Multicenter Prospective Nonrandomized Study of Long-Term Antiarrhythmic Drug Therapy in Patients With Tachyarrhythmias

— Japanese Antiarrhythmics Long-Term Study-2 (JALT-2 Study) —

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Based on the results of the Cardiac Arrhythmia Suppression Trial (CAST), strategies for the treatment of tachyarrhythmias have changed rapidly. The Japanese Antiarrhythmics Long-Term (JALT) study was planned to investigate the present methods for choosing antiarrhythmic drugs, and the effects on long-term prognosis in patients with tachyarrhythmias in Japan. Following a 6-month preliminary study (JALT-1), there was a multicenter nonrandomized prospective study (JALT-2), with a 2-year follow-up, of patients with paroxysmal atrial fibrillation (PAF), sustained ventricular tachycardia (SVT) and nonsustained VT (NSVT). Four hundred fifty-five patients were registered, and 361 of them (79%) were analyzed. Cerebral infarction occurred in 10 of 193 patients (5.2%) with PAF. Transition to chronic AF was observed in 21 patients (10.9%), but in none of the patients receiving Ca antagonist therapy. Twenty-five patients died: 5 deaths were arrhythmic, 10 were because of pump failure, and 9 were noncardiac. The most significant difference in drug selection between JALT-1 and JALT-2 was the increase in the use of slow kinetic Na channel blockers for PAF and the decrease in the use of the same agents for VT in the JALT-2 study. A marked change of therapeutic strategy occurred in JALT-2 compared with JALT-1. Most patients with a poor prognosis had underlying heart diseases and heart failure, but the per annum rate of death by arrhythmia and pump failure in JALT-2 was less than that in JALT-1. (*Jpn Circ J* 2001; 65: 275–278)

Key Words: Antiarrhythmic drugs; Long-term prospective study; Nonsustained ventricular tachycardia; Paroxysmal atrial fibrillation; Sustained ventricular tachycardia

Recent large-scale controlled trials, including the Cardiac Arrhythmia Suppression Trial (CAST)¹ have demonstrated a limited role for long-term antiarrhythmic drug therapy for the treatment of tachyarrhythmias, and some have suggested that certain antiarrhythmic drugs may even exert negative influences on long-term efficacy and prognosis^{2–4}. In contrast, nonpharmacologic therapies, including catheter ablation and implantable cardioverter-defibrillators, have been proven efficacious^{5–8}. In addition, use of the Sicilian Gambit in choosing antiarrhythmic treatment has been widely accepted all over the world^{9–12}.

Based on these findings, the first Japanese Antiarrhythmics Long-Term Study (JALT-1), which analyzed the selection of antiarrhythmic drugs and included a 6-month follow-up in patients with various arrhythmias, was conducted in Japan in 1992^{13,14} and provided important

information. However, the follow-up period was not long enough to evaluate the effect of drug therapy on prognosis. Therefore, the present study, JALT-2, was performed to analyze the choice of antiarrhythmic drug, changes in drug therapy, and the 2-year prognosis for antiarrhythmic drug treatment in patients with tachyarrhythmias.

Methods

The JALT-2 study was designed as a prospective multicenter, nonrandomized follow up study. The goal was to determine the type of antiarrhythmic therapy used as the first agent, its efficacy, long-term complications, and the prognosis for patients with various tachyarrhythmias. Enrollment in the study was based on the intention to treat with antiarrhythmic agents to prevent the recurrence of tachyarrhythmias. The class and dose of medication were not randomized and could be changed during the study period. The types of tachyarrhythmias included were paroxysmal atrial fibrillation (PAF), sustained ventricular tachycardia (SVT), and nonsustained VT (NSVT).

