Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix.

Full list of investigators and participating centers, the distribution of enrolled patients in all centers

List	Investigator	Center	CPVI plus group	CPVI alone group	Enrolled Subjects
1	Minglong Chen Hongwu Chen	The First Affiliated Hospital of Nanjing Medical University	53	35	88
2	Youquan Wei	The First Affiliated Hospital of Wannan Medical College	22	17	39
3	Chengzong Li	The Affiliated Hospital of Xuzhou Medical University	15	14	29
4	Linsheng Shi	The Second Affiliated Hospital of Nantong University	8	8	16
5	Hong Du	The Second Hospital of Hebei Medical University	5	2	7
6	Fangyi Xiao	The First Affiliated Hospital of Wenzhou Medical University	23	31	54
7	Cao Zou	The First Affiliated Hospital of Soochow University	14	11	25
8	Fu Yi	Air Force Military Medical University	19	29	48
9	Bing Han	Xuzhou Central Hospital, the Affiliated Xuzhou Hospital of Medical College of Southeast University	27	37	64
10	Weiming Wang	The Third Affiliated Hospital of Soochow University	8	4	12
11	Chenyang Jiang	Sir Run Run Shaw Hospital, affiliated with the Zhejiang University School of Medicine	15	17	32
12	Wei Ma	Tianjin Chest Hospital	5	10	15
13	Yuegang Wang	The First Affiliated Hospital of Southern Medical University	4	4	8
14	Long Chen	Zhongda Hospital, Southeast University	1	0	1
	Total		219	219	438

Steering committee (SC)

Investigator	Center	Country
Minglong Chen	The First Affiliated Hospital of Nanjing Medical University	China
Bing Han	The Affiliated Xuzhou Hospital of Medical College of Southeast University, Xuzhou Central Hospital	China
Chenyang Jiang	Sir Run Run Shaw Hospital, affiliated with the Zhejiang University School of Medicine	China

Data safety monitoring board (DSMB)

Investigator	Center	Country
Wenxi Wu (Professor of General Surgery)	The First Affiliated Hospital of Nanjing Medical University	China
Fumin Zhang (Professor of Cardiology)	The First Affiliated Hospital of Nanjing Medical University	China
Xin Yao (Professor of Respiratory Diseases)	The First Affiliated Hospital of Nanjing Medical University	China
Hao Yu (Professor of Statistics)	Nanjing Medical University	China
Xiuqing Wang (Member of ethics committee, protection of study subjects)	The First Affiliated Hospital of Nanjing Medical University	China

Event review committee (ERC)

Event adjudicated by an independent blinded committee:

Investigator	Center	Country
Zhibing Lu (Electrophysiologist)	Zhongnan Hospital of Wuhan University	China
Lichun Wang (Electrophysiologist)	The First Affiliated Hospital of Sun Yat-Sen University	China
Jiang Cao (Electrophysiologist)	Changhai Hospital, Naval Medical University	China

Contract research organization (CRO)

Item	Title	Country
Contract Research Organization (CRO)	Guangzhou EnChannel Medical Information Technology Co. Ltd	China

Randomization

Central randomization was issued from The First Affiliated Hospital of Nanjing Medical University. A central computerised simple randomization scheme was used. Patients and the physicians who followed up the patients were blinded to the randomization. All clinical outcomes were collected by the contract research organization (CRO).

Core lab and independent statistical analysis

Each patient’s procedure data were stored and reviewed by the core lab. Core lab would review the procedural electroanatomic map and lesion placement:

Item	Title	Country
Core Lab	Department of Cardiology, the First Affiliated Hospital of Nanjing Medical University	China
Statistical Analysis	Nanjing Lindu Medical Technology Co., Ltd	China

eMethods.

Voltage mapping: impact factors and practical considerations

The voltage of a mapping point depends on the rhythm, rate, contact force, thickness of the local tissue, inter-space of the mapping electrodes, wave front direction as well as other poorly understood tissue factors, all of which highlight the importance of a standardized approach to substrate identification[1,2]. Mapping in sinus rhythm, rather than in AF, was preferred in most previous studies[3-7]. High density mapping, which we used in our STABLE-SR, STABLE-SR-II and other studies, is a fast and time-efficient approach[8-10]. However, the poor contact points can over-estimate the extent of LVA. In this study, LA substrate mapping strategy and the definition of LVAs were similar to other studies[3,4], but with contact force adjudication. We believe that point-by-point mapping fashion—sparsely in the healthy area, densely in areas of interest and verified by contact force—is an acceptable and practical mapping approach. Other factors, such as the inter-space of the mapping electrodes, LVA definition of the different region[2] and wave-front direction were not taken into consideration in our trial. Although the foregoing factors may have impact on substrate identification, our point-by-point approach with contact force adjudication was consistent and parallel in both groups, thus the impact of this potential bias is minimized. Further, we performed voltage mapping after and not before CPVI for the following reasons: 1) Pursuing mapping during sinus rhythm, post CPVI mapping can reduce the possibility of electrical cardioversion, 2) Inadequate ablation because of unstable ablation catheter movement during CPVI adjacent to the lesion line might sometimes be the new iatrogenic areas of arrhythmogenecity. These half-lesion areas need evaluation, 3) Mapping during the waiting period after CPVI does not prolong the procedure time, and allows additional time to check the durability of isolation.

ITT analysis

In this study, the ITT analysis was conducted based on the worst-case analysis, in which all the patients who declined ablation or lost to follow-up during the blanking period were assumed to have ATA recurrence at the first 3-month follow-up.

eReferences

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eTable 1. Baseline characteristics of study patients (modified intention to treat)

Characteristics	CPVI plus, n=209	CPVI alone, n=205
Male, n (%)	107 (51.2)	103 (50.2)
Age, years	70.4±4.4	70.6±4.2
AF history, months	24.0 (6.0, 48.0)	14 (5.0, 48.0)
BMI, kg/m^2	24.2±3.6	24.6±3.0
<25, n (%)	123 (62.8)	122 (60.4)
≥25, n (%)	73 (37.2)	80 (39.6)
Comorbidities, n (%)		
Hypertension	123 (58.9)	132 (64.4)
Diabetes	31 (14.8)	38 (18.5)
CAD	50 (23.9)	46 (22.4)
Stroke or TIA	16 (7.7)	20 (9.8)
Congestive heart failure	2 (1.0)	1 (0.5)
COPD	4 (2.0)	3 (1.5)
OSAS	2 (1.0)	1 (0.5)
CHA_2DS_2-VASc score	2.2±0.9	2.4±1.0
1, n (%)	52 (24.9)	46 (22.4)
2, n (%)	78 (37.3)	65 (31.7)
3, n (%)	57 (27.3)	65 (31.7)
>3, n (%)	22 (10.5)	29 (14.2)
LAD, mm	38.8±5.4	38.8±5.3
LVEF, %	62.5±5.3	62.4±5.5

CPVI, circumferential pulmonary vein isolation; AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; TIA, transient ischaemic attack; COPD, chronic obstructive pulmonary disease; OSAS, obstructive sleep apnoea syndrome; LAD, left atrial diameter; LVEF, left ventricular ejection fraction.

