New drugs vs. old concepts: A fresh look at antiarrhythmics

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ABSTRACT

Common arrhythmias, particularly atrial fibrillation (AF) and ventricular tachycardia/fibrillation (VT/VF) are a major public health concern. Classic antiarrhythmic (AA) drugs for AF are of limited effectiveness, and pose the risk of life-threatening VT/VF. For VT/VF, implantable cardiac defibrillators appear to be the unique, yet unsatisfactory, solution. Very few AA drugs have been successful in the last few decades, due to safety concerns or limited benefits in comparison to existing therapy. The Vaughan-Williams classification (one drug for one molecular target) appears too restrictive in light of current knowledge of molecular and cellular mechanisms. New AA drugs such as atrial-specific and/or multichannel blockers, upstream therapy and anti-remodeling drugs, are emerging. We focus on the cellular mechanisms related to abnormal Na^+ and Ca^{2+} handling in AF, heart failure, and inherited arrhythmias, and on novel strategies aimed at normalizing ionic homeostasis. Drugs that prevent excessive Na^+ entry (ranolazine) and aberrant diastolic Ca^{2+} release via the ryanodine receptor RyR2 (rycals, dantrolene, and flecainide) exhibit very interesting antiarrhythmic properties. These drugs act by normalizing, rather than blocking, channel activity. Ranolazine preferentially blocks abnormal persistent (vs. normal peak) Na^+ currents, with minimal effects on normal channel function (cell excitability, and conduction). A similar "normalization" concept also applies to RyR2 stabilizers, which only prevent aberrant opening and diastolic Ca^{2+} leakage in diseased tissues, with no effect on normal function during systole. The different mechanisms of action of AA drugs may increase the therapeutic options available for the safe treatment of arrhythmias in a wide variety of pathophysiological situations.

Contents

Abbreviations: AA, antiarrhythmic; ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ANS, autonomic nervous system; AP, action potential; AT-1, angiotensin-1; CAMKII, Ca^{2+}/calmodulin kinase type II; CatB, cysteine cathepsin B; CatL, cysteine cathepsin L; CatS, cysteine cathepsin S; CAVB, chronic atrio-ventricular block; CPVT, catecholaminergic polymorphic ventricular tachycardia; DAD, delayed afterdepolarization; DHA, docosahexaenoic acid; EAD, early afterdepolarization; ECG, electrocardiogram; EPA, eicosapentaenoic acid; hERG, human ether-a-go-go-related gene; ICD, implantable cardioverter defibrillator; HF, heart failure; HRV, heart rate variability; I_{CaL}, L-type calcium current; I_f, funny current (hyperpolarization-activated current); I_{KAch}, potassium current activated by acetylcholine; I_{KR}, rapid component of potassium current; I_{KS}, slow component of potassium current; I_{KUR}, ultra-rapid potassium current; I_{Na}, sodium current; I_{NaP}, persistent sodium current; I_{TO}, transient outward current; LQT, long QT syndrome; LV, left ventricle; MAPK, mitogen-activated protein kinase; MI, myocardial infarction; MMP, matrix metalloproteinase; mPTP, mitochondrial permeability transition pore; n-3 LC-PUFA, n-3 long-chain polyunsaturated fatty acid; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; NCX, sodium–calcium exchanger; NOS, nitric oxide synthase; PF, Purkinje fiber; PKA, protein kinase A; PKC, protein kinase C; PLN, phospholamban; QTc, Q-T interval corrected for heart rate; ROS, reactive oxygen species; RP, refractory period; RyR1, ryanodine receptor type 1; RyR2, ryanodine receptor type 2; SCD, sudden cardiac death; SERCA2, sarco/endoplasmic reticulum Ca^{2+} ATPase type 2; SR, sarcoplasmic reticulum; TdP, Torsades de pointes; TGF, transforming growth factor; TNF, tumor necrosis factor; TRPM4, transient receptor potential type M4; TTX, tetrodotoxin; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia; VW, Vaughan Williams.

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1. Introduction

Efficient cardiac contraction depends on the sinus rhythm and atrioventricular as well as inter- and intraventricular synchronization, given the integrity of the cardiac conduction pathway and well-organized excitation–contraction coupling. The term 'arrhythmia' refers to any change in the normal sequence and/or shape of electrical impulses during the cardiac cycle. Arrhythmias are a major public health concern and represent a significant and increasing economic burden for healthcare systems. The most common forms of arrhythmia leading to a high risk of cardiac morbidity and mortality are atrial fibrillation (AF) and ventricular tachycardia/fibrillation (VT/VF). Other rhythm disorders result mostly from unique mechanisms such as intranodal reentry, accessory pathways or focal abnormal automaticity.

Over the last decade, no novel antiarrhythmic (AA) drug has come onto the market. Are there still prospective drugs in the wings? The approaches used for drug development are many and varied. There are a number of excellent recent reviews on arrhythmias and pharmacological approaches to them (Rubart & Zipes, 2005; Nattel & Carlsson, 2006; Nattel et al., 2008; Das & Zipes, 2010; Dobrev & Nattel, 2010; Ravens, 2010). Until now, AAs have been considered modulators of ion channels, and several classifications, mostly based on the targeted protein, have been developed. With this logic in mind, a key question to answer is: which ion channels are the best candidates for new AA drugs? One logical strategy to treat AF is to develop atrial-specific ion channel blockers that are devoid of proarrhythmogenic risks at the ventricular level. Treating ventricular arrhythmia (VA) is more problematic, despite the development of the implantable cardioverter defibrillator (ICD). Novel concepts regarding the origin of arrhythmias are leading to new therapeutic approaches based on recent advances in our understanding of the cellular mechanisms underlying arrhythmias and the normalization of Ca^{2+} cycling, with clinical potential for heart failure (HF), inherited arrhythmias, catecholaminergic polymorphic ventricular tachycardia (CPVT) and AF. Ranolazine and blockers or stabilizers of the ryanodine receptor (RyR2) are emerging as novel drugs or prototypes (Antzelevitch et al., 2004; Wehrens & Marks, 2004; Wehrens et al., 2005; Blayney & Lai, 2009; Kaneko et al., 2009) aimed at preventing Ca^{2+}-dependent arrhythmias and, eventually, structural remodeling as well. Here, after a brief review of established and emerging therapeutic strategies, we will focus on ion-channel blockers, with particular emphasis on concepts that integrate the role of intracellular Ca^{2+} as a key element in arrhythmia generation.

2. Origins of arrhythmias

2.1. Diverse mechanisms: from the tissue to the cell and gene

Arrhythmias are most often caused by an underlying cardiac disease, and can arise from the adverse remodeling associated with morphological and structural alterations of cardiac tissues (Michael et al., 2009). Schematically, the mechanisms underlying arrhythmias can be greatly simplified by saying that there is a substrate and a trigger (e.g., at the cellular level, a disturbance of Ca^{2+} homeostasis leading to delayed afterdepolarization, DAD). In addition, environmental considerations such as the autonomic nervous system (ANS), neurohormones and/or metabolism that regulate the cardiac rhythm to a great extent, are involved in the triggering of arrhythmias as well as in their maintenance, both at the atrial and ventricular levels (Fig. 1) (Corr et al., 1986; Coumel & Maison-Blanche, 1991; Zipes & Wellens, 1998; Zipes & Rubart, 2006; Workman, 2010).

Arrhythmias may also depend on conduction defects, such as reentry, that could lie at the origin of Torsades de pointes (TdP) and VF (Napolitano et al., 1994). Besides enhanced or abnormal impulse formation, reentry occurs when a propagating impulse persists after sinus activation of the heart and re-excites cardiac tissue after the expiration of its refractory period (RP) (Antzelevitch, 2001). Reentry can have two different origins: electrophysiological or structural. Circus movement reentry involves the circuitous propagation of an impulse around an anatomical or functional obstacle, leading to re-excitation of the heart. The first model described for this phenomenon was reentry due to the presence of an anatomical obstacle (Mines, 1913). In this model, there is a circular propagation of the depolarization that is mainly determined by the size of the obstacle (i.e. fibrosis) and the RP (Allessie et al., 1977). In this case, the type of reentry observed is called a macro-reentry. In the presence of slow-conducting tissue (e.g. depolarized cells, and fibrosis), the action potential (AP) can propagate rapidly in normal tissue and return through the area of slow conduction (Fig. 1). However, at least in the atrium, there could be micro-reentry due to a difference as low as 16 ms in the effective RP (Antzelevitch, 2001). This small difference in the RP is enough to maintain the type of circus movement exemplified by the "leading circle model". The same kind of process is thought to occur in the ventricle. Phase 2 reentry occurs due to the electrical heterogeneity of the ventricular myocardium between the endocardial, epicardial and mid-myocardial regions, and in response to pharmacological agents and pathophysiological states (Antzelevitch, 2001, 2007). As a consequence, the right ventricular epicardium displays a much more prominent AP notch than the left ventricular (LV) epicardium. Transmural voltage gradients, generated by differences in the time-course of repolarization of the three cell types, could increase the QT interval and the risk of VA.

At the cellular level, complex mechanisms take part in the genesis of arrhythmias. They depend broadly on aberrant electrical signaling with a multifaceted interplay between different types of ion channels and/or disordered Ca^{2+} signaling. In the normal heart, both mutations in a variety of ion channel genes – like SCN5A or its associated regulating protein (i.e. SCN4B gene) – and drugs that affect cellular AP repolarization may increase the risk of severe arrhythmia (Wilde & van den Berg, 2005; Medeiros-Domingo, 2007; Zhu & Clancy, 2007; Saenen & Vrints, 2008). In addition to contributing to AP duration, Ca^{2+} plays an important role in the triggering of both early afterdepolarizations (EADs; Ca^{2+} entry through L-type Ca^{2+} channels) and DADs. For example during HF, intracellular diastolic Ca^{2+} overload can trigger ectopic activity (Wit & Rosen, 1986) (Fig. 1). The key role played by a panel of Ca^{2+}-handling proteins (Ca^{2+}ATPase SERCA2a, the Na^{+}–Ca^{2+} exchanger NCX, RyR2 channel, and proteolytic enzymes) is now well-established (Shannon & Bers, 2004; Antoons & Sipido, 2008). Overall, some of the mechanisms listed here are involved in both arrhythmias related to remodeling in chronic pathology and inherited arrhythmias (e.g. RyR2), providing relevant avenues of research for new AA drugs and novel concepts, which we will discuss later. Indirect strategies targeting cellular remodeling on a pathological substrate very early in the process are undoubtedly highly relevant to many diseases with structural modifications and deleterious remodeling.

2.2. Tissue sources of arrhythmias

2.2.1. Atrial level

For cardiologists, arrhythmias are mostly characterized by their tissue of origin. AF is a disorder defined by a rapid and irregular rhythm leading to uncoordinated atrial contraction.

AF is initially thought to originate from the ectopic activity of venous structures, mostly the pulmonary veins but also the coronary sinus, the ligament of Marshall or the superior *vena cava*. It is the most complex arrhythmia, frequently associated with an underlying structural and evolutive heart disease. As the AF lasts longer and longer, the mechanisms become more and more complex, involving fibrosis through multiple reentry circuits, rotors considered as "mother" waves, and parasympathetic cardiac innervation (Loomis

