Vernakalant in Atrial Fibrillation: A Relatively New Weapon in the Armamentarium Against an Old Enemy

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ABSTRACT: Atrial fibrillation is the most common sustained cardiac arrhythmia, and its prevalence is increasing with age; also it is associated with significant morbidity and mortality. Rhythm control is advised in recent-onset atrial fibrillation, and in highly symptomatic patients, also in young and active individuals. Moreover, rhythm control is associated with lower incidence of progression to permanent atrial fibrillation. Vernakalant is a relatively new anti-arrhythmic drug that showed efficacy and safety in recent-onset atrial fibrillation. Vernakalant is indicated in atrial fibrillation (⩽7 days) in patients with no heart disease (class I, level A) or in patients with mild or moderate structural heart disease (class IIb, level B). Moreover, Vernakalant may be considered for recent-onset atrial fibrillation (⩽3 days) post cardiac surgery (class IIb, level B). Although it is mainly indicated in patients with recent-onset atrial fibrillation and with no structural heart disease, it can be given in moderate stable cardiac disease as alternative to Amiodarone. Similarly to electrical cardioversion, pharmacological cardioversion requires a minimal evaluation and cardioversion should be included in a comprehensive management strategy for better outcome.

KEYWORDS: Vernakalant, atrial, fibrillation, pharmaceutical, cardioversion

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, its prevalence increases dramatically with age and this prevalence is likely to increase in the next 50 years.[1,2] Moreover, AF is associated with significant mortality and morbidity, and one in five of all strokes is attributed to AF.[3]

Management of AF is a multifaceted strategy: control of underlying heart disease and risk factors, reversal of arrhythmia (rhythm control), controlling the rate (rate control), along with prevention of associated risk of thrombo-embolic events, heart failure, and cardiac ischemia.[3,4] Rate or rhythm control often constitutes a dilemma in the management of AF,[5] and although clinical trials showed no major differences in outcomes in rhythm or rate control strategies, rhythm control is advised in recent-onset AF, highly symptomatic patients, young and active individuals.[6] Moreover, rhythm control provides better clinical benefit when compared with rate control; also it decreases the risk of progression to permanent AF.[7]

Rhythm control can be achieved either by electrical or pharmacological cardioversion. However, acute cardioversion is only one of the strategies for rhythm control, and long-term anti-arrhythmic drug (AAD) therapy and catheter ablation play critical roles in this perspective. Vernakalant is a relatively novel AAD, available in many parts of the world; it has been approved for pharmacological cardioversion of recent-onset AF (⩽7 days) and early (⩽3 days) post cardiac surgery AF.[8,9] This review focuses on the role and benefit of Vernakalant in the management recent-onset AF, on the light of the current available scientific and medical literature.

Methodology

Through a MEDLINE/PubMed research, we used separately the terms "Vernakalant," "RSD1235," "atrial fibrillation." The search started from 2000, selected articles mainly address the clinical use, benefit, and safety rather than the pure pharmacodynamic effect. Editorial reports were excluded, and we retained 51 articles found to be relevant for the study.

Background

The increasing prevalence of AF in the general population, along with the increase in AF complications, makes the burden of AF significantly heavy as a medical condition, also as a socio-economical issue given the cost associated with management, prevention, and complications[3,4] Moreover, despite all recent therapeutic efforts, there appears to be in most cases, an inevitable progression from paroxysmal to persistent and then to permanent form.[3]

There is still some controversy regarding rate vs rhythm control in AF, and a wait-and-see approach with rate control medication may be adopted for patients with recent-onset symptomatic AF in the emergency department, especially that recent-onset AF resolves spontaneously within 24 h in more than 70% of the cases.[10] Moreover, the 2016 ESC Guidelines stated that rhythm control should be considered in patients who remain symptomatic despite rate control approach.[3] However, there is a clinical trend or opinion that rhythm control is better to prevent atrial remodeling and progression from paroxysmal or persistent to permanent AF.[6,7] Rhythm control may be achieved via either electrical or pharmacological cardioversion; in this regard, physician preference plays a role in the

decision process, and this decision varies depending on previous experience, local tradition, and regulations. Of note, pharmacological cardioversion is preferred as a first-line approach in patients who tolerate their arrhythmia especially when no hemodynamic compromise is present.[3] The advantages of pharmacological cardioversion are that there is no need for general anesthesia or conscious sedation with fasting, along with potentially lower psychological impact related to electrical cardioversion and arguably a lower risk of immediate recurrence; the lower risk of immediate recurrence is probably related to better AAD loading ordinarily implemented in pharmacological cardioversion, providing a significant efficacy immediately and for the subsequent hours and days following cardioversion.[9]

