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NEW DRUGS

Vernakalant: Review of a Novel Atrial Selective Antiarrhythmic Agent and its Place in Current Treatment of Atrial Fibrillation

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KEY WORDS: *vernakalant; atrial fibrillation; antiarrhythmics; torsades de pointes; drug cardioversion*

Abbreviations
AADs = antiarrhythmic drugs
AHA = American Heart Association
AF = atrial fibrillation
AV = atrio-ventricular
CABG = coronary artery bypass grafting
ECG = electrocardiogram
EMA = European Medicines Agency
ESC = European Society of Cardiology
FDA = Food & Drug Administration
IV = intravenous
NSR = normal sinus rhythm
NYHA = New York Heart Association
TdP = torsades de pointes

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ABSTRACT

Atrial fibrillation (AF) remains the most common arrhythmia requiring treatment in the emergency department and is the cause of major morbidity and considerable financial burden. Choosing the appropriate therapy to treat recent-onset AF can be extremely demanding and problematic and recent efforts have been focused on identification of an intravenous antiarrhythmic drug that can provide rapid, effective and safe cardioversion of an acute episode. While the currently available antiarrhythmics show moderate efficacy and pose a risk for serious ventricular proarrhythmias, vernakalant, a recently developed relatively atrial-selective multi-channel inhibitor, has consistently proved to be both effective and safe in converting recent-onset AF to normal sinus rhythm (NSR) in randomized clinical trials. Its relatively high atrial selectivity preventing potentially lethal episodes of torsades de pointes (TdP) as well as its prompt onset of action, offer intravenous vernakalant a strong advantage over its competitors and constitutes an attractive option for the physician.

INTRODUCTION

Atrial Fibrillation (AF) is the most common sustained arrhythmia in the modern era affecting 1–2% of the general population,[1] being also the cause of multiple negative implications on the health system and the patient itself. Its current prevalence is high reflecting the incidence of various contemporary risk factors such as latent hypertension, alcohol abuse, obesity and sleep apnea[2] and is expected to increase considerably by 2050, mainly due to the continuously ageing population. Recent epidemiological studies report that more than 6 million people in Europe and approximately 3 million people in the United States have AF, while these numbers are expected to double during the next 30–50 years with a projected prevalence of 7.56 million patients for 2050.[3,4]

There are multiple mechanisms involved in the pathophysiology of AF. Although it is proven that focal triggers, mostly originating in the pulmonary veins, play a significant role in the initiation of AF,[5] it seems that several classic or newer risk factors have a direct impact on atrial myocardium resulting in hypertrophy, fibrosis, apoptosis,

myolysis, dilatation and finally, electrical dissociation between atrial muscle bundles.[6] Thus, electrophysiological remodeling gradually leads to structural remodeling or vice versa that further deteriorates atrial ultrastructure subsequently forming a vicious cycle and perpetuation of AF,[7-9] as the famous Allessie's dictum "AF begets AF" declares.[10] These observations outline the importance of early medical intervention in the history of AF, before electrical remodeling occurs and the arrhythmia becomes persistent or permanent.

The shortening of the atrial refractoriness plays a key role in electrical remodeling and seems to be the result of multiple molecular abnormalities in the atria affecting ion-channels,[11,12] predominantly slow (I_{Ks}), rapid (I_{Kr}), ultrarapid delayed-rectifier (I_{Kur}),[13] acetylcholine-regulated (I_{KACh})[14,15] and transient outward (I_{to}) potassium channels as well as sodium channels (I_{Na}) and cardiac connexins-40 and -43 (Figure 1).[16,17] Among these, I_{Kur}, I_{KACh} and Connexin-40 are only present in the atria, offering possible targets for safe antiarrhythmic therapy in the future (Table 1).

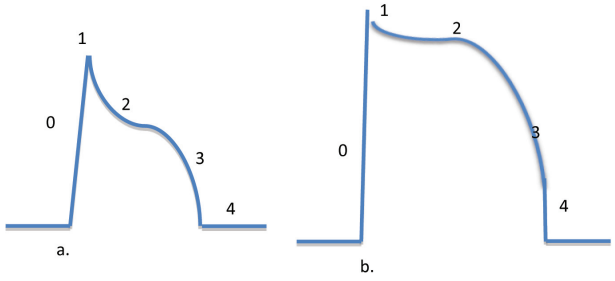

FIGURE 1. Differences between phases of atrial (a) and ventricular (b) action potential. In the atria, phase 2 has a shorter duration than in the ventricles

Although it is widely accepted that AF is a probable cause of mortality and severe morbidity,[18,19] the strategy of long-term normal sinus rhythm (NSR) maintenance has failed to show superiority over rate control strategy in a series of randomized trials and metaanalyses[20-25] excluding the seeming positive outcome on quality of life.[26,27] Possible reasons include "positive patient selection" in these studies (low-risk patients), low long-term maintenance of NSR rate and frequent withdrawal of anticoagulant therapy in the rhythm control groups.[4] Moreover, proarrhythmia, negative inotropy and extracardiac side effects of the currently used antiarrhythmic drugs (AADs) seem to play a consistent role in increasing morbidity and mortality.

