THE EFFICACY OF VERNAKALANT, AN ATRIAL SELECTIVE FIBRILLATING AGENTS

Abstract

An arrhythmia is a disturbance in the rate or rhythm of a normal heartbeat. It indicates that the heart is beating too fast, too slowly, or unevenly. Atrial fibrillation is the most frequent arrhythmia that can lead to blood clotting, which may cause cardiac and related complications. Medication, therapy to reset the heart rhythm, and catheter operations to block incorrect heart signals are all possible treatments for atrial fibrillation. Intravenous Vernakalant is successful regardless of sex, age, or rate of rhythm control treatment usage. It is a safe and well-tolerated medication for patients suffering from atrial fibrillation. In individuals with a history of ischemic heart disease; it also provides a successful treatment option for converting atrial fibrillation with an acceptable safety profile. Vernakalant was faster than placebo, amiodarone, propafenone, and flecainide at converting recent-onset atrial fibrillation to sinus rhythm. Therefore, it is recommended as a therapy of choice based on clinical trials with real-world evidence.

Keywords: Vernakalant, A trialfibrillation, Atrial selectiveagonist, RSD1235.

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I. INTRODUCTION

It was one hundred years; Willem Einthoven reported the electrocardiogram showing atrial fibrillation (AF) in 1906, which affects a minimum of 1-2% of the world's population (1). When a generation reaches the age of seventy-five, 8% of them will have developed AF, up from the period of 65's 5% prevalence. Different modules, such as rate or rhythm control, are used to treat or manage patients in various stages of AF. Both electrical cardioversion and pharmaceutical agents to aid chemical cardioversion were usually considered initial AF therapies. Under the auspices of the European Society of Cardiology, this treatment was observed in 41 nations worldwide in 2016 using the promising novel ligand RSD1235(2).

Under AF-converting agents, RSD1235, later known as Vernakalant, amino cyclohexyl etherproduces vigorous activity in the heart's upper chamber and non-significant effects on the lower region of the heart. Vernakalant, which affects the refractory period of the atria but has little impact on the ventricles, is the preferred marked ant arrhythmic medication for atrial tissue. Vernakalant is intended for persons with no or minimal heart disease and some types of structural heart disease, such as stable coronary heart disease, left ventricular hypertrophy, or mild heart failure, to rapidly terminate acute onset AF. According to prior findings and critical evaluations, Vernakalant is a promising drug for the targeted therapy of AF. As a result of this review, researchers will be reminded to consider Vernakalant as an antiarrhythmic agent for future perspectives in a larger population (3).

Vernakalant is a rapid-acting, relatively a trial-selective ant arrhythmic drug approved inCanadaandEuropeforthepharmacologicalcardioversionofrecent-onset atrial fibrillation. Considering that recent-onset symptomatic AF resolves spontaneously within 24 hours in more than 70% of cases, it may be best to wait and see with rate control medication for patients in the emergency room who have recently developed the condition.In addition, the 2016 European Society of Cardiology (ESC) Guidelines advised that rhythm control should be considered in patients who continue to experience symptoms despite the rate control method.Nonetheless, that rhythm control is preferable to stop atrial remodeling and the development of paroxysmal or persistent AF into permanent AF.Electrical or pharmaceutical cardioversion can be used to control rhythm; the choice depends on the physician's preference and may be influenced by prior knowledge, regional customs, and legal requirements. In particular, where there is no hemodynamic compromise, pharmaceutical cardioversion is chosen as a first-line strategy in patients who tolerate their arrhythmia. Pharmacological cardioversion has the benefit of not requiring general anesthesia or conscious sedation while the patient is fasting, as well as perhaps having less psychological effects than electrical cardioversion and possibly having a lower risk of immediate recurrence; The more muscular antiarrhythmic drug (AAD) loading often used in pharmacological cardioversion, which provides a significant efficacy immediately and for the hours and days following cardioversion, is probably connected to the lower chance of an immediate recurrence. Whether the "pill-in-the-pocket" pharmacological treatment (Flecainide, Propafenone, and Sotalol) can end paroxysmal AF quickly is debatable. The situation's urgency influences the "pill-in-the-pocket" technique's use and effectiveness, the patient's cooperation, the doctor's experience, the drug's availability, any underlying heart conditions, and other factors. There is insufficient data to advocate the "pill-in-the-pocket" approach for treating patients with paroxysmal AF.Furthermore, many AADs (such as amiodarone and beta-blockers) have a sluggish beginning of the action in paroxysmal AF or

may have some limitations for usage in patients with underlying cardiac disease (class 1 AAD). As a result, it was sought after to create innovative and efficient AAD to treat patients with paroxysmal AF.

II. CHEMISTRY OF VERNAKALANT

1. **Chemical Name and Properties:** Chemically Vernakalant is also known as "(1R, 2R)-2-[(3R)-hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy) Cyclohexanemono hydrochloride, with a chemical formula of C20H31NO4.HCl. The basic moiety of Vernakalant belongs to the cyclic class imides with three chiral centres(4).

   - **Synthesis:** Vernakalant hydrochloride is made primarily by chemical synthesis over a five-step procedure that guarantees the chirality of every chiral centre. As a result, a single polymorphism pathway produces the anhydrous, non-solvated substance.

