



HotBalloon Ablation of the Pulmonary Veins for Paroxysmal AF

A Multicenter Randomized Trial in Japan

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ABSTRACT

BACKGROUND Point-by-point catheter ablation is an established treatment for drug-refractory paroxysmal atrial fibrillation (PAF). However, it is time consuming, requires excellent technique to achieve complete pulmonary vein (PV) isolation, and is associated with severe complications.

OBJECTIVES The purpose of this study was to evaluate the safety and effectiveness of a HotBalloon ablation (HBA) compared with antiarrhythmic drug therapy (ADT) for the treatment of PAF.

METHODS A prospective multicenter randomized controlled study was conducted in Japan. Patients with symptomatic PAF refractory to antiarrhythmic drugs (Class I to IV) were randomized to HBA or ADT at a 2:1 ratio and assessed for effectiveness in a comparable 9-month follow-up period.

RESULTS A total of 100 patients in the HBA group and 43 patients in the ADT group received treatment at 17 sites. HBA procedure produced acute complete PV isolation in 98.0% (392 of 400) of the PVs and in 93.0% (93 of 100) of patients in the HBA group. The chronic success rates after the 9-month effective evaluation period were 59.0% in the HBA group (n = 100) and 4.7% in the ADT group (n = 43; p < 0.001). The incidence of major complications was 11.2% (15 of 134 patients). The incidences of PV stenosis (>70%) and transient phrenic nerve injury were 5.2% and 3.7%, respectively. The mean fluoroscopy time was 49.4 ± 26.6 min (n = 134), and the mean procedure duration was 113.9 ± 31.9 min (n = 133).

CONCLUSIONS This study demonstrates the superiority of HBA compared with ADT for treatment of patients with PAF, and a favorable safety profile. (J Am Coll Cardiol 2016;68:2747-57) © 2016 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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ABBREVIATIONS AND ACRONYMS

AADs = antiarrhythmic drugs
ADT = antiarrhythmic drug therapy
AF = atrial fibrillation
HBA = HotBalloon ablation
LA = left atrium
MJC = major complication
PAF = paroxysmal atrial fibrillation
PV = pulmonary vein
SAE = serious adverse event
SF-36v2 = 36-item Short-Form Health Survey Version 2 Japan

Point-by-point catheter ablation is an established treatment for drug-refractory paroxysmal atrial fibrillation (PAF) (1,2). However, it is time consuming, requires excellent technique to achieve complete pulmonary vein (PV) isolation, and is associated with severe complications (1–4). An ideal catheter ablation method to treat atrial fibrillation (AF) would be quicker, less technically difficult, minimize collateral damage, and provide durable PV isolation. A radiofrequency HotBalloon catheter (**Central Illustration**) has been developed to overcome several of these limitations (5,6). The balloon membrane material is elastic and compliant, so it fits the variable

PV anatomy (7). Consequently, this clinical study was undertaken to evaluate if novel HotBalloon ablation (HBA) was safe and effective compared with antiarrhythmic drug therapy (ADT) for the treatment of PAF.

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METHODS

This study was conducted as a prospective multicenter randomized study of patients with drug-refractory (resistant and/or intolerant to) symptomatic PAF comparing treatment with HBA or ADT at 17 sites in Japan. Written informed consent was obtained from all patients. This study protocol was in accord with the Japanese good clinical practice guidance for medical devices and approved by the institutional review board at each site that participated in this study.

STUDY POPULATION AND DESIGN. Patients 20 years of age or older and younger than 75 years of age who were refractory to 1 or more Class I to IV antiarrhythmic drugs (AADs) were enrolled. Primary exclusion criteria were previous left atrium (LA) ablation or surgery for

AF; refractory to all of the following medications: pil-sicainide, cibenzoline, propafenone, disopyramide, and flecainide; New York Heart Association functional class III or IV; history of myocardial infarction or unstable angina pectoris during the previous 6 months; comorbid severe ischemic heart disease, valvular disorder, severe pulmonary hypertension, carotid occlusion, or deep-vein thrombosis; use of an LA appendage closure device, artificial heart valve, pacemaker, implantable-cardioverter-defibrillator or implantable-electrocardiogram recorder, inferior vena cava filter; and a history of cerebral infarction or intracerebral bleeding with apparent neurological symptoms during the previous 6 months.

