Future Perspectives in the Pharmacological Treatment of Atrial Fibrillation and Ventricular Arrhythmias in Heart Failure

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Abstract: Heart failure (HF) is a clinical syndrome characterized by significant impairment of cardiac ventricular function. Atrial fibrillation (AF) is the most commonly observed sustained arrhythmia in clinical practice. Both HF and AF are associated with increased morbidity and mortality and their prevalence increases with age. Approximately 50% of patients with moderate HF die due to ventricular fibrillation that leads to sudden cardiac death. Patients with AF exhibit increased mortality due to HF and stroke. HF and AF often co-exist, and the development of the other condition further deteriorates prognosis. Both chronic HF and AF lead to structural and electrophysiological changes in the heart called remodeling, modifying therapeutic targets including those for antiarrhythmic intervention. Current pharmacological treatment of arrhythmias has major limitations due to low efficacy and serious adverse effects. In this review, the main aspects of electrical remodeling in HF and AF are discussed along with possible novel targets identified for future pharmacological antiarrhythmic therapy.

Keywords: Heart failure, atrial fibrillation, cardiac arrhythmias, electrical remodeling, potassium channel expression, multi-channel blocking drugs.

I. OVERVIEW AND CURRENT STATUS

Epidemiology of Heart Failure, Atrial Fibrillation and their Combination

Heart failure (HF) is a clinical syndrome resulting from a wide range of cardiovascular disorders, featuring significant impairment of cardiac function that leads to reduced ventricular filling or ejection of blood. HF markedly reduces health-related quality of life [1], causes significant morbidity and high mortality and represents an enormous economic burden for the health care system [2]. The incidence of HF is increasing with age, with 20 per 1000 persons 65-69 years old and more than 80 per 1000 persons older than 85 [3] and its prevalence is increasing in a continuously aging population [2]. In spite of the significant advances in the treatment of HF, mortality rates remain poor at approximately 50% of patients dying within 5 years of diagnosis [4]. Serious ventricular arrhythmias are common in HF [5] and approximately 50% of HF patients die due to ventricular fibrillation leading to sudden cardiac death (SCD), the rate of which is several times higher in HF patients compared to the general population [6]. In addition to severe ventricular arrhythmias, atrial arrhythmias often develop in heart failure. Bradycardia can develop due to sinoatrial function impairment [7] that can exacerbate cardiac dysfunction [8], can lead to syncope and haemodynamic collapse and can be resolved by application of implantable devices [9].

Atrial fibrillation (AF) is the most common sustained arrhythmia and it is associated with significant morbidity and mortality, especially due to the increased risk of heart failure and stroke [10-12]. The prevalence of AF increases with age, with 0.5% of patients affected in the 50 year old range, ~10% over the age of 80 [13] and the prediction is that it would increase in the future [14]. Heart failure and atrial fibrillation are often diagnosed in the same patient, and those with HF are more likely to develop AF compared to the

general population [15]. The presence of AF in HF patients with either preserved or reduced left ventricular function carries an increased risk for all-cause mortality [16]. As the New York Heart Association (NYHA) functional classification based severity of HF increases, the prevalence of AF also increases [for a review see [17]. In patients with HF or AF, the development of the other condition leads to further deterioration of an already poor prognosis. The analysis of the temporal relationship of AF and HF in patients from the Framingham Heart Study revealed that in patients with HF, later development of AF was associated with increased mortality both in men and women [15]. It is therefore no coincidence that AF and HF were called the "two new epidemics of cardiovascular disease" [18]. Why do AF and HF so often co-exist? Many cardiovascular diseases are common risk factors for both HF and AF development [19]. These conditions (e.g. hypertension, valvular heart disease, coronary artery disease etc.) may eventually lead to structural and electrophysiological remodeling [20] and chronic neurohormonal activation that promote the development of both AF and HF [21]. In addition, once AF is present, it can facilitate HF due to rapid activation of the ventricles leading to tachycardia induced cardiomyopathy and maladaptive remodeling of the myocardium [22]. Furthermore, AF by itself is associated with decreased cardiac output [23]. Heart failure, on the other hand, can promote AF by increasing atrial pressure and atrial dilatation [24], by inducing atrial fibrosis [25], by its chronic activation of the renin-angiotensin-aldosterone system that leads to further structural and electrophysiological remodeling.

Pharmacological Treatment of AF in HF

Current pharmacological treatment options for the management of AF are sub-optimal, since high rates of AF recurrence are observed following cardioversion using currently available drugs [26-28] and they have even more limited efficacy in patients with persistent/permanent AF and remodeled atria. Furthermore, the majority of these drugs were developed for the treatment of ventricular arrhythmias, therefore their ventricular electrophysiological effects can lead to pro-arrhythmic ventricular side effects. Therefore there is an unmet need for more efficacious and safer pharmacological

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management of AF [29]. The use of antiarrhythmic agents for the management of AF in patients with HF is even more limited, since the mortality increasing pro-arrhythmic side effects of these drugs in HF are of particular concern. Similar to other patient populations with AF, the issue as to whether rhythm control or rate control should be pursued in HF patients with AF was studied in the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial [30]. Rhythm control has not been found to be superior to rate control in patients with HF who develop AF subsequently, in fact, rate control was suggested as the primary approach to manage AF in HF patients [30]. It is not known, however, to what extent the possible pro-arrhythmic side effects of antiarrhythmic drugs negated the advantages of sinus rhythm maintenance in this study. Unless contraindicated, beta-adrenergic blocker drugs are recommended for ventricular rate control due to their beneficial effects on morbidity and mortality in HF patients, in combination with digoxin in case of reduced left ventricular function [31-33]. When ventricular rate control cannot be achieved by pharmacological means, atrioventricular node ablation followed by cardiac resynchronization therapy (CRT) device implantation is often performed [34-35].

In contrast, patients with AF, where HF has developed as the consequence of AF, rhythm control strategies should be chosen [33]. In HF patients with preserved systolic function, AF leads to a more severe functional class of HF and reduced quality of life, and to worse diastolic function compared to those in sinus rhythm [36]. In HF patients, however, the number of antiarrhythmic drugs that can be safely administered is very limited. For rhythm control of AF, Class IC compounds should be avoided in patients with structural heart disease [37], due to considerations based on the results of the Cardiac Arrhythmia Suppression Trial (CAST), where Class IC drugs increased mortality of patients with ischemic heart disease and impaired left ventricular function [38-39]. The Class IA drug quinidine increased the risk of death threefold when used in AF patients for maintenance of sinus rhythm following cardioversion [40]. Some Class III antiarrhythmic drugs are also used and have proven useful for the restoration and maintenance of sinus rhythm in patients with AF [41]. However, so far only amiodarone and dofetilide have exhibited neutral influence on mortality in patients with HF: amiodarone prevented the recurrence of AF far more effectively than propafenone and D, L-sotalol while showing no detrimental effects in patients with reduced left ventricular ejection fraction [26]. Dofetilide did not alter all-cause mortality in patients with left ventricular dysfunction but improved the conversion rate of AF to sinus rhythm in the DIAMOND-CHF trial [42]. Importantly, dofetilide improved mortality in HF patients who had normal QTc intervals before drug treatment compared to those who had a prolonged QTc [43]. D, L-sotalol should be avoided since it increases the incidence of Torsades de Pointes (TdP) arrhythmias in HF [44]. Antiarrhythmic compounds with selective I_{Kr} blocking properties (Class III effect) markedly prolong the action potential, leading to proarrhythmic adverse effects via early afterdepolarization induction and enhancement of ventricular dispersion of repolarization, prerequisites for the development of TdP [45]. Thus, the multi-channel blocker amiodarone remains the most effective antiarrhythmic compound and the drug of choice for the majority of HF patients with AF, however, its chronic use is associated with significant extracardiac side effects [26]. Although amiodarone seems to be the least pro-arrhythmic drug among antiarrhythmic drugs administered for AF [46], it may increase sudden cardiac death risk in patients with advanced HF and with a history of previous TdP arrhythmia [47]. The majority of the extracardiac toxicity of amiodarone were hoped to be avoided with retained antiarrhythmic activity by the development of dronedarone, a newer amiodarone derivative lacking the iodine moiety, with fewer pulmonary and thyroid side effects [48-49]. The disappointing results of the PALLAS trial, however, indicated higher rates of hospitalization, heart failure episodes, stroke and all cause mortality in patients randomized to dronedarone [50-52]. Therefore, dronedarone is now rec-

ommended to be used only in paroxysmal AF or following cardioversion of persistent AF in patients with preserved left ventricular function, and it is contraindicated to use in patients with NYHA IV class HF, and in patients with a prior episode of acute decompensation of HF, especially with left ventricular ejection fraction <35% [53].

Atrial fibrillation carries a significant risk for thromboembolic events irrespective of the type of AF (paroxysmal, persistent or permanent) [11] and their rate increases with age [54], therefore, stroke prevention and antithrombotic therapy are major concerns for AF management. However, antithrombotic therapy in AF is not the subject of this review and the reader is referred to some excellent recent reviews and to the latest guidelines [41, 53, 55-56].

