Safety and efficacy of vernakalant for acute cardioversion of atrial fibrillation: an update

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Abstract: Intravenous vernakalant has recently been approved in Europe as an atrial-selective antiarrhythmic drug for the conversion of recent-onset atrial fibrillation (AF). It inhibits atrial-selective K+ currents (IK,ACh and IKr) and causes rate-dependent atrial-predominant Na+ channel block, with only a small inhibitory effect on the rapid delayed rectifier K+ current (IKr) in the ventricle. Due to its atrial-selective properties, vernakalant prolongs the effective refractory period of the atria with minimal effects on the ventricles, being associated with a low proarrhythmic risk for torsades de pointes arrhythmias. Five pivotal clinical trials consistently demonstrated that vernakalant rapidly terminates AF with stable maintenance of sinus rhythm for up to 24 hours. A head-to-head comparative trial showed that the 90-minute conversion rate of vernakalant was substantially higher than that of amiodarone. Initially, a longer-acting oral formulation of vernakalant was shown to be effective and safe in preventing AF recurrence after cardioversion in a Phase IIb study. However, the clinical studies testing oral vernakalant for maintenance of sinus rhythm after AF cardioversion were prematurely halted for undisclosed reasons. This review article provides an update on the safety and efficacy of intravenous vernakalant for the rapid cardioversion of AF.

Keywords: atrial fibrillation, antiarrhythmic drug, atrial-selective K+ currents, Na+ channel block, ventricles

Introduction

Atrial fibrillation (AF) is the most common arrhythmia and its prevalence is expected to rise dramatically owing to an aging population.1 AF causes symptoms such as palpitations, dizziness, breathlessness, and chest pain, and is associated with cardiovascular morbidity and mortality, mainly due to embolic stroke and heart failure (HF).1 Management of AF patients is focused on reducing symptoms and preventing complications associated with the arrhythmia. Two therapeutic approaches are available: a “rhythm control” strategy, terminating AF and maintaining sinus rhythm, and a “rate control” strategy, allowing the patient to remain in AF but controlling the ventricular response. Both strategies require proper anticoagulation to prevent AF-related risks of thromboembolic complications.1 Since several large randomized trials could not demonstrate the superiority of a rhythm control approach,2 the choice is not imperative. However, restoration and maintenance of sinus rhythm is the most attractive option because of reduction of symptoms and improvement in exercise tolerance and quality of life.2

Antiarrhythmic drugs are considered first-line agents for rhythm control. Currently available and commonly used antiarrhythmic drugs are limited by incomplete efficacy.
for achieving and maintaining sinus rhythm and/or by side effects such as life-threatening ventricular proarrhythmias or severe extra-cardiac toxicities.\textsuperscript{1–5} Amiodarone is the most effective drug for rhythm control but AF recurs in a substantial portion of cases. It is often discontinued due to serious systemic side effects such as thyroid and lung dysfunction.\textsuperscript{1–5} Therefore, there is a clear need for safer and more effective pharmacological strategies for rhythm control.\textsuperscript{6}

Vernakalant is a compound with atrial-selective ion-channel blocking properties that has recently been introduced for the acute management of AF.\textsuperscript{5,7} Its intravenous formulation has been approved for the conversion of recent-onset AF in Europe and other parts of the world, but not in the USA. Vernakalant inhibits atrial-selective K\textsuperscript{+} currents, including the ultra-rapidly activating delayed rectifier K\textsuperscript{+} current (I\textsubscript{Kur}) and acetylcholine-activated inward rectifier K\textsuperscript{+} current (I\textsubscript{K.ACh}), and causes rate-dependent atrial-preferential Na\textsuperscript{+} channel block, with only a small inhibitory effect on the rapidly activating delayed rectifier K\textsuperscript{+} current (I\textsubscript{Kr}) in the ventricle.\textsuperscript{8} Due to its atrial-selective properties, vernakalant prolongs the effective refractory period (ERP) of the atria with minimal effects on the ventricles,\textsuperscript{9} which explains the low proarrhythmic risk for torsades de pointes (TdP) arrhythmias.\textsuperscript{6,7} Several randomized clinical trials consistently demonstrated the efficacy and safety of intravenous vernakalant for the cardioversion of recent-onset AF.\textsuperscript{11–15} A head-to-head comparative trial showed that the 90-minute conversion rate of vernakalant was substantially greater than that of amiodarone.\textsuperscript{16} Although a longer-acting oral formulation of vernakalant showed some efficacy and good safety for prevention of AF recurrence after electrical cardioversion, further development of oral vernakalant was halted,\textsuperscript{17} probably because of insufficient efficacy to maintain sinus rhythm. The lack of an oral formulation for long-term therapy is an obvious limitation for the use of intravenous vernakalant. In addition, one unpublished trial of intravenous vernakalant was suspended following a single unexpected serious adverse event of cardiogenic shock, pending assessment by the US Food and Drug Administration.\textsuperscript{5,7} The aim of this review article is to summarize the putative mechanisms of action of vernakalant and to provide an update on the clinical evidence for efficacy and safety of vernakalant for cardioversion of AF.

