

Preliminary Study on the Safety and Efficacy of One-Stop Treatment of Percutaneous LAAO Combined with Coronary Intervention for Higher Risk of Bleeding in Patients with AF Complicated with CHD

Xiaofei Jiang, MD, PhD,¹ Jie Zeng, MD,² Lintao Zhong, MD, PhD,¹ Weimin Zhu, MD,¹ Jun Li, MD¹

¹Department of Cardiology, Zhuhai People's Hospital (Zhuhai Hospital affiliated with Jinan University), Zhuhai, China;

²Department of Cardiology, Sichuan Province People's Hospital, Chengdu, China

ABSTRACT

Aims: To explore the feasibility, safety, and efficacy of 1-stop treatment of percutaneous left atrial appendage occlusion (LAAO) combined with coronary intervention for patients with nonvalvular atrial fibrillation (AF) complicated with coronary heart disease (CHD).

Methods and Results: We retrospectively analyzed the clinical data of 6 patients with AF combined with CHD admitted from Zhuhai People's Hospital from April 2017 to June 2018. After the operation, all patients were treated with aspirin (100 mg qd) and clopidogrel (75 mg qd) for 1 year, which is considered long-term use of aspirin/clopidogrel. The effects of LAAO and coronary intervention were evaluated immediately. The location of the left atrial appendage occluder, thrombosis, residual leak, and clinical manifestations were observed during the 90-day follow-up. The patients were implanted with Watchman™ devices and coronary stents. After the operation, the immediate sealing effect was satisfactory. The Watchman occluder was used in accordance with the PASS principle (position, anchor, size, seal), and the coronary intervention was satisfactory. During the operation, there were no device-related thrombosis, tamponade, or vascular complications. Follow-up results showed that in the 6 patients, there were no hemorrhagic strokes, worsening heart function, residual leakage, device-related thrombosis, angina pectoris, myocardial infarction, skin ecchymosis, gastrointestinal bleeding, or cerebral hemorrhage.

Conclusion: For patients with nonvalvular AF combined with CHD, the safety and feasibility of 1-stop treatment with left atrial appendage and coronary intervention are reliable, and the curative effects were also satisfactory at short- and medium-term follow-up.

INTRODUCTION

Atrial fibrillation (AF) is one of the most common arrhythmias encountered in clinical practice. The incidence of AF increases with age, especially among elderly individuals, and can increase by 10% with every 5 years of age [Chugh 2014]. AF often coexists with coronary heart disease (CHD), with approximately one-third of patients with AF exhibiting concurrent CHD [Zoni-Berisso 2014]. Owing to the different mechanisms of atrial thrombosis and intracoronary thrombosis, antithrombotic treatment strategies for these 2 diseases are tailored accordingly.

The management of patients with AF complicated by coronary artery disease after percutaneous coronary intervention (PCI) is more difficult because of the increased risk of bleeding resulting from combined antithrombotic therapy. Minimizing the risk of bleeding while achieving maximal benefit is a hot topic in the field of cardiovascular disease. Previous studies have focused on topics related to medication, such as drug selection, drug synergy, and the timing of drug administration. This study aimed to investigate the use of percutaneous left atrial appendage occlusion (LAAO) in place of anticoagulant therapy in patients with nonvalvular AF, CHD, a CHA2DS2-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category) score ≥ 2 , and a HAS-BLED (hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio [INR], elderly, drugs or alcohol) score ≥ 3 to evaluate the feasibility, safety, and efficacy of 1-stop treatment consisting of LAAO combined with PCI followed by antiplatelet therapy after surgery.

METHODS

Study Subjects

We retrospectively analyzed the clinical data of 6 patients, 4 males and 2 females, with nonvalvular AF complicated by CHD who underwent LAAO combined with PCI from April 2017 to June 2018 in Zhuhai People's Hospital. The average age was 71.5 ± 7.7 years (range 59 to 83). The study was approved and conducted by the Research Ethics Committees of Zhuhai People's Hospital, Affiliated Hospital of

Received February 18, 2021; accepted March 22, 2021.

Correspondence: Xiaofei Jiang, MD, PhD, Department of Cardiology, Zhuhai People's Hospital, Zhuhai 519000, China 79 Kang ning Road, Zhuhai 519000, China; 86 20 61642365; fax: 86 20 87712332 (e-mail: jxf_1982@sina.com).

Jinan University. The study conforms to the guiding principles of the Declaration of Helsinki. All subjects signed written informed consent. Clinical information of the patients is shown in Table 1.

