Mechanisms of termination and prevention of atrial fibrillation by drug therapy

Workman AJ, Smith GL, Rankin AC

Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, 126 University Place, Glasgow G12 8TA

Corresponding author: Dr Antony J Workman, Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, 126 University Place, Glasgow G12 8TA, United Kingdom. Tel.: +44 (0)141 330 3451. Fax.: +44(0)141 330 6997. Email: Antony.Workman@glasgow.ac.uk

Abstract
Atrial fibrillation (AF) is a disorder of the rhythm of electrical activation of the cardiac atria. It is the most common cardiac arrhythmia, has multiple aetiologies, and increases the risk of death from stroke. Pharmacological therapy is the mainstay of treatment for AF, but currently available anti-arrhythmic drugs have limited efficacy and safety. An improved understanding of how anti-arrhythmic drugs affect the electrophysiological mechanisms of AF initiation and maintenance, in the setting of the different cardiac diseases that predispose to AF, is therefore required. A variety of animal models of AF has been developed, to represent and control the pathophysiological causes and risk factors of AF, and to permit the measurement of detailed and invasive parameters relating to the associated electrophysiological mechanisms of AF. The purpose of this review is to examine, consolidate and compare available relevant data on *in-vivo* electrophysiological mechanisms of AF suppression by currently approved and investigational anti-arrhythmic drugs in such models. These include the Vaughan Williams class I-IV drugs, namely Na^+ channel blockers, β-adrenoceptor antagonists, action potential prolonging drugs, and Ca^{2+} channel blockers; the "upstream therapies", e.g., angiotensin converting enzyme inhibitors, statins and fish oils; and a variety of investigational drugs such as "atrial-selective" multiple ion channel blockers, gap junction-enhancers, and intracellular Ca^{2+}-handling modulators. It is hoped that this will help to clarify the main electrophysiological mechanisms of action of different and related drug types in different disease settings, and the likely clinical significance and potential future exploitation of such mechanisms.

Keywords
1) Atrial fibrillation
2) Cardiac arrhythmia mechanisms: reentry, afterdepolarisations
3) *In-vivo* animal models
4) Pathological electrical remodelling
5) Pharmacological treatment
6) Anti-arrhythmic drug mechanisms

Contents

Abbreviations
ACE: angiotensin-converting enzyme; AF: atrial fibrillation; AFCL: AF cycle length; APD: action potential duration; DAD: delayed afterdepolarisation; EAD: early afterdepolarisation; ERP: effective refractory period; I_{CaL}: L-type Ca^{2+} current; I_{CaT}: T-type Ca^{2+} current; I_f: funny current; I_{K1}: inward rectifier K^+ current; I_{KACh}: acetylcholine-activated K^+ current; I_{Kr}: rapid delayed rectifier K^+ current; I_{KS}: slow delayed rectifier K^+ current; I_{Kur}: ultra-rapid delayed rectifier K^+ current; I_{Na}: Na^+ current; $I_{Na/Ca}$: Na^+-Ca^{2+} exchanger current; $I_{Na/H}$: Na^+-H^+ exchanger current; I_{NaL}: late I_{Na}; I_{SKCa}: small conductance Ca^{2+}-activated K^+ current; I_{TO}: transient outward K^+ current.

1. Introduction

Atrial fibrillation (AF) is a disturbance of the normally rhythmical beating of the cardiac atria, characterised by rapid (e.g., 400-600 beats/minute), irregular electrical and mechanical activation of the atrial muscle. It is the most common cardiac arrhythmia encountered in clinical practice, and has multiple causes, such as coronary artery disease, heart failure, valve disease and hypertension. Patients with AF have an increased risk of death from stroke, due to embolisation of atrial thrombi which form because the rapid and irregular activation causes uncoordinated atrial contraction and hence disturbed and reduced atrial blood flow. AF can be treated with electrical cardioversion, tissue ablation, and pharmacological therapy; the latter being the mainstay, particularly in the expanding elderly population. However, currently available anti-arrhythmic drugs are only moderately effective in preventing or terminating AF or maintaining sinus rhythm after it is restored, and may also exert adverse effects such as ventricular pro-arrhythmia, organ toxicity, or both (Camm *et al.*, 2010).

Therefore, there is a major unmet need to develop more effective and safe drugs to control the atrial rhythm in patients with AF. This necessitates a drive towards an improved understanding of the various and complex mechanisms by which anti-arrhythmic drugs affect the electrophysiological mechanisms of AF initiation and maintenance, in the setting of the different cardiac pathologies underlying the arrhythmia. An essential part of this is to study patients in the clinic, and their isolated atrial tissues and cells, where possible. However, such studies are usually limited by confounding influences of multiple variables such as patient age, sex, disease history and drug treatments, and also by the difficulty or inability to measure required electrophysiological parameters from human hearts *in-vivo*. For this reason, various *in-vivo* animal models of AF have been developed to permit the necessary control over physiological and pathophysiological variables in different disease states in isolation, and also the continuous measurement of detailed and invasive parameters relating to the associated electrophysiological mechanisms of AF.

The purpose of this review is to examine, consolidate and compare available relevant data on *in-vivo* electrophysiological mechanisms of AF suppression by currently and previously approved, and investigational, anti-arrhythmic drugs in such models. The focus, therefore, is on studies of atrium in *in-vivo* animal models. However, clinical electrophysiological data are utilised where available, and relevant *in-vitro* studies, including of ventricle, are incorporated where *in-vivo* data are lacking. For evaluation of clinical trials of current pharmacological and non-pharmacological interventions, the reader is directed to current European (Camm *et al.*, 2010) and American (Fuster *et al.*, 2006; Wann *et al.*, 2011) guidelines for the management of patients with AF. Details of molecular mechanisms of many of the anti-arrhythmic drugs are found in (Ravens, 2010). It is hoped that this review will help to clarify the main *in-vivo* electrophysiological mechanisms of action of different drug types in different disease settings, and the likely clinical significance and potential future exploitation of such mechanisms.

2. Electrophysiological mechanisms of AF and implications for drug actions

A variety of electrophysiological mechanisms of arrhythmia, reentrant and non-reentrant, likely initiates and maintains AF (Figure 1). Which of these mechanisms predominate in patients and animal models of AF depends partly on the underlying myocardial disease, because of disease-specific patterns of atrial electrical and structural changes, including long term remodelling (Workman *et al.*, 2008). The clinical spectrum of AF ranges from paroxysmal (self-terminating episodes) to persistent (lasting >7 days) to permanent (pharmacologically and electrically inconvertible). The majority of atrial premature beats that initiate AF in patients originate from focal ectopic activity in or near the pulmonary veins, which may be either micro-reentrant or non-reentrant (Haissaguerre *et al.*, 1998). Subsequent progression to persistent or permanent AF likely reflects the time-course and types of the atrial remodelling which, by their effects on the arrhythmia mechanisms, are expected to influence also the efficacy of pharmacological therapy.

2.1. Reentry

Reentry is rapid circuitous myocardial activation by an action potential wavefront as it continuously circulates a region of conduction block, re-exciting previously refractory tissue. This region of conduction block may be functional, i.e., a patch of refractory myocardial tissue, or anatomical/structural, e.g., a coronary vessel or a myocardial lesion; giving rise to functional and anatomical/structural reentry, respectively. The two main competing, but related, concepts of functional reentry are “leading circle reentry” and “spiral wave reentry”. For a comprehensive historical perspective on the development of the theoretical and experimental bases for our understanding of the different mechanisms of reentry, see (Jalife, 2010), which includes the major contributions from the laboratories of Moe, Allessie, Jalife, Haissaguerre, and others.

2.1.1. Leading circle reentry

In leading circle reentry, propagation is at the leading tip of a circuit located around a circle of critical dimensions, with wavelets emanating from that circle constantly maintaining the central core in a refractory state. The circumference of the circle, i.e., the minimum wavelength of the circuit, λ, is the effective refractory period (ERP) x conduction velocity (θ)

(Figure 1). For a reentrant circuit to exist, the wavelength must be shorter than the available conduction pathlength, thus leaving an excitable gap before the propagating wavefront. If atrial ERP or conduction velocity decrease, e.g., as a result of electrical remodelling, or if pathlength increases, e.g., from atrial hypertrophy or dilation, then the smaller wavelength relative to the pathlength will increase the chances of a re-entrant circuit, or multiple circuits, to exist and perpetuate. Furthermore, an increase in the spatial or temporal heterogeneity of electrical activity, e.g., resulting from localised interstitial fibrosis, or discordant alternans of the action potential duration (APD), will increase the likelihood of unidirectional conduction block and reentry (Figure 1). The ERP is determined by membrane excitability, i.e., the availability of Na^+ channels to open and pass inward Na^+ current (I_{Na}) and thus initiate the upstroke of an action potential. I_{Na} is voltage-dependent, and because it becomes available to open only after near full repolarisation of the preceding action potential, the ERP is largely determined by the APD at terminal repolarisation. In turn, this is determined by the magnitude and time course of repolarising K^+ currents such as the ultra-rapid (I_{Kur}), rapid (I_{Kr}), and slow (I_{KS}) delayed rectifier K^+ currents, and inward rectifier K^+ currents such as I_{K1} and the acetylcholine-activated K^+ current (I_{KACh}). Therefore, drugs which inhibit these K^+ currents could inhibit or extinguish reentrant AF, by prolonging APD and ERP and thus increasing wavelength. For further detail on how inhibition of human atrial repolarising ion currents could affect the morphology and duration of the action potential, see illustrations in (Workman, 2010) and (Ravens, 2010). Myocardial conduction velocity is determined partly by the maximum rate of rise of the action potential upstroke, which is dependent on membrane excitability and I_{Na} magnitude. However, conduction velocity also depends largely on the degree of intercellular coupling, which depends on intercellular communication via gap junctions at the intercalated discs, and on the degree of any intercellular fibrosis. Therefore, myocardial diseases which reduce such coupling, and thus conduction velocity and wavelength, particularly in a spatially heterogeneous manner, could promote reentrant AF. Furthermore, drugs which reduce I_{Na} sufficiently to reduce conduction velocity should also be expected, by leading circle reentry, to promote reentrant AF.

2.1.2. Anatomical/structural reentry

For anatomical/structural reentry to occur, as with leading circle reentry, the wavelength of the reentrant circuit must be shorter than the available conduction pathlength. The conduction path is fixed, determined by the size of the anatomical/structural obstacle or feature and may be large, leaving a large excitable gap and producing regular and relatively slow-rate reentry. For example, in the most common form of the supraventricular arrhythmia, atrial flutter, in which reentry rate is typically ~300 beats/minute, the reentry circuit passes through a muscle isthmus adjacent to the tricuspid valve, the neighboring posterior right atrium, and the ostium of the coronary sinus (Gami *et al.*, 2010). Anatomical/structural reentry may also be involved in both the generation and maintenance of AF.

2.1.3. Spiral wave reentry

In spiral wave reentry, curved activation wavefronts propagate outwards into excitable tissue in a spiral fashion, with their tips, which have the highest curvature, revolving around a central core (Figure 1). As with leading circle reentry, changes in ERP will tend to affect core size, but can also cause complex changes in wave tip trajectory that may lead to tip meandering and wave break up. Furthermore, the degree of curvature of the wave tip also affects core size. High curvature produces a small core, short excitable gaps and a high reentry rate, which manifests as a short AF cycle length (AFCL), the minimum interval between successive atrial electrogram deflections. The degree of curvature is determined by the strength of the wavefront "source" (I_{Na}) or "sink" (electrotonic influence of the resting cells). A reduction in I_{Na} reduces curvature, increasing core size and decreasing reentry rate, even when there is a full excitable gap, ultimately potentially blocking reentry. Conversely, reentry rate may increase when I_{K1} is increased, by an increase in electrotonic effects. Furthermore, an increase in ERP, e.g., by decreasing delayed rectifier K^+ current, may cause a transition from a stable circular to a meandering spiral wave. Therefore, the effects of drugs which block, for example, Na^+ or K^+ channels, on reentrant mechanisms of AF are expected to differ according to which of the two models of reentry are considered to operate (Comtois *et al.*, 2005).

2.2. Non-reentry

Non-reentrant mechanisms of arrhythmia include abnormal automaticity and triggered activity (Figure 1). Abnormal automaticity is the premature firing of action potentials due to accelerated diastolic depolarisation. This is favoured by an increase in diastolic inward, depolarising, ion currents such as the funny current (I_f), and also by a decrease in outward, hyperpolarising, currents such as the delayed rectifiers. Triggered activity is premature firing due to afterdepolarisations, which are either early (EAD), occurring during repolarisation, or delayed (DAD) until repolarisation is complete or nearly complete (Wit & Boyden, 2007). EADs are favoured by an increase in the APD that permits reactivation of I_{CaL}, or by abnormalities in I_{Na} activation or inactivation. DADs (and also abnormal automaticity) are favoured by excessive increases in intracellular Ca^{2+} concentration. For example, β-adrenoceptor stimulation may increase the L-type Ca^{2+} current (I_{CaL}) and the sarcoplasmic reticular Ca^{2+} content sufficiently to cause propagating waves of Ca^{2+}-induced Ca^{2+} release via the ryanodine receptors (Eisner *et al.*, 2009). This in turn may

cause DADs by activating a transient inward, depolarising, current carried by the Na^+-Ca^{2+} exchanger ($I_{Na/Ca}$) as each extruded Ca^{2+} is exchanged with 3 Na^+. Therefore, drugs which inhibit ion currents such as I_f and I_{CaL}, or which antagonise β-adrenoceptors or suppress intracellular Ca^{2+} elevation, might be expected, in theory, to suppress non-reentrant mechanisms of AF.
[insert Figure 1]

3. *In-vivo* models of AF used to investigate mechanisms of anti-arrhythmic drugs

3.1. In-vivo model-types and clinical counterparts

A wide variety of *in-vivo* models of AF has been used to study electrophysiological mechanisms of the development of this arrhythmia and, in most cases, to investigate the effects of drugs on such mechanisms. The interventions used generally mimic, as far as possible, clinical risk factors for AF (both established and potential). The major risk factors for AF are heart failure and a variety of associated or causative chronic myocardial diseases such as coronary artery disease, myocardial infarction, hypertrophy, hypertension, atrial dilation and valve disease (Camm *et al.*, 2010). Each may cause chronic adaptational changes, "remodelling", of atrial structure and function, and also neurohumoral imbalance. This may result in an "arrhythmogenic substrate", an atrial myocardium predisposed to reentrant, or non-reentrant, electrical activity (Figure 1). Furthermore, once AF occurs, a persistence of the rapid atrial activation also causes atrial remodelling that promotes AF (Wijffels *et al.*, 1995). Therefore, most of the animal models feature chronic interventions, of at least 2 week's duration. A predisposition to AF also may result from acute risk factors and stimuli (in the presence or absence of remodelling) such as elevated adrenergic and/or cholinergic stimulation, acute atrial dilation and stretch, and cardiac surgery. Therefore, acute models of AF have also been studied. All these chronic and acute models of AF, with the main atrial electrophysiological changes produced in each, are given in Table 1, along with comparative clinical data where available. Each intervention either produced spontaneous AF, eased the induction of AF by electrical stimuli (increased its "vulnerability") or increased its duration before spontaneous reversion to sinus rhythm.
[insert Table 1]

3.1.1. Heart failure and myocardial infarction models of AF

The most extensively studied heart failure model of AF is the dog chronic (2-6 week) ventricular tachypacing model, exemplified by studies from the Nattel laboratory (see (Li *et al.*, 1999) and Table 1). This model reproduced the major haemodynamic, structural and biochemical changes which accompany human heart failure, e.g., left ventricular systolic dysfunction and hypertrophy, increased atrial pressure, dilation and interstitial fibrosis, atrial hypocontraction, and catecholamine elevation (Moe *et al.*, 1989; Li *et al.*, 1999; Stambler *et al.*, 2003; Cha *et al.*, 2004). It also remodelled atrial ion currents, decreasing transient outward K^+ current (I_{TO}), I_{CaL} and I_{KS} and increasing $I_{Na/Ca}$ (Cha *et al.*, 2004), but did not consistently change ERP, conduction velocity or AFCL *in-vivo* (Table 1). The fibrosis caused localised conduction-slowing and increased dispersion (spatial heterogeneity) of conduction velocity (Shinagawa *et al.*, 2002c) which could promote reentry, especially in a dilated atrium, which would increase the available conduction pathlength (Figure 1). However, this model of heart failure could also produce non-reentrant atrial activity, since "spontaneous Ca^{2+} transient events" which may cause DADs were observed *in-vitro* (Yeh *et al.*, 2008). Furthermore, localised, stable, high frequency foci were produced in right atrium and within or near the pulmonary veins (Fenelon *et al.*, 2003; Ryu *et al.*, 2005). While those could be micro-reentrant, the finding that the 1st beat and mean cycle length of atrial tachycardia were directly related to the cycle length of the burst of stimuli that provoked the atrial tachycardia suggests that a triggered mechanism is more likely (Stambler *et al.*, 2003).

Heart failure in patients was associated with a moderate increase or no change in atrial ERP *in-vivo* (Sanders *et al.*, 2003). However, a recent study in our laboratory showed that left ventricular systolic dysfunction in patients was independently associated with a reduction in the ERP of atrial cells *in-vitro*, with decreasing left ventricular ejection fraction correlating with ERP-shortening (Workman *et al.*, 2009). Such ERP-decrease could promote reentry by decreasing wavelength. In support, evidence is emerging that a relatively longer duration of heart failure in dogs (16 weeks ventricular tachypacing) may also decrease atrial ERP, both *in-vivo* (Table 1) and *in-vitro* (Sridhar *et al.*, 2009). The type of AF-promoting atrial electrical remodelling may depend in part, therefore, on the duration of heart failure, with short duration perhaps favouring non-reentry, and long duration perhaps favouring reentry (Rankin & Workman, 2009). However, the arrhythmia mechanism will also be influenced substantially by the degree of atrial structural remodelling, which is also time- as well as aetiology-dependent. There are few studies of atrial remodelling by ventricular myocardial infarction, a major cause of heart failure. In dogs, coronary artery ligation for 8 weeks had no effect on atrial ERP *in-vivo* (Table 1), although it caused APD-alternans, an increased APD-dispersion, a degeneration of activation into multiple wavelets, and a decreased conduction velocity. In rats, chronic myocardial infarction caused atrial fibrosis (Boixel *et al.*, 2003). Preliminary data from our laboratory suggest that chronic myocardial infarction in rabbits causes atrial cellular hypertrophy and defects in atrial excitation-contraction coupling in the presence of β-adrenergic stimulation (Kettlewell *et al.*, 2010).

3.1.2. Acute and chronic atrial dilation models of AF

Acute and chronic atrial dilation has been investigated with a variety of species and interventions. Surgical disruption of tricuspid or mitral valves (Boyden & Hoffman, 1981; Verheule *et al.*, 2003) caused chronic atrial volume overload from valvular regurgitation. Chronic atrial dilation was also produced by atrioventricular node ablation (Greiser *et al.*, 2009) or with an arterio-venous shunt (Remes *et al.*, 2008). Each model produced broadly similar atrial electrophysiological changes, so are grouped in Table 1 as "chronic atrial dilation". The promotion of AF was accompanied by either increased or unchanged ERP, decreased or unchanged conduction velocity, and unchanged AFCL, from which it was suggested that the AF was not caused by wavelength-decrease in this model (Verheule *et al.*, 2003). However, an increase in the available conduction pathlength from the dilation, perhaps coupled with fibrosis, inflammation and increased conduction velocity-dispersion (Verheule *et al.*, 2003) could predispose to reentry, and atrial activation mapping demonstrated reentry *in-vitro* in the rabbit shunt model (Hirose *et al.*, 2005). In patients, it is difficult to isolate effects of chronic atrial dilation from pathological covariables. Nevertheless, atrial enlargement was associated with an increase in atrial ERP (Chen *et al.*, 1998), in line with some of the animal studies. Acute atrial dilation and stretch, precluding remodelling effects, were studied *in-vivo*, including in patients, using balloon catheters, volume-expanding solutions, or simultaneous-atrioventricular-pacing. Each intervention increased AF vulnerability, but effects on ERP were inconsistent (Table 1), including within species. However, ERP-dispersion was increased (Satoh & Zipes, 1996) and conduction velocity was decreased (Solti *et al.*, 1989), both favouring reentry. *In-vivo* studies of hypertension-induced AF, e.g., following renal artery clamping are few (Table 1), and effects on ERP were variable, but a decreased conduction velocity and wavelength, and increased conduction velocity-dispersion (Lau *et al.*, 2010), particularly in enlarged (Kistler *et al.*, 2006) or fibrosed (Kistler *et al.*, 2006; Choisy *et al.*, 2007) atria, could promote reentrant AF.

3.1.3. Autonomic-imbalance models of AF

Variations in autonomic tone profoundly influence the occurrence of AF, with increased cholinergic (vagal) or adrenergic (sympathetic) activity promoting AF. Cholinergic AF has been studied *in-vivo* by stimulating vagal nerves (Wang *et al.*, 1993; Hayashi *et al.*, 1998; Fedorov *et al.*, 2000; Hashimoto *et al.*, 2006; Sarrazin *et al.*, 2007), by using α-chloralose anaesthesia (David *et al.*, 1990) or by delivering acetylcholine, carbachol or methylcholine intraatrially (Rensma *et al.*, 1988), intrapericardially (Kumar *et al.*, 2009), intravenously (Vereckei *et al.*, 2001; Everett *et al.*, 2006), intraperitoneally (Kovoor *et al.*, 2001) or topically (Niu *et al.*, 2009). This invariably produced AF spontaneously or increased its vulnerability. Atrial ERP and wavelength were consistently and markedly decreased, with no effect on conduction velocity (Table 1). The mechanism of ERP-shortening is acceleration of terminal repolarisation as a result of cholinergic activation of I_{KACh}. It is noteworthy that activation of agonist-independent (constitutively active) I_{KACh} (Dobrev *et al.*, 2005) is considered to be a major determinant of atrial ERP-shortening associated with chronic AF in patients (see section 3.1.7). In dogs, a high dominant frequency of activation during cholinergic AF, measured by spectral analysis, indicated multiple high frequency zones (Everett *et al.*, 2006). Focal, rapidly-firing, rotor-like electrograms were also recorded (Niu *et al.*, 2009). An *in-vitro* study showed that the increase in atrial dominant frequency by acetylcholine likely depended both on acetylcholine concentration and I_{KACh} magnitude (Sarmast *et al.*, 2003). The arrhythmia mechanism has been mapped *in-vivo* in dogs, and macro-reentry resulting from unidirectional conduction block was demonstrated (Derakhchan *et al.*, 2001). In patients, promotion of atrial reentry by cholinergic stimulation was suggested by effects of adenosine (which activates the same K^+ channels as acetylcholine) to increase atrial dominant frequency; supported by mathematical modelling of effects of increasing I_{KACh} on reentrant drivers (Atienza *et al.*, 2006). Adrenergic stimulation, with intravenous isoprenaline, was studied in several species including human. AF vulnerability or incidence were consistently increased, but effects on other electrophysiological parameters were variable (Table 1). For example, in patients, isoprenaline caused a marked increase in conduction velocity and a small decrease in ERP, thus increasing wavelength (Shimizu *et al.*, 1994), whereas in dogs, isoprenaline had no effect on wavelength (Rensma *et al.*, 1988). Furthermore, adrenaline prolonged ERP in rabbit atria *in-vitro* (Smeets *et al.*, 1986), whilst isoprenaline had no effect on ERP in human atrial isolated cells (Redpath *et al.*, 2006). It is unclear whether adrenergic stimulation causes AF by reentry *in-vivo*, although isoprenaline sustained reentry in atrial/pulmonary vein tissues *in-vitro* (Arora *et al.*, 2003). Non-reentrant mechanisms are likely prominent, either from DADs or abnormal automaticity resulting from increased intracellular Ca^{2+} and consequent $I_{Na/Ca}$, primarily from stimulation of I_{CaL} and A-kinase mediated phosphorylation of phospholamban (Workman, 2010). Simultaneous cholinergic/adrenergic discharges are common triggers of paroxysmal atrial tachycardia and paroxysmal AF, and the stimulation of ganglionic plexi (sites rich in cholinergic and adrenergic neurons) at the pulmonary vein-left atrial junction can facilitate the onset of these arrhythmias. The mechanism may involve the formation of afterdepolarisations as a result of intracellular Ca^{2+}-elevation in the presence of APD-shortening (Chou & Chen, 2009). In a dog *in-vivo* model of AF ("local nerve-stimulation" in Table 1), high frequency electrical stimulation of the atrial surfaces might induce AF as a result of a simultaneous increase in cholinergic and adrenergic nerve activity.