Pharmacological Management of Ventricular Arrhythmias in HF

Cardiac ventricular arrhythmias significantly contribute to morbidity and mortality in HF. However, most antiarrhythmic agents have been shown to increase mortality in patients with HF [57-58], and the proarrhythmic effects of Class I and III antiarrhythmic compounds are even more pronounced in HF patients [37-38, 40, 58]. Therefore, Class I sodium channel blocking drugs and the Class III drugs d-sotalol and dronedarone [50] should not be administered in HF, and antiarrhythmic drugs in general are listed as compounds that may worsen HF in the current HF management guidelines, including Class IV Ca^{2+} channel blockers [33]. At the time of this review, only the multi-channel blocker amiodarone and dofetilide (Class III) can be recommended for arrhythmia management in HF patients due to their neutral influence on mortality as observed in the GESICA, CHF-STAT and DIAMOND clinical trials [42, 59-61]. However, dofetilide can cause marked QT interval prolongation and can provoke TdP, therefore dofetilide treatment initiation is a mandatory in-hospital procedure in all patients [62-63]. Due to these safety concerns dofetilide is not approved in some countries.

Non-Pharmacological Arrhythmia Management in HF

With the limited efficacy and significant safety concerns regarding antiarrhythmic drug administration for AF treatment [26-27, 64], non-pharmacological approaches to AF management are steadily gaining ground and offer benefits to selected populations of patients. In approximately 10-15 % of patients with AF, appropriate ventricular rate control cannot be obtained pharmacologically [65]. Radiofrequency catheter ablation of the AV node followed by implantation of a permanent pacemaker can be a solution in these cases, improving quality of life, rate control, ventricular function and exercise capacity [66]. Rhythm control by catheter ablation has been used increasingly and has been found to be superior in maintaining sinus rhythm compared to antiarrhythmic drugs [67]. The discovery of the role of pulmonary vein sleeve ectopic triggers in the development of AF [68] has led to the establishment of the pulmonary vein isolation technique [69]. This approach has been shown to be feasible in patients with AF and decreased ventricular function and heart failure, leading to an increase in ejection fraction and improvement in quality of life [70-72]. Ongoing clinical trials will provide more definitive answers on how catheter ablation and conventional therapy influences morbidity and mortality in AF patients with left ventricular ejection fraction <35% (CASTLE_AF) [73] and whether catheter ablation of pharmacological rate or rhythm control is superior for reducing total mortality in untreated AF patients (CABANA) [74]. The success rate of non-pharmacological treatment of AF critically depends on appropriate patient selection for these procedures, summarized by the recently published expert consensus statement [75].

Sudden cardiac death due to ventricular fibrillation is a leading cause of death among HF patients [6]. However, for the treatment of venricular arrhythmias in HF, due to the significantly increased

arrhythmia susceptibility observed in HF patients and because of the proarrhythmic adverse effects of currently available antiarrhythmic drugs, the use of pharmacological agents is very limited. Serious proarrhythmic adverse effects and increased mortality are associated with Class IA, IC and Class III antiarrhythmic drug administration in patient populations with impaired ventricular function [57-58, 76]. Among Class III agents, most likely due to its multi-channel blocking properties, amiodarone has been the most effective and relatively safe drug with the smallest proarrhythmic potential, causing TdP in approximately 1% of cases [45]. However, in patients with previous history of TdP amiodarone is not considered safe and should not be used [47].

The implantable cardioverter defibrillator (ICD) detects and terminates life threatening serious ventricular tachyarrhythmias and was introduced for the primary and secondary prevention of sudden cardiac death in high-risk patients including those with severe left ventricular dysfunction [77-79]. In order to compare the ability of amiodarone and single-lead, conservatively programmed ICD to reduce the risk of death from any cause, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) was conducted involving 2521 patients with mild to moderate heart failure [79]. The main conclusion of the trial was that in patients with left ventricular ejection fraction ≤ 35%, in NYHA functional class II and III, amiodarone did not influence survival, while ICD therapy reduced the relative risk of death by any cause by 23% [79]. The authors compared their results to previous HF trials studying the effects of ICD therapy on mortality and suggested that ICD programming was critical to the final outcome. Indeed, in the Amiodarone versus Implantable Cardioverter Defibrillator (AMIOVIRT) Trial no benefit was offered by ICD therapy over amiodarone therapy, as mortality and quality of life were similar in the two groups involving 103 patients with non-ischaemic dilated cardiomyopathy, non-sustained ventricular tachycardia and with left ventricular ejection fraction ≤ 35% [80]. In the DEFINITE trial comprising 458 patients, again, no beneficial effect on all cause mortality, however, a significant reduction in arrhythmia related sudden cardiac death was observed with ICD application when compared to standard therapy with beta-adrenergic blockers and ACE inhibitors in patients with severe, non-ischaemic dilated cardiomyopathy [81]. In these studies, different thresholds for pacing, different heart rate prompting, different devices (single-, dual or triple-chamber) were applied, emphasizing the importance of device settings and type selection in different subsets of patients with HF. A detailed and comprehensive review on the effectiveness of ICDs for primary prevention of sudden cardiac death has been published very recently [82].

Cardiac resynchronization therapy (CRT) devices represent one of the most promising developments for the treatment of advanced systolic HF [83-84]. It was recognized that patients with severe heart failure frequently had myocardial regions with delayed activation and contraction resulting in dyssynchrony and these alterations influenced mortality and conduction delay was a prognostic marker in patients with heart failure [85]. Cardiac resynchronization therapy aims at the synchronization of electrical activation of the left and right sides of the heart thereby improving cardiac output [86-87]. CRT therapy is now indicated in HF patients with NYHA class II to IV symptoms in spite of adequate therapy, left ventricular ejection fraction ≤ 35% and QRS width ≥ 120 ms [88]. Cardiac resynchronization therapy has been found to reduce mortality and to promote reverse left ventricular remodeling as well as to improve quality of life [89] and these beneficial effects were maintained during long term follow-up [90]. Similar results were observed in patients with moderate (NYHA class II) heart failure [91] and even mild, NYHA class I heart failure, although risks should be weighed carefully against benefits in this group of patients [92]. The effect of CRT therapy on arrhythmias is not fully elucidated. Previously it was accepted that CRT did not decrease AF incidence [93], however, some studies suggest that CRT is associated with increased

resumption of sinus rhythm in patients with persistent AF [94] and even permanent AF [95-96]. Although some case reports described CRT provoking ventricular arrhythmias [97-98], others reported that CRT reduced the burden of ventricular arrhythmias [99], and the analysis of two large CRT trials did not find an increase in polymorhic VT or a decrease in monomorphic VT in 880 patients receiving CRT therapy [100]. Cardiac resynchronization and ICD therapies are frequently combined as cardiac resynchronization therapy with a defibrillator (CRT-D) [88, 101]. Upgrading ICD therapy to CRT-D therapy in HF patients due to worsening of symptoms can significantly reduce the frequency of ventricular tachycardia, fibrillation and device shocks [102].

It should be noted that cardiac electronic device implantations are not without complications, moreover, a higher than expected complication risk was identified in a Danish study involving almost 6000 patients receiving permanent pacemakers, ICDs, CRT and CRT-D devices, at almost 10% of patients experiencing at least one complication [79, 103]. A particularly troublesome complication of CRT device implantation is the markedly increased risk of infection that can be difficult to manage and is associated with significant morbidity [104].

Not all patients who are candidates for CRT respond to therapy, and the exact correlation between QRS widening and developing dys-synchrony needs to be further evaluated, the use of CRT in patients with AF is a subject to controversy [9, 105]. In HF patients with reduced ejection fraction, recurrent ventricular arrhythmias and ICD shocks are observed, leading to significant morbidity and mortality as well as reduced quality of life (for a recent review see [106]). Optimal programming of ICD decreases the number of shocks [107], and ICD application reduces sudden cardiac death [82], however, these devices do not reduce ventricular arrhythmia incidence in HF patients. For the management of recurrent arrhythmias and reduction of ICD shocks in HF patients with reduced ejection fraction and ICD, adjuvant antiarrhythmic therapy is warranted. In this regard, amiodarone has been found to be most effective for ventricular arrhythmia treatment and shock reduction. However, the use of amiodarone is limited by serious extracardiac adverse effects [108].

Need for New, Safer and More Efficacious Antiarrhythmic Compounds

Based on the overview above, there is a clear unmet need for novel antiarrhythmic drugs for the treatment of atrial fibrillation and serious ventricular arrhythmias in HF patients, that are safer and more efficacious compared to currently available compounds. Some promising new drugs, like tedisamil, azimilide, dronedarone and vernakalant have not fulfilled expectations for pharmacological atrial and/or ventricular arrhythmia management in the setting of heart failure with reduced left ventricular function.

In the following part of this review, some of the main aspects and mechanisms of the increased arrhythmia susceptibility observed in HF are described, followed by the discussion of novel and promising targets and investigational compounds for antiarrhythmic intervention in HF.

