaine R, Brugada R, Hong K, Bauersfeld U, Gaita F, Borggrefe M. Further insights into the effect of quinidine in short QT syndrome caused by a mutation in HERG. J Cardiovasc Electrophysiol. 2005;16(1):54–8. https://doi.org/10.1046/j.1540-8167.2005.04470.x.
55. Gaita F, Giustetto C, Bianchi F, Schimpf R, Haissaguerre M, Calo L, Brugada R, Antzelevitch C, Borggrefe M, Wolpert C. Short QT syndrome: pharmacological treatment. J Am Coll Cardiol. 2004;43(8):1494–9. https://doi.org/10.1016/j.jacc.2004.02.034.
56. Haissaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquie JL. Sudden cardiac arrest associated with early repolarization. N Engl J Med. 2008;358:2016–23.
57. Antzelevitch C, Yan GX. J wave syndromes. Heart Rhythm. 2010;7(4):549–58. https://doi.org/10.1016/j.hrthm.2009.12.006.
58. Yan G, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. Circ. 1999;100:1660–6.
59. Gussak I, Antzelevitch C, Bjerregaard P, Towbin J, Chaitman B. The Brugada syndrome: clinical, electrophysiologic and genetic aspects. J Am Coll Cardiol. 1999;33(1):5–15. https://doi.org/10.1016/s0735-1097(98)00528-2.

60. Shimizu W, Antzelevitch C, Suyama K, Kurita T, Taguchi A, Aihara N. Effect of sodium channel blockers on ST segment, QRS duration, and corrected QT interval in patients with Brugada syndrome. J Cardiovasc Electrophysiol. 2000;11:1320–9.
61. Brugada R, Brugada J, Antzelevitch C, Kirsch GE, Potenza D, Towbin JA, Brugada P. Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. Circ. 2000;101:510–5.
62. Morita H, Morita T, Nagase S, Banba K, Nishi N, Tani Y, Watanabe A. Ventricular arrhythmia induced by sodium channel blocker in patients with Brugada syndrome. J Am Coll Cardiol. 2003;42:1624–31. https://doi.org/10.1016/S0735-1097(03)01124-0.
63. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESCEndorsed by the European Stroke Organisation (ESO). Eur Heart J. 2016;37(38):2893–962. https://doi.org/10.1093/eurheartj/ehw210.
64. Roden DM. Cellular basis of drug-induced torsades de pointes. Br J Pharmacol. 2008;154(7):1502–7. https://doi.org/10.1038/bjp.2008.238.
65. Roten L, Derval N, Sacher F, Pascale P, Wilton SB, Scherr D, Shah A, Pedersen ME, Jadidi AS, Miyazaki S, Knecht S, Hocini M, Jais P, Haissaguerre M. Ajmaline attenuates electrocardiogram characteristics of inferolateral early repolarization. Heart Rhythm. 2012;9(2):232–9. https://doi.org/10.1016/j.hrthm.2011.09.013.
66. Postema PG, Wolpert C, Amin AS, Probst V, Borggrefe M, Roden DM, Priori SG, Tan HL, Hiraoka M, Brugada J, Wilde AA. Drugs and Brugada syndrome patients: review of the literature, recommendations, and an up-to-date website (http://www.brugadadrugs.org). Heart Rhythm. 2009;6(9):1335–41. https://doi.org/10.1016/j.hrthm.2009.07.002.

67. Somani R, Krahn AD, Healey JS, Chauhan VS, Birnie DH, Champagne J, Sanatani S, Angaran P, Gow RM, Chakrabarti S, Gerull B, Yee R, Skanes AC, Gula LJ, Leong-Sit P, Klein GJ, Gollob MH, Talajic M, Gardner M, Simpson CS. Procainamide infusion in the evaluation of unexplained cardiac arrest: from the cardiac arrest survivors with preserved ejection fraction registry (CASPER). Heart Rhythm. 2014;11(6):1047–54. https://doi.org/10.1016/j.hrthm.2014.03.022.
68. Fish JM, Antzelevitch C. Role of sodium and calcium channel block in unmasking the Brugada syndrome. Heart Rhythm. 2004;1(2):210–7. https://doi.org/10.1016/j.hrthm.2004.03.061.
69. Fujimura O, Klein GJ, Sharma AD, Yee R, Szabo T. Acute effect of disopyramide on atrial fibrillation in the Wolff-Parkinson-white syndrome. J Am Coll Cardiol. 1989;13(5):1133–7. https://doi.org/10.1016/0735-1097(89)90275-1.
70. Zainal N, Griffiths JW, Carmichael DJS, Besterman EMM, Kidner PH, Gillham AD, Summers GD. Oral disopyramide for the prevention of arrhythmias in patients with acute myocardial infarction admitted to open wards. Lancet. 1977;310(8044):887–9. https://doi.org/10.1016/S0140-6736(77)90829-7.
71. Psotka MA, Lee BK. Atrial fibrillation: antiarrhythmic therapy. Curr Probl Cardiol. 2014;39(10):351–91. https://doi.org/10.1016/j.cpcardiol.2014.07.004.
72. Ito M, Onodera S, Hashimoto J, Noshiro H, Shinoda S, Nagashima M, Suzuki H. Effect of disopyramide on initiation of atrial fibrillation and relation to effective refractory period. Am J Cardiol. 1989;63:561–6.
73. Sherrid MV, Barac I, McKenna WJ, Elliott PM, Dickie S, Chojnowska L, Casey S, Maron BJ. Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005;45(8):1251–8. https://doi.org/10.1016/j.jacc.2005.01.012.
74. Reiffel J, Estes M, Waldo A, Prystowsky E, DiBianco R. A consensus report on antiarrhythmic drug use. Clin Cardiol. 1994;17:103–16.
75. Sherrid MV, Arabadjian M. A primer of disopyramide treatment of obstructive hypertrophic cardiomyopathy. Prog Cardiovasc Dis. 2012;54(6):483–92. https://doi.org/10.1016/j.pcad.2012.04.003.
76. Wellens HJJ, Bär FW, Gorgels AP, Vanagt EJ. Use of ajmaline in patients with the Wolff-Parkinson-White syndrome to disclose short refractory period of the accessory pathway. In: Smeets

JLRM, Doevendans PA, Josephson ME, Kirchhof C, Vos MA, editors. Professor Hein J.J. Wellens: 33 years of cardiology and arrhythmology. Dordrecht: Springer; 2000. p. 215–9. https://doi.org/10.1007/978-94-011-4110-9_20.

77. Khalilullah M, Sathyamurthy I, Singhal NK. Ajmaline in WPW syndrome: an electrophysiologic study. Am Heart J. 1980;99(6):766–71. https://doi.org/10.1016/0002-8703(80)90627-4.
78. Wellens HJJ, Bär FW, Dassen WRM, Brugada P, Vanagt EJ, Farré J. Effect of drugs in the wolff-parkinson-white syndrome. Am J Cardiol. 1980;46(4):665–9. https://doi.org/10.1016/0002-9149(80)90518-4.
79. Rolf S. The ajmaline challenge in Brugada syndrome: diagnostic impact, safety, and recommended protocol. Eur Heart J. 2003;24(12):1104–12. https://doi.org/10.1016/s0195-668x(03)00195-7.
80. Conte G, Sieira J, Sarkozy A, de Asmundis C, Di Giovanni G, Chierchia GB, Ciconte G, Levinstein M, Casado-Arroyo R, Baltogiannis G, Saenen J, Saitoh Y, Pappaert G, Brugada P. Life-threatening ventricular arrhythmias during ajmaline challenge in patients with Brugada syndrome: incidence, clinical features, and prognosis. Heart Rhythm. 2013;10(12):1869–74. https://doi.org/10.1016/j.hrthm.2013.09.060.
81. Nault I, Champagne J. How safe is ajmaline challenge in patients with suspected Brugada syndrome? Heart Rhythm. 2013;10(12):1875–6. https://doi.org/10.1016/j.hrthm.2013.10.047.
82. Mazzanti A, Maragna R, Faragli A, Monteforte N, Bloise R, Memmi M, Novelli V, Baiardi P, Bagnardi V, Etheridge SP, Napolitano C, Priori SG. Gene-specific therapy with mexiletine reduces arrhythmic events in patients with long QT syndrome type 3. J Am Coll Cardiol. 2016;67(9):1053–8. https://doi.org/10.1016/j.jacc.2015.12.033.
83. Badri M, Patel A, Patel C, Liu G, Goldstein M, Robinson VM, Xue X, Yang L, Kowey PR, Yan G-X. Mexiletine prevents recurrent torsades de pointes in acquired long QT syndrome refractory to conventional measures. JACC Clin Electrophysiol. 2015;1(4):315–22. https://doi.org/10.1016/j.jacep.2015.05.008.
84. Shimizu W, Antzelevitch C. Sodium channel block with mexiletine is effective in reducing dispersion of repolarization and preventing torsade de pointes in LQT2 and LQT3 models of the long-QT syndrome. Circ. 1997;96:2038–47.