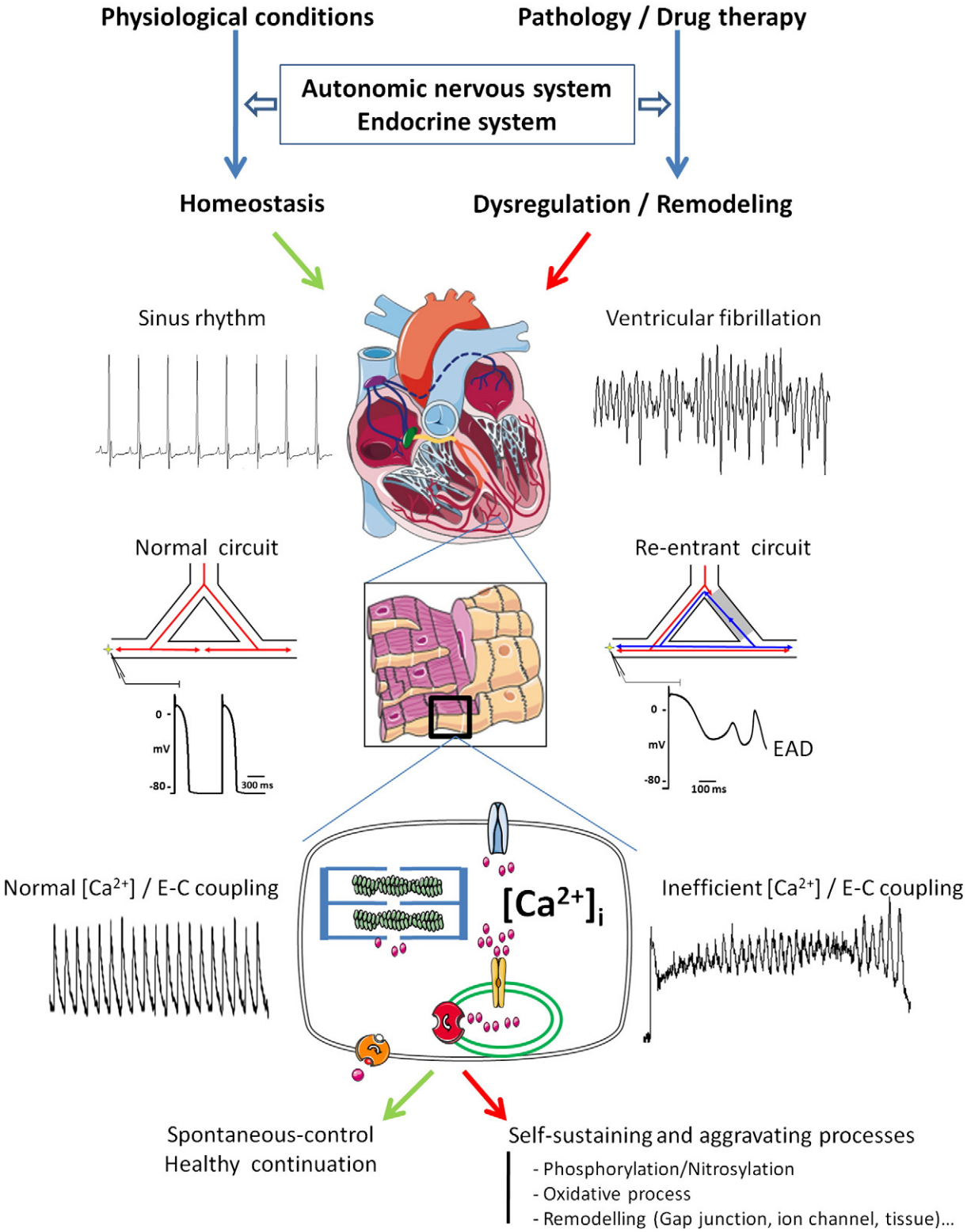

Fig. 1. Schematics of the main mechanisms involved in arrhythmia. The cardiac rhythm is regulated by hormones and the autonomic nervous system. Efficient myocardial contraction depends on a normal sinus rhythm, synchronization among the different cardiac tissues, conduction pathway integrity and well-organized excitation-contraction coupling. Pathological conditions and/or medications can alter or interfere with these regulatory systems at different levels and can lead to cardiac remodeling and rhythm disorders. Complex mechanisms take part in the genesis of arrhythmias. Reentry can lead to ion accumulation (in particular Na^+ and Ca^{2+}) (Munteanu et al., 2008) and, conversely, high intracellular Ca^{2+} can initiate cardiac remodeling that creates a substrate for reentry. AP prolongation can initiate early afterdepolarisations (EADs), and aberrant spontaneous diastolic Ca^{2+} release via leaky RyR2 activates I_{ti} (through NCX) to trigger DAD and, subsequently, VA (typically in HF and CPVT). Environmental conditions (redox status, phosphorylation or nitrosylation) and pathological remodeling can play a pivotal role in susceptibility to arrhythmia.

& Krop, 1955; Yue et al., 2011). Symptoms of AF include palpitations and sometimes weakness, dyspnea and presyncope, and in more severe forms, AF may lead to death.

Clinically, the type of AF is determined based on its duration and its resistance to therapy. As such, AF is classified as paroxysmal (self-terminating, generally >48 h and lasting up to 7 days), persistent (episodes lasting more than 7 days and requiring pharmacological or direct-current cardioversion), long-standing persistent (lasting more than 1 year) and permanent, when the AF is considered as being definitive and accepted by the patient (Camm et al., 2010). In addition to its complex etiology, there is a lack of satisfactory models for sustained AF in connection with specific ion channels. This is especially true for small animals (rodents), and the only valid models for the reproduction of sustained human AF are large animal models (goats, sheep) due to the critical size of their atria (Schotten et al., 2010). This contributes to the difficulty in developing new anti-AF drugs.

The prevalence of AF increases with age (1/25 after 60 years and 1/10 after 80 years in the USA) and is expected to increase by a factor of 2.5 until 2050 (Go et al., 2001). More strikingly, the number of hospitalizations related to AF has increased by 66% in 20 years (Fuster et al., 2006). A study from Olmsted County reports that, from 1980 to 2000, the risk of death related to cardiovascular disease decreased significantly but that the risk of death related to AF remained unchanged (Miyasaka et al., 2007; Miyasaka et al., 2008). The latest guidelines of the *European Society of Cardiology* clearly highlight that AF is an independent risk factor for mortality (Camm et al., 2010). The critical issue is appropriate antithrombotic therapy, but until recently, existing AA drugs were associated with increased mortality. Besides drug therapy to maintain the sinus rhythm, non-drug treatments such as catheter ablation show promising results (Cappato et al., 2005; Ellis et al., 2009), despite a 6–8% global complication rate with a mortality rate as high as 0.5%. Following the recent AFFIRM study (Wyse et al., 2002), it is now commonly accepted that the problem for patients presenting with AF is not rhythm or rate control. A more global approach is desirable in order to decrease the morbidity–mortality linked to AF. Indeed, available AA drugs are associated with an increase in mortality, suggesting that we need better drugs that allow sinus rhythm to be maintained while avoiding iatrogenicity (Wyse et al., 2002).

2.2.2. Ventricular level

At the ventricular level, US vital statistics mortality data for 1989–1998 showed that of 719,456 cardiac deaths among adults aged 35 years in 1998, 456,076 (63%) were defined as sudden cardiac death (SCD) (Zheng et al., 2001). A recently completed large study of 121,701 women (Nurses' Health Study) over a 20-year period estimated that 88% of SCDs were due to arrhythmias (Albert et al., 2003). Deaths from SCD each year outnumber deaths from all cancers (MMWR, 1999; Anderson, 2001). SCD can have multiple origins. Coronary artery disease is present in 80–85% of patients who undergo SCD (Cobb et al., 1975; Myerburg, 2001). A reduced LV ejection fraction remains the single most important risk factor for overall mortality and SCD (Priori et al., 2001b). In HF, QT-prolonging drugs are a major cause for concern. Polytherapy also increases the risk of lethal arrhythmias, estimated to cause 100,000 deaths/year (De Bruin et al., 2007), a figure that is even higher in the presence of underlying heart disease. In a recent study with over 8000 patients, a QTc of greater than 450–470 ms was associated with a tripling of the risk of SCD after adjustment for age, sex, body mass index, hypertension, cholesterol, diabetes, myocardial infarction (MI), HF and heart rate (Straus et al., 2006). Thus, clinical studies have revealed that SCD resulting from arrhythmias is a major and growing public health problem worldwide.

VA is relatively unpredictable, and remains a major source of avoidable SCD. VF is a chaotic VA leading to the disorganized pumping of blood and possibly leading to death. VF occurs consecutive to reentry circuits, but the underlying mechanisms are still not fully understood. It occurs due to reentries that are the result of an increase in transmural dispersion (Antzelevitch & Fish, 2001). It was originally hypothesized that the transmural dispersion was due to an electrical gradient with, notably, the existence of an intermediate cell layer "M" (for mid-myocardial) between the epicardium and the endocardium (Antzelevitch et al., 1996). This gradient was based on differences in the density of various ion currents, including the I_{KS}. Any environmental change that reduced repolarizing currents, such as the I_{KR}, would accentuate the dispersion of repolarization (viewable on an ECG by measuring the Ve–Vp of the T wave) and could result in reentry and thus VF. However, M cells exist in myocardial clusters that vary in spatial location and extent across the heart, and are not present uniformly at a given depth of myocardium (Akar et al., 2002). This heterogeneous distribution of M cells as islands of M cells, coupled with electrophysiological differences between epi- and endocardiomyocytes, reinforces the notion of a heterogeneous repolarization sufficient to cause a functional block and reentry in response to a premature stimulus, and contributing to arrhythmia.

Two different strategies have been adopted in recent decades to reduce the risk of developing lethal arrhythmias, and are used alone or in combination according to ACC/AHA/ESC guidelines (Epstein et al., 2008). These are AA drugs and the implantation of ICD, eventually combined with surgical or percutaneous catheter ablation (Reddy et al., 2007). Currently, no drug is effective enough to obviate the need for ICD implantation, which is not only a palliative but clearly a life-saving treatment. However, although the effectiveness of this therapeutic protocol/strategy is known, it raises a number of problems: 1) it is only a symptomatic treatment, 2) shocks are stressful and may be associated with a deterioration of LV pump function, and 3) it does not prevent disease progression or the development of remodeling. Although their effectiveness in saving lives is high, even for prophylactic indications, ICDs treat but do not prevent SCD (Coats, 2002). Moreover, both appropriate and inappropriate shocks have deleterious effects on the quality of life (Das & Zipes, 2010), suggesting that the development of novel pharmacological therapies is essential.

2.2.3. Purkinje tissue

The role of the Purkinje fibers (PFs) in the triggering and maintenance of VF has been described before (Berenfeld & Jalife, 1998; Haissaguerre et al., 2002a, 2002b; Lindsay, 2009). However, their contribution to the generation of arrhythmias through reentry has probably been underestimated (Sasyniuk & Mendez, 1971; Boyden et al., 2010). The QRS complex of the ECG, which reflects the conduction of electrical activity by PF, has been described as the best predictive factor for VT in patients suffering from perturbations of systolic function (Fazelifar et al., 2009). This suggests that conduction defects are very important in the generation of arrhythmias.

Conduction abnormalities are involved in the genesis of arrhythmias and SCD (Marriott, 1964; Titus, 1973; Herron et al., 2010). This has been shown in ischemic cardiac disease and LV dysfunction after MI, where slowed conduction has been localized to the zone bordering the infarct, as well as in non-ischemic dilated cardiomyopathy, as confirmed by genetic models that exhibit a more global slowing of conduction (Akar & Tomaselli, 2005). A unidirectional conduction block in a branch of a PF can trigger sustained reentry (Gilmour & Watanabe, 1994; Antzelevitch, 2008). Structural heart disease, electrical instability, and increased sympathetic activity provide substrates for ECG changes and arrhythmias in patients with congestive HF (Hombach, 2006). HF patients commonly exhibit prolonged QRS duration and/or ventricular late potentials, predictive of life-threatening VT, aberrant heart rate variability (HRV, an index of MI), and repolarization abnormalities detected by studies of QT dispersion, QT/QTc fluctuation or T-wave alternans (Hombach, 2002).

The impact of conduction delays has been supported by clinical studies, with late potentials on abnormal signal-averaged ECG being an independent predictor of all-cause cardiac death and of great interest for the risk stratification of arrhythmias (Mancini et al., 1993; Lander et al., 1997; Fauchier et al., 2000).

In addition to anisotropic reentry, notably arising in HF after MI-induced injury, inappropriate impulse propagation leading to arrhythmia generation is determined by numerous structural, cellular and molecular changes in fibrosis, extracellular matrix, cell–cell coupling, the expression and function of gap junction proteins (Cx43), and the combination, availability and gating properties of ion channels (Akar & Tomaselli, 2005). Ca^{2+} handling proteins are also involved, in particular the RyR2 Ca^{2+} release channel. It was recently reported that focally activated arrhythmias originate in the specialized electrical conducting cells of the His-Purkinje system in the RyR2(R4496C) mouse model of CPVT (Herron et al., 2010). In this model, PFs have a higher propensity to develop abnormalities in intracellular Ca^{2+} handling than ventricular myocytes, in relation with aberrant Ca^{2+} release events due to the spontaneous opening of RyR2 in diastole, which can be suppressed with flecainide (Kang et al., 2010).

PFs have electrophysiological particularities that are not shared by ventricular cells, such as a longer plateau involving a persistent Na^+ current reflecting a "window" current, considered to be the steady-state component of the fast sodium current (I_{Naf}) resulting from the crossover of the activation and inactivation curves of the Na^+ channel (Attwell et al., 1979; Coraboeuf et al., 1979), rather than slow inactivation due to modified gating properties. Recently, it has also been shown that PFs express channels that are not expressed in ventricular cells, at least under normal conditions. For example, the Ca^{2+}-activated nonselective cation channel TRPM4 is highly expressed in cardiac PFs. Also, recently, a mutation in the TRPM4 channel has been shown to induce a gain-of-function mechanism related to elevated TRPM4 channel density at the cell surface in progressive familial heart block type I, a progressive cardiac bundle branch disease of the His-Purkinje system (Kruse et al., 2009; Liu et al., 2010).

