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INVITED SPOTLIGHT REVIEW

Why translation from basic discoveries to clinical applications is so difficult for atrial fibrillation and possible approaches to improving it

Stanley Nattel [1,2,3,4]*, Philip T. Sager[5], Jörg Hüser [6], Jordi Heijman [4,7], and Dobromir Dobrev[1,4,8]

[1]Department of Medicine, Montreal Heart Institute and Université de Montréal, Montreal, Canada; [2]Department of Pharmacology and Therapeutics, McGill University, Montreal, Canada; [3]IHU LIYRC Institute, Bordeaux, France; [4]Faculty of Medicine, Institute of Pharmacology, West German Heart and Vascular Center, University Duisburg-Essen, Hufelandstrasse 55, 45122 Essen, Germany; [5]Department of Medicine, Cardiovascuar Research Institute, Stanford University, Palo Alto, CA, USA; [6]Research and Development, Preclinical Research, Cardiovascular Diseases, Bayer AG, Wuppertal, Germany; [7]Department of Cardiology, Cardiovascular Research Institute Maastricht, Faculty of Health, Medicine, and Life Sciences, Maastricht University, Universiteitssingel 50, 6229 ER Maastricht, The Netherlands; and [8]Department of Molecular Physiology & Biophysics, Baylor College of Medicine, Houston, USA

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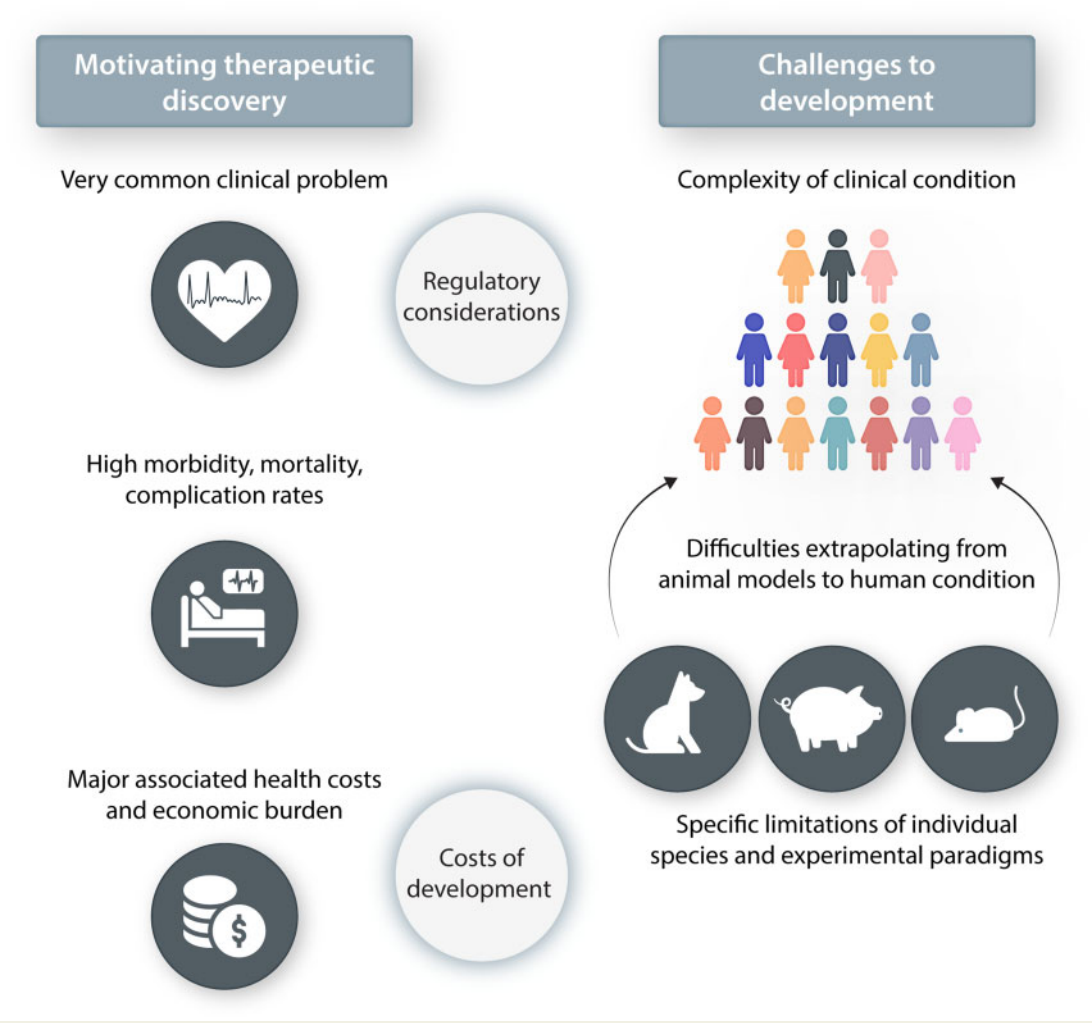
Abstract

Atrial fibrillation (AF) is the most common sustained clinical arrhythmia, with a lifetime incidence of up to 37%, and is a major contributor to population morbidity and mortality. Important components of AF management include control of cardiac rhythm, rate, and thromboembolic risk. In this narrative review article, we focus on rhythm-control therapy. The available therapies for cardiac rhythm control include antiarrhythmic drugs and catheter-based ablation procedures; both of these are presently neither optimally effective nor safe. In order to develop improved treatment options, it is necessary to use preclinical models, both to identify novel mechanism-based therapeutic targets and to test the effects of putative therapies before initiating clinical trials. Extensive research over the past 30 years has provided many insights into AF mechanisms that can be used to design new rhythm-maintenance approaches. However, it has proven very difficult to translate these mechanistic discoveries into clinically applicable safe and effective new therapies. The aim of this article is to explore the challenges that underlie this phenomenon. We begin by considering the basic problem of AF, including its clinical importance, the current therapeutic landscape, the drug development pipeline, and the notion of upstream therapy. We then discuss the currently available preclinical models of AF and their limitations, and move on to regulatory hurdles and considerations and then review industry concerns and strategies. Finally, we evaluate potential paths forward, attempting to derive insights from the developmental history of currently used approaches and suggesting possible paths for the future. While the introduction of successful conceptually innovative new treatments for AF control is proving extremely difficult, one significant breakthrough is likely to revolutionize both AF management and the therapeutic development landscape.

*Corresponding author. Tel: +1 514 376 3330 (ext. 3990); fax: +1 514 376 1355, E-mail: stanley.nattel@icm-mhi.org

Graphical Abstract



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This article is part of the Spotlight Issue on Atrial Fibrillation.

1. Introduction

Atrial fibrillation (AF) is a very common and important clinical problem.[1] The other articles in this issue of *Cardiovascular Research* deal with recent advances in understanding AF, with the mechanistic factors that affect the likelihood of its occurrence and with efforts to apply basic research advances in specific fields to clinical applications. In this article, we aim to provide a general overview of the challenges involved in translating advances in the basic science of AF to clinical medicine. In particular, we discuss the clinical problem of AF and its therapeutics, the basic research models used to study underlying mechanisms and their therapeutic potential, the regulatory constraints and the industry landscape that determines the financial interest/viability of new therapy development. Consideration of these issues makes it clear why advancing AF therapeutics is such an important and challenging goal. We conclude with some ideas about how to approach some of these challenges in order to improve and accelerate the clinical translation of basic discoveries.

2. The problem

2.1 Nature of the problem

AF is the most common sustained arrhythmia, and its prevention and therapy remain a significant unmet medical need.[1] AF is associated with substantial morbidity and mortality and is often difficult to adequately manage. While patients can be asymptomatic, AF is a frequent cause of hospitalizations, thromboembolic events, haemodynamic compromise,

and heart failure (HF), along with symptoms such as fatigue, reduced exercise tolerance, dyspnoea, and syncope, which decrease the quality of life. AF-related stroke appears to be more medically severe than that due to non-AF aetiologies and the stroke risk in non-anticoagulated AF patients is increased ~five-fold.[2] AF is also associated with a two-fold increase in mortality,[3] a three-fold increase in HF,[3] and an increased risk of dementia. Occurring in ~1% of patients <60 years of age, AF has a prevalence that increases in older individuals, affecting up to ~12% of patients aged 75–84 years old; the overall lifetime risk is ~ 37%.[4] The costs associated with AF are large: the incremental associated cost in the USA was estimated at US $6–26 billion per year based on data from 2004 to 2006.[5] A more recent estimate of the incremental annual economic burden of undiagnosed non-valvular AF is US $3.1 billion.[6] Thus, AF is a common, clinically important and economically significant public health problem.

