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Anti-Arrhythmic Agents in the Treatment of Atrial Fibrillation

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Abstract

Although atrial fibrillation (AF) is the most common sustained arrhythmia seen during daily cardiovascular physician practice, its management has remained a challenge for cardiology physician as there was no single anti-arrhythmic agents proved to be effective in converting atrial fibrillation and kept its effectiveness in maintaining sinus rhythm over long term. Moreover all the anti-arrhythmic agents that are used in the treatment of AF were potentially pro-arrhythmic especially in patients with coronary artery disease and structurally abnormal heart. Some of these drugs also have serious non cardiac side effects that limit its long term use in the management of AF. Several new and investigational anti-arrhythmic agents are emerging but data supporting their effectiveness and safety are still limited. In this review we examine the efficacy and safety of these medications supported by the major published randomized trials, meta-analyses and review articles.

Introduction

Atrial fibrillation is the most come type of sustained cardiac arrhythmias that is faced in daily practice of cardiovascular physician all over the world. The incidence and prevalence of atrial fibrillation increases age of the population. Atrial fibrillation comes in a wide spectrum of clinical presentations, ranging from being totally asymptomatic and discovered during routine medical checkup, to presentations related to AF itself like feeling of palpitation which can be sever and affecting the quality of life of the patient and more important that related to its complications including thromboembolic complications and tachycardia induced cardiomyopathy. These complications are responsible for the major part of morbidity and mortality complications of AF and its impact on the quality of life of AF patients.^{1,2}

Key Words:

Atrial fibrillation, anti-arrhythmic agents, treatment, sinus rhythm, conversion

Disclosures:

None.

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Antiarrhythmic Drugs

Anti-arrhythmic drugs (AAD) for AF had been available for long time and used for different indications including cardioversion, as a prophylaxis for maintaining sinus rhythm and preventing recurrence or just controlling the ventricular rate. But at the same time there use was limited by there potential proarrhythmic cardiovascular and non-cardiovascular toxicity and their modest effect on maintaining sinus rhythm.³

The results of the recently published studies over the last several years that compared rhythm control to rate control in form of outcome on the quality of life, thrombo-embolic risk and cardiovascular complications, showed no significant difference in both ways of treatment (table 1).⁴⁻¹¹ These results changed the concept and approach of AF management dramatically from continuous attempt for cardioversion and maintaining sinus rhythm which was difficult to achieve in most of the cases in addition to the potential risk of the treatment, to the rate control approach which is easier and more cost effective than the rhythm control approach. Still in certain circumstances, cardioversion and maintaining sinus rhythm is more recommended like in severely symptomatic patients, new onset AF, young patients and some structural heart conditions.³

Many AAD were used and several of them still currently used for different indications in AF patients including converting the rhythm back to normal, as a prohylaxix to maintain sinus rhythm or to control the ventricular rate. In addition several non-pharmacological treatment methods for the same purpose were used and some of them are still in use.

Because of the limited effectiveness and potential side effects

of the currently used drugs, several newly emerging novel and investigational drugs are under evaluation for their effectiveness and superiority in the management of AF.

In this review, we will try to go through different AAD that are used or still currently used and the newly coming drugs and to review their effectiveness, indications and their potential risks and side effects.

Anti-arrhythmic drugs are classified broadly in to four major groups according to their electrophysiological properties. They are traditionally defined as membrane active agents which modulate the opening and closing of ion channels, change the function of membrane pumps, and activate or block membrane receptors. In electrophysiological terms, such drugs may essentially increase refractoriness of the myocardium, decrease conduction velocity through the myocardium or completely block conduction at vulnerable points, and decrease the firing rate of automatic focal discharges. But a potentially valuable combination of these effects may only be achieved at appropriate concentrations in damaged tissue, with normal electrolyte and acid–base balance, and at certain underlying heart rates. In less favorable circumstances, for example, at the wrong concentration, in less abnormal tissue, at slower heart rates, or in a different milieu, the drug may not only fail to be antiarrhythmic but may also be proarrhythmic. Theoretically, an ideal anti-arrhythmic drug for AF would safely (without producing ventricular proarrhythmia) and effectively terminate and prevent the recurrence of AF in patients with and without structural heart disease, would not exert negative inotropic effect or interfere with thromboembolic prophylaxis, and would provide rate control (atrioventricular node blockade) during the recurrence of AF. Although currently available anti-arrhythmic drugs may theoretically satisfy several of these criteria, in practice, none is sufficiently effective and/or safe in the diverse settings in which AF occurs.¹

Flecainide

Flecainide has local anaesthetic effects and belongs to the class 1C AADs that block sodium channels, thereby slowing conduction through the heart. It selectively increases anterograde and retrograde accessory pathway refractoriness. The action of flecainide in the heart

Table 1:		Sumi	Summary of Kandomized Trials Comparing Knythm and Kate Control.								
Study	# Pat	Follow- up years	primary end point	Difference in primary endpoint RhyC vs RC	ACM RhyC vs RC	TE RhyC vs RC	CHF RhyC vs RC	Hospitalization RhyC vs RC	QoL RhyC vs RC		
PIAF, 2000⁴	252	1	Symptom improvement	Symptoms improved in 70 vs 76 pts (p=0.317)	Not assessed	Not assessed	Not assessed	69% vs 24% (p=0.001)	No difference		
STAF, 2003⁵	200	1.6	ACM, CV events, CPR, TE	5.54%/yr vs 6.09%/yr (p=0.99)	2.5%/yr vs 4.9%/yr	3.1%/yr vs 0.6%/yr	Better with RC	54% vs 26% (p <0.001)	No difference		
Hot-Café, 2004 ⁶	205	1.7	ACM, TE, bleeding	No difference (OR, 1.98; 95% Cl, 0.28-22.3; p >0.71)	3 (2.9%) vs 1 (1%)	3 (2.9%) vs 1 (1%)	No difference	74% vs 12% (p <0.001)	Not reported		
RACE, 2002 ⁷	522	2.3	CV death, hospitaliza- tion for CHF, TE, bleed- ing, pacemaker, AAD adverse effects	22.6% vs 17.2% (HR, 0.73; 90% Cl, 0.53-1.01; p=0.11)	6.8% vs 7%	7.9% vs 5.5% RhyC vs RC	4.5% vs 3.5%	More in RhyC	No differ- ence		
AFFIRM, 2002 ⁸	4060	3.5	ACM	23.8% vs 21.3% (HR, 1.15; 95% Cl, 0.99-1.34; p=0.08)	As above	Stroke: 7.1% vs 5.5% (p=0.79)	2.7% vs 2.1% (p=0.58)	80% vs 73% (p <0.001)	No difference		
AF-CHF, 2008º	1376	3.1	CV mortality	27% vs 25% (HR, 1.06; 95% Cl, 0.86-1.3; p=0.59)	32% vs 33% (p=0.68)	3% vs 4% (p=0.32)	28% vs 31% (p=0.17)	46% vs 39% (p=0.0063)	Not yet available		
CRRAFT, 2004 ¹⁰	144	1	Clinical improvement	Significant improvement with RhyC	0 vs 5 (p=0.023)	1 vs 0	Functional class improved in 60% vs 17.5% (p=0.0014)	8.9% vs 15% (p=0.51)	Improved in 86.7% vs 50% (p=0.033)		
J-RHYTHM, 2009 ¹¹	823	1.6	ACM, TE, bleeding, hospitalization for CHF, adverse effects	15.3% vs 22% (p=0.0128)	4 (1%) vs 3 (0.7%)	2.39% vs 2.97%	0.5% vs 1.5%	Not reported	Better with RhyC		

prolongs the PR interval and widens the QRS complex. The effect on the JT interval is insignificant as flecainide does not lengthen ventricular repolarization.^{13,14}

Because of its electrophysiological properties, flecainide is safe and effective for termination of AF in patients with Wolff Parkinson White (WPW) syndrome. By reducing the conduction over the accessory pathway, flecainide blocks conduction and slows the ventricular rate. Flecainide infusion during AF in WPW patients is extremely safe and in addition to rate slowing, flecainide eventually converts AF to sinus rhythm.¹

Propafenone

Propafenone is a class Ic antiarrhythmic agent. It is a potent sodium channel blocker and substantial beta-adrenoceptor blocking activity at clinical doses. In addition it prolongs APD (class 3) in all cardiac tissues. It seems doubtful, however, whether any calcium antagonist action could contribute substantially to the effects of propafenone in the range of concentrations observed clinically.¹⁶ It has high bioavailability after oral administration (>95%) with > 95% of it is protein bond. It has extensive first pass hepatic metabolism in to two relatively active metabolites through the cytochrome P450 to 5-hydroxypropafenone and non-cytochrome P450 to N-desalkylpropafenone.^{17,18,19}

Propafenone was used since long time in the treatment of different types of arrhythmias including malignant ventricular arrhythmias and atrial fibrillation. But because of its potential proarrhythmic and increase cardiovascular mortality in patients with cardiomyopathies and heart failure as it was shown in CAST study,^{20,21} it is not recommended to be used in such patients.

Ibutilide

Ilbutilide is an intravenous selective class III anti-arrhythmic agent. It is approved by the FDA for conversion of new onset atrial fibrillation. It needs to be given as rapid intravenous bolous or continuous intravenous infusion because of its unique pharmacokinetic properties as it has high plasma clearance rate that approximate the hepatic blood flow with a triexponential course. there is no oral formula for it because of low bioavailability for its extensive hepatic metabolism and needs to be given as intravenous infusion. In patients with low left ventricular ejection fraction, ibutilide had no effect on the cardiac output, mean pulmonary artery pressure or pulmonary capillary wedge pressure. It prolongs the QT-interval but has no effect on the heart rate, blood pressure or QRS duration.²²

Dofetilide

Dofetilide Is a pure potassium channel blocking class III antiarrhythmic agent. It is a selective blocker of the rapid component of the outward delayed rectifier IKr channel which is responsible for terminal repolarization. It was approved for use in atrial fibrillation in United States in 2000. Dofetilide is well absorbed after oral administration, with an absolute bioavailability of 90%. It has 70%-80% renal elimination therefore it needs dose adjustment according to creatinine clearance. Dofetilide has no effect on PR, QRS, or HV intervals. The QT interval and the functional and effective refractory periods of atrial and ventricular muscle are prolonged in a dose dependent fashion. Dofetilide mainly used for maintenance of sinus rhythm and was demonstrated to be safe in patients with left ventricular systolic dysfunction and myocardial infarction.²³

Amiodarone

Amiodarone is a class III antiarrhythmic drug and it has a complex profile of actions on the electrophysiological properties of the cardiac cells and has electrophysiological properties of all the antiarrhythmic classes. Its acute effect includes inhibition of both inward Na and Ca currents resulting in suppression of excitability and conductivity in both INa - and ICa-dependent cardiac tissues and outward IK (IKr and IKs), IK,ACh and IK,Na currents which is more complex to understand. Because of this complex action, its effect on action potential duration is variable depending on its predominant inhibitory action whether on the inward or outward current.²⁴

Amiodarone is a lipophilic compound with a large volume of distribution (66 liters per kilogram of body weight). This property results in a delayed onset of action (an interval of 2 to 3 days). It is metabolized to desethylamiodarone in the liver, and has no clinically significant renal metabolism, and the dose is not affected by renal dysfunction or dialysis.²⁵ Amiodarone crosses the placenta in pregnant women and is excreted in varying amounts in breast milk,²⁶ therefore it is not recommended to be given during pregnancy or breast feeding.