Pharmacological technique using the "pill-in-the-pocket" (ie, Flecainide, Propafenone, Sotalol) as a prompt method to terminate paroxysmal AF is debated. Use and success of the "pill-in-the-pocket" technique depends on the context, urgency of the situation, patient compliance, physician experience, availability of the drug, underlying heart disease, and so on.[11] In this respect, there is currently insufficient evidence to support a recommendation for the use of the "pill-in-the-pocket" strategy in patients with paroxysmal AF.[11] Moreover, in the setting of paroxysmal AF, many AADs have a slow onset of action (ie, amiodarone, beta-blockers) or may have some restrictions for use in patients with underlying heart disease (class 1 AAD). In view of this, the development of new and effective AAD to manage patients with paroxysmal AF was sought.[9,11]

Vernakalant was first used in clinical practice in 2004 by CRAFT investigators,[12] under the investigational product name of RSD1235, and the authors concluded that RSD1235 is a new atrial-selective AAD, which is efficacious and safe for converting recent-onset AF to sinus rhythm. Later on in 2007, Fedida[13] reported on RSD1235 using the term Vernakalant for the first time, which was presented as a novel atrial-selective antifibrillatory agent, with the electrophysiological properties targeting potassium channels that are selectively present in human atria; also they reported that Vernakalant allows a safe and rapid conversion of acute AF back to sinus rhythm.

The 2010 guidelines for the management of AF stated that Vernakalant has recently been recommended for approval for rapid cardioversion of recent-onset AF to sinus rhythm in adults.[14] The 2016 ESC Guidelines for the management of AF classified AF in five categories: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent; also the 2016 ESC Guidelines stated that Vernakalant should be considered for pharmacological cardioversion of recent-onset AF, in patients with no history of ischemic or structural heart disease.[3]

Electrophysiological properties of Vernakalant

Normal atria have a resting membrane potential of (–70) to (–80) mV, about 10 mV more positive than that of the ventricles. During AF, atria fail to fully repolarize, and therefore, the difference in resting membrane between atria and ventricles increases, and this accentuated difference is thought to play a part in Vernakalant selectivity to atria as opposed to normal ventricles.[15]

Vernakalant is a relatively new AAD, and its anti-arrhythmic activity is mainly correlated to the blocking property of the sodium channels (*Ina*).[15] Moreover, Vernakalant action varies with heart rate and with baseline membrane potential; at low rates and at negative membrane potential, Vernakalant has a relatively weak blocking activity of the *Ina*.[13] As the heart rate increases, the affinity of Vernakalant for *Ina* increases and leads to greater *Ina* blockade and fast onset of action, and this phenomenon explains why Vernakalant is not efficient as preventive therapy.[15,16] Interestingly, Vernakalant demonstrates a quick offset of binding once heart rate slows and when *Ina* blockade in no longer required.[15]

Moreover, Vernakalant is able to block certain potassium channels, *Ikur* (atrial-selective potassium channels), involved in atrial repolarization along with other potassium channels (*IkAch*), resulting in prolonged action potential plateau; similarly, Vernakalant blocks potassium channels *Ito*, involved more with atrial than ventricular refractoriness.[13,17] *hERG* is a gene that codes for potassium channel known for its contribution to repolarization through I_{Kr} ("rapid" delayed rectifier current). When this channel is inhibited or compromised, it can result in a long QT interval.[17] Vernakalant is known to partially blocks the *hERG* channel (underlying channel of *Ikr*); this may prolong QT interval; however, this blockade occurs at minimal level and usually has no conclusive clinical effect at target Vernakalant concentrations.[15]

All these properties result in clinical and electrophysiological effects of Vernakalant, with prolongation of atrial refractory period, slowing atrio-ventricular (AV) nodal conduction, but without effect on AV nodal refractoriness or on ventricular cells;[18] moreover, QT interval and ventricular effective refractory period do not significantly change at target dosage.