85. Gao Y, Xue X, Hu D, Liu W, Yuan Y, Sun H, Li L, Timothy KW, Zhang L, Li C, Yan GX. Inhibition of late sodium current by mexiletine: a novel pharmotherapeutical approach in timothy syndrome. Circ Arrhythm Electrophysiol. 2013;6(3):614–22. https://doi.org/10.1161/CIRCEP.113.000092.
86. Chimienti M, Cullen M, Casadei G. Safety of long-term flecainide and propafenone in the management of patients with symptomatic paroxysmal atrial fibrillation: report from the Flecainide and Propafenone Italian Study Investigators. Am J Cardiol. 1996;77:60A–75A.
87. Antman EM, Beamer AD, Cantillon C, McGowan N, Goldman L, Friedman P. Long-term oral propafenone therapy for suppression of refractory atrial fibrillation and atrial flutter. J Am Coll Cardiol. 1988;12:1005–11.
88. Shenasa M, Shenasa H, Rouhani S. Atrial fibrillation in different clinical subsets. In: Shenasa M, Camm J, editors. Management of atrial fibrillation. Oxford: Oxford University Press; 2015. p. 25–73.
89. Kus T, Dubuc M, Lambert C, Shenasa M. Efficacy of propafenone in preventing ventricular tachycardia: inverse correlation with rate-related prolongation of conduction time. J Am Coll Cardiol. 1990;16(5):1229–37.
90. Marchlinski F. Sorting out the mechanisms of antiarrhythmic drug action. J Am Coll Cardiol. 1990;16(5):1238–9.
91. Napolitano C, Bloise R, Monteforte N, Priori SG. Sudden cardiac death and genetic ion channelopathies: long QT, Brugada, short QT, catecholaminergic polymorphic ventricular tachycardia, and idiopathic ventricular fibrillation. Circ. 2012;125(16):2027–34. https://doi.org/10.1161/CIRCULATIONAHA.111.055947.
92. Schwartz PJ, Ackerman MJ, George AL Jr, Wilde AA. Impact of genetics on the clinical management of channelopathies. J Am Coll Cardiol. 2013;62(3):169–80. https://doi.org/10.1016/j.jacc.2013.04.044.
93. Shea P, Lal R, Kim S, Schechtman K, Ruffy R. Flecainide and amiodarone interaction. J Am Coll Cardiol. 1986;7:1127–30.
94. Roden D, Woosley RL. Drug therapy: flecainide. N Engl J Med. 1986;315(1):36–41.
95. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of

sudden cardiac death: the task Force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC) endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015;36(41):2793–867. https://doi.org/10.1093/eurheartj/ehv316.

96. Jazayeri MR, Vanwyhe G, Avitall B, McKinnie J, Tchou P, Akhtar M. Isoproterenol reversal of antiarrhythmic effects in patients with inducible sustained ventricular tachyarrhythmias. J Am Coll Cardiol. 1989;14(3):705–11. https://doi.org/10.1016/0735-1097(89)90114-9.
97. Bannister ML, Thomas NL, Sikkel MB, Mukherjee S, Maxwell C, MacLeod KT, George CH, Williams AJ. The mechanism of flecainide action in CPVT does not involve a direct effect on RyR2. Circ Res. 2015;116(8):1324–35. https://doi.org/10.1161/CIRCRESAHA.116.305347.
98. Smith GL, MacQuaide N. The direct actions of flecainide on the human cardiac ryanodine receptor: keeping open the debate on the mechanism of action of local anesthetics in CPVT. Circ Res. 2015;116(8):1284–6. https://doi.org/10.1161/CIRCRESAHA.115.306298.
99. van der Werf C, Zwinderman AH, Wilde AA. Therapeutic approach for patients with catecholaminergic polymorphic ventricular tachycardia: state of the art and future developments. Europace. 2012;14(2):175–83. https://doi.org/10.1093/europace/eur277.
100. van der Werf C, Kannankeril PJ, Sacher F, Krahn AD, Viskin S, Leenhardt A, Shimizu W, Sumitomo N, Fish FA, Bhuiyan ZA, Willems AR, van der Veen MJ, Watanabe H, Laborderie J, Haissaguerre M, Knollmann BC, Wilde AA. Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. J Am Coll Cardiol. 2011;57(22):2244–54. https://doi.org/10.1016/j.jacc.2011.01.026.
101. Jacquemart C, Ould Abderrahmane F, Massin MM. Effects of flecainide therapy on inappropriate shocks and arrythmias in catecholaminergic polymorphic ventricular tachycardia. J Electrocardiol. 2012;45(6):736–8. https://doi.org/10.1016/j.jelectrocard.2012.05.002.

102. Watanabe H, van der Werf C, Roses-Noguer F, Adler A, Sumitomo N, Veltmann C, Rosso R, Bhuiyan ZA, Bikker H, Kannankeril PJ, Horie M, Minamino T, Viskin S, Knollmann BC, Till J, Wilde AA. Effects of flecainide on exercise-induced ventricular arrhythmias and recurrences in genotype-negative patients with catecholaminergic polymorphic ventricular tachycardia. Heart Rhythm. 2013;10(4):542–7. https://doi.org/10.1016/j.hrthm.2012.12.035.
103. Pellizzon OA, Kalaizich L, Ptacek LJ, Tristani-Firouzi M, Gonzalez MD. Flecainide suppresses bidirectional ventricular tachycardia and reverses tachycardia-induced cardiomyopathy in Andersen-Tawil syndrome. J Cardiovasc Electrophysiol. 2008;19(1):95–7. https://doi.org/10.1111/j.1540-8167.2007.00910.x.
104. Padfield GJ, AlAhmari L, Lieve KV, AlAhmari T, Roston TM, Wilde AA, Krahn AD, Sanatani S. Flecainide monotherapy is an option for selected patients with catecholaminergic polymorphic ventricular tachycardia intolerant of beta-blockade. Heart Rhythm. 2016;13(2):609–13. https://doi.org/10.1016/j.hrthm.2015.09.027.
105. Watanabe H, Chopra N, Laver D, Hwang HS, Davies SS, Roach DE, Duff HJ, Roden DM, Wilde AA, Knollmann BC. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. Nat Med. 2009;15(4):380–3. https://doi.org/10.1038/nm.1942.
106. Meregalli PG, Ruijter JM, Hofman N, Bezzina CR, Wilde AA, Tan HL. Diagnostic value of flecainide testing in unmasking SCN5A-related Brugada syndrome. J Cardiovasc Electrophysiol. 2006;17(8):857–64. https://doi.org/10.1111/j.1540-8167.2006.00531.x.
107. Wolpert C, Echternach C, Veltmann C, Antzelevitch C, Thomas GP, Spehl S, Streitner F, Kuschyk J, Schimpf R, Haase KK, Borggrefe M. Intravenous drug challenge using flecainide and ajmaline in patients with Brugada syndrome. Heart Rhythm. 2005;2(3):254–60. https://doi.org/10.1016/j.hrthm.2004.11.025.
108. Windle J, Geletka R, Moss A, Zareba W, Atkins D. Normalization of ventricular repolarization with flecainide in long QT syndrome patients with SCN5A-DeltaKPQ mutation. Ann Noninvasive Electrocardiol. 2001;6(2):153–8.