II. MYOCARDIAL REMODELING: CREATING ARRHYTHMIA SUBSTRATE AND TRIGGERS IN HEART FAILURE

In an attempt to maintain proper cardiac function and intracellular homeostasis and in response to pathophysiological processes involved in cardiovascular diseases, including HF and AF development, a number of electrophysiological and structural changes are observed in the heart, collectively described as myocardial remodeling. These alterations are partly adaptive in nature, however, when maintained for longer periods they can lead to further deterioration of cardiac function, and importantly, can significantly contribute to arrhythmia development and maintenance. This review

mainly focuses on the arrhythmogenic consequences of electrical remodeling and their possible exploitation for therapy, thus the reader is recommended to refer to previous articles discussing structural remodeling [109-110]. The following sections will deal with three main areas of electrical remodeling in HF and AF: aspects of myocardial repolarization, conduction and impulse generation remodeling.

Remodeling of Atrial and Ventricular Action Potential and Repolarization in AF and HF

The cardiac action potential is a highly regulated and coordinated function of different inward and outward ionic currents and exchangers ensuring proper electrical and electromechanical function of different regions of the heart [111-112]. In a number of pathological settings, including heart failure and atrial fibrillation, fundamental changes appear in the duration and shape of the action potential. Some of these changes are adaptive: it is consistently found that action potential duration is prolonged in HF [113-115] and it may serve to compensate for impaired Ca^{2+} transients and reduced contractility in failing cardiac myocytes by increasing Ca^{2+} load and subsequent release thereby improving cell contractility (Fig. **1**).

Excessive prolongation of repolarization, however, can lead to the development of early afterdepolarizations (EADs) [115, 117] mainly due to recovery of $I_{Ca, L}$ from inactivation [118]. EADs can provoke Torsades de Pointes polymorphic ventricular tachycardia (TdP) in HF patients [119]. TdP leads to syncope and often reverts back to sinus rhythm spontaneously, however, TdP can degenerate into ventricular fibrillation that leads to sudden cardiac death without intervention [118]. Action potential prolongation in HF is due to the remodeling of ion channels carrying inward and outward ionic currents.

Changes in inward currents include the increase of the slowly inactivating, late sodium current ($I_{Na, late}$) that contributes to APD

prolongation and arrhythmogenesis in HF [120-122]. Intracellular calcium handling is significantly influenced by HF on several levels. The L-type calcium current ($I_{Ca, L}$) has been mainly reported to be unchanged in experimental HF models and humans [123-125] or decreased in humans [126]. However, sarcoplasmic reticulum (SR) Ca^{2+} ATPase (SERCA) is downregulated, contributing to decreased SR Ca^{2+} content and increased diastolic Ca^{2+} concentration [127]. The decreased SERCA function impairs Ca^{2+} removal from the cytoplasm and may be the cause for the observed Na^{+}-Ca^{2+} exchanger (NCX) upregulation in HF [128]. The electrogenic NCX exchanges 3 Na^{+} for one Ca^{2+} through the plasma membrane and its main function is the removal of excess intracellular Ca^{2+} during diastole, however, the exchanger can work in both forward (Ca^{2+} extrusion) and reverse (Ca^{2+}-influx) modes, depending on actual membrane potential, intracellular and extracellular Na^{+} and Ca^{2+} concentrations [129]. Since the NCX is responsible for net inward current during the later phase of the action potential, its upregulation may importantly contribute to APD prolongation and arrhythmogenic delayed afterdepolarization (DAD) development in HF [130].

Electrical remodeling includes profound changes in voltage-gated potassium channel expression in HF. Although experimental animal and human studies show some differences, the most consistent changes are downregulation of the transient outward current (I_{to}) [123, 131], the slowly activating component of the delayed rectifier (I_{Ks}) [117, 125, 132] and inward rectifier (I_{K1}) [117, 133], while with the rapid component of the delayed rectifier (I_{Kr}) most studies reported no changes [117, 125, 132].

Therefore, in HF, the repolarization capacity of ventricular myocytes is significantly reduced due to the downregulation of different repolarizing K^{+} channels and increased $I_{Na, late}$, promoting EAD and/or DAD formation and arrhythmia generation, as described above. Also, decreased repolarization capacity means that repolarization reserve [134] is markedly impaired in failing ventricular myocytes. Repolarization reserve refers to the backup
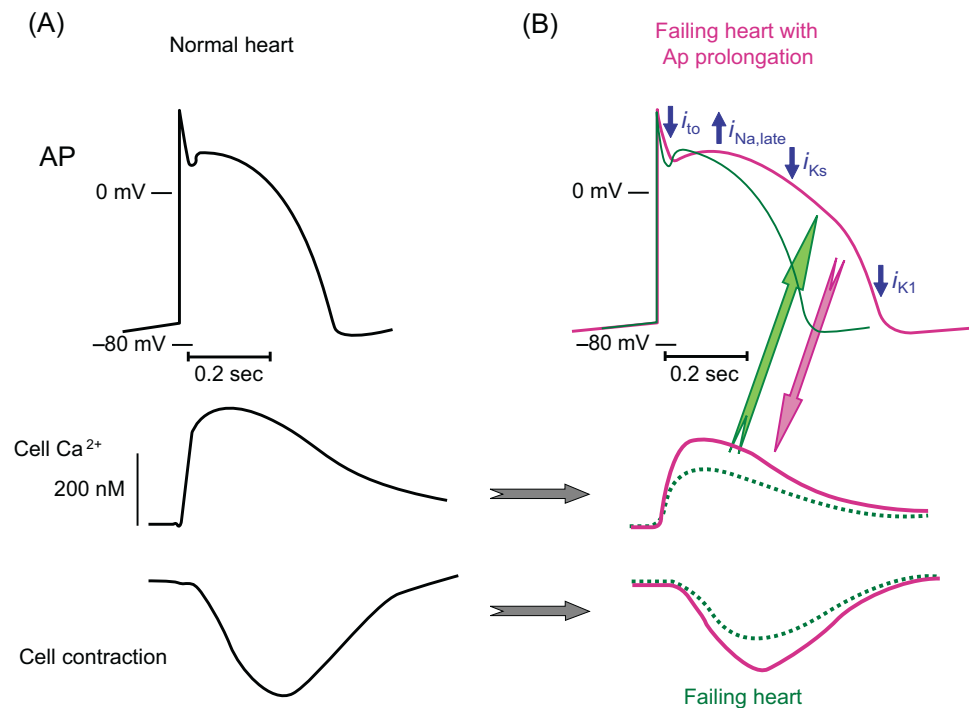

Fig. (1). Schematic illustration of action potentials, Ca^{2+} transients and cell shortening (contraction) from normal (**A**) and failing (**B**) cardiomyocytes showing the compensatory changes in action potential duration by electrical remodeling (indicated by violet lines) in HF. Arrows indicate changes in current densities. Reproduced with permission from [116].

mechanisms of repolarization in the heart, namely the decreased function (by congenital or acquired means) of a repolarizing current can be compensated for by an increase in other potassium currents [135-136]. Impaired repolarization reserve importantly contributes to increased arrhythmia susceptibility in HF patients. In clinical practical terms it means that not only antiarrhythmic drugs with strong potassium channel blocking properties (Class IA, IB and Class III) can provoke TdP, VF and sudden cardiac death in HF patients, but the application of non-cardiovascular drugs that possess weaker K^+ current inhibitory effects, including some antibiotics [137], antimycotics [138], antihistamines [139], antipsychotics [140], NSAIDs [141], even dietary constituents [142], K^+-losing diuretics etc., can further interfere with repolarization [143] and can lead to unexpected and serious ventricular arrhythmia development in this patient population. Importantly, the presence of repolarization prolonging genetic mutations responsible for different forms of long QT (LQT) syndromes can also exacerbate ventricular arrhythmias in HF.

In clinical and experimental settings, the longer AF persists, the harder it becomes to convert AF back to sinus rhythm. This phenomenon was first described by Allessie and colleagues with the now famous expression: "atrial fibrillation begets atrial fibrillation", in their work based on a goat model of AF [144]. The longer AF is present, the more pronounced changes appear in atrial myocardial structure, electrophysiology and function (Fig. **2**).

As (Fig. **3**) illustrates, in contrast to the ventricular AP changes in HF, atrial fibrillation associated remodeling of the atria results in atrial AP shortening and triangulation [145], that leads to shortened atrial effective refractory period and creation of an arrhythmia substrate that is responsible for further maintenance of AF.

Again, the remodeling of the AP, at least in part, is the result of compensatory changes in atrial ion channel expression and function. Rapid atrial rates during AF lead to Ca^{2+} overload of atrial myocytes [146-147], and the consistent finding of reduced $I_{Ca, L}$ [148] that protects the cells from this Ca^{2+} overload and also contributes to APD and refractoriness abbreviation [149-150]. These protective changes, however, become detrimental over longer periods of time since the shortened APD and refractoriness makes the atria more vulnerable to AF initiation and favours the maintenance of the arrhythmia [144].