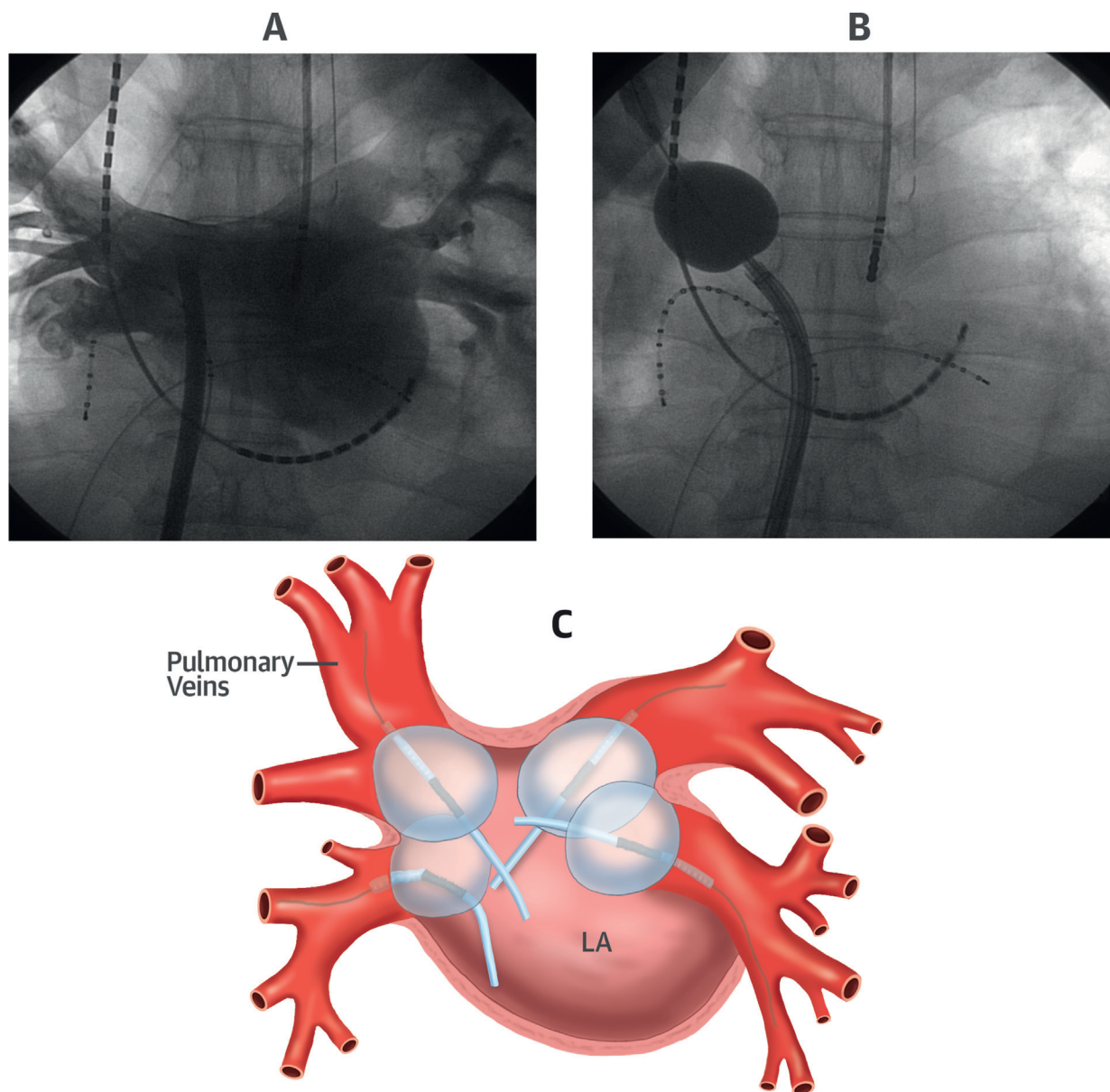
Patients were randomized at a 2:1 ratio to HBA or ADT. Two or more PAF episodes during the 6 months before treatment (ablation or drug therapy) and 1 or more episodes of PAF continuing for more than 30 s recorded by electrocardiogram were required to be enrolled. During the period between randomization and the start of treatment, patients underwent examination. Patients with an LA diameter of 50 mm or greater, a left ventricular ejection fraction of <35%, or an LA thrombus were excluded.

PROTOCOL. Patients were evaluated at the clinical site on day 0 to 7 and at 1, 3, 6, and 12 months after the procedure in the HBA group, and on day 0 and at 1, 4, and 10 months after the start of the drug-adjustment period in the ADT group. Effectiveness was evaluated in the 9-month effectiveness evaluation period after an 84-day blanking period for the HBA group and after a 28-day drug-adjustment period for the ADT group. A 12-lead electrocardiogram was obtained at all follow-up visits. Electrocardiogram monitoring was performed using a portable electrocardiogram monitor in both groups during the effectiveness evaluation period. Patients were required to obtain electrocardiogram readings at least once a week and

for lecture and consulting fees from Toray Industries. Dr. Hirao has received speaker honoraria and/or consulting fees from Boston Scientific Japan, Japan Lifeline, and NIHON KOHDEN. Dr. Shoda has received honoraria for lecture and consulting fees from Toray Industries. Dr. Yasuteru Yamauchi has received honoraria for lecture from Toray Industries. Dr. Yoshio Yamaguchi has received honoraria for lecture from Toray Industries. Dr. Kuwahara has received speaker honoraria and/or consulting fees from Japan Lifeline, Johnson & Johnson K. K. medical, and Toray Industries. Dr. Chun has received speaker honoraria from Boston Scientific Japan, Japan Lifeline, Johnson & Johnson K. K. medical, St. Jude Medical Japan, and Toray Industries. Dr. Kusano has received speaker honoraria from Boston Scientific Japan, Medtronic Japan, and St. Jude Medical Japan. Dr. Kaitani has received honoraria for lecture and consulting fees from Toray Industries. Dr. Fujii has received speaker honoraria from BIOTRONIK Japan, Japan Lifeline, St. Jude Medical Japan, and Toray Industries. Dr. Kumagai has received speaker honoraria and/or consulting fees from Japan Lifeline, NIHON KOHDEN, and Toray Industries. Mr. Matsushita is an employee of Toray Industries. Dr. Satake holds patents related to the HotBalloon catheter. Dr. Aonuma has received speaker honoraria, consulting fees, and/or grants from Boston Scientific Japan, DVx, Japan Lifeline, Johnson & Johnson K. K. medical, Medtronic Japan, and St. Jude Medical Japan. The authors receiving honoraria other than Dr. Ohe received <\$10,000. All other authors reported that they have no relationships relevant to the contents of this paper to disclose.

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CENTRAL ILLUSTRATION Fluoroscopic View of the Radiofrequency HotBalloon PV Ablation for Paroxysmal Atrial Fibrillation Patients



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(A) Left atrigram revealing (B) right superior PV balloon occlusion. The balloon material is very elastic and compliant, allowing single-shot ablation of PVs in the range of 26 to 33 mm. (C) Scheme of PV antrum isolation using a radiofrequency HotBalloon catheter. LA = left atrial; PV = pulmonary vein.

at the time of onset for any AF episodes. The 24-h Holter monitoring was performed at 6 and 12 months (or the final visit) after the procedure in the HBA group, and at 4 and 10 months (or the final visit) after the start of the drug-adjustment period in the ADT group. A 3-dimensional computed tomography

scan was performed at baseline, and at 6 and 12 months after the procedure in the HBA group to detect any PV stenosis. The stenosis rate was defined as reduction in diameter of >70%. All electrocardiograms and 3-dimensional computed tomography images were masked and transmitted to an independent core

laboratory for analysis. Adverse events were adjudicated by the investigator at each site, and were assessed by an independent evaluation committee. The AADs were determined by the investigator using Japanese antiarrhythmic guidelines.