109. Strizek B, Berg C, Gottschalk I, Herberg U, Geipel A, Gembruch U. High-dose flecainide is the most effective treatment of fetal supraventricular tachycardia. Heart Rhythm. 2016;13(6):1283–8. https://doi.org/10.1016/j.hrthm.2016.01.029.
110. Sridharan S, Sullivan I, Tomek V, Wolfenden J, Skovranek J, Yates R, Janousek J, Dominguez TE, Marek J. Flecainide versus digoxin for fetal supraventricular tachycardia: comparison of two drug treatment protocols. Heart Rhythm. 2016;13(9):1913–9. https://doi.org/10.1016/j.hrthm.2016.03.023.
111. Van Hare GF. Flecainide vs digoxin for fetal supraventricular tachycardia: comparison of 2 drug protocols. Heart Rhythm. 2016;13(9):1920–1. https://doi.org/10.1016/j.hrthm.2016.03.045.
112. Vigneswaran TV, Callaghan N, Andrews RE, Miller O, Rosenthal E, Sharland GK, Simpson JM. Correlation of maternal flecainide concentrations and therapeutic effect in fetal supraventricular tachycardia. Heart Rhythm. 2014;11(11):2047–53. https://doi.org/10.1016/j.hrthm.2014.07.031.
113. Cuneo BF, Benson DW. Use of maternal flecainide concentration in management of fetal supraventricular tachycardia: a step in the right direction. Heart Rhythm. 2014;11(11):2054–5. https://doi.org/10.1016/j.hrthm.2014.08.017.
114. Crijns HJ, van Gelder IC, Lie KI. Supraventricular tachycardia mimicking ventricular tachycardia during flecainide treatment. Am J Cardiol. 1988;62(17):1303–6. https://doi.org/10.1016/0002-9149(88)90282-2.
115. Camm J. Antiarrhythmic drugs for the maintenance of sinus rhythm: risks and benefits. Int J Cardiol. 2012;155(3):362–71. https://doi.org/10.1016/j.ijcard.2011.06.012.
116. Ranger S, Talajic M, Lemery R, Roy D, Nattel S. Amplification of flecainide-induced ventricular conduction slowing by exercise. Circ. 1989;79:1000–6.
117. Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, Cobbe S, Breithardt G, Le Heuzey JY, Prins MH, Levy S, Crijns HJ, European Heart Survey Investigators. Atrial fibrillation management: a prospective survey in ESC member countries: the euro heart survey on atrial fibrillation. Eur Heart J. 2005;26(22):2422–34. https://doi.org/10.1093/eurheartj/ehi505.
118. Bailey DDG, Dresser GK. Interactions between grapefruit juice and cardiovascular drugs. Am J Cardiovasc Drugs. 2004;4(5):281–97. https://doi.org/10.2165/00129784-200404050-00002.

119. Fuhr U. Drug interactions with grapefruit juice. Drug safety. 1998;18(4):251–72.
120. Roden D. Antiarrhythmic drugs: from mechanisms to clinical practice. Heart. 2000;84:339–46.
121. Zitron E, Scholz E, Owen RW, Luck S, Kiesecker C, Thomas D, Kathofer S, Niroomand F, Kiehn J, Kreye VA, Katus HA, Schoels W, Karle CA. QTc prolongation by grapefruit juice and its potential pharmacological basis: HERG channel blockade by flavonoids. Circ. 2005;111(7):835–8. https://doi.org/10.1161/01.CIR.0000155617.54749.09.
122. Jaillon P. Antiarrhythmic drug interactions: are they important? Eur Heart J. 1987;8(Suppl A):127–32.
123. Colatsky T, Follmer C, Starmer CF. Channel specificity in antiarrhythmic drug action mechanism of potassium channel block and its role in suppressing and aggravating cardiac arrhythmias. Circ. 1990;82:2235–42.
124. Ravens U. Potassium channels in atrial fibrillation: targets for atrial and pathology-specific therapy? Heart Rhythm. 2008;5(5):758–9. https://doi.org/10.1016/j.hrthm.2007.11.008.
125. Burashnikov A, Antzelevitch C. Atrial-selective sodium channel blockers: do they exist? J Cardiovasc Pharmacol. 2008;52(2):121–8. https://doi.org/10.1097/FJC.0b013e31817618eb.
126. Sicouri S, Glass A, Belardinelli L, Antzelevitch C. Antiarrhythmic effects of ranolazine in canine pulmonary vein sleeve preparations. Heart Rhythm. 2008;5(7):1019–26. https://doi.org/10.1016/j.hrthm.2008.03.018.
127. Sicouri S, Belardinelli L, Carlsson L, Antzelevitch C. Potent antiarrhythmic effects of chronic amiodarone in canine pulmonary vein sleeve preparations. J Cardiovasc Electrophysiol. 2009;20(7):803–10. https://doi.org/10.1111/j.1540-8167.2009.01449.x.
128. Ravens U, Poulet C, Wettwer E, Knaut M. Atrial selectivity of antiarrhythmic drugs. J Physiol. 2013;591(Pt 17):4087–97. https://doi.org/10.1113/jphysiol.2013.256115.
129. Cahalan M, Begenisich T. Sodium channel selectivity: dependence on internal permeant ion concentration. J Gen Physiol. 1976;68:111–25.
130. Comtois P, Sakabe M, Vigmond EJ, Munoz M, Texier A, Shiroshita-Takeshita A, Nattel S. Mechanisms of atrial fibrillation termination by rapidly unbinding Na+ channel blockers: insights from mathematical models and experimental corre-

lates. Am J Physiol Heart Circ Physiol. 2008;295(4):H1489–504. https://doi.org/10.1152/ajpheart.01054.2007.
131. Shenasa M. Ranolazine: electrophysiologic effect efficacy, and safety in patients with cardiac arrhythmias. Card Electrophysiol Clin. 2016;8:467–79.
132. Burashnikov A, Petroski A, Hu D, Barajas-Martinez H, Antzelevitch C. Atrial-selective inhibition of sodium-channel current by Wenxin Keli is effective in suppressing atrial fibrillation. Heart Rhythm. 2012;9(1):125–31. https://doi.org/10.1016/j.hrthm.2011.08.027.
133. Antzelevitch C, Burashnikov A. Atrial-selective sodium channel block as a novel strategy for the management of atrial fibrillation. J Electrocardiol. 2009;42(6):543–8. https://doi.org/10.1016/j.jelectrocard.2009.07.007.
134. Ehrlich JR, Biliczki P, Hohnloser SH, Nattel S. Atrial-selective approaches for the treatment of atrial fibrillation. J Am Coll Cardiol. 2008;51(8):787–92. https://doi.org/10.1016/j.jacc.2007.08.067.
135. Burashnikov A, Di Diego JM, Zygmunt AC, Belardinelli L, Antzelevitch C. Atrium-selective sodium channel block as a strategy for suppression of atrial fibrillation: differences in sodium channel inactivation between atria and ventricles and the role of ranolazine. Circ. 2007;116(13):1449–57. https://doi.org/10.1161/CIRCULATIONAHA.107.704890.
136. Burashnikov A, Di Diego JM, Sicouri S, Ferreiro M, Carlsson L, Antzelevitch C. Atrial-selective effects of chronic amiodarone in the management of atrial fibrillation. Heart Rhythm. 2008;5(12):1735–42. https://doi.org/10.1016/j.hrthm.2008.09.015.
137. Burashnikov A, Di Diego JM, Zygmunt AC, Belardinelli L, Antzelevitch C. Atrial-selective sodium channel block as a strategy for suppression of atrial fibrillation. Ann N Y Acad Sci. 2008;1123:105–12.
138. Dubyak GR. Ion homeostasis, channels, and transporters: an update on cellular mechanisms. Adv Physiol Educ. 2004;28(1–4):143–54. https://doi.org/10.1152/advan.00046.2004.
139. Glaaser IW, Kass RS, Clancy CE. Mechanisms of genetic arrhythmias: from DNA to ECG. Prog Cardiovasc Dis. 2003;46(3):259–70. https://doi.org/10.1016/s0033-0620(03)00073-2.