3.1.4. Models of post-operative AF and atrial ischaemia

AF is common after cardiac surgery, probably from multiple mechanisms such as autonomic imbalance, acute ischaemia, mechanical irritation, and pericarditis. Old age is a strong predictor of post-cardiac surgery AF, likely by conduction disturbances arising from increased atrial fibrosis, whereas pre-surgery atrial cellular electrophysiology probably is not (Workman *et al.*, 2006). The sterile pericarditis model is an experimental counterpart to the patient post-cardiac surgery. It promotes AF, associated with decreased atrial ERP and conduction velocity (Table 1). The primary arrhythmia mechanism is probably reentry (Matsumoto *et al.*, 2010), consistent with reduced wavelength and with functional lines of block due to conduction velocity-dispersion from altered gap junction distribution and/or fibrosis (Ryu *et al.*, 2007). Acute atrial ischaemia was studied independently, by right coronary ligation in dogs. This invariably increased AF duration, and while effects on ERP were highly variable, conduction velocity always decreased (Table 1). Ischaemia also increased atrial conduction velocity-dispersion (Sakabe *et al.*, 2008), impaired conduction between normally- and hypo-perfused atrial myocardium (Shiroshita-Takeshita *et al.*, 2007b), or impaired ERP rate-adaptation; the ability of increasing rate to shorten ERP (Jayachandran *et al.*, 2000). These effects could promote reentry, but triggered activity from increased atrial intracellular Ca^{2+}, e.g., from glycolytic inhibition (Ono *et al.*, 2007), or from a rapid transient increase in APD, as shown in ventricle (Workman *et al.*, 2000), should not be excluded. Chronic atrial infarction has also been studied, in dogs, by ligating the right intermediate atrial artery for 8 days (Table 1). This caused stable reentry circuits in the infarction border zone and increased the duration of burst pacing-induced AF, associated with increased conduction velocity-heterogeneity and fibrosis, and altered intracellular Ca^{2+}-handling (Nishida *et al.*, 2011).

3.1.5. Transgenic mouse and other relevant models of AF

Other *in-vivo* animal models of AF, most of which have been used to investigate anti-arrhythmic mechanisms of drugs, include hypercapnoea or transient asphyxia (relating to AF associated with sleep disordered breathing), hypoglycaemia, atrial mechanical injury (relating to conduction block from, e.g., scar, fibrosis), aconitine ("window" I_{Na} agonist)-induced triggered AF and a variety of transgenic mouse models (Table 1). Persistent conduction-slowing followed hypercapnoea-reversal in sheep, and hypoglycaemia decreased ERP in dogs. The atrial injury models reliably produce reentry, e.g., around Y-shaped lesions (Jalil *et al.*, 1997), and have been used extensively for pharmacological study. Genetically engineered over-expression of the ion channel protein Kir2.1 increased I_{K1} and decreased atrial ERP (Li *et al.*, 2004); electrical changes commonly associated with human chronic AF (Workman *et al.*, 2008). Under-expression (Zhang *et al.*, 2005) or knockout (Mancarella *et al.*, 2008) of Cav1.3 or α_{1D}, to decrease I_{CaL}, increased AF vulnerability without changing ERP. KCNE1-knockout, which paradoxically increased I_{KS}, increased AF incidence (Temple *et al.*, 2005). Connexin40-knockout, to decrease gap junction-coupling, decreased conduction velocity; and Rac1 over-expression, to produce reactive O_2 species and atrial fibrosis, also decreased conduction velocity (Reil *et al.*, 2010). Altered ryanodine receptor function due to mutations (Chelu *et al.*, 2009), or to knockout of an associated regulatory protein, FKBP12.6 (Sood *et al.*, 2008) promoted AF, likely by enhancing spontaneous diastolic sarcoplasmic reticular Ca^{2+} release.

3.1.6. AF causes AF by electrical remodelling: chronic rapid atrial rate models

AF normally occurs initially in short, self-terminating bouts, paroxysms, which may then become progressively longer. A persistence of the rapid atrial activation for several hours is sufficient in itself (i.e., in the absence of initial underlying pathology) to cause substantial AF-promoting atrial electrical remodelling. This was demonstrated first in goats , by the Allessie group: after 24 hr of burst pacing-induced AF, atrial ERP and wavelength were markedly decreased, and AF vulnerability was increased (Wijffels *et al.*, 1995). Similar changes occur after AF-induction lasting 4 days-16 weeks (Table 1). Chronic atrial regular tachypacing, for 24 hr-18 weeks, produced similar electrical remodelling in other species (Table 1). The ERP-shortening occurred in left and right atria and pulmonary veins (Tang *et al.*, 2006) and correlated with both atrial tachypacing duration (Lee *et al.*, 2000) and AF vulnerability (Morillo *et al.*, 1995). It also markedly decreased wavelength whether or not conduction velocity decreased (Table 1). Furthermore, chronic atrial tachypacing increased the dispersion of ERP (Fareh *et al.*, 2001) and AFCL (Gaspo *et al.*, 1997), and produced atrial hypertrophy and fibrosis (Zhao *et al.*, 2010). Each of these promotes reentry, and multiple wavelet reentry was mapped *in-vivo* (Gaspo *et al.*, 1997; Li *et al.*, 2000).

3.1.7. Clinical models of AF

In patients, a history of chronic AF typically was associated with decreased atrial ERP *in-vivo* (Kojodjojo *et al.*, 2007) and *in-vitro* (Workman *et al.*, 2001), and decreased conduction velocity (Kojodjojo *et al.*, 2007) and AFCL (Fujiki *et al.*, 2001). It was also associated with increased APD restitution slope (Kim *et al.*, 2002), and with ERP-dispersion (Kojodjojo *et al.*, 2007) and electrogram fractionation (Kumagai *et al.*, 1991). The concordance between these and the AF/atrial tachypacing-induced changes in the animal models (Table 1) suggests that AF-induced atrial remodelling, probably promoting reentry, occurs in humans also. The ionic mechanisms of the ERP-shortening are probably primarily an increased I_{K1} and constitutively active I_{KACh}, and altered intracellular Ca^{2+}-handling, as identified in studies from several research groups, e.g. (Van Wagoner *et al.*, 1997; Bosch *et al.*, 1999; Workman *et al.*, 2001; Dobrev *et al.*, 2005)

and reviewed in (Workman *et al.*, 2008). An increase in I_{KS} might also be involved (Caballero *et al.*, 2010). A decreased systolic intracellular Ca^{2+} transient, causing contractile dysfunction, may involve a loss of atrial T-tubules, in sheep (Lenaerts *et al.*, 2009). Furthermore, an increase in diastolic sarcoplasmic reticular Ca^{2+} leak (Neef *et al.*, 2010) and in "late" I_{Na}, (I_{NaL}) (Sossalla *et al.*, 2010), both having the potential to cause afterdepolarisations, were associated with human chronic AF. However, it is unclear whether atrial remodelling from chronic AF or atrial tachypacing alters the propensity to afterdepolarisations. AF has been induced acutely in patients, using atrial tachypacing for necessarily brief periods (5-10 min). This caused reversible shortening of atrial ERP and AFCL (Table 1), which was dependent on tachypacing stimulus rate (Yu *et al.*, 1998) and may have involved acute intracellular Ca^{2+}-induced inactivation of I_{CaL}, rather than the type of electrical remodelling that results from chronic AF. Nevertheless, this *in-vivo* model of acute AF has been used extensively to study electrophysiological mechanisms of anti-arrhythmic drugs.

3.2. Model- and disease-dependence of arrhythmia mechanisms and potential drug effects

Among the differing animal models of AF in section 3.1, and very likely, therefore, the clinical disease states they represent, there are wide variations in the atrial electrophysiological changes and mechanisms promoting this arrhythmia, as shown by Table 1. Anti-arrhythmic drugs that target reentrant or non-reentrant mechanisms may be expected, therefore, to affect AF differently depending on the disease state in question. Such drugs, either in clinical use or under investigation, have thus been tested in a variety of *in-vivo* models.

4. Drug types for AF termination and prevention: conventional anti-arrhythmics; upstream therapy; investigational

4.1. Pharmacological management of AF with Vaughan Williams class drugs

Pharmacological treatment of patients with AF is aimed initially at protection against thromboembolic events, with anti-coagulants. The focus is then either to restore sinus rhythm (rhythm control), or to limit the high ventricular rates resulting from the rapid atrial activation, by inhibiting atrioventricular nodal conduction (rate control). Rhythm control, with anti-arrhythmic drugs, is the long term goal in patients for whom rate control offers inadequate symptomatic relief, or in severely compromised patients (Camm *et al.*, 2010). Anti-arrhythmic drugs are conventionally grouped according to their broad mechanism of action (Vaughan Williams, 1984), namely, Na^+ channel blockade (class I), β-adrenoceptor antagonism (II), action potential prolonging (III), and Ca^{2+} channel blockade (IV). Many drugs that prevent AF possess activity in more than one class, and some in none. Nevertheless, this classification serves as a useful basis for assessing and comparing electrophysiological effects of drugs with broadly related activities in the various *in-vivo* models of AF. The current European Society of Cardiology guidelines for the management of AF (Camm *et al.*, 2010) recommends the use of certain drugs from each of these classes for rhythm and/or rate control, depending on the patient's disease state.

4.2. Potential pharmacological management of AF with non-Vaughan Williams class drugs

A variety of non-Vaughan Williams class drugs in clinical use, as well as some naturally occurring substances, can prevent or delay atrial structural remodelling associated with hypertension or heart failure. These "upstream therapies", which include angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, aldosterone antagonists, statins, and poly-unsaturated fatty acids, might deter new onset AF or its progression to permanent AF. Of these agents, the European Society of Cardiology recommends ACE inhibitors, angiotensin receptor blockers and statins to be considered for the treatment of AF, depending on disease state (Camm *et al.*, 2010).

4.3. Investigational drug types and rationale for development

Numerous drugs tested in models of AF have either been approved for the treatment of cardiovascular diseases not including AF, or are currently under investigation for potential clinical use including for AF, or are intended purely for experimental use. These drugs are termed "investigational". Recent development of drugs for rhythm control has focussed on "atrial-selective" and "multi-channel blocking" properties. Atrial-selectivity, in an attempt to avoid ventricular pro-arrhythmia, may be achieved, in theory, by targeting ion channels which occur in atrium and not ventricle (Ravens, 2010). Ion currents such as I_{Kur} and I_{KACh} are generally accepted to contribute substantially to atrial, rather than to ventricular, repolarisation. Nevertheless, since I_{Kur} blockade may affect ventricular repolarisation in some species, e.g., dogs (Sridhar *et al.*, 2007), I_{Kur}-inhibiting drugs perhaps should be considered as having "atrial-predominant" properties. A degree of atrial-selectivity may also be achieved by exploiting ion current characteristics such as availability or kinetics that differ between the chambers, either intrinsically or as a result of differing resting potential or activation rate during AF, e.g., those of I_{Na} (Burashnikov & Antzelevitch, 2010). Multi-channel blocker development is aimed primarily at mimicking the efficacious anti-arrhythmic effects of drugs with multiple actions such as amiodarone, but without their toxicity. Multi-channel blockers also may exhibit atrial-predominance. Other investigational drugs are aimed at improving intercellular coupling, e.g., gap junction-enhancers.

4.4. The need to assess and compare in-vivo mechanistic data on each drug type

The vast majority of Vaughan Williams class drugs and upstream therapies currently recommended for the treatment of patients with AF has been studied extensively in *in-vivo* models of AF. Furthermore, investigational drugs, and many Vaughan Williams class drugs no longer in widespread use, as well as some drugs which have been withdrawn, were also tested in such models. To improve our overall understanding of anti-arrhythmic mechanisms of drugs having related, as well as unique actions, electrophysiological effects of drugs from all of these categories are examined in detail, below, where *in-vivo* mechanistic data are available.

5. Class I drugs (Na^+ channel blockers): *in-vivo* electrophysiological mechanisms of AF termination

5.1. Sub classification of class 1 drugs, and clinical use in AF

Class I drugs are divided into subclasses a, b and c, according to their effects on the ECG and ventricular conduction, APD and ERP (Vaughan Williams, 1984). The 1st available, quinidine, procainamide and disopyramide were designated Ia; lidocaine designated Ib. The subsequently developed class Ic drugs include flecainide, propafenone, pilsicainide and moricizine. Cibenzoline has class Ia and Ic activity. Of these drugs, the current European Society of Cardiology guidelines recommends that flecainide and propafenone can be used, in patients without coronary artery disease or heart failure, for converting short duration or recent onset AF, for reducing AF recurrence following cardioversion, and also for long term rhythm control (Camm *et al.*, 2010). Quinidine is now rarely used owing to risk of ventricular pro-arrhythmia from prolongation of the QT interval, and disopyramide is also rarely used except for cholinergic AF (Camm *et al.*, 2010).

5.2. Inhibition of leading circle reentry by class I drugs

Atrial electrophysiological effects of each of these drugs has been studied in *in-vivo* models of AF. These effects are summarised in Table 2, from which several notable broad patterns emerge.
[insert Table 2]

In keeping with the main recognised action of class I drugs to block I_{Na}, the conduction velocity was reduced in the majority of studies, presumably by decreasing action potential maximum upstroke velocity. Most studies were in dogs, usually using cholinergic stimulation- or atrial injury-induced AF, and chronic AF/atrial tachypacing was studied in dogs and goats. The primary mechanism of AF in each of these models is reentry (see section 3.1). In cholinergic AF and chronic AF/atrial tachypacing, reentry was caused by a marked decrease in wavelength, from ERP-shortening with little or no concurrent change in conduction velocity (see Table 1). The chronic ventricular tachypacing model of heart failure, in which non-reentrant mechanisms may be more prominent, was not used. All class I drugs terminated AF, with varying efficacies, in most of the models and species studied, but tended not to decrease the vulnerability to its re-induction (Table 2). Also, all drugs, irrespective of model or species, increased AFCL where measured, without exception. The AFCL increase, in all the dog cholinergic AF studies, was associated with an increase in atrial ERP and wavelength (Table 2). This represents a partial or full reversal by the drugs of the decrease in ERP and wavelength which was caused by cholinergic stimulation, that was larger than the associated decrease in conduction velocity. Several class I drugs (e.g., flecainide, propafenone, quinidine) inhibit currents such as I_{Kr} or I_{KACh}, in addition to I_{Na}. Such K^+ current inhibition may be expected to increase atrial ERP and/or wavelength by increasing APD. However, inhibition of I_{Na} alone can also increase atrial ERP in the absence of an increase in APD, thus causing post-repolarisation refractoriness. For example, pilsicainide, which may block I_{Na} without also blocking K^+ channels, produced post-repolarisation refractoriness in a dog model of cholinergic AF (Kanki *et al.*, 1998). The effect of pilsicainide, and also of flecainide (Wang *et al.*, 1992) and propafenone (Wang *et al.*, 1993) was use-dependent, i.e., ERP was prolonged preferentially at high atrial rates, such as those encountered during AF. The mechanism of induction of post-repolarisation refractoriness likely involves a depression of I_{Na} reactivation and an increase in the diastolic threshold of excitation. Several I_{Na} blockers, particularly those with rapid unbinding kinetics, may produce post-repolarisation refractoriness in an atrial-predominant manner (Burashnikov & Antzelevitch, 2010). The effect of class I drugs to increase wavelength, by whatever ionic mechanism, in the canine cholinergic AF models is consistent with an anti-reentrant mechanism from an increase in wavelength beyond the available pathlength, according to the concept of leading circle reentry (Figure 1). Consistent with that, procainamide and propafenone (Wang *et al.*, 1993), and flecainide (Wang *et al.*, 1992) increased the size and decreased the number of reentry circuits in this model, and propafenone inhibited macro-reentry without affecting focal AF (Niu *et al.*, 2009). In the non-cholinergic AF models, by contrast, no class 1 drug increased wavelength, and some even reduced it, e.g., flecainide and cibenzoline (Wijffels *et al.*, 2000), despite increasing AFCL and terminating AF. This indicates that suppression of leading circle reentry may not be sufficient alone to explain anti-arrhythmic effects of I_{Na} blockers in these models.

5.3. Inhibition of spiral wave reentry by I_{Na} blockade

An alternative explanation was provided using the goat model of chronic AF, and the concept of spiral wave reentry. Quinidine, cibenzoline and flecainide each were shown to increase not wavelength, but the "temporal excitable gap" (Wijffels *et al.*, 2000). This was calculated as AFCL minus the ERP recorded during AF, the earliest moment at which a premature impulse could capture the fibrillating atrium (Figure 1). It was proposed that the increase in AFCL that widened the excitable gap was caused by a preferential slowing by the drugs of high-curvature wavefronts, due in turn to the reduction in the availability of the source current, I_{Na}. This should increase spiral wave reentry core size and decrease reentry rate, and allow wavelets to fuse and decrease in number, rather than fragment. In support, cibenzoline increased reentry wavelet "linking", i.e., the number of consecutive waves propagating in the same direction, and decreased wavelet "fractionation" (Shan *et al.*, 2004), in this model. Mathematical modelling supports the idea that inhibiting I_{Na} alone is sufficient to terminate AF by suppressing spiral wave reentry. Thus, a simulated reduction in I_{Na} increased the size of generator spirals and slowed their rotation rate by reducing excitability and conduction velocity, despite also decreasing wavelength (Nattel *et al.*, 2003). Mathematical modelling has also highlighted the potential for atrial-selective termination of spiral wave reentry by I_{Na} inhibition (Pandit *et al.*, 2010). The termination of AF by slowing spiral wave reentry is likely not exclusive to the AF/atrial tachypacing models of AF, since in an *in-vitro* study of cholinergic (acetylcholine-induced) AF, pilsicainide increased the reentry core perimeter associated with an increase in the temporal excitable gap, as well as increasing ERP (Kawase *et al.*, 2003). Several class I drugs were studied in canine atrial injury models (Table 2) and, in each case, increased atrial ERP. Atrial wavelength was measured in one study, and was unchanged by quinidine, perhaps suggestive of suppression of spiral wave reentry. The only model in which AF was not terminated was atrial ischaemia. This intervention substantially decreases the conduction velocity (Table 1), and flecainide did not decrease it further (Table 2).

5.4. Clinical mechanistic studies of class I drugs

Atrial electrophysiological effects of several class I drugs were also studied in patients (Table 2). Where it was possible to measure the effect on ERP after conversion of brief episodes of induced AF (acute atrial tachypacing: shortens ERP and AFCL; Table 1), neither procainamide nor propafenone increased ERP, yet they decreased AF duration. Cibenzoline and flecainide increased AFCL and terminated AF. In one study (Brugada *et al.*, 1993) atrial epicardial mapping was possible in one patient, and cibenzoline fused multiple reentry wavelets into a single broad wavefront. These clinical data are consistent with suppression of AF not involving long term atrial remodelling, potentially by inhibition of spiral wave reentry since ERP did not increase. By contrast, in patients with chronic AF (also associated with ERP- and AFCL-shortening; Table 1), disopyramide, flecainide and propafenone increased atrial ERP. The ERP increase by flecainide was associated with APD increase and post-repolarisation refractoriness (Kirchhof *et al.*, 2005). Procainamide, cibenzoline, flecainide and propafenone also increased AFCL (Table 2). Procainamide decreased the number of pulmonary vein ectopic beats (Chen *et al.*, 1999), and a decrease in atrial electrogram fractionation was also observed in several studies (Brugada *et al.*, 1993; Ishibashi *et al.*, 1995; Tuan *et al.*, 2010). It is conceivable, therefore, that class I drug-induced ERP increase in patients with chronic AF could contribute to suppression of leading circle reentry.

5.5. Potential suppression of non-reentrant arrhythmic activity by class I drugs

Anti-arrhythmic effects of some class 1 drugs might involve a contribution from a suppression of non-reentrant arrhythmic activity. For example, in mouse ventricular cells *in-vitro*, flecainide reduced the incidence of isoprenaline-stimulated triggered beats, associated with a reduction in the incidence of spontaneous Ca^{2+} release from the sarcoplasmic reticulum (Watanabe *et al.*, 2009). However, such a mechanism has yet to be demonstrated in atrium.

6. Class II drugs (β-blockers): electrophysiological mechanisms of AF suppression *in-vivo*

6.1. Clinical use of β-blockers in AF

Beta-adrenoceptor antagonists (β-blockers), such as the β_1-blockers esmolol and metoprolol, and the β_1/β_2-blocker propranolol, currently are recommended mainly for rate control and for preventing post-cardiac surgery AF. Carvedilol, a $\beta_1/\beta_2/\alpha_1$-blocker, is also recommended for rate control. However, some β-blockers are also indicated for long term rhythm control, especially in exercise-induced AF (Camm *et al.*, 2010). There are relatively few studies of atrial electrophysiological mechanisms of β-blockers pertaining to rhythm control using *in-vivo* models of AF; summarised in Table 3.

[insert Table 3]

6.2. Studies of acute β-blockade in models of atrial ERP-shortening and reentry

β-blockers suppressed AF induced by a variety of interventions (Table 3). Their effects on atrial ERP, however, were reported in only 3 studies; of chronic AF in goats, acute atrial tachypacing in patients (both of which feature atrial ERP-shortening; Table 1), and acute atrial ischaemia in dogs. In the goat study, propranolol was delivered either before or after

AF induction. It had no effect on ERP before AF, i.e., in the absence of atrial electrical remodelling; consistent with its lack of effect on ERP or conduction velocity in dogs in sinus rhythm (Rensma *et al.*, 1988). Furthermore, its continuous delivery during the first 24 hr of AF did not prevent a marked AF-induced shortening of ERP and AFCL during that time (Wijffels *et al.*, 1997). Moreover, when propranolol was administered acutely after AF had become persistent, i.e., after atrial remodelling, it did not reverse the effects of remodelling: ERP and AFCL were unchanged. Whether this drug affected AF vulnerability or duration was not stated. In the human study, propranolol again had no effect on atrial ERP before AF-induction, and also did not prevent ERP-shortening caused by the brief (~10 min) episode of induced AF. It is possible, therefore, that the anti-arrhythmic action of acute β-blockade in these models does not involve inhibition of reentry. However, data on conduction velocity and wavelength, and ultimately activation mapping during AF, are required to confirm that. By contrast, suppression of atrial ischaemia-induced AF, by the β_1/β_2-blocker nadolol, might involve inhibition of leading circle reentry, since it increased atrial ERP and conduction velocity (Table 3).

6.3. Inhibition of non-reentrant activity by acute β-blockade

In the local nerve-stimulation studies (Table 3), esmolol and propranolol decreased vulnerability to pulmonary vein repetitive focal activity and to atrial premature depolarisations. This could involve inhibition of abnormal automaticity, afterdepolarisations or reentry induced by combined adrenergic-cholinergic activation. A suppression of pulmonary vein electrical activity by propranolol was also reported in patients with paroxysmal AF (Chen *et al.*, 1999). *In-vitro* studies of pulmonary vein/atrial preparations from dogs (Patterson *et al.*, 2005) or rats (Doisne *et al.*, 2009) suggest that β_1-blockade could suppress EADs or abnormal automaticity produced by local nerve stimulation or noradrenaline, respectively. Numerous studies, mainly *in-vitro* and reviewed in (Workman, 2010) indicate that β-blockers can prevent catecholamine-induced non-reentrant activity, mainly by inhibiting phosphorylation of proteins involved in intracellular Ca^{2+}-handling including Ca^{2+} channels and phospholamban, and thus decreasing I_{CaL} and excessive Ca^{2+}-loading. Consistent with these studies, in chronic ventricular tachypacing-induced heart failure, which elevates circulating catecholamines (Moe *et al.*, 1989) and promotes Ca^{2+}-overload and DADs (Stambler *et al.*, 2003), propranolol decreased AF vulnerability (Table 3).