Four hundred fifty-five patients were registered during the 6-month enrollment period from June to November 1994: 244 patients with PAF, 89 patients with SVT, and 122 patients with NSVT. Patients were monitored for 2

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Organizing Members of the JALT Study are listed in Appendix.
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Table 1 Clinical Characteristics of the Patients

	PAF	SVT	NSVT
No. of patients registered	244	89	122
No. of patients analyzed	193	76	92
Age (years)	62.5±11.1	52.5±16.2	55.7±16.6
Sex (M/F)	132/60	59/17	56/34
Follow-up period (days)	756±240	783±241	725±306
Underlying diseases +/-	107/84	54/22	66/25

PAF, paroxysmal atrial fibrillation; SVT, sustained ventricular tachycardia; NSVT, nonsustained ventricular tachycardia.

Table 2 Complications and Prognosis

	PAF	SVT	NSVT
No. analyzed	193	76	92
Complications and events			
Cerebral infarction	10	0	0
Catheter ablation	0	8	0
ICD implantation	0	3	0
Surgical therapy	0	1	0
Death			
Arrhythmic death	0	3	2
Pump failure	0	4	6
Non-cardiac cause	4	3	2
Unknown cause	0	0	1

PAF, paroxysmal atrial fibrillation; SVT, sustained ventricular tachycardia; NSVT, nonsustained ventricular tachycardia; ICD, implantable cardioverter-defibrillator.

Table 3 Characteristics of Patients With Arrhythmic Death

Age (years)	Sex	Arrhythmia	Underlying disease	NYHA	EF (%)	Treatment
52	M	NSVT	Post AVR	II	31	None
49	F	NSVT	CHF, vasospastic angina	II	57	Diltiazem
72	M	SVT	HHD	III	58	Pilsicainide + Verapamil
70	M	SVT	DCM	II	40	Amiodarone
65	M	SVT	DCM	III	37	Metoprolol

NSVT, nonsustained ventricular tachycardia; SVT, sustained ventricular tachycardia; AVR, aortic valve replacement; CHF, congestive heart failure; HHD, hypertensive heart disease; DCM, dilated cardiomyopathy.

years after enrollment for changes in the tachyarrhythmia, the antiarrhythmic drug regimen, and the development of complications. Written informed consent was obtained from all subjects.

Results

Clinical Characteristics of the Patients

The clinical characteristics of the 455 patients, including age, sex, follow-up period and underlying diseases, are summarized in Table 1. Three hundred sixty-one patients (79%) could be analyzed.

Complications and Events During the Follow-Up Period (Table 2)

Cerebral infarction occurred in 10 of 193 patients (5.2%) with PAF, but in none of the patients with SVT or NSVT.

Conversion of PAF to the chronic form occurred in 21 patients (10.9%) after a mean follow-up period of 463 days. The rate of transition to chronic AF was 6.8% (8 of 117) of patients receiving class I drug therapy, 18.9% (7 of 37) of patients receiving β -blocker therapy, 13.7% (7 of 51) of patients receiving digoxin therapy and 0% (0 of 33) of patients receiving Ca antagonist therapy. Nonpharmacologic

therapy (eg, catheter ablation, cardioverter-defibrillator implantation, or surgery) was required in some patients with SVT because the selected drug therapy was thought to be ineffective or had adverse effects during the follow-up period.

Prognosis

Twenty-five of the 455 patients died during the follow-up period: 5 were thought to have experienced an arrhythmic death (Table 3), 10 died of pump failure, 9 died of noncardiac causes and 1 patient died of unknown cause (Table 2). The rate of death during the follow-up period was lower in patients with PAF compared with patients with SVT or NSVT (2.1% vs 13.2% and 12.0%, respectively). None of the patients with PAF died of cardiac disease, including arrhythmia and pump failure. Most of the patients who died of sudden arrhythmias had underlying heart disease and New York Heart Association (NYHA) class II or III heart failure with a low left ventricular ejection fraction.