**Pharmacological actions and therapeutic efficacy of vernakalant**

**Mechanism of action**

Vernakalant is an antiarrhythmic agent that has predominant actions on atrial electrophysiology. A human electrophysiological study demonstrated that vernakalant infusion dose-dependently prolongs atrial ERP but has no significant effect on ventricular ERP or QT interval.\textsuperscript{10} Atrial selectivity, thereby avoiding ventricular proarrhythmia, can be achieved by targeting atrial-selective channels, such as I\textsubscript{Kur} and I\textsubscript{K.ACh}, by atrial-preferential inhibition of excitability through exploiting state-selective Na\textsuperscript{+} channel blocking properties or by high selectivity for rapid rhythms like AF.\textsuperscript{6}

Vernakalant blocks several K\textsuperscript{+} channels. It inhibits I\textsubscript{Kur} in the open state, with preserved efficacy at high stimulation frequencies.\textsuperscript{8} The atrial-selective I\textsubscript{K.ACh} current is potently blocked by vernakalant.\textsuperscript{18–19} Vernakalant also targets Kv4.3 and human ERG (hERG) channels that correspond to the transient outward current (I\textsubscript{to}) and I\textsubscript{Kr}, respectively, although the contribution of I\textsubscript{to} to repolarization is lower in ventricles than in atria.\textsuperscript{8} In contrast, I\textsubscript{Kur} is an important repolarizing current in ventricular cells. Its blockade causes QT interval and action potential duration prolongation, predisposing to TdP arrhythmias through the development of arrhythmia-triggering early afterdepolarization and/or an increased dispersion of repolarization.\textsuperscript{6} However, the potency of vernakalant in blocking hERG channels is up to 100-fold lower than that of class IC antiarrhythmic drugs (flecainide or propafenone).\textsuperscript{5} Late Na\textsuperscript{+} current (I\textsubscript{Na,L}) inhibition by vernakalant is protective against the proarrhythmia from I\textsubscript{to} blockade.\textsuperscript{20} 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.\textsuperscript{5}

Vernakalant causes an open-channel block of Na\textsuperscript{+} channel Nav1.5 α-subunits that underlie the atrial I\textsubscript{Na}.\textsuperscript{8,18} At physiological heart rates, the block of Nav1.5 channels by vernakalant is weak because of its rapid unbinding kinetics from the channel,\textsuperscript{8,18} which is consistent with the small increase in QRS interval (a marker of ventricular conduction velocity) observed in clinical trials.\textsuperscript{12–14} In addition, the effects of vernakalant on Na\textsuperscript{+} channels are voltage and rate dependent, resulting in an enhanced inhibitory potency at depolarized potentials and rapid rates, like in fibrillating atria.\textsuperscript{8} The resting membrane potential of normal atrial myocytes is 10 mV more depolarized than that of normal ventricular myocytes. When atrial myocytes fail to repolarize fully, as can happen during AF, the atrioventricular difference in resting membrane potential is further accentuated and a large fraction of atrial Na\textsuperscript{+} channels is inactivated. This reduces the Na\textsuperscript{+} channel reserve predominantly in the atria and allows vernakalant to inhibit preferentially atrial Na\textsuperscript{+} channels.\textsuperscript{8} Although such voltage and rate dependency
is also typical for flecainide and propafenone, they do not show atrial selectively,\textsuperscript{21,22} and the important difference is that vernakalant exhibits rapid unbinding kinetics from Na\textsuperscript{+} channels.\textsuperscript{6} Therefore, Na\textsuperscript{+} channel block with rapid unbinding kinetics has recently been identified as a promising option for atrial-selective drug treatment of AF.\textsuperscript{23,24} Besides vernakalant, the antianginal agent ranolazine and amiodarone have also been shown to cause atrial-selective Na\textsuperscript{+} channel inhibition.\textsuperscript{22,25–28} A recent ex vivo study of human atrial tissue from sinus rhythm and chronic AF showed that vernakalant causes a rate-dependent reduction in maximum action potential upstroke velocity and that ERP is increased more than action potential duration, resulting in post-repolarization refractoriness.\textsuperscript{19} The ion-channel inhibitory properties and electrophysiological effects of vernakalant are summarized and compared with those of amiodarone and flecainide, the agents most commonly used in AF, in Table 1. Vernakalant exerts antifibrillatory actions that are shared by amiodarone and flecainide by prolonging atrial ERP and/or reducing atrial excitability.