eTable 2. Baseline characteristics (per-protocol set)

Characteristics	CPVI plus, n=205	CPVI alone, n=200
Male, n (%)	107 (52.2)	100 (50.0)
Age, years	70.5±3.9	70.6±4.1
AF history, months	24.0 (6.0, 48.0)	13.0 (4.0, 37.5)
BMI, kg/m^2	24.2±3.6	24.6±3.0
<25, n (%)	120 (58.5)	118 (59.9)
≥25, n (%)	72 (35.1)	79 (40.1)
Comorbidities, n (%)		
Hypertension	120 (58.5)	131 (65.5)
Diabetes	31 (15.1)	38 (19.0)
CAD	50 (24.4)	45 (22.5)
Stroke or TIA	16 (7.8)	20 (10.0)
Congestive heart failure	2 (1.0)	1 (0.5)
COPD	4 (2.0)	2 (1.0)
OSAS	2 (1.0)	1 (0.5)
CHA_2DS_2-VASc score	2.4±1.0	2.2±1.0
1, n (%)	51 (24.9)	43 (21.5)
2, n (%)	78 (38.0)	64 (32.0)
3, n (%)	54 (26.3)	64 (32.0)
>3, n (%)	22 (10.7)	29 (14.5)
LAD, mm	38.8±5.4	38.7±5.3
LVEF, %	62.4±5.3	62.4±5.4

CPVI, circumferential pulmonary vein isolation; AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; OSAS, obstructive sleep apnea syndrome; LAD, left atrial diameter; LVEF, left ventricular ejection fraction.

eTable 3. Procedural characteristics (modified intention to treat)

Characteristics	CPVI plus, n=209	CPVI alone, n=205
ATA at baseline, n (%)	33 (15.8)	33 (16.1)
AF termination during CPVI, n (%)	67 (32.1)	54 (26.3)
CV after CPVI, n (%)	13 (6.2)	2 (1.0)
Non-PV triggers, n (%)	17 (8.1)	20 (9.8)
Concomitant arrhythmia, n (%)	2 (1.0)	5 (2.4)
CTI ablation, n (%)	24 (11.5)	20 (9.8)
LVA, n (%)	86 (41.2)	88 (42.9)
LVA burden 1-10%, n (%)	65 (75.6)	74 (84.1)
Area, cm^2	3.9±2.4	3.6±2.6
LVA burden 11-20%, n (%)	15 (17.4)	8 (9.1)
Area, cm^2	13.2±1.8	13.7±3.5
LVA burden >20%, n (%)	6 (7.0)	6 (6.8)
Area, cm^2	27.9±9.5	40.6±9.5
Total procedure time, min	142.5±39.3	139.4±42.5
Begin-CPVI completed, min	108.9±31.5	106.5±28.0
CPVI completed-end, min	33.6±19.2	32.8±28.0
Total fluoroscopic time, min	9.2±5.3	9.7±7.1
Total RF delivery time, min	43.9±18.3	42.2±17.9

CPVI, circumferential pulmonary vein isolation; ATA, atrial tachyarrhythmia; CV, cardioversion; PV, pulmonary vein; CTI, cavotricuspid isthmus; LVA, low-voltage area, RF, radiofrequency.

eTable 4. Procedural characteristics (per-protocol set)

Characteristics	CPVI plus, n=205	CPVI alone, n=200
ATA at baseline, n (%)	33 (16.1)	31 (15.1)
AF termination during CPVI, n (%)	66 (32.2)	52 (25.4)
CV after CPVI, n (%)	12 (5.9)	2 (1.0)
Non-PV triggers, n (%)	17 (8.5)	20 (9.8)
Concomitant arrhythmia, n (%)	2 (1.0)	5 (2.5)
CTI ablation, n (%)	24 (11.7)	20 (10.0)
LVA, n (%)	84 (41.0)	88 (44.0)
LVA burden 1-10%, n (%)	64 (76.2)	74 (84.1)
Area, cm^2	3.9±2.5	3.63±2.6
LVA burden 11-20%, n (%)	15 (17.9)	8 (9.1)
Area, cm^2	13.2±1.8	13.7±3.5
LVA burden >20%, n (%)	5 (6.0)	6 (6.8)
Area, cm^2	29.5±9.7	40.6±9.5
Total procedure time, min	142.1±39.3	139.1±42.8
Begin-CPVI completed, min	108.5±31.6	106.4±28.9
CPVI completed-end, min	33.6±19.3	32.6±28.2
Total fluoroscopic time, min	9.3±5.4	9.7±7.1
Total RF delivery time, min	43.8±18.3	41.9±18.1

CPVI, circumferential pulmonary vein isolation; ATA, atrial tachyarrhythmia; AF, atrial fibrillation; CV, cardioversion; PV, pulmonary vein; CTI, cavotricuspid isthmus; LVA, low voltage area; RF, radiofrequency.

eTable 5. Baseline characteristics of the four subgroups (modified ITT)

Characteristics	+LVA (CPVI plus), n=86	-LVA (CPVI plus), n=123	-LVA (CPVI only), n=117	+LVA (CPVI only), n=88
Male, n (%)	37 (43.0)	70 (56.9)	70 (59.8)	33 (37.5)
Age, years	71.1±4.0	69.9±4.6	70.3±4.0	71.1±4.4
AF history, months	24.0 (7.0, 48.0)	24.0 (4.0, 49.0)	12.0 (4.0, 48.0)	16.5 (5.5, 42.5)
BMI, kg/m^2	23.9±4.4	24.5±2.8	24.7±3.0	24.5±2.9
<25, n (%)	58 (70.7)	65 (57.0)	69 (59.5)	53 (61.6)
≥25, n (%)	24 (29.3)	49 (43.0)	47 (40.5)	33 (38.4)
Comorbidities, n (%)				
Hypertension	59 (68.6)	64 (52.0)	77 (65.8)	55 (62.5)
Diabetes	16 (18.6)	15 (12.2)	19 (16.2)	19 (21.6)
CAD	26 (30.2)	24 (19.5)	24 (20.5)	22 (25.0)
Stroke or TIA	4 (4.7)	12 (9.8)	12 (10.3)	8 (9.1)
Congestive heart failure	1 (1.2)	1 (0.81)	1 (0.85)	0 (0.0)
COPD	3 (3.5)	1 (0.8)	2 (1.7)	1 (1.1)
OSAS	0 (0.0)	0 (0.0)	2 (1.6)	1 (0.85)
CHA_2DS_2-VASc score	2.4±1.0	2.1±1.0	2.3±1.0	2.5±1.0
1, n (%)	16 (18.6)	36 (29.3)	28 (23.9)	18 (20.5)
2, n (%)	28 (32.6)	50 (40.7)	41 (35.0)	24 (27.3)
3, n (%)	30 (34.9)	27 (22.0)	31 (26.5)	34 (38.6)
>3, n (%)	12 (14.0)	10 (8.1)	17 (14.5)	12 (13.6)
LAD, mm	39.3±5.5	38.4±5.4	38.3±5.2	39.4±5.3
LVEF, %	62.3±6.0	62.5±4.7	62.8±6.1	61.9±4.3