Dronedarone

Dronedarone is a new anti-arrhythmic agent that is used for

Table 2:	Table 2: Randomized Contro			ol Trials on Flecainide Compared with Placebo and Other AADs.			
Study	No. of patients	Onset of AF	Outcome	Comparison	Results		
Donovan KD et a 1992 [51]	102	72Hr	Conversion to SR	IV flecainide vs placebo (digoxin added to all di- goxin naïve patients)	67% vs 35% (6 h); p =0.003		
Capucci A et al 1992 [52]	62	Up to 1 Wk	Conversion to SR	 1) Flecainide vs amioda- rone vs placebo 2) Flecainide vs amio- darone 	1) 91% vs 37% vs 48% (8 h); p < 0.01. 2) 95% vs 89% (24 h); p = insignificant; conversion time was shorter for flecainide		
Donovan KD et al 1995 [53]	95	72Hr	Conversion to SR	IV flecainide vs IV amio- darone vs placebo	59% vs 34% vs 22% (2 h); p < 0.007		
Martinez-Marcos FJ et al [54]	150	48Hr	Conversion to SR	IV flecainide vs IV propafenone vs IV amio- darone	90% vs 72% vs 64% (12 h); p=0.008 for the overall comparison, p < 0.002 for flecainide vs amiodarone, p < 0.022 for flecainide vs propafenone, and p = 0.39 for propafenone vs amiodarone		
Romano S et al/2001 [55]	352	N/A	Conversion to SR	Propafenone vs flecainide vs placebo	92.1% vs 89.8% vs 46.3% (24 h); p < 0.05 (drug vs placebo), P=NS (drug vs. drug)		

conversion of paroxysmal or persistent AF to sinus rhythm or maintenance of sinus rhythm. It is one of the amiodarone derivatives devoid of the iodine which is present in amiodarone and responsible for several of its non-cardiac toxic effects on the thyroid, lungs and liver. A methylsulfonamide group added to it to make it less lipophilic to reduce its neurotoxic effect.²⁷

Dronedarone primarily is class III anti-arrhythmic agent but it has electrophysiological properties of all 4 Vaughan-Williams antiarrhythmic classes.²⁸ In experimental studies, using the whole-cell patch-clamp technique applied to human atrial myocytes, dronedarone inhibited transmembrane potassium currents: ultrarapid-delayed rectifier (IKur), delayed rectifier (IKs and IKr), transient outward (Ito), and inward rectifier (IK1).²⁹

Dronedarone is largely metabolized by the hepatic enzyme cytochrome P450 3A4 isoform (CYP3A4). Only 6% of dronedarone is excreted renally; however, no trial has yet assessed its safety in patients with marked kidney dysfunction.³⁰

It was approved by the US Food and Drug Administration (FDA) in July 2009 for treatment of paroxysmal or persistent AF. It is available only for oral administration at 400 mg twice daily and dose adjustment or titration is not recommended.

Vernakalant (RSD1235)

Table 3:

Vernakalant, 3-pyrrolidinol, 1-[(1R,2R)-2-[2-(3,4dimethoxyphenyl) ethoxy] cyclohexyl]-, hydrochloride (3R)-, is a chemical entity that has been demonstrated to block multiple ionic channels in various atrial tissue models. Atrial and ventricular action potentials currents are not similar. The dominant underlying channels of the ionic currents responsible for generating atrial repolarization differ from the primary underlying channels of the ionic currents causing ventricular repolarization. Kv1.5 channels underlie the ultrarapid delayed rectifier potassium current (IKur), and Kv4.3 channels underlie the transient outward repolarizing potassium current (Ito). The IKur and Ito currents contribute primarily to early atrial repolarization and do not significantly affect ventricular repolarization. Moreover, an atrial-tissue-specific acetylcholineactivated potassium channel (IKACh) has been demonstrated to shorten phase 2 of the atrial action potential and thereby cause earlier termination of atrial repolarization.

In contrast, the late repolarizing delayed rectifier currents (IKr, IKs), with underlying hERG channels, have a much greater role in ventricular repolarization but contribute less to atrial repolarization.^{31,32,33} Vernakalant has a predilection for blocking atrial-specific potassium channels and atrial rate and voltage-dependent sodium-channel blocking properties. Vernakalant is able to selectively affect the atrium because it targets 2 channels that are mainly found in the atria and not in the ventricles. The first is the Kv1.5 channel, which carries the ultra rapid delayed rectifier potassium current (IKur). The second is the Kir3.1/ 3.4 channel, which carries the acetylcholine dependent potassium current (IKACh).³⁴

Ranolazine

Ranolazine is an anti-anginal agent, which inhibits normal and abnormal late Na+ channel currents in the ventricle and peak Na+ channel current in the atrium.^{35,36} By this inhibition, it affects intracellular calcium handling producing an energy sparing effect.³⁸ Ranolazine has also been shown to be a potent inhibitor of after depolarizations produced by a number of mechanisms.³⁷ With this mechanism of action it can be a useful agent in the treatment of

Study	No. of patients	AF onset	outcome	Comparison	results
Capucci A et al 1994 [56]	87	<8 days	Conversion to SR	Oral Propafenone vs IV digoxine=quinidine vs placebo	(62% vs. 17%, 83% vs. 34%; 86% vs. 55%; P < 0.01. 6 h (62% vs. 38%; P < 0.05) dig. 12 h (83% vs. 48%; P < 0.05 dig+quin
Bellandi F et al, 1995 [57]	182		Conversion to SR	IV Propafenone vs IV placebo	90.9% vs 32.1% , P<0.0005.
Boriani G et al 1995 [58]	87	<7 days	Conversion to SR	I.V. propafenone vs oral propafenone vs placebo	66% vs 69% vs 24% (8 h); p < 0.005
Botto GL et al, 1996 [59]	283	<72 hours	Conversion to SR	Oral propafenone vs digoxine and placebo.	57% vs 25%, P<0.001
Fesco et al 1996 [60]	75	<72 Hr	Conversion to SR	IV propafenone vs placebo	58.5% vs 29.4% (within 3 h or until conversion occurred); p < 0.01
Azpitarte et al 1997 [61]	55	<7 days	Conversion to SR	Oral propafenone vs placebo	41% vs 8% (2h) p=0.005. 65% vs 31% (6h) P=0.015
Boriani G et al, 1997 [62]	240		Conversion to SR	Oral propafenone vs placebo	45% vs 18%, P<0.001 (3he).
Bianconi L et al, 1998 [63]	123	<72 hours	Conversion to SR	I.V. propafenone vs I.V. digoxine vs placebo.	50% vs 25%, P<0.01
Botto et al/1998 [64]	123	<72 h	Conversion to SR	IV propafenone vs oral propafenone vs placebo	53% vs 78% vs 48% (8 h); p < 0.03
Ganau et al/1998 [65]	156	<72 h	Conversion to SR	IV propafenone vs placebo	70.3% vs 17.3% (2 h); p < 0.001
Kochiadakis et al/1998 [66]	143	<48 h	Conversion to SR	IV propafenone vs IV amiodarone vs placebo (digoxin added to all digoxin- naive patients)	78.2% vs 83.3% vs 55.1% (within 1 h); p < 0.02 (drug vs placebo)
Blanc JJ et al/1999 [67]	86	<2 weeks	Conversion to SR	Oral propafenone vs oral amiodarone	56% vs 47% (24 h); p = non significant
Romano S et al/2001 [55]	352	N/A	Conversion to SR	Propafenone vs flecainide vs placebo	92.1% vs 89.8% vs 46.3% (24 h); p < 0.05 (drug vs placebo)

Summary of Randomized Trials of Propafenone in New Onset Atrial Fibrillation.

AF. The holter monitor data from the MERLIN trial, showed that ranolazine was associated with a reduction in a number or several arrhythmias, including new episodes of AF.³⁸ On January 31, 2006, ranolazine was approved for use in the United States by the FDA for the treatment of chronic angina pectoris. It is not approved for use in atrial fibrillation because no large randomized trials on its efficacy and safety in atrial fibrillation.

Antazoline

Antazoline is a first generation antihistaminic agent with chinidine-like and anticholinergic properties. Antazoline prolongs action potential duration and lowers its amplitude, prolongs phase 0 duration, reduces phase 4 of resting potential and reduces excitability of cardiac tissue.³⁹ Clinically, antazoline lowers the velocity of intraatrial conduction, prolongs the atrial refraction period and may improve atrioventricular conduction allowing fast ventricular response to supraventricular arrhythmias.⁴⁰ The half-life of antazoline is considered to be about three hours with antiarrhythmic efficacy expiring after about one hour.41 antazoline has been used in clinical practice in Poland for many years due to its efficacy, safety and rapid onset of action within minutes of administration.^{41,42} According to the Summary of Product Characteristics, antazoline is indicated in the treatment of paroxysmal supraventricular tachyarrhythmias including AF and should be administered intravenously in a cumulative dose of 100 to 300 mg during 3 to 10 minutes under strict monitoring of ECG and arterial blood pressure and interrupted after conversion to SR.43,44

Methods

Data Collection

We searched the internet for all clinical, experimental and randomized trials, meta-analyses and the review articles that studied the anti-arrhythmic drug management of atrial fibrillation since 1960 till the writing of this article by using the pub med, Medline and Google search. Using the key words of "atrial fibrillation, antiarrhythmic agents, new onset, conversion, and sinus rhythm", all the published papers that studied the issue of anti-arrhythmic agents in atrial fibrillation were included in this review.

Data Interpretation

We selected five drugs used before or still currently in use for management of atrial fibrillation (fecainide, propafenone, dofetelide, ibutelide and amiodarone). In addition all the newly emerging and investigational agents were also included in this review. All the clinical and randomized placebo and active controlled trials about each selected antiarrhythic agent used in the treatment of AF were included and their results were analysed separately for each selected agent. After the analysis of the results of RCT for each anti-arrhythmic agent in addition to any published meta-analysis concerning the same agents with the support of previous review articles, for each agent discussed to reach a conclusion for its role in AF management and to compare it with the most recent guideline recommendation for its use in AF.