140. Schulze-Bahr E. Arrhythmia predisposition. J Am Coll Cardiol. 2006;48(9):A67–78. https://doi.org/10.1016/j.jacc.2006.07.006.
141. Webster G, Berul CI. An update on channelopathies: from mechanisms to management. Circ. 2013;127(1):126–40. https://doi.org/10.1161/CIRCULATIONAHA.111.060343.
142. Wilde AA, Bezzina CR. Genetics of cardiac arrhythmias. Heart. 2005;91(10):1352–8. https://doi.org/10.1136/hrt.2004.046334.
143. Antzelevitch C. Molecular genetics of arrhythmias and cardiovascular conditions associated with arrhythmias. J Cardiovasc Electrophysiol. 2003;14(11):1259–72. https://doi.org/10.1046/j.1540-8167.2003.03316.x.
144. Ruan Y, Liu N, Priori SG. Sodium channel mutations and arrhythmias. Nat Rev Cardiol. 2009;6(5):337–48. https://doi.org/10.1038/nrcardio.2009.44.
145. Cerrone M, Cummings S, Alansari T, Priori SG. A clinical approach to inherited arrhythmias. Circ Cardiovasc Genet. 2012;5(5):581–90. https://doi.org/10.1161/CIRCGENETICS.110.959429.
146. Kass RS. The channelopathies: novel insights into molecular and genetic mechanisms of human disease. J Clin Invest. 2005;115(8):1986–9. https://doi.org/10.1172/JCI26011.
147. Abriel H, Zaklyazminskaya EV. A modern approach to classify missense mutations in cardiac channelopathy genes. Circ Cardiovasc Genet. 2012;5(5):487–9. https://doi.org/10.1161/CIRCGENETICS.112.964809.
148. Tsai CT, Lai LP, Hwang JJ, Lin JL, Chiang FT. Molecular genetics of atrial fibrillation. J Am Coll Cardiol. 2008;52(4):241–50. https://doi.org/10.1016/j.jacc.2008.02.072.
149. Tfelt-Hansen J, Winkel BG, Grunnet M, Jespersen T. Inherited cardiac diseases caused by mutations in the Nav1.5 sodium channel. J Cardiovasc Electrophysiol. 2010;21(1):107–15. https://doi.org/10.1111/j.1540-8167.2009.01633.x.
150. Watanabe H, Nogami A, Ohkubo K, Kawata H, Hayashi Y, Ishikawa T, Makiyama T, Nagao S, Yagihara N, Takehara N, Kawamura Y, Sato A, Okamura K, Hosaka Y, Sato M, Fukae S, Chinushi M, Oda H, Okabe M, Kimura A, Maemura K, Watanabe I, Kamakura S, Horie M, Aizawa Y, Shimizu W, Makita N. Electrocardiographic characteristics

and SCN5A mutations in idiopathic ventricular fibrillation associated with early repolarization. Circ Arrhythm Electrophysiol. 2011;4(6):874–81. https://doi.org/10.1161/CIRCEP.111.963983.

151. Roberts JD, Gollob MH. A contemporary review on the genetic basis of atrial fibrillation. Methodist Debakey Cardiovasc J. 2014;10(1):18–24.
152. Mestroni L, Brun F, Spezzacatene A, Sinagra G, Taylor MR. Genetic causes of dilated cardiomyopathy. Prog Pediatr Cardiol. 2014;37(1–2):13–8. https://doi.org/10.1016/j.ppedcard.2014.10.003.
153. Remme CA. Cardiac sodium channelopathy associated with SCN5A mutations: electrophysiological, molecular and genetic aspects. J Physiol. 2013;591(17):4099–116. https://doi.org/10.1113/jphysiol.2013.256461.
154. Chockalingam P, Clur SA, Breur JM, Kriebel T, Paul T, Rammeloo LA, Wilde AA, Blom NA. The diagnostic and therapeutic aspects of loss-of-function cardiac sodium channelopathies in children. Heart Rhythm. 2012;9(12):1986–92. https://doi.org/10.1016/j.hrthm.2012.08.011.
155. Schulze-Bahr E, Eckardt L, Breithardt G, Seidl K, Wichter T, Wolpert C, Borggrefe M, Haverkamp W. Sodium channel gene (SCN5A) mutations in 44 index patients with Brugada syndrome: different incidences in familial and sporadic disease. Hum Mutat. 2003;21(6):651–2. https://doi.org/10.1002/humu.9144.
156. Kapplinger JD, Tester DJ, Alders M, Benito B, Berthet M, Brugada J, Brugada P, Fressart V, Guerchicoff A, Harris-Kerr C, Kamakura S, Kyndt F, Koopmann TT, Miyamoto Y, Pfeiffer R, Pollevick GD, Probst V, Zumhagen S, Vatta M, Towbin JA, Shimizu W, Schulze-Bahr E, Antzelevitch C, Salisbury BA, Guicheney P, Wilde AA, Brugada R, Schott JJ, Ackerman MJ. An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for brugada syndrome genetic testing. Heart Rhythm. 2010;7(1):33–46. https://doi.org/10.1016/j.hrthm.2009.09.069.
157. Vatta M, Dumaine R, Varghese G, Richard T, Shimizu W, Aihara N, Nademanee K, Brugada R, Brugada J, Veerakul G, Li H, Bowles NE, Brugada P, Antzelevitch C, Towbin JA. Genetic and biophysical basis of sudden unexplained nocturnal death syndrome (SUNDS), a disease allelic to Brugada syndrome. Hum Mol Genet. 2002;11(3):337–46.

158. Fenske S, Krause SC, Hassan SI, Becirovic E, Auer F, Bernard R, Kupatt C, Lange P, Ziegler T, Wotjak CT, Zhang H, Hammelmann V, Paparizos C, Biel M, Wahl-Schott CA. Sick sinus syndrome in HCN1-deficient mice. Circ. 2013;128(24):2585–94. https://doi.org/10.1161/CIRCULATIONAHA.113.003712.
159. Zhang ZS, Tranquillo J, Neplioueva V, Bursac N, Grant AO. Sodium channel kinetic changes that produce brugada syndrome or progressive cardiac conduction system disease. Am J Physiol Heart Circ Physiol. 2007;292(1):H399–407. https://doi.org/10.1152/ajpheart.01025.2005.
160. Probst V, Allouis M, Sacher F, Pattier S, Babuty D, Mabo P, Mansourati J, Victor J, Nguyen JM, Schott JJ, Boisseau P, Escande D, Le Marec H. Progressive cardiac conduction defect is the prevailing phenotype in carriers of a brugada syndrome SCN5A mutation. J Cardiovasc Electrophysiol. 2006;17(3):270–5. https://doi.org/10.1111/j.1540-8167.2006.00349.x.
161. Schott J-J, Alshinawi C, Kyndt F, Probst V, Hoorntje TM, Hulsbeek M, Wilde AAM, Escande D, Mannens MMAM, Le Marec H. Cardiac conduction defects associate with mutations in SCN5A. Nat Genet. 1999;23(1):20–1.
162. Royer A, van Veen TA, Le Bouter S, Marionneau C, Griol-Charhbili V, Leoni AL, Steenman M, van Rijen HV, Demolombe S, Goddard CA, Richer C, Escoubet B, Jarry-Guichard T, Colledge WH, Gros D, de Bakker JM, Grace AA, Escande D, Charpentier F. Mouse model of SCN5A-linked hereditary Lenegre's disease: age-related conduction slowing and myocardial fibrosis. Circ. 2005;111(14):1738–46. https://doi.org/10.1161/01.CIR.0000160853.19867.61.
163. WP MN, Ku L, Taylor MR, Fain PR, Dao D, Wolfel E, Mestroni L, Familial Cardiomyopathy Registry Research Group. SCN5A mutation associated with dilated cardiomyopathy, conduction disorder, and arrhythmia. Circ. 2004;110(15):2163–7. https://doi.org/10.1161/01.CIR.0000144458.58660.BB.
164. Burkett EL, Hershberger RE. Clinical and genetic issues in familial dilated cardiomyopathy. J Am Coll Cardiol. 2005;45(7):969–81. https://doi.org/10.1016/j.jacc.2004.11.066.
165. Hershberger RE, Siegfried JD. Update 2011: clinical and genetic issues in familial dilated cardiomyopathy. J Am Coll Cardiol. 2011;57(16):1641–9. https://doi.org/10.1016/j.jacc.2011.01.015.
166. Fatkin D. Guidelines for the diagnosis and management of familial dilated cardiomyopathy. Heart Lung Circ. 2011;20(11):691–3. https://doi.org/10.1016/j.hlc.2011.07.008.