HOTBALLOON ABLATION GROUP. The SATAKE HotBalloon ablation system (Toray Industries, Inc., Tokyo, Japan) was composed of a 13-F balloon catheter, an inner diameter 13-F deflectable guiding sheath (Treswartz, Toray Industries, Inc.), and a radiofrequency generator that automatically controls the temperature of the balloon and agitates the fluid inside the balloon. The system uses thermal energy conducted by the heated balloon to ablate the tissue, which does not directly mean radiofrequency ablation. The balloon was inflated up to 26 to 33 mm in diameter with contrast medium diluted 1:1 with normal saline, at a recommended injection volume of 10 to 20 ml. A coil electrode mounted on the catheter shaft within the balloon delivered radiofrequency energy, and a thermocouple near the coil electrode monitored the central balloon temperature. Radiofrequency current of 1.8 MHz was delivered between the coil electrode inside the balloon and the 4 cutaneous electrode patches on the patient's back to induce capacitive-type heating in the balloon. The balloon's central temperature was maintained at a preset value (40°C to 70°C) by the generator's automatic regulation of radiofrequency energy output. The agitation device delivered vibratory waves through a catheter balloon lumen into the balloon to mix the fluid in the balloon to maintain a uniform temperature throughout the balloon.

After transseptal puncture, a deflectable guiding sheath was inserted into the LA by using a guidewire. Subsequently, heparin was administered intravenously to maintain the activated clotting time between 300 and 400 s. Protamine was administered at the end to reverse the heparin. Before ablation, the 4 PVs (right superior, right inferior, left superior, left inferior) were delineated by LA angiography through deflectable guiding sheath, using contrast medium. PV potentials in all veins were recorded using a mapping catheter inserted through the deflectable guiding sheath. Subsequently, the balloon catheter was inserted into the LA using the deflectable guiding sheath.

The operator placed the balloon into the target PV ostium by advancing the J-tip guidewire (Toray Medical Co., Ltd.) through a catheter lumen into the PV. Diluted contrast medium was injected into the balloon through the catheter balloon lumen to inflate the balloon. Balloon positioning in the PV was adjusted by injection volume, so the balloon would

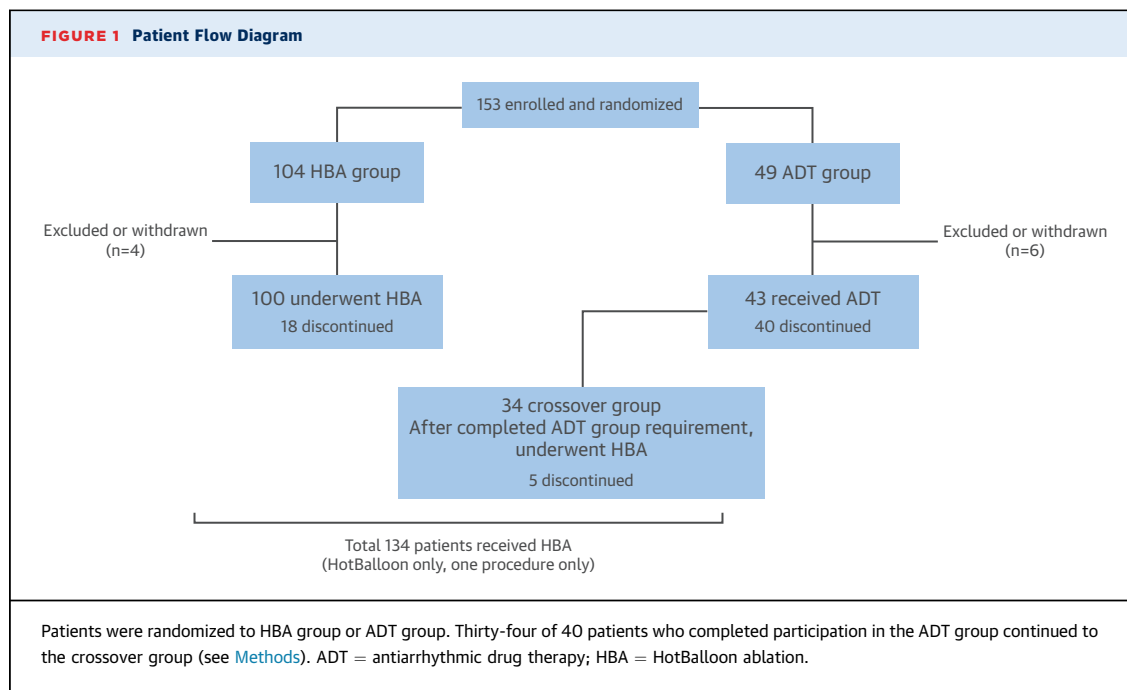
completely appose to the PV wall and occlude the PV. After ablation of the target PV ostium, the operator inflated the balloon slightly as it apposed the PV antrum, and repeated ablation. Subsequently, using similar techniques the operator performed ablation near the carina. After completion of all PV ablations, the operator again inserted the mapping catheter into the deflectable guiding sheath and recorded all PV potentials. If PV potentials remained, the ablation was repeated up to 3 times per location.

To prevent injury to the phrenic nerve, pacing of the diaphragm from an electrode in the superior vena cava was performed (especially during right PV ablations). Ablation energy delivery was terminated if diaphragmatic capture was lost. Furthermore, to avoid damage to the esophagus, the esophageal temperature was monitored (especially left PV ablations) by applying Sensi Therm Esophageal Temperature Monitoring System (St. Jude Medical, Inc., St. Paul, Minnesota). If the temperature exceeded 39°C, cooling water was injected into the esophagus (8). Intraoperative anticoagulation management and anesthesia were performed according to the standard practice of the clinical site. Postoperative anticoagulation was performed based on the judgment of the operators using the most recent guidelines.