Results

Digoxin

Several randomized trials studied digoxin in acute AF and compared it to placebo for its role in acute cardioversion. But no one of

them showed significant cardioversion effect for it in acute AF.45,46 Jordaens et al,47 studied the cardioversion effect of I.V. digoxin in comparison to placebo in acute AF (less than 7 days duration) and after 12 hours there was no significant difference in conversion to sinus rhythm between the digoxin and placebo-treated groups (47.4% vs 40%, respectively). DAAF trial which was a large RCT studied 239 patients with recent onset AF (less than 7 days) and compared I.V. digoxin to placebo,48 showed that acute atrial fibrillation has a high rate of spontaneous conversion to sinus rhythm within 16 h and at 16 h follow-up there was no difference in the restoration of sinus rhythm between the two groups (51% digoxin vs 46% placebo; p = 0.37). However, a significant reduction in ventricular rate was observed in the digoxin treated group at 2 h post therapy (105 beats/ min digoxin vs 117 beats/min placebo; p = 0.0001). An interesting finding was reached by Sticherling C et al ,49 that digoxin not only is not effective in conversion of AF to sinus rhythm but also potentiates the shortening of atrial ERP and predispose toward further episodes of AF that occurs after a short episode of AF and it may facilitate or promote early recurrences of AF after conversion to sinus rhythm not only in patients with vagotonic AF but also among the general population of patients with AF.

Flecainide

Randomized controlled trials that studied flecainide and compared its efficacy in converting new onset AF to sinus rhythm to placebo and/or other AADs have confirmed its effectiveness in cardioversion of acute or new onset loan AF (Table 2).⁵⁰ These trials showed that flecainide was more effective in converting atrial fibrillation to sinus rhythm compared with placebo^{51,52,53,55} and in comparison to amiodarone, conversion rate of flecainide was significantly higher and conversion time was significantly shorter for flecainide compared with amiodarone.^{5,53}

Patients with coronary artery disease, cardiomyopathy, and hemodynamic instability were excluded from these trials. This exclusion was decided because of the consistent results of the Cardiac Arrhythmia Suppression Trial (CAST) study, which showed that encainide/ flecainide increased proarrhythmia risk and mortality in patients with coronary artery disease.^{20,21}

Propafenone

Because of its favorable pharmacokinetics, single oral dose administration and its effectiveness in the conversion of acute or new onset AF was studied in several randomized trials (table 3).^{56,57,68,59,60,61,62} Oral propafenone as compared to placebo was more effective and had significantly higher conversion rate and this difference was clearly significant even in the first 1-3 hours after oral administration of propafenone.^{61,62} Propafenone as oral administration was also compared with other AAD, a study done by Blanc JJ et al⁶⁷ showed that the median time for restoration of sinus rhythm was shorter in the propafenone than in the amiodarone group (2.4 hours vs. 6.9 hours, p = 0.05), while there was no significant difference in the conversion rate between both drugs after 24 hours (56% in the propofenone and 47% in the amiodarone group). On the other hand oral propafenone shown to be superior to oral digoxine and quinidine in converting new onset AF to sinus rhythm.^{56,59}

One study included patients with structural heart disease and compared oral propafenone to placebo conducted by Boriani G et

Table 4:

Summary of Randomized Trials of Ibutilide in New Onset Atrial Fibrillation.

Study	No. of patients	Onset of AF	Endpoint	Comparison	Results
Stambler BS et al, 1996 [68]	266	< 2 weeks	Conversion to SR	lbutilide 1.0 mg/0.5 mg. ibutilide, 1.0 mg/1.0 mg Placebo.	Drug/placebo: 47% vs. 22%, P<0.001. Drug/drug: insignificant (P=0.57). Flutter 63% > fibrillation 31%, P<0.001.
				Ibutilide vs, placebo	Conversion rate: 48% vs. 15%, P<0.0001(1.5 Hr).
VanderLugt JT et al 1999 [69]	302	>7days	Conversion to SR	lbutilide (0.25 mg vs. 0.5 mg vs. 1.0 mg)	40% vs. 47 vs. 57 %, P<0.0001
Bernard EO et al, 2003 [70]	40	3 hr	Conversion to SR	Ibutilide vs. amiodarone	45% vs. 50%
Kafkas NV et al, 2007 [71]	152	3-48 hr	Conversion to SR	Ibutilide vs. amiodarone	$ \begin{array}{l} (80\% \ vs. \ 57\%, \ p = 0.0054). \\ AF: (77\% \ vs. \ 69\%, \ p = ns). \\ AFI: (87\% \ vs. \ 29\%, \ p = 0.003). \end{array} $
Reisinger J et al, 2004 [72]	207	1-48 hr	Conversion to SR	Ibutilide vs. flecainde	50% vs. 56.4%, P=0.34.
Vos MA et al, 1998 [73]	319		Conversion to SR	lbutilide 1 mg vs. 2 mg vs. sotalol	AFI: high dose=low dose (P=0.4). both doses > sotalol (70% and 56% vs. 19%) (P<0.05). AF: high dose > low dose (44% vs. 20%, p < 0.01). High dose > sotalol (44% vs. 11%). Low dose = sotalol.
Volgman AS et al, 1998 [74]	127	3 he-90 days	Conversion to SR	Ibutilide vs. procainamide	58% vs. 18%, P<0.0001. AFI: (76% vs. 14%, p<0.0001). AF: (51% vs. 21%, p<0.005)

al,⁵⁸ showed that oral loading of propafenone was more effective than placebo for conversion to sinus rhythm within 8 hours and had a favorable safety profile and the rate of spontaneous conversion to sinus rhythm was higher in patients without structural heart disease.

Propafenone as I.V. administration is also effective and safe in conversion of new onset atrial fibrillation. A study by Bellandi F et al,⁵⁷ is a randomized placebo controlled trial showed that I.V. propafenone has a high conversion rate in acute or new onset AF (90.9%) as compared to placebo (32.1%) (P<0.0005). In nonresponders to propafenone the duration of AF before trial of conversion was significantly longer (62.26 ±38.22 h vs. 23.42 ±17.96 h, p <0.0005) and the LA size was significantly larger (47.56 ±4.39 vs. 41.64 ±3.3 mm, p < O.OOOS) than in responders. Boriani et al ,58 conducted a study to compare oral and I.V. propafenone to placebo in converting recent onset AF (<7 days) and showed that both ways of propafenone administration are significantly superior to placebo in conversion of AF to sinus rhythm, but at the same time oral propafenone is as effective as intravenous propafenone and at 8 hours there was no difference in the conversion rate between both ways of administration. Paroxysmal Atrial Fibrillation Italian Trial (PAFIT) 2 59 compared intravenous propafenone to placebo in patients with paroxysmal AF and normal heart showed that after 3 hours the conversion rate in the I.V. propafenone group was significantly higher than the placebo group (58.5% vs 29.4% p < 0.01).

Two studies compared propafenone to amiodarone,^{66,67} one of them compared the I.V. administration of both drugs in new onset AF with duration of less than 48 hours and this study used the high dose amiodarone regimen (2100 mg/day). The results of this study showed no significant difference in the conversion rate between both drugs (78.2% vs. 83.3, P=NS), but the mean time to conversion to sinus rhythm was significantly shorter in propafenone group (2±3 hours) than amiodarone group (7±5 hours) (P<0.05).⁶⁶ Blanc JJ et al,⁶⁷ compared oral propafenone to oral amiodarone and showed no significant difference in the conversion rate after 24 hours between both drugs (56% vs 47%; p = non significant).

Ibutilide

Conversion Efficacy

Several randomized trials compared ibutilide to placebo and other anti-arrhythmic drugs (Table 4). A prospective double-blind, placebo-controlled, randomized, dose-response, multicenter trial conducted by Stambler BS et al,68 randomized 266 patients with new onset atrial fibrillation/ flutter into three groups (placebo, 1.0 mg/0.5 mg ibutilide, or 1.0 mg/1.0 mg ibutilide) with a primary endpoint of conversion to sinus rhythm within 1.5 hour. The overall cumulative conversion rate was 47% after two infusions of ibutilide and 2% after placebo. Paired comparisons indicated highly significant differences (both P<.0001) between placebo (2%) and the 1.0 mg/0.5 mg (44%) and the 1.0 mg/1.0 mg (49%) ibutilide doses. There was no significant difference (P=0.57) in the success rates between the 1.0 mg/0.5 mg and the 1.0 mg/1.0 mg ibutilide doses. The conversion rate after two infusions of ibutilide was significantly higher for atrial flutter (63%) than for atrial fibrillation (31%) (P<0.0001) even after adjustment for the arrhythmia duration, percentage of valvular heart disease, ejection fraction and left atrial size. VanderLugt JTet al⁶⁹ conducted a placebo controlled randomized trial on 302 post-operative patients who developed atrial fibrillation/flutter 1-7 days after cardiac surgery and randomized them to placebo or 0.25 mg, 0.5 mg, or 1 mg I.V. ibutilide. After 1.5 hours the conversion rate was significantly higher with ibutilide than placebo (48% vs. 15%, P<0.0001) and the conversion rate in 1.0mg ibutilide group was also significantly higher than the other two ibutilide groups. The conversion rate of atrial flutter was significantly higher that atrial fibrillation at 1.0mg ibutilide (78% vs. 44%).

Trials that compared ibutilide to other anti-arrhythmic drugs showed that ibutilide is not superior to amiodarone in conversion of atrial fibrillation in means of both conversion time and conversion rate (45% vs. 50%),⁷⁰while Kafkas NV et al⁷¹ found that ibutilide is superior to amiodarone in conversion atrial flutter than amiodarone (87% vs. 29%, p = 0.003), but there was no significant difference in the state of atrial fibrillation (77% vs. 69%, p = ns).