+LVA (CPVI plus), patients with LVA who received substrate modification; (2) +LVA (CPVI alone); patients with LVA who received CPVI alone; (3) -LVA (CPVI plus), patients without LVA who received CPVI in the “CPVI plus” group; (4). -LVA (CPVI alone), patients without LVA in the “CPVI alone” group. CPVI, circumferential pulmonary vein isolation; AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; OSAS, obstructive sleep apnea syndrome; LAD, left atrial diameter; LVEF, left ventricular ejection fraction.

eTable 6. Procedural characteristics of four subgroups (modified ITT)

Characteristics	+LVA (CPVI plus), n=86	-LVA (CPVI plus), n=123	-LVA (CPVI only), n=117	+LVA (CPVI only), n=88
ATA at baseline, n (%)	14 (16.3)	19 (15.5)	18 (15.4)	15 (17.1)
AF termination during CPVI, n (%)	21 (24.4)	46 (37.4)	33 (28.2)	21 (23.9)
CV after CPVI, n (%)	8 (9.3)	5 (4.1)	2 (1.7)	0 (0.0)
Non-PV triggers, n (%)	6 (7.1)	11 (8.9)	14 (12.0)	6 (6.8)
Concomitant arrhythmia, n (%)	1 (1.2)	0 (0.00)	0 (0.00)	2 (2.3)
CTI ablation, n (%)	12 (14.0)	12 (9.8)	13 (11.1)	7 (8.0)
LVA, n (%)	86 (100.0)	0 (0.00)	0 (0.00)	88 (100.0)
LVA burden 1-10%, n (%)	65 (75.6)	0 (0.00)	0 (0.00)	74 (84.1)
Area, cm^2	3.93±2.4	0 (0.00)	0 (0.00)	3.6±2.6
LVA burden 11-20%, n (%)	15 (17.4)	0 (0.00)	0 (0.00)	8 (9.1)
Area, cm^2	13.2±1.8	0 (0.00)	0 (0.00)	13.6±3.5
LVA burden >20%, n (%)	6 (7.0)	0 (0.00)	0 (0.00)	6 (6.8)
Area, cm^2	27.9±9.5	0 (0.00)	0 (0.00)	40.6±9.5
Total procedure time, min	147.7±45.0	138.7±34.2	140.6±37.6	137.9±48.4
Begin-CPVI completed, min	108.1±33.7	109.5±30.0	108.4±28.6	104.2±27.2
CPVI completed-end, min	39.6±22.3	29.2±15.2	32.3±21.3	33.6±35.1
Total fluoroscopic time, min	9.6±6.2	9.0±4.7	10.2±6.1	9.1±8.2
Total RF delivery time, min	47.4±19.8	41.3±16.7	42.9±9.1	41.2±16.3

+LVA (CPVI plus), patients with LVA who received substrate modification; (2) +LVA (CPVI alone); patients with LVA who received CPVI alone; (3) -LVA (CPVI plus), patients without LVA who received CPVI in the “CPVI plus” group; (4). -LVA (CPVI alone), patients without LVA in the “CPVI alone” group. LVA, low voltage area; ATA, atrial tachyarrhythmia; AF, atrial fibrillation; CPVI, circumferential pulmonary vein isolation; CV, cardioversion; PV, pulmonary vein; CTI, cavotricuspid isthmus; RF, radiofrequency.

eTable 7. Baseline characteristics of the study population by LVA and treatment (modified intention to treat)

Characteristics	Subgroup A, n=86	Subgroup B, n=88	Subgroup C, n=240
Male, n (%)	37 (43.0)	33 (37.5)	140 (58.3)
Age, years	71.1±4.0	71.1±4.4	70.1±4.3
AF history, months	24.0 (7.0, 48.0)	16.5 (5.5, 42.5)	14.0 (4.0, 48.0)
BMI, kg/m^2	23.9±4.4	24.5±2.9	24.6±2.9
<25, n (%)	58 (70.7)	53 (61.6)	134 (58.3)
≥25, n (%)	24 (29.3)	33 (38.4)	96 (41.7)
Comorbidities, n (%)			
Hypertension	59 (68.6)	55 (62.5)	141 (58.8)
Diabetes	16 (18.6)	19 (21.6)	34 (14.2)
CAD	26 (30.2)	22 (25.0)	48 (20.0)
Stroke or TIA	4 (4.7)	8 (9.1)	24 (10.0)
Congestive heart failure	1 (1.2)	0 (0.0)	2 (0.8)
COPD	3 (3.5)	1 (1.1)	3 (1.3)
OSAS	0 (0.0)	0 (0.0)	3 (1.3)
CHA_2DS_2-VASc score	2.4±1.0	2.5±1.0	2.2±1.0
1, n (%)	16 (18.6)	18 (20.5)	64 (26.7)
2, n (%)	28 (32.6)	24 (27.3)	91 (37.9)
3, n (%)	30 (34.9)	34 (38.6)	58 (24.2)
>3, n (%)	12 (14.0)	12 (13.6)	27 (11.3)
LAD, mm	39.3±5.5	39.4±5.3	38.3±5.3
LVEF, %	62.3±6.0	61.9±4.3	62.7±5.5

Subgroup A, patients with LVA who received “CPVI plus”; Subgroup B, patients with LVA who received “CPVI alone”; Subgroup C; all the enrolled patients without LVA of both groups; LVA, low voltage area; CPVI, circumferential pulmonary vein isolation; AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; OSAS, obstructive sleep apnea syndrome; LAD, left atrial diameter; LVEF, left ventricular ejection fraction.

eTable 8. Procedural characteristics of the study population by LVA and treatment (modified intention to treat)

Characteristics	Subgroup A, n=86	Subgroup B, n=88	Subgroup C, n=240
ATA at baseline, n (%)	14 (16.3)	15 (17.1)	37 (15.4)
AF termination during CPVI, n (%)	21 (24.4)	21 (23.9)	79 (32.9)
CV after CPVI, n (%)	8 (9.3)	0 (0.0)	7 (2.9)
Non-PV triggers, n (%)	6 (7.1)	6 (6.8)	25 (10.7)
Concomitant arrhythmia, n (%)	1 (1.2)	2 (2.3)	4 (1.7)
CTI ablation, n (%)	12 (14.0)	7 (8.0)	25 (10.4)
LVA, n (%)	86 (100.0)	88 (100.0)	0 (0.0)
LVA burden 1-10%, n (%)	65 (75.6)	74 (84.1)	0 (0.0)
Area, cm^2	3.93±2.4	3.6±2.6	0±0
LVA burden 11-20%, n (%)	15 (17.4)	8 (9.1)	0 (0.0)
Area, cm^2	13.2±1.8	13.6±3.5	0±0
LVA burden >20%, n (%)	6 (7.0)	6 (6.8)	0 (0.0)
Area, cm^2	27.9±9.5	40.6±9.5	0±0
Total procedure time, min	147.7±45.0	137.9±48.4	139.6±35.9
Begin-CPVI completed, min	108.1±33.7	104.2±27.2	108.9±29.2
CPVI completed-end, min	39.6±22.3	33.6±35.1	30.7±18.4
Total fluoroscopic time, min	9.6±6.2	9.1±8.2	9.6±5.4
Total RF delivery time, min	47.4±19.8	41.2±16.3	42.1±17.9

