Vernakalant hydrochloride for the treatment of atrial fibrillation: An evaluation of its place in clinical practice

Abstract

Vernakalant is an intravenous anti-arrhythmic drug available in Europe, Canada and some countries in Asia for the restoration of sinus rhythm in acute onset atrial fibrillation. Currently, it is not available in the United States because the Food and Drug Administration have ongoing concerns about its safety. Vernakalant has a unique pharmacological profile of multi-ion channel activity and atrial-specificity that distinguishes it from other anti-arrhythmic drugs. This is thought to enhance efficacy but there are concerns of adverse events stemming from its diverse pharmacology. This ambiguity has prompted a review of the available clinical evidence on efficacy and safety to help re-evaluate its place in clinical practice.

Keywords

Vernakalant, atrial fibrillation, anti-arrhythmic drugs, cardioversion, rhythm control

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice. It represents a global health burden with evidence to suggest a worldwide increase in prevalence and incidence, positively correlated with age [1-3]. In 2016, it was estimated that 7.6 million people in the European Union over 65 years had AF and this has been projected to increase to 14.4 million in 2060, translating to a 22% rise in prevalence [1]. Unsurprisingly, the rate of AF-related hospital admissions has been found to increase so clinical management with rate-controlling or anti-arrhythmic drugs (AADs) has come under scrutiny [4].

Rate-controlling drugs are often recommended for haemodynamically stable patients with acute onset AF in the previous 48 hours for control of ventricular rate and symptom alleviation. [5]. For unstable patients, haemodynamic status guides the choice between electrical or pharmacological (with AADs) cardioversion for restoration of sinus rhythm. The management approach to acute onset AF has been shown to vary considerably across countries, with differences in the use of electrical cardioversion, choice of drugs and rate vs rhythm control strategies [6]. In acute onset AF presenting without haemodynamic instability, the European Society of Cardiology advocate a patient-led decision between pharmacological or electrical cardioversion, provided AF onset is within 48 hours. When pharmacological cardioversion is preferred, intravenous (IV) administration of amiodarone, ibutilide, propafenone, vernakalant or flecainide is recommended, with the choice of drug dependent on patient characteristics (Table 1) [7].

The European Society of Cardiology guidelines recommend restricting the use of IV vernakalant, flecainide, ibutilide and propafenone to patients without structural heart disease for cardioversion [7]. In severe heart failure with reduced ejection fraction (HFrEF) and aortic stenosis, guidelines recommend IV amiodarone. In coronary artery disease (CAD), moderate HFrEF, heart failure with mid-range/preserved ejection fraction (HFmrEF/HFpEF) or abnormal left ventricular hypertrophy, IV vernakalant or IV amiodarone can be used [7]. Despite the subtle differences between AADs and their recommendations for use, most are burdened by a poor safety profile. This is attributed to their narrow therapeutic window and extensive inter-subject variability. Furthermore AADs have different country-specific availability and lower efficacy compared to electrical cardioversion. Nevertheless, AADs continue to be used in the management of patients presenting with new onset AF. Without the need for conscious sedation or general anaesthesia and fasting requirements of electrical cardioversion, they can offer an advantage over this approach by reducing the potential risk of psychological impact on patients. Treatment goals are synonymous for all AADs and include a reduction in the duration and frequency of arrhythmia episodes, a reduction in AF-associated hospitalisations and importantly, improved patient quality of life.

There are many research efforts concentrating on the discovery of new AADs with improved safety, efficacy and less restrictions on use. Novel pharmacological approaches are being investigated to target ion channels specifically in the atria, hypothesised to increase efficacy

and decrease ventricular pro-arrhythmic effects. Recent research has focused on newer agents such as vernakalant, with the potential to mediate atrial specific anti-arrhythmic mechanisms.