Inclusion criteria were as follows: (1) nonvalvular AF >1 year; (2) >18 years old; (3) CHA2DS2-VASc score ≥ 2 ; (4) HAS-BLED score ≥ 3 ; (5) able to tolerate long-term clopidogrel and aspirin use; (6) contraindications to anticoagulant drugs or unable/unwilling to receive long-term anticoagulant therapy; and (7) definitive diagnosis of CHD requiring PCI treatment.

Preoperative Transesophageal Echocardiograph (TEE)

Evaluation

A Philips IE33 ultrasound diagnostic system with an X7-2t esophageal probe was used for TEE. Left atrial appendage (LAA) morphology was observed in the 0°, 45°, 90°, and 135° views, and the diameter of the opening and depth of the LAA were measured. Contraindications for device closure of the LAA were evaluated. Exclusion criteria were as follows: (1) mural thrombus in the left atrium or another heart chamber; (2) LAA maximum diameter >31 or <17 mm; or (3) significantly reduced left ventricular function.

Evaluation of the LAA by Computed Tomography Angiography (CTA) before Surgery

A Siemens Somatom Flash CT scanner (2× Stellar detector, 128-slice CT) and a retrospective electrocardiograph gating technique were used for this evaluation. Patients were asked to hold their breath after a single expiration; breath-hold time was 4 to 7 s. A bolus dose of contrast was administered to view the aortic root, and the 5-second delay from the peak time was used as the delay time in the CTA scan. The reconstruction phase was selected during left ventricular diastole. The maximum diameter and maximum depth of the LAA were measured halfway from the pulmonary vein valve opening.

LAAO Procedure

The Watchman™ occluder was used for LAAO in this group of patients. The detailed procedure is as follows. Patients underwent LAAO under general anesthesia with

tracheal intubation. A TEE probe was placed. The right femoral vein was punctured, followed by placement of an 8F vascular sheath. An SL1 sheath and transeptal needle were inserted through the interatrial septum (at a slightly inferior and posterior site) under TEE guidance. Intravenous heparin was administered according to the patient's body weight (100 IU/kg) at the beginning of the procedure. The activated coagulation time (ACT) was monitored and maintained at >250 s during the procedure.

After the SL1 sheath was inserted into the left atrium, a stiff wire was used to deliver a 14F Watchman delivery sheath to the left atrium, and then a 6F pigtail catheter was inserted and rotated in the left atrium into the LAA. LAA angiography was performed with the patient in the supine position at right anterior oblique 30° and caudal 20°. The diameter of the opening of the LAA and the depth of the LAA were measured by both TEE and angiography. The measurement values were used to ascertain the dimensions of the occluder, and the LAA occluder was selected accordingly. The Watchman occluder was inserted via the delivery sheath. After the occluder reached the expected site, the delivery sheath was withdrawn, and the occluder was released to occlude the LAA. The position and shape of the occluder were observed by TEE, and the compression ratio, excessive shoulder, and leak flow of the device were measured. Under TEE and digital subtraction angiography guidance, the push-pull maneuver was performed to confirm the secure position of the occluder according to the PASS principle (position, anchor, size, seal), and the occluder was released. The position and shape of the device were again examined by TEE. The TEE probe was withdrawn, and PCI was initiated.

PCI Procedure

The radial artery/femoral arteries were punctured, and an arterial sheath was inserted. Different catheters were selected for left and right coronary angiography. The measurement of coronary artery stenosis and target vessel classification was performed according to the criteria of the 1990 American College of Cardiology lesion classification: the reference diameter was 2.5 to 4.0 mm, and target vessel stenosis was >75%. Various guide catheters, guide wires, balloons, and coronary stents were selected; the stents used in PCI were

Table 1. Patient Clinical Information (n = 6)*

No.	Sex	Age (y)	CHA2DS2-VASc	HAS-BLED	NYHA Class	EF (%)	Size of LAAO (mm)
1	M	78	5	4	I	61	23
2	F	83	9	4	III	40	27
3	M	73	4	4	II	45	21
4	F	68	5	3	II	48	24
5	M	59	3	3	I	56	28
6	M	68	5	3	II	50	27

*NYHA indicates New York Heart Association.

drug-eluting stents [Gunnar 1990]. The success criteria for PCI were as follows: residual stenosis of the target vessels <20% after stent placement, thrombolysis in myocardial infarction grade 3 (normal antegrade flow), and no serious complications (Figure 1).