However, there is now strong evidence that the aforementioned neutral effect on hard endpoints is disputable; a clear association between NSR maintenance and improved survival was evident in an on-treatment analysis of the AFFIRM trial, suggesting also that any beneficial antiarrhythmic effects of AADs are offset by their adverse effects.[28] Moreover, a positive outcome on mortality, mainly driven by reduced hospitalizations, was demonstrated after use of dronedarone in the ATHENA trial implying that safely maintained NSR may prevent cardiovascular events in AF.[29] Thus, both recently published ESC and AHA guidelines recommend patient-tailored therapy dependent on the severity of symptoms attributed to AF, how successful rhythm control is expected to be and safety issues concerning use of AADs.[1,30]

Given the fact that currently available AADs show modest efficacy in converting AF and maintaining NSR, while at the same time demonstrate serious adverse events,[31] it is imperative to try to find more effective and much safer drugs especially lacking the potential of causing lethal arrhythmias like polymorphic ventricular tachycardia in the form of torsades de pointes (TdP).

TABLE 1. Cardiac ion Currents, the Genes Encoding Them and Their Distribution in Atrial and Ventricular Myocardium. Ikur and IK.Ach are Only Present in the Atrial Myocardium

Current	Gene	Phase of Action Potential	Ion Direction	Atria	Ventricles
INa	hH1	0	Inward	+	+
Ica.L,T	SCN5A	2	Inward	+	+
Ito	Kv4.2/4.3	1	Inward	+	+
IKs	KCNQ1 (KvLQT1)	3	Outward	+	+
IKr	KCNH2 (HERG)	2,3	Outward	+	+
IKur	KCNA5 (Kv1.5)	2,3	Outward	+	-
ICl	CTRF/TWIK	2,3	Outward	+	+
IK1	Kir2 family	late 3 & 4	Outward	+	+
IK.ATP/ACh	kir6.2+SUR2a/Kir3 family	late 3 & 4	Outward	+	-
If	HCN2/4	4	Inward	+	+

VERNAKALANT

Vernakalant is a recently developed drug that shows several attractive characteristics: it is relatively atrial selective resulting in minimal ventricular proarrhythmia, while at the same time it seems adequately effective in converting new-onset AF. Intravenous vernakalant (Brinavess™, MSD, Dublin, Ireland) was recently approved by the European Medicines Agency (EMA) for the rapid conversion of recent-onset AF lasting less than 7 days in nonsurgical patients and less than 3 days in postoperative AF,[32] therefore achieving a last-minute inclusion in the 2010 ESC Guidelines for treatment of AF. On the contrary, the US Food and Drug Administration (FDA) Cardiovascular and Renal Advisory Committee requires more safety and efficacy data in order to permit its clinical use in the United States.[33]

PHARMACOLOGY

Vernakalant (formerly RSD1235) (Figure 2), a recently developed aminocyclohexyl ether, represents a new category of AF-converting agents that show preferential action on atrial and limited effect on ventricular tissue.[34] It is actually a multi-ion channel blocker, which inhibits several potassium and sodium currents.[35-37] It was discovered more than a decade ago after thorough research in a canine model[38] and its relatively higher effect on prolongation of atrial action repolarization and refractory period is attributed to its novel feature of inhibition of two certain potassium currents, I_{Kur} (IC_{50} = 9μM) and I_{KACh} (IC_{50}=10μM) that are only present in atrial myocardium.[39,40]

Vernakalant modestly inhibits I_{to}, $I_{K.ATP}$, I_{Kr} and late I_{Na} currents, which are expressed in the ventricles as well, rendering its characterization as "atrial selective" rather not fully accurate. However, it shows higher sensitivity for atria-specific I_{Kur} over other channels involved in ventricular repolarization, such as I_{Kr} and I_{Na}, a fact that is mainly responsible for its safety.[35] But despite its large pharmacological spectrum of activity and its prominent action on atrial-selective potassium currents, experimental data suggest that vernakalant's AF-selective actions might be based on state-dependent I_{Na} blockade.[37,41] It seems that vernakalant's action on late I_{Na} current is frequency-dependent with fast offset kinetics, which means that blockage of this current and slowing of atrial conduction is more evident at higher atrial rates, making this agent ideal for the treatment of rapid AF or other atrial tachyarrythmias.[35] In support of this notion, recent experimental data using an isolated canine atrial model confirmed that in higher rates vernakalant prolongs atrial action potential duration significantly more than ranolazine or sotalol.[42] Moreover, other evidence suggests that through late I_{Na} current inhibition, vernakalant shows a ranolazine-like antiarrhythmic effect suppressing drug-induced proarrhythmia from dofetilide, thus having a protective role on ventricular myocardium.[43] Concerning the risk of TdP, balanced competing suppression of these two channels demonstrated in several voltage clamp studies, results in minimal effect on QT duration as I_{Na} blockade shortens QT and I_{Kr} blockade prolongs it.[44]