PFs are also prone to developing EADs, which can be prevented by ryanodine (Boyden et al., 2004). EADs occur against a background in which the AP duration is increased, and are among the first events leading to VF. In addition, it has been shown that in a post-MI animal model, arrhythmias begin at the level of the PFs following the dysregulation of intracellular Ca^{2+} homeostasis (Hirose et al., 2008). These results are of great interest because the origins of CPVT are currently being investigated at the ventricular level, and PFs may also be involved in this process (Hirose et al., 2008). Recent experiments using a mutant mouse model of CPVT have demonstrated that the His-Purkinje system is an important source of focal arrhythmias in CPVT (Cerrone et al., 2007). These findings underline a role for PFs in the generation and maintenance of VA that has been too long ignored, and that could be specifically targeted.

2.3. Pharmacological origin of arrhythmias

2.3.1. Antiarrhythmic therapy and proarrhythmogenicity

The pharmacologic treatment of AF can generate conditions favoring the triggering of VA. There have been dramatic examples in the past of a deleterious effect of AAs on clinical criteria. A classic example of the dangers of the use of intermediate criteria to judge drug efficacy is that of class I AA drugs in post-MI. In the Cardiac Arrhythmia Suppression Trial (CAST), the effects of encainide and flecainide were evaluated in patients with asymptomatic or mildly symptomatic VA after MI (1989). The conclusion was that neither encainide nor flecainide was advisable in the treatment of patients with asymptomatic or minimally symptomatic VA after MI, even though these drugs were initially effective in suppressing VA. Overall, the toxicity associated with class I AA drugs is very common and can be life-threatening (Denaro & Benowitz, 1989; Kim & Benowitz, 1990; Koppel et al., 1990). Examples of poisoning with β-blockers (class III) and Ca^{2+} antagonists (class IV), mostly due to high doses, can also be

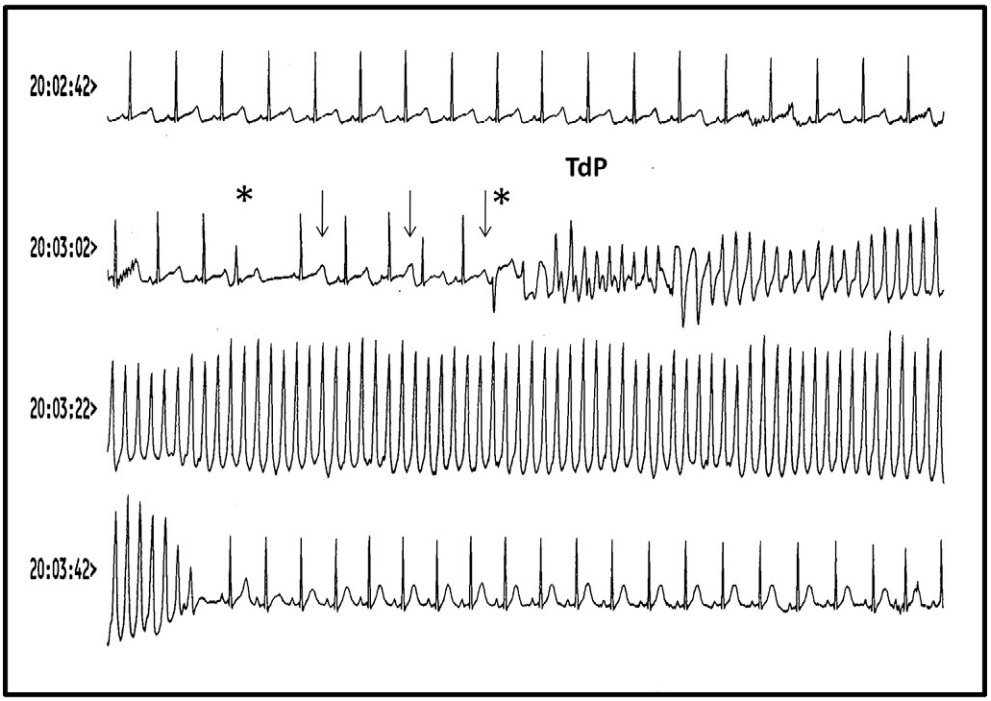

Fig. 2. Example of VT and Torsade de Pointes in a 32-year old woman treated for paroxysmal AF and after attempted suicide using sotalol. In the upper part of the monitor, the trace shows a dramatic prolongation of the QT interval. After an atrial ectopy (first asterisk), there is a pause followed by electrical QT alternans (arrows). A ventricular ectopy (second asterisk) occurs at a vulnerable point during prolonged QT and is responsible for a Torsade de Pointes onset that turns into very fast monomorphic VT and stops after about 30 s (syncope of the patient). After cessation of tachycardia, the sinus rhythm is notably accelerated with a much shorter QT interval.

found (Pearigen & Benowitz, 1991; Reith et al., 1996). This is illustrated in Fig. 2, which shows VT and TdP induced in a 32-year old woman treated for paroxysmal AF after an attempted suicide using sotalol.

Apart from adverse effects related to proarrhythmogenicity, clinical trials have sometimes been discontinued because of other adverse effects as well, suggesting that proarrhythmia is not the only potential safety concern with AA drugs. For instance, amiodarone, in spite of its clearly positive AA effects, was stopped because it was found to induce pulmonary, neurological or liver toxicity as well as thyroid dysfunction in patients under specific circumstances (Kamath & Mittal, 2008). In patients with severe HF and LV systolic dysfunction, treatment with a noniodinated amiodarone derivative, dronedarone, was associated with increased early mortality related to the aggravation of HF (Kober et al., 2008). Since dronedarone was found to block the I_{CaL} current (Gautier et al., 2003), it was hypothesized that a negative inotropic effect may have promoted the worsening of chronic HF in these patients. This propensity of a candidate drug to adversely affect physiological systems other than the cardiovascular system is the second aspect addressed by regulatory authorities in the context of non-clinical safety documentation (Guidance for Industry, S7A, 2001).

2.3.2. Safety concerns

The need to evaluate the proarrhythmic potential of AA drugs was stimulated by the outcomes of the CAST (1989) and SWORD clinical trials (Waldo et al., 1996). It was obvious that AA drugs could also be proarrhythmogenic. Drugs that prolong cellular AP repolarization could increase the risk of severe arrhythmia. After the mid-1990s and the withdrawal from the market of the antihistamine terfenadine because of increasing clinical evidence that the drug induced life-threatening arrhythmias (June & Nasr, 1997), regulatory authorities rapidly addressed the need for improved pre-clinical experiments for the documentation of such safety issues. Therefore, at the end of 1997, the Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Agency first raised a point to be considered in the assessment of the potential for QT-interval prolongation of non-cardiovascular medicinal products (CPMP/SWP/986/96), followed in 2005 by guidelines from the International conference on Harmonization (Guidance for industry, 2005) defining the regulatory requirements for the non-clinical evaluation of this cardiovascular risk. These regulatory guidelines recommend the use of two main approaches: in vitro patch clamp studies to evaluate effects on the hERG current, and in vivo studies dealing with effects on the duration of ventricular repolarization in appropriate species, thereby providing an estimation of the risk of TdP induction. In order to interpret the results and draw appropriate conclusions regarding the proarrhythmic risk, the integration of all these results and others arising from primary pharmacological studies or other safety studies is recommended. Depending on the results of these initial experiments, integrated risk assessment may require additional follow-up experiments, including an assessment of effects on APs in isolated tissues and specific in vivo proarrhythmia models.

Animal models have been developed in order to detect the potential of drugs to induce a rare VA, TdP. The common feature of these models is the achievement of enhanced susceptibility to arrhythmia, to mimic the situation encountered in vulnerable patients. Two models are currently used: the methoxamine-sensitized rabbit model of TdP (Carlsson et al., 1990) and the chronic atrio-ventricular block (CAVB) dog model (Vos et al., 1995). The methoxamine-sensitized rabbit model is considered to be mainly effective in detecting pro-arrhythmic drugs with class III AA features. Likewise, the CAVB dog model is capable of displaying TdP after exposure to class III drugs, but also in response to others such as dronedarone or setindole (Gintant, 2008). Moreover, this model has also helped to highlight the fact that the QT interval duration, the most common biomarker used as a surrogate for drug-induced TdP to estimate pro-arrhythmic potential, could in some ways be misleading. Indeed, drugs like amiodarone and moxifloxacin prolong QT interval duration to a similar extent but fail to induce TdP as expected based on clinical data. From this finding, a new surrogate, the beat-to-beat variability of left ventricular repolarization estimated from short term variability measurements, has been proposed for the evaluation of pro-arrhythmic potential (Gintant, 2008).

Apart from actual regulatory requirements, the patch clamp study on hERG was initially considered a *go/no go* test in the industrial development process because all drugs inducing TdP were identified as hERG channel blockers. The need for the documentation of the electrophysiological effects of all new chemical entities, whatever their therapeutic targets, on the hERG current led to the development of high-throughput methods like automated patch clamp assays to manage the large number of chemical entities, especially for early safety assessment. New methodologies have had a positive impact on the development of new AA drugs because they provide, at an early stage, helpful information for the adjustment of drug design. A variety of relevant cell-based screening assays and systems for arrhythmia assessment have been reviewed recently (Nattel et al., 2008).

3. Antiarrhythmic drugs

3.1. Ion channels: The traditional targets of antiarrhythmic drugs

The electrical activity of the heart is primarily driven by cellular ion currents. Experimental electrophysiology really gave birth to the concept of the "voltage-gated ion channel" more than a half-century ago in a series of remarkable papers (Hodgkin & Huxley, 1952a, 1952b; Hodgkin et al., 1952) and established a theoretical model paving the way for our understanding of how voltage-gated channels work and how drugs could interact with them and modify their function. The "voltage-clamp" technique, and later, the concomitant development of patch clamping methods (Hamill et al., 1981; Sakmann & Neher, 1983; Hille, 1992) and the enzymatic isolation of single cardiomyocytes fostered the emergence of new knowledge and concepts that greatly contributed to mechanistic investigations and the development of AA drugs. Consequently, it became possible to measure ion currents at the level of a single cell or even of a single channel protein, making most tissues (including human tissue samples obtained during surgery) amenable to powerful electrophysiological investigation. These advances made possible the determination of the molecular effects of drugs on the gating of channels for an improved prediction of drug effects on function.

In the meantime, the determination of the protein nature of ion channels, the identification of drug binding sites, and the sequencing of genes encoding these proteins have laid the foundations of "*molecular medicine*" that address the complex problem of cardiac arrhythmias. It has become apparent that numerous mutations in a variety of genes coding for different types of ion channels (channelopathies) are responsible for prolonging the QT interval, which can precipitate TdP and irreversible VF (Shah et al., 2005; Pasquie & Richard, 2009). Thirteen genotypes characterize the long QT syndrome. Hundreds of mutations have been identified for at least eight different ion channel complexes, the structural anchoring protein Ankyrin, and a caveolin protein (Antzelevitch, 2007).

3.2. What is a classic antiarrhythmic drug?

Most voltage-gated ion channels possess druggable binding sites for pharmacological therapy in general and AA drugs in particular (Clarkson & Hondeghem, 1984). These drugs usually prevent channel opening, resulting in a decrease in a given ion current. Interestingly, the biophysical properties of ion channels are important determinants of current amplitude and kinetics, and can strongly modulate/govern

pharmacological effects. In particular, the affinity of a ligand for a channel can be strongly modulated by the conformational state of the protein, which in turn is highly dependent on the membrane potential. In this regard, the modulated receptor hypothesis has been useful in understanding the kinetics of Na^+ channels and the changes produced by various AA drugs (Hondeghem & Katzung, 1984).

3.3. Classification of antiarrhythmic drugs

Based on initial knowledge regarding the origin of arrhythmias (ectopic activity, conduction disorders leading to reentry, and over-excitability), strategies to stop arrhythmias have led to the classification of AA agents since the 70s. The first classification was established by Vaughan Williams (1970) (VW), and was successively completed by Singh and Hauswirth (1974), Harrison et al. (1980) and Hondeghem (1992) (see Table 1). Although other types of classification exist, such as Touboul's classification, which takes into account data from in vivo electrophysiological explorations (Touboul et al., 1979), the autonomic classification of Goldberger and Curtis (1982) or the Gambit (1991), the VW classification has remained robust over time, being by far the most used despite its obvious limitations. It continues to be used for the development of new drugs and the design of approaches to clinical therapy. Its main advantage is that it explains complex effects simply (as a teaching tool), in terms of pharmacological targets. However, it does not address the etiology of the disorder. This classification also does not integrate the concept that AA drugs can be effective in various ways on multiple targets. Indeed, the VW classification was originally based on four classes of drugs that interfered with, respectively, the fast Na^+ current, ß-adrenergic receptor, K^+ channel and Ca^{2+} channel (Vaughan Williams, 1984, 1992). In other words, the VW system enabled the classification of AA drugs based on their effects on the three major types of ion currents identified in the seventies on the one hand, and on sympathetic activity on the other. In all cases, the concept is based on the notion that arrhythmias arise due to abnormal electrical activity and somehow reflect the inappropriate functioning of ion channel proteins. However, the fact that drug action can change during pathology due to channel or receptor modification or a sympathovagal imbalance is not taken into account.