The myocardial sleeves of pulmonary veins (PVs) are an important source of ectopic activities that initiate and maintain paroxysmal AF.\textsuperscript{29} Several studies have proposed enhanced automaticity,\textsuperscript{30} triggered activity,\textsuperscript{31,32} and localized re-entry in PVs\textsuperscript{33} as the underlying mechanisms of chronic AF. The pure Na\textsuperscript{+} channel blocker pilocarpine terminated AF by modifying ERP heterogeneity and conduction properties in the PVs and at the PV-left atrial junction in patients.\textsuperscript{34} A recent study in canine PV sleeve preparations has shown that vernakalant increases the ERP in a rate-dependent manner and that vernakalant suppresses delayed afterdepolarization-mediated triggered activity induced by burst pacing in the presence of isoproterenol and high Ca\textsuperscript{2+}.\textsuperscript{35} The authors speculated that vernakalant may cause a reduction in intracellular Ca\textsuperscript{2+} loading, secondary to the reduction in intracellular Na\textsuperscript{+} loading at rapid rates.\textsuperscript{35} Whether these effects could contribute to the clinical efficacy of vernakalant is unknown.

**Clinical efficacy**

The efficacy of intravenous vernakalant for cardioversion of recent-onset AF has been demonstrated in six clinical trials (Table 2). One of these was the first dose-finding Phase II study (Conversion of Rapid Atrial Fibrillation Trial [CRAFT]). In all subsequent studies (Atrial arrhythmia Conversion Trial [ACT] I, II, III, IV, and A phase III superiority study of Vernakalant vs amiodarone in subjects with Recent Onset atrial fibrillation [AVRO]), vernakalant was administered by a 10-minute infusion of 3 mg/kg followed by a 15-minute observation period then a second 10-minute infusion of 2 mg/kg if still in AF. The results of these trials have been reviewed in excellent articles elsewhere.\textsuperscript{7,36–41} Based on these data, intravenous vernakalant was approved by the European Commission for the rapid cardioversion of recent-onset AF (lasting \(\leq 7\) days for non-surgery patients and \(\leq 3\) days for post-cardiac-surgery patients) to sinus rhythm in adults.\textsuperscript{9} Following, we update the currently available efficacy and safety information obtained in clinical trials and discuss the potential consequences for the clinical use of vernakalant.

The ACT I\textsuperscript{12} and III\textsuperscript{14} tested vernakalant in patients with short-duration AF (3 hours to 7 days) and long-duration AF (8 to 45 days). The primary endpoint in both studies was the proportion of patients with short-duration AF who had treatment-induced conversion of AF to sinus rhythm for at least 1 minute within 90 minutes of treatment infusion. The secondary endpoint in short-duration AF patients included the time to conversion from the first administration and the proportion of patients who remained in sinus rhythm at 24 hours. Another secondary endpoint was conversion of AF in patients with longer-duration AF.

Vernakalant effectively and rapidly converted AF to sinus rhythm compared with placebo. The primary endpoint was

**Table 1 Ion-channel blockade properties and electrophysiological effects**

<table>
<thead>
<tr>
<th>Ion-channel blocking</th>
<th>References</th>
<th>Mechanisms of recent-onset AF conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I_{Na} ) (atrial selectivity)</td>
<td>ERP</td>
<td>Excitability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vernakalant</td>
<td>(\uparrow)</td>
<td>(\downarrow)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>(\uparrow)</td>
<td>(\downarrow)</td>
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<tr>
<td>Flecainide</td>
<td>(\uparrow)</td>
<td>(\downarrow)</td>
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</tbody>
</table>

**Notes:** The \(\ast\) denotes action of agents on ion channel. It is unknown whether an inhibitory effect on ectopic activity can contribute to the clinical efficacy of agents.