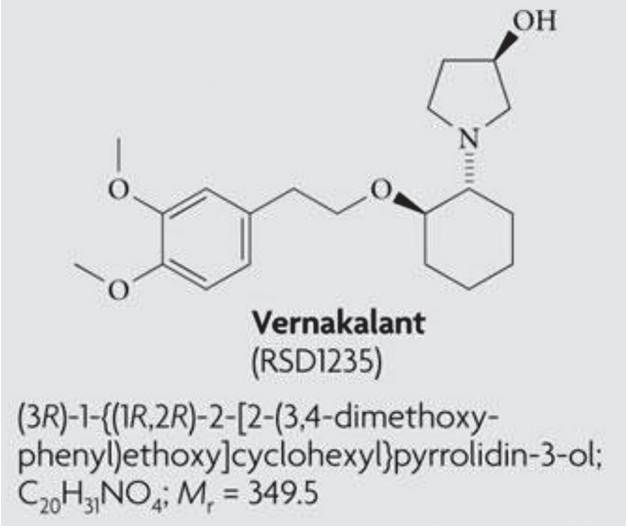

FIGURE 2. Molecular structure of Vernakalant.[76]

PHARMACOKINETICS/ DRUG INTERACTIONS

Pharmacokinetic and pharmacodynamic data for intravenous vernakalant are obtained from four phase II and III clinical trials conducted in patients with AF or atrial flutter (ACT trials[45-48]) and two phase I studies in smaller groups of healthy volunteers.[49,50] Its pharmacokinetic parameters are better described by an open two-compartment mammillary disposition model, with rapid first-order elimination from the central to peripheral compartment. Vernakalant demonstrates linear kinetics following a ten-minute injection period;[51] its metabolism to its major inactive metabolite, RSD1385, is predominantly dependent on 4-O-methylation by cytochrome P-450 (CYP) 2D6 isoenzyme and only 11% of the drug is secreted unchanged in the urine. While average plasma half-life is 3.1 hours in men and 2.9 hours in women, it is critically dependent on CYP2D6 activity classifying patients as poor (half-life 5.6 hours) or extensive metabolizers (half-life 2.2 hours). Same differences are observed in the volume of distribution measured: 85.84L for those with strong CYP2D6 activity and 112.50L for those with weak enzyme activity. Nevertheless, the average maximum plasma concentration (Cmax) is unaffected by CYP2D6 genotype and is 3.29 μg/mL in men and 4.57 μg/mL in women.[52]

Most data obtained from the above studies did not show age, race, sex, hepatic or renal impairment and heart failure to significantly affect vernakalant's pharmacokinetic properties. However, the need for dosage adjustments in hepatic

impairment has not been conclusively determined. Although there is a lack of formal studies regarding drug interactions with vernakalant, there is strong evidence from the ACT I[44] and ACT III[46] clinical trials that CYP2D6 inhibitors do not affect Cmax and do not seem to cause QT prolongation.[53] In addition, vernakalant is not highly bound to serum proteins and as a result, it is not expected that there would be clinically meaningful competition with other highly protein-bound drugs such as amiodarone, warfarin, diltiazem and verapamil.

PHARMACODYNAMICS

Several pharmacodynamic studies have been performed in humans and animals (rabbits, goats and dogs). Vernakalant's ability to prolong the absolute atrial refractory period without affecting ventricular repolarization was consistent in all animal studies. When goats exposed to 48 hours of pacing-induced AF were treated with vernakalant (0.2 mg/kg/h), a significant prolongation of the left atrial effective refractory period from baseline was evident.[54] Even when it was given in higher than its usual human therapeutic concentrations, heart rate, mean arterial blood pressure and various ECG parameters (PR, RR, QT, QRS intervals) were not significantly affected in animals with normal heart rhythm. More specifically, there was a very mild dose-dependent increase in heart rate from 61 to 70 beats/min, PR interval from 169 to 184 ms, QRS interval from 88 to 100 ms and QT interval from 384 to 419 ms. On the contrary, in another study, no significant changes were observed in vital signs or ECG intervals. Although contradictory data were derived from two small Phase I[55] and Phase II[49] studies regarding vernakalant's effect on atrio-ventricular (AV) nodal refractoriness, slight and not statistically significant prolongation of conduction velocity through AV node and His–Purkinje system was seen only at the higher doses.

As already mentioned, animal studies have shown that vernakalant can also have antiarrhythmic effects in the ventricles. Vernakalant significantly decreased the prevalence of drug-induced ventricular arrhythmias in animals which had drug-induced QT prolongation and this action may be attributed to late I_{Na} current inhibition.