RESULTS

The LAA occluder and coronary artery stent were successfully implanted in all 6 patients. The sequence of operation was LAAO first, followed by coronary artery stent

implantation. The Watchman occluder was selected for all patients. The size, compression ratio, excessive shoulder, and leak flow of the Watchman occluder were 30.5 ± 2 mm, $24.8 \pm 2.9\%$, 3.8 ± 1.4 mm, and 0.2 ± 0.44 mm, respectively. One patient suffered chronic total occlusion of the right coronary artery (RCA). Severe stenosis of the left anterior descending (LAD) artery was checked in 3 patients, and the remaining patients suffered severe stenosis of the left circumflex (LCX) artery. Detailed information on the stents is shown in Table 2.

No complications, such as immediate pericardial tamponade, atrioventricular block, or peripheral blood vessels, occurred during or after the procedure. After 45 days of

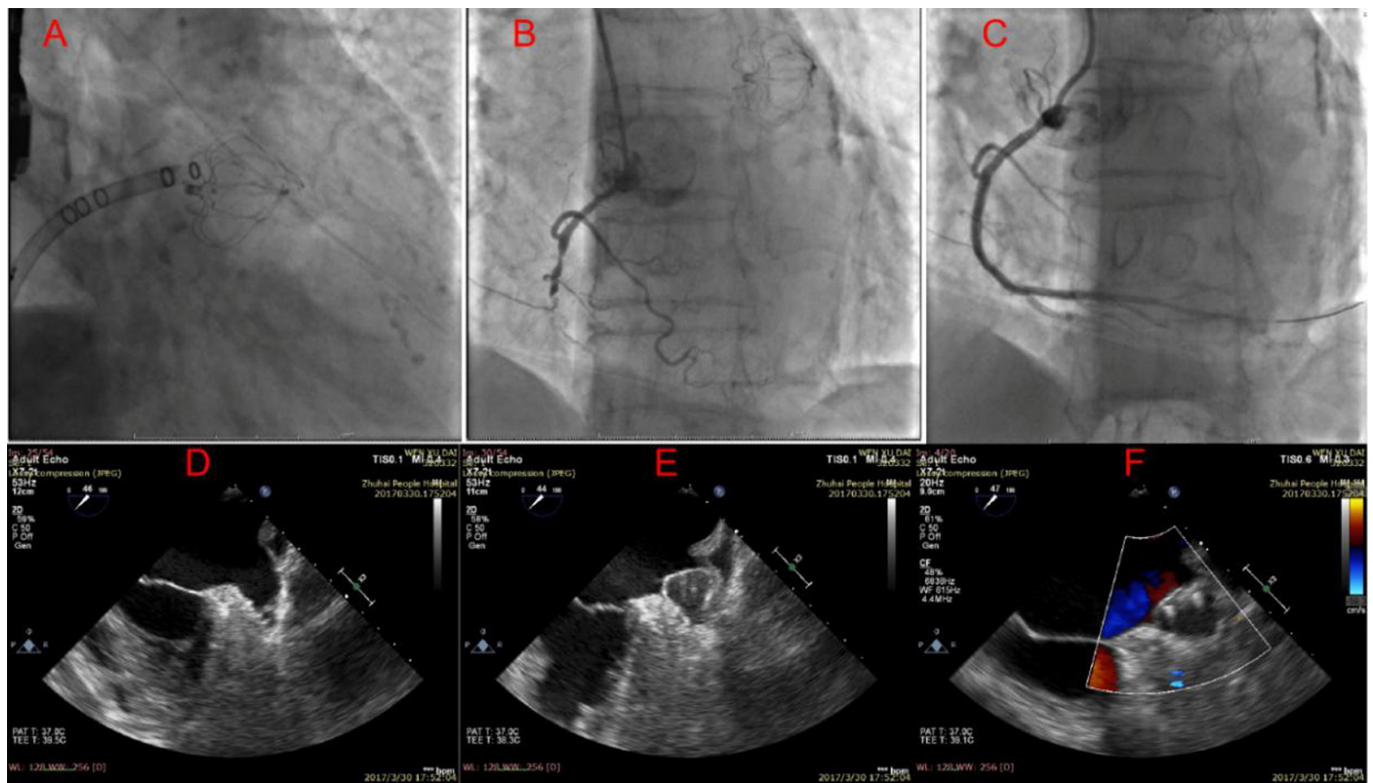


Figure 1. A–C, After placement of a 33-mm Watchman™ occluder, coronary stents of sizes 3.5 × 18 and 2.5 × 38 were placed in the RCA. D–F, Comparison of images before and after LAA closure under 45° esophageal echocardiography.