     This method yields 56% overall yield by three new transformations, comprising a ZnCl$_2$ and pyrrolidine-mediated-etherification, aversatile enzymatic asymmetric transamination (DA-TA) of a -substituted ketone, and an alkyl-B(OH)2-mediated amidation(5).[Fig:1,2]
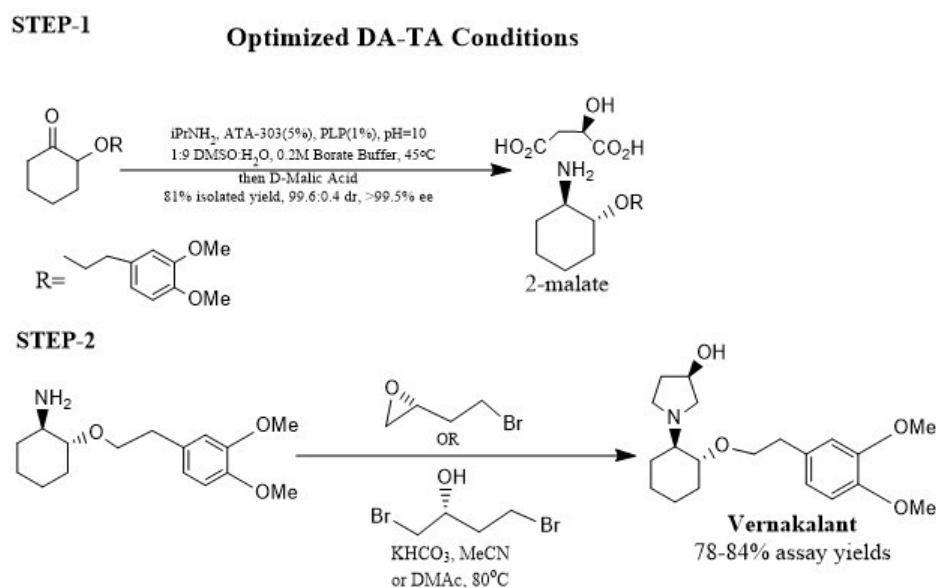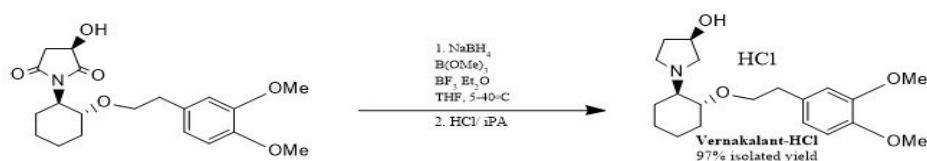

Figure 1: Asymmetric transamination (DA-TA) of a substituted ketone

Formation of Penultimate Imide Intermediate

STEP-1
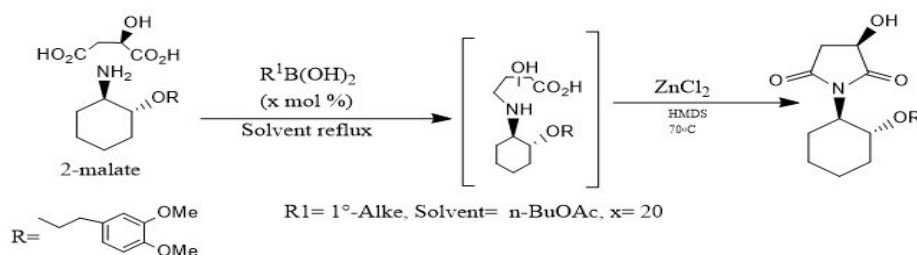
STEP-2

Figure 2: ZnCl₂ and pyrrolidine-mediated-etherification and an alkyl-B(OH)2-mediated amidation

Recently another method has been developed with Ammonium persulfate-dimethyl sulfoxide (APS-DMSO), a new dehydrating agent for a simple one-pot procedure that produces high yields of various cyclic imides from primary amines and cyclic anhydrides which are widely available(4).[Fig:3]
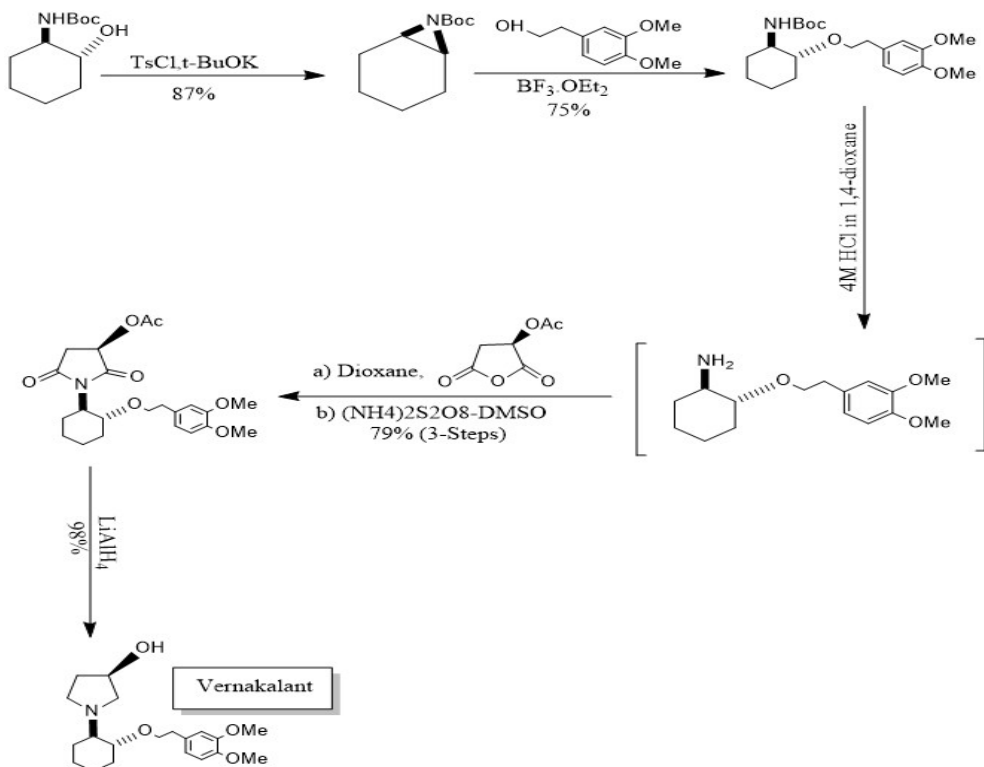
Figure 3: Synthesis of Vernakalant with the help of Ammonium persulfate–dimethyl sulfoxide