CLINICAL EFFICACY AND SAFETY

Intravenous (IV) vernakalant's efficacy in rapidly converting AF in different clinical settings has been assessed in several randomized trials to date. Most of these studies were placebo-controlled and only one was active-comparator (amiodarone used). In addition, one study examined the effectiveness of oral vernakalant in maintaining sinus rhythm after cardioversion (Table 2). Safety issues were also addressed in the majority of them.

Conversion of Recent Onset Atrial Fibrillation Trial (CRAFT) was a phase II, multicenter, double blind, placebo-controlled, step-dose, randomized study assessing the efficacy of IV vernakalant for terminating recent onset AF.[36] A total of 56 patients with AF continuously present for 3 to 72 hours were equally randomized into three groups according to the regimen used: placebo, low dose or high dose vernakalant. Each group received an initial 10-minute infusion followed by a second infusion 30 minutes after completion of first dose, if AF still persisted; the low dose regimen was 0.5 mg/kg IV and 1 mg/kg IV and the high dose regimen was 3.0 mg/kg IV and 2 mg/kg IV for the first and second infusion respectively. The primary end point was termination of AF during infusion or within 30-min after the last infusion and secondary end points included the number of patients in sinus rhythm at 0.5, 1, and 24 hours post-last infusion and time to conversion. The results showed that the high dose of IV vernakalant effectively converted 61% of AF cases to sinus rhythm with a median time to conversion of 11 min as opposed to placebo and low dose regimen (approximately 5%), a statistically significant difference. All secondary end points were also in favor of the high-dose scheme: patients in sinus rhythm at 30 min (56% vs. 5%, p=0.001) and at 1 hour (53% vs. 5%, p=0.0014) and median time to conversion (14 vs. 162 min, p=0.016). Concerning safety, there was no significant QRS or QTc prolongation and no episodes of TdP or other ventricular arrhythmias were observed during the 24 hours of the study. As compared to placebo, no significant changes in blood pressure were seen. Several patients receiving the high-dose regimen experienced a clinically significant decrease in mean heart rate (from 109 bpm to 90 bpm), possibly attributable to their conversion to sinus rhythm.

Intravenous vernakalant was also evaluated in four studies, the Atrial Arrhythmia Conversion Trials (ACT) I, II, III, and IV. **ACT I** was a phase III, randomized, placebo-controlled trial designed to test the efficacy and safety of IV vernakalant for terminating recent onset atrial fibrillation and atrial flutter.[45] A total of 336 patients with AF or atrial flutter from 3 hours to 45 days of duration, were enrolled and then randomized to placebo or IV vernakalant at 3 mg/kg as an initial 10-minute infusion with a provisional infusion of 2 mg/kg if AF persisted after the first dose. All patients were antiarrhythmic- naove for at least 24 hours. Primary end point was conversion of AF to sinus rhythm for at least 1 minute within 90 minutes of the start of drug infusion in the short-duration AF group. Regarding the 220 patients with duration of AF between 3 hours and 7 days, 51% in the vernakalant group were successfully converted to sinus rhythm versus 4.0% in the placebo group (P = 0.0001), after a median time of 11 minutes. On the contrary, in patients with persistent AF (arrhythmia duration more than 7 days), no statistically significant difference between the 2 groups was seen (P = 0.30). Overall, irrespective of duration of AF, 37.6% of patients were cardioverted in the vernakalant group versus 2.6% in the placebo group (p=0.001). Of the 39 patients with atrial flutter, only 1 patient converted to sinus rhythm with IV vernakalant, compared with 0 of 15 for placebo patients. Like CRAFT, there were no episodes of TdP observed during

TABLE 2. Clinical Trials Assessing Efficacy of Vernakalant

CLINICAL TRIAL	Year Published	Type of Trial	N	Formulation	Clinical Setting	Control Group	Primary Endpoint	Vernakalant vs Control (p-Value)	Median Time to Conversion (min)
CRAFT[36]	2004	RCT/ Phase II	56	Intravenous	AF duration 3-72 h	Placebo	AF termination within 30 min	56% vs. 5% (p<0.001)	14
ACT I[44]	2008	RCT/ Phase III	220	Intravenous	AF duration 3h-7d	Placebo	AF termination within 90 min	51.7% vs. 4% (p<0.001)	11
ACT II[45]	2009	RCT/ Phase III	150	Intravenous	AF post-cardiac surgery	Placebo	AF termination within 90 min	47% vs. 14% (p<0.001)	12.4
ACT III[46]	2010	RCT/ Phase III	265	Intravenous	AF duration 3h-7d	Placebo	AF termination within 90 min	51.2% vs. 3.6% (p<0.0001)	8
ACT IV[47]	2010	Open label	167	Intravenous	AF duration 3h-7d	-	AF termination within 90 min	Vernakalant: 50.9%	14
AVRO[56]	2011	RCT	232	Intravenous	AF duration 3-48h	Amiodarone	AF termination within 90 min	53.4% vs. 5.2% (p<0.0001)	11
Torp-Pedersen et al[59]	2011	RCT/ Phase IIb	605	Oral 150/ 300/ 500mg bid	Non-permanent AF	Placebo	Long-term sinus rhythm maintenance	Vernakalant 500 mg bid better, other doses not	-