6.4. Pharmacological remodelling by chronic β-blockade

A potential reentry-inhibiting mechanism of β-blockers is an atrial ERP-prolonging adaptation to their long-term use, so-called pharmacological remodelling. This was demonstrated in rabbits in sinus rhythm, after 6 days of treatment with either a β_1- or a β_1/β_2-blocker (Raine & Vaughan Williams, 1981), and also was independently associated with β_1-blocker therapy in patients in sinus rhythm (Workman *et al.*, 2003b; Workman, 2010). Among the studies in Table 3, β-blockers were probably given acutely in all but the chronic AF model (maximum 3-day treatment) and should not be expected, therefore, to have exerted their effects on AF by such pharmacological remodelling. While it is possible that a sufficiently long period of β-blockade to cause pharmacological remodelling still might not overcome ERP-shortening from AF-induced electrical remodelling, the ERP increase in the absence of AF (Raine & Vaughan Williams, 1981; Workman *et al.*, 2003b) could conceivably contribute to maintenance of sinus rhythm.

7. Class III drugs (APD-prolonging): *in-vivo* electrophysiological mechanisms of AF termination and prevention

7.1. Drug types, clinical uses in AF, and potential risks

The original class III drug, amiodarone, is the most effective available anti-arrhythmic drug. It has multiple actions including inhibition of numerous ion currents (I_{Na}, I_{TO}, I_{CaL}, I_{CaT}, I_{Kur}, I_{Kr}, I_{KS}, $I_{K,Na}$, $I_{Na/Ca}$, I_{K1}, I_{KACh}) and adrenergic/cholinergic receptors. Amiodarone is currently recommended for converting recent onset or persistent AF, for preventing AF recurrence, for long term rhythm control, and also for rate control when other measures are unsuccessful or contraindicated (Camm *et al.*, 2010). However, amiodarone has serious side effects, and while it can be used in patients with structural heart disease, it may adversely affect nearly every organ. Dronedarone, its non-iodinated analogue, is safer but less efficacious (Piccini *et al.*, 2009), and is recommended for long term rhythm and rate control in patients with non-permanent AF who don't have severe or unstable heart failure. Other class III drugs such as dofetilide or ibutilide are recommended for converting AF or atrial flutter (Camm *et al.*, 2010), but risk ventricular pro-arrhythmia, most likely from their inhibition of I_{Kr}. Sotalol is racemic, and the d-,l- form, used clinically and in most *in-vivo* models of AF, has both class III (I_{Kr}-blocking) and II (β_1/β_2-antagonising) action. It may be used for preventing AF recurrence, but is also limited by QT prolongation. Vernakalant, an $I_{Kur}/I_{Na}/I_{KACh}$ blocker, also has class III action and was recently recommended for approval by the European Medicines Agency for treating new onset AF (Camm *et al.*, 2010).

7.2. Suppression of leading circle reentry by class III effect

Atrial electrophysiological effects of most of these drugs were studied *in-vivo* in animal models of a variety of causes and risk factors for AF. All drugs could terminate AF in one or more model, and generally increased atrial ERP and AFCL

(Table 4). The ERP increase often was associated with, and likely resulted from, prolongation of terminal repolarisation, e.g., of APD_{90} by amiodarone (Ashikaga *et al.*, 2006) or ibutilide (Vereckei *et al.*, 2001) in dogs, or by amiodarone (Pandozi *et al.*, 2003) or sotalol (Kirchhof *et al.*, 2005) in patients. The APD increase is generally ascribed to the effect of class III drugs to block atrial I_{Kr}. However, I_{Kr} exists also in ventricle, and ventricular APD increase, e.g., by dofetilide (Chandra *et al.*, 2004), risks QT prolongation and ventricular pro-arryhythmia. The atrial ERP increase frequently was reverse use-dependent, i.e., stronger at low versus high rates (Nattel *et al.*, 1998), one reason why class III drugs can fail to terminate AF yet can prevent its induction (Derakhchan *et al.*, 2001). Class III drugs generally had little or no effect on atrial conduction velocity in animal models, but decreased it in patients with chronic AF, e.g., with amiodarone or ibutilide (Table 4). Atrial wavelength increased in most studies, always associated with ERP increase, suggestive of a general class III effect that could suppress leading circle reentry (Figure 1). In support, sotolol, which increased ERP and wavelength, also increased reentry circuit size and decreased their number, in cholinergic AF (Wang *et al.*, 1993). Dofetilide, ibutilide and nifekalant also increased ERP and/or wavelength in that model (Table 4).
[insert Table 4]

7.3. Loss of class III effect in electrical remodelling

There are exceptions to the rule of atrial ERP increase by class III drugs, however, particularly with the goat chronic AF model (Table 4). Thus, in all reports using this model, any drug effect to increase ERP either before AF or within the first 24 hours of AF, was attenuated or lost subsequently, e.g., with amiodarone (Linz *et al.*, 2007), dofetilide (Blaauw *et al.*, 2004), or ibutilide or sotalol (Duytschaever *et al.*, 2005). Furthermore, in 2 studies, when ERP did not increase, neither did wavelength (Wijffels *et al.*, 1999; Blaauw *et al.*, 2004). Despite this, AFCL-increasing and anti-AF effects could persist (Wijffels *et al.*, 1999; Linz *et al.*, 2007). The reason for the loss of class III effect in the remodelled atria is unclear. However, it could be species-specific, since in dogs, both amiodarone and sotalol reversed chronic atrial tachypacing-induced AF and ERP-shortening when drug delivery was started after electrical remodelling (Shinagawa *et al.*, 2003; Ashikaga *et al.*, 2006; Sakamoto *et al.*, 2009). Nevertheless, an attenuation of class III effect could occur in humans, since sotalol increased ERP less in patients with chronic AF than in those in sinus rhythm (Tse & Lau, 2002).

7.4. Possible class III inhibition of spiral wave reentry

Anti-arrhythmic, but non-ERP-prolonging, effects of class III drugs in the goat models suggest electrophysiological mechanisms other than inhibition of leading circle reentry. Termination of AF with increased AFCL, and not wavelength, by the class I drugs quinidine, cibenzoline and flecainide (Table 2), each of which may block I_{Kr} as well as I_{Na}, was considered due to inhibition of spiral wave reentry (see section 5.3). Such a mechanism is also possible for class III drugs (Figure 1). In support, d-sotalol (specific I_{Kr} blocker) had no effect on ERP or wavelength in the AF-remodelled atrium, yet terminated AF with an approximate doubling of the temporal excitable gap, an effect considered as potentially resulting from preferential slowing of high curvature reentry wavefronts (Wijffels *et al.*, 2000).

7.5. Clinical mechanistic and other studies of class III drugs

Several class III drugs were studied in patients (Table 4). Amiodarone and sotalol decreased the incidence and duration of acutely-induced AF episodes, despite not inhibiting the ERP-shortening that these caused. However, in patients with chronic AF, which also shortens ERP, amiodarone increased ERP in all 4 studies, including in pulmonary vein (Rostock *et al.*, 2005). AFCL was measured in 2 of those, and was increased in both. Ibutilide's effect to terminate AF in patients was also accompanied by increased ERP, as well as decreased conduction velocity and increased AFCL. Sotalol increased ERP in each of 2 studies in patients with chronic AF, and also increased AFCL. Reports of class III drug studies using *in-vivo* models of AF that produce no clear atrial ERP-shortening (see Table 1), e.g., heart failure, atrial dilation, hypertension, adrenergic stimulation and atrial ischaemia, are relatively few (Table 4). In a single study using the dog ventricular tachypacing model of heart failure, dofetilide increased atrial ERP, wavelength and AFCL, with no change in conduction velocity, and blocked reentry and terminated AF (Li *et al.*, 2000). In dogs with chronic atrial dilation, or atrial injury, dofetilide terminated AF, associated with increased ERP and AFCL and decreased conduction velocity, but it was unable to prevent ischaemia-induced AF. In a transient asphyxia model of AF, amiodarone or sotalol decreased AF vulnerability and duration, and amiodarone terminated aconitine-induced AF, presumably by inhibiting triggered activity.

7.6. Recent drugs with class III action: dronedarone and vernakalant

Dronedarone and vernakalant each have class III action, but data on their atrial electrophysiological mechanisms of action in *in-vivo* models of AF are lacking. Dronedarone (SR 33589), like amiodarone, inhibits I_{Na} in a frequency-dependent manner, I_{CaL}, various K^+ currents, and β-adrenoceptors, and it may block I_{KACh} more potently than amiodarone (Ravens, 2010). In dogs in sinus rhythm, intravenous dronedarone increased atrial and ventricular ERP (Manning *et al.*, 1995). A lack of change in ventricular ERP with decreased APD has also been reported (Verduyn *et al.*, 1999). In dog atrial tissues *in-vitro*, acute dronedarone increased atrial ERP, but did not attenuate acetylcholine-induced ERP-

shortening or AF. Acute amiodarone, by comparison, inhibited the ERP-shortening and AF (Burashnikov *et al.*, 2010a). Dronedarone also suppressed dofetilide-induced EADs and ouabain-induced DADs in isolated Purkinje fibres (Varro *et al.*, 2001). In patients with recurrent AF, dronedarone was superior to placebo in maintaining sinus rhythm, but electrophysiological mechanisms were not studied (Singh *et al.*, 2007). Vernakalant increased atrial (and not ventricular) ERP in patients with no history of AF (Dorian *et al.*, 2007). In patients with AF, vernakalant was efficacious in acutely terminating the arrhythmia, but atrial electrophysiological mechanisms were not studied (Roy *et al.*, 2008). Vernakalant may be both atrial-predominant, since it blocks I_{Kur}/I_{KACh}, and disease-specific, since it blocks I_{Na} preferentially at high rates and in depolarised tissue. Mathematical modelling suggested that rapidly-unbinding I_{Na} blockers such as vernakalant may terminate cholinergic AF, not by increasing atrial wavelength, but rather by decreasing atrial conduction velocity and spiral wave reentry rate, and destabilising "primary generator rotors" (Comtois *et al.*, 2008).

7.7. Pharmacological remodelling by amiodarone

Another potentially anti-arrhythmic mechanism of a class III drug is pharmacological remodelling by amiodarone, perhaps analogous to that by chronic β-blockade (Workman, 2010). Thus, chronic (6 weeks) amiodarone treatment in dogs increased APD_{90} and ERP and caused post-repolarisation refractoriness, more so in isolated atrial than ventricular tissues, and inhibited acetylcholine-induced AF (Burashnikov *et al.*, 2008). Increased pulmonary vein APD also was reported in this model (Sicouri *et al.*, 2009), along with prevention of isoprenaline-induced DADs.

8. Class IV drugs (Ca^{2+} channel blockers): electrophysiological effects in *in-vivo* models of AF

8.1. Clinical use of Ca^{2+} channel blockers for rate control, and loss of effects on electrical remodelling

The Ca^{2+} channel blockers verapamil and diltiazem are currently recommended for ventricular rate control (Camm *et al.*, 2010). However, their effects on atrial rhythm have also been studied, and in a wide range of *in-vivo* models of AF, along with those of other Ca^{2+} channel blockers: bepridil and efonidipine (Table 5). Ca^{2+} channel blockers prevented AF or inhibited its induction in 7 of 12 reports, but also could have no effect, or even promote AF (in 4 studies, each in a different model). Most studies were of verapamil and diltiazem, which block I_{CaL}. The most consistent Ca^{2+} channel blocker effect was that of verapamil to increase atrial ERP in acute atrial tachypacing-induced AF in patients (Table 5).
[insert Table 5]

Thus, in each of 3 studies, verapamil, given just before an ~10 min episode of AF, attenuated or prevented AF-induced ERP-shortening. However, verapamil effects on AF were inconsistent, with either suppression (Daoud *et al.*, 1997; Yu *et al.*, 1998) or promotion (Sticherling *et al.*, 2002). Abrupt increase in atrial rate, e.g., as occurs at the onset of an episode of AF in patients, rapidly elevates atrial intracellular Ca^{2+}. By accelerating I_{CaL} inactivation, this Ca^{2+} elevation may rapidly shorten ERP. A reduction in I_{CaL} amplitude by verapamil could attenuate intracellular Ca^{2+} elevation, perhaps explaining its effect to attenuate such ERP-shortening in patients. Alternatively, inhibition of I_{Kr} (Zhang *et al.*, 1999) and/or I_{Kur} (Gao *et al.*, 2004) by verapamil might also contribute to the increase in ERP. Verapamil also increased ERP early on during atrial tachypacing in each of 2 studies using the dog chronic atrial tachypacing model (Table 5). An increase in wavelength (Ohashi *et al.*, 2004) and a decrease in AF vulnerability (Lee *et al.*, 2000) also were found. However, these effects of verapamil on ERP, wavelength and AF were lost after 1 or 2 weeks of continuous atrial tachypacing, despite daily drug administration. There was also a corresponding lack of effect of diltiazem on AF or atrial electrophysiology after 1 week of atrial tachypacing in this model (Table 5). One explanation for the time-dependent loss of effect of these drugs may be the fact that long term remodelling shortens ERP by different mechanisms than short term remodelling, e.g., by (potentially over-riding) increases in I_{K1} and I_{KACh} (Workman *et al.*, 2008). However, the ERP-prolonging effect of efonidipine or bepridil, by contrast with that of verapamil, was not lost (Table 5). Both drugs block I_{CaT} in addition to I_{CaL}, and since a continuous inward leak of Ca^{2+} via I_{CaT} may contribute to long term atrial remodelling (Fareh *et al.*, 2001), the block of I_{CaT} by these drugs might explain the persistence of their atrial electrophysiological/anti-arrhythmic effects.

8.2. Potential of Ca^{2+} channel blockers to inhibit non-reentrant AF

Verapamil was also tested in the dog chronic (2-6 week) ventricular tachypacing model of heart failure which, by contrast with the chronic AF/atrial tachypacing models, does not shorten ERP (Table 1) and the AF it produces likely involves non-reentrant activity. In each of 2 studies (Table 5), verapamil could terminate AF. It had no consistent effect on AFCL (Stambler *et al.*, 2003), and preferentially prevented AF due to atrial "drivers" rather than to "irregular activation" (Ryu *et al.*, 2005). These data, contrasting with the relative lack of anti-AF action of I_{CaL} blockade in the chronic AF/atrial tachypacing models, are in line with a suppression of non-reentrant atrial arrhythmic activity involving I_{CaL}. Data are sparse on atrial electrophysiological mechanisms of Ca^{2+} channel blockers in most of the other models of AF studied, namely, cholinergic stimulation, atrial ischaemia, acute atrial dilation, and transient asphyxia (Table 5), and no consistent patterns emerged. Furthermore, AF was either promoted, inhibited or unchanged among these models. In patients with a

history of AF, atrial electrophysiological effects of Ca^{2+} channel blockers were studied only in those with paroxysmal AF. The ERP, wavelength and AFCL were not measured, and Ca^{2+} channel blocker effects on AF were inconsistent. Thus, verapamil either increased atrial dominant frequency, suggestive of a pro-arrhythmic effect by promoting high frequency zones of activation (Kushiyama *et al.*, 2010), or decreased the incidence of pulmonary vein ectopic activity and "burst AF" (Chen *et al.*, 1999).

9. Upstream therapies and other clinically available agents: *in-vivo* mechanisms

9.1. Atrial electrophysiological mechanisms of upstream therapies

9.1.1. ACE inhibitors and angiotensin receptor blockers

ACE inhibitors and angiotensin receptor blockers are currently recommended for consideration for primary prevention of AF in patients with heart failure and reduced left ventricular function, or with hypertension, and for secondary prevention in patients who have recurrent AF despite receiving anti-arrhythmic drugs (Camm *et al.*, 2010). Several ACE inhibitors and angiotensin receptor blockers in clinical use have been studied in *in-vivo* models of AF, either chronic AF/atrial tachypacing or left ventricular dysfunction, in a variety of species (Table 6).
[insert Table 6]

These drugs were usually anti-arrhythmic, decreasing AF vulnerability, incidence or duration in 8 of 11 studies, irrespective of model type. With remarkable consistency, atrial ERP was unaffected by any ACE inhibitor or angiotensin receptor blocker in either model type. Candesartan also had no effect on the time course of chronic AF-induced shortening of ERP or AFCL (Hall *et al.*, 2010). The duration of AF or atrial tachypacing in all of the chronic AF/atrial tachypacing studies (Table 6) was ≥1 week. However, it should be noted that, in a study of short term (3 hr) atrial tachypacing, either candesartan, or the ACE inhibitor captopril, prevented shortening of the atrial ERP (Nakashima *et al.*, 2000). ACE inhibitor/angiotensin receptor blocker effects on atrial global conduction velocity were less consistent, either leaving it unchanged or increasing it (Table 6). However, no ACE inhibitor or angiotensin receptor blocker decreased conduction velocity. When measured, atrial wavelength was unchanged, always coincident with a lack of change in conduction velocity (Table 6), but wavelength-increase may be expected in the 2 studies in which conduction velocity increased, since ERP was unchanged. An increase in wavelength could inhibit leading circle reentry. However, confirmatory activation mapping evidence with these drugs is lacking. Nevertheless, in the chronic ventricular tachypacing model, enalapril decreased atrial conduction velocity-dispersion, i.e., attenuated local conduction disturbances caused by heart failure (Li *et al.*, 2001). Decreased electrical heterogeneity should oppose reentry, by preventing unidirectional conduction block (Figure 1). The improved conduction was associated with, and likely caused by, attenuation of heart failure-induced atrial fibrosis (Li *et al.*, 2001). That was unlikely to have involved any effect of the drug to improve coronary flow, since fibrosis was unaffected by a non-ACE inhibitor vasodilator (Li *et al.*, 2001). ACE inhibitors/angiotensin receptor blockers also inhibited pathological atrial structural remodelling in other studies in which they inhibited AF (Table 6), preventing fibrosis (Anne *et al.*, 2007), myolysis (Li *et al.*, 2007) and hypertrophy (Li *et al.*, 2007). The reduction in fibrosis occurred whether with chronic atrial tachypacing or chronic ventricular tachypacing, despite atrial tachypacing producing substantially less fibrosis than ventricular tachypacing (Everett *et al.*, 2006). Consistent with this, ACE inhibitor therapy was associated with decreased atrial tissue collagen content in patients with chronic lone AF (Boldt *et al.*, 2006). These effects on fibrosis and myolysis add support to an anti-arrhythmic mechanism involving improved conduction, and the atrial anti-hypertrophic action could also inhibit reentry by reducing the available pathlength (Figure 1). The biochemical mechanisms of increased atrial fibrosis in heart failure are incompletely understood, but likely involve induction of mitogen-activated protein kinases as a consequence of renin-angiotensin-aldosterone system activation. The mechanism of suppression of atrial structural remodelling by the ACE inhibitors and angiotensin receptor blockers most likely involves, therefore, inhibition of pathological angiotensin elevation and associated signalling, as shown with enalapril in heart failure-induced AF (Li *et al.*, 2001) and with quinapril and losartan in chronic atrial tachypacing-induced AF (Anne *et al.*, 2007). Whether the anti-arrhythmic effects of ACE inhibitors and angiotensin receptor blockers involve a contribution from reversal of any acute pro-arrhythmic effects of angiotensin is unclear. Acute angiotensin had no effect on atrial conduction velocity, ERP or ERP-dispersion in patients (Kistler *et al.*, 2005). In guinea pig atrial cells, acute angiotensin increased I_{KS} and shortened APD (Zankov *et al.*, 2006). The contribution of I_{KS} to human atrial repolarisation, however, may be relatively small (Workman, 2010). Nevertheless, acute angiotensin might produce EADs, by increasing the production of reactive O_2 species, as shown in rabbit ventricular cells (Zhao *et al.*, 2011).

9.1.2. Aldosterone antagonists

Aldosterone antagonists, e.g., spironolactone, may reduce AF recurrence in patients with hypertension and mild left ventricular dysfunction, but there is currently no recommendation regarding their use as upstream therapy in the prevention of AF (Camm *et al.*, 2010). In the *in-vivo* models of AF, spironolactone or eplerenone decreased AF vulnerability either in heart failure or chronic atrial tachypacing (Table 6). Spironolactone also prevented atrial

tachypacing-induced atrial fibrosis, apoptosis and myolysis and the associated altered expression of regulatory proteins that could favour extracellular matrix degradation. This could improve local conduction and, coupled with the prevention by spironolactone of atrial hypertrophy (Zhao *et al.*, 2010), might oppose reentry.

9.1.3. Statins

Statins are recommended for consideration for prevention of new-onset AF after cardiac surgery, or in patients with underlying heart disease, particularly heart failure (Camm *et al.*, 2010). Several have been tested in representative animal models, which featured marked atrial fibrosis: pericarditis or heart failure in dogs, and reactive O_2 species over-production in mice. Chronic atrial tachypacing in dogs was also studied (Table 6). In all the dog studies, atorvastatin or simvastatin decreased AF duration and, in each case, increased either ERP, conduction velocity, or both, thus potentially increasing wavelength. However, in the transgenic mouse model, which produced atrial tachycardia rather than AF, rosuvastatin had no effect on ERP, conduction velocity or atrial tachycardia. The prevention by atorvastatin of pericarditis-induced decrease in ERP and conduction velocity is consistent with inhibition of atrial reentry, likely the primary arrhythmia mechanism in this model, and the improved conduction was coupled with decreased fibrosis. Atrial fibrosis and conduction velocity-dispersion were also prevented by simvastatin in the heart failure model. These data point to a contribution from anti-fibrosis to AF suppression by statins. However, numerous additional mechanisms may operate, e.g., improved lipid metabolism, altered membrane fluidity and ion channel conductance, and suppression of atherosclerosis, inflammation, reactive O_2 species, endothelial dysfunction and neurohumoral activation (Savelieva *et al.*, 2010).

9.1.4. Poly-unsaturated fatty acids

There is presently no strong clinical evidence to support the use of n-3 (omega-3; fish oil-derived) poly-unsaturated fatty acids in primary or secondary prevention of AF, as discussed in the current guidelines (Camm *et al.*, 2010) and corroborated by a subsequent randomised double-blind, placebo-controlled clinical trial (Kowey *et al.*, 2010). Among a variety of *in-vivo* animal models, n-3 poly-unsaturated fatty acids either suppressed AF or had no effect, and also exerted minimal effect on atrial electrophysiology (Table 6). Nevertheless, in the 2 dog ventricular tachypacing models, which cause localised atrial conduction disturbances, poly-unsaturated fatty acids reduced atrial conduction velocity-dispersion. In one study, atrial fibrosis was also reduced (Sakabe *et al.*, 2007). Again, such structural effects could oppose reentry. Non-reentry should not be excluded, however, since poly-unsaturated fatty acids inhibited afterdepolarisations in ventricular cells from patients with heart failure, coupled with a lowering of intracellular Ca^{2+} (Den Ruijter *et al.*, 2008). Other putative anti-AF mechanisms of poly-unsaturated fatty acids include plasmalemma stabilisation, vasodilation, and modulation of ion channels or gap junctions. Poly-unsaturated fatty acids may also suppress inflammation, as a result of activation of peroxisome proliferator-activated receptors, and suppress reactive O_2 species production (Savelieva *et al.*, 2010).

9.1.5. Other potential upstream therapies

Fenofibrate and pioglitazone, activators of peroxisome proliferator-activated receptor-α and -γ, respectively, were studied in heart failure models (Table 6). Only pioglitazone suppressed AF, which was associated with increased conduction velocity, likely from a suppression of atrial fibrosis. The anti-inflammatory drugs prednisone and ibuprofen were studied in a chronic atrial tachypacing model of AF (Table 6). Prednisone decreased AF vulnerability and duration and increased ERP, while ibuprofen had no effect. The anti-oxidant vitamin C was also tested, in 2 studies of chronic atrial tachypacing (Table 6). In the 1st, it attenuated atrial ERP-shortening, but AF was not studied. In the 2nd, vitamin C had no effect on ERP-shortening or AF.