2. **The Chemistry behind Vernakalant's High-Affinity Association:** A recent study of Vernakalant's molecular aspects of interaction with the Kv1.5 channel's inner pore is compared to the interactions of the category IC compound flecainide, which shows that Vernakalant effectively inhibits channels that have been triggered and leave the interior vestibule as the track closes. The molecular docking study of Vernakalant binding mechanisms to the openstate of the Kv1.5 channel structure could be explored through modelling utilising AutoDock4. The most convenient conformation hadfree energy of binding (FEB) of 7.12 kcal/mol and an estimated Ki of 6.08 mM (the actual IC_{50} for Vernakalant is 13.8 mM). This conformation appears specifically designed to restrict the channel pore as it interacts with all four T480 residues(2).

- **Mode of Action**: Vernakalant meeklyhinders I_{to}, I_{Kr},$I_{K.ATP}$ and late I_{Na} currents are found in the heart's lower chambers, characterising them as "Atrial selective." It shows dominant sensitivity towards I_{Kur}(atria-specific channel) over the tracks for ventricular depolarization, such as I_{Na} andI_{Kr}. This channel selectivity is chieflyaccountable for the vernakalant's safety(6). Vernakalant inhibits sodium channels; andthis inhibitory activity varies with the potential of membranes and heart rate. When the membrane's resting potentials (INa) are negative, and theheart rate is low, Vernakalant acts as a mild activator of the sodium channel blocker. Due to Vernakalant's increased affinity for I_{Na}, as the heart rate rises, there is a more pronounced I_{Na} blockage, and the medicine starts to work quickly. Vernakalant has a fast binding offset, which is highly desirable in an antiarrhythmic medication after the heart rate lowers and the I_{Na} blockage is no longer necessary. State-dependent I_{Na} blockage may be the basis for Vernakalant's AF-selective activities. However, Vernakalant's late INa kinetics is fast offset and frequency-dependent.

  This property means that at higher atrial rates, the inhibition of late I_{Na}current and deceleration of atrial conduction are more noticeable. Vernakalant isideal for treating rapid atrial fibrillation or other atrial tachyarrhythmias. Furthermore, further data support the idea that Vernakalant exhibits a ranolazine-like antiarrhythmic activity by late I_{Na} current reduction, inhibiting drug-induced proarrhythmic from dofetilide and acting as a protective factor for the ventricular myocardium.

  Normal atria have a resting membrane potential between -70 and -80 mV, roughly ten mV more positive than the ventricles. The discrepancy between the atria and ventricles' resting membrane potentials rises in AF as the atria fail to repolarise entirely. It is theorized that Vernakalant selectively blocks sodium channels in the diseased tissue and atria rather than the healthy ventricles because of this increased disparity in membrane potential. However, Vernakalant's mode of action greatly emphasizes its capacity to block particular potassium channels. It inhibits the potassium current I_{Kur}, which is involved in atrial repolarization-selective. Additionally, Vernakalant blocks the second a trial-selective potassium channel, I_{KACh}, at low concentrations, lengthening the atrial action potential duration and extending the plateau(7).
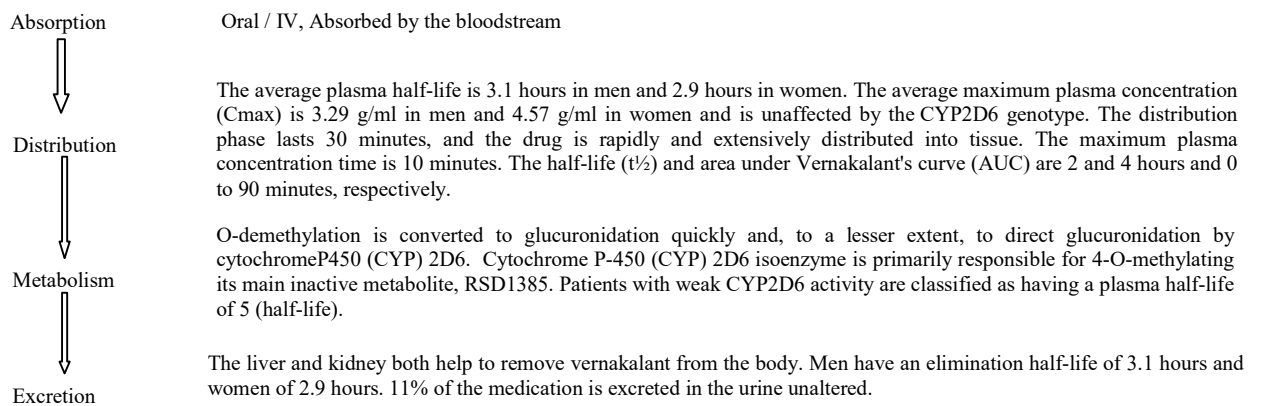
Table 1: Action Potential in Atria and Ventricular Myocardium.