Vernakalant (Brinavess) is already established as an AAD, available as vials of 20mg/ml concentrate to be administered by IV infusion for the rapid termination of recent-onset AF in adults. In non-surgical patients, vernakalant can be used if AF has persisted for up to seven days. In post-cardiac surgery patients, vernakalant can be used for AF of up to three days duration. An initial infusion dose of 3mg/kg should be administered over 10 minutes, and if sinus rhythm is not restored within 15 minutes after the end of the infusion, a second infusion dose of 2mg/kg may be administered over 10 minutes. A pre-infusion checklist should be completed to determine patient eligibility for vernakalant therapy. Owing to the risk of arrythmias and hypotension, blood pressure and electrocardiogram monitoring are recommended for at least 15 minutes after each infusion is complete. The patient should be further observed for two hours after the start of infusion and until clinical and ECG parameters have stabilised. Vernakalant should also be avoided when other intravenous class I and III AADs have been administered within the previous four hours prior to, or first four hours after vernakalant administration [11].

Vernakalant is not available for use in the United States (US) because the Food and Drug Administration (FDA) issued an unfavourable ruling in 2019. Despite sufficient evidence to support the clinical efficacy of vernakalant for conversion to sinus rhythm, the FDA ruled that serious safety liabilities outweighed any potential benefits of treatment [12]. This has prompted a critical review of the clinical data available for vernakalant and the aim of this article is to help re-evaluate its place in clinical practice.

Chemistry

Vernakalant is chemically described as (3R)-1-[(1R, 2R)-2-[2-(3, 4 dimethoxyphenyl)ethoxy]cyclohexyl]pyrrolidin-3-ol. Its molecular weight is 349.5g/mol, its empirical formula is $C_{20}H_{31}NO_4$ and its structural formula is outlined in figure 1 [13].

Pharmacokinetics

Vernakalant exhibits linear pharmacokinetics over the dose range of 0.1mg/kg to 5mg/kg [14]. After an initial infusion of 3mg/kg and a second infusion of 2mg/kg (with 15 minutes in between infusions), average peak plasma concentrations of vernakalant were reported as 3.9 µg/ml and 4.3 µg/ml, respectively. Vernakalant is rapidly distributed to tissues and has a volume of distribution of approximately 2L/kg. Elimination is determined by CYP2D6 metaboliser status; in extensive metabolisers, elimination half-life is approximately 3 hours and in poor metabolisers it is approximately 5.5 hours, corresponding to time taken for full elimination of 15 hours and 27.5 hours, respectively [11].

Pharmacodynamics

Vernakalant sits somewhat uncomfortably in the Vaughan-Williams classification of antiarrhythmic agents because of its unique pharmacological profile. It does possess atrial I_K blocking properties like other class III agents, but much of its clinical efficacy in terminating AF appears to be derived from its modulatory effects on other ion currents, in particular I_{Na}. Vernakalant may be described as a multi-ion channel blocking drug, acting on numerous potassium currents including the transient outward current I_{to1}, the ultra-rapid delayed rectifier current I_{Kur}, the acetylcholine-activated current $I_{K,ACh}$, the ATP-sensitive current controlled by K_{ATP} channels, the rapid delayed rectified current I_{Kr}, and also frequency- and voltage-dependent inhibition of cardiac sodium currents [15]. Because of its complex pharmacology, vernakalant offers a different adverse effect profile to that of other class I or class III agents, and many of the unwanted clinical effects are explained (and indeed may be predicted) by our understanding of vernakalant's multiple ion-channel modulatory actions. The electrophysiological and clinical effects of vernakalant on key ion channels are summarised in table 2.

In AF, the cell membranes of atrial myocytes fail to fully repolarise during the latter phases of the cardiac action potential, leading to a higher resting potential (phase 4) compared to a healthy heart. This is thought to contribute to the state-dependent atrial selectivity of vernakalant in the atria in failing hearts compared to healthier ventricular tissue [16]. Vernakalant blocks the atrial sodium current I_{Na} with relatively weak potency at $Na_V1.5$ channels at more negative resting potentials and slower rhythms [17], but with the more positive resting potentials due to increasing activation rates observed in AF, I_{Na} is blocked more readily and with a faster onset of action [16, 18]. When the heart rate subsequently slows, the affinity of vernakalant for $Na_V1.5$ channels decreases and the drug quickly disassociates itself from the receptor [16]. Vernakalant is therefore suited to rapid pharmacological cardioversion of acute-onset AF rather than prophylaxis.

Probably the most important electrophysiological effect of vernakalant in AF is its inhibition of the peak sodium current, leading to the widening of the QRS complex and slowing conduction, which in turn adds to QT length [19].