2.2 Current therapeutic landscape

AF is most often diagnosed in patients with underlying heart diseases, including hypertension, coronary artery disease, valvular diseases, and HF, and may occur concurrently with an exacerbation of the underlying cardiovascular condition. However, AF can also occur in patients without overt signs of heart disease or detectable structural remodelling. Varying aetiologies, genetic susceptibilities, and comorbidities contribute to substantial patient heterogeneity. Unlike life-threatening ventricular tachyarrhythmias, serious AF-induced haemodynamic instability is uncommon outside acute/intensive care settings. Severe hypotension, altered mental status, cardiac ischaemia, or decompensated HF are the most relevant indicators of such instability and typically prompt immediate (in most cases electrical) cardioversion.[7–9]

Detection or suspicion of AF in haemodynamically stable patients is generally followed by a thorough diagnostic assessment, including routine laboratory investigations (e.g. thyroid hormone status, electrolyte measurements, renal function analysis) as well as cardiac examinations like an electrocardiogram, echocardiography and Holter monitoring, or longer-term patch recordings to identify underlying cardiac diseases and determine the temporal pattern of AF. The treatment of any underlying cardiovascular risk factors and/or other precipitating contributors, like inflammation for post-operative AF, infection, trauma, sleep disordered breathing, obesity, excess alcohol consumption, hypertension, or cigarette smoking generally provides a first step in AF management. Moreover, concomitant heart disease directly affects therapeutic decision-making and the choice of drugs.

Figure 1 shows a simplified schema of the main steps in the management of AF. AF increases the risk of stroke or HF and consequently requires appropriate anticoagulation and control of ventricular rate in affected individuals. Beyond the prevention of any immediately life-threatening sequelae of this rhythm disorder, the consequences of restoring and maintaining sinus rhythm on mortality in AF-patients were assessed in two landmark trials comparing rate vs. rhythm control, the Atrial Fibrillation Follow-up Investigation of Rhythm Management[10] and the Rate Control vs. Electrical Cardioversion for Persistent Atrial Fibrillation (RACE)[11] studies. In both trials, no significant difference between the two treatment approaches could be demonstrated. The more recent Early Treatment of Atrial Fibrillation for Stroke Prevention Trial[12] did show a reduction in significant cardiovascular outcomes with early institution of rhythm-control in AF-patients, perhaps because aggressive rhythm-control therapy was instituted early (before remodelling became advanced),[13] reopening the debate and emphasizing the importance of improving the available pharmacological options for rhythm-control management. This outcome emphasizes the need for further study of the potential value of an early aggressive rhythm-control strategy and the need for improved pharmacological tools to help in achieving better rhythm control. This article will focus primarily on rhythm-control therapy, without delving into the details of aspects like anticoagulation and rate control.

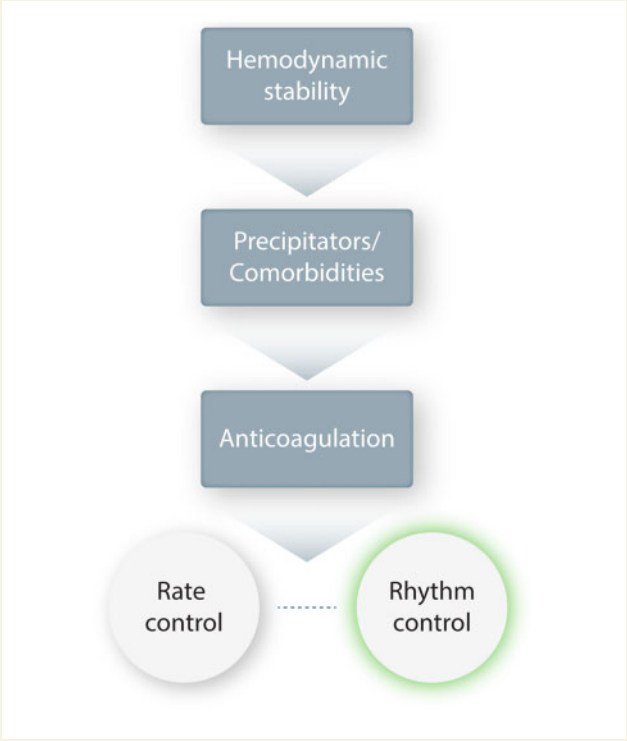

Figure 1 Overall AF treatment strategy schema. This is a simplified schema of the main steps in AF management. Haemodynamic stability must first be ensured, and any precipitators or comorbidities addressed. Anticoagulation is an essential early step in almost all patients to prevent thromboembolic complications. Rate control must be established, even in most patients for whom the primary approach will be rhythm control, since pharmacological rhythm control is not foolproof and rhythm-control drugs can cause a paradoxical acceleration in ventricular rate. The choice between rate control and rhythm control as the principal strategy is based on a variety of patient-specific considerations.

Control of the ventricular response rate is an important component of AF management to control symptoms, prevent ventricular dysfunction, and limit adverse atrial remodelling.[14,15] The RACE-II trial unravelled a somewhat counterintuitive feature of AF therapy by suggesting a lack of benefit from a more strict (<80 beats/min at rest and <110 beats/min during moderate exercise) compared to lenient (<110 beats/min at rest) rate-control strategy.[16] It must be noted that the treating physicians adjusted the treatment in each group according to their clinical judgement, and that while there was a 30 beat/min difference in the target heart-rate cutoffs for the two groups, the difference in mean heart rate was 17 beats/min at the end of dose titration and only 11 beats/min after 1 year in the study (patients were followed for 3 years). Much more needs to be learned to optimize rate-control management and tailor it to the individual patient.