Current	Gene	The phase of action potential	Ion direction	Atria	Ventricles
I_{Na}	hH1	o	Inward	+	+
$I_{Ca, L, T}$	SCN5A	2	Inward	+	+
I_{to}	$K_{v4.2/4.3}$	1	Inward	+	+
I_{Ks}	KCNQ1	3	Outward	+	+
I_{Kr}	HERG	2,3	Outward	+	+
I_{Kur}	$K_{V1.5}$	2,3	Outward	+	-
I_{Cl}	CTRF/TWIK	2,3	Outward	+	+
I_{k1}	Kir 2 family	late 3& 4 family	Outward	+	+
$I_{k.ATP/Ach}$	Kir3 family	late 3& 4 family	Outward	+	-

3. **Electrophysiological & Hemodynamic Effects:** The mean QRS interval ↑increased, the QTc interval prolongedtransiently, and a minimum of 30 msec prolongationwas noted inthe QTcF interval. The meanQTcB (Bazett-corrected QT interval) ↓decreased, monomorphic unsustained ventricular tachycardia (VT) and ventricular extrasystoles decreased. Inpatients treated intravenous (IV) vernakalant, the mean HR (106 beats/min) from baseline ↓decreased. In the 24 hours (from infusion upto 24 hours), Vernakalant caused hypotension. Among those given Vernakalant who remained in AF or atrial flutter (AFL), the decreased in HR [any hr<40 beats/min on Holter (1.7%)], any hypotension event (2.2%), andsystolic blood pressure (SBP)< 90 mmHg (1.3%) was observed(8).

4. **Pharmacokinetics Profile:** Vernakalant IV demonstrated efficacy irrespective ofage, sex, rate, rhythm control therapy and medical histories likeCHF (congestive heart failure), MI (myocardial infarction), hypertension, ischemic heart disease, nephron-impairment, and hepato-injury. However, Vernakalant IV should be given cautiouslyto New York Heart Association (NYHA) class I or II CHFpatients with steady hemodynamics.Vernakalant IV is contraindicated in patients with NYHA class III or IV CHF(7).

   Age, sex, liver, and renal function do not impact the pharmacokinetic properties of Vernakalant orally administered, andVernakalant is transported in the systemic circulationand distributed within 30 mins. It remarked a very short half-life and is metabolized primarily by the hepatic cytochrome P-450 (CYP) 2D6 (CYP2D6) system and excreted within 2 to 5 hours. Oral Vernakalant prescribed doses are150, 300, 500, and 600 mg/kg twice daily. No episodes of torsade de pointes found in the previous activities.The adequateformulation of Vernakalant is intravenous, recommended in an environment where continuous cardiac monitoring is available, at 3 mg/kg (initially) over 10 min. If Vernakalant IV does not restore the sinus rhythm (SR) within 15 min ofthe end of the first administration, a second 2 mg/kg infusion (for 10 min) can be given.Vernakalant is welldistributed (rapid & extensive) into tissue& saliva.Vernakalant's protein binding is 25-50% (low protein binding). The blood: plasma

concentration ratio was usually <1, indicating vaguely bound to erythrocytes. In human serum (EMA), Vernakalant's free fraction rangesfrom 53-63%.Patients are categorized as weak (half-life of 5.6 hours) or extensive metabolizes based on the plasma half-life, dependent on CYP2D6 activity (2.2 hours).The maximum plasma concentration, the area under the plasma concentration curve, is 3.29 µg/ml, 11.64 µg. Hr/ml in the men and 4.57 µg/ml, 11.64 µg.Hr/ml in the woman. The primary inactive metabolite of this substance, RSD1385, is primarily reliant on 4-O-methylation (by cytochrome P-450 (CYP) 2D6 isoenzyme) and fast glucuronidation. Excretion of Vernakalant is taken place in the liver and kidney. Therefore, 11% of the unchanged drug is eliminated in the urine(9).