Change in Antiarrhythmic Therapy for PAF During Follow-Up

The drugs that had been prescribed at the start of the study were sometimes changed to another drug during the

Fig 1. Comparison between JALT-1 and JALT-2 of the initial drug therapy for paroxysmal atrial fibrillation. DISO, disopyramide; CIB, cibenzoline; MEX, mexiletine; APR, aprindine; FLC, flecainide; PIL, pilsicainide; PRF, propafenone; BB, β -blockers; III, amiodarone/sotalol; IV, verapamil/diltiazem; DIG, digoxin.

follow-up period because of treatment failure or side effects, even in patients with PAF. The number of patients who remained on their initial therapy throughout the follow-up period was 10 of 14 patients (71.4%) treated with flecainide, 9 of 11 patients (81.8%) treated with cibenzoline, 2 of 5 patients (40%) treated with pilsicainide, and 6 of 12 patients (50%) treated with disopyramide.

Initial Drug Selection: Comparison Between JALT-1 and JALT-2

Fig 1 shows the frequency of initial selection of the various drugs used to treat PAF. Though disopyramide was most frequently used in JALT-1, its use decreased by almost half in JALT-2. In JALT-2, class Ic drugs (eg, flecainide, cibenzoline and pilsicainide) were used more frequently in patients with PAF. In patients with NSVT or SVT, most of the intermediate and/or slow kinetic Na channel blockers were used less frequently in JALT-2 (Fig 2). Use of mexiletine (a fast kinetic Na channel blocker) and class III drugs (amiodarone and sotalol) almost doubled.

Discussion

From JALT-1 to JALT-2

The treatment of tachyarrhythmias is changing rapidly. Specifically, long-term antiarrhythmic drug therapy using strong Na channel blockers is being reassessed because recent large-scale studies, including CAST, have suggested that such therapy may be associated with a poorer prognosis. In 1992, we conducted the JALT-1 study to determine how Japanese cardiologists chose antiarrhythmic drugs for certain tachyarrhythmias and the results^{13,14} revealed that several kinds of slow kinetic Na channel blockers were still frequently used, even in patients who have underlying organic heart disease. However, the follow-up period for JALT-1 was only 6 months and was considered to be too short to evaluate prognosis. Therefore, the present prospective study was designed to focus on selected arrhythmias with a longer follow-up period, and included the same physicians from the same institutes as in JALT-1.

Conversion to Chronic Atrial Fibrillation

The conversion to chronic AF was observed in about 10% of the patients with PAF and the rate of transition was dependent on the type of antiarrhythmic therapy. Because 2

Fig 2. Comparison between JALT-1 and JALT-2 of initial drug therapy for sustained or nonsustained ventricular tachycardia. DISO, disopyramide; CIB, cibenzoline; MEX, mexiletine; APR, aprindine; FLC, flecainide; PIL, pilsicainide; PRF, propafenone; BB, β -blockers; III, amiodarone/sotalol; IV, verapamil/diltiazem.

or more drugs were used concurrently in some patients, it is sometimes difficult to say which drug is superior in preventing chronic AF. However, it is noteworthy that no patients treated with Ca antagonists progressed to this condition. It has been suggested that Ca antagonists protect against atrial remodeling^{15,16} which is thought to be the main mechanism responsible for the progression to chronic AF.

Factors That Make the Prognosis Worse

Twenty-five patients (about 5%) died during the follow-up period. However, most of them died either of pump failure caused by worsening of their underlying heart disease or of noncardiac causes. None of the patients with PAF died of cardiac causes. Almost all of the patients who died of sudden arrhythmias had underlying heart disease, including dilated cardiomyopathy and heart failure (NYHA class II or III) with a low left ventricular ejection fraction. Neither severe QT prolongation nor torsades de pointes was documented in the patients who died suddenly.

Changes in the Selection of Antiarrhythmic Drugs

As shown in Figs 1 and 2, the selection of antiarrhythmic drugs has changed markedly, not only for PAF but also for NSVT and SVT. The reason why such great changes in the choice of antiarrhythmic agents have occurred within a few years is hard to explain. One reason is the impact of the CAST¹ and ESVEM¹⁷ studies in which it was found that the long-term use of conventional Na channel blockers, especially slow kinetic agents, can worsen patient prognosis. Also, the results of the CASCADE study¹⁸ in which amiodarone was shown to be superior to class I drugs for the management of ventricular arrhythmias, may have greatly influenced the choice of antiarrhythmic agents, as well as the placebo-controlled trials that have proven that amiodarone improves patient prognosis.^{19,20} Finally, it is possible that the Sicilian Gambit,¹⁰ which utilizes a pathophysiologic approach for the selection of drugs instead of empiric selection, has been adopted by Japanese cardiologists.