Class I includes Na^+ channel blockers. Blockade of the Na^+ current slows conduction (Fozzard & Hanck, 1992), which could help prevent arrhythmias by transforming a unidirectional block into a bidirectional one. However, slowing conduction can also promote reentry by decreasing wavelength. This could be the reason for the failure of Class Ic drugs in the CAST (1989). An important aspect of the generation of ectopic beats is linked to the RP. Depending on the type of arrhythmia, ectopic beats can be prevented by increasing the RP following blockade of K^+ currents. Sympathetic innervation also plays an important role in the regulation of cardiac excitation–contraction coupling and in the generation of arrhythmias (Anderson, 2003; Verrier & Antzelevitch, 2004; Vaseghi & Shivkumar, 2008). In the VW classification, this role is undertaken mainly through a regulation of ion currents such as I_{CaL}. Presently, beta-blockers (class II according to the classification) are among the most widely used AA drugs, but the precise reason for their properties is not fully understood. As mentioned above, an important aspect in the generation of arrhythmias is the decrease in the RP. The inhibition of some K^+ channels generally leads to an increase in the AP duration and thus of the RP (Kim & Benowitz, 1990; Ravens & Cerbai, 2008). This is why the VW classification created a particular group, class III, which includes K^+ channel blockers. However, no member of this group is exclusively a K^+ channel blocker. Sotalol, which is the leading molecule in this group, is also a powerful ß-blocker, while amiodarone, which is a powerful AA drug, also inhibits many other channels.

Class IV comprises Ca^{2+} channel blockers including verapamil and diltiazem. These drugs block the I_{CaL} current in all cardiomyocytes but have few effects on the AP waveform. Their effects resemble those of class II AA drugs, with a slowing of the late spontaneous diastolic depolarization of sinus node tissue and an increase of the atrionodal conduction time and RP. With Class IV compounds, the heart rate is not systematically attenuated but the PR interval is often prolonged. Class IV drugs are the reference treatment for reentrant supraventricular tachycardia (Colucci et al., 2010), and the potential decrease of the heart rate could be sufficient to prevent AF (Tsuneda et al., 2006). A major side effect of these drugs is a decrease in contraction, which could be undesirable in HF patients. Finally, a fifth class, whose agents work through other or unknown mechanisms, has been added (Vaughan Williams, 1992). Class V agents include digoxin and adenosine. Digoxin increases vagal activity via its action on the central nervous system, thus decreasing the conduction of electrical impulses through the AV node (van Veldhuisen et al., 1996). It should be noted that Class V agents are not part of the original VW classification. Moreover, new molecules with potential AA properties but that are not compatible with the original VW classification, have emerged: some can be placed in several classes (vernakalant) while others cannot be listed under any of the four original VW classes (ivabradine). This suggests that the VW classification may no longer be best suited to the realities of new AA drug design.

4. Current and future strategies

4.1. Where do we stand?

AA drugs are designed to maintain a normal sinus rhythm and prevent rapid and irregular heartbeats. They are expected to relieve symptoms related to arrhythmias such as palpitations, faintness or HF. Theoretically, the final and ideal goal of AA therapy is to reduce mortality directly related to arrhythmia. So far, this goal has been purely utopian. Currently available pharmacological agents have limited efficacy and/or carry a risk of relevant side effects, such as drug toxicity or proarrhythmic potential (Gramley et al., 2009). As we have all been aware for a very long time, studies of the effectiveness of AA drugs at the atrial (e.g. AFFIRM) and ventricular (e.g. CAST I) levels have shown an increase in mortality directly related to drug side-effects. The only therapies with a mortality-reducing effect are anticoagulants in the case of AF (Hylek et al., 2003; Boden et al., 2007; Connolly & Poston, 2009) and ICDs in VA (Moss, 2003; Cappato et al., 2005; Budde, 2006). In other words, we can reduce mortality by treating the complications of arrhythmias, but we still do not know how to effectively prevent arrhythmias in the long run using drugs or non-drug treatments such as surgery (Klein et al., 1986) or catheter ablation (Wilber, et al., 2010; Pappone et al., 2011).

In complex pathological conditions such as HF, the diversity of the systems that contribute to cardiac remodeling and arrhythmia (beta-adrenergic receptors, renin–angiotensin–aldosterone and endothelin systems or NO synthases) and their polymorphisms necessitates extensive gene cartography in order to understand the different outcomes in patients (Cascorbi et al., 2004). The pharmacogenomic approach has established that individual responses could result from specific gene variants that modify how a drug is absorbed or eliminated. These genetically based differences in drug efficacy, which have long been recognized (Kalow, 2006), are only now on the verge of clinical application in drug development and the design of clinical trials (Shah, 2004; Roden, 2005; Perez et al., 2008; Winkelmann and Herrington, 2010). Gene variants can also hold the key to understanding why individuals who are asymptomatic for cardiac disease are at risk for long QT syndrome, VF, syncope or SCD when under medication or during exercise (Hedley et al., 2009).

A major obstacle in the development of novel AA drugs is related to the complexity of electrical signaling, which in turn introduces safety concerns. The regulation of criteria defining the safety of a drug has been greatly tightened following several cases of malignant

Table 1
Historical and mechanistic classification.

1970 Singh and Vaughan Williams **1974 Singh and Hauswirth** **1981 Harrison** **1992 Hondeghem**	**Class I** Na^+ Channel Blocker Ia ↑ repolarization Ib ↓repolarization Ic No effect on repolarization Slower conduction velocity ↑ QRS, (± ↑ PR) negative inotrope reentry sustaining *disopyramide (a)* *lidocaine (b)* *flecainide (c)*	**Class II** β-adrenergic receptor Blocker β1 or/and β2 receptor blocker Sympatholytic drugs ↑ PR, ↓ HR negative inotrope AV blocks *propranol, atenolol…*	**Class III** K^+ channel Blocker ↑ repolarization ↑ refractory periods ↑ QTc **Class IIIA** acting during HR acceleration **Class IIIB** *acting during* bradycardia *sotalol* **Class IIIAB** *acting independently of heart rate* *amiodarone* Positive inotrope Torsades de pointe	**Class IV** Ca^{2+} Channel blocker Slower conduction velocity ↑ PR, ↑ QTc, ↓ HR negative inotrope AV Blocks *verapamil, diltiazem*	**Class V (1979)** Adenosine Digoxin (↑ vagal activity) *Ivabradine* (specific sinus node action I_f blocker ↓ diastolic depolarization ↓ HR, (± ↑ PR))
Touboul et al., 1979	**Class I** ↓ AV conduction velocity ↑ AH and ↑ ERP *Beta blockers, verapamil, digitalic*	**Class IIA** ↑ His-Purkinje ERP ↑ HV and ↑ atrial RP *quinidine, disopyramide*	**Class IIB** ↓His-Purkinje RP without ↑ HV *phenotoine, lidocaine* ↑His-Purkinje RP without ↑ HV *bretylium*	**Class III** ↑AH conduction velocity and ↑HV ↑ AV RP *aprindine* ↑ Atrial RP ↑ His-Purkinje ERP *Amiodarone*	
1982 Autonomic classification of Goldberger and Curtis	**Class I** Local anesthetics **1A quinidine-like agents with cholinergic 1blocking** **1B agents without autonomic action** *lidocaine*	**Class II** digitalis glycoside with vagotonic effect	**Class III** antiadrenergic agents **Class IIIA** beta-blockers *propranolol* **Class IIIB** norepinephrine-release inhibitors *bretylium* **Class IIIC** non specific adrenergic blockers *amiodarone*	**Class IV** calcium channel blockers	
1991 Taormina "Sicilian gambit"	**Channels** Na^+ Ca^{2+} K^+ I_f	**Receptors** α—adrenergic β—adrenergic M_2-muscarinic Purinergic	**Pumps** Na^+/K^+ ATPase		

arrhythmias and SCD related to medication used in cardiology and non-cardiological fields. Although a drug may prove effective in most patients, rare cases of drug-related SCD support the view that positive results on major safety screening tests (mortality, QT interval, hERG assay …) lead to the exclusion of many molecules of clear therapeutic interest. One immediate consequence is the slowing down of AA drug development, due to the difficulty in equating an hERG block with the actual risk of induction of TdP in humans (Roden, 2008), and the discarding of candidate compounds of possible therapeutic interest (Gintant, 2008). In an attempt to define well-balanced criteria for proarrhythmic risk, it has been proposed that setting an IC50 value for an hERG block at 30 times the maximum calculated unbound effective therapeutic plasma concentration would provide a good safety margin (Redfern et al., 2003). Interestingly, there are examples of drugs with multiple effects on different ion channels that minimize torsadogenic risks, suggesting that combinations of drugs should be taken into account on a more systematic basis.

4.2. Experimental tools available

The starting point in AA development is the availability of relevant experimental models of arrhythmias on the one hand, and for each specific step of efficacy and safety testing on the other hand. Different models are required for different purposes, including the improvement of our understanding of the mechanisms underlying arrhythmia, the identification of "druggable" targets, and the screening and design of molecules (i.e. lead optimization). Very early, extensive consideration has been paid to experimental investigation of arrhythmia in vivo (rat, guinea-pig), particularly at the ventricular level during ischemia, infarction and reperfusion, to provide the Lambeth Convention guidelines covering many practical aspects (definition, classification, quantification, and analysis) (Walker et al., 1988). In vivo models in a number of species allow the induction of AF or VA and aim to reproduce human pathophysiology. However, animal models did not deliver their full potential in this field. In particular, no model covers all aspects of the clinical situation in patients. Therefore, the choice of model used needs to be better defined depending on the goal pursued: identification of mechanisms or development of a therapeutic product.

AF models were developed mainly in large animals (i.e. dogs, pigs, sheep and goat) in order to induce AF associated with electrical (paroxysmal or persistent/permanent models) or structural (persistent/permanent models) remodeling (Nishida et al., 2010; Schotten et al., 2010). These also included the influence of the ANS on the induction of AF. There are now several transgenic mouse models available that exhibit pronounced atrial enlargement and spontaneous or inducible AF, but their comparison with human AF is inherently problematic (for review: Schotten et al., 2010). In different models of VT/VF (iatrogenic, in vivo models of ischemia-induced arrhythmia, Langendorff models and naturally occurring models) the mechanisms involved have been widely documented (for review, Hamlin, 2007). However, due to significant differences in cardiac electrophysiological profiles and heart structure that influence the spatial component of arrhythmia, the translation of these findings to humans also needs to be carried out with caution (Nerbonne et al., 2001). Since the topic of this review is not to describe extensively the limits of all experimental models available for mechanistic investigation of arrhythmia, we invite the reader to consider recent reviews (e.g. Hamlin, 2007 for VF and Schotten et al., 2010 for AF).

Apart from in vivo models for mechanistic studies of arrhythmias, a number of cell-based in vitro assays were developed especially for drug screening and design both for efficacy and safety of new drugs. Ion channel assays based on electrophysiological technologies are essential in drug discovery and evaluation of their potential side effects. Other assays include non-functional tests with ligand-receptor binding techniques targeting ion channels, fluorometric imaging for intracellular Ca^{2+} assessment, and direct ion-flux, which provide more or less functional information. Proceeding beyond the set-up of these new cell-based methods, the achievement of automated assays offers increased drug screening capacity (Nattel et al., 2008). Finally, in combination with the experimental data provided by the models described above, in silico modeling is another emerging technology specifically proposed for the characterization of the mechanisms responsible for efficacy (Vigmond et al., 2009) and adverse effects (Corrias et al., 2010).

The absence of effective drugs in human patients suggests that the relevance of available pre-clinical models is questionable. On the other hand, the absence of reference drugs in the clinical field for VA makes the validation of novel AA molecules difficult to achieve.

4.3. Emerging concepts regarding novel antiarrhythmic drugs

AA drug discovery has been problematic for a long time and development of new AA drugs, notably to treat VA, has failed. The prevailing therapy for VA is the ICD, but this remains a symptomatic treatment which does not prevent disease progression. Interestingly, newly acquired knowledge through genetics of ion channels, functional genomics and use of miniaturized devices (echocardiography, ECG by telemetry, intracardiac electrophysiological exploration), developed in particular for the phenotyping of transgenic mouse models, has advanced our understanding of not only the role of ion channels but also of complex intracellular mechanisms involved critically in the genesis of arrhythmias. Clearly genetic models are easier to study than conventional models of chronic diseases and, although they do not reproduce the complex phenotype of such chronic diseases, they can provide comprehensive mechanistic information. These new approaches are undoubtedly helpful for the development of new AA drugs and for preclinical studies. For example, drugs normalizing altered Na^+ and Ca^{2+} signaling and/or homeostasis were shown to prevent arrhythmias not only in inherited diseases related to ion channels mutations (e.g., LQT3, CPVT) but also in chronic disease. Although they are not always specific, some emerging AA drugs might pose a dual therapeutic benefit at both atrial and ventricular levels where intracellular Na^+ and Ca^{2+} overload has been shown to trigger arrhythmias. Other emerging pharmacological treatments include anti-remodeling drugs targeting primarily factors that are extrinsic to the cardiomyocyte, like mechanistic pathways involved in disease progression (e.g. neurohormonal systems, extracellular matrix remodeling, fibrosis), but involved in its electrical remodeling (ion channels, Ca^{2+} signaling).