**Abbreviations:** AF, atrial fibrillation; ERP, effective refractory period; \(I_{Na}\), ultra-rapidly activating delayed rectifier \(K^+\) current; \(I_{K,CCh}\), acetylcholine-activated inward rectifier \(K^+\) current; \(I_{to}\), rapidly activating delayed rectifier \(K^+\) current; \(I_{Kr}\), Na\textsuperscript{+} current; \(I_{Na,fast}\), late Na\textsuperscript{+} current; \(I_{to}\), transient outward current.
Table 2  Efficacy of intravenous vernakalant in randomized clinical trials of patients with atrial fibrillation (AF) and atrial flutter (AFL)

<table>
<thead>
<tr>
<th></th>
<th>CRAFT11</th>
<th>ACT I12</th>
<th>ACT II13</th>
<th>ACT III14</th>
<th>ACT IV15</th>
<th>AVRO16</th>
<th>Scene 214</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td>RCT/phase II</td>
<td>RCT/phase III</td>
<td>RCT/phase III</td>
<td>RCT/phase III</td>
<td>Open label</td>
<td>RCT</td>
<td>RCT/phase IV/III</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>Sustained AF for 3 to 72 h</td>
<td>Sustained AF for 3 h to 45 d</td>
<td>Postoperative AF/AFL for 3 h to 3 d</td>
<td>Sustained AF for 3 h to 45 d</td>
<td>Sustained AF for 3 h to 45 d</td>
<td>RCT</td>
<td>Sustained AFL for 3 h to 45 d</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>24 h</td>
<td>24 h</td>
<td>7 d</td>
<td>24 h</td>
<td>24 h</td>
<td>7 d</td>
<td>24 h</td>
</tr>
<tr>
<td><strong>Patients, n</strong></td>
<td>56</td>
<td>336</td>
<td>161</td>
<td>276</td>
<td>236</td>
<td>254</td>
<td>54</td>
</tr>
<tr>
<td><strong>Primary efficacy endpoint</strong></td>
<td>AF termination within 30 min: 61% (V) vs 5% (P) (P &lt; 0.0005)</td>
<td>AF termination within 90 min: 45% (V) vs 15% (P) (P &lt; 0.001); AF termination within 90 min: 51.2% (V) vs 3.6% (P) (P &lt; 0.001).</td>
<td>AF (3 h to 7 d) termination within 90 min: 50.9%; median time to conversion to SR: 14 min; patients in SR at 24 h and 7 days: 98% and 89% of responders</td>
<td>AF (3 h to 7 d) termination within 90 min: 51.7% (V) vs 5.2% (A) (P &lt; 0.0001)</td>
<td>AF (8–45 d) termination within 90 min: 51.7% (V) vs 5.2% (A) (P &lt; 0.0001)</td>
<td>AF termination within 90 min: 51.7% (V) vs 5.2% (A) (P &lt; 0.0001)</td>
<td>AF termination within 90 min: 51.7% (V) vs 5.2% (A) (P &lt; 0.0001)</td>
</tr>
<tr>
<td><strong>Secondary efficacy endpoint</strong></td>
<td>Patients in SR at 1 h: 53% (V) vs 5% (P) (P = 0.0014); patients in SR at 24 h: 79% (V) vs 45% (P) (P = NS); median time to SR conversion: 14 min (V) vs 162 min (P) (P &lt; 0.05)</td>
<td>AF (8–45 d) termination: 7.9% (V) vs 0% (P) (P = 0.09); no significant conversion of AFL to SR</td>
<td>Median time to SR conversion with V: 12.3 min (range 0.5–57.1 min); patients in SR at 24 h and 7 d: 60% and 57% of responders</td>
<td>Median time to SR conversion with V: 8 min</td>
<td>AF (8–45 d) termination within 90 min by V: 11.6%</td>
<td>Significantly faster conversion with V than with A; median time to conversion to SR with V: 14 min; patients converted within 240 min: 54.4% (V) vs 22.6% (A) (P &lt; 0.0001)</td>
<td>Ventricular response rate within 50 min: −8.2 bpm (V) vs −0.2 bpm (P) (P = 0.037)</td>
</tr>
</tbody>
</table>

**Abbreviations:** 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.
achieved in 51.7% of vernakalant-treated patients versus 4.0% of placebo (in ACT I\textsuperscript{12}) and in 51.2% versus 3.6% (in ACT III\textsuperscript{14}). Responders given vernakalant showed rapid conversion (median time of 11 and 8 minutes, in ACT I and III, respectively) and a low rate of AF relapse within 24 hours (1.3% and 2.3% in ACT I and III, respectively).\textsuperscript{12,14}

The duration of AF affected the efficacy of vernakalant. Patients with AF lasting 3 to 48 hours given vernakalant demonstrated the highest conversion rate of 62.1% (versus 4.9% for placebo). Conversion rate in patients with AF lasting 3 to 7 days decreased to 23.8% but remained significant (versus 0% for placebo, in ACT I). However, longer-duration AF rarely responded favorably, and the conversion rate was not statistically different from placebo (7.9% vs 0% and 9% vs 3% in ACT I and III, respectively).\textsuperscript{12,14} Similar results were obtained in the open-label ACT IV study.\textsuperscript{15}

The ACT II trial included patients with AF lasting 3 to 72 hours that occurred between 24 hours and 7 days after coronary artery bypass graft and/or valvular surgery.\textsuperscript{13} The primary endpoint was the conversion to sinus rhythm within 90 minutes of dosing, which was met in 47% of vernakalant-treated patients compared with 14% of placebo-treated patients. The median time to conversion was 12 minutes.