AF = atrial fibrillation; bid = twice daily; N= number of patients included; RCT = randomized clinical trial.

the 24-hour period following the drug infusion. Interestingly, two patients experienced episodes of TdP after this 24-hour period but due to the relatively short half-life of the drug (2–3 hours), authors did not attribute these episodes to vernakalant administration. Investigators also reported four serious adverse events that occurred in the vernakalant group, more specifically two episodes of severe hypotension, one episode of complete atrioventricular block and one episode of cardiogenic shock. Statistically significant increases in QRS and QTc duration were observed in vernakalant-treated patients who did not convert from AF.

ACT II[46] was a phase III, multicenter, double-blind, randomized, placebo-controlled clinical trial conducted in patients with new-onset, documented and sustained for 3–72 hours AF (93%) or atrial flutter (6%) after coronary artery bypass graft surgery (CABG) (67%), valvular surgery (24%) or both (9%), in order to provide more evidence about the efficacy and safety of vernakalant administration. Between 24 hours and seven days after cardiothoracic surgery, a total of 190 patients were randomized in a 1:2 ratio to receive either placebo or IV vernakalant (3 mg/kg over ten minutes and provisional second administration of 2 mg/kg over 10 minutes if AF persisted despite the initial infusion). The primary endpoint was conversion to sinus rhythm sustained for at least 1 minute, within 90 minutes of first exposure to the study drug. Cardioversion within 90 minutes occurred in 45% of vernakalant patients (median time to conversion was 12.4 minutes) and 15% of placebo patients (p=0.0002). An additional infusion was needed in only 25% of all patients. Interestingly, none of the 6 patients with atrial flutter receiving vernakalant experienced cardioversion. Although the study included only nine patients with atrial flutter, these data are consistent with those derived from ACT I and suggest that vernakalant is not effective in new onset atrial flutter. In patients who received vernakalant but remained in AF or atrial flutter, a significant increase in QRS and QTc intervals was observed, with the lat-

ter returning to placebo levels within 2 hours. Vernakalant's small but significant heart rate-lowering effect was no longer evident after 90 minutes. Authors reported the occurrence of two serious adverse events within 24 hours of vernakalant administration, one episode of hypotension and one episode of complete atrioventricular block immediately after cardioversion. Both events were successfully treated. There were no cases of TdP, sustained ventricular tachycardia or ventricular fibrillation and no deaths.

The **ACT III** trial[47] shared a similar design with ACT I. It included 276 patients with AF and atrial flutter from 3 hours to 45 days of duration and examined the efficacy of IV vernakalant in converting the arrhythmia. For the patients with short duration of AF (less than 7 days), 51.2% of the vernakalant group were converted to sinus rhythm versus 3.6% of the placebo group (p=0.0001), with a median conversion time of 8 minutes. For the patients whose duration of atrial fibrillation was between 7 days and 45 days, the efficacy difference between the 2 groups was not statistically significant (p=0.33). Intravenous vernakalant successfully converted only 7% of the patients with atrial flutter (0% for placebo patients) suggesting a weak effect of the drug on such context, as the aforementioned trials have demonstrated. The authors did not report any episodes of TdP or ventricular tachycardia. However, one vernakalant patient who had severe aortic stenosis and mild heart failure (NYHA II) died after experiencing severe hypotension and ventricular fibrillation. This event led to addition of a protocol amendment that excluded patients with severe valvular stenosis from future studies. Moreover, the authors reported a reversible episode of hypotension that led to drug discontinuation in a 48-year old man who had NYHA II heart failure with an ejection fraction of 25% and a biventricular pacemaker implanted.

Pooled data derived from ACT I and ACT III trials were used to produce two post-hoc analyses. While for the patients with duration of AF between 7 days and 45 days vernakalant was not more effective than placebo (p=0.142), when AF duration was between 3 hours and 7 days, 51.1% of the vernakalant treated patients achieved NSR in comparison to 3.8% of the placebo group (p = 0.0001).[52] A total of 39.8% of the whole population was converted after the first infusion of the drug (with a median conversion time of 10 minutes), whereas only 19.7% of the remaining patients finally achieved NSR. However, 97.2% of successfully converted patients remained in NSR after 24 hours. The second analysis of pooled data from these two trials focused on the recent-onset AF (>3 and <48 hours) and its treatment in the emergency department.[56] Of the 290 patients included, 79% received IV vernakalant and 59.4% of this group were converted within 90 minutes (the median time to conversion was 12 minutes), as compared to 4.9% of the placebo patients. The authors reported very good tolerance and no cases of TdP.