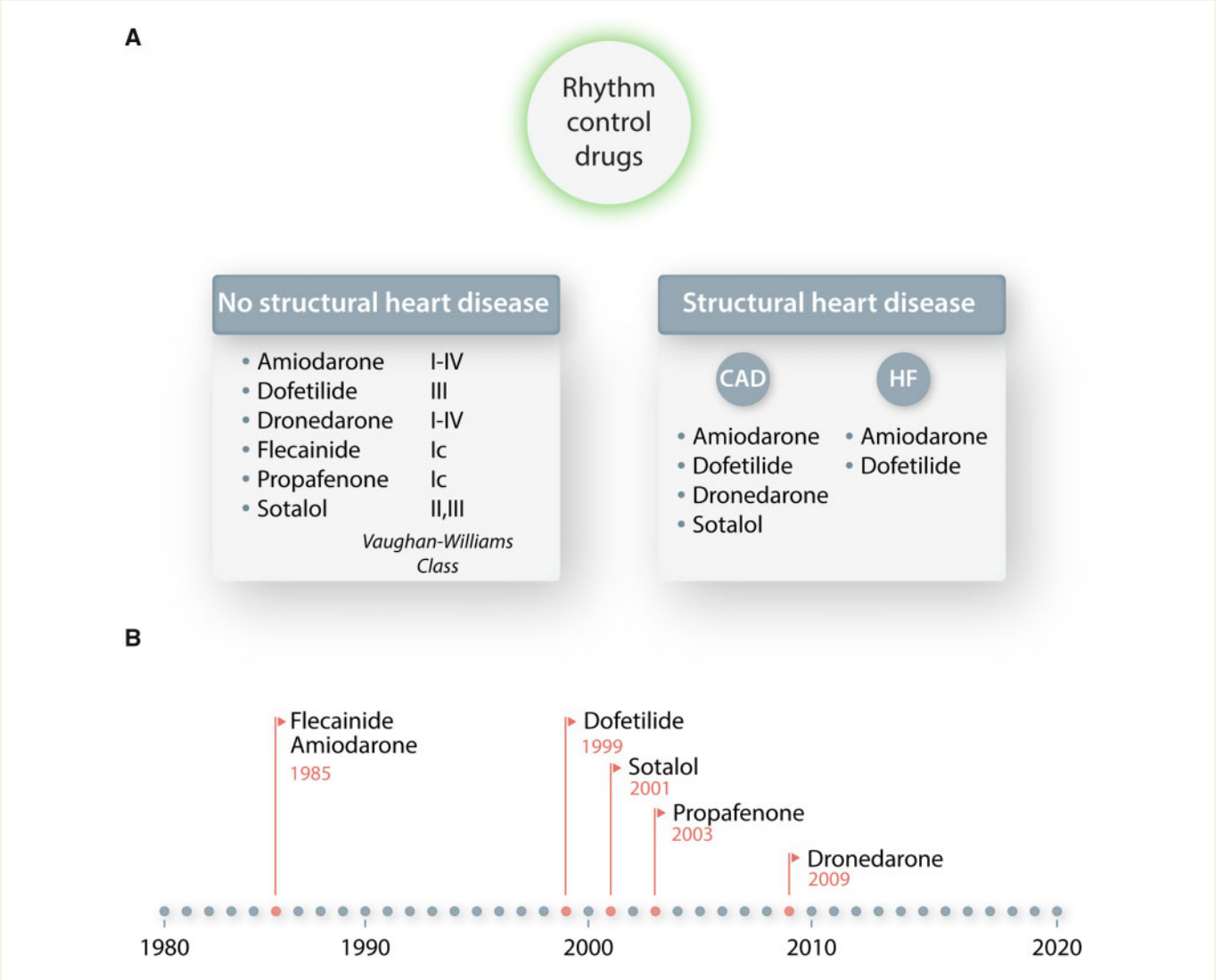

Figure 2 Most commonly used AF rhythm-control drugs (*A*) and a timeline showing their FDA approval year (*B*). In (*A*), the drugs are organized in alphabetical order. The detailed clinical decision-making approach for selection of these drugs is complex and not dealt with in this article. CAD, coronary artery disease; HF, heart failure.

In current clinical practice, the principal motivation for using antiarrhythmic drugs (AADs) is to reduce the symptom burden and improve quality of life in AF-patients.[7–9] Symptoms like palpitations, dyspnoea, fatigue, light-headedness, or chest pain occur in many but not all patients. Their causal and temporal relation to AF episodes is complex and incompletely understood.[17] Rhythm control with AADs and/or catheter ablation traditionally constitutes the last step in the treatment regime, restricted to patients in which symptoms are not adequately controlled by rate control alone. Importantly, because of its limited ability to prevent recurrence of AF, rhythm-control treatment does not obviate the need for anti-thrombotic or rate-control therapy in most patients.

The most commonly used AADs for rhythm control are listed in *Figure 2*. Based on the Singh/Vaughan-Williams classification, they belong to either class III, i.e. potassium channel blockers prolonging the effective refractory period, or class I, i.e. sodium channel blockers reducing excitability and therefore conduction velocity of the action potential, although many of them have actions of more than one class. Drug selection is guided to a significant extent by safety considerations. Many AADs have been associated with risks of bradyarrhythmias, excessive QT prolongation and torsades des pointes, or other types of ventricular tachyarrhythmias. Moreover, patients with underlying heart disease have considerably fewer options because of an increased risk of drug-induced arrhythmias (*Figure 2A*).[7–9] The last significant FDA approval of an AAD in AF was dronedarone in 2009 (*Figure 2B*), which after going through a broad and ambitious development programme eventually fell somewhat short on efficacy and safety grounds and is not widely used today.[18]

The above information makes it clear that the available pharmacological toolbox for rhythm-control treatment is far from optimal. Catheter-based ablation techniques, most prominently pulmonary vein isolation, have emerged as an important alternative, but because of the very large size of the patient population, therapy with AADs still remains the cornerstone of AF treatment, with a clear unmet need for development of more efficient and safer AAD options. Of note, the rate of AAD prescription nearly tripled in the USA between 2004 and 2016.[19] In addition,

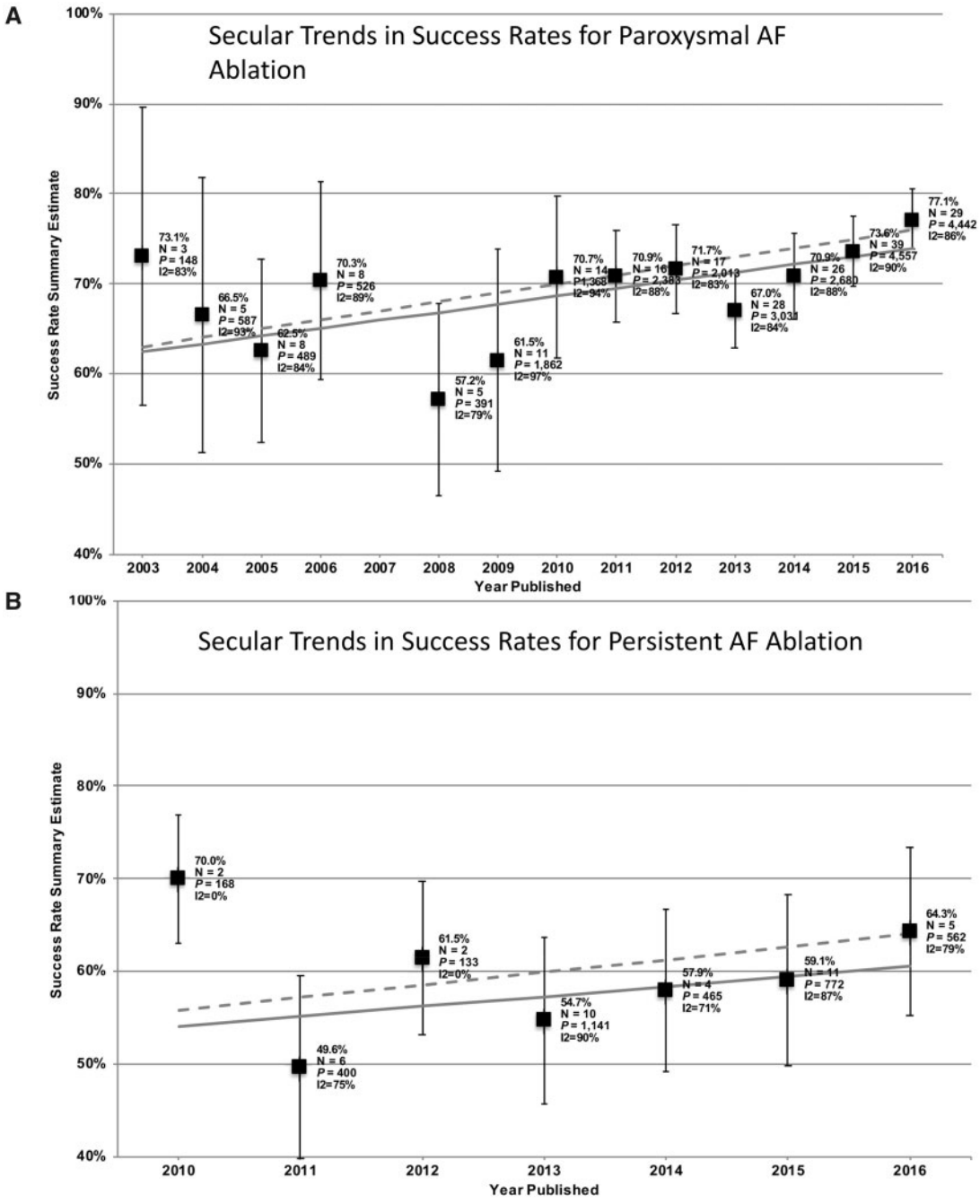

Figure 3 Evolution of success rates of catheter ablation of AF over time. Results shown are those obtained in a meta-analysis by Perino *et al.*[20] (with permission from American Heart Journal and Elsevier). (*A*) Results for paroxysmal AF; (*B*) results for persistent AF. Regression lines suggest adjusted mean improvement rates (dashed lines) that were 1%/year for paroxysmal and 1.4%/year for persistent AF-ablations.

AADs play a significant role in many patients that undergo catheter ablation, whether while waiting for ablation, during the immediate post-ablation period (the 'blanking period') when transient recurrences are common and in cases where ablation is not sufficient and adjunctive AAD therapy is needed.