Other important electrophysiological properties include the inhibition of the atrial early-activating potassium currents I_{to1}, I_{Kur} and $I_{K,ACh}$ [15, 20]. Blocking the transient outward current I_{to1} modulates atrial (rather than ventricular) refractoriness [17, 21]. This is a rapidly activating and deactivating current, activated by the depolarisation during phase 0 and itself contributing to the initial repolarisation of phase 1 of the action potential. The current involves a fast $I_{to1,f}$ variant resulting from the opening of channels formed from $K_V4.2$ and $K_{V4.3}$ subunits, and a slow $I_{to1,s}$ variant from the opening of channels formed from $K_V1.4$ subunits [22]. The rapid inactivation of I_{to1} halts the atrial repolarisation, ending phase I of the action potential. Because of the efflux of K^+ with I_{to1}, this current has an important influence on myocyte Ca^{2+} channel activation during phase 2 and therefore modulates duration of the action potential [22].

The potency of vernakalant on I_{to1} increases with heart rate, so again we observe frequency-dependent block. Yet, in the failing heart, the density of ion channels responsible for I_{to1} in myocyte membranes is decreased [23, 24] and the likely inhibitory effect of vernakalant at clinically relevant concentrations may be small.

I_{Kur} and $I_{K,ACh}$ are currents specific to the atrial myocytes and inhibition of these currents would be expected to prolong the plateau phase of the action potential [19], although this is not observed in healthy subjects at normal heart rate [15]. The original classification of vernakalant as an atrial repolarisation delaying agent stemmed from its effects on these currents [19]. The $K_V1.5$ potassium channel is responsible for the I_{Kur} current and is an attractive target for novel antiarrhythmic agents since it is atrium specific (largely avoiding ventricular effects such as QT prolongation). Vernakalant blocks I_{Kur} via $K_V1.5$ channels with an IC_{50} of 13 µM at a frequency of 1 Hz [25] and $I_{K,ACh}$ is blocked with a very similar IC_{50}. The effects of $I_{K,ACh}$ inhibition may be minimal in practice [26]. However, $K_V1.5$ expression is decreased in chronic AF [27] which reduces its value as a drug target, and at the same time the channel is expressed in non-cardiac tissues [25] meaning adverse effects would be likely from the increased doses required for cardiac arrhythmic activity. The selective IKur inhibitor S66913 was assessed in a clinical trial (the DIAGRAF-IKur study), and no serious adverse events were detected but no clinical benefit was observed at the point when the trial was stopped [28].

The most important drug interactions of vernakalant and those adverse effects which are predictable stem from its interactions with ion channels. Vernakalant weakly inhibits the rapid delayed rectifier current I_{Kr} which contributes to cardiac repolarisation by partially blocking the hERG channel $K_V11.1$ [16], but in experimental studies the potency of vernakalant on this current was 30- to 100-fold less than that for quinidine or propafenone [15]. Compromising this current may prolong the QT interval, although at clinically relevant concentrations vernakalant has minimal inhibitory effect on this ion channel [16]. In practice, precautionary QT monitoring is recommended given the combined risk of hERG channel block and the widening of the QRS complex from peak I_{Na} inhibition.

Adverse arrhythmia is a known risk with vernakalant, given its multi-channel electrophysiological properties. In general, at target doses ventricular refractoriness is not affected and ventricular pro-arrhythmias are less likely given its apparent specificity to atrium currents in experimental studies. Observations of prolonged QT in patients suggests vernakalant is not exclusively atrial specific, and that there is some activity in ventricular tissue [15]. The risk of torsades de points is likely to be small but nevertheless present. Above target dose the risk of ventricular activity increases and therefore careful monitoring is required during treatment.

Hypotension, sometimes severe, has been reported in patients exposed to vernakalant. Experimental studies showed a negative inotropic effect and this is more likely to be clinically significant in patients with a low SBP prior to treatment [15].

Bradycardia is reported in some patients but the mechanism for this is unclear [15]. Vernakalant may slow conduction through the AV node which might show as an increased PR interval [29, 30], though there is limited evidence of this effect on the ECG in the clinic.