Only small, about 10 to 20% changes in I_{Na} density in atrial myocytes of patients with chronic AF have been detected [151-152]. In atrial tachycardia induced AF animal models, however, a marked decrease in I_{Na} was observed [153]. Decreased I_{Na} can slow atrial conduction and may further shorten wavelength [153] already abbreviated by APD and refractoriness shortening, and a shorter wavelength increases the number of atrial re-entry circuits [154]. Some *in vitro* animal experimental data also suggests that an increased $I_{Na, late}$ might play a role in atrial arrhythmia generation [155]. Data regarding NCX expression are inconsistent: a significant increase in protein expression [156] and no change in NCX mRNA have been both described in AF [157]. Voltage-gated potassium currents exhibit significant changes as part of the electrical remodeling in the atria, including an approximately 60% decrease in I_{to} [149, 151], a decrease in the atrial specific acetylcholine-activated K^+ channel ($I_{K, ACh}$) expression [158], but an increased constitutively active (without cholinergic ligand stimulation) $I_{K, ACh}$ component [159], however, I_{K1} upregulation is consistently present in patients with AF [160]. The increases in I_{K1} and constitutive $I_{K, ACh}$ make the membrane potential more hyperpolarized and shorten the APD, therefore contributing to re-entry rotor stabilization [161]. Experimental animal data suggest that I_{Kr} and I_{Ks} are unaltered [162], and the sparse functional data from humans indicated increased I_{Ks} [163]. The atrial specific ultrarapidly activating I_{Kur} [164] expression may be either decreased [163, 165], or unaltered [149, 151]. Importantly, if I_{Kur} expression/activity is decreased this could potentially hinder the further development of the numerous I_{Kur} inhibitory compounds that have been developed for the atrial specific treatment of AF [166-167]. Cardiac ATP-sensitive potassium channels (K_{ATP}) [168] are voltage-independent potassium channels linking cell metabolism to membrane excitability, they are predominantly closed under normoxic conditions and are opened by hypoxia and metabolic stress such as elevated workload [169], considerably shortening the action potential. K_{ATP} channels are responsible for the activation of several cardioprotective mechanisms [170]. Studies on expression of K_{ATP} in AF are inconclusive, with some studies showing no change, increase or decrease in expression [158, 171-172]. Furthermore, while expression of K_{ATP} channels may be unaffected, as increased workload may activate K_{ATP} channels, the relative activity of these channels may actually be increased in HF and/or AF. However, this remains to be
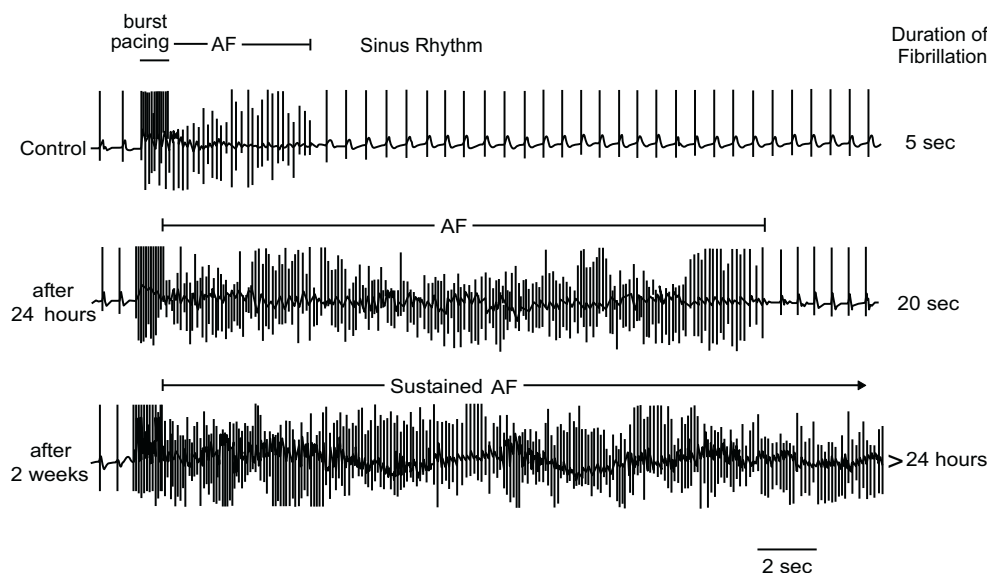

Fig. (2). Representative atrial electrograms recorded from a chronically instrumented goat. The duration of burst-induced AF episodes were prolonged when preceding AF was maintained for longer time periods (24h and then 2 weeks). Upper trace: before the burst, the goat was in sinus rhythm and the induced AF terminated in 5 seconds. Middle trace: The burst induced AF terminated in 20 seconds after 24 h preceding AF. Bottom trace: Burst induced AF did not terminate when the preceding AF lasted for 2 weeks. Reproduced from [144] with permission.
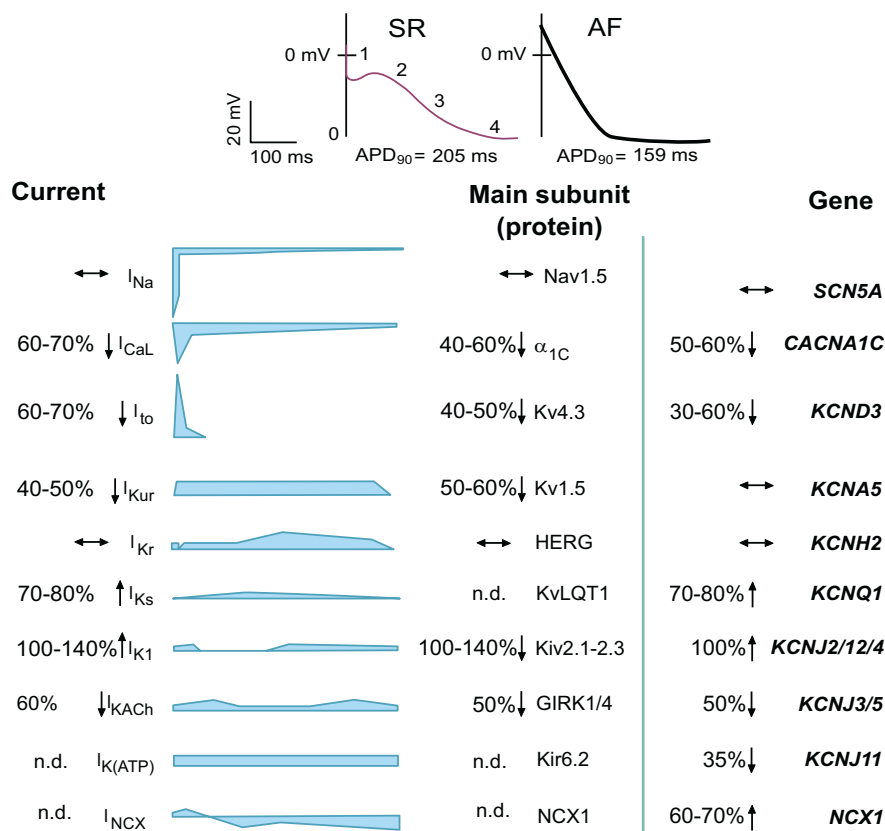
SR — 0 mV — 1, 2, 3, 4, 0 — APD$_{90}$ = 205 ms

AF — 0 mV — APD$_{90}$ = 159 ms

20 mV / 100 ms

Current		Main subunit (protein)		Gene	
↔	I_{Na}	↔ Nav1.5		↔	**SCN5A**
60-70% ↓	I_{CaL}	40-60% ↓ α$_{1C}$		50-60% ↓	**CACNA1C**
60-70% ↓	I_{to}	40-50% ↓ Kv4.3		30-60% ↓	**KCND3**
40-50% ↓	I_{Kur}	50-60% ↓ Kv1.5		↔	**KCNA5**
↔	I_{Kr}	↔ HERG		↔	**KCNH2**
70-80% ↑	I_{Ks}	n.d. KvLQT1		70-80% ↑	**KCNQ1**
100-140% ↑	I_{K1}	100-140% ↓ Kiv2.1-2.3		100% ↑	**KCNJ2/12/4**
60% ↓↓	I_{KACh}	50% ↓ GIRK1/4		50% ↓	**KCNJ3/5**
n.d.	$I_{K(ATP)}$	n.d. Kir6.2		35% ↓	**KCNJ11**
n.d.	I_{NCX}	n.d. NCX1		60-70% ↑	**NCX1**

Fig. (3). Remodeling of the atrial action potential and the underlying alterations of ionic currents and channel subunit expression changes. SR: sinus rhythm; AF: atrial fibrillation. Please see text for detailed discussion on elements of atrial electrical remodeling in AF. Reproduced from [110] with permission.

determined conclusively. Moreover, several cardiac K_{ATP} channel subunit mutations have been found to underlie some rare congenital forms of idiopathic AF [173]. Therefore, K_{ATP} channels may play a role in the development and/or maintenance of AF in HF, where continuously elevated adrenergic stimulation, increased workload and myocardial ischaemia are common features of these diseases.

Remodeling of Conduction in AF and HF

Conduction abnormalities are important contributors to increased arrhythmia susceptibility and creation of an arrhythmia substrate in both HF and AF. Indeed, as already mentioned, reduced intraventricular conduction is prognostic for heart failure [85]. Impairment of gap junction function has been found in different forms of human cardiomyopathies and HF [174], mostly attributed to downregulation and altered distribution of ventricular gap junction constituent connexin43 (Cx43) [175-177]. These changes are further exacerbated by ischaemia increasing the chance for the development of serious ventricular arrhythmias and sudden cardiac death [178]. While increased expression of Cx40 and its lateralization is observed in AF, data regarding Cx43 expression and localization are not conclusive, probably due to different patient populations studied [179-180]. Interestingly, in a recent human study, the application of the beta-adrenergic blocker metoprolol has been found to antagonize the detrimental changes in Cx43 localization and subsequent conduction changes in patients with AF [181]. The detailed discussion of this topic is beyond the scope of this paper and readers are referred to a comprehensive review on this topic published in this issue [182].