Absorption	Oral / IV, Absorbed by the bloodstream
Distribution	The average plasma half-life is 3.1 hours in men and 2.9 hours in women. The average maximum plasma concentration (Cmax) is 3.29 g/ml in men and 4.57 g/ml in women and is unaffected by the CYP2D6 genotype. The distribution phase lasts 30 minutes, and the drug is rapidly and extensively distributed into tissue. The maximum plasma concentration time is 10 minutes. The half-life (t½) and area under Vernakalant's curve (AUC) are 2 and 4 hours and 0 to 90 minutes, respectively.
Metabolism	O-demethylation is converted to glucuronidation quickly and, to a lesser extent, to direct glucuronidation by cytochromeP450 (CYP) 2D6. Cytochrome P-450 (CYP) 2D6 isoenzyme is primarily responsible for 4-O-methylating its main inactive metabolite, RSD1385. Patients with weak CYP2D6 activity are classified as having a plasma half-life of 5 (half-life).
Excretion	The liver and kidney both help to remove vernakalant from the body. Men have an elimination half-life of 3.1 hours and women of 2.9 hours. 11% of the medication is excreted in the urine unaltered.

Figure 4: Pharmacokinetic study of vernakalant

5. **Preclinical Trials:** Vernakalant was used in a rabbit model of acquired Short QT syndrome (SQTS). By injecting 1M pinacidil, the heart's ATP-sensitive K channels are opened. As a result, there is a higher chance that planned stimulations would cause arrhythmias (ventricular fibrillation), which reduce the action potential duration (APD) and QT intervals. Vernakalant increased the APD and QT interval while reducing ventricular fibrillation. However, neither SQTS cardiomyocytes nor SQTS patients have been used in vernakalant studies. The APD-extension and antiarrhythmic effects of Vernakalant in human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) from a patient with SQTS1 have been linked to the pathogenic mutation for SQTS1 known as N588K in the potassium voltage-gated channel subfamily H member 2 (KCNH2) gene. As SQTS1-hiPSC-CMs, these cells are referred to. The Vmax, APD50, and APD90 in the SQTS1-hiPSC-CMs were the three APs that Vernakalant significantly changed. The decrease in Vmax is compatible with its Na channel-blocking effect because peak sodium channel currents are a vital predictor of Vmax in cardiomyocytes. Vernakalant prolonged the APD in SQTS1-hiPSC-CMs, but how this occurred needs to be made clear(10).

6. **Clinical trials**

- Intravenous Vernakalant reported better efficacy than amiodarone for speedy conversion of recent-onset Atrial Fibrillation. The main objective was for patients with sinus rhythm 90 minutes after starting therapy. The treatment with Vernakalant altered 51.7% of patients sinus rhythm at 90 minutes compared with 5.2% of patients treated with amiodarone. The median conversion time of Vernakalant was 11 min.

Furthermore, Vernakalant did not show any significant side effects. Also, there was no ventricular arrhythmia reported(11).

- The safety and efficacy of Vernakalant, in combination with external electrical cardioversion in patients with recent-onset (≤7-day) AF, was studied. After the initial dose of Vernakalant, conversion to SR could be accomplished in 55% of instances. Only 167 individuals (73%) could have their sinus rhythm restored by medication within a median of 11 minutes (IQR 8-29). Within 196 minutes (IQR = 149-300) of the first dose of Vernakalant, electrical cardioversion was accomplished on 62/63 non-responders yielding a total success rate of99%. No patient receiving electrical cardio version showed immediate atrial fibrillation reinitiating. Vernakalant showed no severe rhythm disorders [torsade de pointes tachycardia, polymorphic or sustained/non-sustained VT, ventricular fibrillation, and premature ventricular contractions (PVC)] during or after its administration(11).

- In a phase-3 trial, Vernakalant was given to 161 coronary artery bypass surgery (CABG) patients (placebo=54, Vernakalant=107) to analyze its efficacy and safety. Vernakalant converted AF/AFL to SR in 44.9% (48/107, P<0.001) patients for a minimum of 1 minute within 90 minutes of the first infusion. In contrast, 14.8% (8/54, P<0.001) of placebo patientsexhibited this effect. In patients with AFL at baseline, none of the Vernakalant patients converted to SR. In patients who had CABG surgery alone, the difference in responder rates was significant between Vernakalant 34/71 (47.9%) and placebo 5/37 (13.5%)(P=0.002). The age, gender, left ventricular ejection fraction (LVEF), or left atrial diastolic dimension did not influence the conversion to SR. The median time to conversion for AF-to-SR transformation with Vernakalant was 12.4 minutes. The median time to conversion was 12.3 minutes among AF/AFL patients who responded to Vernakalant treatment (0.5 to 57.1 minutes). In the first 2 hours and 24 hours after beginning dosing, four patients received Vernakalant and witnessed nonsustained ventricular tachycardia lasting 3 to 12 beats. Bradycardia happened more frequently with Vernakalant treatment. The SBP in Vernakalant patients was 90 mmHg. There were no cases of torsade de pointes, sustained ventricular tachycardia, or ventricular fibrillation in either treatment group(14).

- In a cardiovascular emergency care division, Vernakalant (IV) and propafenone (oral) were compared for conversion times of recently developed AF in hemodynamically healthy individuals deprived ofa structural heart ailment. Each patient exhibited hemodynamic stability, symptomatic recent-onset AF (lasting <48 hours), and no structural heart abnormalities. In the propafenone group, there were 19 patients, while in the vernakalant group, there were 17 patients. In the Vernakalant group, sinus rhythm conversion took 9 minutes, whereasthe propafenone group took 166 minutes (P=0.0001) for similar effects.As a result, 7% of Vernakalant-treated and 22% of propafenone-treated patients required electrical cardioversion (ECV).Hospital stay was 43% shorter in the Vernakalant group (P=0.0001).In the Vernakalant group, 47% of patients experienced adverse events, compared to 5% in the case of propafenone treatment. Only one patient in each group experienced a severe adverse event. In those patients, bradycardia lasted<five min at a rate of 40 beats per minute. Coughing

fits and transient dysgeusia was frequent in the Vernakalant group. There were no late adverse events reported(15).