4.3.1. Sino-atrial level

4.3.1.1. Monotask antiarrhythmic drugs: Do they really exist? Although the cause of AF does not primarily involve ion channels, but is more likely due to a remodeling of atrial tissue, the treatment of choice is aimed at ion channels. There are several ways to envisage the development of novel AA drugs that are effective and safe. An ideal approach is to target a specific ion channel involved exclusively at the cardiac stage that exhibits the arrhythmia in question. A good example of this is ivabradine, a novel specific heart-rate lowering drug that acts selectively at the level of the sinoatrial node by inhibiting the pacemaker I_f current involved in setting the sinus rhythm (Thollon et al., 1994; DiFrancesco & Camm, 2004). Recent studies have demonstrated a powerful effect of ivabradine in ischemic patients, in whom it reduces the sinus rhythm to below 70 beats/min ('SHIFT' study) (Cleland et al., 2010; Swedberg et al., 2010). Its place in the treatment of angina pectoris is now established. Due to its own specific effect, we should expect a beneficial effect of this drug on abnormal automaticity of the sinus node. As a matter of fact, ivabradine has recently been shown to be effective, and a safe alternative to Ca^{2+} channel blockers and ß-blockers for the treatment of inappropriate sinus tachycardia (Calo et al., 2010).

In the same vein of specific inhibition of ion channels, a promising AA strategy targeting AF currently under development, is the use of atrial-tissue specific ion channel blockers that do not fit within the classic VW classification. A new family of drugs called ARDAs, for atrial repolarization delaying agents, designed to block the ultra-rapid delayed rectifier current (I_{Kur}) and the acetylcholine-regulated K^+ current (I_{KACh}) that are not expressed at the ventricular stage, is emerging. A more exhaustive treatment of this subject can be found in several recent reviews (Ehrlich & Nattel, 2009; Kozlowski et al., 2009; Ravens, 2010). An example of these new drugs is vernakalant, which has been presented as an atrial-selective compound, with a reduced risk of TdP, and expected to be of use in the acute chemical cardioversion of AF. Its capacity to rapidly reduce AF episodes by 75%, 45 min after IV injection (compared to IV amiodarone; AVRO study) has led to its inclusion in the new *ESC 2010 guidelines* (Camm et al., 2010). Although vernakalant primarily targets the Kv1.5 ion channel, it does, however, have other effects (on I_{Na}, I_{KAch}, I_{To} and I_{KS}), and can be classified as a multichannel blocker, in particular with mixed effects on K^+ and Na^+ channels.

4.3.1.2. Multitask antiarrhythmic drugs. Other AA candidates are multichannel blockers or, may be more appropriately, "multitask" drugs, as some of them have far more complex effects than the modification of AP duration (e.g. effects on Na^+ and Ca^{2+} homeostasis). A good example of a multichannel blocker is amiodarone, which is the oldest and most effective drug used for the maintenance of the sinus rhythm, despite its poor objective efficacy (Lafuente-Lafuente et al., 2007). It is also the AA drug associated with the greatest number and variety of side effects, although its QT-prolonging effect, due to a complex mechanism of action, is unlikely to promote VA. Nowadays, however, new pharmacological agents for AF have to demonstrate a reduction of mortality and a low rate of side effects, in addition to their effect on sinus rhythm maintenance or frequency control. Dronedarone is a derivative of amiodarone that is expected to be devoid of most of its adverse side-effects, particularly on thyroid function (Boden et al., 2007). A benefit of dronedarone treatment on hospitalization rate and cardiovascular mortality was reported in high-risk patients with AF and normal LV function in the ATHENA study (Kober et al., 2008). The EURIDIS and ADONIS studies showed a modest benefit of this drug in reducing the recurrence of AF by, respectively, 22 and 27%, with a clear reduction in the ventricular rate during fibrillation (Singh et al., 2007). Improved rate control during persistent AF was confirmed by the ERATO study (Davy et al., 2008). However, no benefit in terms of mortality was associated with dronedarone in HF patients (Kathofer et al., 2005). Dronedarone is also currently suspected of being hepatotoxic by the EMA (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001043/human_med_001207.jsp&murl=menus/medicines/medicines.jsp&jsenabled=true) and the FDA (http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm240110.htm). In conclusion, while the benefit/risk ratio of dronedarone has not been well evaluated, amiodarone is still, despite its side effects, the best AA available for AF.

4.3.2. Ventricular level

4.3.2.1. Drugs targeting Na^+ and/or Ca^{2+} homeostasis. Among other emerging AA drugs, ranolazine seems to have great potential despite the fact that it has multiple effects on several ion channels. However, ranolazine has a very interesting panel of effects on intracellular Na^+ and Ca^{2+} homeostasis. Similarly, drugs inhibiting or stabilizing RyR2 activity in diastole define a novel therapeutic concept that applies to diverse conditions favoring arrhythmias.

4.3.2.2. Rationale for the normalization of Na^+ and Ca^{2+} homeostasis by antiarrhythmic drugs. VA can be triggered by erratic intracellular Ca^{2+} movements that promote abnormal Ca^{2+}-dependent electrical activity. This can occur in a variety of proarrhythmogenic conditions including chronic diseases, such as congestive HF and ischemic heart disease, and inherited arrhythmogenic diseases such as CPVT. Numerous channels and exchangers regulate Ca^{2+} influx from the extracellular space, Ca^{2+} exchange between intracellular stores and the cytoplasm, as well as Ca^{2+} exit, in order to maintain intracellular Ca^{2+} homeostasis. During each heart beat, fast depolarization of the cardiomyocyte membrane by the AP generates a small Ca^{2+} influx via voltage-gated transmembrane L-type Ca^{2+} channels localized in the transverse tubules. This Ca^{2+} current releases Ca^{2+} stored in the sarcoplasmic reticulum (SR) by triggering the opening of the SR Ca^{2+}-release channel (the cardiac isoform of which is currently referred to as the ryanodine receptor; RyR2) via the "Ca^{2+}-induced Ca^{2+} release" mechanism (Fabiato & Fabiato, 1979; Bers, 2002). This release rapidly increases cytoplasmic Ca^{2+}, thus enabling the activation of contractile proteins. Relaxation occurs with the concerted closing of L-type Ca^{2+} channels, and Ca^{2+} re-uptake into the SR via SERCA2a and/or extrusion via NCX (Bers, 2002; Richard et al., 2006). The rapid return of cytoplasmic Ca^{2+} to its low resting levels determines both the appropriate conditions for full diastolic relaxation as well as its effectiveness.

There is a very close relationship between myocardial contractile dysfunction and the occurrence of VA, most often in chronic cardiac diseases. Patients affected by LV contractile dysfunction are at particular risk for SCD. Ca^{2+} undeniably constitutes a common key factor involved in these two abnormalities, for instance, in HF. Both weaker contraction and the increased propensity for disordered cellular electrical activity result from uncontrolled spontaneous Ca^{2+} release (Pogwizd & Bers, 2004; Tomaselli & Zipes, 2004). In addition to abnormal repolarization, HF is in fact associated with major changes in Ca^{2+} handling, both in experimental and human cell models (Beuckelmann et al., 1992; Bers et al., 2003; Yano et al., 2006). Ca^{2+} homeostasis can also be influenced by changes in Ca^{2+} binding to contractile proteins and/or in Ca^{2+} buffering capacity. The reduced affinity of the troponine C protein (TnC) for Ca^{2+}, which leads to an increase in cytoplasmic Ca^{2+} (Allen & Kentish, 1988), can initiate DADs (Miura et al., 2010). Spatial non-uniformity of excitation–contraction coupling within the border zone between ischemic and healthy cardiac regions promotes DADs (Miura et al., 2008). Myofilament sensitization of contractile proteins, which occurs in pathological situations like hypertrophic cardiomyopathy, has been proposed to cause susceptibility to arrhythmia (Baudenbacher et al., 2008) but the underlying molecular mechanisms are unclear (Huke & Knollmann, 2010). Ca^{2+} buffering within the SR may also be important, as shown by the occurrence of CPVT-2 consecutive to mutations of calsequestrin (CSQ), and the associated reduction in Ca^{2+} buffering capacity (Rizzi et al., 2008; Venetucci & Eisner, 2008).

The electrical abnormalities seen in CPVT are very similar to those associated with cardiotonic steroid (ouabain, digoxin, and digitonin) toxicity (Priori et al., 1988; Priori et al., 2001a). The striking similarity between ECG abnormalities (bidirectional VT) observed with RyR 2 mutations (CPVT) or induced by cardiotonic steroid toxicity is related to aberrant Ca^{2+} overload and RyR2-mediated Ca^{2+} release. Cardiotonic steroids inhibit Na^+/K^+ ATPase leading to the accumulation of diastolic intracellular Na^+, which increases Ca^{2+} influx mediated by NCX during the AP and limits diastolic Ca^{2+} extrusion, which in turn results in SR Ca^{2+} store overfilling, the subsequent activation of a transient inward Na^+ current mediated by NCX (I_{ti}) and the triggering of DADs (Ferrier et al., 1973; Rosen et al., 1973; Lederer & Tsien, 1976; Levi et al., 1997). Recently, Na^+-dependent SR Ca^{2+} overload was shown to induce arrhythmogenic events both in a mouse model with a human CPVT mutation (Sedej et al., 2010) and with oleandrin, a cardiotonic steroid obtained from oleander extract (Poindexter et al., 2007). It should be noted that ouabain-induced abnormalities in Ca^{2+} handling can be partially rescued by the RyR2 stabilizer JTV-519 (Sedej et al., 2010).

4.3.2.3. The ranolazine example

4.3.2.3.1. Ranolazine and cardioprotection. Ranolazine (Ranexa) is a novel anti-ischemic and antianginal drug (Chaitman et al., 2004; Chaitman, 2006) with therapeutic benefits during the early events following MI. Ranolazine, was patented in 1986 and approved in 2006 for patients resistant to standard antianginal therapy (Hale et al., 2008; Keating, 2008; Nash & Nash, 2008). This drug reduces electrical and mechanical dysfunction during myocardial ischemia presumably via the inhibition of persistent Na^+ currents (I_{NaP}). The electrophysiological consequences on AP duration and intracellular Na^+ and Ca^{2+} homeostasis are probably critical for its therapeutic effects. Ranolazine has a structure similar to that of lidocaine (Fredj et al., 2006) and is a class IB AA, according to the VW classification. It blocks a number of ion currents at concentrations approaching the therapeutic plasma level, including both inward depolarizing currents, such as the L-type Ca^{2+} channel current (I_{CaL}) and the persistent I_{NaP}, as well as different outward repolarizing K^+ currents such as I_{Kr} and I_{Ks} (Hale et al., 2008; Saint, 2008). Although ranolazine was not originally proposed as a Na^+ channel inhibitor, its antianginal effect may involve the inhibition of I_{NaP}. The rationale for this mechanism of action can be intuited from several converging observations. First, I_{NaP} is more sensitive to ranolazine than other ion currents (Antzelevitch et al., 2004), which is indeed consistent with its therapeutic effects. Second, ranolazine reduces the intracellular Na^+ and Ca^{2+} overload resulting from any condition that promotes I_{NaP} (Fredj et al., 2006). Finally, like other agents that block I_{NaP}, ranolazine has a protective effect during ischemia–reperfusion. The inhibition of I_{NaP} is recognized as a cardioprotective approach of choice (Hale et al., 2008; Saint, 2008).

4.3.2.3.2. Pathophysiological role and molecular origin of I_{NaP}. Our understanding of the role of I_{NaP} in cardiac pathophysiology today has been influenced by the landmark work of Professor E. Coraboeuf, showing the participation of a Na^+ current in the plateau phase of the AP in PF, although its origin was unclear at the time ('window' current of I_{NaF}) (Coraboeuf et al., 1979). The importance of this finding for the mechanism of action of AA drugs was already evident. Many studies have subsequently demonstrated the existence of I_{NaP} in cardiomyocytes of both humans and animals using the patch-clamp technique (Saint, 2008). The physiological role of I_{NaP} in cardiomyocytes is, however, poorly understood. I_{NaP} is clearly associated with pathological situations, both acquired and genetic. For example, I_{NaP} is induced by hypoxia, present in HF and implicated in the cellular damage that results (Hammarstrom & Gage, 2002). I_{NaP} is also involved in serious genetic arrhythmias (e.g. congenital long QT syndrome type 3 or LQT3, LQT10, and Brugada syndrome) associated with mutations in the cardiac Na^+ channel ($Na_v1.5$ isoform in LQT3; genes encoding a regulatory subunit, such as $Na_v\beta4$ in LQT10; and the gene encoding caveolin in LQT9) (Tan et al., 2003; Vatta et al., 2006; Medeiros-Domingo et al., 2007; Saint, 2008). Finally, I_{NaP} can be induced artificially by the binding of different toxins to the $Na_v1.5$ channel (Quignard et al., 1997; Boccara et al., 1999; Wasserstrom et al., 2009).