Remodeling Leading to Increased Triggered Activity

In addition to increased arrhythmia susceptibility by the development of arrhythmia substrates due to pathological changes in repolarization and conduction in HF and AF, an arrhythmogenic trigger is required for arrhythmia induction. The hyperpolarization-activated, cyclic nucleotide-gated pacemaker "funny current" (I_f), encoded by the HCN genes, plays a key role in sinus node pacemaking [183]. Increased expression of HCN2 and HCN4 in human ventricular myocytes from HF hearts may contribute to the generation of abnormal ventricular-triggered activity in HF [184-185]. Increased HCN subunit expression has been found also in the atria of the failing heart, and increased I_f in atrial tissue may contribute to abnormal ectopic activity in AF [186]. Pulmonary vein foci have been identified as sources of initial triggered activity in AF [68, 187], leading to the development of electrical isolation of these pulmonary vein muscle sleeves via catheter ablation. Remodeling affecting the ryanodine receptors, SERCA and NCX also play important roles in the development of arrhythmic triggers in HF [188-192] and AF [193-195], and the reader is referred to excellent reviews on these topics in the current issue [196-197].

Contribution of Myocardial Ischaemia and Ischaemia-Induced Remodeling to the Development of Arrhythmias in Heart Failure

Myocardial ischaemia and infarction can both cause and be a consequence of HF and AF, and contribute to arrhythmogenic electrophysiological changes and remodeling via their own distinct mechanisms [20, 198]. These mechanisms include increased dispersion of repolarization between regions with different degrees of ischaemia and different degree of activation of K_{ATP} channels [198-201], impairment of conduction in early ischaemia [202], significantly different remodeling of repolarization and conduction in non-infarcted versus infarction border zone tissues [20], potassium loss from ischaemic cardiac tissue leading to heterogenous membrane potential depolarization of tissues with varying degree of

ischaemia [203-204]. These electrical and structural changes can add to the already complex alterations present due to HF and/or AF.

III. NOVEL PHARMACOLOGICAL APPROACHES FOR THE TREATMENT OF ARRHYTHMIAS IN HEART FAILURE

In the final part of this review, the possible antiarrhythmic pharmacological modulation of selected promising targets identified by HF and AF induced remodeling studies are discussed.

$I_{Na, late}$ Inhibitors

In addition to the rapidly inactivated component of the $Na_V1.5$ carried, *SCN5A* gene encoded human voltage dependent peak sodium current (I_{Na}), that is responsible for the fast upstroke of the cardiac action potential and impulse propagation in the myocardium, a slowly inactivating sodium current component has been identified that persists through the action potential plateau [205-206]. The late sodium current ($I_{Na, late}$) has an amplitude 100 fold smaller compared to the peak Na^+ current, however, it may contribute to the plateau phase of the AP and to dispersion of APD in the myocardium [207]. Increased $I_{Na, late}$ has been observed in several cardiovascular diseases, including myocardial ischaemia, angina pectoris, congenital long QT syndrome, HF and AF [208-211]. In the ventricle, increased $I_{Na, late}$ prolongs the action potential duration [205, 209, 212] and facilitates EAD generation [212-213], while in guinea pig atrial myocytes it was shown to play a role in DAD formation and sustained triggered activity [155]. Therefore, the inhibition of the $I_{Na, late}$ current has been proposed as a promising new approach for the treatment of ventricular arrhythmias in HF as well as AF management [214-215]. However, any novel compound developed against this target needs to show considerable selectivity for the inhibition of $I_{Na, late}$ as opposed to peak I_{Na} inhibition to avoid adverse effects on myocardial conduction and contractility, i.e. to be useful in patients with reduced ventricular function and/or structural heart disease. Interestingly, amiodarone, the most effective antiarrhythmic multichannel blocker drug exhibited a 13-fold more potent inhibitory effect on $I_{Na, late}$ than on peak I_{Na} [216]. Resveratrol, a red wine polyphenol with cardioprotective characteristics [217] has been shown to possess a 2-fold selectivity for late over peak I_{Na} inhibition [218]. Ranolazine, a $I_{Na, late}$ blocker approved for the treatment of angina pectoris [219], is considered to have a 30 to 40-fold higher $I_{Na, late}$ inhibitory potency over peak I_{Na} [220]. However, in canine and human cardiac preparations, ranolazine significantly and use-dependently decreased the maximum rate of depolarization (V_{max}) at a concentration of 10 μM, suggesting a peak I_{Na} inhibiting effect with Class I/B antiarrhythmic characteristics in concentrations previously considered to be selective for $I_{Na, late}$ inhibition [221]. In guinea pig ventricular myocytes, ranolazine inhibited the increase of $I_{Na, late}$ induced by sea anemone toxin ATX-II administration [222]. In left ventricular myocytes from failing dog hearts, ranolazine reversed abnormalities of repolarization and contractile dysfunction [223]. Recently, ranolazine has been shown to reduce the I_{Kr} blocker dofetilide induced TdP in dogs with chronic atrioventricular block [224], a large animal proarrhythmia model featuring impaired repolarization reserve due to downregulation of I_{Ks} [225]. It should be noted that ranolazine also blocks I_{Kr} [226], however, its blocking effect is not frequency dependent and recovery from this block is fast [227]. Thus, the antiarrhythmic effects of ranolazine were attributed to $I_{Na, late}$ inhibition rather than I_{Kr} block, and the net effect of the drug on the APD was considered to depend on the magnitudes of $I_{Na, late}$ and I_{Kr} in the given situation. Ranolazine was shown to cause a slight prolongation of the QT interval in patients [228]. In a recent paper in a Langendorff-perfused normal rabbit heart model (without increased $I_{Na, late}$) 10 μM ranolazine further increased d-sotalol induced action potential duration prolongation, however, the compound also reduced the incidence of d-sotalol and low potassium concentration-induced TdP [229]. These results strongly suggest that ranolazine has additional electrophysi-

ological effects that may prove to be beneficial or even detrimental (further prolongation of repolarization) in certain clinical settings. Therefore, compounds with more selective $I_{Na, late}$ over peak I_{Na} effects are desirable and preferably devoid of I_{Kr} blocking properties to prevent ventricular pro-arrhythmic adverse effects in patients with HF and/or diseases impairing ventricular repolarization reserve. In this regard, a novel, highly selective $I_{Na, late}$ inhibitor (100-fold more potent late current than peak current inhibition), GS-458967 (GS967; Fig. **4**) was synthesized, that did not affect other currents [230] and exhibited protective effects against experimental ventricular and atrial arrhythmias [231-232]. In a very recent publication, a novel small molecule targeting multiple mechanisms involved in atrial fibrillation showed a 3-fold higher $I_{Na, late}$ inhibition over peak I_{Na} inhibition, in addition to other ion channel blocking properties, and exhibited efficacy against AF in a chronic atrial tachypacing induced AF dog model [233]. Another novel $I_{Na, late}$ inhibitor, F 15845, reduced the incidence of coronary artery ligation induced arrhythmias in rats [234]. Based on these data, inhibition of $I_{Na, late}$ represents a promising approach for the treatment of both ventricular and atrial arrhythmias in HF. A more detailed discussion of the pathological consequences of increased $I_{Na, late}$ and the potential antiarrhythmic applications of $I_{Na, late}$ blockers is the subject of a pertinent paper in this issue [235].

Potassium Channel Activators

As already discussed, APD prolongation is a consistent finding in ventricular myocytes from failing animal and human hearts [124], and repolarization prolongation is a major cause of serious ventricular arrhythmias and sudden cardiac death in HF [236]. Furthermore, increased spatial dispersion of repolarization due to non-uniform APD prolongation, an important contributor to the creation of an arrhythmia substrate was found in HF and cardiac hypertrophy [237], that can be further exacerbated by K^+ channel blocking drugs in these patients due to the different regional and transmural distribution of expression of these channels. In theory, there are several approaches that can be utilized to limit excessive AP prolongation in congenital and acquired long QT via the activation of different voltage dependent potassium channels. Below, the effects of novel compounds developed for the pharmacological activation of I_{Kr}, I_{Ks} and I_{to} are discussed.

