REVIEW ARTICLE

Vernakalant for the Conversion of Atrial Fibrillation: The New Kid On the Block?

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Conversion of recent onset atrial fibrillation (AF) to sinus rhythm with antiarrhythmic drugs reduces the risk of hemodynamic instability, hospitalizations, and atrial remodeling seen with persistent AF. This is the main reason for pharmacological or electrical cardioversion to be considered first line of treatment for recent onset AF. Is there a role for new antiarrhythmic drugs in the conversion of AF as the first approach to a rhythm-control strategy? Vernakalant is a novel and relativity atrial selective drug which inhibits atrial-selective K^+ currents, with only a small inhibitory effect on the rapidly activating delayed rectifier K^+ current (IKr) in the ventricle. In this brief Review, we tell the journey of vernakalant to become an attractive alternative to achieve pharmacological cardioversion of AF.

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Atrial fibrillation (AF) is the most common arrhythmia and its prevalence is expected to rise dramatically, owing to an aging population. Conversion of recent onset AF to sinus rhythm with antiarrhythmic drugs reduces the risk of hemodynamic instability, hospitalizations, and atrial remodeling seen with persistent AF. This is the main reason for pharmacological or electrical cardioversion to be considered first line of treatment for recent onset AF.[1]

In many centers around the world, electrical cardioversion is considered the first line of treatment for paroxysmal AF. The benefit to use pharmacological cardioversion instead of electrical cardioversion relies in avoiding sedation and fasting for 3–6 hours. The reduction of length of stay in the emergency department may represent an important reduction in costs at the time of deciding the method for cardioversion into sinus rhythm.[2] The aim of this brief Review is to analyze the mechanism of action and pivotal studies that used vernakalant for the conversion of AF.

Vernakalant: Mechanism of Action

The atrial-selective $I_{K,ACh}$ current is potently blocked by vernakalant that also targets Kv4.3 and human ERG (hERG) channels that correspond to the transient outward current (I_{to}) and I_{Kr}, respectively.[3–6]

I_{Kr} is an important repolarizing current in ventricular cells, and its blockade causes QT interval and action potential duration prolongation, predisposing to ventricular arrhythmias.[7] Late Na^+ current ($I_{Na,late}$) inhibition by vernakalant is protective against the proarrhythmia from I_{Kr} blockade. Accordingly, clinical trials showed little changes in QT interval and a very low incidence of ventricular tachyarrhythmia following vernakalant infusion, which was not significantly different from placebo recipients.[8]

The effects of vernakalant on Na^+ channels are voltage and rate dependent, resulting in an enhanced inhibitory potency at depolarized potentials and rapid rates, like in fibrillating atria.

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It reduces the Na^+ channel reserve predominantly in the atria.[9]

Na^+ channel block with rapid unbinding kinetics has recently been identified as a promising option for atrial-selective drug treatment of AF. Besides vernakalant, the antianginal agent ranolazine and amiodarone have also been shown to cause atrial-selective Na^+ channel inhibition. Vernakalant exerts antifibrillatory actions that are shared by amiodarone and flecainide by prolonging atrial ERP and/or reducing atrial excitability.[10–14]

PIVOTAL STUDIES

Currently, there are six randomized trials which showed the proportion of patients who converted from AF to sinus rhythm versus placebo and amiodarone (Table 1).

The first dose-finding Phase II study (CRAFT study) evaluated AF termination using vernakalant versus placebo. Vernakalant converted AF into sinus rhythm within 30 minutes of the infusion 61% of the patients while only 5% of the placebo group converted to sinus, being this difference statistically significant ($P < 0.0005$).[15]

In the ACT I trial, vernakalant converted to sinus rhythm 51.7% of the patients versus 4.0% of the placebo group ($P < 0.001$).[16]

The ACT II trial included patients with AF lasting 3–72 hours that occurred between 24 hours and 7 days after coronary artery bypass graft and/or valvular surgery and 47% of vernakalant-treated patients were converted to sinus rhythm versus 14% of the placebo-treated patients ($P < 0.001$). The median time to conversion was 12 minutes.[17]

In the ACT III trial, the proportion of patients who converted from AF to sinus rhythm was 51.2% in the vernakalant group versus 3.6% in the placebo group ($P < 0.001$), a similar trial to ACT I.[18]

The ACT IV trial, vernakalant versus placebo, was an open label study where AF (3 hours to 7 days) termination within 90 minutes by vernakalant was 50.9% with a median time to conversion to sinus rhythm: 14 minutes.[19]

In the AVRO study, vernakalant was compared with intravenous amiodarone, and converted 51.7% of patients to sinus rhythm at 90 minutes, compared to 5.2% of patients treated with amiodarone ($P < 0.0001$).[20]