After the procedure, an 84-day blanking period was set. The effectiveness evaluation period was defined as the 9 months after the end of the blanking period (to 12 months after ablation).

ANTIARRHYTHMIC DRUG THERAPY GROUP. Patients in the ADT group received treatment with AADs. A 28-day drug-adjustment period was set to determine the AADs to be used. The effectiveness evaluation period was defined as 9 months after the end of the drug-adjustment period. Patients who experienced 30 s or more of confirmed AF (meeting the criteria for failure of the effectiveness endpoints) within 3 months after the end of the drug-adjustment period were allowed to cross over to HBA treatment. Crossover data were used only to investigate the safety of HBA.

RESTRICTIONS ON CONCOMITANT DRUGS AND THERAPIES DURING THE STUDY. In the HBA group during the effectiveness evaluation period, the use of Classes I to IV AADs resulted in effectiveness failure except for AADs to which patients were preoperatively determined to be refractory could be used at the same or lower dose; and Class II and IV AADs could be used for indications other than the treatment of AF. In the ADT group, the use of AADs other than those determined during the drug-adjustment period resulted in effectiveness failure. Any of the following resulted in effectiveness failure for patients



in the HBA group: 1) LA ablation using other ablation devices during the index procedure; 2) redo procedures; 3) electrocardioversion during the effectiveness evaluation period; or 4) undergoing a surgical procedure or use of an implantable device that might affect the evaluation of this study. Ablation or 3) or 4) above resulted in effectiveness failure for patients in the ADT group.

EFFECTIVENESS ENDPOINTS. Acute success (PV isolation). Success was defined as a potential ≤ 0.1 mV or no synchronization of the PV and LA potentials.

Chronic success. The primary effectiveness endpoint was chronic success, defined as no documented AF episode continuing for 30 s or more, regardless of the presence or absence of symptoms, and no use of restricted concomitant drugs or therapies. Patients who discontinued this study after the start of ablation or the drug-adjustment period were defined as cases of treatment failure in both groups, regardless of the reasons or timing.

Quality of life. Quality of life was investigated at baseline and at the end of this study (or at study discontinuation) using the 36-item Short-Form Health Survey Version 2 Japan (SF-36v2).

Safety endpoints. Serious adverse events (SAEs) and major complications (MJs) were investigated. SAE was defined as any untoward medical occurrence that: 1) resulted in death; 2) was life threatening; 3) resulted in disability (dysfunction affecting patient's

normal daily activity); 4) might result in disability; 5) required or prolonged hospitalization for treatment; 6) was as serious as the conditions mentioned in 1) to 5) above; or 7) was a congenital disease or anomaly in the offspring. MJC in the HBA group and the crossover group was defined as category 1) SAEs that occurred within 7 days after the procedure; 2) all postoperative severe PV stenosis ($>70\%$) or esophageal perforation, cardiac tamponade, phrenic nerve paralysis, or cerebral infarction accompanied by apparent neurological symptoms; and 3) postoperative PV stenosis ($\leq 70\%$) that required invasive treatment such as stenting or was accompanied by severe clinical symptoms.

STATISTICAL ANALYSIS. A 2-tailed test was conducted for hypothesis testing without multiplicity adjustment with a significance level of 5%. Intergroup comparison by Fisher's exact test was conducted for the primary analysis of chronic success, the primary effectiveness endpoint. In addition, the following analysis was performed as an exploratory analysis. A Kaplan-Meier curve was plotted for the time to first AF recurrence, use of restricted concomitant drugs, and performance of restricted concomitant therapies; and an intergroup comparison was conducted using a log-rank test. We used Cox's proportional hazard model to estimate the hazard ratio and its Wald-type 95% confidence interval (CI). Events that had occurred during the blanking period and termination were treated as those occurring at the first day of the evaluation period (day 0).

TABLE 1 Baseline Characteristics			
	HBA (n = 100)	ADT (n = 43)	HBA and Crossover (n = 134)
Age, yrs	58.8 ± 10.4	61.0 ± 10.0	58.9 ± 10.3
Male	80.0	81.4	82.1
AF duration, yrs	5.3 ± 6.8 (n = 97)	4.6 ± 4.6 (n = 41)	5.1 ± 6.3 (n = 130)
Hypertension	51.0	55.8	50.7
Diabetes	3.0	9.3	4.5
Hyperlipidemia	19.0	14.0	16.4
Coronary artery disease	3.0	4.7	3.7
History of atrial flutter	18.0	14.0	17.9
CHADS ₂ score	0.8 ± 0.9	0.9 ± 1.0	0.8 ± 0.9
LA diameter, mm	38.3 ± 5.6	38.3 ± 4.9 (n = 42)	38.1 ± 5.4
% Left ventricular ejection fraction	66.7 ± 6.1	66.5 ± 6.5 (n = 42)	66.0 ± 6.4
LA volume, ml	66.5 ± 30.1	65.2 ± 24.5 (n = 42)	66.8 ± 30.2
Number of AADs*	1.4 ± 0.8	1.2 ± 0.8	1.4 ± 0.8
AADs*			
Pilsicainide	35.0	37.2	33.6
Cibenzoline	14.0	20.9	14.2
Propafenone	6.0	0.0	6.7
Disopyramide	2.0	0.0	1.5
Flecainide	6.0	0.0	6.7
Others	57.0	41.9	54.5
Refractory AADs*			
Class I/III	79.0	67.4	76.1
Class II/IV only	15.0	9.3	12.7
SF-36v2			
Role physical	45.8 ± 12.7	47.1 ± 10.0	
Role emotional	47.3 ± 11.2	48.1 ± 9.5	
Mental health	49.0 ± 9.9	50.3 ± 8.4	
Role/social component summary	45.7 ± 13.2	48.3 ± 12.3	

Values are mean ± SD or %. *Used at the time of signing the informed consent.
 AADs = antiarrhythmic drugs; ADT = antiarrhythmic drug therapy; AF = atrial fibrillation;
 CHADS₂ = congestive heart failure, hypertension, age 75 or older, diabetes, and stroke scale;
 HBA = HotBalloon ablation; LA = left atrial; SF-36v2 = 36-item Short-Form Health Survey
 Version 2 Japan.