167. Laurent G, Saal S, Amarouch MY, Beziau DM, Marsman RF, Faivre L, Barc J, Dina C, Bertaux G, Barthez O, Thauvin-Robinet C, Charron P, Fressart V, Maltret A, Villain E, Baron E, Merot J, Turpault R, Coudiere Y, Charpentier F, Schott JJ, Loussouarn G, Wilde AA, Wolf JE, Baro I, Kyndt F, Probst V. Multifocal ectopic Purkinje-related premature contractions: a new SCN5A-related cardiac channelopathy. J Am Coll Cardiol. 2012;60(2):144–56. https://doi.org/10.1016/j.jacc.2012.02.052.
168. Wan X, Chen S, Sadeghpour A, Wang Q, Kirsch GE. Accelerated inactivation in a mutant Na1 channel associated with idiopathic ventricular fibrillation. Am J Physiol Heart Circ Physiol. 2001;280:H354–60.
169. Hu D, Viskin S, Oliva A, Carrier T, Cordeiro JM, Barajas-Martinez H, Wu Y, Burashnikov E, Sicouri S, Brugada R, Rosso R, Guerchicoff A, Pollevick GD, Antzelevitch C. Novel mutation in the SCN5A gene associated with arrhythmic storm development during acute myocardial infarction. Heart Rhythm. 2007;4(8):1072–80. https://doi.org/10.1016/j.hrthm.2007.03.040.
170. Delisle BP, Anson BD, Rajamani S, January CT. Biology of cardiac arrhythmias: ion channel protein trafficking. Circ Res. 2004;94(11):1418–28. https://doi.org/10.1161/01.RES.0000128561.28701.ea.
171. Sarkozy A, Brugada P. Sudden cardiac death and inherited arrhythmia syndromes. J Cardiovasc Electrophysiol. 2005;16(Suppl 1):S8–20. https://doi.org/10.1111/j.1540-8167.2005.50110.x.
172. Remme CA, Verkerk AO, Nuyens D, van Ginneken AC, van Brunschot S, Belterman CN, Wilders R, van Roon MA, Tan HL, Wilde AA, Carmeliet P, de Bakker JM, Veldkamp MW, Bezzina CR. Overlap syndrome of cardiac sodium channel disease in mice carrying the equivalent mutation of human SCN5A-1795insD. Circ. 2006;114(24):2584–94. https://doi.org/10.1161/CIRCULATIONAHA.106.653949.
173. Grant AO, Carboni MP, Neplioueva V, Starmer CF, Memmi M, Napolitano C, Priori S. A spontaneous mutation identifies a residue critical for closed-state inactivation of cardiac sodium channels. Circ. 2001;104(suppl II):II–310.
174. Havakuk O, Viskin S. A tale of 2 diseases: the history of long-QT syndrome and brugada syndrome. J Am Coll Cardiol. 2016;67(1):100–8. https://doi.org/10.1016/j.jacc.2015.10.020.

175. Gourraud JB, Kyndt F, Fouchard S, Rendu E, Jaafar P, Gully C, Gacem K, Dupuis JM, Longueville A, Baron E, Karakachoff M, Cebron JP, Chatel S, Schott JJ, Le Marec H, Probst V. Identification of a strong genetic background for progressive cardiac conduction defect by epidemiological approach. Heart. 2012;98(17):1305–10. https://doi.org/10.1136/heartjnl-2012-301872.
176. Korkmaz S, Zitron E, Bangert A, Seyler C, Li S, Hegedus P, Scherer D, Li J, Fink T, Schweizer PA, Giannitsis E, Karck M, Szabo G, Katus HA, Kaya Z. Provocation of an autoimmune response to cardiac voltage-gated sodium channel NaV1.5 induces cardiac conduction defects in rats. J Am Coll Cardiol. 2013;62(4):340–9. https://doi.org/10.1016/j.jacc.2013.04.041.
177. Lee HC, Huang KT, Wang XL, Shen WK. Autoantibodies and cardiac arrhythmias. Heart Rhythm. 2011;8(11):1788–95. https://doi.org/10.1016/j.hrthm.2011.06.032.
178. Kovach JR, Benson DW. Conduction disorders and Nav1.5. Card Electrophysiol Clin. 2014;6(4):723–31. https://doi.org/10.1016/j.ccep.2014.07.008.
179. Tester DJ, Valdivia C, Harris-Kerr C, Alders M, Salisbury BA, Wilde AA, Makielski JC, Ackerman MJ. Epidemiologic, molecular, and functional evidence suggest A572D-SCN5A should not be considered an independent LQT3-susceptibility mutation. Heart Rhythm. 2010;7(7):912–9. https://doi.org/10.1016/j.hrthm.2010.04.014.
180. Lin H, Dolmatova EV, Morley MP, Lunetta KL, McManus DD, Magnani JW, Margulies KB, Hakonarson H, del Monte F, Benjamin EJ, Cappola TP, Ellinor PT. Gene expression and genetic variation in human atria. Heart Rhythm. 2014;11(2):266–71. https://doi.org/10.1016/j.hrthm.2013.10.051.
181. Amin AS, Boink GJ, Atrafi F, Spanjaart AM, Asghari-Roodsari A, Molenaar RJ, Ruijter JM, Wilde AA, Tan HL. Facilitatory and inhibitory effects of SCN5A mutations on atrial fibrillation in brugada syndrome. Europace. 2011;13(7):968–75. https://doi.org/10.1093/europace/eur011.
182. Muggenthaler M, Behr ER. Brugada syndrome and atrial fibrillation: pathophysiology and genetics. Europace. 2011;13(7):913–5. https://doi.org/10.1093/europace/eur094.
183. Giustetto C, Cerrato N, Gribaudo E, Scrocco C, Castagno D, Richiardi E, Giachino D, Bianchi F, Barbonaglia L, Ferraro