The final Atrial Arrhythmia Conversion Trial published so far, **ACT IV**,[48] was an open-label study conducted with the objective to further evaluate the safety and efficacy of vernakalant in a larger group of patients. It specifically focused on the same population as the previously mentioned post-hoc analysis: those with recent-onset AF, lasting >3 hours to ≤7 days. Patients received the usual 3-mg/kg plus 2-mg/kg dosing regimen. The primary efficacy end point was the proportion of patients with recent-onset AF who converted to sinus rhythm within 90 minutes of the start of the first infusion. Successful cardioversion was observed in 51% of the eligible patients (N=167), with a median time of 14 minutes. Serious adverse events, most commonly bradycardia (2.1%) and hypotension (1.7%), leading to drug discontinuation occurred in 4.2% of the patients. Although non-sustained ventricular tachycardia episodes were reported in 8% of the patients who received vernakalant, the majority of them were asymptomatic and occurred 2-24 hours post-dosing. There were no episodes of TdP, ventricular fibrillation, or sustained ventricular tachycardia.

The limited effectiveness of vernakalant in successfully converting recent onset atrial flutter was recently confirmed by the Steno-2 investigators in a phase II/III randomized, double-blind, placebo-controlled trial.[57] Vernakalant, although well tolerated, did not restore sinus rhythm in patients with atrial flutter (3% vs. 0% in the placebo group) and only modestly increased atrial flutter's cycle length (average 55 ms) and decreased ventricular response rates (-8.2 bpm).

The results of the Active Controlled, Multicenter Study of Vernakalant Injection Versus Amiodarone in Subjects with Recent Onset Atrial Fibrillation (**AVRO**) were published in 2011.[58] It was the first double blind randomized study that did not use placebo in the control arm. A total of 254 patients with symptomatic AF (>3 hours and <48 hours) were equally randomized to receive either vernakalant (3 mg/kg for 10 minutes followed by a 15-minute observation period and a second 10-minute infusion of 2 mg/kg) or intravenous amiodarone (1 hour loading dose of 5 mg/kg, followed by a 1 hour maintenance infusion of 50 mg). Primary endpoint of the study was the conversion from AF to NSR with a minimum duration of 1 minute within 90 minutes of the first exposure of the study drug. In AVRO, vernakalant was proven to be significantly faster than intravenous amiodarone in converting AF patients to NSR: conversion rate within 90 minutes was 51.7% in patients receiving vernakalant versus 5.2% of patients on amiodarone (median time to conversion 11 minutes). Moreover, more patients reported no symptoms at 90 minutes compared with amiodarone. Interestingly, there was a higher incidence of atrial flutter within 4-hours post dose in the vernakalant group (8.6%) as compared with amiodarone (0.9%). Both study drugs were well-tolerated and serious events leading to the discontinuation of drugs were uncommon. The incidence of hypotension was lower compared with the ACT trials. There was an episode of non-sustained monomorphic ventricular tachycardia in the vernakalant group that was

not associated with QT prolongation. The authors reported no cases of TdP, ventricular fibrillation or polymorphic or sustained ventricular tachycardia.

Given the limited data available, a specific analysis of the ACT trials was conducted to assess the efficacy and safety of IV vernakalant for the rapid conversion of AF in patients with a history of ischemic heart disease.[59] While the efficacy analysis included only patients with recent onset AF, the safety analysis included all patients with AF or atrial flutter receiving vernakalant. Results showed that conversion rate was not influenced by the presence of ischemic heart disease. Concerning safety, serious adverse events and discontinuations due to adverse events were similar in both groups and authors reported no cases of TdP, ventricular fibrillation or death in patients with ischemic heart disease.

A phase IIIb study in 470 patients with recent onset symptomatic atrial fibrillation, ACT V, was specifically requested by the FDA in 2008 in order to further evaluate the safety and efficacy of vernakalant versus placebo. ACT V enrollment was prematurely suspended following a single serious case of cardiogenic shock in a patient who received the drug.

Evidence regarding oral vernakalant and its efficacy in maintaining NSR after successful cardioversion are still scarce. While the manufacturing company had previously completed Phase II testing of oral vernakalant, phase III trials were halted from its rights-holder partner company during 2010 and 2011. Two phase II studies assessing oral vernakalant's safety, dosing and efficacy are published up to date. The first one[60] was a phase IIa study carried out in 159 patients with AF duration of >30 and <180 days were randomized into 3 treatment groups: placebo twice daily, oral vernakalant 300 mg twice daily or 500 mg twice daily. After 3 days of therapy, patients remaining in AF were cardioverted with DC shock and continued their drug treatment for 25 more days. A total of 61% of the patients receiving vernakalant maintained NSR at the end of the observing period versus 43% of the placebo group (p=0.028). Serious adverse events were present in 1% of the placebo group, 4% in the 300-mg group, and 6% in the 500-mg group. There were no episodes of TdP. The second one[60] was a phase 2b study that randomized 605 patients to receive oral vernakalant 150 mg, 300 mg or 500 mg twice daily or placebo for a total period of 90 days. At the end of the treatment time, only the 500 mg group reached statistical significance versus placebo (p = 0.027). Patients' hemodynamic tolerance was very good, the incidence of serious adverse events was similar among the two treatment groups and bradycardia occurred in 2.7% in the 500-mg group and in 1.1% in each of the other groups. There were no episodes of TdP observed.