9.2. Atrial electrophysiological mechanisms of digoxin in rate and rhythm control

Digoxin is neither a Vaughan Williams class drug nor upstream therapy. It is a Na^+,K^+ pump blocker, recommended for rate control at rest (due to its vagotonic effect) (Camm *et al.*, 2010). This drug was studied in a goat chronic AF model, to assess its potential to affect mechanisms of rhythm control and atrial remodelling. Digoxin either moderately increased AF vulnerability and duration, or had no effect (Table 6). It had no effect on atrial ERP, conduction velocity, AFCL or electrogram fractionation (Duytschaever *et al.*, 2000). Such a lack of effect of Na^+,K^+ pump blockade on atrial electrophysiology in this model is consistent with the reported absence of change in atrial Na^+,K^+ pump current density in patients with chronic AF (Workman *et al.*, 2003a). However, digoxin delayed ERP-recovery after cessation of AF in goats, perhaps by a persistent effect to elevate intracellular Ca^{2+} (Tieleman *et al.*, 1999). Such an effect could theoretically increase AF recurrence in patients after cardioversion. In line with this, digoxin exacerbated AF re-induction and atrial ERP-shortening following acute atrial tachypacing-induced AF in patients (Table 6). It was noted that, because all patients underwent autonomic blockade (Sticherling *et al.*, 2000), the AF-promoting effect of digoxin was more likely due to its effect to increase intracellular Ca^{2+} than to increase vagal tone.

10. Investigational anti-arrhythmic drugs: *in-vivo* electrophysiological mechanisms of AF termination and prevention

10.1. Types of investigational drugs and AF models studied

Numerous investigational drugs have been studied in *in-vivo* animal models of AF (Table 7). Many are being tested as potential treatments for AF, and some have already been approved for other conditions. Others were withdrawn, or are intended purely for experimental use. Most studies were in dogs, usually in ERP-shortening, reentry-promoting, models: chronic AF/atrial tachypacing or cholinergic stimulation. Reentry-promoting atrial injury models were also widely used. Relatively few drugs were tested in models of atrial structural remodelling, such as heart failure or pericarditis. This may reflect the primary mechanism of action of most drugs tested: APD-prolonging ion channel blockers. The relatively selective blockers are shown first in Table 7, followed by multi-channel blockers, then gap junction-enhancers and others.

10.2. Investigational ion channel blockers: in-vivo electrophysiological mechanisms

The ion channel blockers as a group increased atrial ERP with remarkable consistency: in 23 of 25 studies in which it was measured (Table 7). Atrial wavelength was increased in 5 of 6 studies, always as a result of ERP-increase, and AFCL was also consistently increased: in 19 of 20 studies. These drugs tended to terminate AF more effectively than inhibit its induction.

10.2.1. Selective ion channel blockers

Of the selective ion channel blockers, three: DPO-1 (a diphenylphosphine oxide), NIP-151 (a benzopyrane derivative) and tertiapin (a bee venom peptide) target I_{Kur} or I_{KACh} and are thus atrial-predominant. In line, AF-termination by each was accompanied by an increase in atrial ERP without effect on ventricular ERP. This is desirable as it minimises ventricular pro-arrhythmia risk from ventricular afterdepolarisations. The likely anti-AF mechanism was suppression of reentry by the ERP increase. However, NIP-151 and tertiapin also terminated aconitine-induced AF (Table 7), presumably by suppressing afterdepolarisations. The selective I_{Kr} blockers all terminated AF and prolonged atrial ERP, except for almokalant. However, several also prolonged the QT interval and/or ventricular ERP: e.g., almokalant, KCB-328 and MK499. The anti-arrhythmic mechanism presumably involved suppression of reentry, the predominant arrhythmia mechanism in the models used. In support, KCB-328 also decreased ERP-dispersion (Rahme *et al.*, 2001), potentially inhibiting unidirectional conduction block (Figure 1). Atrial flutter was mapped during azimilide (I_{Kr}/I_{KS} blocker) treatment in the chronic atrial dilation model. Azimilide terminated this arrhythmia by increasing ERP and preferentially decreasing conduction velocity in slowly-conducting zones of atrial reentry circuits (Restivo *et al.*, 2001). It should be noted, however, that since the electrophysiological mechanisms of atrial flutter may differ from those of AF (see section 2.1.2), the effects of azimilide on these arrhythmias also may differ. Azimilide also increased ERP in the cholinergic AF model, terminating AF when AFCL-increase was greatest. Selective I_{Ks} blockade with HMR 1556 also terminated AF, including in pigs (Table 7). However, it increased ventricular as well as atrial ERP (Nakashima *et al.*, 2004). The aminobenzimidazole NS8593 blocks the small conductance Ca^{2+}-activated K^+ current (I_{SKCa}). An increase in I_{SKCa} may contribute to APD-shortening from rapid atrial pacing (Ozgen *et al.*, 2007). In an *in-vivo* rat model, NS8593 decreased AF duration (Table 7) associated with, and considered to be caused by, increased ERP as measured *in-vitro* in the same study. NS8593 did not prolong the QT interval, in guinea pig hearts (Diness *et al.*, 2010). The Na^+-H^+ exchanger current ($I_{Na/H}$) inhibitor cariporide (HOE642) did not affect atrial electrophysiology in a chronic atrial tachypacing model (Table 7). Nevertheless, it prevented atrial ERP-shortening and loss of ERP rate-adaptation due to atrial ischaemia, both effects which could oppose reentry. However, it is presently unclear whether atrial $I_{Na/H}$ is altered in AF-remodelling (Workman *et al.*, 2008).

[insert Table 7]

10.2.2. Multi-channel blockers

All the multi-channel blockers (Table 7) inhibit at least one K^+ current (most commonly I_{Kr}), and over half block I_{Na}. Those that block I_{Kur} and/or I_{KACh} may possess some degree of atrial-predominance: ambasilide, AVE0118, AZD7009, nibentan, NIP-142, SD-3212, SSR149744C, and tedisamil. Furthermore, those which block I_{Na} with marked voltage-dependence also may be atrial-predominant, by producing greater block in atrium than ventricle, e.g., ranolazine (anti-anginal), AZD7009, and possibly SSR149744C (celivarone; structural analogue of amiodarone). Additional block of I_{NaL}, e.g., with ranolazine (Sossalla *et al.*, 2010), could also counterbalance any ventricular APD-prolonging effect of I_{Kr} block and thus potentially lower pro-arrhythmic risk. For detailed ionic mechanisms of such atrial-predominance, refer to (Ravens, 2010). Most multi-channel blockers terminated AF (Table 7). All except vanoxerine (dopamine transporter antagonist) increased ERP, likely by increasing atrial APD, e.g., AVE0118 (Blaauw *et al.*, 2007) and SD-3212. AVE0118 (a biphenyl derivative) did not affect QT (Blaauw *et al.*, 2007), consistent with atrial-selectivity. By contrast, ambasilide, AZD7009, nibentan, ranolazine and tedisamil all could increase QT and/or ventricular ERP. Furthermore, the effects of AVE0118 were not lost as electrical remodelling progressed (Linz *et al.*, 2007), unlike those of, for example,

the I_{Kr} blockers d-sotalol and ibutilide (see section 7.3). AVE0118 also attenuated an increase in both ventricular repolarisation-heterogeneity and fibrillation caused by ventricular ischaemia in dogs (Billman & Kukielka, 2008). In Table 7, the consistently increased atrial ERP (and wavelength where measured) suggest an effect of the multi-channel blockers to inhibit leading circle reentry (Figure 1), as considered in the study of AVE0118 (Blaauw *et al.*, 2004). Supporting evidence was provided by mapping: ambasilide (Wang *et al.*, 1994) and nibentan (Fedorov *et al.*, 2000) terminated AF by decreasing the number and increasing the size of co-existing reentrant circuits required to support AF. However, some I_{Na}-blocking drugs might inhibit spiral wave reentry (see section 5.3): AZD7009 terminated pericarditis-induced AF by slowing conduction at wavefront "pivot points" (Goldstein *et al.*, 2004), and vanoxerine reduced the "safety factor for conduction" in slow zones of reentry circuits (Matsumoto *et al.*, 2010). Ranolazine's anti-arrhythmic mechanism was not determined, and an effect to reduce atrial dominant frequency was considered as due to its inhibition of either macro-reentry or focal atrial tachycardia (Kumar *et al.*, 2009). In support of an anti-reentrant mechanism, ranolazine increased atrial ERP and post-repolarisation refractoriness (without affecting ventricular ERP) in dog atria *in-vitro* (Sicouri *et al.*, 2010). However, ranolazine could also suppress triggered activity, as demonstrated in dog pulmonary veins *in-vitro* (Sicouri *et al.*, 2008), perhaps by its inhibition of I_{NaL}; an effect potentiated in cells isolated from patients with chronic AF (Sossalla *et al.*, 2010). Data are emerging on a synergism between effects of ranolazine and other anti-arrhythmic drugs. In atrial tissues isolated from dogs treated chronically with amiodarone, acute ranolazine produced a synergistic, use-dependent and atrium-predominant depression of I_{Na}-dependent action potential parameters, and abolished acetylcholine plus burst pacing-induced AF (Sicouri *et al.*, 2010). Furthermore, acute ranolazine plus acute dronedarone produced post-repolarisation refractoriness in dog atrial tissues, in a synergistic, use-dependent and atrial-predominant manner. This drug combination also markedly reduced the incidence of acetylcholine-induced AF, and of isoprenaline plus high extracellular Ca^{2+}-induced DADs and triggered activity in isolated pulmonary vein sleeves (Burashnikov *et al.*, 2010b).

10.3. Gap junction-enhancers

Gap junction-enhancing peptides were tested in a wide range of animal models (Table 7), most of which reduce atrial conduction velocity (see Table 1) and/or increase its dispersion (see section 3.1). Uncoupling of atrial cells by interstitial fibrosis is a prominent feature of some of these models, e.g., ventricular tachypacing-induced heart failure, and pericarditis. However, the contribution to uncoupling from gap junction remodelling in those, or in chronic AF/atrial tachypacing models, is unclear. By contrast, loss of gap junction communication in acute ischaemia is considered to contribute substantially to conduction-slowing and arrhythmogenesis. GAP-134 (small molecule gap junction-modifier) and rotigaptide (stable derivative of the anti-arrhythmic peptide AAP10) increased atrial conduction velocity and did not affect atrial ERP in all *in-vivo* studies (Table 7). However, any consequent increase in wavelength generally was accompanied by disparate effects on AF: rotigaptide was ineffective in chronic ventricular tachypacing or atrial tachypacing, and GAP-134 suppressed AF in the ventricular tachypacing plus atrial tachypacing model only in animals with minimal atrial dilation. Furthermore, GAP-134 increased atrial dominant frequency and electrogram disorganisation (Laurent *et al.*, 2009), consistent with AF promotion, rather than inhibition. However, in atrial ischaemia or pericarditis, gap junction-enhancers suppressed AF (Table 7). The anti-AF mechanism in ischaemia may have been due in part to the decrease in conduction velocity-dispersion, an effect not produced by rotigaptide in the heart failure model, in which AF was not inhibited. The biochemical mechanism of the enhanced gap junction communication likely involved enhanced phosphorylation and/or suppressed dephosphorylation of connexins (Shiroshita-Takeshita *et al.*, 2007b).

10.4. Other investigational drugs

Other investigational drugs include those that affect intracellular Ca^{2+}-handling: mibefradil (withdrawn from clinical use), K201 (JTV-519), ryanodine and tetracaine (local anaesthetic); as well as an anti-fibrotic and a 5-hydroxytryptamine antagonist (Table 7). Mibefradil, an I_{CaT} blocker, decreased the duration of chronic atrial tachypacing-induced AF in dogs, associated with an increase in atrial ERP and a decrease in its dispersion (it prevented atrial tachypacing-induced ERP-remodelling), without changing conduction velocity, and consequently increased wavelength. The anti-arrhythmic mechanism may have involved an attenuation of intracellular Ca^{2+} elevation-induced atrial remodelling, by block of inward Ca^{2+} leak via I_{CaT} which, unlike I_{CaL}, is not downregulated in atrial tachypacing-remodelling (Yue *et al.*, 1997). K201 (benzothiazepine derivative) has multiple actions: inhibition of I_{Na}, I_{CaL} and various K^+ channels, and stabilisation of ryanodine receptor conformation which may reduce a potentially arrhythmogenic diastolic sarcoplasmic reticular Ca^{2+} leak. *In-vivo*, K201 suppressed AF, associated with an increase in atrial ERP, and with no change in conduction velocity (Table 7). It also prolonged the QT interval, however. The anti-AF mechanism was considered to be inhibition of reentry, the likely predominant cause of AF in the pericarditis model. In support, K201 decreased the vulnerability to carbachol-induced AF in guinea pig hearts *in-vitro*, associated with atrial ERP-increase, likely from an observed inhibition of I_{KACh} and I_{Kr} (Nakaya *et al.*, 2000). However, K201 could also suppress non-reentrant AF since it reduced DAD amplitude or the rate of spontaneous activity, associated with a decreased intracellular Ca^{2+} transient and $I_{Na/Ca}$, in rabbit pulmonary vein isolated cells (Chen *et al.*, 2008). Furthermore, K201 attenuated diastolic spontaneous sarcoplasmic reticular Ca^{2+}

release caused by intracellular Ca^{2+} elevation in rabbit ventricular cells (Loughrey *et al.*, 2007). The ryanodine receptor inhibitor ryanodine terminated atrial tachycardia after increasing its cycle length in a heart failure model of AF (Table 7). The anti-arrhythmic mechanism is unknown, but since this drug inhibits sarcoplasmic reticular Ca^{2+} release and this model produces spontaneous atrial depolarisations (Stambler *et al.*, 2003), a suppression of non-reentrant activity is possible. Tetracaine, which also inhibits ryanodine receptors, suppressed AF in a transgenic mouse model (Table 7). An associated reduction in the incidence of spontaneous sarcoplasmic reticular Ca^{2+} release events in atrial cells (Sood *et al.*, 2008) again suggests suppression of non-reentrant activity. However, an anti-reentrant contribution from I_{Na} blockade should not be excluded. The anti-fibrotic, pirfenidone, attenuated heart failure-induced atrial conduction-slowing in dogs, in line with an observed attenuation of fibrogenesis and associated cytokine disruption, and did not affect ERP (Table 7). It also attenuated conduction velocity-dispersion which, by reducing electrical heterogeneity, could inhibit reentry. Finally, the 5-hydroxytryptamine$_4$ antagonist RS-100302 terminated AF in a pig model. This was associated with an increase in atrial wavelength from increased ERP with minimal conduction-slowing, and with no change in ventricular ERP or QT. The increased wavelength, coupled with decreased ERP-dispersion, could inhibit reentry, the main mechanism of AF in this model. However, suppression of non-reentrant activity should not be excluded since, in human atrial isolated cells, another 5-hydroxytryptamine$_4$ antagonist, GR-113808, suppressed "cellular arrhythmic depolarisations", which may represent abnormal automaticity or afterdepolarisations (Pau *et al.*, 2007).

11. Concluding remarks and future directions

An overview of these data on *in-vivo* electrophysiological mechanisms of pharmacological termination and prevention of AF, as represented in Figure 1, allows several conclusions to be drawn. Studies of effects of class I drugs suggest that Na^+ channel blockade *per se* can terminate AF by decreasing atrial conduction velocity and slowing spiral wave reentry. Any effect of these drugs to increase atrial ERP, including from concurrent block of K^+ channels, and particularly in disease states that shorten the ERP, should contribute to AF termination by increasing wavelength. From the limited available data on effects of class II drugs in *in-vivo* models of AF, the mechanisms by which acute β-blockade suppresses AF are rather unclear. However, numerous *in-vitro* studies suggest a prominent contribution from inhibition of atrial pro-arrhythmic effects of catecholamines, likely involving a reduction in non-reentrant mechanisms by limiting excessive Ca^{2+} influx. This is in line with clinical effects of these drugs to suppress AF associated with elevated adrenergic tone. The chronic use of β-blockers may provide an additional, potentially anti-reentrant action, by an adaptive prolongation of the atrial ERP; so called pharmacological remodelling. Class III drugs may block I_{Kr} only or multiple ion currents, but a general effect of inhibiting atrial reentry by increasing atrial ERP is likely their main anti-arrhythmic mechanism, in a variety of disease settings. However, a diminution or loss of class III effect of some of these drugs may occur as a result of electrical remodelling. Furthermore, many of the class III drugs risk ventricular pro-arrhythmia. Mechanistic data on the influence of class IV drugs on AF suggest that any beneficial effect of the rate-controlling Ca^{2+} channel blockers on atrial rhythm during AF may be lost as a result of electrical remodelling. Limited data suggest that Ca^{2+} channel blockers might be more effective in suppressing heart failure-induced AF, possibly by inhibiting non-reentrant mechanisms. However, these drugs cannot be used in patients with heart failure because of their ventricular negative inotropic effects. The main atrial anti-arrhythmic mechanism of most of the upstream therapies was a potentially reentry-inhibiting improvement in atrial conduction resulting from inhibition of atrial fibrosis and myocyte degradation, rather than from any substantial effects on repolarisation. Thus, in heart failure models of AF, which feature prominent atrial structural remodelling, ACE inhibitors, statins and poly-unsaturated fatty acids each decreased atrial conduction-heterogeneity. The predominant atrial anti-arrhythmic mechanism of many investigational ion channel blockers was probably suppression of leading circle reentry, by an increase in ERP and wavelength, without a decrease in conduction velocity. However, inhibition of spiral wave reentry and/or non-reentry likely contributed in some cases. Many of these drugs increased the QT interval and thus risked ventricular pro-arrhythmia. However, some were relatively atrial-, and also potentially disease-, selective, and did not prolong QT. Gap junction-enhancers tended to improve atrial conduction, but were only moderately effective in preventing AF. A multitude of actions of some investigational drugs, including atrial-predominant modulation of multiple ion channels, autonomic receptors, and intracellular Ca^{2+}-handling, likely contributed to their anti-AF effects in highly complex, pathology-dependent ways.

It may be noted that extensive investigation of *in-vivo* mechanistic electrophysiological effects of drugs in different models of AF seems not to be a requirement for their approval for the treatment of patients with AF, e.g., for the recently approved dronedarone, or the first available class III drug, amiodarone. However, as highlighted by this review, such investigations have demonstrated that the efficacy of drugs to suppress AF may be quite different in different disease states underlying the arrhythmia, and at different time points during the progression of electrical and structural remodelling. Perhaps future drug-testing may focus more on models of AF that produce marked atrial structural as well as electrical remodelling (and not necessarily primarily in dogs, e.g., see Table 7), including for ion channel blockers, i.e. non-upstream therapies. Studies of ventricular tissue have highlighted temporal heterogeneities of APD and restitution as pro-arrhythmic, particularly those resulting from alternating changes (alternans) of APD and the systolic intracellular

Ca^{2+} transient. Such alternans could be pro-arrhythmic in atrium also (Blatter *et al.*, 2003), but this will require further investigation, including *in-vivo*. Current theories concerning the cellular mechanisms of alternans infer a pathological disruption of sarcoplasmic reticular function; the prevention of which could provide a novel route for pharmacological intervention independent of classic ion channel blockade. The study of mechanisms of atrial-predominant, multiple-action drugs in development, as well as of currently available drugs, in *in-vivo* models of AF should help inform about patient groups most likely to benefit from such treatments, and potentially about appropriate timing of differing drug therapy-types during the progression of AF, as the predominating arrhythmia mechanisms change. Furthermore, as mathematical models of atrial electrophysiology incorporate increasingly realistic anatomical and functional parameters relating to the development of AF, these should also help inform about potential electro-pharmacological mechanisms of AF termination and prevention.

It is hoped that the study of electrophysiological mechanisms of acute and chronic effects of anti-arrhythmic drugs in a variety of types of *in-vivo*, and *in-vitro*, models of AF, aided by mathematical modelling, will improve our understanding of how we might increase the efficacy and safety of pharmacological treatments for preventing AF in patients.

References

Anne, W., Willems, R., Holemans, P., Beckers, F., Roskams, T., Lenaerts, I., Ector, H., & Heidbuchel, H. (2007). Self-terminating AF depends on electrical remodeling while persistent AF depends on additional structural changes in a rapid atrially paced sheep model. *J Mol Cell Cardiol* 43, 148-158.

Arora, R., Verheule, S., Scott, L., Navarrete, A., Katari, V., Wilson, E., Vaz, D., & Olgin, J. E. (2003). Arrhythmogenic substrate of the pulmonary veins assessed by high-resolution optical mapping. *Circulation* 107, 1816-1821.

Ashikaga, K., Kobayashi, T., Kimura, M., Owada, S., Sasaki, S., Iwasa, A., Furukawa, K., Motomura, S., & Okumura, K. (2006). Effects of amiodarone on electrical and structural remodeling induced in a canine rapid pacing-induced persistent atrial fibrillation model. *Eur J Pharmacol* 536, 148-153.

Atienza, F., Almendral J, Moreno J, Vaidyanathan R, Talkachou A, Kalifa J, Arenal A, Villacastin JP, Torrecilla EG., Sanchez A, Ploutz-Snyder R, Jalife J, & Berenfeld O (2006). Activation of inward rectifier potassium channels accelerates atrial fibrillation in humans. Evidence for a reentrant mechanism. *Circulation* 114, 2434-2442.

Bauer, A., Koch, M., Kraft, P., Becker, R., Kelemen, K., Voss, F., Senges, J. C., Gerlach, U., Katus, H. A., & Schoels, W. (2005). The new selective I_{Ks}-blocking agent HMR 1556 restores sinus rhythm and prevents heart failure in pigs with persistent atrial fibrillation. *Basic Res Cardiol* 100, 270-278.

Biffi, M., Boriani, G., Bronzetti, G., Capucci, A., Branzi, A., & Magnani, B. (1999). Electrophysiological effects of flecainide and propafenone on atrial fibrillation cycle and relation with arrhythmia termination. *Heart* 82, 176-182.

Billman, G. E. & Kukielka, M. (2008). Novel transient outward and ultra-rapid delayed rectifier current antagonist, AVE0118, protects against ventricular fibrillation induced by myocardial ischemia. *J Cardiovasc Pharmacol* 51, 352-358.

Blaauw, Y., Gogelein, H., Tieleman, R. G., van Hunnik, A., Schotten, U., & Allessie, M. A. (2004). "Early" class III drugs for the treatment of atrial fibrillation: efficacy and atrial selectivity of AVE0118 in remodeled atria of the goat. *Circulation* 110, 1717-1724.

Blaauw, Y., Schotten, U., van Hunnik, A., Neuberger, H. R., & Allessie, M. A. (2007). Cardioversion of persistent atrial fibrillation by a combination of atrial specific and non-specific class III drugs in the goat. *Cardiovasc Res* 75, 89-98.

Blatter, L. A., Kockskamper, J., Sheehan, K. A., Zima, A. V., Huser, J., & Lipsius, S. L. (2003). Local calcium gradients during excitation-contraction coupling and alternans in atrial myocytes. *J Physiol* 546, 19-31.

Boixel, C., Fontaine, V., Rucker-Martin, C., Milliez, P., Louedec, L., Michel, J. B., Jacob, M. P., & Hatem, S. N. (2003). Fibrosis of the left atria during progression of heart failure is associated with increased matrix metalloproteinases in the rat. *J Am Coll Cardiol* 42, 336-344.

Boldt, A., Scholl, A., Garbade, J., Resetar, M. E., Mohr, F. W., Gummert, J. F., & Dhein, S. (2006). ACE-inhibitor treatment attenuates atrial structural remodeling in patients with lone chronic atrial fibrillation. *Basic Res Cardiol* 101, 261-267.

Bosch, R. F., Zeng, X., Grammer, J. B., Popovic, K., Mewis, C., & Kuhlkamp, V. (1999). Ionic mechanisms of electrical remodeling in human atrial fibrillation. *Cardiovasc Res* 44, 121-131.

Boyden, P. A. & Hoffman, B. F. (1981). The effects on atrial electrophysiology and structure of surgically induced right atrial enlargement in dogs. *Circ Res* 49, 1319-1331.

Brugada, J., Gursoy, S., Brugada, P., Atie, J., Guiraudon, G., & Andries, E. (1993). Cibenzoline transforms random re-entry into ordered re-entry in the atria. *Eur Heart J* 14, 267-272.

Burashnikov, A. & Antzelevitch, C. (2010). New developments in atrial antiarrhythmic drug therapy. *Nat Rev Cardiol* 7, 139-148.

Burashnikov, A., Belardinelli, L., & Antzelevitch C (2010a). Acute dronedarone is inferior to amiodarone in terminating and preventing atrial fibrillation in canine atria. *Heart Rhythm* 7, 1273-1279.

Burashnikov, A., Di Diego, J. M., Sicouri, S., Ferreiro, M., Carlsson, L., & Antzelevitch C (2008). Atrial-selective effects of chronic amiodarone in the management of atrial fibrillation. *Heart Rhythm* 5, 1735-1742.