Clinical Efficacy

A total of nine randomised controlled trials (RCTs) (seven multi-centre and two single-centre) have been conducted to investigate the clinical efficacy and safety of vernakalant for the treatment of acute onset AF by comparing to placebo [31-36], ibutilide [37, 38] and amiodarone [39]. Study characteristics, clinical and safety outcomes are summarised in Table 3.

In eight of the trials, clinical efficacy was universally defined as conversion to sinus rhythm for ≥1 minute within 90 minutes from the start of drug infusion [31-34, 36-39]. In one trial, it was defined as conversion to sinus rhythm or another atrial rhythm (such as atrial flutter) for any length of time within 30 minutes from the end of drug infusion [35]. Median conversion times to sinus rhythm were in the range of 8-14 minutes in seven of the trials [31, 33-37, 39]. Pooled analysis of all nine RCTs demonstrated that vernakalant significantly increased the rate of conversion to sinus rhythm within 90 minutes (Relative Risk [RR] 5.15; 95% Confidence Interval [95% CI] 2.24–11.84, I^2 = 91%) [40]. Overall, 50% of vernakalant-treated patients converted within 90 minutes. A sensitivity analysis of the six RCTs that compared vernakalant to placebo [31-36] found 48% of vernakalant-treated patients converted within 90 minutes (RR 7.49; 95% CI 3.57-15.72, I^2 = 63%). When compared to an active comparator (ibutilide and amiodarone), 56% of vernakalant treated patients converted within 90 minutes compared to 24%, although heterogeneity limits the conclusions that can be drawn from this comparison (RR 2.40; 95% CI 0.76–7.58, I^2 = 94%, *P* for interaction = 0.10). Another sensitivity analysis [40] also revealed vernakalant was less effective in patients after recent cardiac surgery [34] (45% conversion, RR 3.03; 95% CI 1.54–5.94) when comparing to trials which excluded patients after cardiac surgery (49% conversion, RR 9.62; 95% CI 4.46–20.77, I^2 = 48%, *P* for interaction = 0.03) [31-33, 35, 36]

A systematic review by Ma et al [41] included the same nine RCTs in addition to 15 observational studies, with meta-analysis results presented for RCTs. Similarly to McIntrye et al [40], analysis of the six RCTs comparing vernakalant to placebo [31-36] found vernakalant was associated with a significantly increased rate of cardioversion, but different values were reported (49.7% vs. 6.2%, RR 8.13, 95% CI 5.35 to 12.36, I^2 = 60%, P<0.00001). Ma et al [41] used a fixed-effects model whereas McIntyre et al[40] used random-effects. There were also differences in the total number of events reported for two RCTs by Ma et al and McIntyre et al because of different approaches whether or not to include patients with atrial flutter [34] and patients from both (n=2) vernakalant dose groups [35].

Meta-analysis was also presented comparing vernakalant to an active comparator, but results were presented separately for two RCTs comparing to ibutilide [37, 38] and one RCT comparing to amiodarone [39]. Vernakalant was superior to amiodarone for cardioversion of

recent-onset AF within 90 minutes (RR 10.00, 95% CI 4.50-22.23), but not ibutilide (62.4% vs. 47.3%, RR 1.32, 95% CI 1.00 to 1.73, I^2 = 63%, P=0.05) [41].

In another systematic review and meta-analysis to identify the most effective AAD for pharmacological cardioversion in acute onset AF, Bayesian network meta-analysis using a random-effects model demonstrated that vernakalant (Odds Ratio [OR] 7.5, 95% CI 3.1-18.6), flecainide (OR 6.1, 95% CI 2.9-13.2), propafenone (OR 6.8, 95% CI 3.6-13.8) and ibutilide (OR 4.1, 95% CI 1.8-9.6) increased the likelihood of conversion within 4 hours compared to placebo or control, but treatment effect differences between drugs were small and potentially not clinically meaningful. The review alluded to the need for other factors such as cost, patient preference and adverse effects to guide drug selection [42].