The recently updated ESC guidelines for the management of AF[1] suggest avoiding the use of vernakalant in patients with systolic blood pressure less than 100 mm Hg, severe aortic stenosis, heart failure (class NYHA III and IV) or acute coronary syndromes within the previous 30 days. The authors also recommend adequate prehydration to avoid the risk of hypotension and ECG and hemodynamic monitoring. Finally, it should be noted that although vernakalant seems not to significantly prolong the QT interval, patients with preexisting QTc prolongation were excluded from participating in the clinical trials and consequently we should avoid its use in this setting.

DOSING REGIMEN

The intravenous vernakalant hydrochloride dosing regimen approved by the EMA is the one determined in CRAFT trial and therefore used in all of the ACT and the AVRO trials: 3 mg/kg infusion over 10 minutes followed by 2 mg/kg over 10 minutes administered at 15 minutes later if AF persists.

SIDE EFFECTS

Due to relatively short half-life of IV vernakalant (2-3 hours) all the adverse events recorded in the above mentioned phase II and III trials were evaluated within the first 24 hours after drug infusion. Findings from CRAFT, ACT I, II, III, IV and AVRO trials demonstrated that the side effects mostly experienced by patients were dysgeusia (20.4%), sneezing (15%), paresthesias (8.8%), nausea (6.5%), cough, pruritus, dizziness, hyperhidrosis and hypotension (5.8%).[52] Nevertheless, all these effects were transient.

VERNAKALANT'S PLACE IN CURRENT PRACTICE

Although a significant proportion of patients with AF duration <48 hours seem to spontaneously cardiovert to sinus rhythm, the use of an antiarrhythmic agent to promote conversion and shorten the length of stay in the emergency department is usually preferred. However, currently available antiarrrhythmic agents (amiodarone, ibutilide, flecainide, propafenone) show several limitations concerning efficacy and safety.

Amiodarone has a relatively slow onset of action and, therefore offers little to our efforts to rapidly convert AF in the emergency department,[62-64] nevertheless, it is the drug most commonly used in the acute setting due to safety reasons, especially when the clinical background of the patient reveals structural heart disease or is unknown. Amiodarone actually poses a small risk of proarrhythmia, while at the same time it is considered to be the only available drug that is safe for use in patients with heart failure and ischemic heart disease, a quite common clinical setting in AF patients. These assets seem to offset its limited efficacy to promptly convert recent-onset AF, in the short or medium term. The AVRO trial, as already mentioned, showed that IV vernakalant is significantly more rapid and effective than amiodarone (52% vs 5% within 90 minutes post-infusion) while at the same time it is equally

safe. However, the quite short 90-minute efficacy period was undoubtedly unfair on amiodarone whose conversion rates at 24 hours are 80-90%, while vernakalant seems to have limited benefit in the medium term, with only few patients converted beyond the first hour post-infusion.[65]

Flecainide is a class IC antiarrhythmic agent that has been studied for recent-onset AF conversion either in IV formulation (2 mg/kg over 10 min; not available in many countries) or in a single 300-mg oral loading dose. Efficacy rates were 67-92% at 6 hours post-infusion and 57–68% at two to four hours and 75–91% at eight hours post-oral dose.[66-68] Adverse effects observed were conversion to atrial flutter with rapid ventricular response, QRS widening, transient hypotension and mild neurologic and visual disturbances. Propafenone is another IC agent that has been studied in several randomized trials. When propafenone was given either as an intravenous infusion (not available in many countries) of 2mg/kg over 10 minutes or as a single 600-mg oral loading dose was found to succeed in conversion of recent-onset AF in 41-91% for the intravenous drug and 45-94% for the "pill-in-the-pocket" approach.[69] Reported adverse effects were rapid atrial flutter, ventricular tachycardia, intraventricular conduction disturbances and hypotension. With regard to vernakalant, indirect comparison using data from the ACT trials suggests similar efficacy to the IC agents, ranging from 51% to 79% for recent-onset AF. Both flecainide and propafenone are contraindicated in patients with heart failure or structural heart disease and ESC guidelines recommend patients should be screened for indications and contraindications before implementing the 'pill-in-the pocket' technique and their efficacy and safety should have been previously tested in hospital. Intravenous ibutilide (up to two infusions of 1 mg over 10 min each, with a wait of 10 min between the two doses) is associated with a dose dependent efficacy rate of approximately 50% in 90 minutes with a median time to conversion of 30 minutes (Table 3).[70,71] It is, however, more effective for conversion of atrial flutter than AF and moreover, due to significant I_{Kr} blockade, significantly prolongs QTc carrying thus the important risk of serious proarrhythmia and TdP. For that reason, guidelines recommend a 6-hour post-infusion ECG monitoring, rendering it an unattractive option in the Emergency Department. Head to head comparative trials with these antiarrhythmics as well as other rate control agents are lacking to better define the role of vernakalant in acute AF management.[72] Because of the fact that in most European countries IV flecainide and propafenone are not available, vernakalant is currently the only parenteral drug that could offer an alternative to IV amiodarone (and less often procainamide) for the treatment of recent onset AF, let alone its higher short-term efficacy. Indeed, its rapid onset of action and the short median time to conversion make vernakalant a possible alternative to the more invasive option of electrical cardioversion, especially in hemodynamically stable patients.[73]