Burashnikov, A., Sicouri, S., Di Diego, J. M., Belardinelli, L., & Antzelevitch C (2010b). Synergistic effect of the combination of ranolazine and dronedarone to suppress atrial fibrillation. *J Am Coll Cardiol* 56, 1216-1224.

Caballero, R., de la Fuente, M. G., Gomez, R., Barana, A., Amoros, I., Dolz-Gaiton, P., Osuna, L., Almendral, J., Atienza, F., Fernandez-Aviles, F., Pita, A., Rodriguez-Roda, J., Pinto, A., Tamargo, J., & Delpon, E. (2010). In humans, chronic atrial fibrillation decreases the transient outward current and ultrarapid component of the delayed rectifier current differentially on each atria and increases the slow component of the delayed rectifier current in both. *J Am Coll Cardiol* 55, 2346-2354.

Camm, A. J., Kirchof P, Lip GYH, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Goronek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, & Rutten FH (2010). Guidelines for the management of atrial fibrillation. The task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 31, 2369-2429.

Carnes, C. A., Chung, M. K., Nakayama, T., Nakayama, H., Baliga, R. S., Piao, S., Kanderian, A., Pavia, S., Hamlin, R. L., McCarthy, P. M., Bauer, J. A., & Van Wagoner, D. R. (2001). Ascorbate attenuates atrial pacing-induced peroxynitrite formation and electrical remodeling and decreases the incidence of postoperative atrial fibrillation. *Circ Res* 89, E32-E38.

Cha, T. J., Ehrlich, J. R., Zhang, L., Shi, Y. F., Tardif, J. C., Leung, T. K., & Nattel, S. (2004). Dissociation between ionic remodeling and ability to sustain atrial fibrillation during recovery from experimental congestive heart failure. *Circulation.* 109, 412-418.

Cha, Y., Wales, A., Wolf, P., Shahrokni, S., Sawhney, N., & Feld, G. K. (1996). Electrophysiologic effects of the new class III antiarrhythmic drug dofetilide compared to the class IA antiarrhythmic drug quinidine in experimental canine atrial flutter: role of dispersion of refractoriness in antiarrhythmic efficacy. *J Cardiovasc Electrophysiol* 7, 809-827.

Chandra, P., Rosen, T. S., Yeom, Z. H., Lee, K., Kim, H. Y., Danilo, P., Jr., & Rosen MR (2004). Evaluation of KCB-328, a new IKr blocking antiarrhythmic agent in pacing induced canine atrial fibrillation. *Europace* 6, 384-391.

Chelu, M. G., Sarma, S., Sood, S., Wang, S., van Oort, R. J., Skapura, D. G., Li, N., Santonastasi, M., Muller, F. U., Schmitz, W., Schotten, U., Anderson, M. E., Valderrabano, M., Dobrev, D., & Wehrens XHT (2009). Calmodulin kinase II-mediated sarcoplasmic reticulum Ca^{2+} leak promotes atrial fibrillation in mice. *J Clin Invest* 119, 1940-1951.

Chen, S. A., Hsieh, M. H., Tai, C. T., Tsai, C. F., Prakash, V. S., Yu, W. C., Hsu, T. L., Ding, Y. A., & Chang, M. S. (1999). Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins. Electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. *Circulation* 100, 1879-1886.

Chen, Y. J., Chen Y-C, Wongcharoen, W., Lin C-I, & Chen S-A (2008). Effect of K201, a novel antiarrhythmic drug on calcium handling and arrhythmogenic activity of pulmonary vein cardiomyocytes. *Br J Pharmacol* 153, 915-925.

Chen, Y. J., Chen, S. A., Tai, C. T., Yu, W. C., Feng, A. N., Ding, Y. A., & Chang, M. S. (1998). Electrophysiologic characteristics of a dilated atrium in patients with paroxysmal atrial fibrillation and atrial flutter. *J Interv Card Electrophysiol* 2, 181-186.

Choisy, S. C. M., Arberry, L. A., Hancox, J. C., & James, A. F. (2007). Increased susceptibility to atrial tachyarrhythmia in spontaneously hypertensive rat hearts. *Hypertension* 49, 498-505.

Chou, C. C. & Chen, P. S. (2009). New concepts in atrial fibrillation: neural mechanisms and calcium dynamics. *Cardiol Clin* 27, 35-43.

Comtois, P., Kneller, J., & Nattel, S. (2005). Of circles and spirals: bridging the gap between the leading circle and spiral wave concepts of cardiac reentry. *Europace* 7, S10-S20.

Comtois, P., Sakabe, M., Vigmond, E. J., Munoz, M., Texier, A., Shiroshita-Takeshita, A., & Nattel, S. (2008). Mechanisms of atrial fibrillation termination by rapidly unbinding Na^{+} channel blockers: insights from mathematical models and experimental correlates. *Am J Physiol* 295, H1489-H1504.

Daoud, E. G., Knight, B. P., Weiss, R., Bahu, M., Paladino, W., Goyal, R., Man, K. C., Strickberger, S. A., & Morady, F. (1997). Effect of verapamil and procainamide on atrial fibrillation-induced electrical remodeling in humans. *Circulation* 96, 1542-1550.

David, D., Lang, R. M., Neumann, A., Borow, K. M., Akselrod, S., & Mor-Avi, V. (1990). Parasympathetically modulated antiarrhythmic action of lidocaine in atrial fibrillation. *Am Heart J.* 119, 1061-1068.

Den Ruijter, H. M., Berecki, G., Verkerk, A. O., Bakker, D., Baartscheer, A., Schumacher, C. A., Belterman CNW, de Jonge, N., Fiolet JWT, Brouwer, I. A., & Coronel, R. (2008). Acute administration of fish oil inhibits triggered activity in isolated myocytes from rabbits and patients with heart failure. *Circulation* 117, 536-544.

Derakhchan, K., Page, P., Lambert, C., & Kus, T. (1994). Effects of procainamide and propafenone on the composition of the excitable gap in canine atrial reentry tachycardia. *J Pharmacol Exp Ther* 270, 47-54.

Derakhchan, K., Villemaire, C., Talajic, M., & Nattel, S. (2001). The class III antiarrhythmic drugs dofetilide and sotalol prevent AF induction by atrial premature complexes at doses that fail to terminate AF. *Cardiovasc Res.* 50, 75-84.

Deroubaix , E., Folliguet, T., Rucker-Martin, C., Dinanian, S., Boixel, C., Validire, P., Daniel, P., Capderou, A., & Hatem, S. N. (2004). Moderate and chronic hemodynamic overload of sheep atria induces reversible cellular electrophysiologic abnormalities and atrial vulnerability. *J Am Coll Cardiol* 44, 1918-1926.

Diness, J. G., Sorensen US, Nissen JD, Al-Shahib B, Jespersen T, Grunnet M, & Hansen RS (2010). Inhibition of small-conductance Ca^{2+}-activated K^+ channels terminates and protects against atrial fibrillation. *Circ Arrhythmia Electrophysiol* 3, 380-390.

Dobrev, D., Friedrich, A., Voigt, N., Jost, N., Wettwer, E., Christ, T., Knaut, M., & Ravens, U. (2005). The G protein-gated potassium current $I_{K,ACh}$ is constitutively active in patients with chronic atrial fibrillation. *Circulation.* 112, 3697-3706.

Doisne, N., Maupoil, V., Cosnay, P., & Findlay, I. (2009). Catecholaminergic automatic activity in the rat pulmonary vein: electrophysiological differences between cardiac muscle in the left atrium and pulmonary vein. *Am J Physiol* 297, H102-H108.

Dorian, P., Pinter, A., Mangat, I., Korley, V., Cvitkovic, S. S., & Beatch, G. N. (2007). The effect of vernakalant (RSD1235), an investigational antiarrhythmic agent, on atrial electrophysiology in humans. *J Cardiovasc Pharmacol* 50, 35-40.

Duytschaever, M., Blaauw, Y., & Allessie, M. (2005). Consequences of atrial electrical remodeling for the anti-arrhythmic action of class IC and class III drugs. *Cardiovasc Res* 67, 69-76.

Duytschaever, M. F., Garratt CJ, & Allessie MA (2000). Profibrillatory effects of verapamil but not of digoxin in the goat model of atrial fibrillation. *J Cardiovasc Electrophysiol* 11, 1375-1385.

Eijsbouts, S., Ausma, J., Blaauw, Y., Schotten, U., Duytschaever, M., & Allessie, M. A. (2006). Serial cardioversion by Class IC drugs during 4 months of persistent atrial fibrillation in the goat. *J Cardiovasc Electrophysiol* 17, 648-654.

Eisner, D. A., Kashimura, T., O'Neill, S. C., Venetucci, L. A., & Trafford, A. W. (2009). What role does modulation of the ryanodine receptor play in cardiac inotropy and arrhythmogenesis? *J Mol Cell Cardiol* 46, 474-481.

Everett, T. H., Wilson, E. E., Verheule, S., Guerra, J. M., Foreman, S., & Olgin, J. E. (2006). Structural atrial remodeling alters the substrate and spatiotemporal organization of atrial fibrillation: a comparison in canine models of structural and electrical atrial remodeling. *Am J Physiol* 291, H2911-H2923.

Fareh, S., Benardeau, A., & Nattel, S. (2001). Differential efficacy of L- and T-type calcium channel blockers in preventing tachycardia-induced atrial remodeling in dogs. *Cardiovasc Res* 49, 762-770.

Fedorov, V. V., Sharifov, O. F., Beloshapko, G. G., Yushmanova, A. V., & Rosenshtraukh, L. V. (2000). Effects of a new class III antiarrhythmic drug nibentan in a canine model of vagally mediated atrial fibrillation. *J Cardiovasc Pharmacol* 36, 77-89.

Feld, G. K. & Shahandeh-Rad, F. (1992). Mechanism of double potentials recorded during sustained atrial flutter in the canine right atrial crush-injury model. *Circulation* 86, 628-641.

Fenelon, G., Shepard, R. K., & Stambler, B. S. (2003). Focal origin of atrial tachycardia in dogs with rapid ventricular pacing-induced heart failure. *J Cardiovasc Electrophysiol* 14, 1093-1102.

Fischbach, P. S., Barrett, T. D., Goyal, R., Tran, B. C., Syed, Z. A., Hennan, J. K., & Lucchesi, B. R. (2001). Conversion of atrial fibrillation by the experimental antiarrhythmic drug tedisamil in two canine models. *J Cardiovasc Electrophysiol* 12, 1138-1144.

Fischbach, P. S., Johnston, P. V., Friedrichs, G. S., & Lucchesi, B. R. (1999). Tedisamil in a chronic canine model of atrial flutter. *J Cardiovasc Pharmacol* 34, 212-218.

Fujiki, A., Nagasawa, H., Sakabe, M., Sakurai, K., Nishida, K., Mizumaki, K., & Inoue, H. (2001). Spectral characteristics of human atrial fibrillation waves of the right atrial free wall with respect to the duration of atrial fibrillation and effect of Class I antiarrhythmic drugs. *Jpn Circ J* 65, 1047-1051.

Fujiki, A., Tani, M., Hayashi, H., Mizumaki, K., Inoue, H., Uemura, H., & Nakaya, H. (1997). Electrophysiologic effects of SD-3212, a new class I antiarrhythmic drug, on canine atrial flutter and atrial action-potential characteristics. *J Cardiovasc Pharmacol* 29, 471-475.

Fuster, V., Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, & Wann S (2006). ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. Executive summary. *J Am Coll Cardiol* 48, 854-906.

Gami, A. S., Edwards, W. D., Lachman, N., Friedman, P. A., Talreja, D., Munger, T. M., Hammill, S. C., Packer, D. L., & Asirvatham, S. J. (2010). Electrophysiological anatomy of typical atrial flutter: the posterior boundary and causes for difficulty with ablation. *J Cardiovasc Electrophysiol* 21, 144-149.

Gao, Z., Lau CP, Chiu SW, & Li GR (2004). Inhibition of ultra-rapid delayed rectifier K^+ current by verapamil in human atrial myocytes. *J Mol Cell Cardiol* 36, 257-263.

Gaspo, R., Bosch, R. F., Talajic, M., & Nattel, S. (1997). Functional mechanisms underlying tachycardia-induced sustained atrial fibrillation in a chronic dog model. *Circulation* 96, 4027-4035.

Gautier, P., Serre, M., Cosnier-Pucheu, S., Djandjighian, L., Roccon, A., Herbert, J. M., & Nisato, D. (2005). In vivo and in vitro antiarrhythmic effects of SSR149744C in animal models of atrial fibrillation and ventricular arrhythmias. *J Cardiovasc Pharmacol* 45, 125-135.

Goldstein, R. N., Khrestian, C., Carlsson, L., & Waldo, A. L. (2004). AZD7009: a new antiarrhythmic drug with predominant effects on the atria effectively terminates and prevents reinduction of atrial fibrillation and flutter in the sterile pericarditis model. *J Cardiovasc Electrophysiol* 15, 1444-1450.

Greiser, M., Neuberger, H. R., Harks, E., El-Armouche, A., Boknik, P., de Haan, S., Verheyen, F., Verheule, S., Schmitz, W., Ravens, U., Nattel, S., Allessie, M. A., Dobrev, D., & Schotten, U. (2009). Distinct contractile and molecular differences between two goat models of atrial dysfunction: AV block-induced atrial dilatation and atrial fibrillation. *J Mol Cell Cardiol* 46, 385-394.

Hagendorff, A., Schumacher, B., Kirchhoff, S., Luderitz, B., & Willecke, K. (1999). Conduction disturbances and increased atrial vulnerability in Connexin40-deficient mice analyzed by transesophageal stimulation. *Circulation* 99, 1508-1515.

Haissaguerre, M., Jais, P., Shah, D. C., Takahashi, A., Hocini, M., Quiniou, G., Garrigue, S., Le Mouroux, A., Le Metayer, P., & Clementy, J. (1998). Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 339, 659-666.

Hall, M. C. S., Kirubakaran, S., Choudhury, R., Abidin, N., Peters, N. S., & Garratt, C. J. (2010). Effects of angiotensin receptor blockade on atrial electrical remodelling and the 'second factor' in a goat burst-paced model of atrial fibrillation. *J Renin-Angiotensin-Aldosterone Syst* 11, 222-233.

Hashimoto, N., Yamashita, T., & Tsuruzoe, N. (2006). Tertiapin, a selective IK_{ACh} blocker, terminates atrial fibrillation with selective atrial effective refractory period prolongation. *Pharmacol Res* 54, 136-141.

Hashimoto, N., Yamashita, T., & Tsuruzoe, N. (2008). Characterization of in vivo and in vitro electrophysiological and antiarrhythmic effects of a novel I_{KACh} blocker, NIP-151: a comparison with an I_{Kr}-blocker dofetilide. *J Cardiovasc Pharmacol* 51, 162-169.

Haugan, K., Lam, H. R., Knudsen, C. B., & Petersen, J. S. (2004). Atrial fibrillation in rats induced by rapid transesophageal atrial pacing during brief episodes of asphyxia: a new *in vivo* model. *J Cardiovasc Pharmacol* 44, 125-135.

Hayashi, H., Fujiki, A., Tani, M., Usui, M., & Inoue, H. (1998). Different effects of class Ic and III antiarrhythmic drugs on vagotonic atrial fibrillation in the canine heart. *J Cardiovasc Pharmacol* 31, 101-107.

Hirose, M., Takeishi, Y., Miyamoto, T., Kubota, I., Laurita, K. R., & Chiba, S. (2005). Mechanism for atrial tachyarrhythmia in chronic volume overload-induced dilated atria. *J Cardiovasc Electrophysiol* 16, 760-769.

Huang, C. X., Zhao, Q. Y., Liang, J. J., Chen, H., Yang, B., Jiang, H., & Li, G. S. (2006). Differential densities of muscarinic acetylcholine receptor and $I_{K,ACh}$ in canine supraventricular tissues and the effect of amiodarone on cholinergic atrial fibrillation and $I_{K,ACh}$. *Cardiology* 106, 36-43.

Inoue, H., Yamashita, T., Usui, M., Nozaki, A., Saihara, S., & Sugimoto, T. (1991). Effects of pentisomide and E-4031 on canine atrial flutter due to reentry: a comparative study with disopyramide and propafenone. *J Cardiovasc Pharmacol* 18, 137-143.

Ishibashi, K., Inoue, D., Sakai, R., Inoue, M., Shirayama, T., Asayama, J., & Nakagawa, M. (1995). Effects of disopyramide on the atrial fibrillation threshold in the human atrium. *Int J Cardiol* 52, 177-184.

Jalife, J. (2010). Deja vu in the theories of atrial fibrillation dynamics. *Cardiovasc Res* (In Press. DOI: 10.1093/cvr/cvq364).

Jalil, E., Laflamme, M., & Kus, T. (1997). Effects of procainamide on the excitable gap composition in a canine model of atrial flutter. *Can J Physiol Pharmacol* 75, 1-8.

Jayachandran, J. V., Zipes, D. P., Weksler, J., & Olgin, J. E. (2000). Role of the Na^+/H^+ exchanger in short-term atrial electrophysiological remodeling. *Circulation* 101, 1861-1866.

Kanki, H., Mitamura, H., Takatsuki, S., Sueyoshi, K., Shinagawa, K., Sato, T., & Ogawa, S. (1998). Postrepolarization refractoriness as a potential anti-atrial fibrillation mechanism of pilsicainide, a pure sodium channel blocker with slow recovery kinetics. *Cardiovasc Drugs Ther* 12, 475-482.

Kawase, A., Ikeda, T., Nakazawa, K., Ashihara, T., Namba, T., Kubota, T., Sugi, K., & Hirai, H. (2003). Widening of the excitable gap and enlargement of the core of reentry during atrial fibrillation with a pure sodium channel blocker in canine atria. *Circulation* 107, 905-910.

Kettlewell, S., Smith, G. L., & Workman, A. J. (2010). Left atrial cellular hypertrophy accompanying a left ventricular infarction is accompanied by altered intracellular Ca^{2+} handling in the presence of adrenergic stimulation. *Cardiovasc Res* 87, S63.

Kim, B. S., Kim, Y. H., Hwang, G. S., Pak, H. N., Lee, S. C., Shim, W. J., Oh, D. J., & Ro, Y. M. (2002). Action potential duration restitution kinetics in human atrial fibrillation. *J Am Coll Cardiol* 39, 1329-1336.

Kirchhof, P., Engelen, M., Franz, M. R., Ribbing, M., Wasmer, K., Breithardt, G., Haverkamp, W., & Eckardt, L. (2005). Electrophysiological effects of flecainide and sotalol in the human atrium during persistent atrial fibrillation. *Basic Res Cardiol* 100, 112-121.

Kiss, O., Zima, E., Soos, P., Kekesi, V., Juhasz-Nagy, A., & Merkely, B. (2004). Intracoronary endothelin-1 infusion combined with systemic isoproterenol treatment: antagonistic arrhythmogenic effects. *Life Sci* 75, 537-548.

Kistler, P. M., Davidson, N. C., Sanders, P., Fynn, S. P., Stevenson, I. H., Spence, S. J., Vohra, J. K., Sparks, P. B., & Kalman, J. M. (2005). Absence of acute effects of angiotensin II on atrial electrophysiology in humans. *J Am Coll Cardiol* 45, 154-156.

Kistler, P. M., Sanders, P., Dodic, M., Spence, S. J., Samuel, C. S., Zhao, C., Charles, J. A., Edwards, G. A., & Kalman, J. M. (2006). Atrial electrical and structural abnormalities in an ovine model of chronic blood pressure elevation after prenatal corticosteroid exposure: implications for development of atrial fibrillation. *Eur Heart J* 27, 3045-3056.

Kojodjojo, P., Peters, N. S., Davies, D. W., & Kanagaratnam, P. (2007). Characterization of the electroanatomical substrate in human atrial fibrillation: the relationship between changes in atrial volume, refractoriness, wavefront propagation velocities, and AF burden. *J Cardiovasc Electrophysiol* 18, 269-275.

Kovoor, P., Wickman, K., Maguire, C. T., Pu, W., Gehrmann, J., Berul, C. I., & Clapham, D. E. (2001). Evaluation of the role of I_{KACh} in atrial fibrillation using a mouse knockout model. *J Am Coll Cardiol* 37, 2136-2143.

Kowey, P. R., Reiffel, J. A., Ellenbogen, K. A., Naccarelli, G. V., & Pratt, C. M. (2010). Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation. A randomized controlled trial. *JAMA J Am Med Assoc* 304, 2363-2372.

Kumagai, K., Akimitsu, S., Kawahira, K., Kawanami, F., Yamanouchi, Y., Hiroki, T., & Arakawa, K. (1991). Electrophysiological properties in chronic lone atrial fibrillation. *Circulation* 84, 1662-1668.

Kumagai, K., Nakashima, H., Gondo, N., & Saku, K. (2003a). Antiarrhythmic effects of JTV-519, a novel cardioprotective drug, on atrial fibrillation/flutter in a canine sterile pericarditis model. *J Cardiovasc Electrophysiol* 14, 880-884.

Kumagai, K., Nakashima, H., & Saku, K. (2004). The HMG-CoA reductase inhibitor atorvastatin prevents atrial fibrillation by inhibiting inflammation in a canine sterile pericarditis model. *Cardiovasc Res* 62, 105-111.

Kumagai, K., Nakashima, H., Urata, H., Gondo, N., Arakawa, K., & Saku, K. (2003b). Effects of angiotensin II type 1 receptor antagonist on electrical and structural remodeling in atrial fibrillation. *J Am Coll Cardiol* 41, 2197-2204.

Kumar, K., Nearing, B. D., Carvas, M., Nascimento BCG, Acar, M., Belardinelli, L., & Verrier, R. L. (2009). Ranolazine exerts potent effects on atrial electrical properties and abbreviates atrial fibrillation duration in the intact porcine heart. *J Cardiovasc Electrophysiol* 20, 796-802.

Kushiyama, Y., Osaka, T., Yokoyama, E., Hasebe, H., Kuroda, Y., Kamiya, K., & Kodama, I. (2010). Verapamil eliminates the hierarchical nature of activation frequencies from the pulmonary veins to the atria during paroxysmal atrial fibrillation. *Heart Rhythm* 7, 577-583.

Lau, D. H., Mackenzie L, Kelly DJ, Psaltis PJ, Worthington M, Rajendram A, Kelly DR, Nelson AJ, Zhang Y, Kuklik P, Brooks AG, Worthley SG, Faull RJ, Rao M, Edwards J, Saint DA, & Sanders P (2010). Short-term hypertension is associated with the development of atrial fibrillation substrate: a study in an ovine hypertensive model. *Heart Rhythm* 7, 396-404.

Laurent, G., Leong-Poi H, Mangat I, Moe GW, Hu X, So PPS, Tarulli E, Ramadeen A, Rossman EI, Hennan JK, & Dorian P (2009). Effects of chronic gap junction conduction-enhancing antiarrhythmic peptide GAP-134 administration on experimental atrial fibrillation in dogs. *Circ Arrhythmia Electrophysiol* 2, 171-178.

Laurent, G., Moe, G., Hu, X., Holub, B., Leong-Poi, H., Trogadis, J., Connelly, K., Courtman, D., Strauss, B. H., & Dorian, P. (2008a). Long chain n-3 polyunsaturated fatty acids reduce atrial vulnerability in a novel canine pacing model. *Cardiovasc Res* 77, 89-97.

Laurent, G., Moe, G., Hu, X., Leong-Poi, H., Connelly, K. A., So, P. P., Ramadeen, A., Doumanovskaia, L., Konig, A., Trogadis, J., Courtman, D., Strauss, B., & Dorian, P. (2008b). Experimental studies of atrial fibrillation: a comparison of two pacing models. *Am J Physiol* 294, H1206-H1215..

Lee, K. W., Everett, T. H., Rahmutula, D., Guerra, J. M., Wilson, E., Ding, C., & Olgin, J. E. (2006). Pirfenidone prevents the development of a vulnerable substrate for atrial fibrillation in a canine model of heart failure. *Circulation* 114, 1703-1712.

Lee, S. H., Yu, W. C., Cheng, J. J., Hung, C. R., Ding, Y. A., Chang, M. S., & Chen, S. A. (2000). Effect of verapamil on long-term tachycardia-induced atrial electrical remodeling. *Circulation* 101, 200-206.