Pharmacokinetics of Vernakalant

When Vernakalant hydrochloride is infused at a dose of 0.1 to 5 mg/kg, intravenously over 10 min, the maximum plasma concentration (C_{max}) reaches 0.08 to 4 µg/mL and increases linearly with dose, the average C_{max} reaches 3.9 µg/mL after a single 10-min infusion of 3 mg/kg, and the average C_{max} is 4.3 µg/mL after 15 min of a second infusion of 2 mg/kg.[19]

Moreover, the dose-normalized values for the area under the concentration-time curve (AUC) do not differ significantly among doses, although the C_{max} is dose proportional. Vernakalant half-life ($t_{½}$) is between 2 and 4 h according to cytochrome P450 enzyme metabolizing activity.[19]

Of note, the AUC between 0 and 90 min after infusion of Vernakalant is estimated to be 15% higher in CYP2D6 poor metabolizers than extensive metabolizers, with age and serum

creatinine having smaller influences on exposure; therefore, dose adjustments based on patient characteristics (concomitant drugs, renal function, age, etc) are unnecessary for intravenous Vernakalant.[20,21] In this regard, there is no dosage adjustment required in patient with renal or hepatic failure, or in the elderly; however, there is currently not enough data to recommend use of Vernakalant in patients below 18 years old.[21]

The drug is extensively and rapidly distributed in the body after intravenous infusion, with a serum free fraction of 53% to 63% at concentration range of 1 to 5 μg/mL.[20] Vernakalant is not highly protein bound and accordingly, there is no significant competition between Vernakalant and other highly protein-bound drugs such as amiodarone, warfarin, propranolol, diltiazem, and verapamil.[21,22]

Clinical use of Vernakalant

Since 2004, Vernakalant (RSD1235) was presented by the CRAFT investigators as a new atrial-selective AAD, efficacious and safe for converting recent-onset AF to sinus rhythm.[12] Later on, Vernakalant has been tested in three placebo-controlled trials (ACT I, ACT II, and ACT III) and was more effective than placebo for the rapid conversion of recent-onset AF, and without significant adverse events.[23–25] Further studies showed that Vernakalant is efficacious in converting recent-onset (⩽7 days) AF; also it is efficacious for recent-onset AF (⩽3 days) occurring following heart surgery.[26,27]

In the AVRO study, Vernakalant demonstrated superior efficacy compared with Amiodarone for acute conversion of recent-onset AF, and success rate was 51.7%, with a median time of conversion of 11 min; moreover, there were no significant side effects, also there were no cases of ventricular arrhythmia.[28] Table 1 illustrates key studies addressing Vernakalant.

The 2010 guidelines for the management of AF recommended Vernakalant for approval for rapid cardioversion of recent-onset AF to sinus rhythm in adults.[14] The 2012 focused update of the 2010 ESC guidelines stated that Vernakalant should be considered for recent-onset AF (⩽7 days) in patients with mild or moderate structural heart disease (class IIb, Level B); also Vernakalant may be considered for recent-onset AF post cardiac surgery (⩽3 days) (class IIb, level B).[34]

The 2016 ESC Guidelines for the management of AF[3] recommended Vernakalant for pharmacological cardioversion (rhythm control) of recent-onset AF, in patients with no history of ischemic or structural heart disease (recommendation: class I, level A). According to the same study,[3] Vernakalant may be considered as alternative to Amiodarone in patients with stable ischemic and/or moderate structural heart disease, including mild to moderate heart failure (class II, level B). Figure 1 illustrates these clinical scenario.

In a randomized controlled trial including 100 patients with recent-onset AF, Vernakalant was superior to Ibutilide in converting AF to sinus rhythm (shorter time to conversion to sinus rhythm and higher conversion rate at 90 min).[30] Of note, Vernakalant is significantly more expensive when compared with Ibutilide; however, fewer side effects and more rapid restoration of sinus rhythm are observed with Vernakalant, reducing the overall cost of hospitalization in recent-onset AF patients.[35]

In a meta-analysis conducted by Bash et al, the efficacy of cardioversion of recent-onset AF by Vernakalant and by "comparators" (Propafenone and Flecainide) was studied, and the authors concluded that all these AADs are efficient for rapid restoration of sinus rhythm; however, there was no mention regarding the time to conversion observed with each drug.[36]