Reisinger J et al compared ibutilide to flecainide and did not show superiority for ibutilide over flecainide (50% vs. 56.4%, P=0.34.⁷² A study conducted by Vos MA et al compared ibutlide to sotaltol, showed that ibutilide is superior to sotalol in converting atrial flatter to sinus rhythm at both low and high dose, but in case of atrial fibrillation high dose ibutilide was superior to both low dose ibutilide and sotalol while low dose ibutilide was not superior to sotalol.⁷³ The conversion time for ibutilide was significantly shorter than sotalol. A randomized trial compared ibutilide to procainamide and showed that ibutilide is superior to procainamide in converting both AF and AFI to sinus rhythm.⁷⁴ significantly (P<.0001) prolonged from baseline in the ibutilidetreated patients and also significantly more than the placebo group, but the QRS duration was not altered significantly across dose groups from baseline to minute 30. Polymorphic ventricular tachycardia developed in 8.3% of ibutilide-treated patients and in no placebotreated patients. There was no significant change in the systolic blood pressure from the baseline or the placebo group. There was a consistent and statistically significant (P=.0094) decrease in heart rate in both ibutilide dose groups compared with placebo. This decrease in heart rate was most likely due to termination of the arrhythmia because in patients who did not convert, a statistically significant decrease in heart rate was not seen.68 VanderLugt JT et al in his study found that there was a statistically significant prolongation in the QT and QTc intervals in the ibutilide group in comparison to baseline and the magnitude of QT prolongation was proportional to the ibutilide dose. There was no significant effect on the blood pressure and the drop in heart rate was related to the conversion to sinus rhythm.⁶⁹ Also there was no significant difference in the proarrhythmic side effect with Ibutilide in comparison to flecainide or amiodarone.^{68,69}

Safety

In Stambler BS et al study the QT and QTc intervals were

Table 5: Summary of Randomized Trials of Dofetilide in Atrial Fibrillation. Onset of AF Results Study No. of patients Endpoint Comparison 30.3% vs. 3.3%. P<0.006. I.V. dofetilide 8 mcg/kg Nørgaard BL et al, 1999 [75] 96 1-180 days Conversion to SR AFI>AF, 64% vs. 24%, P<0.012 vs. placebo I.V. dofetilide 8 mcg/kg, Frost L et al. 1997 [76] 98 1-6 davs Conversion to SR After 3 hr: 44% vs. 36% vs. 24%. P=insignificant. 4mcg/kg vs. placebo 31% vs. 12.5% vs 0% I.V. dofetilide 8 mcg/kg, Falk RH et al. 1997 [77] 91 Sustained AF/AFI Conversion to SR AFI>AF: (54% versus 12.5%) 4mcg/kg vs. placebo 3 hr: 35%, 4%, and 4%, P<0.001. LV dofetilide vs. LV amio-Bianconi L et al, 2000 [78] 150 2 hr-6 Mn AFI > AF (75% vs. 22%, P=0.004) darone vs. placebo Lindeboom JE et al. 2000 [79] (6.1%, 9.8%, and 29.9%) vs. 1.2%, P=0.015 and dofetilide (1250mcg. P<0.001. Conversion to SR. SR at 1 yr (0.40, 0.37, 0.58) vs. 0.25, (500 mcg vs. Singh S et al, (SAFIRE-D) 2000 [80] 325 Persistent AF/AFI 250 mcg, 500 mcg) vs. SR at 1 vr. placebo, P < 0.001). placebo dofetilide (1250mcg. Conversion to SR (5.9%, 10.5%, and 29.5%) vs. 5.1% vs. 1.5% Greenbaum RE et al (EMERALD) 1998 250 mcg, 500 mcg) BID 546 Persistent AF/AFI SR at 1 vr SR at 1 yr: (30%, 45%, and 51%) vs. 38% vs. 16%. [81] vs. Sotalol 80 BID vs. placebo 59% vs. 34%. Conversion to SR SR at 1 year: 79% vs. 42%, P<0.001. Reduced Pedersen OD et al, (DIAMOND AF) 506 Persistent AF/AFI SR at 1 yr. dofetilide vs. placebo hospitalizations for worsening of heart failure (29% 2001 [82] vs. 40%) At 1 vr: 61% vs. 33%. P<0.001 No effect on mortality. Torp-Pedersen CT et al (DIAMOND-CHF), 1518 NA dofetilide vs. placebo Reduced hospitalizations for worsening of heart SR at 1 yr 2000 [83] failure HR 0.75 (0.63-0.89). At 1 yr: survival 79% vs 77%. Hospitalizations for DIAMOND-MI, 1997 [84] 1510 NA SR at 1 vr dofetilide vs. placebo worsening of heart failure 27% for each Jun-Jul, 2013 | Vol-6 | Issue-1 www.jafib.com

Dofetilide

Featured Review

Table 5 summarizes the randomized trials of dofetilide in atrial fibrillation. Small trials that compared I.V. dofetilide to placebo in new onset atrial fibrillation showed that the conversion rate of dofetilide is significantly higher than placebo and it is more effective in conversion of atrial flutter than fibrillation.^{75,76,77} Bianconi L et al⁷⁸ compared the conversion rate of I.V. dofetilide to I.V. amiodarone in new onset atrial fibrillation andflutter and reported that after 3 hr dofetilide is superior to amiodarone and placebo in converting Af/AF1 to sinus rhythm (35%, 4%, and 4%, P<0.001) and the conversion rate of atrial flutter is significantly higher than that of atrial fibrillation (75% vs. 22%, P=0.004). Two trials were large placebo controlled double blind and studied the efficacy of dofetilide in persistent AF.^{80,84} SAFIRE-D trial 80 enrolled 325 patients with persistent atrial fibrillation and randomized them to either placebo or dofetilide (125 mg BID, 250 mg BID, and 500 mg BID). During the initial phase, pharmacological cardioversion occurred in 1.2%, 6.1%, 9.8%, and 29.9% of patients in the placebo, 125 mg BID, 250 mg BID and 500 mg BID groups, respectively. Dofetilide 500 mg BID was superior to placebo in maintaining sinus rhythm at 6 and

12 months (62% and 58% vs. 37% and 25%, P<0.001). The lower doses of dofetilide did not show a statistically significant difference from placebo. The European and Australian Multicenter Evaluative Research on Atrial Fibrillation Dofetilide (EMERALD) study was a randomized, double-blind, placebo-controlled trial in patients with persistent atrial fibrillation.⁸¹ As in SAFIRE-D, there was both a conversion phase and a maintenance phase. Five hundred forty-six patients were randomized to receive either placebo, 1 of 3 doses of dofetilide (125, 250, or 500 mg BID), or sotalol 80 mg BID. Pharmacological conversion was noted in 5.9%, 10.5%, and 29.5% of patients on the 3 ascending doses of dofetilide, in 5.1% of those randomized to sotalol, and in 1.5% of the placebo group. Between 76% and 90% of patients in the 5 groups achieved sinus rhythm after either pharmacological or electrical cardioversion and entered the maintenance portion of the study. At 1 year, 30%, 45%, and 51% of the 125 mg BID, 250 mg BID, and 500 mg BID dofetilide groups, 38% of the sotalol group, and 16% of the placebo group remained in sinus rhythm. All of the active drug groups were statistically different from placebo. The DIAMOND studies were big randomized studies

Table 6:		Summary of Randomized Trials of Amiodarone in Atrial Fibrillation.					
Study	No. of patients	AF onset	Amiodarone dose	outcome	Comparison	results	
Cowan et al, 1986 [86]	34	<48 h compli- cating MI	1500 mg	Conversion to SR	Amiodarone Digoxin	A: 83 D: 75	
Noc M et al, 1990 [87]	24	< 2 days	350 mg		Amiodarone vs. Verapamil	77% vs. 0, P<0.05	
Capucci A et al 1992 [52]	62	Up to 1 Wk	2150 mg	Conversion to SR	 Flecainide vs amiodarone vs placebo Flecainide vs amiodarone. 	1) 91% vs 37% vs 48% (8 h); p < 0.01. 2) 95% vs 89% (24 h); p = insignificant; conversion time was shorter for flecainide.	
Donovan KD et al 1995 [53]	95	72Hr	490 mg	Conversion to SR	IV flecainide vs IV amiodarone vs placebo	59% vs 34% vs 22% (2 h); p = 0.007	
Hou et al/1995 [88]	50	<10 days	1620 mg	Conversion to SR	IV amiodarone vs IV digoxin	92% vs $71%$ (within 24 h; apparent difference seen in first hour); $p=0.0048$	
Galve E et al 1996 [89]	100	< 72h	1550 mg	Conversion to SR	I.V. amiodarone vs placebo	68% vs 60%, P=0.532 (after 24h)	
Kochiadakis GE et al/1998 [66]	143	<48 h	3500 mg	Conversion to SR	IV propafenone vs IV amiodarone vs placebo (digoxin added to all digoxin- naive patients)	78.2% vs 83.3% vs 55.1% (within 1 h); p < 0.02 (drug vs placebo	
Cotter G et al 1999 [90]	100	<48 h	3000 mg	Conversion to SR	I.V. amiodarone vs placebo	62% vs 58% (8 h). 92% vs 64%, P<0.0017 (24 h)	
Peuhkurinen et al/2000 [91]	62	<48 h		Conversion to SR	Oral amiodarone vs placebo	87% vs 35% (24 h); p < 0.0001	
Joseph et al/2000 [92]	120	<24 h	1150 mg	Conversion to SR	Active treatment (amiodarone/so- talol) vs control group (digoxin) Amiodarone vs sotalol	95% vs 78% (48 h); p < 0.05 No significant difference	
Vardas PE et al 2000 [93]	208		2300 mg	Conversion to SR	Amiodarone vs placebo.	38% vs 25%, P<0.05 (after 1 h). 61.1% vs 40%, P< 0.001 (after 24 h).	
Hilleman et al/2002 [94]	Metaanalys	is <7 days	NA	Conversion to SR	Amiodarone vs placebo. Amiodarone vs other AAD.	Pooled cohort estimates: 82.4% vs 59.7%; p = 0.03 72.1% vs 71.9%; p = 0.84	
Thomas et al/2004 [95]	140	N/A	1200 mg	Conversion to SR	IV sotalol vs IV amiodarone vs IV digoxin	44% vs 51% vs 55% (12 h); p = nonsignificant	
Boriani et al, 1998 [96]	417	<7 days	2150 mg	Conversion to SR	I.V. amiodarone vs oral fecainide vs I.V. propafenone vs oral propafenone vs placebo		
Hofmann et al/2006 [97]	100	N/A	750 mg	Conversion to SR	IV amiodarone vs IV digoxin	42% vs 18% (1 h); p = 0.012	

to assess the safety of dofetilide in patients with left ventricular dysfunction, one was conducted on patients with left ventricular dysfunction and NYHA class II-IV heart failure (DIAMOND-CHF) and the other one done on patients with recent myocardial

infarction and left ventricular dysfunction (DIAMOND-MI).⁸⁴ There were 506 patients with persistent atrial fibrillation at study entry to the DIAMOND studies.⁸⁴ A sub-study conducted by Pedersen OD et al⁸² that included these patients randomized them