As for AAD therapy, the primary indication for catheter ablation is to reduce symptoms and improve quality of life, with ablation generally reserved for patients that have failed to respond to one or more AADs.[7–9] The effectiveness of this intervention is greatest in patients with paroxysmal AF, followed by persistent AF, and even long-standing (>12 months) AF can be a therapeutic target.[7–9] A steadily growing number of interventions and corresponding trials to assess sinus-rhythm maintenance with catheter ablation in AAD resistant and naïve patients have finally resulted in changed society guidelines[7–9] that consider ablation as first-line treatment in selected AF-patients. Nevertheless, a recent meta-analysis demonstrated only incrementally improved success rates of

Asset	Originator	Description	Development status (Preclin Ph1 Ph2 Ph3 Reg)
RyR2 inhibitor	Elex Biotech Inc.	Cardiac ryanodine receptor inhibitor	Preclin
CaMKII inhibitor	Sanofi	CaMKII inhibitor	Preclin
NOX4 inhibitor	UCLA	NOX4 inhibitor	Preclin
$I_{K,ACh}$ channel inhibitor	Tufts University	$I_{K,ACh}$ channel inhibitor	Preclin
M201	Acetas	RyR2 modulator, iv	Ph1
HBI-3000	Huya	Multi-ion channel inhibitor, iv	Ph1
HSY244	Novartis	Undisclosed	Ph1
Flecainide acetate	InCardia	Na^+ channel blocker, intranasal	Ph2
AP30663	Acesion	SK channel inhibitor, iv	Ph2
OMT-28	Omeicos	Omega-3 epoxyeicosanoids, oral	Ph2
AGN-151607, Botulinum Toxin A	Allergan	Acetylcholine release inhibitor, inject	Ph2
IncobotulinumtoxinA	Merz Pharm.	Acetylcholine release inhibitor, inject	Ph3
Bisoprolol	Toa Eiyo	Beta blocker, transdermal	Reg

Figure 4 Present development pipeline for AF antiarrhythmic agents in the pharmaceutical industry. The agent being developed is shown at the left, followed by the originating entity, a description of the product and the present developmental stage. CaMKII, calcium/calmodulin dependent protein-kinase type II; $I_{K,ACh}$, acetylcholine-gated potassium channel; Na^+ channel, sodium channel; NOX4, NADPH oxidase type 4; RyR2, ryanodine receptor type 2; SK channel, small-conductance calcium-dependent potassium channel; UCLA, University of California at Los Angeles.

catheter ablation for both paroxysmal and persistent AF between 2006 and 2016 (*Figure 3*), with present sinus-rhythm-maintenance rates averaging around 80% for paroxysmal AF and 65% for non-paroxysmal AF,[20] suggesting that ablation is far from being a cure for AF. Moreover, outcome trials like CABANA have thus far been unable to show definitively a clear benefit of ablation vs. standard therapy.[21] Part of the reason might be extensive crossovers from pharmacological to ablation therapy: both a treatment-received analysis and a per-protocol treatment comparison suggested all-cause mortality reductions with ablation therapy in CABANA.[21] Although the Catheter Ablation vs. Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) trial did suggest improved outcomes with a catheter-ablation rhythm-control strategy in HF patients,[22] the subsequent Atrial Fibrillation Management in Congestive Heart Failure With Ablation (AMICA) study did not demonstrate similar improvement[23] and the question remains open. Differences between the trials that might explain the discrepant outcomes include the number of patients per group (179/184 in CASTLE-AF vs. 68/72 in AMICA), the overall illness of the study populations (CASTLE-AF patients were less sick, with 30/35% in paroxysmal AF vs. 19/28% in AMICA, LV ejection fraction averaging 32/33% vs. 25/28%, respectively, class III or greater HF in 28/31% vs. 59/62%) and the follow-up duration (>3 years vs. 1 year, respectively).

2.3 Drug development pipeline

With respect to pharmacological therapies, it is clear that despite their reasonably extensive continuing use, the currently available AADs have at most moderate efficacy and are associated with a risk of pro-arrhythmia, particularly in structurally remodelled heart. As shown in *Figure 2*, it has been over 10 years since the introduction of any new drug for AF treatment. Enthusiasm for AF drug development has been dampened by

many factors, including rigorous regulatory requirements and a history of limited efficacy and well-recognized risk for cardiac and non-cardiac side effects. *Figure 4* shows the current status of the AF development pipeline in the pharmaceutical industry and provides only limited hope for short-term progress, considering the notoriously low success rates for this indication. Pipeline assets offer limited innovation beyond already known motifs, including beta blockers, K^+ channel blockers, modulators of cardiomyocyte Ca^{2+} handling, antioxidants, or parasympatholytics. The rationale and experimental basis for these specific targets goes beyond the scope of the present article—the interested reader is directed to recent detailed review articles.[24,25] It is quite unclear whether the efforts in *Figure 4* will be sufficient to produce an effective and widely usable new drug for AF.

2.4 Upstream pharmacologic approaches

The idea that targeting development of the substrate leading to AF might be a more promising approach than attacking the final electrical end-product has been around for over 20 years.[26] Upstream therapies, as such treatments have come to be called, aim to reduce or prevent structural and/or electrical remodelling that promotes AF and thus reduce the likelihood of the primary occurrence or progression of the arrhythmia. Structural remodelling results in fibrosis and other changes in the extracellular matrix, that promote atrial reentry.[27] Electrical remodelling involves shortening of the atrial action potential duration and the atrial refractory period, also favouring reentry.[27] In addition, abnormal cellular Ca^{2+}-handling may lead to arrhythmogenic afterdepolarizations and spontaneous ectopic beats, while contributing to the progression of the arrhythmogenic substrate that initiates and maintains reentry.[28]

Approaches to upstream therapy that have been applied clinically include angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), aldosterone antagonists, beta blockers, mineralocorticoid inhibitors, statins, and polyunsaturated fatty acids.[29–40] While there have been a number of disappointing trials, the available data point to the value of ACE inhibitors, ARBs and aldosterone inhibitors in preventing new-onset AF among patients with established stimuli to structural remodelling, like hypertension or HF associated with reduced ejection fraction.[29–34,36] However, studies investigating ACE inhibitors and ARBs for secondary prevention are controversial and inconsistent, without a clear efficacy advantage.[35] Although observational findings suggest potential value, the weight of available data suggest limited benefit, if any, for statins, beta blockers and polyunsaturated fatty acids in AF-prevention.[35,37–40]

3. Experimental development of new anti-AF approaches and challenges

3.1 Why are experimental models needed?

The development of new pharmacological therapies for AF, as for many other clinical conditions, is closely linked to an improved understanding of critical basic mechanisms.[41] Experimental models are needed that mimic aspects of the complex clinical condition, in order to discover novel mechanisms that control the occurrence and progression of AF and to test specific mechanistic hypotheses. In addition, preclinical models are needed for the evaluation of candidate drugs and interventions for desired effects, ranging from the putative cellular or molecular mechanism of action to the desired beneficial effect on AF occurrence, maintenance, or progression.

3.2 What are the principal properties of the available preclinical models?

A variety of approaches and tools are available for the evaluation and discovery of tractable mechanisms at the organismal, organ, cellular, and molecular levels. *Figure 5* summarizes the types of models that are used to investigate AF pathophysiology. Considerations within each model include the species to be studied and the manipulations used to create an arrhythmic substrate relevant to clinical AF.

AF itself induces AF-promoting remodelling, largely through the effects of a very rapid atrial rate, often referred to as 'AF begets AF'.[42,43] Tachypacing models of the AF-substrate, which can involve very rapid regular atrial pacing or electrically induced AF, are limited to large animals in which tachycardia-pacemakers can be implanted, and have been predominantly created in dogs, pigs, and sheep. The development of the AF-substrate has a complex time-course.[44,45] Electrical remodelling due to changes in ion-current function occurs within days and is primarily manifested as action potential/refractory period abbreviation, whereas structural remodelling consisting of extracellular matrix changes including atrial fibrosis develops much more slowly, over weeks to months.[44,45] Rapid atrial activation is sufficient to cause both types of remodelling, but structural remodelling is enhanced when ventricular dysfunction occurs in response to poor ventricular rate control.[15] Atrial tachycardia-remodelling provides insights into the mechanisms by which AF becomes progressively more resistant to therapy. A significant limitation of these models is that they provide no information about the mechanisms leading to the initial occurrence of AF, since AF has to start somehow before it can beget itself.