The active-controlled AVRO trial compared the efficacy of vernakalant with amiodarone (a 1 hour infusion of 5 mg/kg followed by a maintenance infusion of 50 mg over 1 additional hour) in recent-onset AF (of 3 to 48 hours duration).\textsuperscript{16} The primary endpoint was the proportion of patients who achieved sinus rhythm at 90 minutes after initiating infusion. Treatment with vernakalant converted 51.7% of patients to sinus rhythm at 90 minutes compared with 52.2% of patients treated with amiodarone. The proportion of vernakalant- or amiodarone-treated patients converted to sinus rhythm within 240 minutes was 54.4% and 22.6%, respectively. These results are attributed to a slow onset of action of amiodarone and do not indicate that vernakalant is superior to amiodarone in treating recent-onset AF.

These pivotal Phase III trials included patients with a history of hypertension, mild to moderate HF (except New York Heart Association functional class IV), myocardial infarction, ischemic heart disease, and valvular heart disease. There were no significant differences in response to vernakalant injection in any subgroup. However, there was a trend toward decreased efficacy in patients with a history of HF (26.9% vs 50.0% for no HF history).\textsuperscript{9} A sub-analysis of patients with a history of ischemic heart disease showed that the rate of AF conversion by vernakalant was not influenced by the presence of ischemic heart disease.\textsuperscript{42} Serious adverse events and drug discontinuations due to adverse events were similar in patients with and without ischemic heart disease. No cases of TdP, ventricular fibrillation, or death were recorded in patients with ischemic heart disease. Of note, since patients were excluded in these trials if they had acute myocardial infarction, acute coronary syndrome, or cardiac surgery within 30 days before enrollment (except for the ACT II trial just discussed), the results cannot be extrapolated to patients with acute ischemia.

Vernakalant was ineffective for the treatment of atrial flutter in nonsurgical patients and cardiac surgery patients in the ACT II\textsuperscript{13} and ACT III\textsuperscript{14} trials, respectively. Moreover, these studies showed that approximately 10% of AF patients treated with vernakalant developed atrial flutter in the first 90 minutes, which either restored to sinus rhythm spontaneously or was restored by electrical cardioversion. A recent Phase II/III randomized, double-blind, placebo-controlled trial (Scene 2, Table 2) has confirmed the ineffectiveness of vernakalant in converting atrial flutter.\textsuperscript{41} Vernakalant did not restore sinus rhythm in patients with atrial flutter (3% versus 0% in the placebo group). The treatment increased the atrial flutter cycle length by an average of 55 milliseconds and decreased ventricular response rates by 8.2 bpm from baseline. Importantly, there was no occurrence of 1:1 AV conduction. This is explained by the combined effects of vernakalant on flutter cycle length and AV nodal refractoriness.\textsuperscript{43} Besides increasing the atrial flutter cycle length, vernakalant causes a small but significant prolongation of AV nodal refractoriness.\textsuperscript{10} The lack of 1:1 AV conduction appears a clinically important advantage of vernakalant over class IC drugs like flecainide and propafenone that can cause atrial flutter, termed “IC flutter,” which is often associated with a 1:1 AV conduction. Although infrequent, this pattern of proarrhythmia has been reported in a patient receiving vernakalant infusion.\textsuperscript{44}

Oral vernakalant initially showed promise for maintenance of sinus rhythm in a Phase Ib study.\textsuperscript{17} Patients with symptomatic AF persisting for 72 hours to 6 months were randomized to receive oral vernakalant (150, 300, or 500 mg) or placebo twice daily for up to 90 days. The efficacy analysis was conducted on 605 patients who entered the maintenance phase on day 3 after cardioversion. At day 90, 49% of the 500 mg vernakalant group maintained sinus rhythm versus 36% of the placebo group ($P = 0.021$). The median time to the first recurrence of AF was >90 days in the vernakalant group versus 29 days with placebo. The drug was well tolerated during exposure for up to 90 days, and no proarrhythmic reactions were observed. Vernakalant was not effective at the lower doses.
Side effects and safety
Clinical trials have consistently demonstrated that vernakalant is a well-tolerated and safe antiarrhythmic agent. Due to the short half-life of vernakalant (~2 hours), safety evaluations have focused mainly on adverse events within the first 24 hours of administration. The most common adverse events are dysgeusia (19%), sneezing (13%), paresthesia (7%), and nausea (7%), which are likely to be related to Na+ channel blockade in the central nervous system. These side effects have been considered mild or moderate and not treatment limiting. Related serious adverse events are mostly of cardiovascular origin and include hypotension, bradycardia, and ventricular arrhythmia. The data obtained from clinical trials are summarized in Table 3.