In cardiomyocytes, the fast inactivating Na^+ current (referred to as I_{NaF} for simplicity) is responsible for the rapid depolarization of the AP and closely determines cell excitability. The opening of Na^+ channels is initiated by slight membrane depolarizations. Under normal conditions, the Na^+ channel opens quickly and briefly (for a few milliseconds) after membrane depolarization, which accounts for the transitory properties of I_{NaF}. When depolarization is maintained, typically during the plateau of the AP, all Na^+ channels inactivate by rapidly entering a non-conductive and absorbing state (non-activatable). Compared to these "normal" gating properties, I_{NaP} hardly inactivates (it can last for seconds), even for large depolarizations far above the voltages that determine the so-called 'window' current (Boccara et al., 1999). At the single-channel level, longer openings and/or re-openings during depolarization have been demonstrated in different experimental models, including in human cardiomyocytes (Maltsev & Undrovinas, 2006). This biophysical behavior of the Na^+ channel most probably determines the pharmacological efficacy of ranolazine.

The molecular origin of I_{NaP} is still undefined. Although I_{NaF} and I_{NaP} could be generated by distinct Na^+ channel isoforms (splice variants), a single isoform ($Na_v1.5$) has been shown to generate both fast- and slow-inactivating components (Maltsev & Undrovinas, 2006), which is the case for mutations of the SCN5A gene (LQT3) (Fredj et al., 2006). Although the mechanistic details are unclear, the promotion of I_{NaP} under various pathological situations induces similar changes in the biophysical properties (gating) of the $Na_v1.5$ Na^+ channel.

4.3.2.3.3. Ranolazine normalizes Na^+ channel gating and inhibits I_{NaP}. What is the molecular mechanism of action of ranolazine on I_{NaP}? Ranolazine inhibits I_{NaP} with a much higher affinity than I_{NaF} (Fredj et al., 2006), by a factor of 40 to 60, in terms of EC_{50}, according to some reports (Undrovinas et al., 2006; Keating, 2008). This suggests that ranolazine is capable of inhibiting I_{NaP} with no effect on I_{NaF} (Fig. 3), a mechanism that is fundamentally different from the effect of tetrodotoxin (TTX) which is expected to block both I_{NaF} and I_{NaP} (Quignard et al., 1997; Boccara et al., 1999). In other words, the strategic effect of ranolazine may be associated with a normalization of the kinetics of global I_{Na}, then turned into a fast inactivating current I_{NaF}, and ideally with little or no effect on the peak current as a whole. The observed effects of the molecule correspond to the underlying mechanistic concept: at concentrations that selectively block I_{NaP}, ranolazine does not affect global current amplitude (indicating that all channels open normally), as shown with channels carrying a mutation implicated in the LQT3 syndrome (Fredj et al., 2006), but the time spent in the open state is limited by the drug. At the physiological level, ranolazine is expected not to affect the participation of the Na^+ current in cell excitability or conduction, in stark contrast to the effect of an inhibitor such as TTX, which blocks the channel and prevents its opening (Fig. 3). Consistent with this supposition, ranolazine shortens the AP in the presence of an I_{NaP} component, as in the case of a LQT3 mutation (Fredj et al., 2006; Moss et al., 2008).

4.3.2.3.4. Ranolazine as a novel antiarrhythmic drug? Despite a selective effect on I_{NaP}, ranolazine blocks different types of ion channels. In particular, ranolazine inhibits I_{Kr}, a major proarrhythmogenic ion current, thereby causing a modest but significant dose-dependent prolongation of the cellular AP and of the QT interval, events regarded as predictive of VA and TdP (Singh & Wadhani, 2004). In fact, several studies suggest that proarrhythmic risk, usually associated with I_{Kr} blockers, is limited in the case of ranolazine, an effect that could, among other things, arise from its concomitant effect on I_{NaP}. Blocking the inward depolarizing I_{NaP} is expected to counterbalance the inhibitory effect of ranolazine on the repolarizing I_{Kr} current, thereby resulting in a 'neutral' or minor effect on the AP plateau. In fact, ranolazine has remarkable AA properties and, in addition, may prevent the deleterious effects of various I_{Kr} blockers (Antzelevitch et al., 2004; Keating, 2008; Moss et al., 2008; Wang et al., 2008; Antoons et al., 2010). Ranolazine is a promising new treatment option for patients with atrial rhythm disturbances (AF-terminating drug) and diastolic dysfunction (Nattel & Carlsson, 2006; Dobrev & Nattel, 2010; Sossalla et al., 2010). It has also been shown to exhibit a marked AA effect in the setting of acute ischemia/reperfusion at low doses, consistent with its inhibition of I_{NaP} (Kloner et al., 2010).

At the cellular level, a normalization of the ventricular AP duration, in association with an I_{NaP} blockade, is expected to decrease the risk of developing EADs during the plateau phase (Fig. 3). More importantly, an overload of intracellular diastolic Na^+ (linked to a 'window' I_{NaP} or after a rise in heart rate) plays a role in inducing a Ca^{2+} overload and the occurrence of arrhythmias via Ca^{2+}-dependent DADs. These abnormal depolarizations are associated with the existence of spontaneous Ca^{2+} waves (not triggered by an AP) (Wasserstrom et al., 2009), resulting from intracellular Ca^{2+} overload and increased activity of RyR2, which initiate a transient inward depolarizing

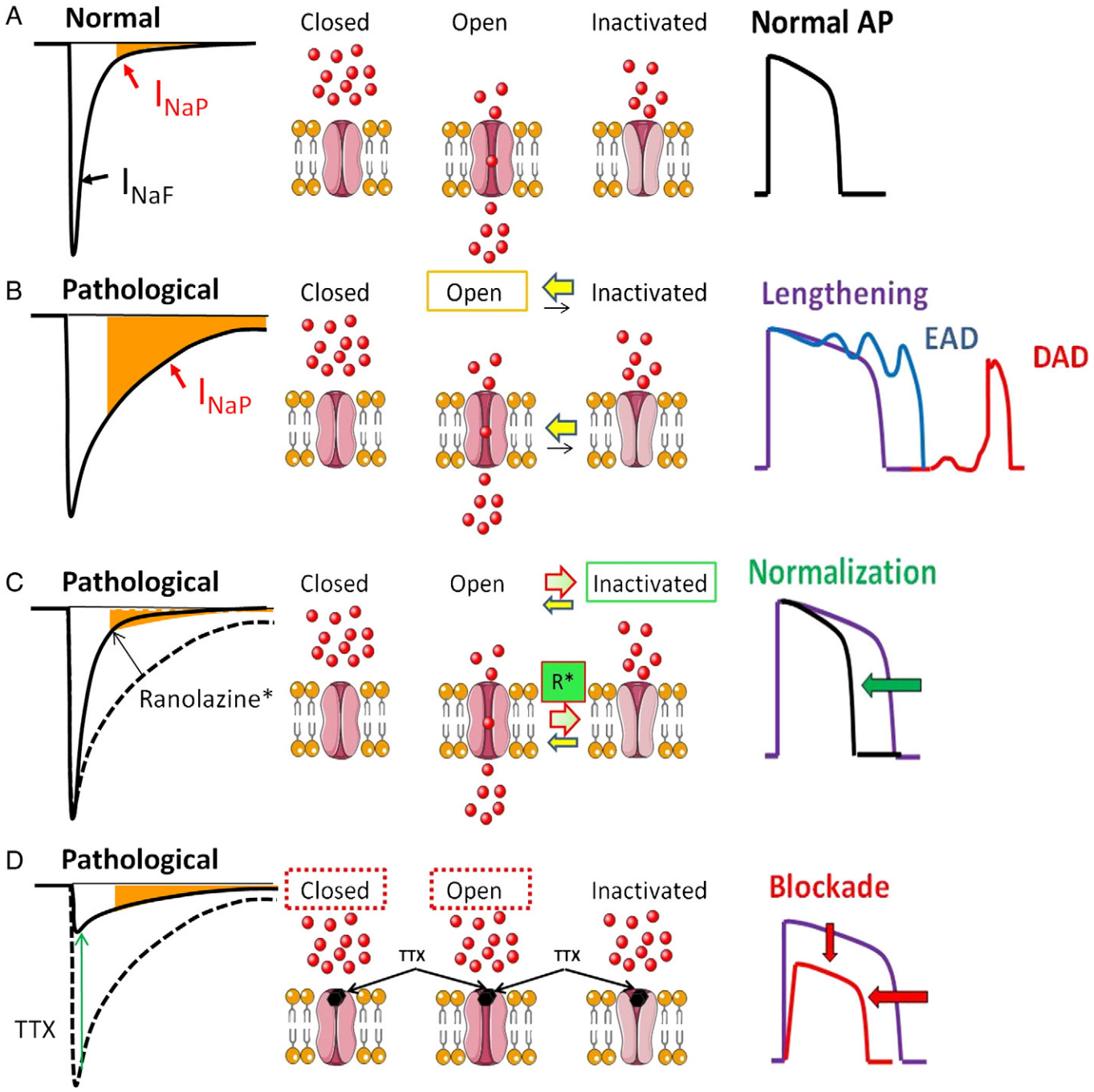

Fig. 3. Ranolazine normalizes Na^+-channel gating and macroscopic current kinetics. The typical I_{Na} current is characterized by fast activation and rapid inactivation. Na^+ channels normally fluctuate in a voltage-dependent manner between three distinct fundamental conformational states: closed, open (permeant) and inactivated (non-permeant, non-activatable). The persistent I_{NaP} current reflects the promotion of the open state under pathological conditions, which contributes to AP prolongation and favors the occurrence of cellular arrhythmias. Ranolazine preferentially inhibits I_{NaP} vs. I_{Na} peak (with no effect on I_{NaF}) thereby normalizing I_{Na} and AP duration and preventing cellular arrhythmias. The Na^+-channel blocker TTX has a very different mechanism of action. Ranolazine has a higher affinity for the open state (vs. the closed state) and induces Na^+-current fast inactivation.

current (I_{ti}) generated by NCX. Thus, ranolazine may prevent both I_{NaP}-induced EADs and DADs resulting from chronic disease or gene mutations (Kaufman, 2008; Moss et al., 2008).

4.3.2.4. RyR2 blockers and stabilizers

4.3.2.4.1. RyR2 as a privileged direct pharmacological target. Although there are other druggable targets among Ca^{2+} handling proteins, like SERCA2a and NCX, RyR2 is probably the most relevant for the prevention of abnormal spontaneous openings in diastole. Enhancing SR Ca^{2+} load, which has been tested via overexpression of SERCA2a or knocking out PLN, is an interesting therapeutic approach (Periasamy & Huke, 2001). However, persistent SR Ca^{2+} leakage, which could be further aggravated by enhanced SR Ca^{2+} load, might limit its therapeutic potential in terms of arrhythmias. Thus, targeting leaky RyR2 to prevent abnormal SR Ca^{2+} release appears to be a more promising pharmacological approach (Wehrens & Marks, 2004; Wehrens et al., 2004, 2005; George et al., 2007; Gyorke & Carnes, 2008; Blayney & Lai, 2009).

4.3.2.4.2. Ca^{2+} leakage via RyR2, I_{ti} and arrhythmias. The electrical imbalance between repolarizing and depolarizing ion currents during the cellular AP is a source of arrhythmias, namely EADs. These occur in HF, for instance, which is characterized by a prolongation of the AP

resulting mainly from the attenuation of outward repolarizing K^+ currents and possibly from the slowing of Ca^{2+} current decay (Janse, 2004; Pogwizd & Bers, 2004; Tomaselli & Zipes, 2004; Richard et al., 2006). Consistent with the latter phenomenon, the abnormal inactivation caused by the G406R mutation of the $Ca_V1.2$ isoform of the Ca^{2+} channel (associated with Timothy syndrome) delays AP repolarization, thus explaining the associated arrhythmia (Splawski et al., 2004). Altered intracellular Ca^{2+}-handling also can promote VA and SCD, a fact that has been established both in chronic diseases like HF and in inherited malignant arrhythmogenic disorders such as CPVT.