Subgroup A, patients with LVA who received “CPVI plus”; Subgroup B, patients with LVA who received “CPVI alone”; Subgroup C; all the enrolled patients without LVA of both groups; LVA, low voltage area; ATA, atrial tachyarrhythmia; AF, atrial fibrillation; CPVI, circumferential pulmonary vein isolation; CV, cardioversion; PV, pulmonary vein; CTI, cavotricuspid isthmus; RF, radiofrequency.

eTable 9. Baseline characteristics of the study population by LVA and treatment (per-protocol set)

Characteristics	Subgroup A, n=84	Subgroup B, n=88	Subgroup C, n=233
Male, n (%)	37 (44.1)	33 (37.5)	137 (58.8)
Age, years	71.0±4.1	71.1±4.4	70.2±3.8
AF history, months	24.0 (6.5, 48.0)	16.5 (5.5, 42.5)	14.0 (4.0, 48.0)
BMI, kg/m^2	23.9±4.5	24.5±2.9	24.6±2.9
<25, n (%)	56 (70.0)	53 (61.6)	129 (57.9)
≥25, n (%)	24 (30.0)	33 (38.4)	94 (42.6)
Comorbidities, n (%)			
Hypertension	57 (67.9)	55 (62.5)	139 (59.7)
Diabetes	16 (19.1)	19 (21.6)	34 (14.6)
CAD	26 (31.0)	22 (25.0)	47 (20.2)
Stroke or TIA	4 (4.8)	8 (9.1)	24 (10.3)
Congestive heart failure	1 (1.2)	0 (0.0)	2 (0.9)
COPD	3 (3.6)	1 (1.1)	2 (0.9)
OSAS	0 (0.0)	0 (0.0)	3 (1.3)
CHA_2DS_2-VASc score	2.4±1.0	2.5±1.0	2.2±1.0
1, n (%)	16 (19.1)	18 (20.5)	60 (25.8)
2, n (%)	28 (33.3)	24 (27.3)	90 (38.6)
3, n (%)	28 (33.3)	34 (38.6)	56 (24.0)
>3, n (%)	12 (14.3)	12 (13.6)	27 (11.6)
LAD, mm	39.4±5.4	39.4±5.3	38.27±5.3
LVEF, %	62.3±6.1	61.9±4.3	62.7±5.5

Subgroup A, patients with LVA who received “CPVI plus”; Subgroup B, patients with LVA who received “CPVI alone”; Subgroup C; all the enrolled patients without LVA of both groups; CPVI, circumferential pulmonary vein isolation; AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; OSAS, obstructive sleep apnea syndrome; LAD, left atrial diameter; LVEF, left ventricular ejection fraction.

eTable 10. Procedural characteristics of the study population by LVA and treatment (per-protocol set)

Characteristics	Subgroup A, n=84	Subgroup B, n=88	Subgroup C, n=233
ATA at baseline, n (%)	14 (16.7)	15 (17.1)	35 (15.0)
AF termination during CPVI, n (%)	20 (23.8)	21 (23.9)	77 (33.1)
CV after CPVI, n (%)	7 (8.3)	0 (0.0)	7 (3.0)
Non-PV triggers, n (%)	6 (7.1)	5 (5.7)	25 (10.7)
Concomitant arrhythmia, n (%)	1 (1.2)	2 (2.3)	3 (1.3)
CTI ablation, n (%)	12 (13.4)	7 (8.0)	25 (10.4)
LVA, n (%)	84 (100.0)	88 (100.0)	0 (0.0)
LVA burden 1-10%, n (%)	64 (76.2)	74 (84.1)	0 (0.0)
Area, cm^2	3.9±2.5	3.6±2.6	0±0
LVA burden 11-20%, n (%)	15 (17.9)	8 (9.1)	0 (0.0)
Area, cm^2	13.2±1.8	13.7±3.5	0±0
LVA burden >20%, n (%)	5 (6.0)	6 (6.8)	0 (0.0)
Area, cm^2	29.5±9.7	40.6±9.5	0±0
Total procedure time, min	146.9±45.0	137.9±48.4	139.3±36.2
Begin-CPVI completed, min	107.3±33.6	104.2±27.2	108.8±29.4
CPVI completed-end, min	39.5±22.5	33.6±35.1	30.6±18.4
Total fluoroscopic time, min	9.7±6.2	9.1±8.2	9.6±5.5
Total RF delivery time, min	47.1±19.9	41.2±16.3	42.0±18.1

Subgroup A, patients with LVA who received “CPVI plus”; Subgroup B, patients with LVA who received “CPVI alone”; Subgroup C; all the enrolled patients without LVA of both groups; LVA, low voltage area; ATA, atrial tachyarrhythmia; AF, atrial fibrillation; CPVI, circumferential pulmonary vein isolation; CV, cardioversion; PV, pulmonary vein; CTI, cavotricuspid isthmus; RF, radiofrequency.

eTable 11. Peri-procedural safety data

Adverse events	CPVI plus, n=209	CPVI alone, n=205
VF during peri-procedure, n	0	1
Vascular access complication, n	1	1
Hemoptysis, n	1	1
Total, n	2	3

CPVI, circumferential pulmonary vein isolation; VF, ventricular fibrillation.

eTable 12. Adverse events during follow-up

Adverse events	CPVI plus, n=209	CPVI alone, n=205
Death, n	1	0
Cancer, n	1	2
Total, n	2	2

CPVI, circumferential pulmonary vein isolation.

eTable 13. Baseline characteristics of the study population by sex

Characteristics	Male, n=210	Female, n=204
Age, years	70.6±3.9	70.5±4.7
AF history, months	12 (3.0, 36)	24 (6.0, 48)
BMI, kg/m^2	24.4±3.1	24.7±3.2
<25, n (%)	125 (62.5)	120 (60.6)
≥25, n (%)	75 (37.5)	78 (39.4)
Comorbidities, n (%)		
Hypertension	128 (61.0)	127 (62.3)
Diabetes	37 (17.6)	32 (15.7)
CAD	49 (23.3)	47 (23.0)
Stroke or TIA	25 (11.9)	11 (5.4)
Congestive heart failure	2 (1.0)	1 (0.5)
COPD	6 (2.9)	1 (0.5)
OSAS	1 (0.5)	2 (1.0)
CHA_2DS_2-VASc score	2.0±1.0	2.7±1.0
1, n (%)	77 (36.7)	21 (10.3)
2, n (%)	80 (38.1)	63 (30.9)
3, n (%)	36 (17.1)	86 (42.2)
>3, n (%)	17 (8.1)	34 (16.7)
LAD, mm	39.0±5.5	38.5±5.2
LVEF, %	62.3±5.7	62.6±4.9
LVA prevalence, n (%)	63 (30.0)	104 (50.9)
LVA burden, %	4.6±4.3	9.0±7.8