Pharmacological activators of I_{Kr} have been the most intensively studied among voltage gated K^+ channel activators so far. A number of I_{Kr} activators have been developed by different companies in recent years (Fig. **5**) [238-240]. NS1643 and NS3623 (by NeuroSearch) influence hERG1 inactivation, both causing a rightward shift on the inactivation curve of the current [238, 241]. It is important to note that NS1643 blocks I_{Ks} too, albeit only at slow pacing rates [242]. Since I_{Ks} plays a critical role in cardiac ventricular repolarization reserve [243], it is not yet clear how this effect influences the antiarrhythmic activity of NS1643. Another hERG1 channel agonist, RPR260243 (by Sanofi-Aventis), influences channel deactivation properties [239] and also causes a rightward shift on the inactivation curve of the current [244], similarly to the NS hERG1 activator compounds. Additional hERG1 activator compounds were developed by Pfizer, PD-118057 and PD-307243 [240], and the latter has been shown to slow both deactivation and inactivation of the channel. ICA-105574 was developed by Icagen (later acquired by Pfizer) and was shown to be a potent inhibitor of hERG channel inactivation and to shorten action potentials in guinea pig ventricular cardiomyocytes [245]. A very recent study compared the effects of NS1643 and ICA-105574 in guinea pig preparations and found that both compounds shortened action potentials in isolated ventricular cardiomyocytes and QT intervals in isolated hearts, however, only ICA-105574 prevented I_{Kr} and I_{Ks} inhibitor induced arrhythmias in isolated hearts [246]. Importantly, ICA-105574 exhibited proarrhythmic adverse effects in normal hearts when applied in higher concentrations in the same study. Although NS1643 did not show antiarrhythmic effects in isolated
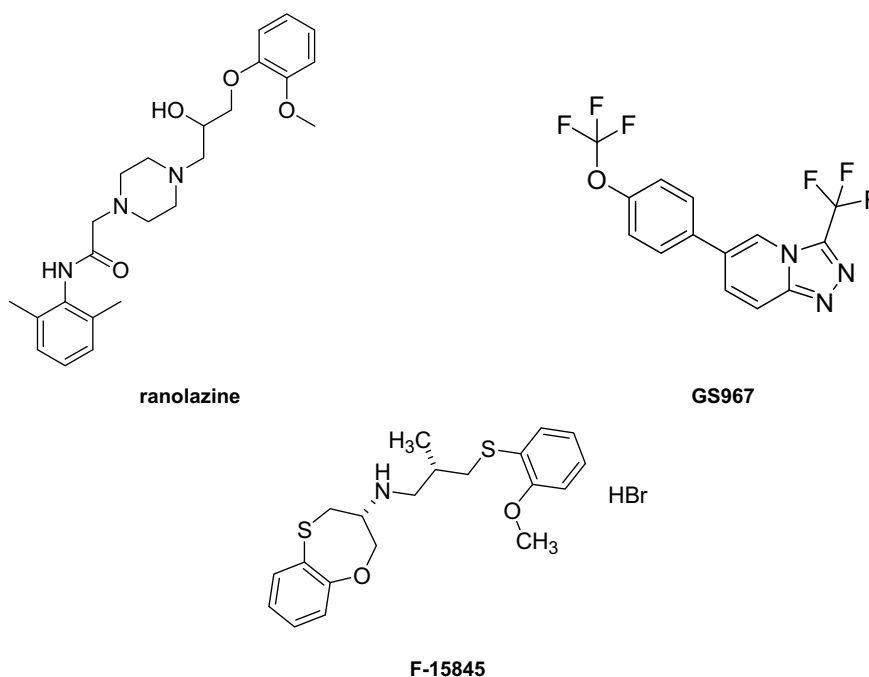
ranolazine

GS967

F-15845

Fig. (4). Chemical structures of representative $I_{Na, late}$ blockers.

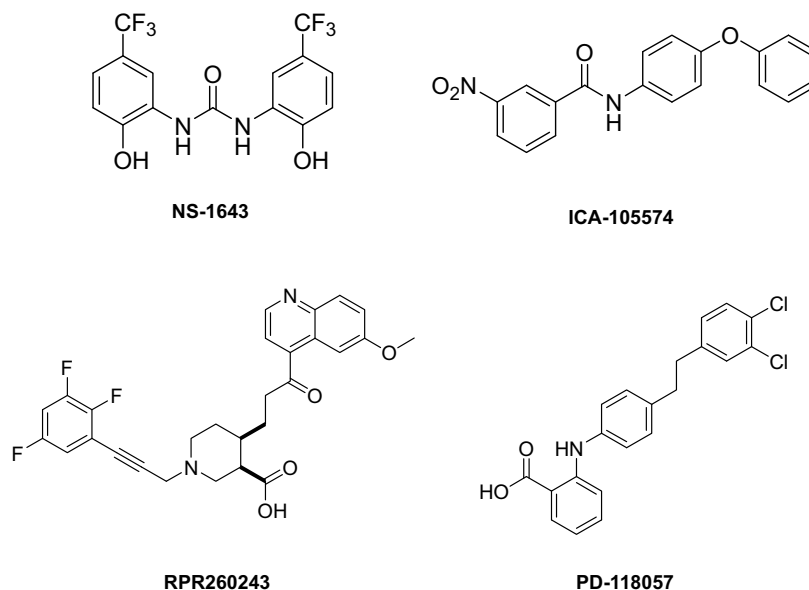**NS-1643**

ICA-105574

RPR260243

PD-118057

Fig. (5). Chemical structures of representative I_{Kr} activators.

guinea pig hearts [246], in isolated guinea pig ventricular cardio-myocytes NS1643 prevented triggering activity due to early after-depolarizations [242]. NS1643 convincingly exhibited antiarrhythmic activity in two different rabbit models of TdP [247]: in rabbits with chronic atrioventricular block and bradycardia [248], and in the classical methoxamine-sensitized rabbit model [249]. In a transgenic rabbit model of congenital LQT1 syndrome, NS1643 significantly shortened the QTc interval, however, it increased the incidence of arrhythmias in this model and the proarrhythmic effect was attributed to the excessive repolarization shortening in these animals [250]. NS3623 shortened the QTc interval in anesthetized and conscious guinea-pigs, and reversed QTc prolongation induced by the I_{Kr} blocker E-4031 [251]. Interestingly, NS3623 impaired conduction in optical mapping experiments in Langendorff-

perfused guinea-pig hearts, however, the authors found that di-4-ANEPPS, the voltage sensitive dye itself decreased conduction velocity, raising the possibly of confounding these results [252].

The slow component of the delayed rectifier potassium current, I_{Ks}, plays a critical role in cardiac ventricular repolarization reserve [136, 243, 253], and its downregulation has been confirmed in animal models of HF and cardiac hypertrophy as well as in human HF [20, 117, 125, 132, 225]. Its pharmacological activation could be used for increasing repolarization reserve and for the prevention of excessive prolongation of action potentials at slow heart rates in clinical settings associated with I_{Ks} downregulation and/or dysfunction. Surprisingly, few compounds have been developed for this purpose and very few studies have investigated the effect of I_{Ks} activators on repolarization. An I_{Ks} activator, L-364, 373 (Fig. **6**)
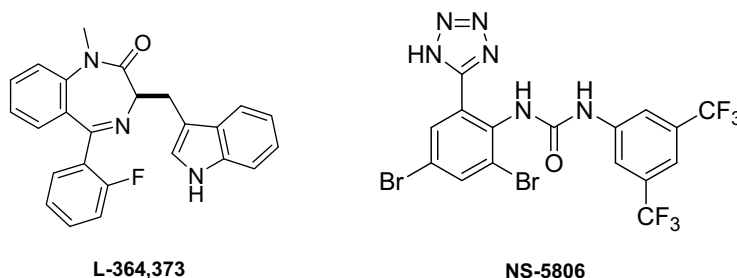
Fig. (6). Chemical structure of the I_{Ks} activator L-364, 373 and I_{to} activator NS5806.

developed more than 15 years ago [254] was shown to enhance I_{Ks} by causing a negative shift in the voltage dependence of channel activation and by slowing channel deactivation [255]. The shortening of the APD was observed in control, hypertrophied and dofetilide (I_{Kr} blocker) treated rabbit ventricular myocytes accompanied by EAD elimination in hypertrophied cardiomyocytes in the same study. Some investigators failed to find any I_{Ks} activating effect of this compound [256], while others found the drug rescued repolarization in a guinea-pig cellular model of LQT2 syndrome [257]. However, according to the results of a recent study, the two enantiomers of L-364, 373 had opposing effects on I_{Ks}, explaining why the racemic drug was devoid of any I_{Ks} activating effect in other studies [258]. In order to properly investigate the putative beneficial effect of I_{Ks} activation in pathological settings with impaired repolarization reserve and arrhythmogenesis, additional I_{Ks} activator compounds need to be studied in different models of congenital and acquired models of prolonged repolarization. Importantly, further elucidation of the roles and tissue distribution of different KCNQ1 channel complexes formed with different regulatory β-subunits are needed before meaningful cardiac selective I_{Ks} activator development becomes feasible [259].