Electrocardiogram parameters and risk of ventricular arrhythmias
An in vivo human electrophysiology study and the CRAFT trial did not find a significant change in QRS or heart rate-corrected QT interval (QTc) by the infusion of vernakalant. In contrast, pivotal trials (ACT I, II, and III) showed that vernakalant increases the QRS and QTc intervals between 5 minutes and 2 hours after the start of infusion. This finding suggests that the atrial selectivity of vernakalant is not absolute and that the drug carries a proarrhythmic risk. Overall, no TdP has been documented within 24 hours of vernakalant administration, except for one case in which the class III antiarrhythmic drug ibutilide was given on top of vernakalant (Scene 2). Two patients experienced TdP episodes 32 hours and 16–17 days, respectively, after vernakalant administration (ACT I). QT interval prolongation led to drug discontinuation in one case only (ACT I). The incidence of non-sustained ventricular tachycardias reported in vernakalant-treated patients appears comparable to that in placebo-treated patients. However, some cases had drug discontinuation because of ventricular bigeminy (ACT I), monomorphic sustained (ACT III), and non-sustained VT (AVRO) during the first 2 hours. In addition, ventricular arrhythmias occurred more frequently in patients with a history of HF. Ventricular arrhythmias unrelated to TdP have been identified as an adverse event of special significance.

Serious adverse events
There was one case of death considered related to vernakalant and 26 cases (2.9%) of serious adverse events within the first 24 hours out of 889 vernakalant-treated patients in clinical trials. Hypotension was the most frequent vernakalant-related serious adverse event (eight patients, 1.0%). Others include bradycardia (seven patients), complete AV block (two patients), and cardiogenic shock (one patient). One death that occurred in the ACT III study was a 64-year-old patient with a history of severe aortic stenosis and New York Heart Association class II HF. At the time of admission, he was suffering from acute coronary syndrome and AF with a ventricular rate of ~150 bpm. The intravenous metoprolol used for ventricular rate control caused transient hypotension. Despite the hemodynamic instability, the patient received the two infusions of vernakalant and became hypotensive after each infusion. Subsequently, the patient developed ventricular fibrillation and resuscitation was unsuccessful.

Hypotensive episodes usually occur within 15 minutes of following vernakalant infusion, are transient, and generally resolve without pharmacological intervention. However, significant hypotension that required treatment with intravenous fluids and/or norepinephrine was reported in four cases (ACT I, II, and III trials), two of which had HF. Bradycardia events are primarily associated with AF termination. A clinically significant bradycardia that lasted ≤ 20 minutes from the time of conversion of AF was documented in four patients (ACT IV). Complete AV block occurred in a 90-year-old woman (ACT I) and a cardiac surgery patient (ACT II). In the former case, it occurred after electrical cardioversion, which was performed ~2.5 hours after the second infusion and, in the latter case, during the first infusion of vernakalant. Cardiogenic shock occurred in a patient who was diagnosed later as having tachycardia-induced cardiomyopathy (ACT I). The patient had hypotension after the first infusion, which responded to a saline intravenous bolus injection, and did not receive the second infusion. He underwent electrical cardioversion a few hours later then developed cardiogenic shock.

Deaths occurred up to 30 days after study drug infusion in five vernakalant patients (ACT I, ACT IV, and AVRO), but none was considered related to this medication. Clinical considerations
The conventional class IC (flecainide, propafenone) and class III (amiodarone and ibutilide) antiarrhythmic drugs that are commonly used for the acute termination of recent-onset AF have shown limited efficacy and raised substantial safety concerns. In particular, amiodarone’s onset of action is extremely slow, lasting up to 24 hours; flecainide and propafenone cannot be given when HF, coronary artery disease, or acute ischemia are present; and ibutilide carries a high risk of causing life-threatening TdP arrhythmias,
### Table 3: Safety of intravenous vernakalant in randomized clinical trials of patients with atrial fibrillation (AF) and atrial flutter (AFL)