CPVI, circumferential pulmonary vein isolation; AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; OSAS, obstructive sleep apnea syndrome; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVA, low voltage area.

eTable 14. Hazard ratio for primary endpoint after adjustment of study centers, sex, and BMI

		mITT		PPS	
	CPVI alone	CPVI plus	P value	CPVI plus	P value
HR (95% CI), Model 1	1 (reference)	0.58 (0.37-0.92)	0.021	0.56 (0.35-0.89)	0.014
HR (95% CI), Model 2	1 (reference)	0.61 (0.39-0.95)	0.030	0.58 (0.37-0.92)	0.020
HR (95% CI), Model 3	1 (reference)	0.59 (0.37-0.94)	0.025	0.56 (0.35-0.90)	0.016
HR (95% CI), Model 4	1 (reference)	0.57 (0.36-0.92)	0.020	0.55 (0.34-0.88)	0.013

Model 1: adjusted for study centers;

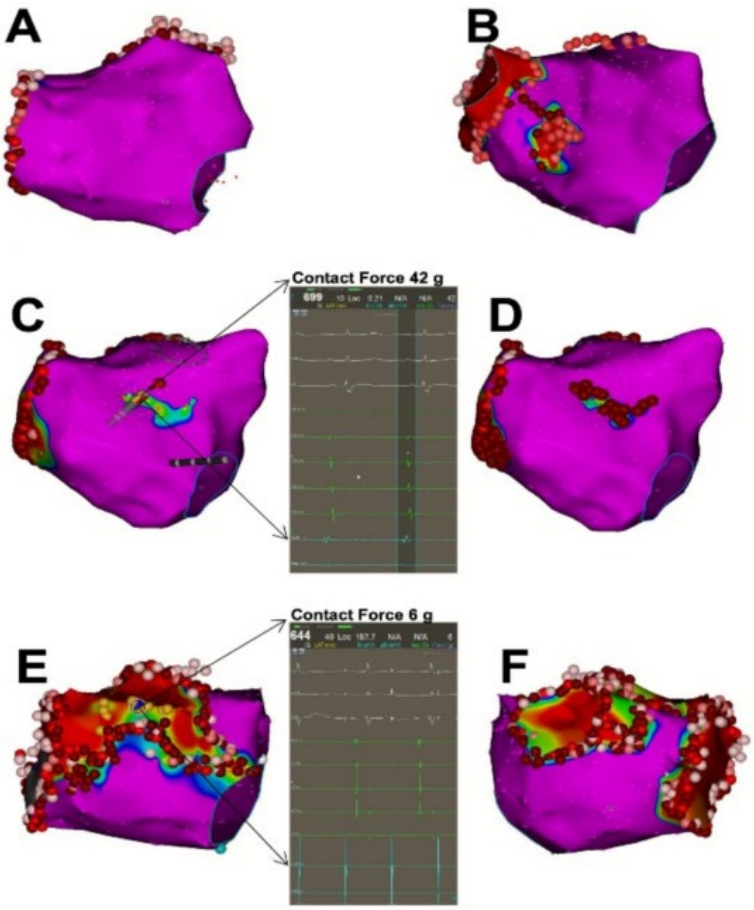
Model 2: adjusted for sex;

Model 3: adjusted for BMI;

Model 4: adjusted for study centers, sex and BMI;

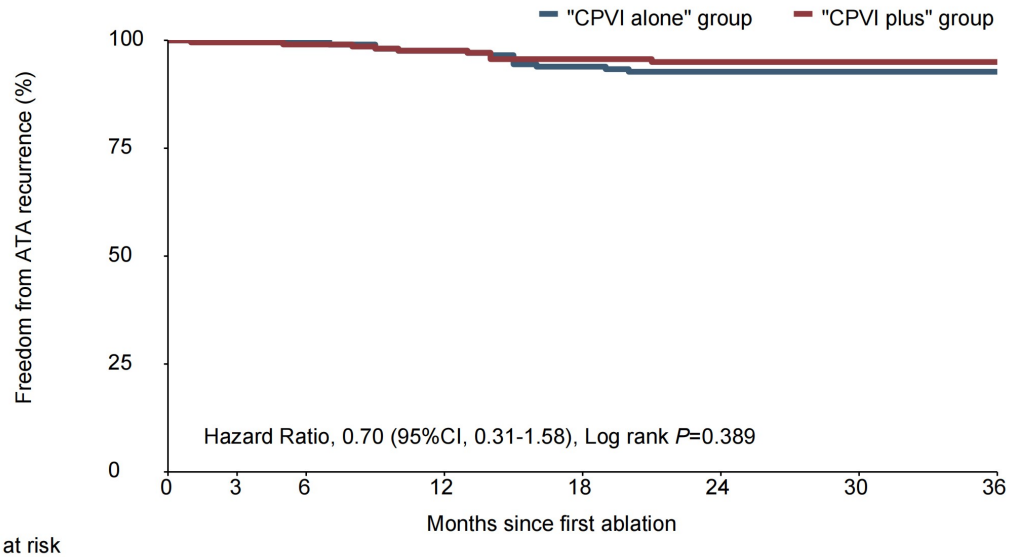
mITT, modified intention to treat; PPS, per-protocol analysis, BMI, body mass index; CPVI, circumferential pulmonary vein isolation.

eFigure 1. Sample images of LVA distribution and the corresponding ablation strategies



A: Patients without LVA after CPVI and no additional ablation was needed; **B:** LVA homogenization was performed in the left anterior atrial wall with a short lesion line extended to the right-side PV line; **C and D:** Isolated small patches of LVAs in left anterior atrial body and exterior RIPV antrum, localized homogenizations were performed accordingly; **E and F,** Extensive LVA was mapped in the anterior wall and posterior region of the left atrium. Scar isolation was conducted by placing the lesions encircling the LVA areas. Note that there was an apparent dissociation between the high-voltage pacing within the box area (blue dot) and the left atrial activation. CPVI, circumferential pulmonary vein isolation; LVA, low-voltage area; RIPV, right inferior pulmonary vein.

eFigure 2. Kaplan-Meier curve of the freedom from ATA after single procedure by specificity analysis of clinical-detected event-based finding between CPVI plus and CPVI alone groups by modified intention-to-treat analysis