Concerning long-term management, since survival benefit from rhythm control has been disputed in most clinical trials, recent ESC guidelines suggest that the choice of therapy between rate and rhythm control is mostly dependent on clinical setting and patients' preferences. Currently used oral

TABLE 3. Comparison Between Vernakalant and Ibutilide

	Vernakalant	**Ibutilide**
Vaughan-Williams class	Not classified	Class III
Mechanism of action	Prolongation of refractoriness	Prolongation of refractoriness
Atrial selectivity	Yes	No
Effectiveness in acute AF	≈50% converted in 90 min	≈50% converted in 90 min
Effectiveness in acute AFl	No	Yes
Median Time to conversion (min)	11	30
Proarrhythmic effect	None or minimal	Risk of ventricular proarrhythmia (TdP 1.7%)
Contraindications	SBP <100 mmHg; Severe aortic stenosis; Heart failure (NYHA III/IV); ACS in the last 30 days; QTc prolongation	Heart failure (NYHA III/IV); Recent ACS; QTc prolongation; Co-administration with class I AADs and other QT-prolonging drugs; hypokalemia
Dosing regimen (IV)	3 mg/kg over 10 min followed by a second infusion of 2 mg/kg over 10 min if arrhythmia persists	1 mg over 10 min followed by a second infusion of 1 mg over 10 min if arrhythmia persists

AADs = antiarrhythmic drugs; ACS = acute coronary syndromes; AF = atrial fibrillation; AFl = atrial flutter; NYHA= New York Heart Association; IV = intravenous; TdP= torsades de pointes.

antiarrhythmics are flecainide, propafenone, sotalol, amiodarone and dronedarone but limitations arise, particularly concerning safety when dealing with patients with structural heart disease. While physicians are surely familiar with the serious extracardiac toxicity of amiodarone rendering it the last resort, recent safety evidence derived from dronedarone trials, especially ANDROMEDA[74] and PALLAS,[75] raise doubts about its future in AF management. Moreover, the risk of TdP with the other antiarrhythmics prevents many clinicians from deciding to follow a rhythm control strategy. If we could improve the efficacy and minimize the risk of proarrhythmia caused by class IA, IC and III antiarrhythmic agents, rhythm control could become a more attractive strategy to most clinicians than rate control strategy. With data available to-date, oral vernakalant appears to have an acceptable efficacy and a low risk of TdP but phase III studies are lacking. Given the fact that the IV formulation has proved to be safe in patients with heart failure[76] and ischemic heart disease, manufacturers aspire the oral drug to become a reliable alternative to more toxic drugs like dronedarone and amiodarone.

CONCLUSIONS

Atrial fibrillation is the most commonly treated arrhythmia in the emergency department.[31] Intravenous vernakalant is a novel, relatively atrial-selective antiarrhythmic agent that has shown to be efficacious in converting recent onset AF but not atrial flutter in several phase III clinical studies. Vernakalant is the first in a class of new pharmacologic agents developed for the acute conversion of AF and works predominantly by blocking early-activating K+ channels and frequency-dependent Na+ channels.

Intravenous vernakalant has already been approved in the European Union, Iceland, and Norway for the rapid conversion of recent-onset AF to sinus rhythm in adult nonsurgical patients with AF duration of seven days or less and post-cardiac surgery patients with AF duration of three days or less. However, the FDA has been reluctant to approve its use due to limited safety data, especially after the preliminary termination of ACT V following the unfortunate outcome in a single patient. Although the risk of serious ventricular proarrhythmia seems to be minimal, hypotension often observed after its use is a concern,[77,78] particularly in patients with symptomatic left ventricular dysfunction, aortic stenosis and pre-existing low blood pressure, situations in which the use of this new drug should be avoided. Finally, cost issues will constitute an important hindrance to expanded use of IV vernakalant.

Preliminary data on the oral formulation of vernakalant have become available but while phase III studies were pending to provide more clinical data concerning efficacy and safety, in the first quarter of 2012, the drug maker decided to halt further development of oral vernakalant.

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