As discussed earlier, HF associated electrical remodeling involves the downregulation of different potassium channels responsible for repolarization, including I_{to} [20]. Impairment of the early phase of repolarization governed by I_{to} can lead to pathological alterations in calcium homeostasis, reduced calcium-induced calcium release and reduced contractility [260]. Therefore, the pharmacological activation of I_{to} may be a suitable target for improving calcium homeostasis and increasing contractility in HF. A recently developed I_{to} activator, NS5806 (Fig. **6**) increased I_{to} by 80% in canine epicardial right ventricular cells, only by 16% in endocardial cells, and increased peak I_{to} in atrial myocytes by 25% [261]. Importantly, in the same study NS5806 was found to strongly inhibit atrial I_{Na}, while the compound had little effect on ventricular I_{Na} [261]. The antianginal and $I_{Na, late}$ inhibitor ranolazine exhibited efficacy against AF and this effect was attributed to its atrial selective I_{Na} blocking properties [262]. Therefore, it would be very interesting to see whether NS5806 had any beneficial effect in an animal model of atrial fibrillation. In a canine model of rapid ventricular pacing induced heart failure, where reduced I_{to} density, slowed recovery of I_{to} from inactivation were observed, the I_{to} activator NS5806 increased I_{to} recovery from inactivation and restored the action potential notch in epicardial cells [263], leading the authors to conclude that some aspects of HF induced electrical remodeling can be reversed by pharmacological activation of I_{to}.

It is important to note that there are differences in the antiarrhythmic effects of these novel voltage gated potassium channel activators, and some exhibited proarrhythmic effects in certain animal models, therefore more, sufficiently detailed studies are needed to elucidate the cellular cardiac electrophysiological effects of these compounds to assess their effects on other ionic currents.

Another approach to APD prolongation limitation and facilitation of repolarization is the pharmacological activation of sar-

colemmal K_{ATP} channels to activate steady-state, voltage-independent potassium current. Figure **7** illustrates that activation of sarcolemmal K_{ATP} can indeed reduce the dispersion of repolarization between canine ventricular papillary muscle and Purkinje fibers elicited by selective I_{Kr} block at slow pacing frequences [170]. Pharmacological activators of K_{ATP} have been shown to protect against arrhythmias induced by triggered activity, EADs and DADs [264-266]. The K_{ATP} opener nicorandil reduced EADs, shortened monophasic action potential duration and prevented syncope recurrence in patients with congenital LQT and in animal models of LQT [267-269]. Pharmacological activation of K_{ATP} can reduce calcium overload and improve contractile function [270], and at least in part, this protective mechanism involves resting membrane potential hyperpolarization and reduction in reverse-mode NCX activity [271-272].

However, the activation of sarcolemmal K_{ATP} can lead to proarrhythmic side effects, most likely due to excessive APD shortening [273-274]. In a recent optical mapping study the K_{ATP} openers diazoxide and pinacidil decreased APD and promoted burst pacing induced arrhythmias in coronary-perfused human atria and ventricles isolated from failing hearts [275]. To reduce myocardial ischemia induced sarcolemmal K_{ATP} activation that can result in increased dispersion of repolarization between cardiac tissue regions with different degrees of ischemia, the cardioselective inhibition of K_{ATP} channels has been proposed [276]. In addition, the presently available sarcolemmal K_{ATP} openers are not selective for cardiac K_{ATP} channels and activate vascular smooth muscle K_{ATP} channels, reducing total peripheral resistance and decreasing blood pressure [170] that can lead to reflex tachycardia. Therefore, cardiac sarcolemmal K_{ATP} activators are needed to properly assess the antiarrhythmic and proarrhythmic effects of cardiac sarcolemmal K_{ATP} activation in different pathological settings. The different molecular composition of sarcolemmal K_{ATP} channels in different tissue types certainly suggest that this aim can be achieved [277-278].

In summary, K_{ATP} channel activation can be both antiarrhythmic and proarrhythmic based on actual cardiac pathological settings and degree of ischemia, and the inhibition of sarcolemmal K_{ATP} has been suggested as an ischemia selective antiarrhythmic therapeutic modality. The detailed discussion of the role of K_{ATP} channels in cardiac arrhythmias is beyond the scope of this paper and the reader is referred to a recent review [170] and an update on this topic in this issue [279].

I_{Kur} Blockers

The atrial specific ultrarapidly activating I_{Kur} channel [164, 280] has been identified as a very promising target for drug development for the atrial selective pharmacological treatment of AF with little or no ventricular side effects. In line with these expectations, a large number of I_{Kur} inhibitor compounds have already been developed and tested in different experimental models in the last 15 years. The comprehensive discussion of these compounds is well beyond the scope of this review and the reader is referred to an excellent re-
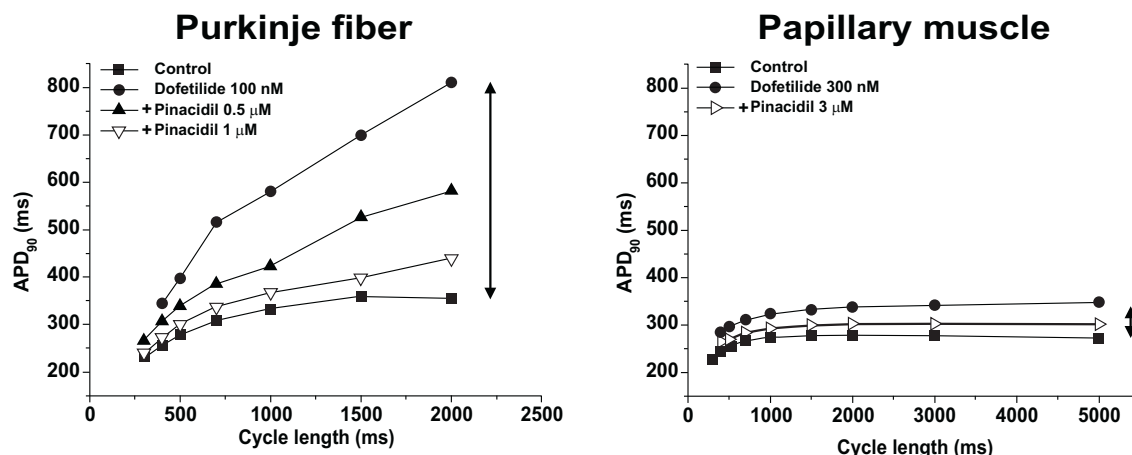
Fig. (7). The cardiac sarcolemmal K_{ATP} channel activator pinacidil reduces reverse use-dependent repolarization prolongation and dispersion of repolarization following the administration of the I_{Kr} blocker dofetilide in canine Purkinje fibers and papillary muscle. Please note the large difference in cycle length dependent repolarization prolongation in the two preparations. APD_{90}: action potential duration at 90% repolarization. Reproduced from [170] with permission.

view on this topic [281]. It is important to note, however, that the selective inhibition of these channels by pure I_{Kur} blockers might be somewhat disappointing, since downregulation of I_{Kur} in prolonged AF has been reported [149, 151, 282].

$I_{K, ACh}$ Inhibitors

GIRK1 and GIRK4 channels conducting acetylcholine-activated potassium current, $I_{K, ACh}$, can be found predominantly in the atria [283], and they mediate the effects of vagal nerve stimulation on the atria via M_2 receptors and can induce AF [284]. The activation of these channels shortens atrial APD, atrial effective refractory period and hyperpolarizes the resting membrane potential - all these effects favour the stabilization of AF rotors and promoting re-entry. The constitutive activation of these channels in AF has been shown [159], therefore their inhibition is expected to abolish AF. Indeed, the application of a derivative of the honey bee venom toxin tertiapin, tertiapin-Q inhibited constitutive $I_{K, ACh}$ in nanomolar concentrations [285] and was shown to terminate AF in a canine aconitine-induced AF model [286]. Subsequently, the $I_{K, ACh}$ blocking effects and efficacy in experimental AF were reported for a series of novel compounds, including NIP-141, NIP-142, NIP-151 and NTC-801 [287-290]. Some of these compounds inhibit other ionic currents also targeted in the treatment of AF, such as the already discussed I_{Kur} [291]. It is not known yet, however, whether these compounds influence ventricular contractility that would interfere with their beneficial effects against AF in the setting of reduced left ventricular function, and few data is available on their effects on chronic AF with atrial remodeling.

NCX Inhibitors

The Na^+/Ca^{2+} exchanger is upregulated and its function is enhanced in HF and AF [192-193]. Increased NCX activity can contribute a significant inward current leading to the development of DADs in HF [130]. In a canine heart failure model, inhibition of NCX led to normalization of cellular calcium handling [292], and inhibition of the NCX by SEA-0400 (Fig. **8**) prevented EADs and DADs in dog ventricular tissue [293]. However, previously available NCX blockers lacked selectivity, most importantly they also blocked $I_{Ca, L}$ [294], making it very difficult to separate the relative contribution of their NCX blocking and calcium channel blocking effects to the observed results. A very recent publication introduced a novel NCX blocker compound with improved selectivity for the NCX over $I_{Ca, L}$, ORM-10103 (Fig. **8**) [295]. With the identification of this compound it now seems to be feasible to more critically assess the physiological role of the NCX in calcium homeostasis, as

well as the effect of NCX inhibition on arrhythmias in the setting of HF.