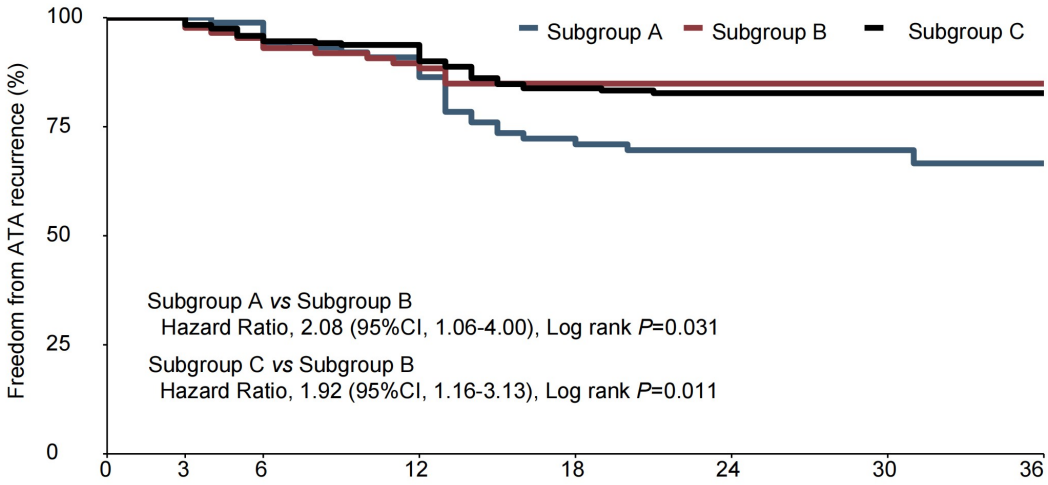


Number at risk

"CPVI alone" group	205	205	205	200	163	120	65	30
"CPVI plus" group	209	208	207	206	164	120	77	33

This graph shows freedom from recurrent ATA following the post-blanking period after a single procedure between CPVI plus and CPVI alone groups by specificity analysis of clinical-detected event-based finding between two groups. ATA recurrence referred to the situation where patients experienced symptoms of palpitation and had documented AF recurrence on an ECG during unscheduled clinical visits. The recurrent events in the proposal-scheduled follow-up were neglected. There was no significant difference in ATA recurrence between the two groups (Hazard Ratio 0.70 [95% CI, 0.31-1.58], Log rank P=0.389).

eFigure 3. Kaplan-Meier curve of the freedom from ATA after single procedure among three subgroups by mITT

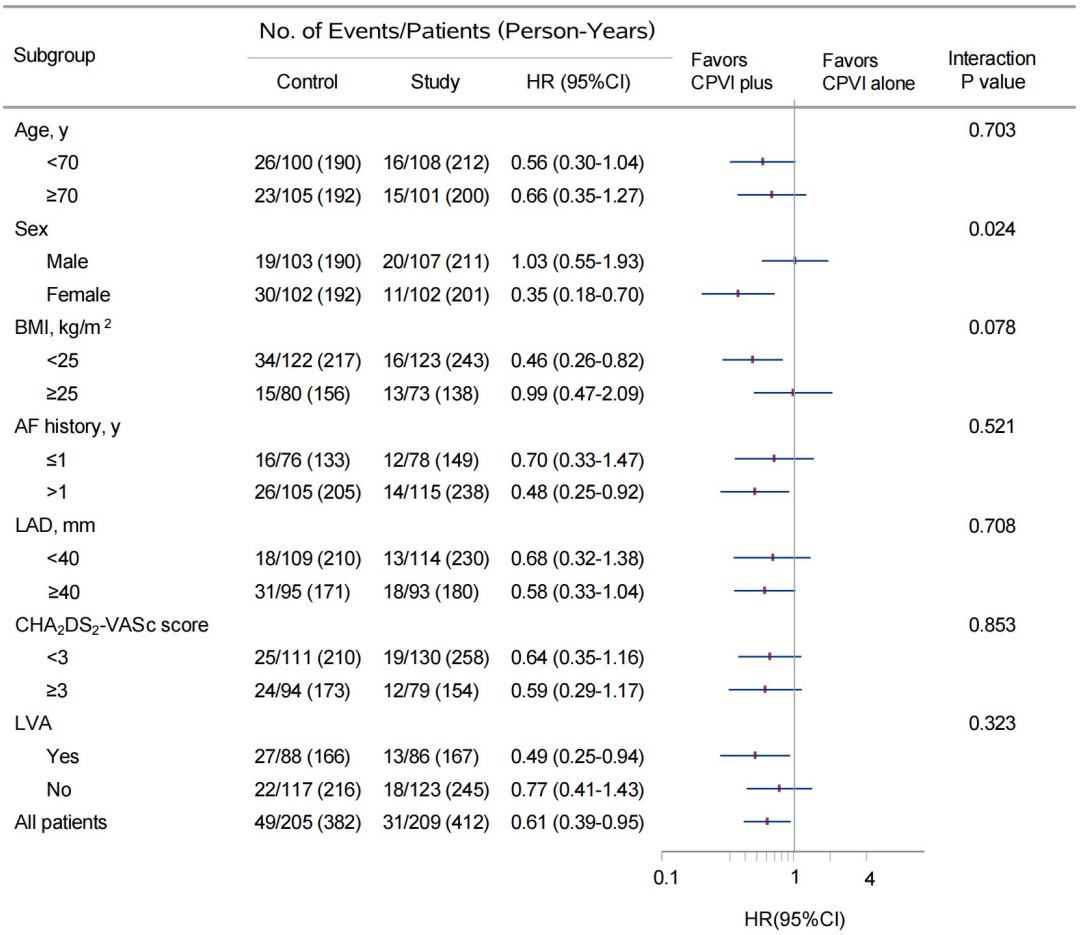


Number at risk

Subgroup A	88	88	87	80	55	41	23	10
Subgroup B	86	86	82	77	59	44	27	10
Subgroup C	240	240	230	225	165	112	64	30

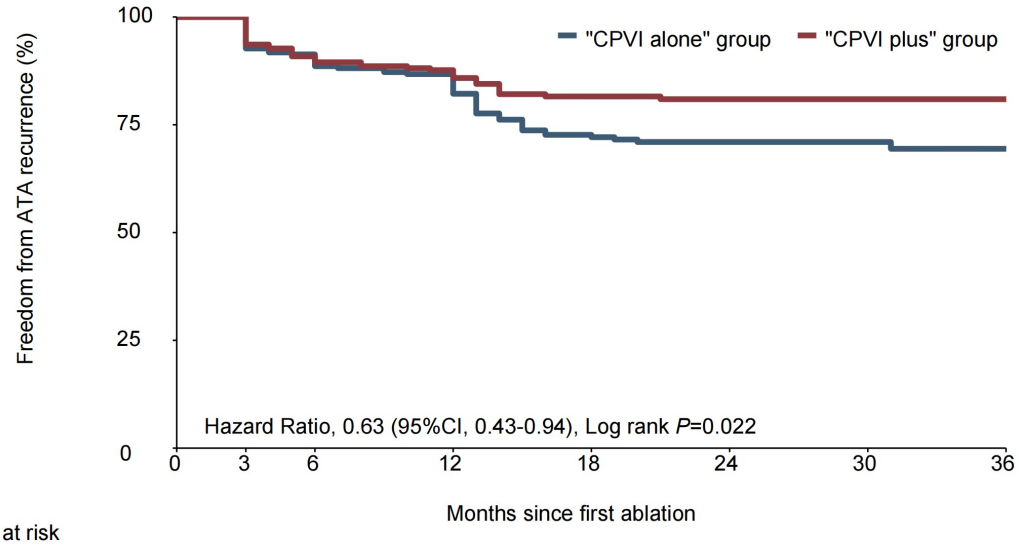
The graph demonstrates that patients with LVA who received CPVI alone (Subgroup B) had significantly higher recurrence rate than those without LVA (Subgroup C, P=0.011), and those with LVA receiving modification (Subgroup A, P=0.031), respectively. Note that the curves begin to diverge at 1 year, coinciding with the 12 month 7-day ambulatory monitoring. ATA, atrial tachyarrhythmia; Based on the presence of LVA and the 2 ablation strategies described in protocol section (Supplemental materials, page 18), all patients were divided into three subgroups: Subgroup A, patients with LVA who received “CPVI plus”; Subgroup B, patients with LVA who received “CPVI alone”; Subgroup C, all the enrolled patients without LVA of both groups; CPVI, circumferential pulmonary vein isolation; HR, hazard ratio; CI, confidence interval.