CPVT is a rare cause of syncope and SCD in children, adolescents and young adults with a structurally normal heart (Leenhardt et al., 1995; Priori et al., 2002; Francis et al., 2005). Clinically, the VA occurs in the absence of a repolarization defect and is triggered by physical exercise or emotional stress, with a higher risk associated with males (Priori et al., 2002; Mohamed et al., 2007). The diagnosis of CPVT cannot be based on resting ECG, as no abnormality is present at rest, and the typical ECG pattern only becomes apparent during a stress test. ß-blockers reduce arrhythmias, but in 30% of patients, an ICD is required although not completely effective and painful (Priori et al., 2002; Mohamed et al., 2006; Pizzale et al., 2008). Extended clinical phenotypes (e.g. dysfunction of the sinoatrial and atrioventricular nodes, AF, atrial standstill, and dilated cardiomyopathy) and, eventually, LV dysfunction and dilatation, have also been described in individuals with a large genomic deletion in the RyR2 gene (Bhuiyan et al., 2007).

Genetic investigations have now revealed the involvement of many mutations in the genes encoding RyR2 and CSQ (Lahat et al., 2001; Laitinen et al., 2001; Priori, et al., 2001a; Postma et al., 2002; Priori et al., 2002; Viatchenko-Karpinski et al., 2004; di Barletta et al., 2006; Lehnart et al., 2008; Gyorke, 2009). The functional characterization of these mutations has demonstrated that CPVT is caused by increased spontaneous openings of the RyR2 in diastole, which results in altered control of local intracellular Ca^{2+}, spontaneous Ca^{2+} release, Ca^{2+} waves and DADs (Fig. 4) (Terentyev et al., 2006; George et al., 2007; Gyorke & Carnes, 2008; Fernandez-Velasco et al., 2009). Leaky RyR2 may also cause seizures in addition to SCD, in keeping with the idea that CPVT is a combined neurocardiac disorder in which RyR2 channels in the brain cause epilepsy, while their cardiac counterparts lead to arrhythmia (Lehnart et al., 2008). VA can be triggered by unprompted APs arising from DADs related to the spontaneous release of Ca^{2+} through RyR2 induced Ca^{2+} waves. RyR2-mediated SR Ca^{2+} leakage is critically involved in the triggering of Ca^{2+}-mediated arrhythmia in HF and CPVT (Fig. 4) (Bers et al., 2003; Lehnart et al., 2004; Yano et al., 2006). It should be noted that SR Ca^{2+} overload may play a critical role in determining whether Ca^{2+} waves occur (Jiang et al., 2004; Eisner et al., 2009). Catecholamines may also cause arrhythmia in CPVT because they increase SR Ca^{2+} content up to the threshold required for Ca^{2+} release (for review, see: Venetucci & Eisner, 2008). Decreased levels of CSQ and, thereby, of Ca^{2+} buffering capacity within the SR in a knock-in mouse model have been associated with high susceptibility to arrhythmia (Rizzi et al., 2008).

The concept of an association between defective SR Ca^{2+} release and arrhythmia also applies to AF (Hove-Madsen et al., 2004; Vest et al., 2005). Acute atrial arrhythmogenic properties in the RyR2-P2328S mouse are correlated with altered Ca^{2+} homeostasis in the absence of repolarization abnormalities (Zhang et al., 2011). Interestingly, it has been shown that the antihistamine terfenadine and adenosine A(2A) receptor stimulation increases spontaneous Ca^{2+} release in human atrial myocytes and may contribute to atrial arrhythmogenesis (Hove-Madsen et al., 2006a, 2006b). In addition, endocardial mapping has confirmed the PF origin of focal arrhythmias associated with aberrant RyR2 activity (Cerrone et al., 2007).

4.3.2.4.3. Normalizing RyR2 activity to prevent arrhythmias. The discovery of new AA drugs capable of both preventing Ca^{2+}-dependent arrhythmias and rescuing contraction by sealing leaky RyR2 channels has emerged as a major challenge. This can be achieved in different ways by drugs targeting multiple facets of RyR2 function, either directly, or indirectly, by using well-established drugs to delay adverse cardiac remodeling (see below). An example of a direct effect is provided by dantrolene, primarily used to treat malignant hyperthermia by targeting the skeletal muscle ryanodine receptor (RyR1). Dantrolene also prevents abnormal SR Ca^{2+} leakage through cardiac RyR2 through a similar mechanism (correction of domain unzipping-induced channel dysfunction) (Kobayashi et al., 2005). Dantrolene has been shown to both improve contractile function in pacing-induced HF (Kobayashi et al., 2009) and prevent CPVT induced by either epinephrine or exercise, while improving exercise tolerance,

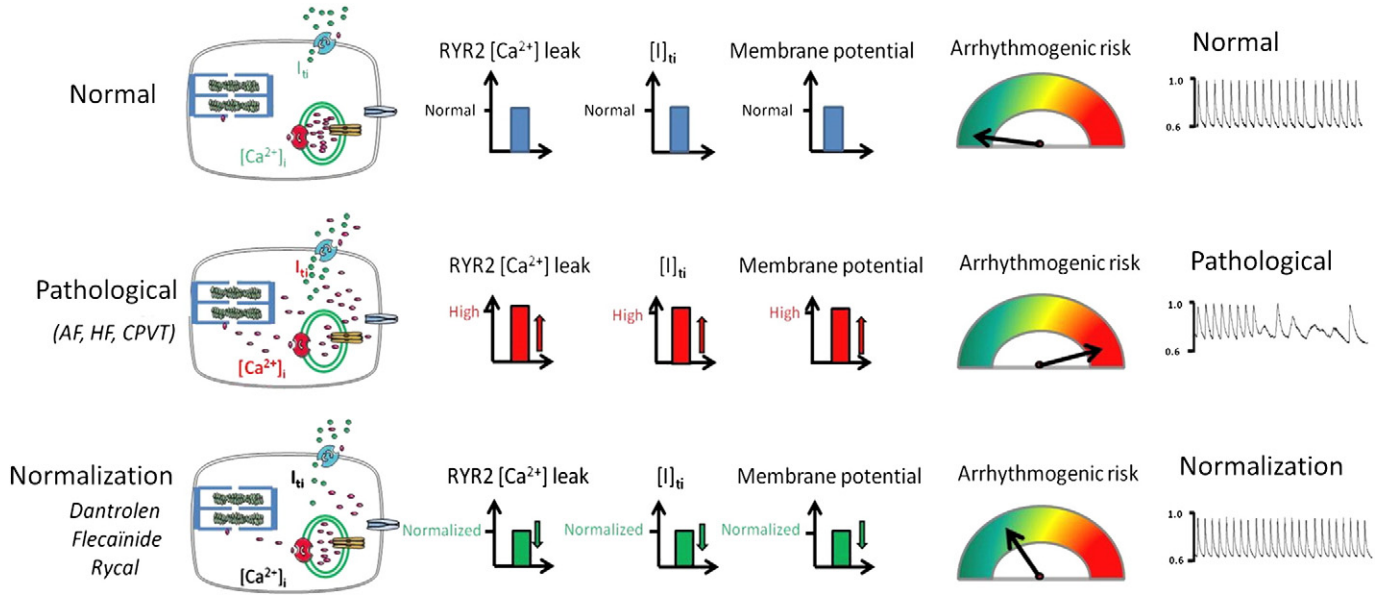

Fig. 4. Blockers and stabilizers of RyR2 prevent arrhythmia. Under normal conditions, RyR2 rarely opens in diastole. Spontaneous opening leads to leaky RyR2 in various pathophysiological situations, generating aberrant Ca^{2+} sparks and Ca^{2+} waves that activate inward depolarizing I_{ti} currents via NCX, that in turn generate DADs and arrhythmia. Compounds that block or stabilize the RyR2-FKBP12.6 interaction (Rycals) prevent Ca^{2+} leakage and arrhythmogenic risk.

in a mouse model carrying a human RyR2 mutation (KI, RyR2 (R2474SQ/+) (Kobayashi et al., 2010)). Dantrolene probably has no effect on normal cardiac function (Kobayashi et al., 2009), which is in line with the concept of the normalization of RyR2 function.

Flecainide also targets RyR2, reminding one of the effect of another local anesthetic, tetracaine, although the mechanisms of action on spark frequency and Ca^{2+} waves are different (Hilliard et al., 2010). It was shown to prevent arrhythmias in a mouse model of CPVT, by inhibiting RyR2-mediated Ca^{2+} release, and in two human subjects who had remained highly symptomatic on conventional drug therapy (Watanabe et al., 2009). Consistent with this mechanism, flecainide inhibits arrhythmogenic Ca^{2+} waves by an open-state blockade of RyR2 Ca^{2+} release channels and a reduction of Ca^{2+} spark mass (Hilliard et al., 2010). Blocking the RyR2 open state provides a new therapeutic strategy for the prevention of diastolic Ca^{2+} waves. Despite the inhibition of Na^{+} channels and its proarrhythmogenic effect, notably in HF, flecainide has been proposed as a promising drug for CPVT (Watanabe et al., 2009).

Stabilizers of the binding of calstabin to leaky RyR2 (also referred to as Rycals), such as the benzothiazepine derivatives S-107 and JTV-519, prevent the erratic opening of the channels in diastole, while they are devoid of effect on normal RyR2 (Wehrens & Marks, 2004; Wehrens et al., 2004, 2005; Blayney & Lai, 2009). Proof of concept has been provided with the 1,4-benzothiazepine derivative JTV519 (or K201), which also exhibits a cardioprotective effect against Ca^{2+} overload via improved contractility and delayed LV remodeling in HF, presumably by stabilizing RyR2 (Fig. 4) (Yano et al., 2003; Yano, 2008; Kaneko et al., 2009). JTV519 has been shown to reduce the arrhythmogenic activity of pulmonary vein cardiomyocytes (Chen et al., 2008) and micro Ca^{2+} waves in arrhythmogenic PF cells following infarction in the canine heart (Boyden et al., 2004).

4.3.2.4.4. Ryanodine receptor stabilizers, Ca^{2+} handling and remodeling. The majority of heart diseases, such as HF, ischemic disorders and hypertrophy, may exacerbate arrhythmia through electrical and structural remodeling, creating a substrate for reentry and ectopic activity that could lead to SCD (Tomaselli & Marban, 1999). Such arrhythmogenic remodeling involves alterations in ion channels. In HF, major electrophysiological remodeling occurs, prolonging the AP as a result of a decrease in the density of repolarizing K^{+} currents (Janse, 2004), the appearance of I_{NaP} (Valdivia et al., 2005), the uncoupling of gap junctions, (Severs et al., 2008) and alterations in Ca^{2+} handling (Pogwizd & Bers, 2004). Ca^{2+} is critically involved in the initiation of cardiac remodeling through genetic effects (Berridge, 2006). There is increasing evidence that cardiac hypertrophy and HF may arise from an inappropriate phenotypic remodeling of the signalosome. The alteration of the Ca^{2+} transient during these disorders leads to increased diastolic Ca^{2+}. These changes in Ca^{2+} homeostasis may be sufficient to activate the transcriptional events that are responsible for the phenotypic remodeling that leads to hypertrophy (Williams & Rosenberg, 2002). Ca^{2+} is capable of initiating and modifying the protein expression profile of excitable cells by direct or indirect actions at the level of the gene (Rosen et al., 1995; Wankerl & Schwartz, 1995; Williams & Rosenberg, 2002).

RyR2 plays a critical role in the pathogenesis/pathology of HF. One proposed mechanism is through 'hyperphosphorylation' mediated by the cAMP-dependent protein kinase (PKA) due to sympathetic nervous system activation, which results in the dissociation of the RyR2-stabilizing subunit calstabin2 (or FKBP12.6) and causes RyR2 instability in diastole and subsequent SR Ca^{2+} leakage not only in HF but also in AF (Reiken et al., 2001; Doi et al., 2002; Vest et al., 2005; Sood et al., 2008; Yano, 2008). This can be corrected by ß-blockers (Reiken et al., 2001; Doi et al., 2002). Enhanced Ca^{2+}/calmodulin-dependent protein kinase (CaMKII) activity is also involved in the promotion of diastolic SR Ca^{2+} leakage, and increased diastolic Ca^{2+} levels contribute to arrhythmogenesis both in HF (Guo et al., 2006; Sag et al., 2009) and in AF (Chelu et al., 2009; Neef et al., 2010). CaMKII inhibition therefore has good potential as an antiarrhythmic strategy, although we could wonder about the specificity of a pathway with such a ubiquitous and important role in cellular physiology. Defective regulation of inter-domain interactions within the RyR2 may play a key role in the pathogenesis of HF (Oda et al., 2005), which could be corrected by antioxidant edaravone preventing Ca^{2+} leak and LV remodeling (Yano et al., 2005).