<table>
<thead>
<tr>
<th></th>
<th>CRAFT&lt;sup&gt;1&lt;/sup&gt;</th>
<th>ACT I&lt;sup&gt;12&lt;/sup&gt;</th>
<th>ACT II&lt;sup&gt;13&lt;/sup&gt;</th>
<th>ACT III&lt;sup&gt;14&lt;/sup&gt;</th>
<th>ACT IV&lt;sup&gt;15&lt;/sup&gt;</th>
<th>AVRO&lt;sup&gt;16&lt;/sup&gt;</th>
<th>Scene 2&lt;sup&gt;4&lt;/sup&gt;</th>
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<tr>
<td>Patients given V, n</td>
<td>36</td>
<td>221</td>
<td>107</td>
<td>134</td>
<td>236</td>
<td>116</td>
<td>39</td>
</tr>
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<td>QRS 15% increase from baseline (P = NS)</td>
<td>7% increase from baseline (P &lt; 0.001)</td>
<td>10% increase from baseline (P &lt; 0.001)</td>
<td>7% increase from baseline (P &lt; 0.001)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>QTc 3% increase from baseline (P = NS)</td>
<td>6% increase from baseline (P &lt; 0.001)</td>
<td>5% increase from baseline (P &lt; 0.001)</td>
<td>20–25 ms increase from baseline</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>TdP within 24 h</td>
<td>0</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
<td>1</td>
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<tr>
<td>Incidence of VAs within 24 h</td>
<td>4 patients: VPC NSVT (6.3% V, 14.8% P)</td>
<td>NSVT (16.8% V, 13.0% P)</td>
<td>NSVT (11.9% V, 10% P), mono-SVT in 1 given V</td>
<td>NSVT 8.4%</td>
<td>Mono-NSVT in 1 given V</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Death within 24 h</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Serious AEs 1 patient: VF induced by asynchronous electrical CV</td>
<td>3 patients (1 in P): hypotension 1, CAVB 1, cardiogenic shock 1</td>
<td>2 patients (0 in P): hypotension 1, CAVB 1</td>
<td>3 patients (6 in P): hypotension 1, bradycardia 2</td>
<td>12 patients: hypotension 4, bradycardia 5</td>
<td>3 patients: NSVT 1, pulmonary embolism 2</td>
<td>2 patients: hypotension in 1, feeling of suffocation in 1</td>
<td></td>
</tr>
<tr>
<td>Discontinuations due to AEs</td>
<td>–</td>
<td>4 patients (1 in P): bradycardia 1, hypotension 1, prolonged QT 1, VPC bigeminy 1</td>
<td>3 patients (0 in P): hypotension 1, CAVB in 1, RBBB 1</td>
<td>6 patients (0 in P): hypotension 1, tachycardia 1</td>
<td>10 patients (4.2%): bradycardia &gt; 1, LBBB &gt; 1, hypotension 4</td>
<td>3 patients: NSVT 1, pulmonary embolism 2</td>
<td>3 patients: (0 in P): hypotension 1, QRS prolongation 2</td>
</tr>
<tr>
<td>AE, others 2 patients: sinus bradycardia</td>
<td>Hypotension (6.3% V, 3.5% P)</td>
<td>Hypotension, SBP &lt; 90 mmHg (7.5% V, 0% P), bradycardia (14% V, 3.7% P)</td>
<td>Bradycardia (6% V, 0% P), hypotension (5% V, 1% P)</td>
<td>Bradycardia Hypotension, SBP &lt; 90 mmHg (5.5%, bradycardia 5.9%</td>
<td>AFL (8.6% V, 0.9% A)</td>
<td>Bradycardia (10% V, 0% P), hypotension (13% V, 7% P)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** A, amiodarone; ACS, acute coronary syndrome; ACT, Atrial arrhythmia Conversion Trial; AE, adverse effect; AS, aortic stenosis; AVRO, A phase III superiority study of Vernakalant vs amiodarone in subjects with Recent Onset atrial fibrillation; CAVB, complete AV block; CRAFT, Conversion of Rapid Atrial Fibrillation Trial; CV, cardioversion; HF, heart failure; NSVT/SVT, non-sustained/sustained ventricular tachycardia; NYHA, New York Heart Association; P, placebo; QTC, heart rate-corrected QT interval; RBBB/LBBB, right/left bundle branch block; SBP, systolic blood pressure; TdP, torsades de pointes; V, vernakalant; VAs, ventricular tachyarrhythmias; VF, ventricular fibrillation; VPC, ventricular premature complex.
especially in patients with HF. Based on data from the six randomized clinical trials, intravenous vernakalant has a strong advantage over the traditional competitors because of its prompt onset of action, atrial selectivity, and low risk of TdP proarrhythmia. Moreover, vernakalant can be used for a broad range of patients with structural heart diseases and is not contraindicated in patients with stable coronary heart disease, hypertensive heart disease, or HF.\textsuperscript{45} However, with the exception of the AVRO study, clinical trials comparing the efficacy of intravenous vernakalant with other antiarrhythmic drugs have not been published. Ongoing trials are being carried out for direct comparison with flecainide\textsuperscript{46} and ibutilide.\textsuperscript{47} Recently, a meta-analysis was undertaken using a mixed-treatment comparison method to assess the relative efficacy of intravenous vernakalant compared with the more commonly used antiarrhythmic drugs in eliciting cardioversion within 2 hours among patients with short-duration AF (<48 hours).\textsuperscript{48} Vernakalant (intravenous), flecainide (intravenous and oral), and propafenone (intravenous) were more efficacious in pair-wise comparisons than placebo. Vernakalant (intravenous) was observed to be statistically more effective than propafenone (intravenous). Results on the comparative efficacy of vernakalant (intravenous) versus flecainide (intravenous and oral) were not definitive, potentially due to a lack of power to show a difference between treatments or a lack of comparability between patient samples.\textsuperscript{48} These results suggest vernakalant is an efficient and relatively safe antiarrhythmic drug that can be effectively used for the cardioversion of short-duration AF, regardless of presence of structural heart disease.