eFigure 4. Primary endpoint subgroup by mITT analysis



Primary endpoint subgroup analyses. Squares represent point estimates calculated by Cox regression analysis with lines representing the 95% CI. Sensitivity analysis is shown in eTable 14. CI, confidence interval; CPVI, circumferential pulmonary vein isolation; BMI, body mass index; AF, atrial fibrillation; LAD, left atrial diameter; CHA2DS2-VASc score, congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke/transient ischemic attack/thromboembolism (doubled), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age 65-75 years, sex category (female); LVA, low-voltage area.

eFigure 5. Kaplan-Meier estimates of the freedom from ATA after single procedure between CPVI plus and CPVI alone groups by intention-to-treatment

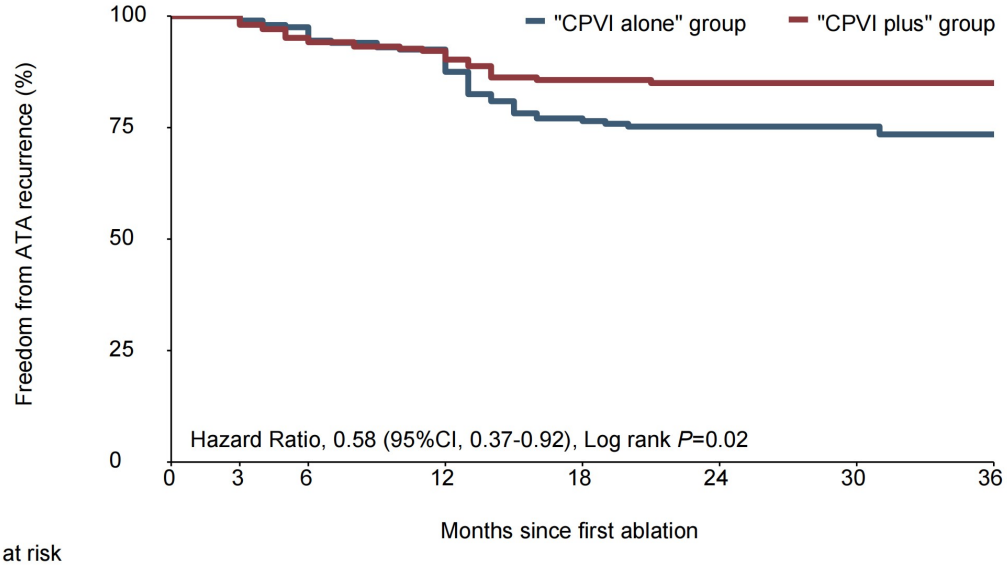


Number at risk

"CPVI alone" group	219	219	200	190	133	92	49	21
"CPVI plus" group	219	219	199	192	146	105	65	29

This graph shows freedom from recurrent ATA following the post-blanking period after a single procedure between CPVI plus and CPVI alone groups by intention-to-treatment depend on “worst-case” analysis, which means all the patients who declined ablation (one case in study group) or lost to follow-up during the blanking period (9 cases in study group and 14 cases in control group) were assumed to have ATA recurrence at the first 3month follow-up. There is significant reduction in CPVI plus group compared with CPVI alone group (18.7% vs. 28.8%, HR 0.63, [95% CI, 0.43-0.94], P=0.022). Note that the curves begin to diverge at 1 year, coinciding with the 12 month 7-day ambulatory monitoring. CPVI, circumferential pulmonary vein isolation; ATA, atrial tachyarrhythmia; HR, hazard ratio; CI, confidence interval.

eFigure 6. Kaplan-Meier estimates of the freedom from ATA after single procedure between CPVI plus and CPVI alone groups by per-protocol analysis

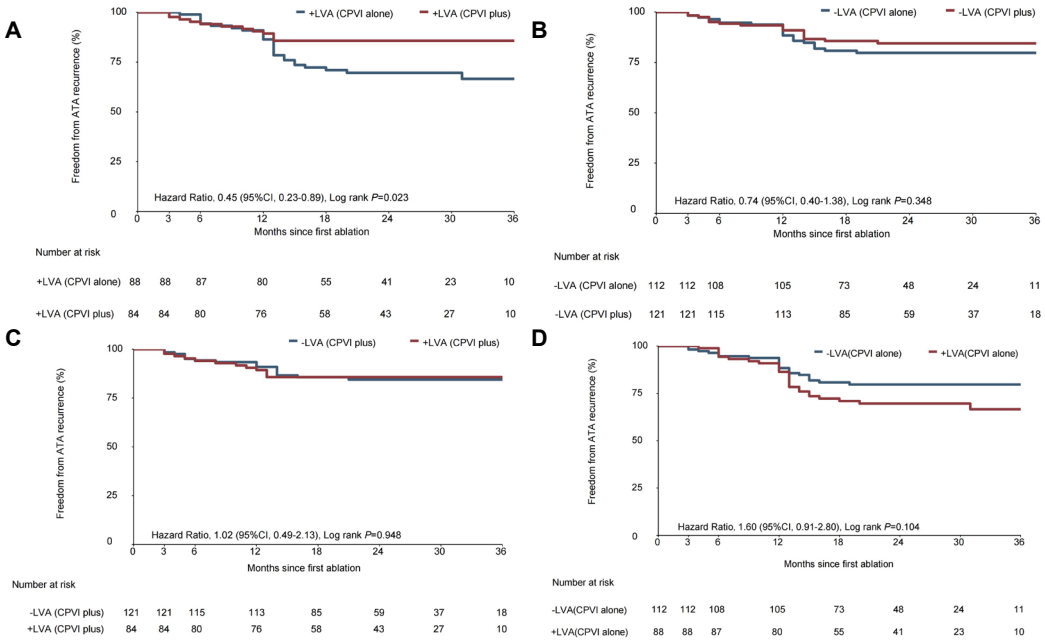


Number at risk

"CPVI alone" group	200	200	195	185	128	89	47	21
"CPVI plus" group	205	205	195	189	143	102	64	28