4.3.3. Anti-remodeling drugs with antiarrhythmic properties: Control of fibrosis and arrhythmia

4.3.3.1. Neurohormonal control. The importance of preexisting structural abnormalities in the development of AF has been amply demonstrated (Goette et al., 2002; Goette & Lendeckel, 2004). Concomitant with electrophysiological remodeling, structural and ultrastructural changes in atrial tissue are of particular importance, and worsened with the perpetuation of AF (Ausma et al., 1997). During the development/evolution of the pathology, the activation of the angiotensin system and inflammatory cascades in atrial tissue leads to fibrosis and provides a substrate for the maintenance of AF. Fibrosis is a key determinant of AF (Goette & Lendeckel, 2004), and the characterization of the signal transduction pathways leading to the development of such structural and molecular abnormalities may offer new therapeutic approaches to AF through the prevention of the remodeling processes. According to this concept, some non-AA drugs appear to be effective in the treatment of arrhythmias. For example, angiotensin-converting enzyme (ACE) inhibitors and blockers of the angiotensin receptor AT-1 appear to be effective in AF by reducing atrial fibrosis (Van Den Berg et al., 1995; Carnes et al., 2001), a finding that has been confirmed in the clinic (Madrid et al., 2002; Vermes et al., 2003).

4.3.3.2. Matrix metalloproteinase, cathepsin and fibrosis. Other molecules participating in fibrosis are also being explored, such as matrix metalloproteinases (MMPs), whose expression and activity are increased by angiotensin secretion (Coker et al., 2001). Inhibiting MMPs could limit atrial fibrosis during AF (Moe et al., 2008). Cysteine cathepsins are proteolytic enzymes less famous than MMP, but their role in some chronic diseases like cancers is emerging (Reiser et al., 2010). These proteases were initially thought to be located exclusively in the lysosomal compartment, but there is now quite some evidence that they can also be secreted by cells. The dysregulation of cathepsins, mainly cathepsin L (CatL), may play a role in cardiomyopathy. Mice knocked out for CatL (−/−) have been shown to develop fibrosis, impaired cardiac contraction and ventricular dilatation (Stypmann et al., 2002; Petermann et al., 2006). Associated with the development of cardiomyopathy, these mice present supraventricular tachycardia, ventricular extrasystoles and atrioventricular block (Stypmann et al., 2002). In addition, even though there have been no reports regarding arrhythmias, it has to be pointed out that other cysteine cathepsins, CatB and CatS, can be overexpressed in patients with hypertensive HF. These cathepsins are likely involved in the turnover of the extracellular matrix and cardiac remodeling (Cheng et al., 2006).

4.3.3.3. Electrical remodeling. In addition to their antifibrotic role, angiotensin II antagonists can prevent the electrical remodeling that occurs during AF (Nakashima et al., 2000) and limit their electrical triggering (Haissaguerre et al., 1998). There is some evidence to suggest interplay between the adrenergic system and the renin–angiotensin–aldosterone system (Musgrave et al., 1991). Beta blockade may also exert AA actions by preventing a relapse into AF after cardioversion (Kuhlkamp et al., 2000; Workman et al., 2003) and by initiating adaptive electrophysiological remodeling (Workman et al., 2003). The combination of angiotensin antagonists and ß-blockers deserves to be studied. The importance of reactive oxygen species

(ROS) and reactive nitrogen species (RNS) in AF and in HF has also been shown in electrical remodeling (Carnes et al., 2001; Rennison & Van Wagoner, 2009; Brown & O'Rourke, 2010). Mitochondria are a major source of ROS and RNS and their production is increased with the alterations in energy metabolism that occurs during AF (Kalifa et al., 2008) and HF (Rosca & Hoppel, 2010). During ischemia–reperfusion injury, the opening of the mitochondrial permeability transition pore (mPTP) can also lead to ROS production and to cell death via a Ca^{2+}-dependent mechanism (Abdallah et al., 2010). ROS can modulate the function of Ca^{2+} regulating proteins such as the L-type Ca^{2+} channel, SERCA2a, NCX or RyR2 (Zima & Blatter, 2006; Kuster et al., 2010). In addition, RNS like peroxynitrite can induce Ca^{2+} leakage from the SR by increasing the probability of RyR2 opening through S-nitrosylation (Fauconnier et al., 2010). All these modifications lead to increased diastolic Ca^{2+} and a depletion of SR Ca^{2+} and promote Ca^{2+}-dependent arrhythmias (Donoso et al., 2010; Fauconnier et al., 2010). Prophylactic therapy with vitamin C can reduce the incidence of AF after surgery through a mechanism involving the regulation of Ca^{2+} handling proteins like RyR2 and SERCA2a (Carnes et al., 2001). Indirectly limiting ROS production by modulating several pathways (MAPK, and NADPH oxidase) could be an alternative strategy against arrhythmia (Jones et al., 2003; Goette & Lendeckel, 2004). Statin treatment is another strategy involving the mitochondria (Jones et al., 2003). For example, simvastatin seems to have the potential for pharmacological preconditioning via NOS and the mitochondrial potassium channel (mK_{ATP} channel) (Shiroshita-Takeshita et al., 2004). The mPTP inhibitor ciclosporin has been proven to reduce myocardial injury due to ischemia–reperfusion in infarcted patients (Piot et al., 2008). Its effectiveness in reducing VA in animals has yet to be confirmed in humans (Arteaga et al., 1992). Cell death promotes VA via conduction defects. Thus, the prevention of arrhythmia could repose on the indirect AA effects of several drugs, and multiple strategies must therefore be explored.

During the establishment of remodeling, gap junctions undergo severe alterations. In this context, the use of AAP10, a peptide modulator of gap junctional communication through a mechanism involving the PKCα pathway, has been proposed (Muller et al., 1997; Weng et al., 2002; Dhein et al., 2010). This molecule and its derivatives were capable of reducing TdP in LQT syndrome (Hirose et al., 2008) and AF in an animal model of acute MI (Shiroshita-Takeshita et al., 2007), but the potential use of this kind of molecule in the clinic is still under discussion (Dhein et al., 2010). Recently, the direct modulation of fibrosis by a regulator of profibrotic cytokines and fibroblasts, pirfenidone, has shown a beneficial effect on VT after MI in rats (Nguyen et al., 2010). However, other studies have revealed serious cases of VT after infliximab therapy in humans (Lazzerini et al., 2008). For now, direct action by anti-TGFβ or anti-TNFα has not proven to be of real efficacy in the clinic as an AA strategy.

4.3.3.4. Omega-3 fatty acids. Mid-way between protective dietary compounds and AA drugs, there is the case of the long-chain n-3 poly-unsaturated fatty acids (n-3 LC-PUFAs). It has been known since the mid-1970s that a diet principally composed of marine products like fatty fish (rich in n-3 PUFAs) is associated with lower mortality due to cardiovascular diseases (Bang et al., 1976). Many studies have confirmed the putative cardioprotective role of n-3 LC-PUFAs, leading to a large prospective randomized clinical trial of 11,324 patients reporting a recent MI (GISSI Prevenzione Trial, 1999). In this study, it was shown that a daily dose of 850 mg of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) was associated with a reduction of 45% in SCD at 42 months (Marchioli et al., 2002). This reduced mortality involved AA effects. Presently, several hospitals in France, including in Montpellier, provide n-3 LC-PUFAs (Omacor®) as an adjuvant therapy to patients with MI. The protective role of n-3 LC-PUFAs against AF is still under debate, with some groups finding a beneficial effect (Virtanen et al., 2009), while others do not (Berry et al., 2010). However, these have been case–control studies. To the best of our knowledge, there has been only one interventional study, started in 2009, but its results have not yet been released (Macchia et al., 2009). Contrary to pharmacological AA agents, n-3 PUFAs can be used at present only as an adjuvant therapy. There are many hypotheses that attempt to explain the AA effects of n-3 LC-PUFAs at the cellular level, involving the modulation of ion channels directly or indirectly through signaling pathways such as PKC. While this is slightly outside the scope of this review, more information can be found in a review dedicated to this topic (Jude et al., 2006).

5. Conclusion

In the search for new AA drugs, there are several important issues to consider. Despite recent advances, several problems are still pending and a key question remains: what makes a successful AA drug? Or better yet: what makes successful AA drugs that can treat different types of arrhythmias with minimal side effects and an absence of proarrhythmogenicity? The classification of AA based on

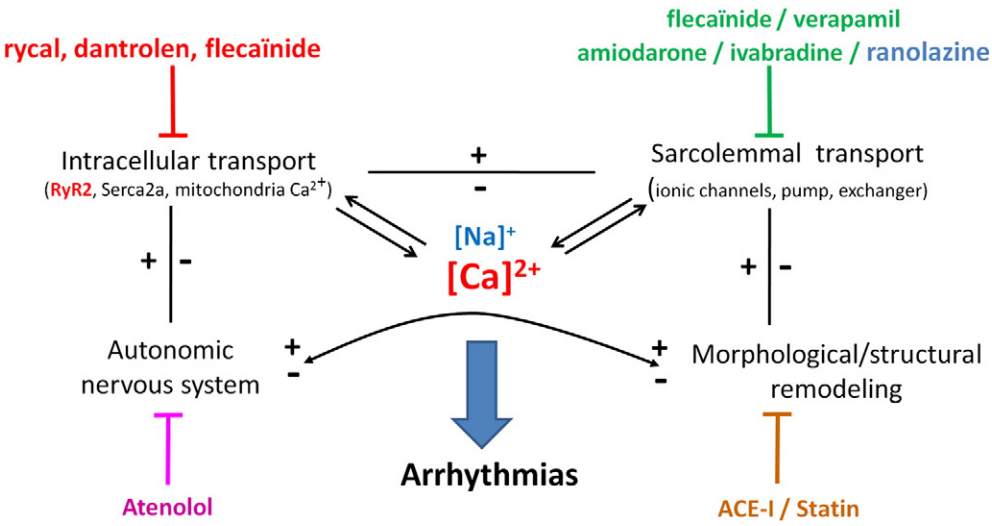

Fig. 5. Intracellular Ca^{2+} as a key element of ectopic activity. Regardless of the primary mechanism leading to arrhythmia, Ca^{2+} is most often involved. Ca^{2+} lies at the crossroads of different pathways and cellular mechanisms of arrhythmias targeted by AA and non-AA drugs.

their target led to the paradigm that AAs have to be modulators of ion channels (inhibitors of ion channels or agents interfering with the ANS, which modulates ion channel activity). Perhaps new classifications more specifically based on original mechanisms of arrhythmia might help to generate new therapeutic concepts. Thinking that specific drug-target interactions could provide a way to catch or prevent arrhythmias has failed. Occam's razor, which roughly states that *no more assumptions should be made than the minimum needed to explain a phenomenon*, should not govern AA drug development. One could even ask the question of whether specific AA drugs exist! Moreover, ion channels are rarely completely tissue specific. Practical approaches must thus go beyond basic pharmacological concepts and be holistic rather than reductionist. Arrhythmias are hard to control because they are particularly complex, with different types, causes and/or substrates that can evolve over time as with any disorder. In this sense, upstream therapy (inhibitors of the renin–angiotensin–aldosterone system, statins, ω-3 fatty acids, ß-blockers, modulators of protease activity etc.) may show promise. Secondly, although the risk of proarrhythmogenicity may increase with multichannel blockers (notably with AA drugs that block hERG), several AA drugs that act on different ion channels exhibit interesting and relatively safe clinical effects. Atrial-specific and/or multiple ion channel blockers (e.g. vernakalant, and amiodarone derivatives) may fulfill this criterion. By blocking both inward and outward currents, multichannel blockers may create steady-state conditions that avoid large variations in AP repolarization, thereby preventing the development of electrical instability. Thirdly, intracellular Na^+ and/or Ca^{2+} overload (the two can be linked) promoting spontaneous depolarization and APs during diastole seems to be critically involved in the occurrence of common arrhythmias (Fig. 5). Interestingly, drugs that prevent excessive Na^+ entry and its intracellular accumulation (e.g. ranolazine) or/and aberrant intracellular Ca^{2+} release and Ca^{2+} waves in diastole (rycals, dantrolene, and flecainide) may confer AA benefits at all cardiac levels (atrial, ventricle, and PF). These drugs act by normalizing – rather than blocking – channel activity, with minimal interactions with the normal functioning of the protein, thereby minimizing potentially undesirable effects at any cardiac level. Indeed, ranolazine does not block peak I_{Na} but only abnormal I_{NaP}, which does not hamper the normal functioning of the I_{Na} (excitability, and conduction). This concept of "normalization" also applies to RyR2 stabilizers that only prevent aberrant opening. Interestingly, as evidenced for some local anesthetics or some Ca^{2+} channel blockers with vascular selectivity in the past, the blocking effect of flecainide on RyR2 in the open state illustrates how the power of a drug may be in the "details". In conclusion, the emergence of novel AA drugs that rely on different concepts and mechanisms of action may provide a wider panel of therapeutic options to better and more specifically treat arrhythmias in a wide variety of pathophysiological situations.

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Conflict of interest

None declared.

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