Safety and Tolerability

Safety data collected from all nine RCTs suggest that vernakalant is generally safe and well tolerated. This is supported by a meta-analysis of pooled adverse event data from seven RCTs [31-34, 36, 37, 39] that found no overall significant difference in the rate of adverse events between vernakalant and its comparators (placebo/amiodarone/ibutilide) (RR 0.95; 95% Confidence Interval [95% CI] 0.70–1.28; I^2 = 0%) [40]. There was no significant difference in risk between treatment groups for the following adverse events: ventricular arrhythmia (RR 0.61; 95% CI 0.31–1.22, P = 0.2); death (RR 1.89; 95% CI 0.42–8.48, P = 0.4), and heart failure (RR 0.94; 95% CI 0.15–5.93, P = 1.0) [40]. The fixed-effect meta-analysis by Ma et al [41] also reported there was no significant difference in occurring serious adverse events (9.9% vs 10.4%, RR 0.91, 95% CI 0.67-1.25, P=0.57) and hypotension (5.3% vs 3.3%, RR 1.53, 95% CI 0.86-2.73, P=0.15) between vernakalant and its comparators.

Dysgeusia was reported as a mild adverse event in seven RCTs [31-33, 36-39]. Paresthesia [31, 32, 35-37], sneezing [31-33, 36, 37, 39] and nausea [31, 32, 34-36] were also commonly reported. In regards to cardiac adverse events, there was only one RCT that reported torsades de pointes in two patients post-vernakalant infusion (after 32 hours and on days 16 and 17) [36]. Another trial reported rates of ventricular tachycardia as similar between placebo and vernakalant groups, noting vernakalant patients to show statistically significant increases in the QRS duration, Bazett-corrected QT interval and QTcF but no associations of pro-arrhythmia [31].

Four RCTs reported serious adverse events that were considered to be related to vernakalant to include dyspnoea (in one patient) [33], nausea, headache, confusional state and cold sweat (in one patient) [32], sinus arrest (in one patient) [32], cardiogenic shock (in one patient) [32], severe hypotension (one patient in each trial) [31, 34] and atrio-ventricular block (in one patient) [34]. Out of the nine RCTs, there were a total of seven deaths [31-33, 36, 39]and only two of these were related to vernakalant [31, 32]. One patient, with no previous cardiac history, suffered with cardiogenic shock 10 minutes post-vernakalant infusion and went on to experience a number of complications leading to death [32]. The other patient presented with acute coronary syndrome and AF and had a history of severe valvular stenosis and New York

Heart Association class II heart failure. The patient suffered with ventricular fibrillation leading to death 47 minutes after the start of the vernakalant infusion [31].

Real-world data

A real-world post-authorisation safety study (SPECTRUM) was carried out in six western European countries. The registry consisted of 1,778 patients with 2,009 episodes of AF. All patients received vernakalant and were followed up for 24 hours after the last infusion, until hospital discharge/end of medical encounter and information on adverse events such as significant hypotension, significant ventricular arrhythmia, significant atrial flutter and significant bradycardia was recorded. The cumulative data demonstrated an incidence of adverse events and serious adverse events that was similar or lower than available vernakalant clinical trial safety data. The observed conversion rate was also found to be higher than that reported in clinical trials, providing further evidence to support vernakalant's efficacy [43].

There have been a number of other smaller scale studies reporting on real-world safety data of vernakalant in the acute hospital setting. One study of 47 patients administered vernakalant in the Emergency Department reported mild and transient adverse effects in five patients [44]. Another single-centre study of 42 patients reported no serious adverse events during, immediately after, or within the monitoring period following vernakalant infusion (6 months) [45]. There were 30 adverse events reports from a multi-centre cohort study of 165 patients who were recruited from five hospitals in Spain and administered vernakalant, but none had clinically important consequences [46]., A retrospective study comparing 200 patients treated with vernakalant (n=100) or flecainide (n=100) reported no serious adverse effects of treatment with flecainide or vernakalant that required intensive care or prolonged follow up [48]. No serious adverse events were reported in a prospective cohort study of 230 patients treated with vernakalant [50].