For the SF-36v2, analysis of covariance was performed using changes from baseline at the end of this study or study discontinuation, with the baseline as a covariate. SAS version 9.3 software (SAS Institute Inc., Cary, North Carolina) was used.

RESULTS

PATIENT CHARACTERISTICS. A total of 153 patients were enrolled, with 104 and 49 patients randomized to the HBA group and the ADT group, respectively. Four patients in the HBA group and 6 patients in the ADT group did not receive ablation or start the drug-adjustment period. As a result, interventional treatment was performed in 100 patients in the HBA group and 43 patients in the ADT group. Thirty-four patients

TABLE 2 Procedural Characteristics		
	HBA (n = 100)	HBA and Crossover (n = 134)
Conscious sedation (patients)	99.0	99.3
Procedure time, min*	113.8 ± 33.2 (n = 99)	113.9 ± 31.9 (n = 133)
Ablation time, min†	28.0 ± 4.4	28.4 ± 4.6
Fluoroscopy time, min	49.5 ± 27.4	49.4 ± 26.6
Ablation time per PV, min		
Right superior	8.1 ± 2.1	8.3 ± 2.2
Right inferior	4.5 ± 1.0	4.4 ± 0.9
Left superior	10.2 ± 2.9	10.5 ± 3.1
Left inferior	5.2 ± 1.6	5.2 ± 1.6
Number of ablations per PV		
Right superior	3.5 ± 0.7	3.5 ± 0.8
Right inferior	2.1 ± 0.4	2.1 ± 0.4
Left superior	3.4 ± 0.9	3.5 ± 0.9
Left inferior	2.3 ± 0.7	2.3 ± 0.7
Volume in the balloon per PV, ml		
Right superior	9.5 ± 1.6	9.7 ± 1.7
Right inferior	7.9 ± 1.8	8.1 ± 1.9
Left superior	10.1 ± 2.0	10.2 ± 1.9
Left inferior	8.8 ± 1.6	8.9 ± 1.6

Values are % or mean ± SD. *From the time of transseptal puncture to the time of protamine administration after ablation. †The sum of ablation time for each PV.
 HBA = HotBalloon ablation; PV = pulmonary vein.

(79.1%) in the ADT group continued to the crossover group. Accordingly, a total of 134 patients underwent HBA (Figure 1).

Baseline characteristics in the HBA group were similar to those in the ADT group (Table 1). The mean CHADS₂ (congestive heart failure, hypertension, age 75 or older, diabetes, and stroke scale) score was <1 in both groups, indicating that patients with a low risk of embolism were enrolled.

PROCEDURAL CHARACTERISTICS. Procedural characteristics are shown in Table 2. There was no patient who could not undergo appropriate ablation because of the anatomy of the PVs (i.e., form and diameter of the openings of the PVs). Because the carina ablation was counted as superior PV ablation, the duration and number of ablations was greater for superior PVs than for inferior PVs. The mean total fluoroscopic time in the HBA and crossover groups was 49.4 ± 26.6 min (minimum: 12 min; maximum: 132 min), and the mean total duration of the procedure was 113.9 ± 31.9 min (minimum: 57 min; maximum: 215 min). Shorter fluoroscopic and procedure times were achieved by the sites that had experience from previous HotBalloon studies.

EFFECTIVENESS OUTCOMES. Acute success (PV isolation). Ablation in the HBA group resulted in isolation of all 4 PVs in 93.0% (95% CI: 86.1 to 97.1; 93

of 100) of the patients. The percentage of PVs isolated was 98.0% (95% CI: 96.1 to 99.1; 392 of 400 PVs) (Table 3).

Chronic success. The chronic success rate, the primary effectiveness endpoint, was 59.0% (95% CI: 48.7 to 68.7; 59 of 100) in the HBA group and 4.7% (95% CI: 0.6 to 15.8; 2 of 43) in the ADT group, showing a statistically significant difference ($p < 0.001$) (Table 3). All 7 patients with acute HBA failure resulted in chronic failure.

The Kaplan-Meier plot with AF recurrence and the use of restricted concomitant drugs or therapies as events are presented in Figure 2. The event-free rates at the end of the effectiveness evaluation period at week 36 were 60.0% in the HBA group and 8.3% in the ADT group, showing a statistically significant difference ($p < 0.001$).

Quality of life. In the HBA group, 8 of 11 items in the SF-36v2 quality-of-life form significantly increased at the end of this study or at study discontinuation compared to baseline (Table 4). In the ADT group, 9 of 11 items slightly decreased. The role physical, role emotional, mental health, and role/social component summary items significantly increased in the HBA group compared with those in the ADT group.

SAFETY OUTCOMES. Adverse events were assessed by the investigators and the independent evaluation committee. There were no differences in assessment results, other than for 1 event of cerebral infarction. For 1 event of cerebral infarction, the independent evaluation committee considered that the causal relationship with HotBalloons could not be completely ruled out, whereas the investigator did not consider it to be related.

MJCs. The incidence of MJCs in all patients undergoing HBA was 11.2% (95% CI: 6.4 to 17.8; 15 patients, 17 events) (Table 5). There was no esophageal perforation, cardiac tamponade, cerebral infarction which was classified as category 2 of MJC, or PV stenosis which was classified as category 3 of MJC.

Phrenic nerve injury. The incidence of phrenic nerve paralysis was 3.7% (5 of 134). The events in the 5 patients were recovered within 9 to 13 months, and inpatient hospitalization or prolongation of existing hospitalization was not needed.