Та	Table 7: Summary of Randomized Trials of Dronidarone in Atrial Fibrillation.							
Study	Number of patients	Patient characteristics	Dose of dronedarone	Placebo controlled	Primary endpoint	Follow-up, months	Outcome	Comments
DAFNE 2003 [98]	270	Post-cardiover- sion	400 mg b.i.d. 600 mg b.i.d. 800 mg b.i.d.	Yes	Time to first AF recurrence	6	Dronedarone 400 mg b.i.d. significantly prolonged median time to first AF recurrence vs. placebo: 60 vs. 5.3 days, P = 0.026); rela- tive risk reduction 55% (95% Cl, 28–72% P = 0.001)	Higher doses were ineffective and were associated with discontinuation rates of 7.6 and 22.6%; conversion rates were 5.8, 8.2, and 14.8% vs. 3.1% on placebo
EURIDIS. 2007 [99]	615	Post-cardiover- sion	400 mg b.i.d	Yes	Time to first AF recurrence	12	Median time to first AF recur- rence was 41 days on droneda- rone vs. 96 days on placebo, P < 0.01	Ventricular rates during AF recurrence were significantly lower on dronedarone
ADONIS 2007 [99]	630	Post-cardiover- sion	400 mg b.i.d	Yes	Time to first AF recurrence	12	Median time to first AF recur- rence was 59 days on droneda- rone vs. 158 days on placebo, P = 0.002	Dronedarone reduced ventricular rates during AF recurrence vs
EURIDIS / ADONIS Pooled 2007 [99]	1237	Post-cardiover- sion	400 mg b.i.d.	Yes, n = 409	All-cause mortality and hospitalizationsa	12	Dronedarone reduced the primary endpoint vs. placebo by 27% (95% Cl, 7-43%, P = 0.01)	Trend towards reduced all-cause mortality and hospitalizations from cardiac causes was ob- served with dronedarone; relative risk reduction 20%, P = 0.164
ERATO, 2008 [100]	630	Permanent AF with ventricular rates .80 b.p.m. on rate-controlling thera	400 mg b.i.d.	Yes	Mean 24-h ventricular rate at 2 weeks	1	Ventricular rates were 12 b.p.m. lower on dronedarone vs. placebo	Peak heart rates during exercise were 24 b.p.m. lower on droneda- rone vs. placebo
ANDROMEDA , 2008 [101]	627	Congestive heart failure; EF < 0.35	400 mg b.i.d.	Yes	All-cause mortal- ity or hospitalization for worsening heart failure	6	Stopped early because of increased mortality in the dronedarone arm (8 vs. 3.8% on placebo; hazard ratio 2.3)	Possible explanation for increased mortality is more frequent discontinuation of ACE inhibitors in the dronedarone arm secondary to an increase in plasma creatinine
ATHENA, 2009 [102	4628	Paroxysmal or persistent AF with risk factors	400 mg b.i.d.	Yes	All-cause mortality and hospitalizations for cardiac causes	21±5	Dronedarone reduced the primary endpoint vs placebo by 24% (P < 0.001)	CV hospitalizations, cardiovascular mortality, and hospitalizations for AF were reduced by 25% (P < 0.001), 29% (P = 0.034), and 37% (P < 0.001); no significant difference in all cause mortality
PALLAS, 2011 [103]	3236	Permanent AF, age≥65 yr	400 mg b.i.d.	Yes	Composite of stroke, MI, systemic embo- lism, or death from CV causes. Unplanned hospitalization for a CV cause or death.	3.5	CV Death, MI, Stroke, Sys- temic Embolism. (2% vs. 0.9%) P =0.009. Death, Unplanned CV Hospital- ization (7.5% vs. 5.1%) P 0.006. HF Hospitalization (2.2% vs. 1%) P=0.008	This trial was suspended due to an increase in CV events with dronedarone (significant increase in major cardiovascular events defined as a composite of stroke, MI, systemic embolism, or cardiovascular
Dionysos, 2009 [104]	Meta- analysis	Post-cardiover- sion	400 mg b.i.d.	Drone- darone vs. amiodarone	AF recurrence. CV death, CV hospital- ization		Amiodarone superior to droneda- rone (OR: 0.49; 95% CI: 0.37 to 0.63; p < 0.001) for the preven- tion of recurrent AF. Higher all-cause mortality (OR: 1.61; 95% CI: 0.97 to 2.68; p = 0.066) and adverse events re- quiring drug discontinuation with amiodarone than dronedarone (OR: 1.81; 95% CI: 1.33 to 2.46; p < 0.001).	

to receive dofetilide 250mg BID or placebo and followed for 1 month and assessed the efficacy of dofetilide in patients with left ventricular dysfunction and atrial flutter or fibrillation and showed that dofetilide is superior to placebo in converting AF/AF1 to sinus rhythm and maintaining sinus rhythm at 1 year. 56 of 249 (22.5%) patients taking dofetilide versus 7 of 257 (2.7%) patients receiving placebo converted to sinus rhythm. At one year 79% of dofetilide patients versus 42% of placebo-treated patients were in sinus rhythm. Dofetilide showed no effect on all-cause mortality, but restoration and maintenance of sinus rhythm was associated with significant reduction in mortality (RR, 0.44; 95% CI, 0.30 to 0.64; P<0.0001). In addition, dofetilide therapy was associated with a significantly lower risk for either all-cause (RR, 0.70; 95% CI, 0.56 to 0.89; P<0.005) or congestive heart failure rehospitalization (RR, 0.69; 95% CI, 0.51 to 0.93; P<0.02). Among those patients who were originally in sinus rhythm, the dofetilide group also had a lower incidence of new onset of atrial fibrillation (2.0% versus 10.5%, P<0.001). The DIAMOND-CHF trial was double-blind, placebo-controlled trials designed to evaluate the efficacy and safety of dofetilide in high-risk patients with congestive heart failure.83 It was mortality trial, and specific antiarrhythmic effects were not primary end points. It randomized 1518 patients with left ventricular ejection fraction < 35%. Patients were randomized to either dofetilide 500 mg BID or to matching placebo. Patients with atrial fibrillation or flutter by protocol received 250 mg BID. The mortality rate at one year was 41% in dofetilide

Table 8:	Sumr Fibril	Summary of Randomized Trials of Vernakalant in Atrial Fibrillation.							
Study	No. of patients	AF du- ration	Primary end point	Comparison	Results				
CRAFT 2004 [105]	56	<72 hr	Conversion to sinus rhythm	RSD1235 (2.0 and 3.0 mg/kg) vs RSD1235 (0.5 and 1.0 mg/kg) vs Placebo.	61% vs 11% vs 5%. RSD1235 (2.0 and 3.0 mg/kg) vs Placebo P<0.0005. RSD1235 (0.5 and 1.0 mg/kg) vs Placebo, insignificant				
ACT I 2005 [106]	356	3hr- 45days	Conversion to sinus rhythm in short dura- tion AF	Vernakalant vs Placebo	51.7% vs 4.0% (P<0.001) (< 7 days). 7.9% vs 0 P=0.09 (>7- 45 days)				
ACT II, 2009 [107]	190	24 hr-7 days after cardiac surgery	Conversion to sinus rhythm	Vernakalant vs Placebo	At 90 min: 47% vs. 14%, P<0.0001				
ACT III [108]	276	3hr- 45days	Conversion to sinus rhythm	Vernakalant vs Placebo	51.2% vs 3.6% P<0.0001 (short dura- tion) 39.8% vs 3.3% P <0.0001 (overall)				
ACT IV	167	3 h-45 days	Conversion to SR within 90 min of drug initiation	Non-placebo dose com- parison	SR: 50.9%. Median time to conver- sion 14 min.				
ACT V 2013 [109]	470	3 Hr7 days	Safety and efficacy of vernakalant	Vernakalant vs Placebo	Stopped because of reported cases of car- diogenic shock related to vernakalant				
AVRO 2011 [110]	232	3-48 Hr	Conversion to SR within 90 min of drug initiation	Vernakalant vs. amioda- rone	At 90 min: 51.7% vs 5.2% (P<0.0001). At 4 Hr: 54.4% vs. 22.6% (P<0.0001)				

group patients compared with 42% in placebo group patients (P=insignificant).

Amiodarone

The efficacy of amiodarone in converting atrial fibrillation to sinus rhythm was studied since long time in several randomized trials [Table 6]. The conversion rate of amiodarone in comparison to placebo was variable and was not always consistently superior to placebo in the placebo controlled studies. This wide range in conversion rate and inconsistent superiority of amiodarone over placebo or other AAD comes from the fact that these studies used different doses and protocols, seven published studies used low or conventional doses (<1600mg) of amiodarone (table 6),^{86,87,53,89,92,95,97} the largest of them was conducted by Galve E and colleagues,⁸⁹ in which 100 patients were randomized to amiodarone (5 mg/kg IV over 30 min, followed by 1200 mg IV over 24 hours) or saline placebo showed no difference in conversion rates at 24 hours, and similar 2-week recurrence rates (12% with amiodarone vs. 10% with placebo). Also a study done by Donovan KD et al, showed that amiodarone at a dose of 7 mg/kg had a similar conversion rate to placebo after 2 and 8 hours.⁵³

Noc M et al ,⁸⁷ showed that a bolus of 5 mg/kg of amiodarone was superior to IV verapamil at 3 hours. Cowan and coworkers studied patients with recent- onset AF complicating myocardial infarction and found that 24-h conversion rate of amiodarone (7 mg/kg bolus followed by an infusion rate up to 1500 mg/d) was comparable to IV digoxin .⁸⁶

On the other hand six trials have evaluated high-dose IV amiodarone (>1600 mg/d) either by administering larger IV doses or by combining IV and oral administration (Table 6). 52,88,90,91,93,96 In a small trial, Capucci and colleagues 52 compared a 5-mg/kg IV amiodarone bolus followed by a 75-mg/h infusion (1800 mg/d) vs. a single dose of flecainide or placebo. Amiodarone was as effective as placebo at any point within 24 hours, and in comparison to flecainide, there was no significant difference in conversion rate at 24 hours but flecainide was faster than amiodarone in conversion to sinus rhythm and conversion rate of flecainide was significantly higher at 3, 8 and 12 hours. Boriani et al⁹⁶ compared the same amiodarone regimen to oral flecainide, I.V. propafenone, oral propafenone and placebo involving 417 patients. Intravenous amiodarone was not different from placebo until 8 hours when it was associated with 57% of conversion rate. At 8 hours, amiodarone conversion rate was significantly higher than placebo but less than flecainide or propafenone. A study conducted by Hou et al,⁸⁸ which randomized a tailored infusion of high-dose IV amiodarone against digoxin in recent-onset AF in an attempt to attain therapeutic plasma concentrations within 1 hour and maintain them for 24 hours. At 24 hours the conversion rate in amiodarone group was significantly higher than digoxin group (92% vs 71%, p = 0.0048) and the difference appeared since the first hour and maintained throughout the 24 hours. A randomized placebocontrolled trial done by Cotter G et al,⁹⁰ compared a high-dose I.V. amiodarone infusion (125 mg/h) to placebo and found no difference at 8 hours (62% vs 58%), but higher conversion rates at 24 hours with amiodarone (92% vs 64%, P <0.0017). Kochiadakis GE and colleagues 66 found that amiodarone (300-mg bolus plus 20-mg/kg/d infusion, with concomitant oral amiodarone at 600 mg three times daily) led to significantly higher 24-h conversion rates than placebo. Vardas PE and colleagues showed that this IV amiodarone regimen,

with an oral amiodarone 600mg daily in three divided doses was associated with more successful conversions than placebo at 1 and 24 hours in a mix of recent onset and chronic AF patients; however, benefit was limited to patients with recent-onset AF. It showed that patients with atrial fibrillation lasting less than 24 h had a high probability of conversion (> 95%) with amiodarone regardless of the left atrial size. While none of the chronic AF patients converted to NSR within 24 hours .⁹³

Dronedarone

Several randomized trials conducted to assess the effectiveness and safety of dronedarone in AF patients (Table 7). Most of these trial were placebo controlled trials.^{98,99,100,101,102,103} ATHENA trial¹⁰² was a prospective, double-blind study included 4,628 patients with atrial fibrillation or atrial flutter and at least one other cardiovascular risk factor to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular hospitalization or death from any cause. It showed that dronedarone, in addition to standard therapy, significantly reduced the risk of a first cardiovascular hospitalization or death by 24% in patients with atrial fibrillation or atrial flutter. The study excluded patients with decompensated heart failure.