- Phase 3 arrhythmia conversion trials I (ACT I) and ACT IV sought to evaluate the efficacy and safety of Vernakalant for patients with recent-onset AF. The sample was 290 individuals with AF lasting > 3 to ≤48 hours.Vernakalant and placeboswere given to 229 (ACT I=99 and ACT IV=130) and 61 (in ACT I) patients, respectively. Vernakalant converted 136/229 [59.4%; 95% confidence interval (CI)=53% to 66%, p<0.0001]to SR within 90 min. But, the placebo converted only 3/61 (4.9%; 95% CI=1% to 14%, p<0.0001) to SR. Here, Vernakalant showed a median conversion time of 12 min. Between 2 and 24 hours, Vernakalant patients (33.6%) received ECV and other AAD, less than placebo patients (80.3%). Among no responders (patients not converting within 90 min), 93 (59.1%) Vernakalant patients received ECV or AADs between 2 and 24 hours, compared to 58 (84.5%) no responders in the case of placebo. Severe AEs like bradycardia and hypotension were noted in 7 (3.1%) patientswithin the first 2 hours of Vernakalant administration. But, the placebo did not show any such effects. From 2-24 hours after administration of a drug, the most common AEs were dysgeusia (weird taste), sneezing, paresthesia, nausea, pruritus, and cough. Vernakalant and placebo-treated patients showed similar ventricular arrhythmia, bradycardia, and hypotension incidence. No torsade de pointes, ventricular fibrillation, or sustained ventricular tachycardia (VT) were observed(16).

- To analyze the predictors of conversion in 2years of experience, Vernakalant IV was given to 121 patients for treatment ofrecent-onset AF. Hypertension was present in 46.4% of the patients, and only 1.8% had diabetes. Structural heart disease (13.4%) existedwith an average of 60.2±6.4 of ejection fraction and 20.6±4.4 of left atrial area. The SR was returned in 84.5% of patients; however, a second Vernakalant dose was needed for 46% of patients. The time for conversion to SR was 10 min.The group without modification showed more significant structural heart disease (35.3 vs. 9.7%; P=0.02). The group with and without conversion showed a mean EF of 61.05±5.7% and 54.9±8.4%, respectively (P=0.016). In addition, a lower rate of conversion was achieved in the patients with EF less than 55%(15).

- To safely and quickly restore sinus rhythm and promote same-day discharge, the researcher examined the viability of chemical cardioversion of recently developed AF in the emergency room using Vernakalant hydrochloride. Vernakalant (42 doses) was given to 32-82 years (mean=57.7) with a 76.2% male preponderance. At an average of 8.8 minutes (2-30), 83% of patients had their sinus rhythm back, and nine required a second injection. Symptoms lasted an average of 11.9 hours (2-36). Sneezing (15%) and brief (20%)taste alterations were noted. The cardioversion/noncardioversion groups were not significantly differentconcerning age (57.6/56.2 years), symptoms duration (mean=12.54/9.54 hours), and heart rate (mean=141/140 bpm). After two hours of monitoring in the ED, two Vernakalant non-responders were cardioverted electrically, fourpatients got discharged for cardioversion at the outpatient department (because of resource limitations), and 1 patient was hospitalized for additional diagnostic testing. Four (9.5%) patients experienced a recurrence of AF, but no patientshad thrombotic/bleeding episodes within the six-month follow-up. Same-day discharge from the ED accounted for97.5% (41/42)(18).

- The influence of Vernakalant on the hemodynamics of ten intensive care unit (ICU) patients developing post-operative atrial fibrillation (POAF) after elective cardiac surgery was studied. All ten patients were awake and breathing spontaneously. The patients before 20 min and after 120 min of the first dose of Vernakalantwere clinically observed and monitored for heart rate, invasive blood pressure, pulse oximetry, and central venous pressure (CVP) in 1 min. From the end of surgery until the occurrence of POAF, the median time was 52.8 (45.9–77.4) hours. From the circumstance of POAF until the Vernakalant's first application, the median time was 3.5 (1.2–10.1) hours. The patients were supported with catecholamine (epinephrine)during the observational phase. A stable hemodynamic state was noted, with a tendency to fall in heart rate (HR) throughout the 120 minutes after the administration of Vernakalant. In 70% (7) of patients, conversion to sustained SRwas obtained within 8.0 min (6.0–9.0). No SAEs were recorded during the observation span. Conclusively, the Vernakalant could not produce a significant adverse effect on the hemodynamics of the patients (ICUpatients showing POAF after cardiac surgery). Still, it had sustained SR conversion in 70% of patientsafter a median of 8.0 min(20).

7. **Interaction with Other Drugs:** Vernakalant's pharmacokinetic profile shows fast dispersion and a brief half-life, which reduces the likelihood of drug-drug interactions.Vernakalant established synergistic, antagonistic, additive effects with many following drugs, but no interaction was found with food.No pharmacodynamic interactions were found between Vernakalant and propranolol, verapamil, or the anticoagulant warfarin. Several authors have hypothesized drug-drug interaction resulting from protein displacement.