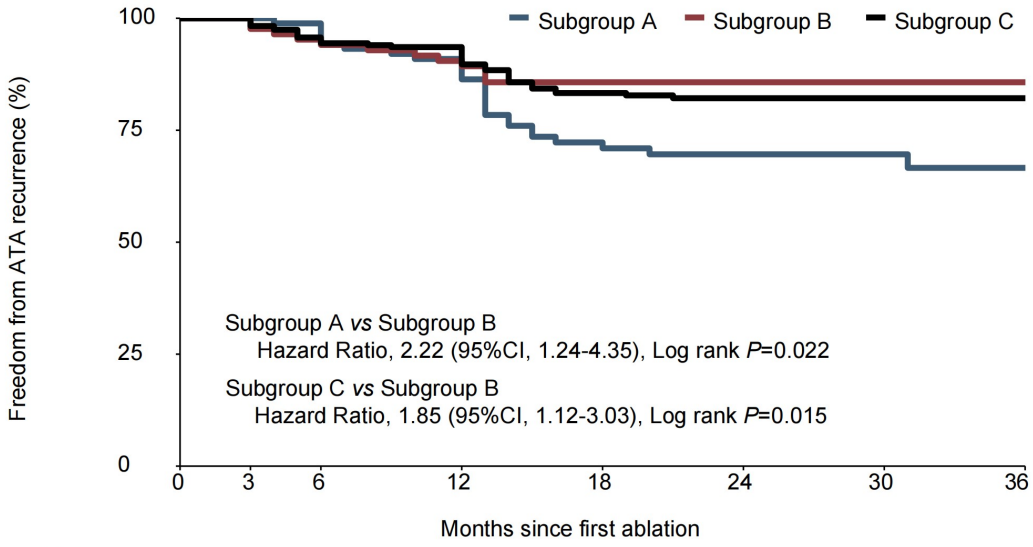
This graph shows freedom from recurrent ATA following the post-blanking period after a single procedure. There is significant reduction in CPVI plus group compared with CPVI alone group (P=0.02). Note that the curves begin to diverge at 1 year, coinciding with the 12 month 7-day ambulatory monitoring. CPVI, circumferential pulmonary vein isolation; ATA, atrial tachyarrhythmia; HR, hazard ratio; CI, confidence interval.

eFigure 7. Kaplan-Meier curve of the freedom from ATA after single procedure among four subgroups by per-protocol analysis



The graph demonstrates that patients with LVA who received CPVI plus had significantly higher recurrence rate than those with LVA who received CPVI alone (P=0.023). Based on randomization assignment and the existence of LVA, all patients were divided into four subgroups: (1) +LVA (CPVI plus), patients with LVA who received substrate modification; (2) +LVA (CPVI alone); patients with LVA who received CPVI alone; (3) -LVA (CPVI plus), patients without LVA who received CPVI in the “CPVI plus” group; (4). -LVA (CPVI alone), patients without LVA in the “CPVI alone” group. Patients with LVA who received modification in the study group had a significant reduction of ATA recurrence compared to those who did not in the control group (A). Note that the ascertainment of recurrent ATA episodes differed at 12 vs. 3 or 6 months. CPVI, circumferential pulmonary vein isolation; HR, hazard ratio; CI, confidence interval; - LVA = without low voltage area, + LVA = with low voltage area.

eFigure 8. Kaplan-Meier curve of the freedom from ATA after single procedure among three subgroups by per-protocol analysis

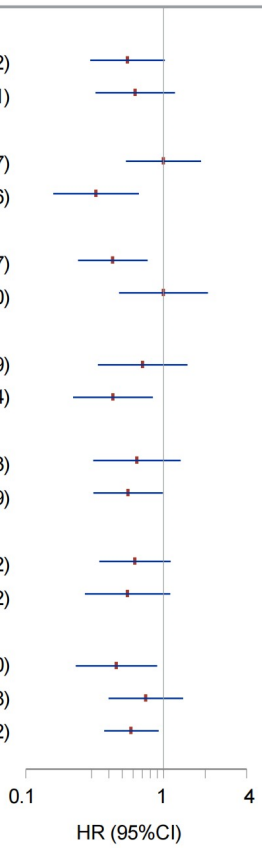


Number at risk								
Subgroup A	88	88	87	80	55	41	23	10
Subgroup B	84	84	80	76	58	43	27	10
Subgroup C	233	233	223	218	158	107	61	29

The graph demonstrates that patients with LVA who received CPVI alone (Subgroup B) had significantly higher recurrence rate than those without LVA (Subgroup C, P=0.015), and those with LVA receiving modification (Subgroup A, P=0.022), respectively. Note that the curves begin to diverge at 1 year, coinciding with the 12 month 7-day ambulatory monitoring. ATA, atrial tachyarrhythmia. Based on the presence of LVA and the 2 ablation strategies, all patients were divided into three subgroups: Subgroup A, patients with LVA who received “CPVI plus”; Subgroup B, patients with LVA who received “CPVI alone”; Subgroup C, all the enrolled patients without LVA of both groups; CPVI, circumferential pulmonary vein isolation; HR, hazard ratio; CI, confidence interval.

eFigure 9. Primary endpoint subgroup by per-protocol analysis

Subgroup	No. of Events/Patients (Person-Years)			Interaction P value
	Control	Study	HR (95%CI)	
Age, y				0.772
<70	26/97 (182)	16/107 (209)	0.55 (0.29-1.02)	
≥70	23/103 (189)	14/98 (195)	0.62 (0.32-1.21)	
Sex				0.021
Male	19/100 (183)	20/107 (211)	1.00 (0.53-1.87)	
Female	30/100 (189)	10/98 (193)	0.32 (0.16-0.66)	
BMI, kg/m^2				0.055
<25	34/118 (209)	15/120 (238)	0.43 (0.24-0.77)	
≥25	15/79 (154)	13/72 (135)	1.00 (0.47-2.10)	
AF history, y				0.393
≤1	16/75 (131)	12/76 (144)	0.70 (0.33-1.49)	
>1	26/101 (196)	13/114 (238)	0.43 (0.22-0.84)	
LAD				0.720
<40	18/109 (210)	12/111 (224)	0.64 (0.31-1.33)	
≥40	31/90 (160)	18/92 (177)	0.55 (0.31-0.99)	
CHA_2DS_2-VASc score				0.801
<3	25/107 (200)	19/129 (255)	0.62 (0.34-1.12)	
≥3	24/93 (171)	11/76 (149)	0.55 (0.27-1.12)	
LVA				0.297
Yes	27/88 (166)	12/84 (164)	0.45 (0.23-0.90)	
No	22/112 (205)	18/121 (240)	0.74 (0.40-1.38)	
All patients	49/200 (371)	30/205 (404)	0.58 (0.37-0.92)	



Squares represent point estimates calculated by Cox regression analysis with lines representing the 95% CI. Note that LVA ablation in female patients were more beneficial in “CPVI plus” group compared with “CPVI alone” group (P=0.021) according to subgroup interactions analyses. CI, confidence interval; CPVI, circumferential pulmonary vein isolation; BMI, body mass index; AF, atrial fibrillation; LAD, left atrial diameter; CHA_2DS_2-VASc score, congestive heart failure, hypertension, age≥75 years (doubled), diabetes, stroke/transient ischemic attack/thromboembolism (doubled), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age 65-75 years, sex category (female); LVA, Low-voltage area.