Touboul P et al,⁹⁸ in the Dronedarone Atrial Fibrillation Study after Electrical Cardioversion (DAFNE) which was a double-blind, randomized, placebo-controlled, dose-finding trial, included 270 patients with persistent AF. This study was conducted to compare different doses of dronidarone and to determine which dose is the most appropriate to prevent AF recurrence after cardioversion in comparison to placebo with a mean follow up of 6 months. The conversion rate was dose dependant and high doses associated with higher conversion rate (5.8% with 800 mg vs. 14.8% with 1600 mg),

Table 9:	Summary of Studies That Assessed the Association of Amiodarone with Cardiovascular Mortality.								
Study	No. of patients	Type of study	Comparison	Results					
Saksena S et al, 2011 ¹²⁵	2027	Post-Hoc analysis	Amiodarone, sotalol, 1c agents vs. rate control.	non-CV death: amiodarone: (HR: 1.11, 95% Cl: 1.01 to 1.24, p = 0.04). First CVH: Amiodarone: 47% vs. 40% (HR: 1.20, 95% Cl: 1.03 to 1.40, p = 0.02). Sotalol: 50% vs.40% (HR: 1.364, 95% Cl: 1.16 to 1.611, p < 0.001) 1c agents: 44% vs. 36% (HR: 1.24, 95% Cl: 0.96 to 1.60, p = 0.09).					
Torp-Pedersen C et al, 2007 ¹²⁶	3029	Post-Hoc analysis	Amiodarone vs. control.	All cause mortality: NYHA II: 38.7% vs. 26.2%, P<0.001. NYHA III + IV : 58.9% vs. 43.3, P<0.001. Circulatory failure: amiodarone > control, P<0.001. SCD: (HR 1.07, Cl 0.8–1.4, P = .7).					
Thomas KL et al, 2008 ¹²⁷	14700	Post-Hoc analysis	Amiodarone vs. control.	Amiodarone associated with early and late mortality.					
Piccini JP et al, 2009 ¹²⁸	6522	Meta- analysis	Amiodarone vs. placebo/ inactive	SCD: 7.1% vs. 9.7% P<0.001. CV mortality: 14% vs. 16.3%, P=0.004. All cause mortality: 18.1% vs. 19.6%, P=0.093					

but in both doses the conversion rate was significantly higher than placebo (3.1%). For the maintenance of sinus rhythm and prevention of recurrence, dronedarone at the lowest dose (800 mg daily) was associated with a significantly lower recurrence rate at 6 months than placebo with 35% remaining in sinus rhythm as compared to 10% in placebo group. In addition the median time to first AF recurrence was 5.3 days in the placebo group, and 60 days in the dronedarone 800 mg group (RRR 55%, 95% CI 72–28%, P=0.001). This difference in recurrence rate was not seen at higher doses of dronedarone. This dose independent effect observed with dronedarone was not seen with other new antiarrhythmic agents and could not be explained by its pharmacokinetic parameters, one hypothesis for this effect is the multifactor mode of action of dronedarone, would result in a bellshaped response curve, a notion that has never been documented with dronedarone in animal models. In addition the higher proportion of patient censoring in the 1200 and 1600 mg dronedarone groups, mainly due to adverse events resulting in drug discontinuation.

Two phase 3 identical, placebo- controlled, multicenter, doubleblind, parallel group trials sponsored by Sanofi-Aventis, The European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) 99 conducted in 12 European countries and the American-Australian-African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS) 99 conducted in the United States, Canada, Australia, South Africa, and Argentina, tested the effectiveness of dronedarone 800 mg twice daily in maintaining sinus rhythm. These two trials randomized 1237 patients in sinus rhythm with a history of at least one attack of AF in the last 3 months before inclusion and mean age of 63 years, in a 2:1 ratio of active drug to placebo. The studies included patients with structural heart disease, but the mean left ventricular ejection fraction was 58%. Patients were followed for 12 months and their primary end point was time for first recurrence of AF. Dronedarone significantly reduced the risk of a first recurrence of atrial fibrillation by 22% in ADONIS and 27.5% in EURIDIS. Also dronedarone was associated with significantly lower median time to first AF recurrence than placebo (41 days vs. 96 days, P < 0.01) in EURIDIS trial and 59 days on dronedarone vs. 158 days on placebo, P = 0.002 in ADONIS trial. Both trials showed that dronedarone reduced ventricular rates during AF recurrence significantly as compared to placebo.

ANDROMEDA trial¹⁰¹ included patients with heart failure and NYHA III-IV and were randomized in a 1:1 ratio to double-blind treatment with either dronedarone or matching placebo and followed for 6 months. A total of 627 patients with EF< 35% were studied with primary end point was death from any cause or hospitalization for worsening heart failure. Mortality was higher in dronedarone treated group 25 (8%) vs. 12 (3.8%) in the placebo group (HR 2.13; 95% CI=1.07 - 4.25; P = 0.03) and the death was mainly related to worsening of heart failure and there was no significant difference in the incidence of death related to arrhythmia or sudden death. First hospitalization for an acute cardiovascular cause was higher in the dronedarone group (71 patients vs. 50 patients) (P = 0.02) and the main cause for hospital admission was also worsening heart failure.

The most recent study, PALLAS,¹⁰³ a randomized, double blind, placebo controlled, parallel group trial conducted at 489 sites in 37 countries for assessing the clinical benefit of dronedarone 400mg bid

on top of standard therapy in patients with permanent atrial fibrillation and additional risk factors including heart failure with NYHA class II-III. It randomized a total of 3236 patients with permanent AF to receive either dronedarone (at a dose of 400 mg twice daily) or matching placebo with median follow-up of 3.5 months. The results of this trial showed higher total mortality in dronedarone group (25 vs. 13, HR=1.94; 95% CI, 0.99 to 3.79; P = 0.049) and cardiovascular death (21 vs. 10, HR=2.11; 95% CI, 1.00 to 4.49; P = 0.046). In addition arrhythmic cardiovascular death was also higher in dronedarone group (13 vs. 4, HR=3.26; 95% CI, 1.06 to 10.00; P = 0.03). Stroke occurred in 23 patients in the dronedarone group and 10 in the placebo group (hazard ratio, 2.32; 95% CI, 1.11 to 4.88; P = 0.02). Unplanned hospitalization for cardiovascular causes was significantly higher in dronedarone group (113 vs. 59, HR=1.97; 95% CI, 1.44 to 2.70; P<0.001). Hospitalization for heart failure was also higher in dronedarone group (43 vs. 24, HR=1.81; 95% CI, 1.10 to 2.99; P = 0.02). With subgroup analysis an interesting significant association found for unplanned hospitalization for cardiovascular causes or death with diabetes (P < 0.03).

One meta-analysis used 4 placebo controlled trials for amiodarone and 4 placebo controlled trials for dronedarone is the DIONYSOS study.¹⁰⁴ Its results showed that amiodarone superior to dronedarone (OR: 0.49; 95% CI: 0.37 to 0.63; p < 0.001) for the prevention of recurrent AF. Also it showed a trend toward greater all-cause mortality (OR: 1.61; 95% CI: 0.97 to 2.68; p = 0.066) and greater overall adverse events requiring drug discontinuation with amiodarone versus dronedarone (OR: 1.81; 95% CI: 1.33 to 2.46; p < 0.001).

Vernakalant

Vernakalant studied in several randomized studies to assess its effectiveness and safety in conversion of new onset AF and the appropriate dose of it. CRAFT trial was a prospective doubleblinded, placebo controlled, randomized, dose-response trial. It included patients with new onset AF (less than 72 hours) and it was highly selective in enrolment of patients and excluded any patient with evidence of CAD, structural heart disease or conductive abnormality. It randomized patients into two vernakalant regimen (2.0 and 3.0 mg/kg) vs (0.5 and 1.0 mg/kg) and compared them with placebo. It showed that the conversion rate of vernakalant at higher dose regimen was significantly superior to the lower dose vernakant group and placebo (61% vs 11% vs 5%, P<0.0005), but the low dose vernakalant group did not show a superiority over placebo in conversion rate. High dos vernaka lant as compared to placebo had higher conversion rate at 30 minutes (56 versus 5%; p<0.001) and one hour (53 versus 5%; p=0.0014), and median time to conversion (14 versus 162 minutes; p=0.016). No serious adverse events, including torsade de pointes, were noted with vernakalant group.¹⁰⁵

A larger phase III trial, the ACT I study,¹⁰⁶ compared intravenous vernakalant with placebo in 416 patients with atrial fibrillation duration of 3 hours-7 days. Of vernakalant group, 52% converted to sinus rhythm compared with 4% of placebo patients (p<0.001). However, in the overall study, when one looked at the atrial fibrillation duration of three hours to 45 days, only 38% of patients receiving intravenous vernakalant had their atrial fibrillation terminated compared with 3% of placebo patients (p<0.001). Intravenous vernakalant was ineffective in converting atrial flutter, with only one of 39 drug-treated patients converted compared with 0 of 15 atrial flutter patients treated

with placebo. No drug-related torsade de pointes was noted with vernakalant group.