LV dysfunction causes atrial fibrosis and thereby creates a clinically relevant substrate for AF-maintenance.[46] AF-promoting LV-dysfunction can be induced by ventricular tachypacing,[46] which is only feasible in larger animals, or by the induction of acute myocardial infarction in smaller animals like rodents. These models can be used to provide insights into the mechanisms that lead to fibrosis, a common and prominent component of the clinical AF-substrate.[47] Limitations include the direct consequences of HF *per se* (like hypotension, neurohumoral changes, and acute atrial stretch) or of the intervention used to cause LV dysfunction, like the myocardial ischaemia associated with coronary artery occlusion.

The autonomic nervous system (ANS) plays an important role in determining AF initiation and maintenance, and ANS-manipulations can be used to create models of AF occurrence.[48] Vagal-nerve stimulation produces a predictable and reversible substrate for AF-maintenance that can be used to screen antiarrhythmic-drug effectiveness for acute AF termination.[49] Of note, the acetylcholine-gated potassium current $I_{K,ACh}$, the main effector of vagal-nerve activity, develops agonist-independent constitutive $I_{K,ACh}$ activity mimicking persistent vagal-nerve function in atrial tachycardia-remodelled dog atria[50] and in atria of patients with persistent AF,[51] although the precise clinical role of this activity remains unclear. AF and various clinical AF-paradigms alter atrial autonomic innervation in ways that contribute to AF-promoting remodelling.[48] Chronic alterations in autonomic function, like those induced by nerve growth-factor injection into sympathetic ganglia, create atrial profibrillatory changes that can result in spontaneous AF.[48] Investigations in ANS-

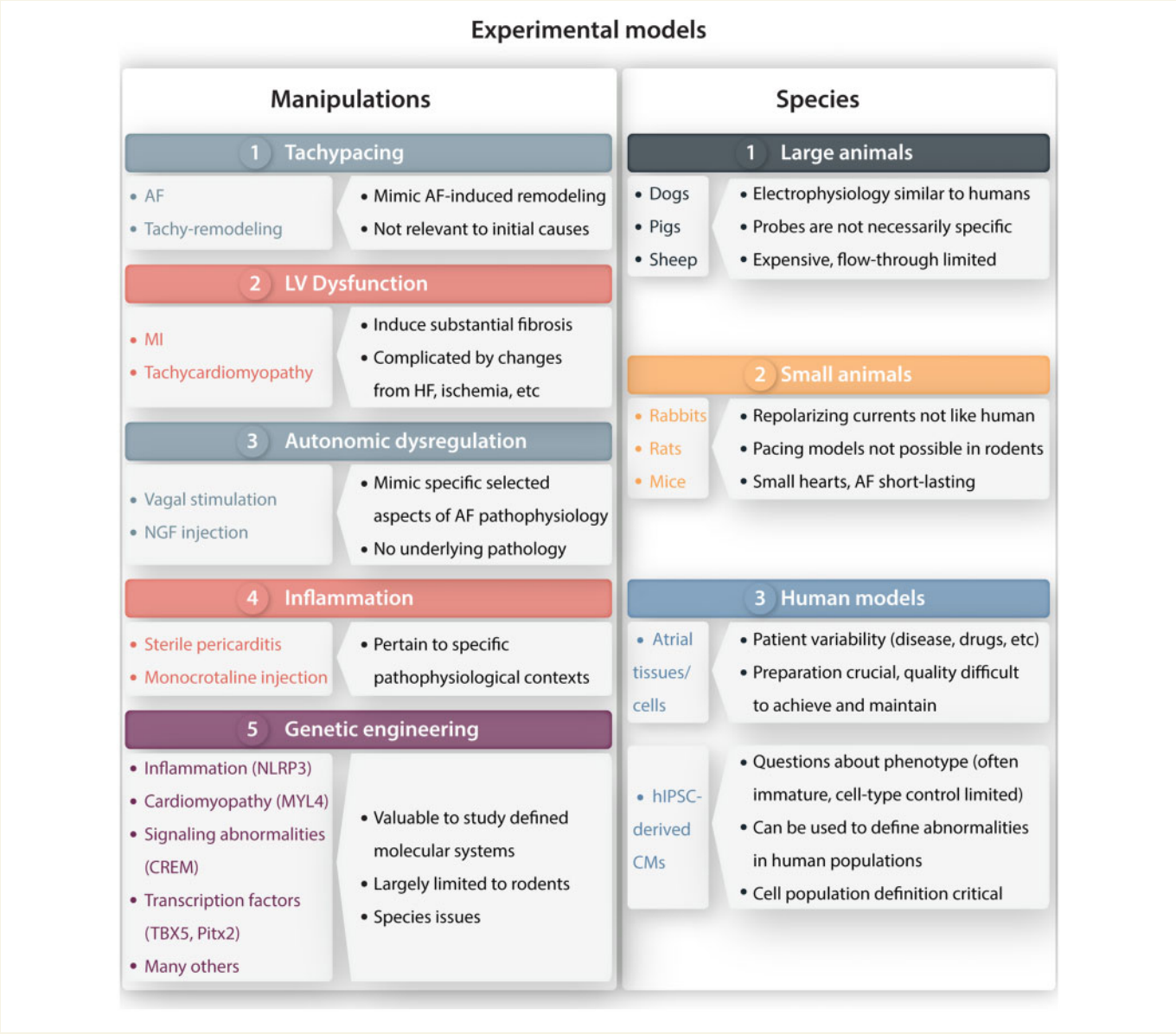

Figure 5 Summary of principal preclinical AF-models. Left: manipulations used to create experimental models of AF. Right: principal species in which various types of preclinical models have been created. CMs, cardiomyocytes; HF, heart failure; hIPSCs, human induced pluripotent stem cell; MI, myocardial infarction; NGF, nerve growth factor.

dependent animal models have been used to develop clinically applicable therapies that target the ANS.[48]

There is evidence for an important role of sterile inflammation in the development of the AF-substrate.[52] Recent work shows that cardiomyocyte inflammatory signalling is enhanced in AF-patients and that activation of NLRP3-inflammasome signalling may be a common pathway involved in various clinical forms, including paroxysmal, persistent, and post-operative AF,[53,54] as well as in conditions that promote AF (e.g. diabetes and obesity).[55,56] Endurance exercise training in mice produces an inflammation-driven arrhythmogenic AF-substrate involving tumour necrosis factor-α activation.[57] Thus, inflammation plays a key role in a number of animal models of AF, which can be used to explore novel interventions. The sterile pericarditis model typically involves substantial pericardial inflammation and is relevant to post-operative AF.[58] Monocrotaline injection produces pulmonary hypertension and right-heart remodelling, with right-atrial dependent AF that shows enhanced inflammatory signalling.[59] Inflammation resolution-promoting therapy prevents development of the AF-substrate in this model, showing the feasibility of acting on inflammation to prevent AF-related remodelling.[60]

Genetically engineered animals provide unmatched precision in identifying specific molecular mechanisms contributing to AF. Most of these are produced in mice, because of their well-characterized genetic structure and the ability to rapidly produce usable mouse lines bearing knock-in mutations, knockouts of specific genes (including inducible models to circumvent neonatal lethality and developmental effects), and animals with two or more simultaneous genetic alterations for complex hypothesis-testing.[61] The recent development of atrial-targeted gene manipulation employing adeno-associated viruses and atrial-selective promoters allows for the alteration of atrial gene expression without confounding changes from ventricular effects.[62] Limitations of these mouse models

include small atrial size, which makes protein-expression analysis challenging, and aspects of electrophysiology not directly translatable to humans (like different ion-channel systems controlling repolarization, very rapid resting heart rates and possibly different AF-inducing and maintaining mechanisms). It is feasible to create genetically engineered AF-models in rats,[63] but the longer production and breeding times make practical use more challenging. While rat atria are substantially larger than those of mice, significant electrophysiological differences from humans are present.

Atrial cardiomyocytes from AF-patients have been used extensively to study AF-related cellular electrophysiological and molecular abnormalities associated with AF.[53,54,64] The results of such studies provide valuable information about clinical importance and relevance that is most powerful when used in conjunction with studies in animal models to address specific hypotheses and study cause–effect relationships.[53,65] Limitations of studies in human tissues and cells relate primarily to the variability introduced by tissue procurement from patients: subjects of different ages, with various associated cardiac pathologies and different drug treatments. Careful control for these factors can deal with some of these concerns,[54] but the associated extraneous sources of variance can never be completely eliminated even with careful propensity matching. Constant care is needed to ensure a reproducible yield of high-quality cardiomyocytes from the often very small atrial tissue-samples obtained from the operating room.