Regulatory affairs

The regulatory environment for vernakalant differs markedly across the globe. Notably, whilst the drug is approved for use in Europe, Canada and other countries in Asia, lack of FDA approval means that it is not available in the US. This fact limits the worldwide market for vernakalant and impacts its future development. Vernakalant was first approved by the European Medicines Agency (EMA), the medicines regulatory body of the European Union (EU) in September 2010 [15] [11] under the trade name 'Brinavess' on the agreement that a real-world post-authorisation safety study would be conducted (SPECTRUM) [43] Vernakalant received market authorization in Canada in 2017 [51]. However, repeated applications in the US have not resulted in FDA approval. In 2007, the Cardiovascular and Renal Drugs Advisory Committee of the FDA recommended that vernakalant be approved for the rapid conversion of AF to sinus rhythm, however in August 2008, the FDA withheld approval for the drug on the basis of safety concerns, and a perceived lack of evidence demonstrating efficacy [19]. After European approval, the FDA requested a further phase 3 study (Beatch et al) [32] but after a patient death from cardiogenic shock, a meeting was held with the FDA in 2011 where

the sponsors and investigators deemed that the study would not meet regulatory expectations and it was terminated early. In 2012 Merck halted its developmental programme for an oral dosage form of vernakalant based upon its 'assessment of the regulatory environment and projected development timeline' [52]. In 2019, the SPECTRUM registry data (conducted from September 2011 to April 2018) was presented to the Cardiovascular and Renal Drugs Advisory Committee of the FDA as part of a resubmitted New Drug Application to provide evidence of safety. However, the panel voted overwhelmingly against the approval of vernakalant for recent onset AF in the US [12]. Panel members cited concerns that the risk of serious adverse effects may not outweigh the benefits of treatment and that the pre-infusion checklist might not reliably identify individuals at high risk of side effects. It is possible that the repeated unfavourable FDA rulings have been influenced by standard clinical practice in the US, comprised of a conservative management approach for acute onset AF favouring rate control over rhythm control [6]. It seems unlikely; therefore, that vernakalant will gain regulatory approval in the US, without further studies to evaluate the safety and efficacy of the drug or a marked change in the clinical management approach to acute onset AF.

Conclusion

Vernakalant is effective for rapid restoration of sinus rhythm in acute onset AF and represents an alternative to amiodarone for patients with coronary artery disease, moderate HFrEF, HFmrEF, HFpEF and left ventricular hypertrophy. Safety data from RCTs and post-marketing studies is reassuring and vernakalant appears to carry a risk of adverse events that is similar to ibutilide, amiodarone and flecainide. Further research to address the paucity of evidence on the effect of CYP2D6 metaboliser status and different patient subgroups on the risk of suffering from adverse effects would provide valuable, additional safety information.

Executive Summary

Indication for use

- Rapid conversion of recent onset atrial fibrillation (≤ 7 days duration in non-surgery patients and ≤ 3 days duration in post-cardiac surgery patients) to sinus rhythm.

Dosage and administration

- Available as vials of 20mg/ml concentrate to be administered by IV infusion.
- Initial infusion dose: 3mg/kg (administered over 10 minutes).
- Second infusion dose (if sinus rhythm is not restored within 15 minutes after the end of the initial infusion): 2mg/kg (administered over 10 minutes).

Mechanism of action

- Vernakalant is as multi-ion channel blocking drug with atrial-specific activity.
- It acts on numerous potassium currents including the transient outward current I_{to1}, the ultra-rapid delayed rectifier current I_{Kur}, the acetylcholine-activated current $I_{K,ACh}$, the ATP-sensitive current controlled by K_{ATP} channels and the rapid delayed rectified current $I_{Kr.}$
- It acts on frequency- and voltage-dependent cardiac sodium currents.

Pharmacokinetic properties

- Vernakalant is rapidly distributed to tissues and has a volume of distribution of approximately 2L/kg.
- Elimination is determined by CYP2D6 metaboliser status; in extensive metabolisers, elimination half-life is approximately 3 hours and in poor metabolisers it is approximately 5.5 hours.