When compared head-to-head with Flecainide in patients with recent-onset AF, Vernakalant was more effective in cardioversion to sinus rhythm; moreover, Vernakalant allowed faster restoration of sinus rhythm, and therefore, patients can be discharged earlier from the emergency department.[33,37] Similarly, when compared head-to-head with Propafenone in patients with recent-onset AF, Vernakalant showed higher efficacy and a shorter time to conversion of AF to sinus rhythm and was associated with shorter hospital stay.[29]

Vernakalant is usually a well-tolerated drug and most common side effects include paresthesia, dysgeusia, dizziness, sneezing, and nausea and these effects are probably related to the inhibition of the sodium channels in the central nervous system; also most of these side effects are mild and transient.[38] Of note, de Riva-Silva et al[39] reported a case of 1:1 AV conduction atrial flutter after Vernakalant administration for AF conversion; however, Guerra et al[38] reported that no cases of significant arrhythmia or hemodynamic dysfunction are generally observed when cautions and contraindications are respected.

Vernakalant is contraindicated in patients with hypersensitivity to the drug, high-grade AV block which is not backed up by pacemaker, hypotension as defined by systolic blood pressure less than 100 mm Hg, recent (<30 days) acute coronary syndrome, heart failure with NYHA class III and IV, severe aortic stenosis, and long QT interval; also Vernakalant is contraindicated within 4 h after use of Amiodarone (oral or IV).[34,38]

Vernakalant did not restore sinus rhythm in patients with atrial flutter in ACT II and ACT III trials,[24,25] and only a reduced mean ventricular response rate was mostly observed in the studied patients. Vernakalant has rate related blocking effects on sodium channels (*Ina*), which is the probable explanation for the lack of efficacy on atrial flutter patients; of note, no cases of 1:1 AV conduction with rapid ventricular response are observed when Vernakalant is used in atrial flutter.[40]

Oral Vernakalant (150, 300, and 500 mg) was studied in a single Phase IIb trial as a prophylactic drug for sinus rhythm maintenance after direct current cardioversion;[41] the 150 and 300 mg doses did not show superiority against placebo, and

Table 1. Main studies addressing Vernakalant.

STUDY/AUTHOR/DESIGN/OBJECTIVE	DATE	PATIENTS	CONVERSION RATE	RESULTS REGARDING VERNAKALANT
CRAFT[12] Multi-centered, randomized, double-blinded (VKL vs placebo)	2004	56 pts recent-onset AF	53%	RSD1235: efficacious and safe for converting recent-onset AF
ACT I[23] Randomized, double-blind, placebo-controlled	2008	336 pts recent-onset AF	51.7%	Rapid conversion of short-duration AF
ACT II[24] Randomized, double-blind, placebo-controlled	2009	100 pts AF or AFL post cardiac surgery	47%	Safe and effective in the rapid conversion of AF post cardiac surgery
ACT III[25] Randomized, double-blind, placebo-controlled	2010	138 pts AF or AFL of recent onset	51.2%	Rapid and efficient for conversion of short-duration AF
Stiell et al[26] (ACT IV) Multicenter, open-label study	2010	236 pts recent-onset AF	50.9%	VKL rapidly converted recent-onset AF to SR, was well tolerated
AVRO[28] Randomized, double-blind, active-controlled with Amd	2011	254 pts recent-onset AF	51.7% VKL vs 5.2% Amd	VKL was superior to Amd for acute conversion of recent-onset AF
Conde et al[29] Prospective trial	2013	36 pts recent-onset AF	93% VKL vs 78% Propafenone	VKL was superior to Propafenone
Simon et al[30] Randomized controlled trial	2017	100 pts recent-onset AF	69% VKL vs 43% Ibutilide	VKL was superior to Ibutilide
Carbajosa Dalmau et al[31] Prospective multicenter	2017	165 pts recent-onset AF	77.6%	VKL is effective and safe for restoring SR in the emergency department
Akel and Lafferty[32] Meta-analysis	2018	1421 pts recent-onset AF	NA	VKL is effective for rapid conversion of AF
Pohjantähti-Maaroos et al[33] Monocentric, retrospective	2019	200 pts recent-onset AF	67% with VKL vs 46% Flecainide	VKL was more effective and faster than Flecainide in cardioversion of AF

Abbreviations: AFL, trial flutter; Amd, Amiodarone; NA, non available; pts, patients; SR, sinus rhythm; VKL, Vernakalant.