Table 2: Pharmacokinetic Interaction of Vernakalant on the following Drugs.

Metabolism of Vernakalant ↑	Metabolism of Vernakalant ↓	↑es arrhythmogenic activity of Vernakalant	The risk or severity of QTc prolongation	The risk or severity of adverse effects
Abatacept	Selegiline, Rosiglitazon,Ranitidine, Omeprazole, Mepyramine, celecoxib, Chloroquine, Cimetidine, Cyclosporine, Hydroxycholroquine, Imipramine	Verapamil, Propafenone, Norfloxacin, Losartan, Lidocaine, Acetyldigitoxin, Amlodipine, Bretylium, digitoxin, Ethosuximide, Hyoscyamine	Sulfamethoxazole, Valproic acid, Salbutamol, Oxytocin, Ondansetron, Ofloxacin, Nalidixic acid, Metronidazole, Acrivastine, Amantadine, Apomorphine, Azithromycin, Cetrizine, Chlorpheniramine, Ciprofloxacin, Clarithromycin, Cocaine, disulfiram, domperidone, Famotidine,Haloperidol, Levocetrizine	Amiodarone

8. **Contraindication:** Acute coronary syndrome, critical aortic stenosis, extreme heart failure, SBP less than 100 mmHg, acute coronary syndrome during the past 30 days, and QT prolongation more significant than 440 msec are all contraindications to using Vernakalant. Vernakalant is also not advised if someone recently received class I/class III antiarrhythmic intravenously. Not many individuals have severe liver disease, restrictive

cardiomyopathy, hypertrophic obstructive cardiomyopathy, constrictive pericarditis, or clinically significant valvular stenosis. The left ventricular ejection fraction is rarely less than 35%.

9. **Adverse events and serious adverse events:** The safety profile of oral Vernakalant is similar to intravenous Vernakalant in the first 24 hours. In addition, there were no episodes of torsade de pointes in both formulation studies(8).

Table 3: Commonly developed AE and SAE of Vernakalant

Adverse event	Serious Adverse event
Cardiac disorders	Ventricular fibrillation
Ventricular tachycardia	Arterial BP (49/39 mmHg)
Sinus arrest	Complete AV block
Dysgeusia	Ventricular tachycardia
Sneezing	Sustained zoomorphic
Paresthesia	Ventricular fibrillation
Dizziness	Bradycardia
Bradycardia	Sinus arrest
Nausea	Urinary retention
Hyperhidrosis	Troponin T increase
Hypotension	Atrial thrombosis
Pruritus	Syncope (related to pulmonary embolism)
Cough	Bradycardia of 40 beats per min lasting <5 min
Lacrimation increased	
Transiently altered taste	

10. **Toxicology:** Rat shows the highest resistance among laboratory animals due to ion channel blockade. No observed adverse effect was established from the single and repeated dose study on Vernakalant. In addition, the mating, oestrouscycle, sperm parameters, pregnancy, litter parameters, or other fertility indices are not affected.

III. CONCLUSION

Neurological effects such as ataxia, splayed posturing, head shaking, coarse tremor, lower proprioception, and reduced locomotor activity were reported in atrial fibrillation screening on laboratory animals. Vernakalant hydrochloride is a marked atrial selective ant arrhythmic agent. According to clinical trials, the most effective formulation of Vernakalant is intravenous formulation. It is a potassium channel blocker (I_{Kur}) and sodium channel blocker, which defines it as responsible for antiarrhythmic potency.Twenty-four hours after infusion, Vernakalant prolonged QRS, QT, QTcF, and QTcB and induced hypotension and Bradycardia.Theexistingstudies reveal its efficacy in itsparenteral formulation in terminating event-onset AF. Sex, age, hepatic, and kidney function do not intend to affect the

pharmacokinetic properties of Vernakalant.The most severe adverse event was of cardiac origin with hospitalization. During the first 24 hours, adverse events in patients were dysgeusia, sneezing, paresthesia, nausea, and hypotension. The oral formulation is being studied for long-term maintenance of sinus rhythm after its first attempt, is currently under development, and has shown significant yield. It also provides an effective therapeutic alternative for converting AF with an acceptable safety profile in patients with a history of ischemic heart disease (IHD).

REFERENCES

[1] Lindmayr T, Schnaubelt S, Sulzgruber P, Simon A, Niederdoeckl J, Cacioppo F, et al. Body Weight Counts—Cardioversion with Vernakalant or Ibutilide at the Emergency Department. J Clin Med. 2022;11(17).

[2] Eldstrom J, Wang Z, Xu H, Pourrier M, Ezrin A, Gibson K, et al. The molecular basis of high-affinity binding of the antiarrhythmic compound vernakalant (RSD1235) to Kv1.5 channels. Mol Pharmacol. 2007;72(6):1522–34.

[3] Lévy S, Hartikainen J, Ritz B, Juhlin T, Carbajosa-Dalmau J, Domanovits H. Vernakalant for Rapid Cardioversion of Recent-Onset Atrial Fibrillation: Results from the SPECTRUM Study. Available from: https://doi.org/10.1007/s10557-020-07103-9

[4] Garad DN, Tanpure SD, Mhaske SB. Radical-mediated dehydrative preparation of cyclic imides using (NH4)2S2O8-DMSO: Application to the synthesis of Vernakalant. Beilstein J Org Chem. 2015;11:1008–16.