Lenaerts, I., Bito V, Heinzel FR, Driesen RB, Holemans P, D'hooge J, Heidbuchel H, Sipido KR, & Willems R (2009). Ultrastructural and functional remodeling of the coupling between Ca^{2+} influx and sarcoplasmic reticulum Ca^{2+} release in right atrial myocytes from experimental persistent atrial fibrillation. *Circ Res* 105, 876-885.

Li, D., Benardeau, A., & Nattel, S. (2000). Contrasting efficacy of dofetilide in differing experimental models of atrial fibrillation. *Circulation* 102, 104-112.

Li, D., Fareh, S., Leung, T. K., & Nattel, S. (1999). Promotion of atrial fibrillation by heart failure in dogs. Atrial remodeling of a different sort. *Circulation* 100, 87-95.

Li, D., Shinagawa, K., Pang, L., Leung, T. K., Cardin, S., Wang Z, & Nattel S (2001). Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. *Circulation* 104, 2608-2614.

Li, J., McLerie, M., & Lopatin, A. N. (2004). Transgenic upregulation of I_{K1} in the mouse heart leads to multiple abnormalities of cardiac excitability. *Am J Physiol* 287, H2790-H2802.

Li, Y., Li WM, Gong YT, Li BX, Liu W, Han W, Dong D, Sheng L, Xue JY, Zhang L, Chu S, & Yang BF (2007). The effects of cilazapril and valsartan on the mRNA and protein expressions of atrial calpains and atrial structural remodeling in atrial fibrillation dogs. *Basic Res Cardiol* 102, 245-256.

Linz, D. K., Afkham, F., Itter, G., Rutten, H., & Wirth, K. J. (2007). Effect of atrial electrical remodeling on the efficacy of antiarrhythmic drugs: comparison of amiodarone with I_{Kr}- and I_{to}/I_{Kur}-blockade in vivo. *J Cardiovasc Electrophysiol* 18, 1313-1320.

Loughrey, C. M., Otani, N., Seidler, T., Craig, M. A., Matsuda, R., Kaneko, N., & Smith, G. L. (2007). K201 modulates excitation-contraction coupling and spontaneous Ca^{2+} release in normal adult rabbit ventricular cardiomyocytes. *Cardiovasc Res* 76, 236-246.

Mancarella, S., Yue, Y., Karnabi, E., Qu, Y., El-Sherif, N., & Boutjdir, M. (2008). Impaired Ca^{2+} homeostasis is associated with atrial fibrillation in the α_{1D} L-type Ca^{2+} channel KO mouse. *Am J Physiol* 295, H2017-H2024.

Manning, A., Thisse, V., Hodeige, D., Richard, J., Heyndrickx, J. P., & Chatelain, P. (1995). SR 33589, a new amiodarone-like antiarrhythmic agent: electrophysiological effects in anesthetized dogs. *J Cardiovasc Pharmacol* 25, 252-261.

Matsumoto, N., Khrestian, C. M., Ryu, K., Lacerda, A. E., Brown, A. M., & Waldo, A. L. (2010). Vanoxerine, a new drug for terminating atrial fibrillation and flutter. *J Cardiovasc Electrophysiol* 21, 311-319.

Maury, P. & Zimmermann, M. (2004). Effect of chronic amiodarone therapy on excitable gap during typical human atrial flutter. *J Cardiovasc Electrophysiol* 15, 1416-1423.

Minami, T., Isomoto, S., Nakao, K., Komiya, N., Fukae, S., Centurion, O. A., & Yano, K. (2004). Effects of intravenous nifekalant, a class III antiarrhythmic drug, on atrial vulnerability parameters in patients with paroxysmal atrial fibrillation. *PACE-Pacing Clin Electrophysiol* 27, 212-217.

Miyauchi, Y., Zhou, S., Okuyama, Y., Miyauchi, M., Hayashi, H., Hamabe, A., Fishbein, M. C., Mandel, W. J., Chen, L. S., Chen, P. S., & Karagueuzian, H. S. (2003). Altered atrial electrical restitution and heterogeneous sympathetic hyperinnervation in hearts with chronic left ventricular myocardial infarction. Implications for atrial fibrillation. *Circulation* 108, 360-366.

Moe, G. W., Stopps, T. P., Angus, C., Forster, C., De Bold, A. J., & Armstrong, P. W. (1989). Alterations in serum sodium in relation to atrial natriuretic factor and other neuroendocrine variables in experimental pacing-induced heart failure. *J Am Coll Cardiol* 13, 173-179.

Morillo, C. A., Klein, G. J., Jones, D. L., & Guiraudon, C. M. (1995). Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. *Circulation* 91, 1588-1595.

Nagasawa, H., Fujiki, A., Fujikura, N., Matsuda, T., Yamashita, T., & Inoue, H. (2002). Effects of a novel class III antiarrhythmic agent, NIP-142, on canine atrial fibrillation and flutter. *Circ J* 66, 185-191.

Nakashima, H., Gerlach, U., Schmidt, D., & Nattel, S. (2004). In vivo electrophysiological effects of a selective slow delayed-rectifier potassium channel blocker in anesthetized dogs: potential insights into class III actions. *Cardiovasc Res* 61, 705-714.

Nakashima, H. & Kumagai, K. (2007). Reverse-remodeling effects of angiotensin II type 1 receptor blocker in a canine atrial fibrillation model. *Circ J* 71, 1977-1982.

Nakashima, H., Kumagai, K., Urata, H., Gondo, N., Ideishi, M., & Arakawa, K. (2000). Angiotensin II antagonist prevents electrical remodeling in atrial fibrillation. *Circulation* 101, 2612-2617.

Nakaya, H., Furusawa, Y., Ogura, T., Tamagawa, M., & Uemura, H. (2000). Inhibitory effects of JTV-519, a novel cardioprotective drug, on potassium currents and experimental atrial fibrillation in guinea-pig hearts. *Br J Pharmacol* 131, 1363-1372.

Nattel, S., Kneller, J., Zou, R., & Leon, L. J. (2003). Mechanisms of termination of atrial fibrillation by class I antiarrhythmic drugs: evidence from clinical, experimental, and mathematical modeling studies. *J Cardiovasc Electrophysiol* 14, S133-S139.

Nattel, S., Liu, L., & St-Georges, D. (1998). Effects of the novel antiarrhythmic agent azimilide on experimental atrial fibrillation and atrial electrophysiologic properties. *Cardiovasc Res* 37, 627-635.

Neef, S., Dybkova, N., Sossalla, S., Ort, K. R., Fluschnik, N., Neumann, K., Seipelt, R., Schondube, F. A., Hasenfuss, G., & Maier, L. S. (2010). CaMKII-dependent diastolic SR Ca^{2+} leak and elevated diastolic Ca^{2+} levels in right atrial myocardium of patients with atrial fibrillation. *Circ Res* 106, 1134-1144.

Neuberger, H. R., Schotten, U., Verheule, S., Eijsbouts, S., Blaauw, Y., van Hunnik, A., & Allessie, M. (2005). Development of a substrate of atrial fibrillation during chronic atrioventricular block in the goat. *Circulation* 111, 30-37.

Nishida, K., Fujiki, A., Sakamoto, T., Iwamoto, J., Mizumaki, K., Hashimoto, N., & Inoue, H. (2007). Bepridil reverses atrial electrical remodeling and L-type calcium channel downregulation in a canine model of persistent atrial tachycardia. *J Cardiovasc Electrophysiol* 18, 765-772.

Nishida, K., Yan X, Wakili R, Comtois P, Chartier D, Harada M, Iwasaki Y, Romeo P, Maguy A, Dobrev D, Michael G, Talajic M, & Nattel S (2011). Mechanisms of atrial tachyarrhythmias associated with coronary artery occlusion in a chronic canine model. *Circulation* 123, 137-146.

Niu, G., Scherlag, B. J., Lu, Z., Ghias, M., Zhang, Y., Patterson, E., Dasari, T. W., Zacharias, S., Lazzara, R., Jackman, W. M., & Po, S. S. (2009). An acute experimental model demonstrating 2 different forms of sustained atrial tachyarrhythmias. *Circ Arrhythmia Electrophysiol* 2, 384-392.

Ohashi, N., Mitamura, H., Tanimoto, K., Fukuda, Y., Kinebuchi, O., Kurita, Y., Shiroshita-Takeshita, A., Miyoshi, S., Hara, M., Takatsuki, S., & Ogawa, S. (2004). A comparison between calcium channel blocking drugs with different potencies for T- and L-type channels in preventing atrial electrical remodeling. *J Cardiovasc Pharmacol* 44, 386-392.

Ono, N., Hayashi, H., Kawase, A., Lin, S. F., Li, H., Weiss, J. N., Chen, P. S., & Karagueuzian, H. S. (2007). Spontaneous atrial fibrillation initiated by triggered activity near the pulmonary veins in aged rats subjected to glycolytic inhibition. *Am J Physiol* 292, H639-H648.

Ortiz, J., Nozaki, A., Shimizu, A., Khrestian, C., Rudy, Y., & Waldo, A. L. (1994). Mechanism of interruption of atrial flutter by moricizine. Electrophysiological and multiplexing studies in the canine sterile pericarditis model of atrial flutter. *Circulation* 89, 2860-2869.

Ozgen, N., Dun, W., Sosunov, E. A., Anyukhovsky, E. P., Hirose, M., Duffy, H. S., Boyden, P. A., & Rosen MR (2007). Early electrical remodeling in rabbit pulmonary vein results from trafficking of intracellular SK2 channels to membrane sites. *Cardiovasc Res* 75, 758-769.

Pandit, S. V., Zlochiver S, Filgueiras-Rama D, Mironov S, Yamazaki M, Ennis SR, Noujaim SF, Workman AJ, Berenfeld O, Kalifa J, & Jalife J (2010). Targeting atrio-ventricular differences in ion channel properties for terminating acute atrial fibrillation in pigs. *Cardiovasc Res* -(In press. DOI: 10.1093/cvr/cvq359).

Pandozi, C., Gentilucci, G., Calo, L., Castro, A., Lamberti, F., Loricchio, M. L., Santini, L., Magris, B., Bulava, A., Peichl, P., & Santini, M. (2003). Relations between monophasic action potential duration and refractoriness after cardioversion of persistent atrial fibrillation: results in wash-out and amiodarone-treated patients. *Ital Heart J* 4, 257-263.

Patterson, E., Po, S. S., Scherlag, B. J., & Lazzara, R. (2005). Triggered firing in pulmonary veins initiated by *in vitro* autonomic nerve stimulation. *Heart Rhythm* 2, 624-631.

Pau, D., Workman, A. J., Kane, K. A., & Rankin, A. C. (2007). Electrophysiological and arrhythmogenic effects of 5-hydroxytryptamine on human atrial cells are reduced in atrial fibrillation. *J Mol Cell Cardiol* 42, 54-62.

Piccini, J. P., Hasselblad, V., Peterson, E. D., Washam, J. B., Califf, R. M., & Kong, D. F. (2009). Comparative efficacy of dronedarone and amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation. *J Am Coll Cardiol* 54, 1089-1095.

Power, J. M., Beacom, G. A., Alferness, C. A., Raman, J., Wijffels, M., Farish, S. J., Burrell, L. M., & Tonkin, A. M. (1998). Susceptibility to atrial fibrillation: a study in an ovine model of pacing-induced early heart failure. *J Cardiovasc Electrophysiol* 9, 423-435.

Rahme, M. M., Cotter, B., Leistad, E., Wadhwa, M. K., Mohabir, R., Ford APDW, Eglen, R. M., & Feld, G. K. (1999). Electrophysiological and antiarrhythmic effects of the atrial selective 5-HT_4 receptor antagonist RS-100302 in experimental atrial flutter and fibrillation. *Circulation* 100, 2010-2017.

Rahme, M. M., Ungab G, Wadhwa, M., Al-Kandari, F., Yao, B., Gupta, A., Lee, K., Kim, H. Y., & Feld, G. K. (2001). Electrophysiologic and antiarrhythmic effects of the new class III antiarrhythmic drug KCB-328 in experimental canine atrial flutter. *J Cardiovasc Pharmacol Ther* 6, 297-306.

Raine, A. E. G. & Vaughan Williams, E. M. (1981). Adaptation to prolonged β-blockade of rabbit atrial, Purkinje, and ventricular potentials, and of papillary muscle contraction. Time-course of development of and recovery from adaptation. *Circ Res* 48, 804-812.

Ramadeen, A., Laurent, G., dos Santos, C. C., Hu, X., Connelly, K. A., Holub, B. J., Mangat, I., & Dorian, P. (2010). n-3 Polyunsaturated fatty acids alter expression of fibrotic and hypertrophic genes in a dog model of atrial cardiomyopathy. *Heart Rhythm* 7, 520-528.

Rankin, A. C. & Workman, A. J. (2009). Duration of heart failure and the risk of atrial fibrillation: different mechanisms at different times? *Cardiovasc Res* 84, 180-181.

Ravens, U. (2010). Antiarrhythmic therapy in atrial fibrillation. *Pharmacol Ther* 128, 129-145.

Redpath, C. J., Rankin, A. C., Kane, K. A., & Workman, A. J. (2006). Anti-adrenergic effects of endothelin on human atrial action potentials are potentially anti-arrhythmic. *J Mol Cell Cardiol* 40, 717-724.

Reil, J. C., Hohl, M., Oberhofer, M., Kazakov, A., Kaestner, L., Mueller, P., Adam, O., Maack, C., Lipp, P., Mewis, C., Allessie, M., Laufs, U., Bohm, M., & Neuberger, H. R. (2010). Cardiac Rac1 overexpression in mice creates a substrate for atrial arrhythmias characterized by structural remodelling. *Cardiovasc Res* 87, 485-493.

Remes, J., van Brakel, T. J., Bolotin, G., Garber, C., de Jong, M. M., van der Veen, F. H., & Maessen, J. G. (2008). Persistent atrial fibrillation in a goat model of chronic left atrial overload. *J Thorac Cardiovasc Surg* 136, 1005-1011.

Rensma, P. L., Allessie, M. A., Lammers, W. J. E. P., Bonke, F. I. M., & Schalij, M. J. (1988). Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. *Circ Res* 62, 395-410.

Restivo, M., Hegazy, M., El-Hamami, M., Yin, H., Caref, E. B., Assadi, M. A., Brooks, R. R., & El-Sherif, N. (2001). Efficacy of azimilide and dofetilide in the dog right atrial enlargement model of atrial flutter. *J Cardiovasc Electrophysiol* 12, 1018-1024.

Rivard, L., Sinno, H., Shiroshita-Takeshita, A., Schram, G., Leung, T. K., & Nattel, S. (2007). The pharmacological response of ischemia-related atrial fibrillation in dogs: evidence for substrate-specific efficacy. *Cardiovasc Res* 74, 104-113.

Rossman, E. I., Liu, K., Morgan, G. A., Swillo, R. E., Krueger, J. A., Gardell, S. J., Butera, J., Gruver, M., Kantrowitz, J., Feldman, H. S., Petersen, J. S., Haugan, K., & Hennan, J. K. (2009). The gap junction modifier, GAP-134 [(2*S*,4*R*)-1-(2-aminoacetyl)-4-benzamido-pyrrolidine-2-carboxylic acid], improves conduction and reduces atrial fibrillation/flutter in the canine sterile pericarditis model. *J Pharmacol Exp Ther* 329, 1127-1133.

Rostock, T., Servatius, H., Risius, T., Ventura, R., Weiss, C., Meinertz, T., & Willems, S. (2005). Impact of amiodarone on electrophysiologic properties of pulmonary veins in patients with paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 16, 39-44.

Roy, D., Pratt, C. M., Torp-Pedersen, C., Wyse, D. G., Toft, E., Juul-Moller, S., Nielsen, T., Rasmussen, S. L., Stiell, I. G., Coutu, B., Ip, J. H., Pritchett ELC, & Camm, A. J. (2008). Vernakalant hydrochloride for rapid conversion of atrial fibrillation: a phase 3, randomized, placebo-controlled trial. *Circulation* 117, 1518-1525.

Ryu, K., Li, L., Khrestian, C. M., Matsumoto, N., Sahadevan, J., Ruehr, M. L., Van Wagoner, D. R., Efimov, I. R., & Waldo, A. L. (2007). Effects of sterile pericarditis on connexins 40 and 43 in the atria: correlation with abnormal conduction and atrial arrhythmias. *Am J Physiol* 293, H1231-H1241.

Ryu, K., Shroff, S. C., Sahadevan, J., Martovitz, N. L., Khrestian, C. M., & Stambler, B. S. (2005). Mapping of atrial activation during sustained atrial fibrillation in dogs with rapid ventricular pacing induced heart failure: evidence for a role of driver regions. *J Cardiovasc Electrophysiol* 16, 1348-1358.

Sakabe, M., Shiroshita-Takeshita A, Maguy A, Dumesnil C, Nigam A, Leung TK, & Nattel S (2007). Omega-3 polyunsaturated fatty acids prevent atrial fibrillation associated with heart failure but not atrial tachycardia remodeling. *Circulation* 116, 2101-2109.

Sakabe, M., Shiroshita-Takeshita, A., Maguy, A., Brundel BJJM, Fujiki, A., Inoue, H., & Nattel, S. (2008). Effects of a heat shock protein inducer on the atrial fibrillation substrate caused by acute atrial ischaemia. *Cardiovasc Res* 78, 63-70.

Sakamoto, T., Fujiki, A., Nakatani, Y., Sakabe, M., Mizumaki, K., Hashimoto, N., & Inoue, H. (2009). d,l-Sotalol reverses abbreviated atrial refractoriness and prevents promotion of atrial fibrillation in a canine model with left ventricular dysfunction induced by atrial tachypacing. *Circ J* 73, 1820-1828.

Sampson, K. J., Terrenoire C, Cervantes DO, Kaba RA, Peters NS, & Kass RS (2008). Adrenergic regulation of a key cardiac potassium channel can contribute to atrial fibrillation: evidence from an I_{Ks} transgenic mouse. *J Physiol* 586, 627-637.

Sanders, P., Morton, J. B., Davidson, N. C., Spence, S. J., Vohra, J. K., Sparks, P. B., & Kalman, J. M. (2003). Electrical remodeling of the atria in congestive heart failure. Electrophysiological and electroanatomic mapping in humans. *Circulation* 108, 1461-1468.

Santos, P. E., Duytschaever, M., & Allessie, M. A. (2008). Low-frequency oscillations of atrial fibrillation cycle length in goats: characterization and potentiation by class III antiarrhythmic almokalant. *J Electrocardiol* 41, 711-723.

Sarmast, F., Kolli, A., Zaitsev, A., Parisian, K., Dhamoon, A. S., Guha, P. K., Warren, M., Anumonwo JMB, Taffet, S. M., Berenfeld, O., & Jalife, J. (2003). Cholinergic atrial fibrillation: $I_{K,ACh}$ gradients determine unequal left/right atrial frequencies and rotor dynamics. *Cardiovasc Res* 59, 863-873.

Sarrazin, J. F., Comeau, G., Daleau, P., Kingma, J., Plante, I., Fournier, D., & Molin, F. (2007). Reduced incidence of vagally induced atrial fibrillation and expression levels of connexins by n-3 polyunsaturated fatty acids in dogs. *J Am Coll Cardiol* 50, 1505-1512.

Satoh, T. & Zipes, D. P. (1996). Unequal atrial stretch in dogs increases dispersion of refractoriness conducive to developing atrial fibrillation. *J Cardiovasc Electrophysiol* 7, 833-842.

Savelieva, I., Kourliouros, A., & Camm, J. (2010). Primary and secondary prevention of atrial fibrillation with statins and polyunsaturated fatty acids: review of evidence and clinical relevance. *Naunyn-Schmied Arch Pharmacol* 381, 207-219.

Sawaya, S. E., Rajawat, Y. S., Rami, T. G., Szalai, G., Price, R. L., Sivasubramanian, N., Mann, D. L., & Khoury, D. S. (2007). Downregulation of connexin40 and increased prevalence of atrial arrhythmias in transgenic mice with cardiac-restricted overexpression of tumor necrosis factor. *Am J Physiol* 292, H1561-H1567.

Schauerte, P., Scherlag, B. J., Patterson, E., Scherlag, M. A., Matsudaria, K., Nakagawa, H., Lazzara, R., & Jackman, W. M. (2001). Focal atrial fibrillation: experimental evidence for a pathophysiologic role of the autonomic nervous system. *J Cardiovasc Electrophysiol* 12, 592-599.

Shan, Z., Van Der Voort, P. H., Blaauw, Y., Duytschaever, M., & Allessie, M. A. (2004). Fractionation of electrograms and linking of activation during pharmacologic cardioversion of persistent atrial fibrillation in the goat. *J Cardiovasc Electrophysiol* 15, 572-580.

Shimano, M., Tsuji, Y., Inden, Y., Kitamura, K., Uchikawa, T., Harata, S., Nattel, S., & Murohara, T. (2008). Pioglitazone, a peroxisome proliferator-activated receptor-gamma activator, attenuates atrial fibrosis and atrial fibrillation promotion in rabbits with congestive heart failure. *Heart Rhythm* 5, 451-459.

Shimizu, A., Fukatani, M., Tanigawa, M., Kaibara, M., Konoe, A., Isomoto, S., Centurion, O. A., Yano, K., & Hashiba, K. (1994). Mechanism of the suppression of repetitive atrial firing by isoproterenol-comparison with disopyramide. *Int J Cardiol* 43, 175-183.

Shinagawa, K., Li, D., Leung, T. K., & Nattel, S. (2002a). Consequences of atrial tachycardia-induced remodeling depend on the preexisting atrial substrate. *Circulation* 105, 251-257.

Shinagawa, K., Mitamura, H., Ogawa, S., & Nattel, S. (2002b). Effects of inhibiting Na^+/H^+-exchange or angiotensin converting enzyme on atrial tachycardia-induced remodeling. *Cardiovasc Res* 54, 438-446.

Shinagawa, K., Mitamura, H., Takeshita, A., Sato, T., Kanki, H., Takatsuki, S., & Ogawa, S. (2000). Determination of refractory periods and conduction velocity during atrial fibrillation using atrial capture in dogs: direct assessment of the wavelength and its modulation by a sodium channel blocker, pilsicainide. *J Am Coll Cardiol* 35, 246-253.

Shinagawa, K., Shi, YF., Tardif, JC., Leung, TK., & Nattel, S. (2002c). Dynamic nature of atrial fibrillation substrate during development and reversal of heart failure in dogs. *Circulation* 105, 2672-2678.

Shinagawa, K., Shiroshita-Takeshita, A., Schram, G., & Nattel, S. (2003). Effects of antiarrhythmic drugs on fibrillation in the remodeled atrium: insights into the mechanism of the superior efficacy of amiodarone. *Circulation* 107, 1440-1446.

Shiroshita-Takeshita, A., Brundel BJJM, Burstein, B., Leung, TK., Mitamura, H., Ogawa, S., & Nattel, S. (2007a). Effects of simvastatin on the development of the atrial fibrillation substrate in dogs with congestive heart failure. *Cardiovasc Res* 74, 75-84.

Shiroshita-Takeshita, A., Brundel BJJM, Lavoie, J., & Nattel, S. (2006). Prednisone prevents atrial fibrillation promotion by atrial tachycardia remodeling in dogs. *Cardiovasc Res* 69, 865-875.

Shiroshita-Takeshita, A., Sakabe, M., Haugan, K., Hennan, J. K., & Nattel, S. (2007b). Model-dependent effects of the gap junction conduction-enhancing antiarrhythmic peptide rotigaptide (ZP123) on experimental atrial fibrillation in dogs. *Circulation* 115, 310-318.

Shiroshita-Takeshita, A., Schram, G., Lavoie, J., & Nattel, S. (2004). Effect of simvastatin and antioxidant vitamins on atrial fibrillation promotion by atrial-tachycardia remodeling in dogs. *Circulation* 110, 2313-2319.

Shroff, S. C., Ryu, K., Martovitz, N. L., Hoit, B. D., & Stambler, B. S. (2006). Selective aldosterone blockade suppresses atrial tachyarrhythmias in heart failure. *J Cardiovasc Electrophysiol* 17, 534-541.

Sicouri, S., Belardinelli, L., Carlsson, L., & Antzelevitch C (2009). Potent antiarrhythmic effects of chronic amiodarone in canine pulmonary vein sleeve preparations. *J Cardiovasc Electrophysiol* 20, 803-810.