ACT-II study evaluated the efficacy and safety of intravenous vernakalant for the treatment of 190 patients who developed atrial fibrillation or atrial flutter between 24 hours and seven days following coronary artery bypass graft or valve replacement surgery. In the atrial fibrillation group, 47% of intravenous vernakalant group converted to sinus rhythm within 90 minutes compared with only 14% of placebo patients (p=0.0001). The median time to conversion was around 12 minutes for the vernakalant responders. No torsade de pointes was reported and 0 out of 10 patients who had atrial flutter converted to sinus rhythm with intravenous vernakalant.¹⁰⁷

ACT-III was a pivotal phase III trial very similar in structure to ACT-I, randomizing 276 patients. Intravenous vernakalant converted 51% of the patients with recent-onset atrial fibrillation of three hours to seven days to sinus rhythm compared with only 4% of placebo patients (p<0.001). Similar to ACT-I, in the population of three hours to 45 days, 40% of patients receiving intravenous vernakalant had their atrial fibrillation terminated compared with 4% of placebo patients (p<0.001). Only 7% of patients with atrial flutter receiving vernakalant converted to sinus rhythm compared with 0% of placebo patients. There were no documented cases of torsade de pointes in this trial.¹⁰⁸

A randomized trial compared I.V. vernakalant to I.V. amiodarone (AVRO Trial)¹⁰⁹ conducted on 232 patients with acute onset AF. This study showed that the conversion rate of vernakalant at 90 minutes and 4 hours was significantly higher than that of I.V. amiodarone (51.7% and 54.4% vs. 5.2% and 22.6% respectively, P<0.0001). In addition vernakalant was associated with higher rate of symptoms relief at 90 minutes than amiodarone (53.4% vs. 32.8% p= 0.0012).

Oral vernakalant for maintenance of sinus rhythm was evaluated in several trials. A trial conducted by Pratt CM et al¹¹¹ studied the oral vernakalant in maintaining sinus rhythm after cardioversion of sustained atrial fibrillation demonstrated that oral vernakalant at 300 and 600mg twice daily was superior to placebo in maintaining sinus rhythm over a 28-day treatment. In the placebo group, 57% of patients had atrial fibrillation recurrence compared with 39% in the vernakalant 300mg twice-daily group (p=0.048) and 39% in the 600mg twice-daily group (p=0.06). Another large phase IIIb trial conducted by Torp-Pedersen C et al¹¹² compared the efficacy of oral vernakalant at 150mg, 300 mg and 500 mg doses in maintaining sinus rhythm as compared to placebo. This study found that the time to the first recurrence of symptomatic sustained AF was significantly longer in the 500 mg vernakalant group than in the placebo group (>90 days vs. 29 days, HR 0.735, P = 0.0275). No significant effect was seen at the lower doses of vernakalant. The percent of patients in sinus rhythm at Day 90 was 41%, 39%, and 49% in the 150 mg, 300 mg, and 500 mg vernakalant groups, respectively, compared to 36% in the placebo group. There were no vernakalant-related proarrhythmic events.

Ranolazine

No large randomized trials done on the efficacy of ranolazine in atrial fibrillation A small study of 7 patients, ranolazine was initiated soon after atrial fibrillation ablation and was found to be useful in maintaining sinus rhythm.¹¹³ A single-center retrospective cohort

study conducted by Miles RH et al¹¹⁴ enrolled total of 393 consecutive patients undergoing CABG and received either amiodarone or ranolazine. AF occurred in 26.5% of the amiodarone-treated patients compared to 17.5% of the ranolazine-treated patient (p = 0.035). No difference was found in the risk of adverse events between the 2 therapies. This study concluded that ranolazine was independently associated with a significant reduction of AF compared to amiodarone after CABG, with no difference in the incidence of adverse events.

Antazoline

The antiarrhythmic effect of antazoline specifically in atrial fibrillation was not studied in a randomized trial before. It was studied in single-arm clinical trials with no control group and they suggested high efficacy of antazoline in rapid conversion of AF to SR if administered intravenously up to the cumulated dose of 350 mg.

A retrospective study conducted by Kuch M et al ,¹¹⁵ analyzed the efficacy of intravenous antazoline in converting paroxysmal atrial fibrillation into sinus rhythm. It included 1325 consecutive patients with paroxysmal atrial fibrillation admitted to Coronary Care Unit between 1985 and 1997 and treated with antazoline intravenously. It showed a total efficacy of 52%. The efficacy in relation to total dose was: 100 mg - 46%; 200 mg - 54.4%; 300 mg - 50%; >300 mg - 20.5% (significance between 100-300 mg and >300 mg - p<0.01). He concluded that antazoline is an efficient and relatively safe drug in converting paroxysmal atrial fibrillation to sinus rhythm and its high efficacy seen at a dose of 100 to 300 mg. There was no difference in efficacy in relation to sex and age. The AnPAF Study is the first randomized placebo controlled trial on the efficacy of antazoline in rapid conversion of atrial fibrillation to sinus rhythm. It is still ongoing and expected to finish on 2014.¹¹⁶

Discussion

Flecainide is highly effective in the acute setting for cardioversion of AF. In haemodynamically stable patients with acute-onset AF (<48 h duration) and preserved LV function, flecainide restores SR in up to 95% of patients within 1h from the start of the I.V. infusion. A pooled analysis of eight randomized controlled trials by the US Agency for Healthcare Research and Quality (AHRQ) showed that acute treatment with flecainide was associated with conversion rates of between 52 and 95%. ²⁰ Therefore flecainide is contraindicated in patients with a history of acute coronary ischemia, structural heart disease or cardiomyopathy and hemodynamic instability due to the risk of cardiac decompensation.

For all of this evidence, flecainide is recommended by the ACC/ AHA and ESC guidelines as one of the first line therapy for rhythm control in patients with recurrent PAF particularly young age patients and patients with structurally normal heart with normal ventricular function .^{117,118,119}

Propafenone is effective and safe agent in converting AF to sinus rhythm. It is as effective as flecainide, though flecainide is faster in conversion and both are having the same incidence of side effects and negligible pro-arrhythmic potential for malignant arrhythmias especially in structurally normal heart. Also it is more effective than amiodarone in form of mean time for conversion and its oral administration is as effective as its intravenous administration. For all of this propafenone is recommended as first line agent for conversion of new onset AF with structurally normal hearts.^{117,118,119} Dofetilide was the first selective class III potassium channel blocker and proved to be effective in maintaining sinus rhythm after conversion of atrial fibrillation to sinus rhythm. After publication of SAFIRE-D and EMERALD studies results, which are large randomized clinical trials in patients with persistent atrial fibrillation, dofetilide got a preliminary approval in the United States in 2000. The Danish Investigations on Arrhythmia and Mortality on Dofetilide (DIAMOND) study and its subgroup analysis done to assess the effect of dofetilide on the mortality and hospitalization in high risk patients (i.e. low ejection fraction and post myocardial infarction). The results of these trials support a role for dofetilide in patients with advanced heart disease and atrial fibrillation, but because atrial fibrillation was not used to stratify randomization, they are less conclusive than data from the SAFIRE-D and EMERALD studies.

Amiodarone

High-dose amiodarone regimen, using large daily IV doses (more than 1600 mg) or combining oral and IV doses, is more effective than placebo for converting recent-onset AF to normal sinus rhythm as compared to low dose regimen. Nevertheless, amiodarone needed longer time for cardioversion than class 1c agents, despite that conversion rate at 24 hours was sometimes comparable to these agents. Amiodarone trials that used high dose regimen had restricted their inclusion criteria and excluded patients with NYHA Class II–IV functional status, acute myocardial infarction, recent cardiac surgery or cardiogenic shock.

Amiodarone was considered as relatively safe drug to be used for a trial of cardioversion in atrial fibrillation especially when used in patients with structural heart disease and patients with LV systolic dysfunction. Earlier studies that assessed the safety of amiodarone in heart failure patients showed that amiodarone was associated with significant improvement in left ventricular ejection fraction compared with placebo,^{120,121} significantly reduced admission to hospital for CHF and improved functional class¹²² or no significant effect on left ventricular ejection fraction.¹²³ Therefore the ACC/AHA, ESC AF management guidelines recommended it as a first choice agent for cardioversion in such patients.^{117,118,119}

The hemodynamic effects of intravenous amiodarone was studied long time before, Kosinski EJ et al¹²⁴ was one of those who studied this effect. He conducted a double blind study on patients with LV systolic dysfunction and divided them into two groups with EF > 35% or < 35% and he reached a conclusion that IV amiodarone results in negative inotropic and peripheral vasodilatory effects and reduced coronary blood flow, therefore it should be reserved as a second or third line anti-arrhythmic agent in patients with moderate left ventricular dysfunction. Also patients with impaired left ventricular function who are receiving intravenous amiodarone need careful hemodynamic monitoring. It is advised that those patients with chronic ventricular arrhythmias are best treated with the safer, method of high oral loading dose of amiodarone.

But recent studies that evaluated its cardiovascular safety in such patients raised an issue that amiodarone is not that safe and need to be cautious in using amiodarone especially when it is used for cardioversion or for ventricular arrhythmias as I.V. form. A study done by Saksena S et al,¹²⁵ to assess the impact of individual anti-arrhythmic drug therapy as compared with rate control with propensity score-

matched analyses which analyzed the AFFIRM trial results, showed that Clinical characteristics and initial AAD selection rather than treatment strategy influenced cardiovascular hospitalization risk, and death. Intensive care unit hospital stay and non-CV death were more frequent with amiodarone. Turp-Pedersen C and colleges¹²⁶ did reanalysis of the results of COMIT trial which randomized 3029 patients with chronic heart failure to receive carvedilol or metoprolol and followed patients for a median of 58 months. One hundred fifty-five of 1466 patients in NYHA Class II and 209 of 1563 in Class III or IV received amiodarone at baseline. After about 4 years follow up, 38.7% of patients in NYHA Classes II and 58.9% of patients in class III + IV who receive amiodarone died versus 26.2% and 43.3% in those who did not receive amiodarone (P < .001). This increase in mortality rate was mainly due to circulatory failure and there was no difference in sudden death.

A study conducted by Thomas KL et al,¹²⁷ used data from VAL-IANT, a randomized comparison of valsartan, captopril, or both in patients with acute myocardial infarction with heart failure and/or left ventricular systolic dysfunction. They compared baseline characteristics of 825 patients treated with amiodarone at randomization with 13 875 patients not treated with amiodarone using Cox models. The association of amiodarone use with subsequent mortality after randomization was examined, and found that amiodarone use was associated with excess early and late all-cause and cardiovascular mortality. A meta-analysis done by Piccini et al,¹²⁸ analyzed the data from all randomized placebo controlled trials done over the period from 1966 till 2007. He reached a conclusion that amiodarone reduced the SCD by 26% and CV death by 18% but did not reduce the overall mortality.

Dronedarone

Dronedarone emerged as a substitute for amiodarone lacking the iodine molecule to reduce the non-cardiac toxicity associated with last agent. DAFNE trial⁹⁹ was the most important early clinical trial done on dronedarone and as the aim of it is to determine the most effective as well as safe dose of dronedarone to maintain sinus rhythm after cardioversion. It was a prospective phase II, placebocontrolled, dose-ranging study and showed that an 800 mg daily dose of dronedarone is the most suitable dose as it was effective for the prevention of AF relapses after cardioversion, reduced time to AF recurrence compared with placebo, longer median time to AF recurrence, lower discontinuation rate as compared to higher doses with no significant effect on the QT interval.