PV stenosis. The incidence of PV stenosis ($>70\%$) was 5.2% (7 of 134; 2 right superior PVs, 1 right inferior PV, 1 left superior PV, 3 left inferior PVs). During the follow-up period, no clinical symptoms associated with PV stenosis were reported, and no invasive treatments were required.

TABLE 3 Effectiveness Outcomes of Radiofrequency HotBalloons PV Ablation

Acute HBA Success Rate		
By patient		By pulmonary vein
93.0% (93/100)		98.0% (392/400)
Chronic Success Rate†		
HBA group	ADT group	p value*
59.0% (59/100)	4.7% (2/43)	<0.001

*Fisher's exact test. †Defined as freedom from AF at 36-week effectiveness evaluation period. Outcomes were achieved without using "touch-up" ablation using a conventional ablation catheter.

Abbreviations as in [Tables 1](#) and [2](#).

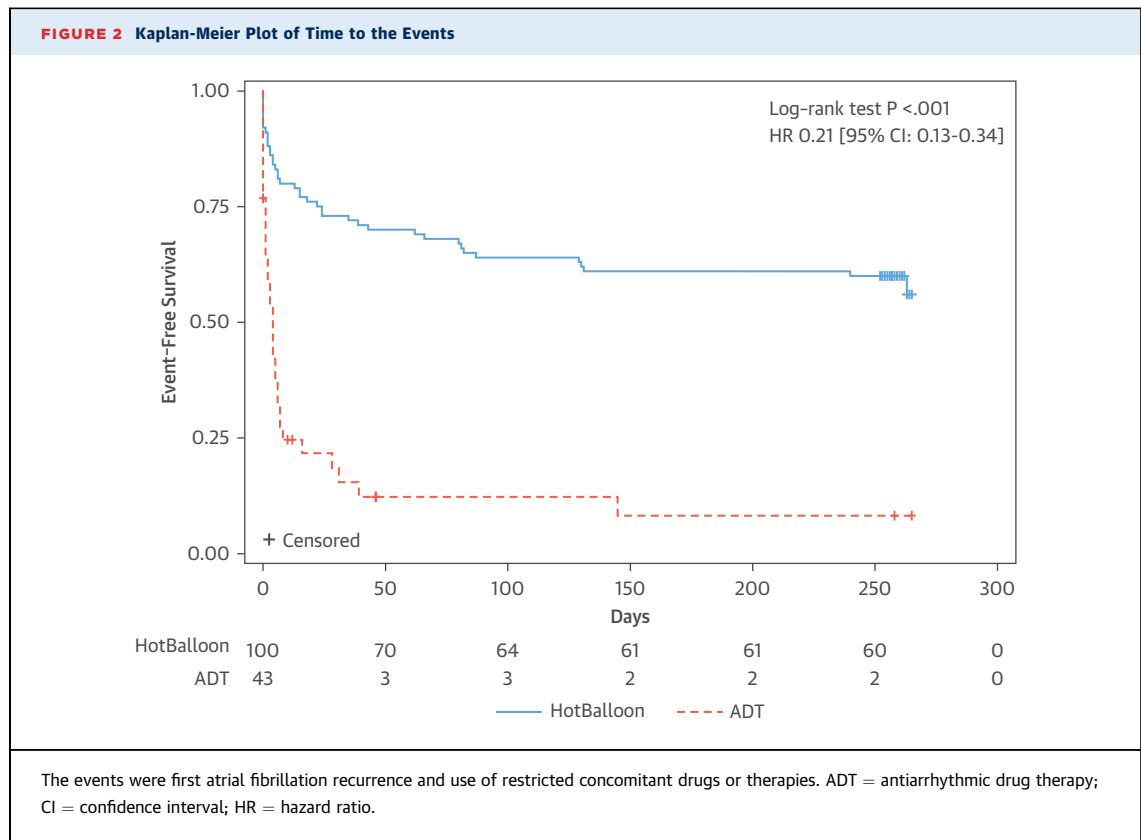
Cerebral infarction. The incidence of cerebral infarction was 1.5% (2 of 134). Two patients had onset of cerebral infarction on the day of the ablation procedure. One patient had paralysis of the left upper limb that resolved 2 days later and was attributed to an air embolism during basket mapping catheter insertion after ablation. The other patient had paralysis of the right lower limb with a small cerebral infarct area on magnetic resonance imaging that resolved 27 days after the ablation procedure. The patient had a background of patent foramen ovale, and the investigator expressed the opinion that the venous thrombus formed at the puncture site could have entered the left heart system through the patent foramen ovale.

SAEs. The incidence of SAEs was 10.4% (14 of 134 patients) in all patients undergoing HBA (Table 6) and 4.7% (2 of 43 patients) in the ADT group. For all events, a causal relationship with the HotBalloons catheter and/or AADs was ruled out by the investigator. The independent evaluation committee concluded that the causal relationship with the HBA could not be completely ruled out for a case of cerebral infarction.

Adverse events. There was no occurrence of heart wall perforation, cardiac tamponade, injury of a coronary artery, valve, or chordae tendineae, atrial-esophageal fistula, or esophageal perforation. The incidence of adverse events related to vascular access sites whose causal relationship with the HotBalloons catheter could not be ruled out was 20.9% (28 of 134 patients); however, none of the events was reported to be SAEs, and none required surgical treatment or blood transfusion.

DISCUSSION

The main finding of this study is the demonstration of the superiority of HBA compared with ADT in the treatment of patients with PAF refractory to AADs.



Several studies involving other ablation therapies for AF have reported significant adverse events such as PV stenosis requiring intervention, atrial-esophageal fistula, permanent phrenic nerve paralysis, pyloric spasm, and death (1,4). None of the patients in this study experienced these serious events.

