Clinical Relevance of Incomplete Device Endothelialization After Left Atrial Appendage Closure

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Abstract

Purpose

This study aimed to assess the incidence, potential risk factors and clinical impact of incomplete device endothelialization (IDE) after left atrial appendage closure (LAAC).

Methods

A total of 101 consecutive patients with nonvalvular atrial fibrillation (AF) who underwent successful LAAC and received antithrombotic treatment using a standard regimen were prospectively followed up to 6 months after the procedure. The status of device endothelialization and device-related thrombus (DRT) were evaluated using cardiac computed tomography (CT). Major adverse cardio-cerebral events (MACCE) including all-cause death, heart failure(HF) hospitalization, acute ischemic stroke, transient ischemic attack(TIA), peripheral vascular embolism, and major bleeding were recorded.

Results

IDE was detected in 65 (64.4%) patients. Patients with IDE or complete device endothelialization (CDE) did not significantly differ with respect to baseline clinical characteristics and interventional procedure features. Multivariate analysis model revealed that persistent AF, left atrial appendage ostial diameter and left atrial size were independent risk factors for IDE. During 6-month follow-up, the incidence of DRT was 4.6% in patients with IDE and 2.8% in those with CDE, respectively ($p > 0.05$), and the overall rate of MACCE was non-significantly higher in the IDE group (7.7% vs. 2.8%, $p = 0.32$).

Conclusions

IDE is common after LAAC, especially in patients with persistent AF, higher left atrial appendage ostial diameter and left atrial size. IDE confers an increased risk for DRT, but may be not necessarily associated with thromboembolic events and poor clinical outcome, providing careful monitoring and continued antithrombotic therapy are given.

1. Introduction

Atrial fibrillation (AF) is associated with a 4- to 5-fold increased risk of ischemic stroke [1]. Oral anticoagulation with non-vitamin K oral anticoagulants (NOACs) or vitamin K antagonists are recommended as the first-line treatment for reducing stroke risk, but bleeding complications and nonadherence are barriers to effective anticoagulation therapy[2]. Considering more than 90% of the thrombus locating inside the left atrial appendage [3], percutaneous left atrial appendage closure(LAAC)

emerged in recent years for stroke risk reduction in nonvalvular AF patients, particularly in those with contraindications, intolerance or refusal to oral anticoagulation therapy[4–6].

Device related thrombus (DRT) formation, one of the main concerns after LAAC, is generally reported to be 2–5% in larger cohorts [7–10]. Especially, it may develop on the poorly endothelialized device following intervention, and have a potential negative impact on the risk of stroke and thromboembolic events [7, 11–13]. Since animal studies suggest that device endothelialization was completed within 45–90 days after LAAC procedure [14, 15], antithrombotic therapy for a similar period was recommended to prevent DRT formation in patients with a newly implanted LAAC device[16]. In fact, incomplete device endothelialization (IDE) at 6 months or later after implantation was frequently described in humans [11, 13, 17, 18], necessitating the need for investigating the risk factors and therapeutic regimens. However, data on this issue are still limited. In the present study, we sought to investigate the incidence, risk factors, and clinical impact of IDE following LAAC.

2. Methods

Study population

A total of 108 consecutive patients with AF undergoing successful percutaneous LAAC from February to December 2019 were prospectively recruited. Of them, 7 patients with severe renal failure (n = 5) or poor cardiac CT imaging (n = 2) at 6-month follow-up were excluded. The remaining 101 patients who had good cardiac CT quality and completed clinical follow-up at 6-month were eligible for final analysis (Fig. 1).

This study was carried out according to the principles of the declaration of Helsinki and was approved by the hospital ethics committee. All patients provided their written informed consents.

LAAC procedure and anticoagulation regimen

LAAC procedure was performed under fluoroscopy and trans-esophageal echocardiography guidance by the standard technique described previously [19]. In brief, intravenous heparin was administered following transseptal puncture and introduction of delivery system to the left atrial appendage. The type and size of LAAC devices were selected upon the orifice diameter, depth, and morphology of the left atrial appendage, including Watchman™ (Boston Scientific, Marlborough, MA, USA), Lambre™ (Lifetech Scientific Corp, Shenzhen, China), and Leftear™ (Guangdong Pulse Medical Technology Co., Ltd. Zhuhai, China).

Anticoagulation (warfarin or NOACs) was prescribed in the initial 45 days post-implant, or until 3 months for those who underwent one-stage LAAC and catheter ablation [20], dual anti-platelet therapy with aspirin 100mg/d and clopidogrel 75mg/d were prescribed after cessation of anticoagulant therapy according to the current guideline recommendation[21]. The choice of angiotensin-converting-enzyme inhibitor(ACEI) or angiotensin II-receptor blocker(ARB), beta-blocker and statins, was based on patients'

features and current guideline recommendation [22, 23]. For those with DRT at 6-month CT examination, anticoagulant therapy was re-prescribed, replacing the anti-platelet therapy.