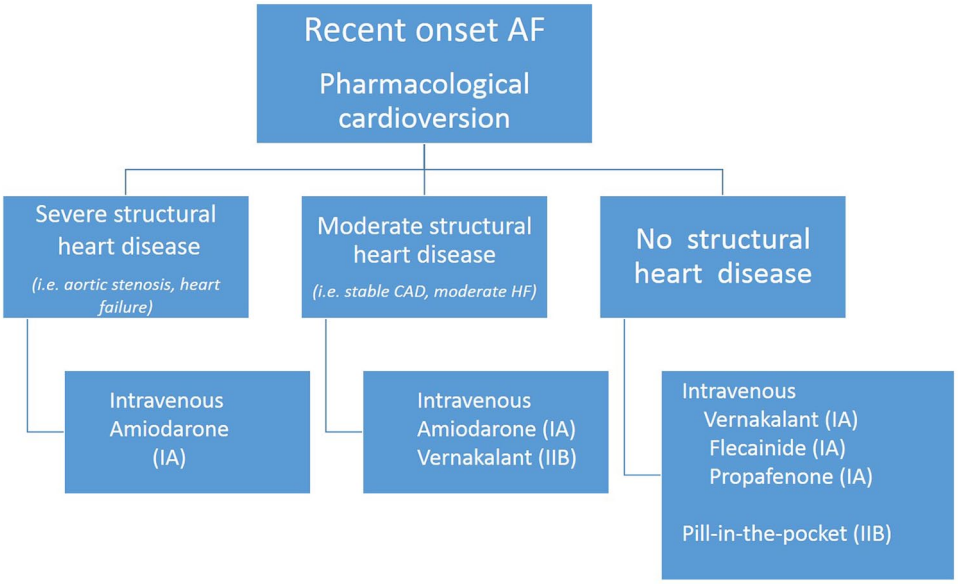

Figure 1. Clinical scenario and management strategy according to each case. *Class and level of evidence are represented between parentheses.* AF indicates atrial fibrillation.

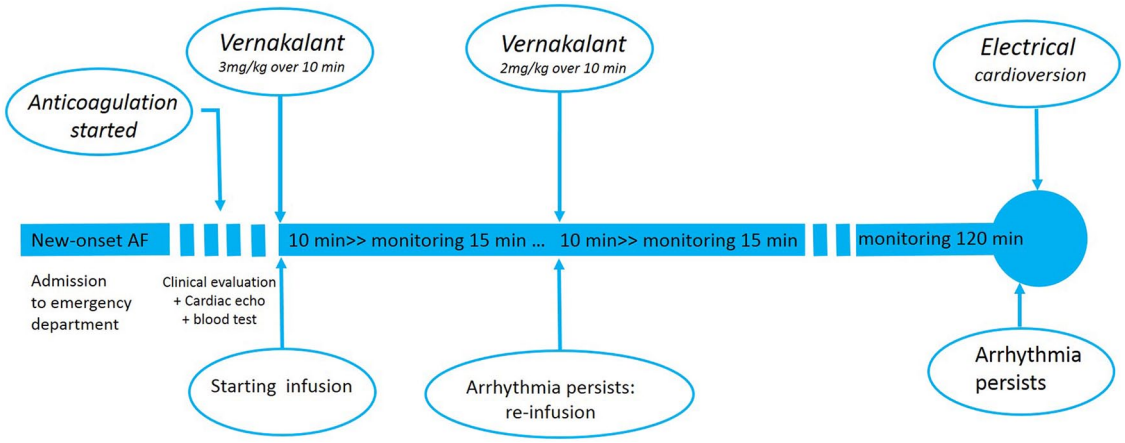

Figure 2. Image showing the infusion scenario with dosage and monitoring time, ending with electrical cardioversion if AF persists. AF indicates atrial fibrillation.

only the 500 mg dose showed a slight superiority in preventing recurrence of AF at 3 months. Nevertheless, in March 2012, Cardiome and Merck announced the discontinuation of further research on oral Vernakalant.[38]

Vernakalant was approved in 2010 by the European Union for cardioversion of AF which was less than 7 days in duration, or for post-operative AF less than 3 days in duration.[9] Vernakalant is still not approved by the United States Food and Drug Administration, namely after the study "ACT V" was discontinued following the death of a single patient, and therefore, further safety data and protocol revision regarding drug administration were required for approval by the Food and Drug Administration.[9,38]