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References

1. Echt DS, for the CAST investigators: Mortality and morbidity in patients receiving encainide, flecainide or placebo; the cardiac arrhythmia suppression trial. *N Engl J Med* 1991; **324**: 781–788
2. The Cardiac Arrhythmia Suppression Trial II investigators: Effects of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med* 1992; **327**: 227–233
3. IMPACT research group: International mexiletine and placebo antiarrhythmic coronary trial: Report on arrhythmia and other findings. *J Am Coll Cardiol* 1984; **4**: 1148–1163
4. Waldo AL, for the SWORD investigators: Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet* 1996; **348**: 7–12
5. Connolly SJ, for the CIDS investigators: Canadian implantable defibrillator study (CIDS): Study design and organization. *Am J Cardiol* 1993; **72**: 103F–108F
6. The Antiarrhythmics Versus Implantable Defibrillators (AVID) investigators: A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997; **337**: 1576–1583
7. Moss AJ, for the Multicenter Automatic Defibrillator Implantation Trial investigators: Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996; **335**: 1933–1940
8. Buxton AE, and the MUSTT investigators: Prevention of sudden death in patients with coronary artery disease: The Multicenter Unsustained Tachycardia Trial (MUSTT). *Prog Cardiovasc Dis* 1993; **36**: 215–226
9. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology: The Sicilian Gambit: A new approach to the classification of antiarrhythmic drugs based on their action on arrhythmogenic mechanisms. *Circulation* 1991; **84**: 1831–1851
10. Members of the Sicilian Gambit: Antiarrhythmic therapy: A pathophysiological approach. Armonk, NY: Futura; 1994
11. Members of the Sicilian Gambit: The search for novel antiarrhythmic strategies. *Jpn Circ J* 1998; **62**: 633–648
12. Kodama I, Ogawa S, Inoue H, Kasanuki H, Kato T, Mitamura H, et al: Profiles of aprindine, cibenzoline, pilsicainide and pirmenol in the framework of the Sicilian Gambit. *Jpn Circ J* 1999; **63**: 1–12
13. JALT-1 Investigators: Recent strategy for antiarrhythmic drug therapy in Japan: First report. *Nihon Iji Shinpo* 1994; **3654**: 47–52 (in Japanese)
14. JALT-1 Investigators: Recent strategy for antiarrhythmic drug therapy in Japan: Second report. *Nihon Iji Shinpo* 1994; **3687**: 25–27 (in Japanese)
15. Wijffels MC, Kirchhof CJ, Dorland R, Allesie MA: Atrial fibrillation begets atrial fibrillation: A study in awake chronically instrumented goats. *Circulation* 1995; **92**: 1954–1967
16. Daoud EG, Knight BP, Weiss R, Bahu M, Paladino W, Goyal R, et al: Effects of verapamil and procainamide on atrial fibrillation-induced electrical remodeling in humans. *Circulation* 1997; **96**: 1542–1550
17. Mason JW for ESVEM Investigators: A comparison of seven antiarrhythmic drugs in patients with ventricular tachycardias. *N Engl J Med* 1993; **329**: 452–458
18. The CASCADE Investigators: Randomized antiarrhythmic drug therapy in survivors of cardiac arrest (the CASCADE study). *Am J Cardiol* 1993; **72**: 280–287
19. Julian DG, for EMIAT Investigators: Randomized trial of effect of amiodarone on mortality in patients with left ventricular dysfunction after recent myocardial infarction; EMIAT. *Lancet* 1997; **349**: 667–674
20. Cairns JA, for CAMIAT Investigators: Randomized trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarizations. *Lancet* 1997; **349**: 675–682

Appendix

Organizing Members of JALT Study (from the outset)

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