A. Atrial fibrillation in a large population with brugada electrocardiographic pattern: prevalence, management, and correlation with prognosis. Heart Rhythm. 2014;11(2):259–65. https://doi.org/10.1016/j.hrthm.2013.10.043.
184. Smith JG, Melander O, Sjogren M, Hedblad B, Engstrom G, Newton-Cheh C, Platonov PG. Genetic polymorphisms confer risk of atrial fibrillation in patients with heart failure: a population-based study. Eur J Heart Fail. 2013;15(3):250–7. https://doi.org/10.1093/eurjhf/hfs176.
185. Lubitz SA, Rienstra M. Genetic susceptibility to atrial fibrillation: does heart failure change our perspective? Eur J Heart Fail. 2013;15(3):244–6. https://doi.org/10.1093/eurjhf/hft005.
186. Gollob M, Jones D, Krahn A, Danis L, Gong X, Shao Q, Liu X, Veinot J, Tang A, Stewart A, Tesson F. Somatic mutations in the connexin 40 gene (GJA5) in atrial fibrillation. N Engl J Med. 2006;354:2677–88.
187. Darbar D, Kannankeril PJ, Donahue BS, Kucera G, Stubblefield T, Haines JL, George AL Jr, Roden DM. Cardiac sodium channel (SCN5A) variants associated with atrial fibrillation. Circ. 2008;117(15):1927–35. https://doi.org/10.1161/CIRCULATIONAHA.107.757955.
188. Ellinor PT, Nam EG, Shea MA, Milan DJ, Ruskin JN, MacRae CA. Cardiac sodium channel mutation in atrial fibrillation. Heart Rhythm. 2008;5(1):99–105. https://doi.org/10.1016/j.hrthm.2007.09.015.
189. Francis J, Antzelevitch C. Atrial fibrillation and Brugada syndrome. J Am Coll Cardiol. 2008;51(12):1149–53. https://doi.org/10.1016/j.jacc.2007.10.062.
190. Rodriguez-Manero M, Namdar M, Sarkozy A, Casado-Arroyo R, Ricciardi D, de Asmundis C, Chierchia GB, Wauters K, Rao JY, Bayrak F, Van Malderen S, Brugada P. Prevalence, clinical characteristics and management of atrial fibrillation in patients with Brugada syndrome. Am J Cardiol. 2013;111(3):362–7. https://doi.org/10.1016/j.amjcard.2012.10.012.
191. Enriquez A, Antzelevitch C, Bismah V, Baranchuk A. Atrial fibrillation in inherited cardiac channelopathies: from mechanisms to management. Heart Rhythm. 2016;13(9):1878–84. https://doi.org/10.1016/j.hrthm.2016.06.008.
192. Horne AJ, Eldstrom J, Sanatani S, Fedida D. A novel mechanism for LQT3 with 2:1 block: a pore-lining mutation in Nav1.5 significantly affects voltage-dependence of activa-

tion. Heart Rhythm. 2011;8(5):770–7. https://doi.org/10.1016/j.hrthm.2010.12.041.
193. Moss AJ, Kass RS. Long QT syndrome: from channels to cardiac arrhythmias. J Clin Invest. 2005;115(8):2018–24. https://doi.org/10.1172/JCI25537.
194. Moss AJ, Zareba W, Schwarz KQ, Rosero S, McNitt S, Robinson JL. Ranolazine shortens repolarization in patients with sustained inward sodium current due to type-3 long-QT syndrome. J Cardiovasc Electrophysiol. 2008;19(12):1289–93. https://doi.org/10.1111/j.1540-8167.2008.01246.x.
195. Chockalingam P, Wilde A. The multifaceted cardiac sodium channel and its clinical implications. Heart. 2012;98(17):1318–24. https://doi.org/10.1136/heartjnl-2012-301784.
196. Schwartz PJ, Priori SG, Cerrone M, Spazzolini C, Odero A, Napolitano C, Bloise R, De Ferrari GM, Klersy C, Moss AJ, Zareba W, Robinson JL, Hall WJ, Brink PA, Toivonen L, Epstein AE, Li C, Hu D. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long-QT syndrome. Circ. 2004;109(15):1826–33. https://doi.org/10.1161/01.CIR.0000125523.14403.1E.
197. Silver ES, Liberman L, Chung WK, Spotnitz HM, Chen JM, Ackerman MJ, Moir C, Hordof AJ, Pass RH. Long QT syndrome due to a novel mutation in SCN5A: treatment with ICD placement at 1 month and left cardiac sympathetic denervation at 3 months of age. J Interv Card Electrophysiol. 2009;26(1):41–5. https://doi.org/10.1007/s10840-009-9428-1.
198. Horowitz L, Zipes D, Bigger JT, Campbell R, Morganroth J, Podrid PJ, Rosen MR, Woosley RL. Proarrhythmia, arrhythmogenesis or aggravation of arrhythmia-a status report, 1987. Am J Cardiol. 1987;59(11):54E–6E.
199. Josephson ME. Antiarrhythmic agents and the danger of proarrhythmic events. Ann Intern Med. 1989;111(2):101–3. https://doi.org/10.7326/0003-4819-111-2-101.
200. Echt D, Liebson PR, Mitchell B, Peters R, Obias-Manno D, Barker A, Arensberg D, Baker A, Friedman L, Greene L, Huther M, Richardson D. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: the cardiac arrhythmia suppression trial. N Engl J Med. 1991;324(12):781–8.
201. Fenichel R, Malik M. Drug-induced torsades de pointes and implications for drug development. J Cardiovasc Electrophysiol. 2004;15(4):475–95.

202. Liu J, Laurita KR. The mechanism of pause-induced torsades de pointes in long QT syndrome. J Cardiovasc Electrophysiol. 2005;16(9):981–7. https://doi.org/10.1111/j.1540-8167.2005.40677.x.
203. Kay GN, Plumb VJ, Arciniegas JG, Henthorn R, Waldo A. Torsades de pointes: the long-short initiating sequence and other clinical features: observations in 32 patients. J Am Coll Cardiol. 1983;2(5):806–17.
204. Vandersickel N, de Boer TP, Vos MA, Panfilov AV. Perpetuation of torsades de pointes in heterogeneous hearts: competing foci or re-entry? J Physiol. 2016;594(23):6865–78. https://doi.org/10.1113/JP271728.
205. El-Sherif N, Chinushi M, Caref EB, Restivo M. Electrophysiological mechanism of the characteristic electrocardiographic morphology of torsades de pointes tachyarrhythmias in the long-QT syndrome. Detailed analysis of ventricular tridimensional activation patterns. Circ. 1997;96(12):4392–9. https://doi.org/10.1161/01.cir.96.12.4392.
206. Viskin S, Justo D, Halkin A, Zeltser D. Long QT syndrome caused by noncardiac drugs. Prog Cardiovasc Dis. 2003;45(5):415–27. https://doi.org/10.1053/pcad.2003.00101.
207. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. Heart. 2003;89:1363–72.
208. Roden DM, Viswanathan PC. Genetics of acquired long QT syndrome. J Clin Invest. 2005;115(8):2025–32. https://doi.org/10.1172/JCI25539.
209. Camm AJ, Malik M, Yap YG. Acquired long QT syndrome. Hoboken: Wiley-Blackwell; 2004.
210. Riad FS, Davis AM, Moranville MP, Beshai JF. Drug-induced QTc prolongation. Am J Cardiol. 2017;119(2):280–3. https://doi.org/10.1016/j.amjcard.2016.09.041.
211. Locati EH, Zareba W, Moss A, Schwartz PJ, Vincent M, Lehmann MH, Towbin JA, Priori SG, Napolitano C, Robinson JL, Andrews M, Timothy K, Hall W. Age- and sex-related differences in clinical manifestations in patients with congenital long-QT syndrome. Circ. 1998;97:2237–44.
212. Roden DM, Johnson JA, Kimmel SE, Krauss RM, Medina MW, Shuldiner A, Wilke RA. Cardiovascular pharmacogenomics. Circ Res. 2011;109(7):807–20. https://doi.org/10.1161/CIRCRESAHA.110.230995.