Table 1. Efficacy of Intravenous Vernakalant in Randomized Clinical Trials

	CRAFT	ACT I	ACT II	ACT III	ACT IV	AVRO	Scene 2
Type	RCT/phase II	RCT/phase III	RCT/phase III	RCT/phase III	Open label	RCT	RCT/phase II/III
Inclusion criteria	AF for 3–72 h	AF for 3 h to 45 d	Postoperative AF/AFL for 3 h to 3 d	AF for 3 h to 45 d	AF for 3 h to 45 d	AF for 3 to 48 h	AFL for 3 h to 45 d
Follow-up	24 h	24 h	7 d	24 h	7 d	24 h	30 d
Patients, n	56	336	161	276	236	254	54
Primary efficacy endpoint	AF termination within 30 min: 61% (V) vs 5% (P) ($P < 0.0005$)	AF (3 h to 7 d) termination within 90 min: 51.7% (V) vs 4.0% (P) ($P < 0.001$); median time to conversion to SR: 11 min; patients in SR at 24 h: 98%	AF/AFL termination within 90 min: 45% (V) vs 15% (P) ($P < 0.001$); AF termination within 90 min: 47% (V) vs 14% (P) ($P < 0.001$); no conversion of AFL to SR: 0/6 patients given V	AF (3 h to 7 d) termination within 90 min: 51.2% (V) vs 3.6% (P) ($P < 0.001$). AF (8–45 d) termination within 90 min: 9.4% (V) vs 2.7% (P) ($P = NS$). Patients in SR at 24 h: 98% (V)	AF (3 h to 7 d) termination within 90 min by V: 50.9%; median time to conversion to SR: 14 min; patients in SR at 24 h and 7 days: 98% and 89% of responders	AF termination within 90 min: 51.7% (V) vs 5.2% (A) ($P < 0.0001$)	AFL conversion within 90 min: 3% (V) vs 0% (P) ($P = NS$)

A, amiodarone; ACT, atrial arrhythmia conversion trial; AVRO, a phase III superiority study of vernakalant vs amiodarone in subjects with recent onset atrial fibrillation; CRAFT, conversion of rapid atrial fibrillation trial; d, days; h, hours; min, minutes; NS, not significant; RCT, randomized controlled trial; P, placebo; SR, sinus rhythm; V, vernakalant.

The encouraging results of vernakalant for the conversion of AF have not been reproduced for the conversion of atrial flutter. Vernakalant was ineffective for the treatment of atrial flutter in nonsurgical patients and cardiac surgery patients in the ACT II and ACT III trials, respectively.[3]

A recent Phase II/III randomized, double-blind, placebo-controlled trial (Scene 2) has confirmed the ineffectiveness of vernakalant in converting atrial flutter. Vernakalant did not restore sinus rhythm in patients with atrial flutter in a significant manner (3% vs 0% in the placebo group).[21]

In terms of safety, vernakalant showed to be a safe and well tolerate drug in all these trials, no different to placebo or amiodarone regarding major events, and with only one death over 889 enrolled patients (one patient with aortic stenosis in the ACT III trial). There was also no difference in other serious adverse events like ventricular arrhythmia.[3]

PAST PUBLICATIONS

Some other studies using vernakalant are also worth to mention. Few sequential studies have compared vernakalant versus oral loading dose of propafenone and flecainide, in patients without structural heart disease.

The first study which compared vernakalant with propafenone showed a median conversion time for vernakalant group of 9 minutes versus 166 minutes in the propafenone group ($P = 0.001$),[22] while another study showed 10 minutes in the vernakalant group versus 163 minutes in the flecainide group ($P = 0.001$).[23] In both studies vernakalant was safe and well tolerated.

A third study compared vernakalant with intravenous Amiodarone in patients with mild left ventricular dysfunction and the results showed that vernakalant was superior to amiodarone (conversion rate was 87% vs 33.3% respectively; $P = 0.005$) without serious adverse events in both groups.[24]

There is a retrospective study which compared vernakalant versus electrical cardioversion (EC) of recent onset AF and the results showed a conversion rate of 91% in the vernakalant group at 2 hours and 100% in the EC group ($P = NS$), with a hospital length of stay of 246 minutes in the vernakalant group versus 263 minutes in the EC group ($P = NS$).[25] The results of this study are relevant. Both treatments had the same hospital length of stay but cardioversion with vernakalant did not need sedation, thus, no anesthesiologist was involved in patient care and fasting was not necessary.

Safety Concerns

Cardiogenic shock occurred in two patients in ACT I and unpublished ACT V trials, one of whom died. Serious hypotension and clinically significant bradycardia were more frequently documented in vernakalant-treated patients. Two patients had complete AV block, one during vernakalant infusion and the other within hours of vernakalant infusion.[16,17]

Vernakalant-related hypotension can be attributed to its negative inotropic effect, which has been shown in experimental studies, although the underlying mechanisms have not been directly addressed. The negative inotropic effect of vernakalant observed in anaesthetized dogs occurred only at high plasma concentrations (a threefold or greater margin above the maximum concentration observed at therapeutic doses).[26]

REMARKS

The currently available clinical studies have shown that intravenous vernakalant is safe, well tolerated and highly efficacious for cardioversion of recent-onset AF. Vernakalant should be considered within the emergency department therapeutic arsenal as per the European guidelines recommendation.[27]

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