Clinical efficacy and safety

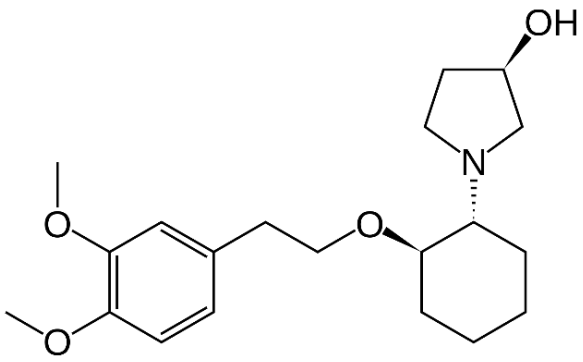
- There are six RCTs that compare vernakalant to placebo (ACT I, ACT II, ACT III, ACT V, CRAFT, ASIA-PACIFIC), two that compare vernakalant to ibutilide (Simon et al, Vogiatzis et al) and one that compares vernakalant to amiodarone (AVRO).
- Pooled analysis of all nine RCTs showed vernakalant significantly increased the rate of conversion to sinus rhythm within 90 minutes (Relative Risk [RR] 5.15; 95% Confidence Interval [95% CI] 2.24–11.84, $I^2 = 91\%$).
- Pooled analysis of seven RCTs showed there was no significant difference in the rate of adverse events between vernakalant and its comparators (placebo/amiodarone/ibutilide) (RR 0.95; 95% CI 0.70–1.28; $I^2 = 0\%$).
- A real-world post-authorisation study (SPECTRUM) of 1,778 patients treated with vernakalant reported an incidence of adverse events/serious adverse events that was similar or lower than available clinical trial safety data. It also reported a higher conversion rate than that reported in clinical trials.

Regulatory affairs

- Vernakalant is available in Europe, Canada and some countries in Asia but continues to be unavailable in the US after failing to gain FDA approval because of ongoing safety concerns.

Figures

Figure 1. Structural formula of vernakalant hydrochloride.



Tables

Table 1. Anti-arrhythmic drugs recommended for pharmacological cardioversion.

Vaughan Williams classification	Drug	Available route(s) of administration (PO/IV)	Main contraindications
III	Amiodarone	PO /IV	Bradycardia, thyroid dysfunction [53]
III	Ibutilide	IV	QT prolongation [54]
III & I	Vernakalant	IV	Bradycardia, hypotension, QT prolongation, severe aortic stenosis , severe heart failure, heart block without pacemaker, recent acute coronary syndrome [11]
IC	Propafenone	PO/IV	Heart failure, QT prolongation, significant valvular disease [55]
IC	Flecainide	PO/IV	Heart failure, QT prolongation, significant valvular disease [56]

PO, oral; IV, intravenous.

Table 2. Summary of the electrophysiological and clinical effects of vernakalant on key ion cardiac channels.

Channels affected	Current inhibition	Effect on cardiac AP	Clinical effects
$Na_V1.5$	I_{Na}	State-dependent block – acts in atria more readily and with a faster onset of action in AF	Slower conduction, leading to widening of QRS complex and lengthened QT interval → increased effective refractory period
$K_V4.2$, $K_V4.3$ and $K_V1.4$	I_{to1}	Rapid inactivation of I_{to1} halts atrial repolarisation, ending phase I of the action potential	Increased QT interval, although clinical effects may be small/insignificant
$K_V1.5$	I_{Kur}	Elevation of the atrial AP plateau voltage	Increased APD may lead to delayed atrial repolarisation in acute AF, but effect may be diminished in chronic AF
$K_{ir}3.4$	$I_{K,ACh}$	Theoretical increase in APD	No clear evidence that any clinical effects of vernakalant are due to $I_{K,ACh}$ inhibition
Partial block of $K_V11.1$	I_{Kr}	Partial inactivation of cardiac repolarisation	Probably little effect on QT interval at clinically relevant concentrations

Table 3. Study characteristics of randomised-controlled trials assessing the efficacy of vernakalant for conversion of acute onset AF to sinus rhythm.

Study, Author (Year)	Comparator, total dosing of vernakalant	Number of participants receiving vernakalant/comparator	Participant age, mean (SD), vernakalant/ comparator,	AF duration	Time to conversion (Median) in vernakalant responders	Conversion to sinus rhythm within 90 minutes vernakalant vs comparator, n (%), p value	Safety and tolerability
ACT III, Pratt et al (2010)	Placebo, 3mg/kg followed by 2 mg/kg if required	86/84	60 (16)/60 (15) (short duration AF)	3 hours to 7 days	8 minutes	44 (51.2%) vs 3 (3.6%), p <0.0001	Transient dysgeusia, paresthesia and sneezing. Similar incidence of ventricular tachycardia between the vernakalant and placebo group, vernakalant patients showed statistically significant increases in QRS duration, Bazett-corrected QT interval and QTcF that were not associated with proarrhythmia.
ACT V, Beatch et al (2016)	Placebo, 3mg/kg followed by 2	129/68	63.7 (12.7)/60.8 (14.1)	3 hours to 7 days	Not reported	59 (45.7%) vs 1 (1.5%), p <0.0001	Transient dysgeusia, paraesthesia and sneezing.