Table 2. Stent Details

No.	Size (mm)	Watchman Occluder			Coronary Stent	
		Compression ratio (%)	Excessive Shoulder (mm)	RCA (mm)	LAD (mm)	LCX (mm)
1	30	20.0	2	1.2		3.5 × 28
2	33	24.2	6	0	3.5 × 18, 2.5 × 28	
3	27	25	4	0	4.0 × 23	
4	27	30	4	0		3.0 × 23
5	33	24	5	0		3.0 × 33
6	30	26	2	0	3.0 × 23	

follow-up, esophageal echocardiography revealed that the position of the occluder was fixed in the 6 patients. The leak flow showed no significant change compared with the postoperative measurement. No device-related thrombosis or other chamber thrombosis was found. After 90 days of follow-up, transthoracic echocardiography showed that the occluder position was fixed appropriately.

Although the symptoms of heart failure improved in all patients, there was no significant difference in ejection fraction (EF) between the measurement after 90 days of follow-up and immediately after the procedure ($P > .01$). During the 90-day follow-up period, no stroke, angina pectoris, myocardial infarction, skin echymosis, digestive tract hemorrhage, or cerebral hemorrhage occurred.

DISCUSSION

AF is one of the most common arrhythmias encountered in clinical practice, and its incidence increases with age. Non-valvular AF is more common than valvular AF. The danger of AF to patients, in addition to causing palpitations, cardiac structural changes, and heart failure, is embolism formation in peripheral blood vessels, which frequently leads to stroke. The incidence of stroke in patients with nonvalvular AF is 5 times that in patients without AF. Therefore, in addition to rhythm control and heart rate control, another treatment objective for AF is thrombosis prevention.

Anticoagulant therapy is applied depending on a patient's risk of stroke. Currently, the main scoring system used is CHA₂DS₂-VASc [January 2019]: congestive heart failure/left ventricular dysfunction has a weight of 1 point; hypertension, 1 point; age ≥ 75 years, 2 points; diabetes, 1 point; stroke, transient ischemic attack, or thromboembolism, 2 points; vascular disease (previous myocardial infarction, peripheral arterial disease, aortic plaque), 1 point; 65 to 74 years of age, 1 point; and female sex, 1 point. The maximum possible score is 9 points for female patients and 8 points for male patients. Nonvalvular AF with a CHA₂DS₂-VASc score of 0 indicates no need for antithrombotic therapy (IIa, B) and that with a CHA₂DS₂-VASc score of 1 indicates no antithrombotic therapy (IIb, C), although treatment with an oral anticoagulant or aspirin may be considered based on bleeding risk and patient preference. A score ≥ 2 warrants oral anticoagulation treatment with warfarin (I, A) and novel oral anticoagulants (I, B).

Anticoagulant therapy inevitably causes an increased risk of bleeding; therefore, bleeding risk assessment is required for patients with AF. Currently, HAS-BLED [Pisters 2010; January 2014] is the main system used to assess bleeding risk according to the weights of different conditions: hypertension has a weight of 1 point; liver and kidney dysfunction, 1 point; a history of stroke, 1 point; a history of bleeding, 1 point; a labile INR, 1 point; age > 65 years, 1 point; drug therapy (antiplatelet drugs or nonsteroidal anti-inflammatory drugs), 1 point; and alcoholism, 1 point. The maximum possible score is 9 points. A score ≥ 3 reflects a high risk of bleeding, and antithrombotic therapy should be used with caution.

AF and CHD have many common risk factors, such as age, hypertension, and diabetes. Patients with AF and CHD often have a high risk of stroke or bleeding. Atrial thrombosis and coronary thrombosis have different mechanisms. Therefore, secondary prevention of CHD includes antiplatelet therapy, whereas prevention of thromboembolic events in patients with AF mainly includes oral anticoagulant drugs. Therefore, in patients with AF and CHD, the difficulty in treatment is that antiplatelet drugs cannot be completely replaced by anticoagulant drugs and vice versa, and their combined application is associated with an increased risk of bleeding [Dewilde 2013; Gibson 2016; Lopes 2019].