Opinions, clinical implications

A lot of progress has occurred in rhythm control strategies for AF, especially with the development of ablation procedures; however, pharmacological cardioversion should be preserved as first and integrated approach for the management of AF. Vernakalant showed a superior efficacy to Amiodarone and to other AAD for rapid conversion of recent-onset AF;[29,33,36,37,42] although it can be given in patients with mild to moderate cardiovascular conditions, the absence of structural heart disease is associated with greater conversion rate to sinus rhythm.[43] Vernakalant is a relatively safe drug and Manolis et al[44] reported successful utilization of intravenous Vernakalant for AF conversion in the regular ward under only bedside monitoring.

Anticoagulation should be started promptly in all patients presenting with AF, not only in those presenting with AF lasting since more than 48 h.[45–48] Moreover, cardioversion should not be attempted in those presenting with AF lasting since more than 48 h before effective anticoagulation has been established for at least 3 weeks (except for patients with hemodynamic compromise requiring immediate cardioversion). However, if cardioversion needs to be performed sooner, then transesophageal echo guidance is recommended.[49]

Clinical risk scores for stroke and systemic embolism including the CHA2DS2-VASc score should be implemented more frequently in real practice.[3,47] In this regard, a patient presenting to the emergency department needs a minimum workup to ensure that it is a recent-onset AF, and this is required for evaluating potential underlying cardiopathy, and for assessment of the relevance of Vernakalant use according to the estimated AF duration.

The new AF guidelines[3] classify a first time diagnosed AF as "first diagnosed AF," which is defined as AF that has not been diagnosed before, irrespective of its duration or severity. Accordingly, patients presenting to emergency room for a first episode of AF are classified as "first diagnosed AF," and this AF may be otherwise paroxysmal or even persistent. In other terms, a patient may present to the emergency department with AF only when symptoms become severe; however, he may be asymptomatic or pauci-symptomatic with an AF lasting since days, weeks, or months, especially if the AF is intermittent.

Before using Vernakalant, patients should be adequately hydrated; the current dosage recommendation consists of a first infusion 3 mg/kg over 10 minutes, then a monitoring period of 15 minutes, and if AF persists, a second infusion of 2 mg/kg over 10 minutes with a second monitoring period of 15 minutes, the maximal dose over 24 hours being 5 mg/kg[3]. Interestingly, electrical cardioversion is still feasible after administration of Vernakalant, and it enhances restoration of sinus rhythm as integrated approach for AF; however, its use is recommended only 120 min after Vernakalant administration; therefore, Vernakalant may be considered as a useful agent for facilitated electrical cardioversion in resistant and recent-onset AF;[50] Figure 2 illustrates this scenario.

Of note, Vernakalant is indicated for recent-onset AF; nonetheless, the indication is not extended to atrial flutter.[3] Carbajosa Dalmau et al[31] showed that AF duration of less than 12 h was significantly associated with greater effectiveness in the hospital emergency department. Finally, cost-effectiveness studies of Vernakalant applied in "real world" remain to be

evaluated; moreover, caution about safety and use of Vernakalant within specific patients' subgroups must be considered.[32,51]

Conclusions

AF is the most common arrhythmia in patients admitted to emergency departments or hospitalized in intensive care units; also it is associated with increased morbidity and mortality. The increasing incidence of AF has prompted researches to find new therapeutic alternatives for such common and refractory arrhythmia.

Vernakalant, a relatively new AAD with atrial-selective anti-arrhythmic activity, is currently approved in the European Union and in many other countries for pharmacological cardioversion of recent-onset AF. Of note, the drug is still not approved in the United States; also multicentric cost-effectiveness studies evaluating Vernakalant in "real world" are still missing. Nevertheless, current medical literature showed that Vernakalant is safe and efficacious as anti-arrhythmic agent for terminating recent-onset AF.

Author Contributions

Conceived the concepts: AK. Analyzed the data: AK. Wrote the first draft of the manuscript: AK. Contributed to the writing of the manuscript: AK. Agree with manuscript results and conclusions: AK. Developed the structure and arguments for the paper: AK. Made critical revisions and approved final version: AK.

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