Results of clinical trials showed that the efficacy of vernakalant decreases with the duration of AF. The conversion rate was substantially lower in AF lasting 3 to 7 days than 3 to 48 hours. Longer-duration AF (8 to 45 days) rarely responded to vernakalant. This is in line with previous findings that showed that the efficacies of cardioversion by conventional antiarrhythmic drugs are diminished along with the duration of AF.\textsuperscript{49} This therapeutic resistance to antiarrhythmic drugs is attributed to the progression and severity of atrial remodeling, possibly involving both electrophysiological and structural changes.\textsuperscript{50,51} These findings, together with the fact that there was a trend toward decreased efficacy of vernakalant in patients with a history of HF,\textsuperscript{9} suggest a lower efficacy of vernakalant to cardiovert AF and maintain sinus rhythm in structurally remodeled atria. The development of oral vernakalant for sinus rhythm maintenance was terminated in 2012, probably because of its low efficacy in maintaining sinus rhythm.

In a recently published systematic review and meta-analysis, vernakalant was not associated with a significant difference in serious adverse events compared with controls.\textsuperscript{52} Nevertheless, its safety remains a matter of concern. Cardiogenic shock occurred in two patients (in ACT I\textsuperscript{12} and unpublished ACT V), 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.\textsuperscript{12,13}

Vernakalant-related hypotension can be attributed to its negative inotropic effect, which has been shown in experimental studies,\textsuperscript{53} 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 three-fold or greater margin above the maximum concentration observed at therapeutic doses).\textsuperscript{9} A recent experimental study using human isolated subcutaneous resistance artery and ventricular trabecular muscle preparations showed that, at test concentrations encompassing free plasma concentrations associated with clinical efficacy for conversion of AF, vernakalant had no significant direct effects on human resistance artery tone or ventricular contractility.\textsuperscript{54} No case of HF worsening with vernakalant treatment has been reported in clinical trials.\textsuperscript{9}

The superior efficacy of vernakalant in treating recent-onset AF is in great contrast with the suspended clinical trial and halted development of an oral formulation of vernakalant. A recently published short report showed in 51 recent-onset AF patients without structural heart diseases that AF conversion to sinus rhythm is faster and the length of hospital stay is shorter with vernakalant than with flecainide or propafenone.\textsuperscript{55} Although vernakalant is more expensive than amiodarone and flecainide,\textsuperscript{55} this reduction in length of hospital stay should reduce patient costs. In addition, rapid conversion to sinus rhythm may prevent or reverse development of the atrial electrical and structural remodeling associated with AF, potentially reducing disease progression and likelihood of stroke; however, no data are yet available on the long-term effects of vernakalant. Many more studies on the safety and efficacy of vernakalant are required to determine its clinical benefits and therapeutic value.

\textbf{Conclusion}

The currently available clinical studies have shown that intravenous vernakalant is highly efficacious in acute cardioversion of recent-onset short-duration AF, without any documented vernakalant-related life-threatening TdP arrhythmias.
The antifibrillatory effect of vernakalant rapidly decreases with the duration of AF and longer-duration (persistent) AF rarely responds to the drug. In addition, vernakalant appears less effective for acute conversion of AF in association with HF and the incidence of serious hypotension and ventricular arrhythmia is higher in this patient population. Future studies are warranted to clarify the efficacy of the drug in AF associated with structural heart diseases and to assess its safety profile in high-risk patients with structural heart disease and left-ventricular dysfunction.

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Disclosure

Dr Dobrev is an advisor and lecturer for Sanofi and Merck-Sharp-Dohme. Dr Tsuji declares no conflicts of interest in this work.

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