213. Lin CY, Lin YJ, Lo LW, Chen YY, Chong E, Chang SL, Chung FP, Chao TF, Hu YF, Tuan TC, Liao JN, Chang Y, Chien KL, Chiou CW, Chen SA. Factors predisposing to ventricular proarrhythmia during antiarrhythmic drug therapy for atrial fibrillation in patients with structurally normal heart. Heart Rhythm. 2015;12:1490–500. https://doi.org/10.1016/j.hrthm.2015.04.018.
214. Behr ER, Roden D. Drug-induced arrhythmia: pharmacogenomic prescribing? Eur Heart J. 2013;34(2):89–95. https://doi.org/10.1093/eurheartj/ehs351.
215. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med. 2004;350(10):1013–22. https://doi.org/10.1056/NEJMra032426.
216. Padfield GJ, Escudero CA, De Souza AM, Steinberg C, Gibbs KA, Puyat JH, Lam PY, Sanatani S, Sherwin E, Potts JE, Sandor G, Krahn AD. Characterization of myocardial repolarization reserve in adolescent females with anorexia nervosa. Circ. 2016;133:557–65. https://doi.org/10.1161/CIRCULATIONAHA.115.016697.
217. Frommeyer G, Eckardt L. Drug-induced proarrhythmia: risk factors and electrophysiological mechanisms. Nat Rev Cardiol. 2016;13(1):36–47. https://doi.org/10.1038/nrcardio.2015.110.
218. Schimpf R, Veltmann C, Papavassiliu T, Rudic B, Goksu T, Kuschyk J, Wolpert C, Antzelevitch C, Ebner A, Borggrefe M, Brandt C. Drug-induced QT-interval shortening following antiepileptic treatment with oral rufinamide. Heart Rhythm. 2012;9(5):776–81. https://doi.org/10.1016/j.hrthm.2012.01.006.
219. Behr ER, January C, Schulze-Bahr E, Grace AA, Kaab S, Fiszman M, Gathers S, Buckman S, Youssef A, Pirmohamed M, Roden D. The international serious adverse events consortium (iSAEC) phenotype standardization project for drug-induced torsades de pointes. Eur Heart J. 2013;34(26):1958–63. https://doi.org/10.1093/eurheartj/ehs172.
220. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, Philippides GJ, Roden DM, Zareba W, American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology, the Council on Cardiovascular Nursing, and the American College of Cardiology Foundation. Prevention

of torsades de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. Circ. 2010;121(8):1047–60. https://doi.org/10.1161/CIRCULATIONAHA.109.192704.
221. Kowey PR, Malik M. The QT interval as it relates to the safety of non-cardiac drugs. Eur Heart J Suppl. 2007;9(Suppl G):G3–8. https://doi.org/10.1093/eurheartj/sum047.
222. Vincent GM. Risk assessment in long QT syndrome: the Achilles heel of appropriate treatment. Heart Rhythm. 2005;2(5):505–6. https://doi.org/10.1016/j.hrthm.2005.03.002.
223. Colman MA, Aslanidi OV, Kharche S, Boyett MR, Garratt C, Hancox JC, Zhang H. Pro-arrhythmogenic effects of atrial fibrillation-induced electrical remodelling: insights from the three-dimensional virtual human atria. J Physiol. 2013;591(Pt 17):4249–72. https://doi.org/10.1113/jphysiol.2013.254987.
224. Nattel S, Maguy A, Le Bouter S, Yeh YH. Arrhythmogenic ion-channel remodeling in the heart: heart failure, myocardial infarction, and atrial fibrillation. Physiol Rev. 2007;87(2):425–56. https://doi.org/10.1152/physrev.00014.2006.
225. Shinagawa K. Effects of antiarrhythmic drugs on fibrillation in the remodeled atrium: insights into the mechanism of the superior efficacy of amiodarone. Circ. 2003;107(10):1440–6. https://doi.org/10.1161/01.cir.0000055316.35552.74.
226. Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implications. Circ Arrhythm Electrophysiol. 2008;1(1):62–73. https://doi.org/10.1161/CIRCEP.107.754564.
227. Gaspo R, Bosch RF, Bou-Abboud E, Nattel S. Tachycardia-induced changes in Na current in a chronic dog model of atrial fibrillation. Circ Res. 1997;81(6):1045–52. https://doi.org/10.1161/01.res.81.6.1045.
228. Yue L, Melnyk P, Gaspo R, Wang Z, Nattel S. Molecular mechanisms underlying ionic remodeling in a dog model of atrial fibrillation. Circ Res. 1999;84(7):776–84. https://doi.org/10.1161/01.res.84.7.776.
229. Gaborit N, Steenman M, Lamirault G, Le Meur N, Le Bouter S, Lande G, Leger J, Charpentier F, Christ T, Dobrev D, Escande D, Nattel S, Demolombe S. Human atrial ion channel and transporter subunit gene-expression remodeling associated with valvular heart disease and atrial fibrillation. Circ. 2005;112(4):471–81. https://doi.org/10.1161/CIRCULATIONAHA.104.506857.

230. Piccini JP, Pritchett EL, Davison BA, Cotter G, Wiener LE, Koch G, Feld G, Waldo A, van Gelder IC, Camm AJ, Kowey PR, Iwashita J, Dittrich HC. Randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of a single oral dose of vanoxerine for the conversion of subjects with recent onset atrial fibrillation or flutter to normal sinus rhythm: RESTORE SR. Heart Rhythm. 2016;0:1–7. https://doi.org/10.1016/j.hrthm.2016.04.012.
231. Henry BL, Gabris B, Li Q, Martin B, Giannini M, Parikh A, Patel D, Haney J, Schwartzman DS, Shroff SG, Salama G. Relaxin suppresses atrial fibrillation in aged rats by reversing fibrosis and upregulating Na+ channels. Heart Rhythm. 2016;13(4):983–91. https://doi.org/10.1016/j.hrthm.2015.12.030.
232. Hou JW, Li W, Guo K, Chen XM, Chen YH, Li CY, Zhao BC, Zhao J, Wang H, Wang YP, Li YG. Antiarrhythmic effects and potential mechanism of WenXin KeLi in cardiac Purkinje cells. Heart Rhythm. 2016;13(4):973–82. https://doi.org/10.1016/j.hrthm.2015.12.023.
233. Xiao YF, Ma L, Wang SY, Josephson ME, Wang GK, Morgan JP, Leaf A. Potent block of inactivation-deficient Na+ channels by n-3 polyunsaturated fatty acids. Am J Physiol Cell Physiol. 2006;290(2):C362–70. https://doi.org/10.1152/ajpcell.00296.2005.
234. Xiao YF, Kang JX, Morgan JP, Leaf A. Blocking effects of polyunsaturated fatty acids on Na+ channels of neonatal rat ventricular myocytes. Proc Natl Acad Sci U S A. 1995;92:1100–11004.
235. Leaf A, Albert CM, Josephson M, Steinhaus D, Kluger J, Kang JX, Cox B, Zhang H, Schoenfeld D, Fatty Acid Antiarrhythmia Trial Investigators. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. Circ. 2005;112(18):2762–8.
236. Raitt MH, Connor WE, Morris C, Kron J, Halperin B, Chugh SS, McClelland J, Cook J, MacMurdy K, Swenson R, Connor SL, Gerhard G, Kraemer DF, Oseran D, Marchant C, Calhoun D, Shnider R, McAnulty J. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. JAMA. 2005;293(23):2884–91.
237. Goette A, Schon N, Kirchhof P, Breithardt G, Fetsch T, Hausler KG, Klein HU, Steinbeck G, Wegscheider K, Meinertz T. Angiotensin II-antagonist in paroxysmal atrial fibrillation