Induced pluripotent stem cells differentiated into cardiomyocytes (iPSC-CMs) are being used increasingly as models of heart disease.[66] Protocols have been developed to preferentially drive iPSC differentiation towards an atrial cardiomyocyte phenotype, and such cells have been used to create 2-dimensional cell-sheets that show many atrial properties including the occurrence of arrhythmias with features of AF.[67] However, caution is needed because these cells demonstrate many features of immature cell-types, including depolarized resting potentials with high levels of sodium-current inactivation and very slow conduction velocities (1–2 orders of magnitude slower than physiological).

3.3 What are the principal challenges to using experimental models?

Table 1 indicates some of the main challenges when using animal models for AF research. The first, and probably most important, is the clinical complexity of the condition being studied. Clinical AF varies enormously among different patient groups in its underlying pathophysiology and mechanisms. AF in a foetus in utero has very different mechanisms from familial AF in a 30 year-old, from paroxysmal AF in an otherwise healthy 50 year-old, from persistent AF in a 75 year-old patient with severe ischaemic cardiomyopathy and HF or from AF in a 45 year-old individual with thyrotoxicosis. These pathophysiological differences make it essential to be sure what questions are being asked about AF mechanisms, what target population is being considered for an intervention under development or what clinical condition is being mimicked. When it comes to AF, one size definitely does not fit all.

A second important consideration is that all of the available experimental paradigms have limitations that must be considered. Rodent models do not realistically mimic the human electrophysiological phenotype in some important respects (e.g. basal heart rate and ion-currents governing repolarization) and certainly do not come close to human atrial dimensions, but large-animal models have other important drawbacks in terms of restricted availability of animals, larger purchase and handling costs and limited knowledge and manipulability of genetic make-up. Additional concerns include (i) the limited incorporation of clinically important risk factors like aging and comorbidities (e.g. hypertension and diabetes); (ii) the lack of models that manifest spontaneous AF, requiring AF induction to analyse markers of the AF-substrate like AF inducibility and duration; and (iii) the potential complicating effects of anaesthesia and invasive procedures required to obtain arrhythmia readouts. The human-cell models require great skill and sustained technical attention (with atrial-biopsy cellular/tissue studies), and are subject to contaminating effects by uncontrollable clinical variability. Studies with iPSC-CMs are limited by their often immature and poorly controllable phenotype, which tends to change over time in culture.

Extrapolating from animal systems to man is always challenging because of species differences, but also because the animal models are much more controlled and limited than the complex picture presented by patients. Patients are generally older, have multiple and varying comorbidities and take various drugs not usually present in animal models. In addition, each experimental system studied has technical limitations intrinsic to the methods used to develop and study it. Finally, the selected model system usually recapitulates only one or two aspects of the arrhythmogenic substrate, whereas in patients the AF-inducing and maintaining substrate results from the mixed effects of multiple comorbidities, risk factors, genetic determinants and medications, most of which act over much longer time periods than can be reproduced in experimental animal paradigms.

Overall, given the deficiencies of the different models available, it is important to be very clear on what one expects from a model, to what clinical paradigm(s) it is relevant and what the intrinsic limitations are of the information obtained. It is therefore key to use more than one model in order to obtain reliable insights, to replicate and to validate the findings.

4. Regulatory hurdles and considerations

Despite technological and methodological advances in catheter ablation, pharmacologic rhythm-control therapy remains an important component of the therapeutic strategy for many patients, particularly those who are highly symptomatic. In addition to their primary role, AADs are often needed as adjuncts to maintain sinus rhythm at various times after ablation. The regulatory threshold for approval of a drug to maintain sinus rhythm is challenging and has focused on endpoints that are clinically meaningful to patients, such as a reduction in symptoms (e.g. dyspnoea, fatigue, palpitations, and light-headedness), hospitalization, morbidity (e.g. new or worsening congestive HF, stroke, myocardial infarction, etc.), or mortality. The impact of drugs (as well as ablation) on symptoms does not necessarily correlate with sinus-rhythm maintenance, adding to the complexity of the regulatory pathway. Potential secondary outcome measures, which are generally not sufficient for a primary indication, include improved quality of life and exercise tolerance. For drugs with the potential to be proarrhythmic, the financial burden of development is complicated by the need for a cardiac outcome study, focused on cardiovascular mortality in higher risk patients, to demonstrate safety. Included in this category are agents whose mechanism of action is to modulate cardiac ion channels, with the potential to slow conduction and or prolong repolarization in the ventricles. Of course, the clinical benefit of any drug needs to be balanced against potential risks.

A drug that is safe and fully eliminates the recurrence of AF would be expected to have meaningful health benefits, but such a 'magic bullet' scenario is rather unlikely. Increases in the maintenance of sinus rhythm or prolongation of the time to first recurrence of AF alone (without improvement in other clinical endpoints) are only surrogate outcomes, which despite having been sufficient for approval of AADs in the past are no longer expected to constitute valid endpoints for the regulatory process. The reason for the insufficiency of such surrogate endpoints is that it is difficult to show that such an endpoint results in a meaningful health benefit to patients. An argument can also be made that a drug that converts persistent AF to a clinical picture in which patients go in and out of AF for significant periods of time might even increase the risk of thrombus dislodgment and embolic events.

The availability of multiple long-term ECG recording technologies, including implantable ECG recorders and ECG patches, has made it possible to study the effect of a drug on AF burden, and it may be possible to pursue this as a regulatory endpoint in certain situations. The focus would be to show that while AF is not obliterated, the episodes are likely insufficiently frequent and lasting to permit the formation of an atrial thrombus. Such a drug might potentially reduce the need for anticoagulation. Nevertheless, the patient population would need to be carefully defined and selected, since it is possible that such a drug would be less effective in patients with considerable electrical or structural remodelling. No drug has been approved using such a strategy, but it has potential value and would merit discussion with regulators.

5. Industry concerns and strategies

Despite the significant limitations of currently available AADs, AF pharmacotherapy has not seen any major innovation over the last three decades (*Figure 2*). Most of the advances in disease understanding documented in detail elsewhere[28] have not yet been successfully translated to pharmacological application and/or clinical validation. Moreover, the research and development (R&D) pipeline analysis (*Figure 4*) reveals a quite sobering picture of the state of affairs of AF drug development across the industry, with only a few new molecular entities, most of which still lack crucial proof-of-concept in humans. It is also remarkable that 'big pharma' rarely shows up in the list. Does this reflect a generally low level of interest of major pharma companies to invest in R&D for AF drugs? There are many valid arguments to the contrary.

As already pointed out, the size of the problem related to the number of patients and AF-inflicted costs is enormous. The aging population and the constant increase in type 2 diabetes and obesity, two important AF risk factors, will further increase the unmet medical need. Non vitamin-K anticoagulants introduced for stroke prevention in AF-patients turned out to be a great success, not only for the patients (for whom devastating strokes could be avoided) and for the pharmaceutical industry, which produced blockbuster drugs, but also for society and healthcare systems, generating overall savings on the direct costs for stroke treatment and the enormous indirect costs associated with disability.[68,69] But stroke is only one complication precipitated by AF. The majority of patients suffer from concomitant ischaemic heart disease and/or HF and these comorbid cardiovascular-risk patients are hospitalized twice as often compared to otherwise similar patient cohorts without AF. Irrespective of whether exacerbations of the underlying heart disease triggered by AF episodes (or vice versa) or symptomatic AF alone drives the patient to the emergency room, the number and costs of such hospitalizations—more than 550 000 hospitalizations per year (2010) in the USA,[70] with concomitant AF adding another 70% to the costs[5]—provide the grounds to construct value propositions for AAD candidates. This approach obviously challenges the controversial notion of equivalence in outcomes between rhythm and rate control, an idea that has also been challenged by recent clinical data showing superiority of rhythm control in cardiac risk patients early in the natural history of AF (diagnosis within the last 12 months).[12] Of note, only 20% of the patients assigned to early rhythm-control received AF-ablations; the rest were treated with AADs, clearly illustrating the great relevance of AAD approaches for rhythm-control strategies.