EURIDIS and ADONIS trials⁹⁹ studied the efficacy of dronedarone (400 mg BID) for the maintenance of sinus rhythm after electrical, pharmacological, or spontaneous conversion of AF or AFL, but they excluded patients with NYHA class III or IV heart failure, and severe renal impairment. Over half of the patients in both trials had a history of hypertension, approximately 25% coronary heart disease, and just fewer than 20% had a history of heart failure. Dronedarone at 800mg daily was significantly effective in reducing the risk of recurrence of AF/AFL over 1 year compared with placebo. In addition the median time to first recurrence of AF/AFL for dronedarone in EURIDIS was 2.3 times longer and 2.7 times longer in ADONIS than placebo group. This effectiveness was consistent even after dividing the patients in dronedarone group in to three subgroups [those with recent cardioversion (within 5 days of randomization), prior Featured Review

treatment with amiodarone, and structural heart disease]. Both trials also showed that dronedarone is effective for rate control after recurrence of AF which was a secondary endpoint in these studies and the mean ventricular rate during first AF/AFL documented recurrence was significantly lower in the dronedarone-treatment groups (102.3 and 104.4 vs. 117.5 and 116.6) of EURDIS and ADONIS, re respectively, (P<0.0001 and P<0.001, respectively). ERATO study, 100 a phase III study, examined the rate control benefit of dronedarone in 174 elderly patients with permanent AF as compared to placebo. In this study, 38.9% had structural heart disease and 39.7% NYHA class I or II heart failure. The ERATO trial showed that the addition of dronedarone to standard therapy produced a statistically significant decrease in ventricular response rate to AF at rest as well as during exercise, but no significant change in exercise tolerance.

Safety

The ADONIS and EURIDIS trials⁹⁹ used the low dose of dronedarone (800 mg daily) did not report any pro-arrhythmia or pulmonary or thyroid toxicity among the 828 dronedarone-treated patients. In addition no cases of torsade de pointes were reported over the 12-month course of these studies. Serious adverse events were rare and occurred with similar frequency in the two cohorts (16.5% dronedarone vs. 13.5% placebo). Rates of premature discontinuation for adverse events were also similar (15.3% dronedarone vs. 9% placebo).

The two major randomized placebo controlled trials that examined the safety of dronedarone in high risk patients (left ventricular dysfunction and NYHA class III-IV heart failure) were stopped prematurely as both showed a trend toward increased mortality in the dronedarone treated group. The ANDROMEDA trial¹⁰¹ was planned for a total of 1,000 patients with follow up period of 6 months, but only 627 patients had been enrolled as the trial was stopped prematurely at a median follow-up of approximately 2 months. During this period, mortality was significantly higher in dronedarone group (8% vs. 3.8%, P=0.027). This trial reached a three relevant findings; First, the excess deaths related to dronedarone were largely due to heart failure, Second, the risk of death with dronedarone was greatest among patients with the most severely reduced left ventricular systolic function. Third, treatment with dronedarone led to a small increase in hospitalizations for heart failure. The other study, PAL-LAS trial,¹⁰³ which included patients with permanent AF and at least one risk factor includ ing NYHA III-IV heart failure, evaluated the effect of dronedarone on the composite of stroke, MI, systemic embolism, or death from cardiovascular causes as a primary endpoint, and unplanned hospitalization for a cardiovascular cause or death as a secondary endpoint. This study can be considered as the continuation of ATHENA trial as both were assessing the same endpoints but differ in the NYHA functional class and left ventricular systolic function. PALLAS trial selected the high risk patients and its results were totally the opposite of ATHENA trial, as it showed that dronedarone significantly increases the total mortality, risk of stroke, cardiovascular mortality and hospitalization for cardiovascular causes and this increase in mortality and hospitalization was mainly related to heart failure.

The ATHENA trial was the first large trial to study the all cause mortality or hospitalization for any cardiac reason with rhythm control agent. It included 4628 patients with at least one cardiovascu-

lar risk factor but excluded high risk patients and randomized them to 400 mg BID versus placebo. The study included some patients with NYHA class III symptoms, but the majority of the heart failure patients were NYHA class II. It showed a 24.2% reduction in the risk of cardiovascular hospitalization or death from any cause (P=0.001) and 30% reduction in cardiovascular death (P=0.03). There was a 25.5% reduction in cardiovascular hospitalizations and a trend toward 16% less death from any cause (P=0.18). In addition there was 45% reduction in arrhythmia death. Dronedarone showed a low risk of pro-arrhythmia and no excess hospitalizations for CHF in comparison to placebo as well as similar rate of drug discontinuation to placebo group. Following the publication of ATHENA results, dronedarone was resubmitted for approval by the U.S. Food and Drug Administration and the European Medicines Agency and gate approval on July 2009.

A consistent finding in all the abovementioned studies is the rise in serum creatinine in the dronedarone treated patients. EURIDIS/ ADONIS trials⁹⁹ demonstrated that the dronedarone group had a 2.4% incidence of serum creatinine rise versus 0.2% in the placebo group (P=0.004). A retrospective analysis of ANDROMEDA study data has reported inappropriate withdrawal of angiotensin-converting enzyme inhibitor (ACE) and/or angiotensin receptor blocker (ARB) therapy following transient rises in serum creatinine levels after the initiation of dronedarone treatment. This may explain the early excess mortality seen in the ANDROMEDA trial. No cases of torsade de pointes were recorded with dronedarone in the trial, so proarrhythmias can not explain the increase in the mortality.

DIONYSOS¹⁰⁴ is a meta-analysis of the randomized trials of amiodarone and dronedarone comparing the efficacy of maintaining sinus rhythm and effect on cardiovascular mortality and hospitalization of both agents. This study demonstrated that dronedarone is less effective for the prevention of recurrent AF compared with amiodarone but on the other hand, dronedarone is associated with fewer adverse events requiring discontinuation of treatment. Dronedarone does not significantly prolong the QTc, and no proarrhythmic events have been observed in the randomized trials performed to date. Additionally no thyroid, pulmonary, ocular, hepatic, cutaneous, or neurologic toxic effects have been observed in up to 12-month chronic dosing with dronedarone.

In light of the available data, dronedarone is a suitable choice for maintaining sinus rhythm especially young patients eliminating the non-cardiac toxic effect seen with amiodarone. Also it is preferred in hemodynamically stable patients and those with NYHA class I-II heart failure. On the other hand it has to be avoided in high risk patients with advanced age, NYHA class III-IV heart failure and hemodynamically unstable patients.

Vernakalant (RSD1235)

Vernakalant was significantly more effective than placebo in converting AF of more than 7 days. In ACT I and III, the conversion rates in the treatment arm were 51.7 and 51.2%, respectively, compared with 4 and 3.6% in the placebo arm.^{107,109} In the open-label ACT IV study ,110 the results were identical (50.9%). Vernakalant cardioverted 47% of the patients with post-operative AF enrolled in ACT II compared with 14% who converted spontaneously on placebo.¹⁰⁸ The median time to conversion was 11, 12, 8, and 14 min in ACT I to IV respectively. The majority of patients (75–82%)

for AF of less than 72 h duration (70-80%). On the other hand conversion rate of vernakalant dropped dramatically when AF lasted more than 7 days (8% in ACT I and 9% in ACT III). Also vernalakant was ineffective in atrial flutter with conversion rate of only 2.5% in ACT I and 7% in ACT III. The drug was well tolerated, with no significant QTc prolongation or drug-related torsades de pointes. The most common side effects of vernakalant were dysgeusia, sneezing, and nausea. The moderate overall anti-arrhythmic efficacy of veranakalant and particularly the absence of the anti-arrhythmic effect of IKur blockade in AF of more than 7 days may be explained by complex ionic remodelling during AF, including downregulation of Ito, INa, and ICaL currents. Blockade of Ito and INa by vernakalant may be more beneficial for prevention than conversion of AF. An oral formulation of vernakalant has been investigated in a phase IIa study .¹¹⁰ Two doses of the drug (300 and 600 mg twice daily) were compared with placebo. The follow-up period was limited to 28 days because of available toxicology data and because the efficacy of anti-arrhythmic agents in the early post-cardioversion period is of particular interest. Both doses of vernakalant were equally effective in preventing recurrence (61% vs. 43%) at the end of the study. No drug-related torsades de pointes were reported. The preliminary results of a phase IIb randomized, double blind study of three doses of vernakalant (150, 300, or 500 mg twice daily) in 446 patients after conversion with vernakalant or electrical cardioversion were released on 2008. Patients treated with the highest dose were more likely to maintain sinus rhythm at 3 months compared with placebo (52 vs. 39%, P< 0.05); the median time to recurrence of AF was significantly longer with vernakalant 500 mg group as compared to placebo (90 days vs. 39 days) while with the 150mg and 300 mg twice daily it was not significant. ATC 5 study that conducted to assess the safety of I.V. vernakalant in acute conversion of new onset atrial fibrillation was terminated prematurely by the cosponsors as requested by the FDA because of reported serious hypotension and bradycardia with one fatal cardiogenic shock case. This questioned the safety of I.V. vernakalant and strengthened the need for close monitoring of blood pressure and heart rate during and after the I.V. infusion of vernakalant.

converted after the first dose. The highest efficacy was observed

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In a subgroup analysis of the MERLIN-TIMI 36 trial,¹²⁹ which studied the effect of ranolazine on the recurrence of cardiovascular events after non-ST elevation acute coronary syndrome, the continuous ECGs of 6,351 patients were analyzed. The results showed that, in comparison with placebo, treatment with ranolazine resulted in fewer episodes of ventricular tachycardia that lasted 8 beats or longer (5.3% vs. 8.3%; P <0.001), and in fewer episodes of supraventricular tachycardia (44.7% vs 55%; P <0.001) and new-onset atrial fibrillation (1.7% vs 2.4%; P=0.08). In addition, there were no differences in the incidence of polymorphic ventricular tachycardia or sudden cardiac death, a concern that had arisen after previous observations of prolonged QT intervals.⁴⁰ At therapeutical concentrations (2-6 mmol/L), ranolazine also affects IKr (50% inhibition at 12 mmol/L) and can potentially prolong the action potential, but this effect is offset by more potent late INa blockade. The net effect and clinical consequence of multiple channel blockade by ranolazine is a modest increase in the mean QT interval by 2-6 ms. A phase III study in patients with AF is planned as the therapeutical dose is established, there will no need for dose-ranging phase II studies.

Conclusions:

Numerous retrospective and prospective clinical studies have been undertaken for the evaluation of antiarrhythmic drug therapy for the treatment of AF. However, currently available agents remain limited in safety and efficacy and represent an area for further research and development. In the meanwhile therapy should be targeted according to the individual patient`s symptoms and functional status.

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