EFFECTIVENESS OF HOTBALLOON ABLATION. The single-procedure chronic success rate after 12 months was 59.0% in the HBA group. This shows sufficient effectiveness, especially considering that the procedures were performed by Japanese operators with little balloon ablation experience. The chronic success rates of other types of ablation catheters in recent clinical studies have been reported to be 70% to 80% (3,4,9). These may reflect improved treatment results due to the effect of the operator's experience with the ablation therapy being used. It is expected that additional experience with HBA will result in improved future outcomes. However, comparison of effectiveness results among studies must be performed carefully. In pivotal clinical trials such as this one, AF recurrences are investigated strictly compared with those occurring in many post-marketing studies, and chronic success rates may appear low. In fact, the single-procedure chronic success rate of a well-established radiofrequency

ablation method that served as the control device in the HeartLight trial was 61.7% (10). The differences in the protocols and the definition of success must be noted.

The effectiveness comparisons among the initial pivotal clinical trials experience are more accurate than comparisons to post-marketing studies. The chronic success rates reported were 63% in the Thermocool AF trial including redo procedures (11); 65.8% in the SMART-AF (THERMOCOOL SMART-TOUCH Catheter for the Treatment of Symptomatic Paroxysmal Atrial Fibrillation) trial (12); 57.7% in the STOP AF (Sustained Treatment of Paroxysmal Atrial Fibrillation) trial (13); and 61.1% in the HeartLight trial (10). In this study, weekly portable electrocardiogram monitoring was performed, asymptomatic and short episodes of AF (≥ 30 s) were defined as recurrence, touch-up tools were not used and LA linear ablation was not performed during ablation, and redo procedures were not performed. In view of the above, this study shows sufficient effectiveness.

ANTIARRHYTHMIC DRUG THERAPY. The chronic success rate in the ADT group was 4.7% in this study. The event rate by Kaplan-Meier method was 7.3% in STOP AF trial (13); 8.3% in this study; and 16.0% in Thermocool AF trial (11). These results were similar.

TABLE 4 Quality of Life (SF-36v2)

Scale	HBA (n = 100)	ADT (n = 32)	Differences Between Groups
Physical functioning	1.9 ± 0.9	-1.3 ± 1.7	3.2 ± 1.9
p Value	0.048	0.434	0.099
Role physical	3.0 ± 1.0	-1.5 ± 1.8	4.4 ± 2.0
p Value	0.004	0.406	0.031
Body pain	1.1 ± 0.9	-0.4 ± 1.7	1.4 ± 1.9
p Value	0.260	0.826	0.456
General health perceptions	2.4 ± 0.7	0.3 ± 1.2	2.1 ± 1.4
p Value	<0.001	0.800	0.129
Vitality	2.1 ± 1.0	-0.1 ± 1.7	2.2 ± 2.0
p Value	0.035	0.949	0.273
Social functioning	2.5 ± 1.0	-0.0 ± 1.8	2.6 ± 2.0
p Value	0.012	0.979	0.208
Emotional role	3.4 ± 0.9	-0.9 ± 1.5	4.3 ± 1.8
p Value	<0.001	0.559	0.017
Mental health	2.7 ± 0.9	-1.0 ± 1.6	3.8 ± 1.9
p Value	0.004	0.539	0.049
Physical component summary	0.8 ± 0.7	-0.5 ± 1.3	1.3 ± 1.5
p Value	0.273	0.691	0.376
Mental component summary	1.6 ± 0.9	0.3 ± 1.6	1.3 ± 1.8
p Value	0.065	0.849	0.455
Role/social component summary	3.1 ± 1.0	-1.4 ± 1.8	4.5 ± 2.0
p Value	0.002	0.433	0.029

Values are least squares means of change from baseline ± SE by analysis of covariance.
Abbreviations as in Table 1.

TABLE 5 Tabulation of Major Complications

Category	Type of Adverse Events	HBA and Crossover (n = 134)
1	Serious adverse events within 7 days of the ablation procedure (day 0-7)	
	Cerebral infarction	1.5 (2)
	Complete atrioventricular block	0.7 (1)
	Sick sinus syndrome aggravated	0.7 (1)
	Pseudoaneurysm	0.7 (1)
2	PV stenosis (>70%)	5.2 (7)
	Esophageal perforation	0
	Cardiac tamponade	0
	Phrenic nerve paralysis	3.7 (5)
	Cerebral infarction accompanied with apparent neurological symptom	0
3	PV stenosis (≤70%) that meets 1 of the following criteria: requires an invasive intervention, such as PV stenting; results in clinically significant symptoms	0
Total MJCs rate*		11.2 (15 patients, 17 events)

Values are % (number of events). *Total MJCs rate means the number of patients experiencing MJC.
MJCs = major complications; other abbreviations as in Tables 1 and 2.

TABLE 6 List of Serious Adverse Events in HBA Group and Crossover Group

SAE Reported Term	Seriousness Criteria	Time to Onset From Ablation Procedure
Cerebral infarction	5	0 day
Cerebral infarction	5	0 day
Complete atrioventricular block	5,6	0 day
Pseudoaneurysm	5	0 day
Sick sinus syndrome aggravated	5	2 days
Bradycardia	5	20 days
Loss of consciousness	4, 5	21 days
Cardiac failure acute	5	22 days
Coronary spastic angina (VSA)	5	22 days
Bladder cancer	5, 6	33 days
Sick sinus syndrome	5	73 days
Large intestine carcinoma	5	126 days
Acute bronchitis	5	166 days
Pneumonia	5	166 days
Gastric cancer	6	About 6 months
Anxiety neurosis	5	215 days
Total SAEs rate: 10.4% (14 patients, 16 events)*		

Seriousness criteria are defined as: 1) results in death; 2) is life threatening; 3) results in disability (dysfunction affecting patient's normal daily activity); 4) may result in disability; 5) requires or prolongs hospitalization for treatment; 6) is as serious as the conditions mentioned in events 1) to 5) above; 7) is a congenital disease or anomaly in the offspring. *Total SAEs rate means the rate of patients experiencing SAE(s) in HBA and crossover group (n = 134).
HBA = HotBalloon ablation; SAEs = serious adverse events; VSA = vasospastic angina.