Sicouri, S., Burashnikov, A., Belardinelli, L., & Antzelevitch C (2010). Synergistic electrophysiologic and antiarrhythmic effects of the combination of ranolazine and chronic amiodarone in canine atria. *Circ Arrhythmia Electrophysiol.* 3, 88-95.

Sicouri, S., Glass, A., Belardinelli, L., & Antzelevitch C (2008). Antiarrhythmic effects of ranolazine in canine pulmonary vein sleeve preparations. *Heart Rhythm* 5, 1019-1026.

Singh, B. N., Connolly, S. J., Crijns HJGM, Roy, D., Kowey, P. R., Capucci, A., Radzik, D., Aliot, E. M., & Hohnloser, S. H. (2007). Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 357, 987-999.

Smeets, J. L. R. M., Allessie, M. A., Lammers WJEP, Bonke FIM, & Hollen, J. (1986). The wavelength of the cardiac impulse and reentrant arrhythmias in isolated rabbit atrium. The role of heart rate, autonomic transmitters, temperature, and potassium. *Circ Res* 58, 96-108.

Solti, F., Vecsey, T., Kekesi, V., & Juhasz-Nagy, A. (1989). The effect of atrial dilatation on the genesis of atrial arrhythmias. *Cardiovasc Res* 23, 882-886.

Sood, S., Chelu, M. G., van Oort, R. J., Skapura, D., Santonastasi, M., Dobrev, D., & Wehrens XHT (2008). Intracellular calcium leak due to FKBP12.6 deficiency in mice facilitates the inducibility of atrial fibrillation. *Heart Rhythm* 5, 1047-1054.

Sossalla, S., Kallmeyer, B., Wagner, S., Mazur, M., Maurer, U., Toischer, K., Schmitto, J. D., Seipelt, R., Schondube, F. A., Hasenfuss, G., Belardinelli, L., & Maier, L. S. (2010). Altered Na^+ currents in atrial fibrillation. Effects of ranolazine on arrhythmias and contractility in human atrial myocardium. *J Am Coll Cardiol* 55, 2330-2342.

Sridhar, A., da Cunha DNQ, Lacombe, V. A., Zhou, Q., Fox, J. J., Hamlin, R. L., & Carnes, C. A. (2007). The plateau outward current in canine ventricle, sensitive to 4-aminopyridine, is a constitutive contributor to ventricular repolarization. *Br J Pharmacol* 152, 870-879.

Sridhar, A., Nishijima Y, Terentyev D, Khan M, Terentyeva R, Hamlin RL, Nakayama T, Gyorke S, Cardounel AJ, & Carnes CA (2009). Chronic heart failure and the substrate for atrial fibrillation. *Cardiovasc Res* 84, 227-236.

Stambler, B. S., Fenelon, G., Shepard, R. K., Clemo, H. F., & Guiraudon, C. M. (2003). Characterization of sustained atrial tachycardia in dogs with rapid ventricular pacing-induced heart failure. *J Cardiovasc Electrophysiol* 14, 499-507.

Stambler, B. S., Wood, M. A., & Ellenbogen, K. A. (1996). Pharmacologic alterations in human type I atrial flutter cycle length and monophasic action potential duration. Evidence of a fully excitable gap in the reentrant circuit. *J Am Coll Cardiol* 27, 453-461.

Stevenson, I. H., Roberts-Thomson KC, Kistler PM, Edwards GA, Spence S, Sanders P, & Kalman JM (2010). Atrial electrophysiology is altered by acute hypercapnia but not hypoxemia: implications for promotion of atrial fibrillation in pulmonary disease and sleep apnea. *Heart Rhythm* 7, 1263-1270.

Sticherling, C., Hsu, W., Tada, H., Bares, A. C., Oral, H., Pelosi, F., Knight, B. P., Strickberger, S. A., & Morady, F. (2002). Effects of verapamil and ibutilide on atrial fibrillation and postfibrillation atrial refractoriness. *J Cardiovasc Electrophysiol* 13, 151-157.

Sticherling, C., Oral, H., Horrocks, J., Chough, S. P., Baker, R. L., Kim, M. H., Wasmer, K., Pelosi, F., Knight, B. P., Michaud, G. F., Strickberger, S. A., & Morady, F. (2000). Effects of digoxin on acute, atrial fibrillation-induced changes in atrial refractoriness. *Circulation* 102, 2503-2508.

Stump, G. L., Wallace, A. A., Regan, C. P., & Lynch, J. J., Jr. (2005). In vivo antiarrhythmic and cardiac electrophysiologic effects of a novel diphenylphosphine oxide I_{Kur} blocker (2-isopropyl-5-methylcyclohexyl) diphenylphosphine oxide. *J Pharmacol Exp Ther* 315, 1362-1367.

Tai, C. T., Chen, S. A., Feng, A. N., Yu, W. C., Chen, Y. J., & Chang, M. S. (1998). Electropharmacologic effects of class I and class III antiarrhythmia drugs on typical atrial flutter: insights into the mechanism of termination. *Circulation* 97, 1935-1945.

Tang, M., Zhang, S., Sun, Q., Hua, W., & Huang, C. X. (2006). Effect of nifekalant on acute electrical remodelling in rapid atrial pacing canine model. *Chin Med J* 119, 2056-2061.

Temple, J., Frias, P., Rottman, J., Yang, T., Wu, Y., Verheijck, E. E., Zhang, W., Siprachanh, C., Kanki, H., Atkinson, J. B., King, P., Anderson, M. E., Kupershmidt, S., & Roden, D. M. (2005). Atrial fibrillation in KCNE1-null mice. *Circ Res* 97, 62-69.

Tieleman, R. G., Blaauw Y, Van Gelder IC, De Langen CDJ, de Kam PJ, Grandjean JG, Patberg KW, Bel KJ, Allessie MA, & Crijns HJGM (1999). Digoxin delays recovery from tachycardia-induced electrical remodeling of the atria. *Circulation* 100, 1836-1842.

Tse, H. F. & Lau, C. P. (2002). Electrophysiologic actions of *dl*-sotalol in patients with persistent atrial fibrillation. *J Am Coll Cardiol* 40, 2150-2155.

Tse, H. F., Pelosi, F., Oral, H., Knight, B. P., Strickberger, S. A., & Morady, F. (2001). Effects of simultaneous atrioventricular pacing on atrial refractoriness and atrial fibrillation inducibility: role of atrial mechanoelectrical feedback. *J Cardiovasc Electrophysiol* 12, 43-50.

Tuan, J., Osman, F., Jeilan, M., Kundu, S., Mantravadi, R., Stafford, P. J., & Ng, G. A. (2010). Increase in organization index predicts atrial fibrillation termination with flecainide post-ablation: spectral analysis of intracardiac electrograms. *Europace* 12, 488-493.

Van Wagoner, D. R., Pond, A. L., McCarthy, P. M., Trimmer, J. S., & Nerbonne, J. M. (1997). Outward K^+ current densities and Kv1.5 expression are reduced in chronic human atrial fibrillation. *Circ Res* 80, 772-781.

Vardas, P. E., Vemmos, K., Sideris, D. A., & Moulopoulos, S. D. (1993). Susceptibility of the right and left canine atria to fibrillation in hyperglycemia and hypoglycemia. *J Electrocardiol* 26, 147-153.

Varro , A., Takacs, J., Nemeth, M., Hala, O., Virag, L., Iost, N., Balati, B., Agoston, M., Vereckei, A., Pastor, G., Delbruyere, M., Gautier, P., Nisato, D., & Papp, J. G. (2001). Electrophysiological effects of dronedarone (SR 33589), a noniodinated amiodarone derivative in the canine heart: comparison with amiodarone. *Br J Pharmacol* 133, 625-634.

Vaughan Williams, E. M. (1984). A classification of antiarrhythmic actions reassessed after a decade of new drugs. *J Clin Pharmacol* 24, 129-147.

Verduyn, S. C., Vos, M. A., Leunissen HDM, van Opstal, J. M., & Wellens HJJ (1999). Evaluation of the acute electrophysiologic effects of intravenous dronedarone, an amiodarone-like agent, with special emphasis on ventricular repolarization and acquired torsade de pointes arrhythmias. *J Cardiovasc Pharmacol* 33, 212-222.

Vereckei, A., Gorski, J. C., Ujhelyi, M., Mehra, R., & Zipes, D. P. (2004). Intrapericardial ibutilide administration fails to terminate pacing-induced sustained atrial fibrillation in dogs. *Cardiovasc Drugs Ther* 18, 269-277.

Vereckei, A., Warman, E., Mehra, R., & Zipes, D. P. (2001). Comparison of the effects on drug concentrations, electrophysiologic parameters, and termination of atrial fibrillation in dogs when procainamide and ibutilide are delivered into the right atrium versus intravenously. *J Cardiovasc Electrophysiol* 12, 330-336.

Verheule, S., Wilson, E., Everett, T., Shanbhag, S., Golden, C., & Olgin, J. (2003). Alterations in atrial electrophysiology and tissue structure in a canine model of chronic atrial dilatation due to mitral regurgitation. *Circulation* 107, 2615-2622.

Wang , Z., Page P, & Nattel S (1992). Mechanism of flecainide's antiarrhythmic action in experimental atrial fibrillation. *Circ Res* 71, 271-287.

Wang, J., Bourne, G. W., Wang Z, Villemaire, C., Talajic, M., & Nattel, S. (1993). Comparative mechanisms of antiarrhythmic drug action in experimental atrial fibrillation. Importance of use-dependent effects on refractoriness. *Circulation* 88, 1030-1044.

Wang, J., Feng, J., & Nattel, S. (1994). Class III antiarrhythmic drug action in experimental atrial fibrillation. Differences in reverse use dependence and effectiveness between *d*-sotalol and the new antiarrhythmic drug ambasilide. *Circulation* 90, 2032-2040.

Wann, L. S., Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes III NAM, Page RL, Ezekowitz MD, Slotwiner DJ, Jackman WM, Stevenson WG, & Tracy CM (2011). 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline). A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Heart Rhythm* 8, 157-176.

Watanabe, H., Chopra, N., Laver, D., Hwang, H. S., Davies, S. S., Roach, D. E., Duff, H. J., Roden, D. M., Wilde AAM, & Knollmann, B. C. (2009). Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. *Nat Med* 15, 380-383.

Wijffels, M. C. E. F., Dorland, R., & Allessie, M. A. (1999). Pharmacologic cardioversion of chronic atrial fibrillation in the goat by class IA, IC, and III drugs: a comparison between hydroquinidine, cibenzoline, flecainide, and d-sotalol. *J Cardiovasc Electrophysiol* 10, 178-193.

Wijffels, M. C. E. F., Dorland, R., Mast, F., & Allessie, M. A. (2000). Widening of the excitable gap during pharmacological cardioversion of atrial fibrillation in the goat: effects of cibenzoline, hydroquinidine, flecainide, and d-sotalol. *Circulation* 102, 260-267.

Wijffels, M. C. E. F., Kirchhof CJHJ, Dorland R, & Allessie, MA. (1995). Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation* 92, 1954-1968.

Wijffels, M. C. E. F., Kirchhof, C., Dorland, R., Power, J., & Allessie, M. A. (1997). Electrical remodeling due to atrial fibrillation in chronically instrumented conscious goats. Roles of neurohumoral changes, ischemia, atrial stretch, and high rate of electrical activation. *Circulation* 96, 3710-3720.

Winslow, E. (1981). Hemodynamic and arrhythmogenic effects of aconitine applied to the left atria of anesthetized cats. Effects of amiodarone and atropine. *J Cardiovasc Pharmacol* 3, 87-100.

Wit, A. L. & Boyden, P. A. (2007). Triggered activity and atrial fibrillation. *Heart Rhythm* 4, S17-S23.

Workman, A. J. (2010). Cardiac adrenergic control and atrial fibrillation. *Naunyn-Schmied Arch Pharmacol* 381, 235-249.

Workman, A. J., Kane KA, & Rankin AC (2001). The contribution of ionic currents to changes in refractoriness of human atrial myocytes associated with chronic atrial fibrillation. *Cardiovasc Res* 52, 226-235.

Workman, A. J., Kane KA, & Rankin AC (2003a). Characterisation of the Na, K pump current in atrial cells from patients with and without chronic atrial fibrillation. *Cardiovasc Res* 59, 593-602.

Workman, A. J., Kane KA, & Rankin AC (2008). Cellular bases for human atrial fibrillation. *Heart Rhythm* 5, S1-S6..

Workman, A. J., Kane KA, Russell JA, Norrie J, & Rankin AC (2003b). Chronic beta-adrenoceptor blockade and human atrial cell electrophysiology: evidence of pharmacological remodelling. *Cardiovasc Res* 58, 518-525.

Workman, A. J., MacKenzie I, & Northover BJ (2000). Do K_{ATP} channels open as a prominent and early feature during ischaemia in the Langendorff-perfused rat heart? *Basic Res Cardiol* 95, 250-260.

Workman, A. J., Pau D, Redpath, C. J., Marshall GE, Russell JA, Norrie J, Kane KA, & Rankin AC (2009). Atrial cellular electrophysiological changes in patients with ventricular dysfunction may predispose to AF. *Heart Rhythm* 6, 445-451.

Workman, A. J., Pau, D., Redpath, C. J., Marshall, G. E., Russell, J. A., Kane, K. A., Norrie, J., & Rankin, A. C. (2006). Post-operative atrial fibrillation is influenced by beta-blocker therapy but not by pre-operative atrial cellular electrophysiology. *J Cardiovasc Electrophysiol* 17, 1230-1238.

Yeh, Y. H., Wakili R, Qi XY, Chartier D, Boknik P, Kaab S, Ravens U, Coutu P, Dobrev D, & Nattel S (2008). Calcium-handling abnormalities underlying atrial arrhythmogenesis and contractile dysfunction in dogs with congestive heart failure. *Circ Arrhythmia Electrophysiol* 1, 93-102.

Yu, W. C., Chen, S. A., Lee, S. H., Tai, C. T., Feng, A. N., Kuo BIT, Ding, Y. A., & Chang, M. S. (1998). Tachycardia-induced change of atrial refractory period in humans: rate dependency and effects of antiarrhythmic drugs. *Circulation* 97, 2331-2337.

Yue, L., Feng, J., Gaspo, R., Li, G. R., Wang, Z., & Nattel, S. (1997). Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation. *Circ Res* 81, 512-525.

Zankov, D. P., Omatsu-Kanbe, M., Isono, T., Toyoda, F., Ding, W. G., Matsuura, H., & Horie, M. (2006). Angiotensin II potentiates the slow component of delayed rectifier K^+ current via the AT_1 receptor in guinea pig atrial myocytes. *Circulation* 113, 1278-1286.

Zhang, C., Yasuno, S., Kuwahara, K., Zankov, D. P., Kobori, A., Makiyama, T., & Horie, M. (2006). Blockade of angiotensin II type 1 receptor improves the arrhythmia morbidity in mice with left ventricular hypertrophy. *Circ J* 70, 335-341.

Zhang, S., Zhou Z, Gong Q, Makielski JC, & January CT (1999). Mechanism of block and identification of the verapamil binding domain to HERG potassium channels. *Circ Res* 84, 989-998.

Zhang, Z., He, Y., Tuteja, D., Xu, D., Timofeyev, V., Zhang, Q., Glatter, K. A., Xu, Y., Shin, H. S., Low, R., & Chiamvimonvat, N. (2005). Functional roles of $Ca_v1.3(\alpha_{1D})$ calcium channels in atria. Insights gained from gene-targeted null mutant mice. *Circulation* 112, 1936-1944.

Zhao, J., Li J, Li W, Li Y, Shan H, Gong Y, & Yang B (2010). Effects of spironolactone on atrial structural remodelling in a canine model of atrial fibrillation produced by prolonged atrial pacing. *Br J Pharmacol* 159, 1584-1594.

Zhao, Z., Fefelova N, Shanmugam M, Bishara P, Babu GJ, & Xie LH (2011). Angiotensin II induces afterdepolarizations via reactive oxygen species and calmodulin kinase II signaling. *J Mol Cell Cardiol* 50, 128-136.

Acknowledgements

British Heart Foundation for financial support (Basic Science Lectureship Award, renewal: BS/06/003)

[Figure legend]

Figure 1

Overview of *in-vivo* electrophysiological mechanisms of AF and their pharmacological termination or prevention. Diagram shows main reentrant and non-reentrant arrhythmia mechanisms predisposing to (constituting a “substrate” for) AF, along with the drug types which inhibit them. λ=reentry circuit wavelength; ERP=effective refractory period; θ=conduction velocity; EG=excitable gap; AFCL=AF cycle length; AA=abnormal automaticity; EAD=early afterdepolarisation; DAD=delayed afterdepolarisation; TA=triggered activity; class I-IV=Vaughan Williams class of anti-arrhythmic drug; UT=upstream therapy; ID=investigational anti-arrhythmic drug; “?”=potential drug action or non-reentrant mechanism: requires confirmation *in-vivo*

[Tables, with legends]

Table 1

In-vivo animal models and clinical studies of AF used, or not used* for drug investigations, showing pathology-induced changes in atrial electrophysiology

***In-vivo* model /clinical study**	**Species**	**AF**	**ERP**	**θ**	**λ**	**CL**	**Refs**
Ventricular MI*	Dog	↑inc/dur	↔	↓			Miyauchi *et al.*, 2003
HF: VTP 16wk*	Dog	↑dur	↓				Sridhar *et al.*, 2009
HF: VTP 2-6wk	Sheep, dog, rabbit	↑vul/inc /dur	↔/↑	↔/↓	↔	↑/↔	Power *et al.*, 1998; Li *et al.*, 1999; Shinagawa *et al.*, 2002c; Stambler *et al.*, 2003; Cha *et al.*, 2004; Shroff *et al.*, 2006; Shimano *et al.*, 2008; Laurent *et al.*, 2008b
HF: VTP+ATP	Dog	↑/↔vul /↑dur	↔/↓	↓			Shinagawa *et al.*, 2002a; Shinagawa *et al.*, 2002c; Laurent *et al.*, 2008a; Ramadeen *et al.*, 2010
LVH	Mouse	↑vul	↔				Zhang *et al.*, 2006
Clinical HF*	Human	↑vul	↔/↑	↓			Sanders *et al.*, 2003
Chronic atrial dilation	Goat, sheep dog	↑vul/↔inc /↑dur	↑/↔	↓/↔		↔	Boyden & Hoffman, 1981; Restivo *et al.*, 2001; Verheule *et al.*, 2003; Deroubaix *et al.*, 2004; Neuberger *et al.*, 2005; Remes *et al.*, 2008; Greiser *et al.*, 2009
Clinical atrial dil.*	Human		↑				Chen *et al.*, 1998
Acute atrial dil.	Human goat, dog	↑vul	↓/↑/↔	↓		↔	Solti *et al.*, 1989; Satoh & Zipes, 1996; Wijffels *et al.*, 1997; Tse *et al.*, 2001
Hypertension*	Sheep	↑vul/dur	↔/↑	↓	↓		Kistler *et al.*, 2006; Lau *et al.*, 2010
Cholinergic-stim.	Dog, mouse	↑vul/inc	↓	↔	↓		Rensma *et al.*, 1988; Hayashi *et al.*, 1998; Fedorov *et al.*, 2000; Kovoor *et al.*, 2001; Sarrazin *et al.*, 2007
Adrenergic-stim.*	Human, dog, mouse	↑vul/inc	↔/↓	↔/↑	↔/↑	↓	Rensma *et al.*, 1988; Shimizu *et al.*, 1994; Stambler *et al.*, 1996; Kiss *et al.*, 2004; Sampson *et al.*, 2008
Local nerve-stim.	Dog	↑inc	↓				Schauerte *et al.*, 2001
Pericarditis	Dog	↑vul/dur	↓	↓			Kumagai *et al.*, 2004; Ryu *et al.*, 2007
Atrial ischaemia	Dog	↑dur	↔/↑/↓	↓		↔	Jayachandran *et al.*, 2000; Rivard *et al.*, 2007; Sakabe *et al.*, 2008
Atrial infarction*	Dog	↔vul/↑dur	↔				Nishida *et al.*, 2011
Hypercapnoea-reversal*	Sheep	↑vul	↓	↓			Stevenson *et al.*, 2010
Asphyxia	Rat	↑vul/dur					Haugan *et al.*, 2004; Diness *et al.*, 2010
Hypoglycaemia*	Dog	↑vul	↓				Vardas *et al.*, 1993
Atrial injury	Dog	↑vul					Feld & Shahandeh-Rad, 1992; Jalil *et al.*, 1997
Aconitine	Dog, cat	↑inc					Winslow, 1981; Hashimoto *et al.*, 2006
↓/↑ ion channel*	T-mouse	↑vul/inc	↓/↔				Li *et al.*, 2004; Temple *et al.*, 2005; Zhang *et al.*, 2005; Mancarella *et al.*, 2008
↓connexin*	T-mouse	↑vul		↓			Hagendorff *et al.*, 1999
↑ROS/fibrosis/inflam.	T-mouse	↑vul/inc	↔/↑	↓			Sawaya *et al.*, 2007; Reil *et al.*, 2010
↓/↑Ca^{2+}_i protein	T-mouse	↑vul	↔	↔			Sood *et al.*, 2008; Chelu *et al.*, 2009
Chronic AF	Pig, goat	↑vul/dur	↓	↔	↓	↓/↔	Wijffels *et al.*, 1995; Bauer *et al.*, 2005; Eijsbouts *et al.*, 2006; Greiser *et al.*, 2009
Chronic ATP	Sheep, dog	↑vul/↔/↑inc /↑dur	↓	↓/↔	↓	↓	Morillo *et al.*, 1995; Gaspo *et al.*, 1997; Li *et al.*, 1999; Fareh *et al.*, 2001; Tang *et al.*, 2006; Anne *et al.*, 2007; Nakashima & Kumagai, 2007; Lenaerts *et al.*, 2009; Zhao *et al.*, 2010
Clinical AF	Human		↓	↓		↓	Kumagai *et al.*, 1991; Fujiki *et al.*, 2001; Kim *et al.*, 2002; Kojodjojo *et al.*, 2007
Acute ATP	Human	↑inc	↓			↓	Yu *et al.*, 1998; Biffi *et al.*, 1999; Sticherling *et al.*, 2000

Arrows show reported direction of change in atrial fibrillation (AF) vulnerability (vul), incidence (inc) and duration (dur); atrial effective refractory period (ERP), conduction velocity (θ) and reentry wavelength (λ); and AF cycle length (CL), in various animal models of AF, relative to a pre-intervention control; or associated with the presence of a clinical disease; from selected representative references. MI=myocardial infarction; HF=heart failure; VTP=ventricular tachypacing; ATP=atrial tachypacing; LVH=left ventricular hypertrophy; T-mouse=transgenic mouse; ROS=reactive O_2 species; Ca^{2+}_i=intracellular Ca^{2+}; Acute ATP=atrial tachypacing-induced brief (5-10min) episodes of AF in patients

Table 2

In-vivo effects of class I anti-arrhythmic drugs (Na^+ channel blockers) on AF and atrial electrophysiology in animal models or clinical studies of AF