Among the guidelines available for the treatment of patients with AF and CHD, the 2016 ESC Guidelines for the management of AF developed in collaboration with EACTS [Kirchhof 2016] recommends triple antithrombotic therapy for 1 month (HAS-BLED score ≥ 3) or 6 months (IIa, B), followed by dual antithrombotic therapy (oral anticoagulant and clopidogrel or aspirin) for 12 months (IIa, C), and then oral anticoagulant drug therapy for life (I, B) for patients with acute coronary syndrome and AF, according to the risk of bleeding. Patients with stable CHD and AF (IIa, B) should take triple antithrombotic therapy for 1 month after the PCI procedure, then dual antithrombotic therapy (oral anticoagulant and clopidogrel or aspirin) for 12 or 6 months (HAS-BLED score ≥ 3) (IIa, C), and then oral anticoagulant drugs for life (I, B), according to the risk of bleeding.

LAAO is an alternative to anticoagulant therapy for patients with AF and is recommended for patients with nonvalvular AF, CHA₂DS₂-VASc score ≥ 2 , and HAS-BLED score 3 who have contraindications to anticoagulation, who are unwilling to receive anticoagulation, or who experience thromboembolic events after standard anticoagulant therapy [January 2019; Glikson 2019]. The ASAP study [Reddy 2013] demonstrated that in patients with nonvalvular AF and contraindications to anticoagulation, the incidence of stroke was significantly reduced after placement of a Watchman occluder and antiplatelet therapy (1.7% versus 7.3%). The EWOLUTION registration study published in the 2018 American Conference on Transcatheter Cardiovascular Therapy showed that the success rate of LAAO with a Watchman device is high, and the risk of stroke is significantly reduced. After 2 years of follow-up, 5 patients were taking only 1 antiplatelet agent or were not using any antithrombotic agents.

For patients with AF complicated by CHD, long-term anticoagulant therapy is inevitable, and multiple PCI treatments may be required. Therefore, these patients may have repeated triple anticoagulant treatments, which cause an increased risk of bleeding. If LAAO is used as an alternative to anticoagulant therapy in these patients, the risk of bleeding from anticoagulation does not need to be considered in future treatment of the patient; only antiplatelet therapy is needed, which can significantly reduce the bleeding risk in these patients. Therefore, the patients in this study received 1-stop treatment involving LAAO and PCI at the same time to observe the feasibility, safety, and efficacy of the technique.

Considering that the required heparin dose is smaller for LAAO than for PCI, the patients underwent LAAO first,

followed by PCI after adding heparin based on the ACT. All patients underwent the procedures in the same operation, and no intraoperative complications occurred. After the operation, the patients were treated with dual anticoagulation (aspirin plus clopidogrel). After 45 and 90 days of follow-up, the occluder remained in place. The patients had no device surface-related thrombosis and no worsening symptoms, such as cerebral infarction, angina pectoris, myocardial infarction, or heart failure, or antithrombotic complications, such as ecchymosis, bleeding gums, or digestive tract or cerebral hemorrhage.

This pilot study with 6 patients proved the feasibility, safety, and effectiveness of concurrent application of the 2 well-accepted techniques. Further large-scale clinical trials are necessary to elucidate conflicting results. Additionally, the current regulations of medical insurance companies in China limit the compensation for 2 types of surgery at the same time during hospitalization. We hope this study helps develop insurance guidelines that are more flexible and beneficial to patients and their families.

REFERENCES

- Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: A Global Burden of Disease 2010 Study. *Circulation* 2014;129:837-847.
- Dewilde WJM, Oirbans T, Verheugt FWA, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: An open-label, randomised, controlled trial. *Lancet* 2013;381:1107-1115.
- Gunnar RM, Bourdillon PD, Dixon DW, et al. ACC/AHA guidelines for the early management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (subcommittee to develop guidelines for the early management of patients with acute myocardial infarction). *Circulation* 1990;82:664-707.
- Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;375:2423-2434.
- Glikson M, Wolff R, Hindricks G, et al. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion—An update. *EuroIntervention* 2019;EIJY19M08_1.
- January CT, Wann LS, Alpert JS, et al. AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;64:e1-e76.
- January CT, Wann LS, Calkins H, et al. AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2019;74:104-132.
- Kirchhof P, Benussi S, Kotecha D, et al. ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893-2962.
- Lopes RD, Heizer G, Aronson R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med* 2019;380:1509-1524.
- Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The Euro Heart Survey. *Chest* 2010;138:1093-1100.
- Reddy VY, Mobius-Winkler S, Miller MA, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: The ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *J Am Coll Cardiol* 2013;61:2551-2556.
- Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol* 2014;6:213-220.