[5] Limanto J, Ashley ER, Yin J, Beutner GL, Grau BT, Kassim AM, et al. A highly efficient asymmetric synthesis of Vernakalant. Org Lett. 2014;16(10):2716–9.

[6] Marinelli A, Ciccarelli I, Capucci A. Vernakalant hydrochloride in the treatment of atrial fibrillation: a review of the latest clinical evidence. Clin Investig (Lond). 2011;1(4):579–88.

[7] Ritchie LA, Qin S, Penson PE, Henney NC, Lip GYH. Vernakalant hydrochloride for the treatment of atrial fibrillation: Evaluation of its place in clinical practice. Vol. 16, Future Cardiology. Future Medicine Ltd.; 2020. p. 585–95.

[8] Savelieva I, Graydon R, Camm AJ. Pharmacological cardioversion of atrial fibrillation with Vernakalant: Evidence in support of the ESC Guidelines. Vol. 16, Europace. 2014. p. 162–73.

[9] Hall AJM, Mitchell ARJ. Introducing vernakalant into clinical practice. Arrhythmia Electrophysiol Rev. 2019 Mar 1;8(1):70–4.

[10] Xu Q, Huang X, Meng Z, Li Y, Zhong R, Li X, et al. Antiarrhythmic Effects of Vernakalant in Human-Induced Pluripotent Stem Cell-Derived Cardiomyocytes from a Patient with Short QT Syndrome Type 1. J Cardiovasc Dev Dis. 2022;9(4):1–14.

[11] Kossaify A. Vernakalant in Atrial Fibrillation: A Relatively New Weapon in the Armamentarium Against an Old Enemy. Drug Target Insights. 2019;13.

[12] Roy D, Pratt CM, Torp-Pedersen C, Wyse DG, Toft E, Juul-Moller S, et al. Vernakalant hydrochloride for rapid conversion of atrial fibrillation: A phase 3, randomized, placebo-controlled trial. Circulation. 2008;117(12):1518–25.

[13] Yu C, Li J, Zhao C, Guan Y, Wu D, Sun B, et al. Effectiveness and Safety Profiles of Vernakalant for Cardioversion of Acute-onset Atrial Fibrillation: A Systematic Review and Meta-analysis. Clin Ther [Internet]. 2023;45(3):218–31. Available from: https://www.sciencedirect.com/science/article/pii/S0149291823000346

[14] Randomized A, Trial P, Kowey PR, Dorian P, Mitchell LB, Pratt CM, et al. Vernakalant Hydrochloride for the Rapid Conversion of Atrial Fibrillation After Cardiac Surgery. 2009;652–9.

[15] Costabel JP, Lambardi F, Aragón M, Campos R, Urdapilleta M, Ariznavarreta P, et al. Predictors of conversion of recent-onset atrial fibrillation treated with Vernakalant. PACE - Pacing Clin Electrophysiol. 2015 Feb 1;38(2):196–200.

[16] Stiell IG, Dickinson G, Butterfield NN, Clement CM, Perry JJ, Vaillancourt C, et al. Vernakalant hydrochloride: A novel a trial-selective agent for the cardioversionof recent-onset atrial fibrillation in the emergency department. Acad Emerg Med. 2010 Nov;17(11):1175–82.

[17] Roy D, Rowe BH, Ms C, Stiell IG, Ms C, Coutu B, et al. A Randomized , Controlled Trial of RSD1235 , a Novel Antiarrhythmic Agent , in the Treatment of Recent Onset Atrial Fibrillation. J Am Coll Cardiol [Internet]. 2004;44(12):2355–61. Available from: http://dx.doi.org/10.1016/j.jacc.2004.09.021

[18] Stoneman P, Gilligan P, Mahon P, Sheahan R. Chemical cardioversion of recent-onset atrial fibrillation in the emergency department using vernakalant hydrochloride achieves safe and rapid restoration of sinus rhythm and facilitates same day discharge. Ir J Med Sci. 2017;186(4):903–8.

[19] Roy D, Rowe BH, Stiell IG, Coutu B, Ip JH, Phaneuf D, et al. A randomized, controlled trial of RSD1235, a novel antiarrhythmic agent, in the treatment of recent onset atrial fibrillation. J Am Coll Cardiol [Internet]. 2004;44(12):2355–61. Available from: http://dx.doi.org/10.1016/j.jacc.2004.09.021

[20] Schnaubelt S, Niederdöckl J, Simon A, Schütz N, Holaubek C, Edlinger-Stanger M, et al. Hemodynamic effects of Vernakalant in cardio-surgical ICU-patients treated for recent-onset postoperative atrial fibrillation. Sci Rep. 2020 Dec 1;10(1).

[21] Minassian AM, Silk SE, Barrett JR, Nielsen CM, Miura K, Diouf A, et al. Reduced blood-stage malaria growth and immune correlates in humans following RH5 vaccination. Med [Internet]. 2021;2(6):701-719.e19. Available from: https://doi.org/10.1016/j.medj.2021.03.014