Poor efficacy and safety concerns associated with the currently used AADs provide ample opportunities for new-generation antiarrhythmic compounds with improved efficacy and safety profiles. It is important to note that the relatively rapid action of rhythm-control agents and readily accessible electrophysiological readouts in humans render antiarrhythmic efficacy (maintenance of sinus rhythm) and safety (signs of ventricular pro-arrhythmia) to be readily probed in smaller size studies of short duration before considering investing in costly outcome trials. Technical advances like the use of rhythm monitoring with smart-phone applications and patch-based remote recording devices are facilitating these types of approaches. Possible regulatory approaches to using AF burden as an approvable endpoint may also be helpful for highly efficacious agents. Today's sparsely populated pipeline might partially reflect a well-functioning test cascade eliminating flawed candidates at early stages.

Table 1 Limitations to clinical translation of results from current experimental models of AF

- Complexity of the clinical condition
  - Range of clinical presentations and underlying mechanisms
  - Variation in features over the life-course
  - Complexity of human condition, often involving multiple pathologies and conditions
- Limitations of experimental paradigms
  - Limitations imposed by species differences in cardiac electrophysiology, heart size, availability etc.
  - Lack of models manifesting spontaneous AF
  - Complications due to anaesthesia, need for chronic instrumentation or acute surgery for arrhythmia susceptibility testing
  - Technical challenges and patient variability for human atrial-biopsy studies
  - Often immature and incompletely controlled IPSC-CM phenotype
- Problems extrapolating from animal models to humans
  - Animal models lack complexity of human condition
  - Differences in ion-channel properties, anatomy, structure etc.
- Intrinsic limitations of the model systems studied
  - Each experimental system extrapolates with restrictions to specific human scenarios and AF phenotypes
  - Inference to clinical pathophysiology must be careful and guarded

Obviously, no candidate yet has been identified combining robust antiarrhythmic efficacy with the sufficient atrial specificity to prevent ventricular pro-arrhythmia risk, central nervous system or other unwanted target-related adverse effects.

It is conceivable that the efficacy of AADs—similar to ablation therapy—is limited to a large extent by the degree and anatomical complexity of atrial remodelling.[71] This complex relationship is only partially captured by the current AF classification exclusively based on AF duration, which in itself cannot be defined precisely. While future clinical practice might further tolerate some degree of 'trial-and-error' to this end, especially for AADs with improved safety, there is a clear unmet need for clinical trials involving patients stratified according to 'disease staging' and ideally dominant AF mechanism.

Costs and risks are viewed significantly less favourably by many experts in industry when it comes to AF-prevention by targeting mechanisms acting to halt or potentially reverse the age- and heart disease-related remodelling processes that generate and contribute to the arrhythmogenic atrial substrate. The sample sizes and trial durations required to demonstrate efficacy substantially exceed those used for acute arrhythmia-treatment testing efficacy. Moreover, suitable dynamically responsive clinical surrogate markers (or 'intermediate traits') to indicate target engagement are needed to steer dose finding and de-risk the programme by generating initial relevant efficacy signals. At present, progression-specific markers are available for only a minority of the mechanisms linked to AF. Most importantly, despite being a central theme in AF research, atrial fibrosis remains a process difficult to monitor using biomarkers. The complexity of the issue is well-illustrated by the case of renin–angiotensin–aldosterone system (RAAS) inhibitors. While RAAS inhibitors appear to be of value for primary AF-prevention in studies of groups at high risk for fibrosis development (e.g. patients with substantial LV dysfunction post-myocardial infarction and those with severe hypertension),[34] they have shown limited efficacy in secondary AF-prevention.[35] The major challenge is that in the absence of reliable surrogate markers of fibrosis or fibrotic signalling, the only evidence for effectiveness is AF-prevention, which requires very large numbers of patients who are both at increased risk for developing a fibrotic AF-substrate and yet have not developed advanced atrial fibrosis. Thus, it is not surprising that the beneficial effects of 'upstream therapy' with RAAS blockers have been limited and difficult to demonstrate.[72]

Inflammation and inflammatory signalling are emerging as a second intensely studied driver mechanism, which combines the availability of relevant markers (e.g. interleukin-6 and high-sensitivity C-reactive protein), multiple candidate drugs, and a clinically relevant condition (post-operative AF) considered to be predominantly driven by inflammation of atrial tissue (target engagement).[73] While this AF population might serve as a reasonable entry indication for anti-inflammatory drugs, the relevance of inflammatory signalling to the broader AF population is not well established. Nevertheless, recent evidence for a role of cardiomyocyte inflammatory signalling in varied forms of AF, including post-operative, paroxysmal, and persistent AF, points to potential therapeutic value of specific targeting of inflammatory signalling.[53,54,74]

Finally, patient heterogeneity with multiple different disease processes interacting at the individual patient level require considerably improved clinical classification schemes ('disease staging') to further personalize treatment and improve therapeutic efficacy.[75] These considerations emphasize the need and relevance of further basic/translational and clinical research in AF to uncover novel and specific mechanisms for pharmacological intervention, while advancing our clinical tools to precisely define AF pathophysiology at the individual patient level. These efforts will benefit also from a constantly growing repertoire of therapeutic modalities, e.g. cell and gene therapies, potentially allowing for innovative interventions to tackle disease processes previously deemed 'undruggable'.

6. Where do we go from here—possible paths forward

6.1 Consideration of basis for current therapies

In thinking about possible strategies to improve the development of new clinical approaches to treating AF, it may be instructive to evaluate the sources of therapies that are currently used. *Figure 6* presents a variety of presently used rhythm-control interventions for AF, along with a statement of how they were developed.

Figure 6A summarizes the basis for the development of the AADs used to treat AF. Quinidine was first introduced for AF termination and sinus-rhythm maintenance about 100 years ago, as a safer and more effective analogue of quinine, which had been noted by Wenckebach to have effectiveness in AF conversion.[76] Flecainide emerged as a result of chemical synthesis of a series of antiarrhythmic compounds,[77] and was targeted for ventricular arrhythmia suppression.[78] Its use as an AF-suppressing antiarrhythmic agent was subsequently noted empirically[79] and created a challenge to prevailing mechanistic notions.[80] Propafenone, like flecainide a class Ic AAD, was similarly first introduced as a drug to suppress ventricular ectopy,[81] although its effectiveness in AF was observed early in its clinical development.[82] Amiodarone was initially introduced as a vasodilator and anti-anginal drug, found to have selective action potential prolonging properties by Singh and Vaughan Williams[83] and noted to be effective for a wide range of arrhythmias, including AF, by Rosenbaum.[84] Dofetilide was identified in a search for novel molecules with class III properties,[85] and soon noted to be of value in AF.[86] Sotalol (initially known as MJ1999) was the first prototype class III agent as described in the classical Singh and Vaughan Williams' article of 1972[87] and found to be highly effective in AF.[88] Dronedarone was developed in a search for less toxic amiodarone congeners,[89] but unlike most of the other agents was introduced primarily for the treatment of AF.[90]

Figure 6B summarizes the principal interventional approaches presently used for AF management and the basis for their development. The surgical maze procedure is the first approach to AF management targeted specifically to AF pathophysiology,[91] has passed through many subsequent modifications[92] and is probably still the most effective therapeutic modality for sinus-rhythm maintenance. Pulmonary vein-directed catheter procedures were initially described by Haissaguerre *et al.*[93] based on empiric observations and remain the mainstay of catheter-based AF-ablation procedures.[9] Linear catheter-ablation lesions are used for AF-ablation to mimic the therapeutic mechanisms of the maze procedure.[94] Likely because of difficulties in successfully and safely creating linear lesions with complete bidirectional block by catheter ablation, the success of the maze procedure has yet to be replicated by catheter-based procedures. Based on experimental observations consistent with a role for a small number of discrete rotors in AF-maintenance,[95] ablation procedures have been developed to target these rotors.[96] Despite some initial success,[96] procedures targeting cardiac rotors have overall been found to have limited efficacy to date,[97] possibly related to observations showing that rotors tend to be multiple, short-lived, and spatially unstable.[98]