Drug Class I	*In-vivo* model /clinical study	Species	AF	ERP	θ	λ	CL	Refs
Cibenzoline	Chronic AF	Goat	Term/↔vul	↑	↓	↔/↓	↑	Wijffels *et al.*, 1999; Wijffels *et al.*, 2000; Shan *et al.*, 2004; Eijsbouts *et al.*, 2006
	Acute ATP	Human	Term				↑	Brugada *et al.*, 1993
	Clinical AF	Human	Term				↑	Brugada *et al.*, 1993; Fujiki *et al.*, 2001
Disopyramide	Atrial injury	Dog	Term	↑			↑	Inoue *et al.*, 1991
	Clinical AF	Human	↓vul	↑	↓			Ishibashi *et al.*, 1995
Flecainide	Cholinergic-stim.	Dog	Term/↓dur	↑	↓	↑	↑	Wang *et al.*, 1992; Rivard *et al.*, 2007
	Atrial ischaemia	Dog	↔dur	↔	↔		↑	Rivard *et al.*, 2007
	Asphyxia	Rat	↓dur/↔vul					Haugan *et al.*, 2004
	Chronic AF/ATP	Goat, dog	Term/ ↔vul/dur	↔/↑	↔/↓	↔/↓	↑	Wijffels *et al.*, 1999; Wijffels *et al.*, 2000; Shinagawa *et al.*, 2003; Duytschaever *et al.*, 2005; Eijsbouts *et al.*, 2006
	Acute ATP	Human	Term				↑	Biffi *et al.*, 1999
	Clinical AF	Human	Term	↑			↑	Kirchhof *et al.*, 2005; Tuan *et al.*, 2010
Lidocaine	Cholinergic-stim.	Dog	Term					David *et al.*, 1990
Moricizine	Pericarditis	Dog	Term	↑	↓		↑	Ortiz *et al.*, 1994
Pilsicainide	Cholinergic-stim.	Dog	Term	↑	↓	↑	↑	Hayashi *et al.*, 1998; Kanki *et al.*, 1998; Shinagawa *et al.*, 2000
Procainamide	Cholinergic-stim.	Dog	Term/↓inc	↑	↓	↑	↑	Wang *et al.*, 1993; Vereckei *et al.*, 2001
	Atrial injury	Dog		↑			↑	Derakhchan *et al.*, 1994; Jalil *et al.*, 1997
	Acute ATP	Human	↓inc/dur	↔				Yu *et al.*, 1998
	Clinical AF	Human	Term				↑	Fujiki *et al.*, 2001
Propafenone	Cholinergic-stim.	Dog	Term/↓inc /↔dur	↑	↓	↑	↑	Wang *et al.*, 1993; Niu *et al.*, 2009
	Atrial injury	Dog	Term	↑			↑	Inoue *et al.*, 1991; Derakhchan *et al.*, 1994
	Chronic ATP	Dog	Term	↑	↓		↑	Chandra *et al.*, 2004
	Acute ATP	Human	Term/↓inc/dur	↔			↑	Yu *et al.*, 1998; Biffi *et al.*, 1999
	Clinical AF	Human	Term	↑	↓		↑	Tai *et al.*, 1998
Quinidine	Atrial injury	Dog	Term	↑	↓	↔	↑	Cha *et al.*, 1996
	Chronic AF	Goat	Term/↔vul	↔/↑	↔/↓	↔	↑	Wijffels *et al.*, 1999; Wijffels *et al.*, 2000

Term=acute termination of AF after drug administration. See legend of Table 1 for other definitions

Table 3

In-vivo effects of class II anti-arrhythmic drugs (β-blockers) on AF and atrial electrophysiology in animal models or clinical studies of AF

Drug Class II	***In-vivo* model /clinical study**	**Species**	**AF**	**ERP**	**θ**	**λ**	**CL**	**Refs**
Esmolol	Local nerve-stim.	Dog	↓vul					Schauerte *et al.*, 2001
Nadolol	Cholinergic-stim.	Dog	↔dur					Rivard *et al.*, 2007
	Atrial ischaemia	Dog	↓inc/dur	↑	↑		↔	Rivard *et al.*, 2007
Propranolol	HF: VTP 2-6wk	Dog	↓vul					Stambler *et al.*, 2003
	Local nerve-stim.	Dog	↓vul					Schauerte *et al.*, 2001
	Asphyxia	Rat	↔vul/↓dur					Haugan *et al.*, 2004
	Chronic AF	Goat		↔			↔	Wijffels *et al.*, 1997
	Acute ATP	Human	↓inc/dur	↔				Yu *et al.*, 1998

See legend of Table 1 for definitions

Table 4

In-vivo effects of class III (action potential-prolonging) anti-arrhythmic drugs on AF and atrial electrophysiology in animal models or clinical studies of AF

Drug class III	*In-vivo* model /clinical study	Species	AF	ERP	θ	λ	CL	Refs
Amiodarone	Cholinergic-stim.	Dog	↓vul					Huang *et al.*, 2006
	Asphyxia	Rat	↓vul/dur					Haugan *et al.*, 2004; Diness *et al.*, 2010
	Aconitine	Cat	Term					Winslow, 1981
	Chronic AF/ATP	Goat, dog	Term/↓vul/ inc/dur	↑/↔	↑/↓		↑	Shinagawa *et al.*, 2003; Ashikaga *et al.*, 2006; Linz *et al.*, 2007
	Acute ATP	Human	↓inc/dur	↔				Yu *et al.*, 1998
	Clinical AF	Human	Term	↑	↔/↓		↑	Tai *et al.*, 1998; Pandozi *et al.*, 2003; Maury & Zimmermann, 2004; Rostock *et al.*, 2005
Dofetilide	HF: VTP 2-6wk	Dog	Term/↓vul/dur	↑	↔	↑	↑	Li *et al.*, 2000
	Chronic atrial dil.	Dog	Term/↓vul	↑	↓		↑	Restivo *et al.*, 2001
	Cholinergic-stim.	Dog	Term/↔term /↓vul/↔dur	↑	↔	↑	↑	Nattel *et al.*, 1998; Derakhchan *et al.*, 2001; Rivard *et al.*, 2007
	Atrial ischaemia	Dog	↔dur	↑	↔		↑	Rivard *et al.*, 2007
	Atrial injury	Dog	Term	↑	↓	↑	↑	Cha *et al.*, 1996
	Chronic AF/ATP	Goat, dog	↔Term/↔vul /dur	↔/↑	↔	↔/ ↑	↑	Li *et al.*, 2000; Shinagawa *et al.*, 2003; Blaauw *et al.*, 2004; Chandra *et al.*, 2004; Linz *et al.*, 2007
Ibutilide	Cholinergic-stim.	Dog	Term	↑				Vereckei *et al.*, 2001
	Atrial injury	Dog	Term	↑				Stump *et al.*, 2005
	Chronic AF/ATP	Goat, dog	↔Term/↔vul /dur	↔/↑	↔	↑	↑	Blaauw *et al.*, 2004; Vereckei *et al.*, 2004; Duytschaever *et al.*, 2005
	Acute ATP	Human	Term	↑			↑	Sticherling *et al.*, 2002
	Clinical AF	Human	Term	↑	↓		↑	Tai *et al.*, 1998
Nifekalant	Cholinergic-stim.	Dog	Term	↑	↔	↑	↑	Hayashi *et al.*, 1998
	Chronic ATP	Dog	↓vul/dur	↑	↔	↑		Tang *et al.*, 2006
	Clinical AF	Human		↑	↓			Minami *et al.*, 2004
Sotalol	Cholinergic-stim.	Dog	↔Term/Term/ ↔vul/↓vul	↑	↔	↑	↑	Wang *et al.*, 1993; Wang *et al.*, 1994; Derakhchan *et al.*, 2001
	Asphyxia	Rat	↓vul/dur					Haugan *et al.*, 2004
	Chronic AF/ATP	Goat, dog	Term/↔vul/dur /↓vul/dur	↑/↔	↔	↔	↑	Wijffels *et al.*, 1999; Wijffels *et al.*, 2000; Duytschaever *et al.*, 2005; Sakamoto *et al.*, 2009
	Acute ATP	Human	↓inc/dur	↔				Yu *et al.*, 1998
	Clinical AF	Human	↔vul	↑			↑	Tse & Lau, 2002; Kirchhof *et al.*, 2005

See legend of Table 1 for definitions

Table 5

In-vivo effects of class IV anti-arrhythmic drugs (Ca^{2+} channel blockers) on AF and atrial electrophysiology in animal models or clinical studies of AF

Drug class IV	*In-vivo* model /clinical study	Species	AF	ERP	θ	λ	CL	Refs
Bepridil	Chronic ATP	Dog	↓vul/dur	↑			↑	Nishida *et al.*, 2007
Diltiazem	Cholinergic-stim.	Dog	↔inc/dur					Rivard *et al.*, 2007
	Atrial ischaemia	Dog	↓inc/dur	↔	↑		↔	Rivard *et al.*, 2007
	Chronic ATP	Dog	↔dur	↔	↔	↔		Fareh *et al.*, 2001
Efonidipine	Chronic ATP	Dog		↑	↔	↑		Ohashi *et al.*, 2004
Verapamil	HF: VTP 2-6wk	Dog	Term/↔term/↓vul					Stambler *et al.*, 2003; Ryu *et al.*, 2005
	Acute atrial dil.	Human	↓vul	↑				Tse *et al.*, 2001
	Asphyxia	Rat	↔vul/↑dur					Haugan *et al.*, 2004
	Chronic AF	Goat	↑dur	↓	↔		↓	Duytschaever *et al.*, 2000
	Chronic ATP	Dog	↓vul/↔vul/dur/↑dur	↑/↔	↔	↑/↔		Lee *et al.*, 2000; Ohashi *et al.*, 2004
	Acute ATP	Human	↔Term/↓vul/inc/dur/↑dur	↑			↓	Daoud *et al.*, 1997; Yu *et al.*, 1998; Sticherling *et al.*, 2002

See legend of Table 1 for definitions

Table 6

In-vivo effects of upstream therapies & other clinically-available non-Vaughan Williams class agents on AF and atrial electrophysiology in animal models of AF

Agent	*In-vivo* model	Species	AF	ERP	θ	λ	CL	Refs
Cilazapril: ACEI	Chronic ATP	Dog	↓vul/dur					Li *et al.*, 2007
Enalapril: ACEI	HF: VTP 2-6wk	Dog	↓dur	↔	↔	↔		Li *et al.*, 2001
	Chronic ATP	Dog	↔vul/dur	↔	↔	↔		Shinagawa *et al.*, 2002b
Quinapril: ACEI	Chronic ATP	Sheep	↓inc	↔	↔	↔		Anne *et al.*, 2007
Candesartan: ARB	HF: VTP 2-6wk	Rabbit	↓dur	↔	↑			Shimano *et al.*, 2008
	LVH	Mouse	↓vul	↔				Zhang *et al.*, 2006
	Chronic AF/ATP	Goat, dog	↔vul/dur/↓dur	↔	↑		↔	Kumagai *et al.*, 2003b; Hall *et al.*, 2010
Losartan: ARB	Chronic ATP	Sheep	↓inc	↔	↔	↔		Anne *et al.*, 2007
Olmesartan: ARB	Chronic ATP	Dog	↔dur	↔	↔			Nakashima & Kumagai, 2007
Valsartan: ARB	Chronic ATP	Dog	↓vul/dur					Li *et al.*, 2007
Eplerenone: A-A	HF: VTP 2-6wk	Dog	↓vul	↑	↔			Shroff *et al.*, 2006
Spironolactone: A-A	Chronic ATP	Dog	↓vul/dur					Zhao *et al.*, 2010
Atorvastatin: statin	Pericarditis	Dog	↓dur	↑	↑			Kumagai *et al.*, 2004
Rosuvastatin: statin	↑ROS/fibrosis	T-mouse	↔inc	↔	↔			Reil *et al.*, 2010
Simvastatin: statin	HF: VTP 2-6wk	Dog	↓dur	↔	↑			Shiroshita-Takeshita *et al.*, 2007a
	Chronic ATP	Dog	↓vul/dur	↑				Shiroshita-Takeshita *et al.*, 2004
PUFA	HF: VTP 2-6wk	Dog	↔vul/↓dur	↔	↔			Sakabe *et al.*, 2007
	HF: VTP+ATP	Dog	↓vul/dur	↔	↔			Laurent *et al.*, 2008a
	Cholinergic-stim.	Dog	↓vul	↔				Sarrazin *et al.*, 2007
	Chronic ATP	Dog	↔vul/dur	↔	↔			Sakabe *et al.*, 2007
Fenofibrate: PPAR-α↑	HF: VTP 2-6wk	Dog	↔dur	↔	↔			Shiroshita-Takeshita *et al.*, 2007a
Pioglitazone: PPAR-γ↑	HF: VTP 2-6wk	Rabbit	↓dur	↔	↑			Shimano *et al.*, 2008
Prednisone: A-I	Chronic ATP	Dog	↓vul/dur	↑				Shiroshita-Takeshita *et al.*, 2006
Ibuprofen: A-I	Chronic ATP	Dog	↔vul/dur	↔				Shiroshita-Takeshita *et al.*, 2006
Vitamin C	Chronic ATP	Dog	↔vul/dur	↔/↑				Carnes *et al.*, 2001; Shiroshita-Takeshita *et al.*, 2004
Digoxin: glycoside	Chronic AF	Goat	↑vul/dur/↔dur	↔	↔		↔	Tieleman *et al.*, 1999; Duytschaever *et al.*, 2000
	Acute ATP	Human	↑inc	↓				Sticherling *et al.*, 2000

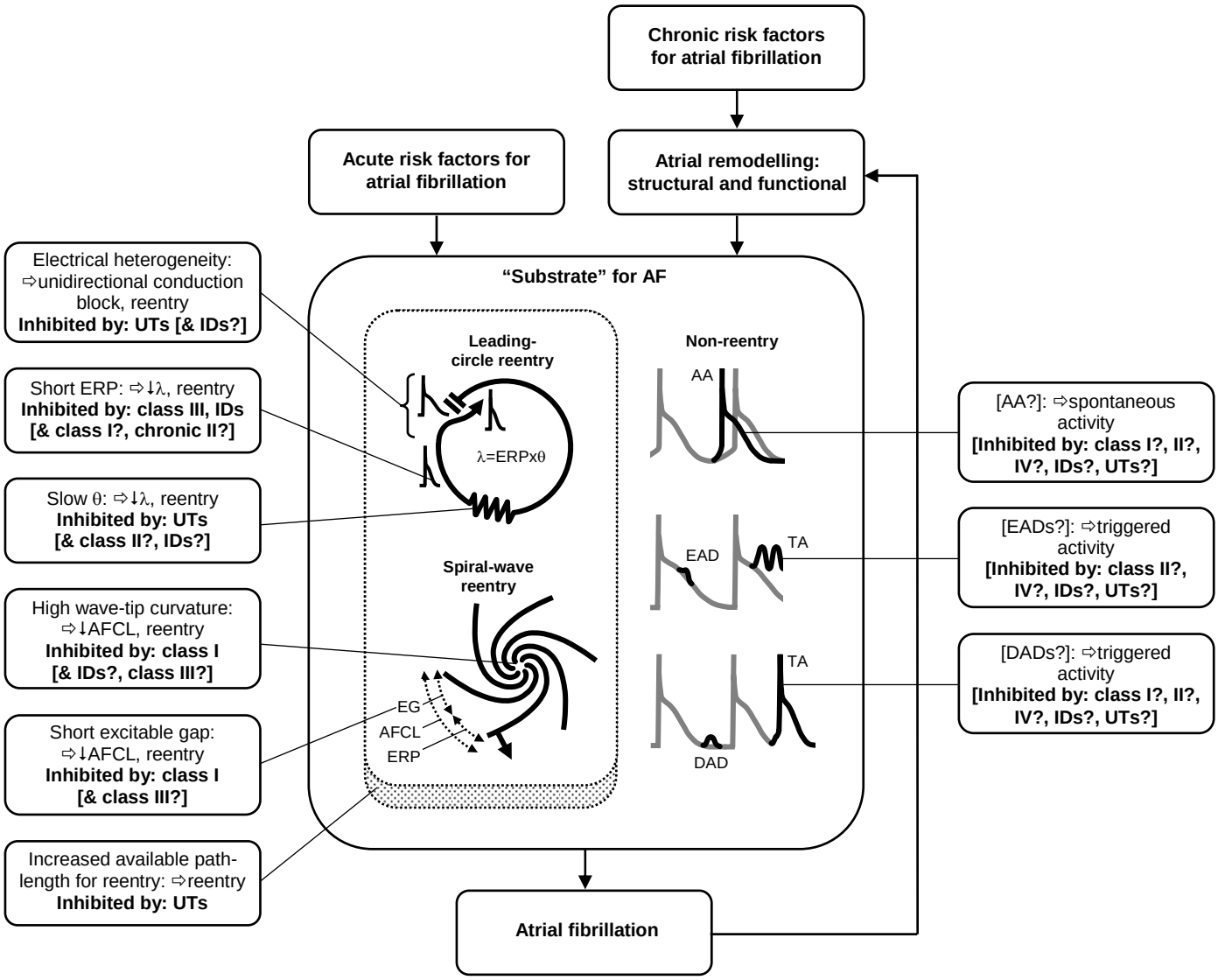
ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; A-A=aldosterone receptor antagonist; PUFA=poly-unsaturated fatty acid; PPAR=peroxisome proliferator-activated receptor; A-I=anti-inflammatory; See legend of Table 1 for other definitions

Table 7
In-vivo effects of investigational anti-arrhythmic drugs on AF and atrial electrophysiology in animal models of AF

Investigational drug	*In-vivo* model	Species	AF	ERP	θ	λ	CL	Refs
DPO-1: ↓I_{Kur}	Atrial injury	Dog	Term	↑				Stump *et al.*, 2005
Almokalant: ↓I_{Kr}	Chronic AF	Goat	↔Term				↑	Santos *et al.*, 2008
E-4031: ↓I_{Kr}	Atrial injury	Dog	Term	↑			↑	Inoue *et al.*, 1991
KCB-328: ↓I_{Kr}	Atrial injury	Dog	Term	↑	↓	↑	↑	Rahme *et al.*, 2001
	Chronic ATP	Dog	Term	↑	↓		↑	Chandra *et al.*, 2004
MK499: ↓I_{Kr}	Atrial injury	Dog	Term	↑				Stump *et al.*, 2005
Azimilide: ↓I_{Kr}/I_{Ks}	Chronic atrial dil.	Dog	Term/↓vul	↑	↓		↑	Restivo *et al.*, 2001
	Cholinergic-stim.	Dog	Term	↑	↔		↑	Nattel *et al.*, 1998
HMR 1556: ↓I_{Ks}	Cholinergic-stim.	Dog	↓dur	↑			↑	Nakashima *et al.*, 2004
	Chronic AF	Pig	Term					Bauer *et al.*, 2005
NS8593: ↓I_{SKCa}	Asphyxia	Rat	↓dur					Diness *et al.*, 2010
NIP-151: ↓I_{KACh}	Cholinergic-stim.	Dog	Term	↑				Hashimoto *et al.*, 2008
	Aconitine	Dog	Term					Hashimoto *et al.*, 2008
Tertiapin: ↓I_{KACh}	Cholinergic-stim.	Dog	Term	↑	↔			Hashimoto *et al.*, 2006
	Aconitine	Dog	Term/↓dur					Hashimoto *et al.*, 2006
Cariporide: ↓$I_{Na/H}$	Atrial ischaemia	Dog		↑				Jayachandran *et al.*, 2000
	Chronic ATP	Dog	↔vul/dur	↔	↔	↔		Shinagawa *et al.*, 2002b
Ambasilide: ↓I_{TO}/I_{Kur}/I_{Na}/I_{Kr}/I_{Ks}	Cholinergic-stim.	Dog	Term/↓inc	↑	↔	↑	↑	Wang *et al.*, 1994
	Pericarditis	Dog	↓inc	↑	↔	↑		Wang *et al.*, 1994
AVE0118: ↓I_{Kur}/I_{TO}/I_{KACh}	Chronic AF	Goat	Term/↓vul	↑	↔	↑	↑	Blaauw *et al.*, 2004; Blaauw *et al.*, 2007; Linz *et al.*, 2007
AZD7009: ↓I_{Kr}/I_{Na}/I_{TO}/I_{Kur}	Pericarditis	Dog	Term/↓vul	↑	↓		↑	Goldstein *et al.*, 2004
Nibentan: ↓I_{K}/I_{KACh}	Cholinergic-stim.	Dog	Term/↓vul	↑	↔	↑	↑	Fedorov *et al.*, 2000
NIP-142: ↓I_{KACh}/I_{Kur}/I_{Ks}/I_{Kr}/I_{TO}/I_{CaL}/I_{CaT}	Cholinergic-stim.	Dog	Term/↓vul	↑	↔		↑	Nagasawa *et al.*, 2002
	Atrial injury	Dog	Term/↓vul				↔	Nagasawa *et al.*, 2002
Ranolazine: ↓I_{Kr}/I_{KS}/I_{Na}/I_{NaL}	Cholinergic-stim.	Pig	↓vul/dur	↑	↓			Kumar *et al.*, 2009
SD-3212: ↓I_{Na}/I_{CaL}/I_{K}/I_{KACh}	Atrial injury	Dog	Term	↑	↓		↑	Fujiki *et al.*, 1997
SSR149744C: ↓I_{Na}/I_{CaL}/I_{Kur}/I_{Kr}/I_{KS}/ $I_{KACh,}$ α-/β-/angiotensin receptors	Cholinergic-stim.	Dog	Term/↓vul	↑			↑	Gautier *et al.*, 2005
Tedisamil: ↓I_{TO}/I_{Kur}/I_{Kr}/I_{Ks}/I_{KATP}	Cholinergic-stim.	Dog	Term				↑	Fischbach *et al.*, 2001
	Atrial injury	Dog	Term/↓vul	↑	↔		↑	Fischbach *et al.*, 1999
	Chronic ATP	Dog	Term/↓vul				↑	Fischbach *et al.*, 2001
Vanoxerine: ↓I_{Kr}/I_{CaL}/I_{Na}	Pericarditis	Dog	Term	↔	↔		↑	Matsumoto *et al.*, 2010
AAP10: ↑I_{gap}	Asphyxia	Rat	↔vul/dur					Haugan *et al.*, 2004
GAP-134: ↑I_{gap}	HF: VTP+ATP	Dog	↔vul/dur/ ↓vul/dur	↔	↑	↑		Laurent *et al.*, 2009
	Pericarditis	Dog	↓vul/dur	↔	↑			Rossman *et al.*, 2009
Rotigaptide: ↑I_{gap}	HF: VTP 2-6wk	Dog	↔vul/dur	↔	↑			Shiroshita-Takeshita *et al.*, 2007b
	Atrial ischaemia	Dog	↓dur	↔	↑			Shiroshita-Takeshita *et al.*, 2007b
	Chronic ATP	Dog	↔vul/dur	↔	↑			Shiroshita-Takeshita *et al.*, 2007b
Mibefradil: ↓I_{CaT}	Chronic ATP	Dog	↓dur	↑	↔	↑		Fareh *et al.*, 2001
K201: ↓Ca^{2+}/I_{Na}/I_{CaL}/I_{KACh}/I_{Kr}/I_{K1}	Pericarditis	Dog	↓vul/↓dur	↑	↔		↑	Kumagai *et al.*, 2003a
Ryanodine: RyR inhibitor	HF: VTP 2-6wk	Dog	Term/↓vul				↑	Stambler *et al.*, 2003
Tetracaine: ↓I_{Na}/I_{K1}/Ca^{2+}_{i}	↓Ca^{2+}_{i} protein	T-mouse	↓vul	↔				Sood *et al.*, 2008
Pirfenidone: ↓fibrosis	HF: VTP 2-6wk	Dog	↓dur	↔	↑			Lee *et al.*, 2006
RS-100302: 5-HT_4 antagonist	Atrial injury	Pig	Term/↓vul	↑	↓	↑	↑	Rahme *et al.*, 1999

See text for definitions of ion currents. Ca^{2+}_{i}=intracellular Ca^{2+}; RyR=ryanodine receptor; 5-HT=5-hydroxytryptamine

[Figure 1]


Chronic risk factors for atrial fibrillation
Acute risk factors for atrial fibrillation
Atrial remodelling: structural and functional
Electrical heterogeneity: ⇨unidirectional conduction block, reentry
Inhibited by: UTs [& IDs?]
Short ERP: ⇨↓λ, reentry
Inhibited by: class III, IDs [& class I?, chronic II?]
Slow θ: ⇨↓λ, reentry
Inhibited by: UTs [& class II?, IDs?]
High wave-tip curvature: ⇨↓AFCL, reentry
Inhibited by: class I [& IDs?, class III?]
Short excitable gap: ⇨↓AFCL, reentry
Inhibited by: class I [& class III?]
Increased available path-length for reentry: ⇨reentry
Inhibited by: UTs
"Substrate" for AF
Leading-circle reentry
λ=ERPxθ
Spiral-wave reentry
EG
AFCL
ERP
Non-reentry
AA
EAD
TA
TA
DAD
[AA?]: ⇨spontaneous activity
[Inhibited by: class I?, II?, IV?, IDs?, UTs?]
[EADs?]: ⇨triggered activity
[Inhibited by: class II?, IV?, IDs?, UTs?]
[DADs?]: ⇨triggered activity
[Inhibited by: class I?, II?, IV?, IDs?, UTs?]
Atrial fibrillation