(ANTIPAF) trial. Circ Arrhythm Electrophysiol. 2012;5(1):43–51. https://doi.org/10.1161/CIRCEP.111.965178.
238. Schmieder R, Kjeldsen S, Julius S, McInnes G, Zanchetti A, Hua TA. Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial. J Hypertens. 2008;26:403–11.
239. GISSI-AF Investigators, Disertori M, Latini R, Barlera S, Franzosi MG, Staszewsky L, Maggioni AP, Lucci D, Di Pasquale G, Tognoni G. Valsartan for prevention of recurrent atrial fibrillation. N Engl J Med. 2009;360:1606–17.
240. Investigators ACTIVEI, Yusuf S, Healey JS, Pogue J, Chrolavicius S, Flather M, Hart RG, Hohnloser SH, Joyner CD, Pfeffer MA, Connolly SJ. Irbesartan in patients with atrial fibrillation. N Engl J Med. 2011;364:928–38.
241. Tayebjee MH, Creta A, Moder S, Hunter RJ, Earley MJ, Dhinoja MB, Schilling RJ. Impact of angiotensin-converting enzyme-inhibitors and angiotensin receptor blockers on long-term outcome of catheter ablation for atrial fibrillation. Europace. 2010;12(11):1537–42. https://doi.org/10.1093/europace/euq284.
242. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. 2011;8(8):1308–39. https://doi.org/10.1016/j.hrthm.2011.05.020.
243. Verma A, Cairns JA, Mitchell LB, Macle L, Stiell IG, Gladstone D, McMurtry MS, Connolly S, Cox JL, Dorian P, Ivers N, Leblanc K, Nattel S, Healey JS, Committee CCSAFG. 2014 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. Can J Cardiol. 2014;30(10):1114–30. https://doi.org/10.1016/j.cjca.2014.08.001.
244. Pedersen CT, Kay GN, Kalman J, Borggrefe M, Della-Bella P, Dickfeld T, Dorian P, Huikuri H, Kim YH, Knight B, Marchlinski F, Ross D, Sacher F, Sapp J, Shivkumar K, Soejima K, Tada H, Alexander ME, Triedman JK, Yamada T, Kirchhof P, Document R, Lip GY, Kuck KH, Mont L, Haines D, Indik

J, Dimarco J, Exner D, Iesaka Y, Savelieva I. EHRA/HRS/APHRS expert consensus on ventricular arrhythmias. Europace. 2014;16(9):1257–83. https://doi.org/10.1093/europace/euu194.
245. Nattel S. New ideas about atrial fibrillation 50 years on. Nature. 2002;415:219–26.
246. Bagwe S, Leonardi M, Bissett J. Novel pharmacological therapies for atrial fibrillation. Curr Opin Cardiol. 2007;22:450–7.
247. Van Norman GA. Drugs, devices, and the FDA: part 1. JACC Basic Transl Sci. 2016;1(3):170–9. https://doi.org/10.1016/j.jacbts.2016.03.002.
248. Van Norman GA. Drugs, devices, and the FDA: part 2. JACC Basic Transl Sci. 2016;1(4):277–87. https://doi.org/10.1016/j.jacbts.2016.03.009.
249. Sanguinetti MC, Bennett PB. Antiarrhythmic drug target choices and screening. Circ Res. 2003;93(6):491–9. https://doi.org/10.1161/01.RES.0000091829.63501.A8.
250. Cho HC, Marban E. Biological therapies for cardiac arrhythmias: can genes and cells replace drugs and devices? Circ Res. 2010;106(4):674–85. https://doi.org/10.1161/CIRCRESAHA.109.212936.
251. Wood AJJ. Racial differences in the response to drugs — pointers to genetic differences. N Engl J Med. 2001;344(18):1394–6. https://doi.org/10.1056/NEJM200105033441811.
252. Cambien F, Tiret L. Genetics of cardiovascular diseases: from single mutations to the whole genome. Circ. 2007;116(15):1714–24. https://doi.org/10.1161/CIRCULATIONAHA.106.661751.
253. Roden DM. Cardiovascular pharmacogenomics: current status and future directions. J Hum Genet. 2016;61(1):79–85. https://doi.org/10.1038/jhg.2015.78.
254. Roden DM. Cardiovascular pharmacogenomics. Circ. 2003;108(25):3071–4. https://doi.org/10.1161/01.CIR.0000110626.24310.18.
255. Milan DJ, Lubitz SA, Kaab S, Ellinor PT. Genome-wide association studies in cardiac electrophysiology: recent discoveries and implications for clinical practice. Heart Rhythm. 2010;7(8):1141–8. https://doi.org/10.1016/j.hrthm.2010.04.021.
256. Luo X, Yang B, Nattel S. MicroRNAs and atrial fibrillation: mechanisms and translational potential. Nat Rev Cardiol. 2015;12(2):80–90. https://doi.org/10.1038/nrcardio.2014.178.
257. Yang B, Lin H, Xiao J, Lu Y, Luo X, Li B, Zhang Y, Xu C, Bai Y, Wang H, Chen G, Wang Z. The muscle-specific microRNA miR-1 regulates cardiac arrhythmogenic potential by targeting

GJA1 and KCNJ2. Nat Med. 2007;13(4):486–91. https://doi.org/10.1038/nm1569.
258. Eloff BC, Gilat E, Wan X, Rosenbaum DS. Pharmacological modulation of cardiac gap junctions to enhance cardiac conduction: evidence supporting a novel target for antiarrhythmic therapy. Circ. 2003;108(25):3157–63. https://doi.org/10.1161/01.CIR.0000101926.43759.10.
259. Priori SG. The fifteen years of discoveries that shaped molecular electrophysiology: time for appraisal. Circ Res. 2010;107(4):451–6. https://doi.org/10.1161/CIRCRESAHA.110.226811.
260. Priori SG, Napolitano C. Role of genetic analyses in cardiology: part I: mendelian diseases: cardiac channelopathies. Circ. 2006;113(8):1130–5. https://doi.org/10.1161/CIRCULATIONAHA.105.563205.
261. van Asselt KM, Kok HS, van der Schouw YT, Peeters PH, Pearson PL, Grobbee DE. Role of genetic analyses in cardiology: part II: heritability estimation for gene searching in multifactorial diseases. Circ. 2006;113(8):1136–9. https://doi.org/10.1161/CIRCULATIONAHA.105.563197.
262. Odenstedt J, Linderoth B, Bergfeldt L, Ekre O, Grip L, Mannheimer C, Andrell P. Spinal cord stimulation effects on myocardial ischemia, infarct size, ventricular arrhythmia, and noninvasive electrophysiology in a porcine ischemia-reperfusion model. Heart Rhythm. 2011;8(6):892–8. https://doi.org/10.1016/j.hrthm.2011.01.029.
263. Ackerman JP, Bartos DC, Kapplinger JD, Tester DJ, Delisle BP, Ackerman MJ. The promise and peril of precision medicine: phenotyping still matters most. Mayo Clin Proc. 2016;91(11):1606–16. https://doi.org/10.1016/j.mayocp.2016.08.008.
264. Marsman RF, Bezzina CR, Freiberg F, Verkerk AO, Adriaens ME, Podliesna S, Chen C, Purfurst B, Spallek B, Koopmann TT, Baczko I, Dos Remedios CG, George AL Jr, Bishopric NH, Lodder EM, de Bakker JM, Fischer R, Coronel R, Wilde AA, Gotthardt M, Remme CA. Coxsackie and adenovirus receptor is a modifier of cardiac conduction and arrhythmia vulnerability in the setting of myocardial ischemia. J Am Coll Cardiol. 2014;63(6):549–59. https://doi.org/10.1016/j.jacc.2013.10.062.
265. Denegri M, Bongianino R, Lodola F, Boncompagni S, De Giusti VC, Avelino-Cruz JE, Liu N, Persampieri S, Curcio A, Esposito F, Pietrangelo L, Marty I, Villani L, Moyaho A, Baiardi P, Auricchio A, Protasi F, Napolitano C, Priori SG. Single delivery

of an adeno-associated viral construct to transfer the CASQ2 gene to knock-in mice affected by catecholaminergic polymorphic ventricular tachycardia is able to cure the disease from birth to advanced age. Circ. 2014;129(25):2673–81. https://doi.org/10.1161/CIRCULATIONAHA.113.006901.

266. Fordyce CB, Roe MT, Ahmad T, Libby P, Borer JS, Hiatt WR, Bristow MR, Packer M, Wasserman SM, Braunstein N, Pitt B, DeMets DL, Cooper-Arnold K, Armstrong PW, Berkowitz SD, Scott R, Prats J, Galis ZS, Stockbridge N, Peterson ED, Califf RM. Cardiovascular drug development: is it dead or just hibernating? J Am Coll Cardiol. 2015;65(15):1567–82. https://doi.org/10.1016/j.jacc.2015.03.016.