	mg/kg if required						Three patients had serious adverse effects considered to be related to vernakalant (nausea, headache, confusional state and cold sweat, sinus arrest and cardiogenic shock).
ACT II, Kowey et al (2009)	Placebo, 3mg/kg followed by 2 mg/kg if required	100/50	68.3 (7.7)/67.8 (6.4)	3 to 72 hours	12 minutes	47 (47%) vs 7 (14%), p < 0.001	Two patients had serious adverse events considered to be related to vernakalant (severe arterial hypotension and complete AV block). There were no cases of torsades de pointes, sustained ventricular tachycardia or ventricular fibrillation.
ASIA-PACIFIC, Beatch et al (2017)	Placebo, 3mg/kg followed by 2 mg/kg if required	55/56	60.7 (13.7)/59.2 (12.0)	3 hours to 7 days	11 minutes	29 (52.7%) vs 7 (12.5%), p < 0.001	Similar incidence of adverse effects between vernakalant and placebo group. Dyspnoea (reported in one patient) was the only serious adverse event considered to be related to vernakalant.

CRAFT, Roy et al (2004)	Placebo, 0.5mg/kg + 1 mg/kg treatment group 1, 2mg/kg + 3 mg/kg treatment group 2	36/20	67.4 (treatment group 1), 60.8 (treatment group 2)/64	3 to 72 hours	14 minutes	Treatment group 2: 11 (61%) vs 1 (5%), p = <0.0005 **within 30 minutes**	There were no serious adverse events reported considered to be related to vernakalant. Mild adverse events considered to be related to vernakalant included paresthesia, nausea and hypotension.
ACT I, Roy et al (2008)	Placebo, 3mg/kg followed by 2 mg/kg if required	145/75	60.4 (14)/59.9 (11.8)	3 hours to 7 days	11 minutes	75 (51.7%) vs 3 (4%), p <0.001	Four serious adverse events reported in three patients were considered to be related to vernakalant (hypotension [2 events], cardiogenic shock, complete heart block). Mild adverse events considered to be related to vernakalant included dysgeusia, paresthesia and sneezing. There were 3 reports of torsades de pointes in 2 patients 32 hours post infusion and 16

							and 17 days post infusion (not related to vernakalant).
AVRO, Camm et al (2011)	Amiodarone, 3mg/kg followed by 2 mg/kg if required	116/116	63.1 (10.81)/62.2 (11.63)	3 to 48 hours	11 minutes	60 (51.7%) vs 6 (5.2%), p < 0.0001)	There were no cases of torsades de pointes, ventricular fibrillation or sustained ventricular tachycardia in either group. Mild adverse events including dysgeusia, sneezing and cough were reported in the vernakalant group but not in the amiodarone group.
Simon et al (2017)	Ibutilide, 3mg/kg followed by 2 mg/kg if required	49/51	56.2 (14.32)/56.7 (15.77)	No longer than 48 hours	10 minutes	34 (69%) vs 22 (43%), log-rank p = 0.002)	No serious adverse events reported. Mild adverse events including paresthesia and dysguesia were reported in the vernakalant group but not in the ibutilide group. Premature ventricular contraction (8), aberrant conduction (7), and non-sustained

							ventricular tachycardia (7) were observed only in the ibutilide group, one leading to discontinuation. There were no cases of torsades de pointes, ventricular fibrillation or sustained ventricular tachycardia in either group.
Vogiatzis et al (2017)	Ibutilide, 3mg/kg followed by 2 mg/kg if required	36/42	62.44 (7.24)/64.81 (6.1)	1 to 48 hours	11.8 minutes (mean)	19 (52.78%) vs 22 (52.38%), p = 0.58	Vernakalant was discontinued in one patient due to severe hypotension with sweating, dizziness and nausea. Ibutilide was discontinued in 3 patients due to non-sustained ventricular tachycardia.

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