In the case of a similar study design, the effectiveness of AADs therapy in drug-refractory symptomatic PAF patients has been reported to typically result in a 5% to 20% chronic effectiveness success rate.

QUALITY OF LIFE. The SF-36v2 form, a comprehensive quality of life scale not limited to some diseases (14), has been widely used to evaluate symptom change and symptomatic arrhythmia burden as an AF ablation outcome. In this study, many items for patients in the HBA group improved significantly compared to their baseline values and the values of the ADT group (Table 4), suggesting that HBA may not only provide rhythm control but also decrease symptoms and improve physical and mental health.

COMPLIANT BALLOON FITS VARIATIONS IN PV ANATOMY. The HotBalloon material is compliant enough to accommodate variations in PV anatomy. As previously reported, compliance of the balloon membrane also allows the device to be used to perform a box isolation procedure for the treatment of various types of AF (7).

The temperature of the fluid in the HotBalloon during radiofrequency energy delivery is not susceptible to the effects of the temperature of the circulating blood in the surrounding vessel.

Accordingly, the hyperthermic effect is maintained. Therefore, operators do not need to completely block blood circulation to perform PV antrum and carina ablation, and vein occlusion should be maintained during ostial PV ablation. In addition, the size and form of the HotBalloon can be altered. The balloon expands from 26 to 33 mm in size with a recommended injection volume of 10 to 20 ml. A single balloon catheter can perform ablation in PVs of various sizes and shapes. These factors demonstrate the potential merit.

PULMONARY VEIN STENOSIS. In this study, 7 patients developed PV stenosis (>70%). All patients with PV stenosis were asymptomatic, and no interventions were required during the follow-up period. Investigation of the fluoroscopic images during ablation for these 7 patients confirmed a trend toward the balloon being located deeper in the PV. It is considered that distal PV ablation is a risk factor for the development of PV stenosis. In addition, in all 7 patients, the fluid volume injected into the PV ablation balloon was 8 ml or less. When the fluid volume in the balloon is small, the balloon becomes smaller in diameter and more prone to inadvertently advance deeper into the PV. Even if the balloon is confirmed to be located at an appropriate site by radiography before ablation, the balloon may inadvertently advance deeper into the PV, such as by a sudden motion of a patient during radiofrequency energy delivery. Therefore, verifying proper balloon position using radiography every 30 s during ablation and a higher balloon injection volume (10 to 20 ml) are strongly recommended. It is believed that mastering such skills will lead to future reductions in the risk of PV stenosis.

ESOPHAGEAL INJURY. Although complications related to esophageal injury have been reported with other types of ablation catheters (15), there were no symptomatic serious esophageal injuries using the HotBalloon, including esophageal ulceration, pyloric spasm, and atrial-esophageal fistula detected. The esophageal cooling method (8) performed intraoperatively might contribute to the prevention of these complications. The ability to immediately stop ablation by deflating the balloon and immediately reduce radiofrequency power and temperature in the balloon also may contribute to the avoidance of serious esophageal injury. However, it should be noted that no routine endoscopy was performed; therefore no data about the incident of esophageal injury can be provided.

PHRENIC NERVE INJURY. Phrenic nerve injury is a well-documented complication of ablation for AF

(1–4,13). In this study there were 5 events of phrenic nerve paralysis. However, all 5 patients recovered. The HotBalloon does not adhere to the tissue, so ablation can be immediately halted by ceasing radiofrequency energy delivery and deflating the balloon. This might be the reason that the 5 events were transient. However, despite this potential advantage, efforts should be made to avoid phrenic nerve injury during HBA. In these 5 patients, the balloon fluid volume during right superior PV ablation was 8 ml or less. When the balloon is small in diameter, it is more prone to inadvertently advance deeper into the PV, increasing the risk of injury. In some cases the balloon may advance into the distal portion of the right superior PV beyond the cardiac border where the phrenic nerve is typically immediately posterior to the right atrium. Therefore, proper balloon position within the cardiac shadow should be maintained and the recommended balloon injection volume should be used.

CEREBRAL INFARCTION. There were 2 events of cerebral infarction in this study. One of them occurred when, after ablation, a basket mapping catheter was inserted in the sheath. During the insertion, the sound of air sucked in the sheath was heard and ST-segment elevation was detected. In the other event, the investigator reported that the venous thrombus formed at the puncture site could have entered the left heart system through the patent foramen ovale. However, with regard to the second cerebral infarction, the independent evaluation committee concluded that the causal relationship with HotBalloon could not be completely ruled out.

The authors thought that these 2 events were important “procedure-related SAE” as both of the incidents occurred within 24 h after the procedure. Although both events were fully resolved 2 and 27 days after the procedure, respectively, careful attention must be paid to the proper use of HotBalloon and other devices, with proper care of puncture sites and anticoagulation treatment.

STUDY LIMITATIONS. Although this trial was a prospective multicenter randomized study, there were several limitations to be considered. The evaluation period was 48 weeks. A longer period trial should be conducted in the future to investigate the effectiveness and safety of the thermal properties of HBA.

There were no devices in widespread use that were approved for PAF treatment in Japan at the time (2011) of planning this study, so HBA was not comparable with other ablation devices as controls. In addition, the definitions of recurrence of AF and of the chronic success were different in the trials for

other ablation devices. The effectiveness of HBA showed superiority to ADT, but it was difficult to simply compare the HBA with other ablation devices.

In this trial, no routine esophageal endoscopy was performed to investigate esophageal injury. In addition, the interpretation of the quality-of-life data is limited due to the high crossover rate.

CONCLUSIONS

This clinical trial demonstrates the superiority of HBA over ADT in the treatment of patients with PAF with a favorable safety profile.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL

SKILLS: In patients with PAF, ablation is more effective than ADT in maintaining sinus rhythm. HBA is superior to ADT in maintaining sinus rhythm in patients with PAF.

TRANSLATIONAL OUTLOOK: Multicenter, randomized studies are needed to assess the potential benefits of compliant HBA in patients with non-PAF.

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