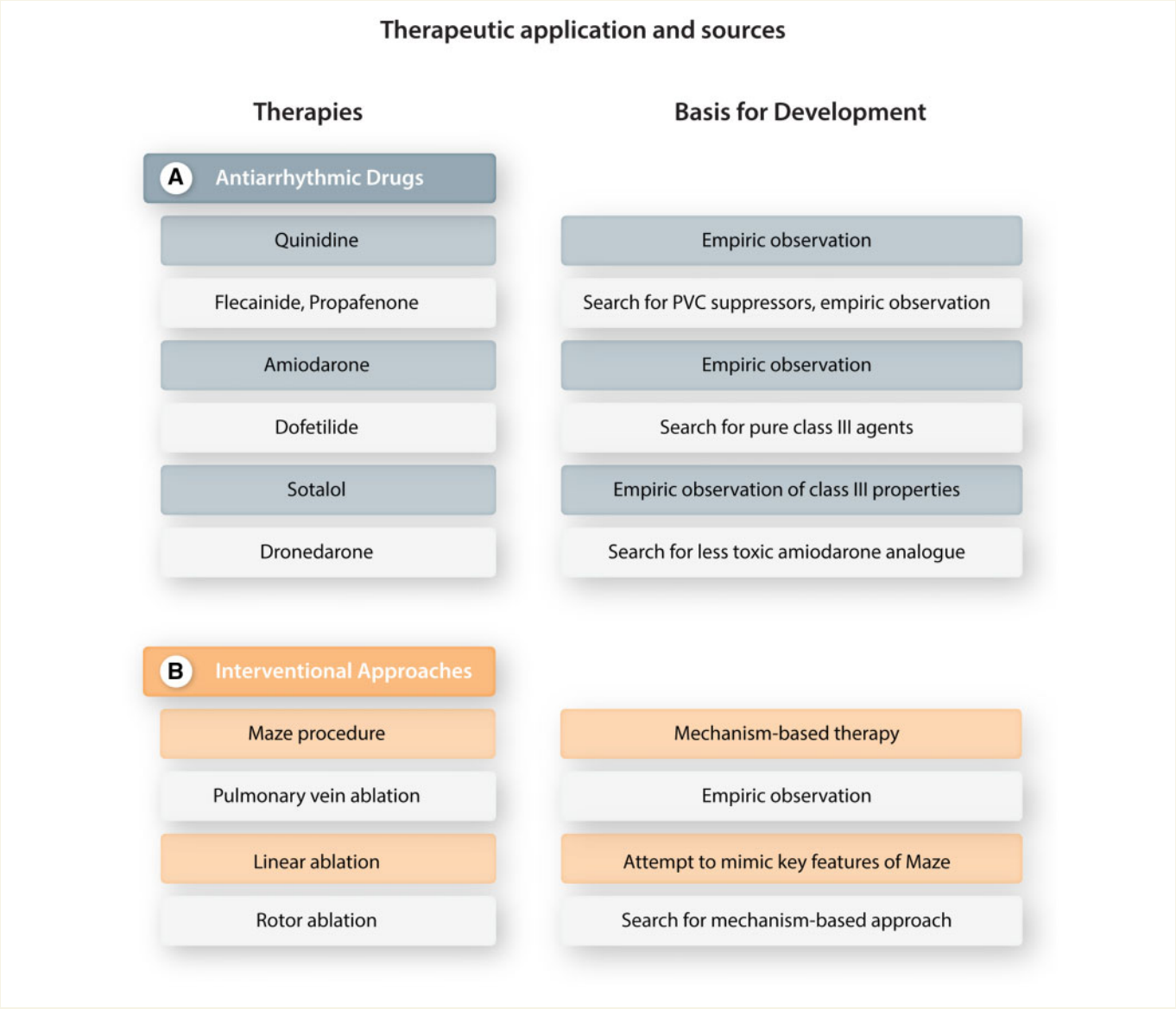

Figure 6 Principal currently used therapies for AF rhythm control (left) and their developmental origins (right). (*A*) Antiarrhythmic drugs. (*B*) Interventional methods.

6.2 Challenges and possible paths forward

A few conclusions may be drawn from the history of AF therapy development. The first is that relatively few of the drugs in present use to treat AF were actually developed specifically to target AF. This fact relates to the compelling importance of ventricular tachyarrhythmias as a potentially lethal clinical target, notwithstanding the emerging great public health importance of AF. Nevertheless, there may be opportunities for the specific development of AF-targeting therapies. The single most effective treatment for AF, the surgical maze procedure, was targeted against the mechanisms underlying AF,[83] providing some support for the promise of mechanistic targeting. On the other hand, the most effective catheter-based procedure for AF, pulmonary vein isolation, was an empirical development and the underlying mechanisms of pulmonary vein involvement in AF remain incompletely understood. Furthermore, the apparent failure of rotor ablation to date illustrates the challenges of developing new mechanism-based interventional AF therapies.

Efforts have been made to target atrial-specific ion channels like the ultra-rapid delayed rectifier K^+-channel and $I_{K,ACh}$.[24] Neither of these targets have shown promise in initial clinical trials,[99–101] illustrating the challenges in extrapolating from observations in experimental models and human tissue samples[50,51,102] to clinical use. Novel ion-channel targeting drugs may still have promise. While the risk of pro-arrhythmia with Na^+ and K^+ channel blocking drugs are well recognized,[103] it is interesting that such agents are still in wide clinical use for AF management.[12] Harnessing advanced *in silico* approaches to help in designing AF-selective drug therapy[104,105] and *in silico*/human pluripotent stem cell models to minimize proarrhythmic liability[106,107] may allow for the development of improved ion-channel targeting AF therapies for clinical use. Late Na^+-current and/or L-type Ca^{2+} current inhibition can reduce

or eliminate torsades de pointes risk and may be a useful component of multiple-channel blocking drugs to reduce proarrhythmic propensities.

A wide range of potential molecular targets have been identified for prevention of AF-substrate development.[28,41] A major limitation to their development is the lack of a clear development pathway. Interventions that prevent development of the AF-substrate must have acceptably low toxicity and clinical risk potential. Drugs that target pathways that can be beneficial for the primary disease in high-risk patients, like RAAS inhibitors in patients with HF or severe hypertension, have potential value,[34] but in most cases will already be in common use for the primary pathology. For lower-risk patients, the toxicity/adverse effect potential would have to be extremely low. Drugs that promote the resolution of inflammation are thought to have very limited risk and might be potential candidates.[60] Given the very high costs for the development of AADs, repurposing of existing drugs with anti-inflammatory actions (e.g. colchicine) might also constitute an alternative option for treatment targeting the atrial substrate that promotes AF. Classical anti-inflammatory agents have not emerged as practical because of limited efficacy and adverse effects,[108,109] perhaps in part because they fail to target the specific forms of inflammation (e.g. preferably expressed in cardiomyocytes[53,54]) that appear to be important in more common forms of AF. The success of lifestyle interventions in controlling AF with substantial effectiveness over a practical timeframe[110,111] points to the viability of substrate-prevention as a clinical approach to AF. Interestingly, there is an interaction between polygenic risk scores and lifestyle-factor associations with cardiovascular disease, arguing for the further investigation of novel approaches to guide and personalize AF interventions with the use of genetic information.[112]

7. Conclusions

It is clear that there is an important unmet need for improved therapeutic options for AF. There remains a paradox between the wide continuing use of electrically active AADs (with recognized limitations) and the limited ongoing efforts to develop better alternatives. Upstream therapy remains an attractive approach, but its clinical application presents both theoretical and practical obstacles. While the majority of AF treatments in present clinical use resulted from empirical development, new approaches based on arrhythmia mechanisms have yielded highly effective therapies in the past. Despite significant challenges, therapeutic innovation based on the translation of basic research findings to clinical applications remains a promising path towards the introduction of effective new treatment modalities for AF. While the introduction of successful, conceptually innovative approaches to AF control is a challenging objective, one significant breakthrough will clearly revolutionize both AF management and the therapeutic development landscape.

Conflict of interest: S.N. is a consultant for LQT Therapeutics. J.H. is an employee of Bayer AG, Germany. P.S. is Co-Founder, Board of Director member, and equity holder in Long QT Therapeutics, Consultant to Milestone Pharma, Acesion Pharma, Lilly, Cydan Pharma, MyoKardia, Pharmaron. J.H. has no disclosures. D.D. is member of the Scientific Advisory Boards of Omeicos Therapeutics GmbH and Acesion Pharma.

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