I_f Blockers

An association between elevated resting heart rate and increased risk of mortality has been established in heart failure patients [296]. Therefore, reduction of elevated heart rate in HF patients seems beneficial. Moreover, the increased HCN2 and HCN4 expression in human failing ventricular and atrial cardiomyocytes may contribute to abnormal ectopic activity and trigger arrhythmias in HF [184-186]. In theory, isoform selective I_f blockers could prevent the triggering activity in HF occurring through HCN2 and HCN4 pathological activation. The most prominent representative I_f blocker compound, ivabradine is approved for the treatment of angina pectoris in patients who do not tolerate beta adrenergic blockers [297]. In pooled data from the BEAUTIFUL and SHIFT trials, in patients with reduced left ventricular function and elevated heart rate, ivabradine decreased HF associated hospitalization and cardiovascular mortality [298]. Ivabradine is a reasonably selective I_f current blocker [299], however, additional ion channel blocking effects of ivabradine have been identified that could contribute to its antiarrhythmic activity [300]. Recently, some important steps have been made in the development of new I_f blockers showing relative isoform selectivity [301], and EC18 was identified as a selective HCN4 blocker that slowed the slope of diastolic depolarization in canine Purkinje fibers [302]. Further studies are needed, however, to determine the effects of isoform selective I_f blockers on enhanced triggered activity in experimental HF.

Potential Candidates with Combined Mechanism of Action: the Way Forward?

The development of most of the compounds discussed so far have been following the concept of creating relatively selective ion channel blockers for the treatment of arrhythmias. However, sobering lessons learnt from clinical trials following selective sodium and potassium channel blocker administration in patients with reduced left ventricular function [57-58], and the exceptional efficacy of amiodarone suggests that novel antiarrhythmic drugs with modulatory effects on multiple ion channels may exert beneficial effects in the treatment of atrial and ventricular arrhythmias.

Dronedarone

Dronedarone is a new multichannel blocker antiarrhythmic drug approved for the treatment of AF. The drug was developed as an amiodarone structural analogue without the iodine moiety in an effort to reduce the serious extracardiac side effects of chronic
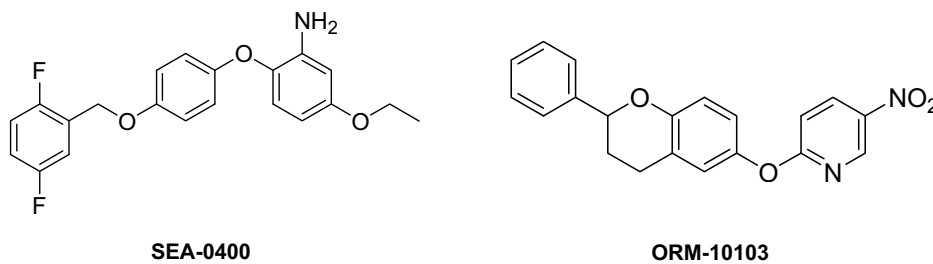
Fig. (8). Chemical structures of the Na^+/Ca^{2+} exchanger inhibitors SEA-0400 and ORM-10103.
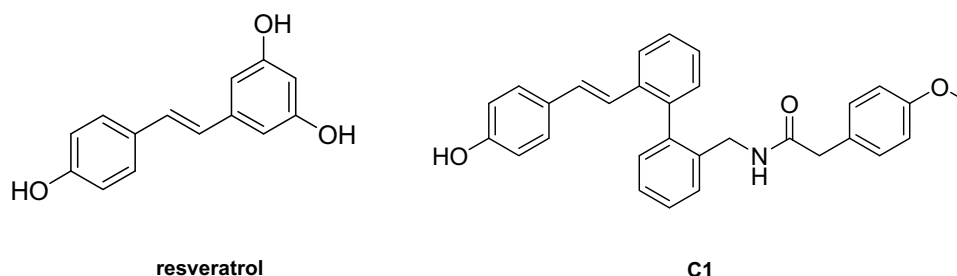

Fig. (9). Chemical structures of resveratrol and Compound 1 (C1).

amiodarone treatment [48]. Dronedarone blocks I_{Kr}, I_{Ks}, I_{K1}, I_{to}, I_{Na} and $I_{Ca, L}$ [303]. However, dronedarone was found later in the PAL-LAS clinical trial to increase heart failure events [52], and in the ANDROMEDA trial to increase mortality in patients with severely impaired left ventricular function [50]. Therefore, dronedarone is not recommended to treat arrhythmias in patients with structural heart disease and reduced left ventricular function [33].

Vernakalant

Vernakalant is a recently introduced antiarrhythmic drug that is relatively atrial specific and blocks several ionic currents, such as I_{Kur}, I_{to}, $I_{K, ACh}$ and I_{Na} [304], and was developed for the treatment of AF. Following intravenous administration, vernakalant effectively converted AF to sinus rhythm in recent onset and postoperative AF [305-307]. In a recent clinical trial oral vernakalant was found to be effective for maintaining sinus rhythm following cardioversion of AF [308]. Vernakalant does not exhibit proarrhythmic effects in dogs with chronic atrioventricular block, a model featuring I_{Ks} downregulation, bradycardia and increased susceptibility to arrhythmias [309]. No proarrhythmic adverse effects were found in a rabbit proarrhythmia model [310] or in a recent clinical trial [308]. In AF associated with HF, vernakalant appears to be less effective for cardioversion and increased incidence of serious hypotensive episodes and ventricular arrhythmias were detected in patients with left ventricular dysfunction [311]. Vernakalant is currently approved in Europe for the conversion of recent onset AF.

The complex etiology of AF and the multiple mechanisms responsible for the development and maintenance of AF led to the suggestion that novel compounds targeting several pathways involved in AF may exhibit improved efficacy [312-313]. In this regard, resveratrol, an intensively investigated red grape polyphenol that possesses cardioprotective properties [216] could serve as a potential parent compound for the development of future drugs to treat both AF and heart failure associated ventricular arrhythmias. Resveratrol has been shown to inhibit NFAT activation [314], a pathway implicated in AF [315] and pathological cardiac hypertrophy [316]. Resveratrol also inhibited hypertrophic remodeling [317], as well as late I_{Na} with preference over peak I_{Na} [218]. Indeed, in a very recent study Compound 1 (C1; Fig. **9**), a resveratrol derivative was shown to possess multi-channel blocking properties and exhibited efficacy against AF in a chronic atrial tachypacing

induced atrial fibrillation dog model [233]. This novel compound inhibited peak and late I_{Kur} (IC$_{50}$: 0.36 and 0.11 µmol/l, respectively), $I_{K, ACh}$ (IC$_{50}$: 1.9 µmol/l), peak I_{Na} and $I_{Na, late}$ (IC$_{50}$: 3.0 and 1 µmol/l, respectively), demonstrated NFAT inhibitory and antioxidant properties that were similar to those of resveratrol. Importantly, C1 showed only weak hERG channel inhibition and did not prolong the QT interval in conscious dogs, suggesting that the compound did not significantly influence ventricular repolarization and was unlikely to provoke ventricular arrhythmias. Based on these effects, it was concluded that C1 as a multifunctional small molecule targeting several key pathways involved in the development and maintenance of AF.

IV. SUMMARY

Heart failure and atrial fibrillation are the "two new epidemics of cardiovascular disease" [18]. Both HF and AF are associated with significant morbidity and mortality and their prevalence icreases with age. The two conditions are often diagnosed together and the development of the other condition further deteriorates the prognosis. Almost half of HF patients die due to ventricular fibrillation, and AF leads to increased mortality due to increased risk for stroke and heart failure. Both chronic HF and AF lead to structural and electrical remodeling of the heart that can significantly alter targets for pharmacological antiarrhythmic treatment. Current pharmacological approaches for the management of HF associated ventricular arrhythmias and AF lack efficacy and often lead to serious cardiovascular and/or extracardiac adverse events. For the treatment of ventricular arrhythmias in HF, novel approaches may include improving electrical remodeling impaired repolarization capacity via the activation of selected potassium currents and/or inhibition of abnormal depolarizing currents, normalization of impaired conduction and improving dysfunctional intracellular calcium homeostasis. Future pharmacological treatment of AF may focus on atrial selective modulation of ionic currents to avoid ventricular side effects and targeting other mechanisms involved in AF generation and maintenance with multifunctional compounds, with particular attention paid to avoid adverse effects in patients with left ventricular dysfunction. However, the upstream treatment of both conditions aiming at the reduction of disease induced remodeling is also emphasized. Due to the heterogenous mechanisms involved in ventricular and atrial arrhythmia development, it is expected that

compounds with multiple mechanisms of action may show improved efficacy in the treatment of arrhythmias in heart failure.

ABBREVIATIONS

AF	=	Atrial fibrillation
APD	=	Action potential duration
Cx43	=	Connexin 43
HF	=	Heart failure
I_{K1}	=	Inwardly rectifying potassium current
I_{Kr}	=	Rapid component of the delayed rectifier potassium current
I_{Ks}	=	Slow component of the delayed rectifier potassium current
I_{Kur}	=	Ultra-rapidly activating potassium current
I_{to}	=	Transient outward potassium current
$I_{Na, L}$	=	Late or persistent sodium current
I_{KATP}	=	Adenosine-triphosphate sensitive potassium current
$I_{K, ACh}$	=	Acetylcholine-regulated potassium current
NCX	=	Na^+/Ca^{2+} exchanger
SCD	=	Sudden cardiac death
TdP	=	Torsades de Pointes
VF	=	Ventricular fibrillation
V_{max}	=	Maximum rate of depolarization

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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