Cardiac CT assessment

Cardiac CT was performed using a 320-detector row CT system (Aquilion ViSION, Canon Medical Systems corporation, Otawara, Japan) with a collimation of 320×0.5mm. Each patient received an injection of 40 to 70 mL of contrast medium (Iopamidol, 370mgI/ml) at 4.0 to 5.0 mL/s. Tube current was adapted automatically according to body mass index (BMI) of each individual. After first-pass imaging, the second set of images were acquired for 45 seconds to assess delayed contrast opacification.

Image analysis was made by two blinded and experienced radiologists with Vitrea Workstation™ (Vital, Canon Medical Systems corporation, Zoetermeer, Netherlands). All scan images were reconstructed to 0.5mm slice thickness with a 0.5mm increment and a medium sharp convolution kernel (FC47). Left atrial appendage patency was determined by Hounsfield unit (HU) in the left atrial appendage distal to the device and comparison of contrast density between the left atrial appendage and the left atrium [24]. Trans-fabric leak was defined as contrast entering into the left atrial appendage through the fabric rather than around the device [24, 25].

Definitions

IDE was defined as left atrial appendage attenuation > 100 HU or left atrial appendage / left atrium attenuation ratio ≥ 0.25 and presence of trans-fabric leak on cardiac CT at 6 months post-procedure(Fig. 2B-C) [24, 26]. Filling defects on the atrial aspect of the LAAC device images was diagnosed as DRT (Fig. 2D)[27]. Clinical composite endpoint of major adverse cerebro-cardiac events (MACCE) were compared between two groups, which included all-cause death, heart failure(HF) hospitalization, acute ischemic stroke documented by CT or magnetic resonance imaging(MRI), transient ischemic attack(TIA), peripheral vascular embolism, and major bleeding [Bleeding score as defined by the Bleeding Academy (BARc) > 3 points] [28].

Statistical Analysis

Continuous variables are presented as mean ± SD, and were compared between two groups using independent t test or Mann-Whitney U test. Categorical data are summarized as proportions and frequencies and were compared by Chi-squared tests. Univariable and multivariable stepwise logistic regression analyses were used to determine the predictors of IDE. The multivariable model was created using stepwise regression, where variables (in Tables I and II) were entered into the model at the 0.20 significance level and removed at the 0.05 level. A value of $p < 0.05$ was considered statistically significant. All statistical analysis was carried out with the software SPSS (SPSS Inc, version 22.0, Chicago, IL, USA).

3. Result

Baseline clinical and procedural characteristics

IDE and complete device endothelialization were detected in 65 (64.4%) and 36 (35.6%) patients, respectively. Patients with IDE had a larger left atrial appendage(LAA) ostial diameter and left atrial(LA) size than those with CDE. There was no significant difference in terms of age, gender, body mass index(BMI), risk factors for coronary artery disease, history of persistent AF, hepatic and renal function disease history, and other transthoracic and trans-esophageal echocardiographic measurements between the two groups (table 1). Likewise, procedural characteristics of LAAC and anticoagulant medications after intervention were similar between the two groups (Table 2).

Table 1 Baseline Clinical Characteristics of all patients

Variables	Total(N=101)	IDE(N=65)	CDE(N=36)	P
Age, years	71.31±7.99	71.49±7.81	70.97±8.41	0.756
Male gender, n (%)	54（53.5）	33（50.8）	21（58.3）	0.470
BMI, kg/m^2				0.112
≤24.5	51(50.5)	29(44.6)	22(61.1)	
>24.5	50(49.5)	36(55.4)	14(38.9)	
Laboratory values				
Hb, g/L	133.1±15.8	133.4±16.3	132.4±15.0	0.762
ALT, U/L	21.4±15.0	20.9±16.2	22.0±12.8	0.747
AST, U/L	22.9±19.1	23.1±21.8	22.7±12.9	0.915
Cr, umol/l	80.8±30.2	80.4±30.0	81.7±30.9	0.838
eGFR, ml/min（per1.73m^2	76.2±28.7	76.5±29.3	75.6±28.2	0.888
NT-proBNP, ng/L	1155.3±1308.2	1217.7±1358.6	1042.6±1222.3	0.522
FBG, mmol/L	5.9±1.8	5.9±1.8	5.9±1.9	0.927
$HbA1_C$, %	6.6±1.3	6.4±0.9	6.8±1.8	0.250
Previous history, n (%)				
Persistent AF	57（56.4）	34（52.3）	23（63.9）	0.299
Smoking	22(21.8)	14（21.5）	8（22.2）	1.000
Hypertension	76(75.2)	52（80）	24（66.7）	0.155
Diabetes	34(33.7)	20（30.8）	14（38.9）	0.510
CAD	33(32.7)	22（33.8）	11（30.6）	0.826
CHD	3(3.0)	2（3.1）	1（2.8）	1.000
Stroke	42(41.6)	30（46.2）	12（33.3）	1.000
Major bleeding	9(8.9)	5（7.7）	4（11.1）	0.718
CHA_2DS_2-VAS_C score				0.402
≤4.4	58(57.4)	35（53.8）	23（63.9）	
>4.4	43(42.6)	30（46.2）	13（36.1）	
HAS-BLED score				0.408
≤2.7	42(41.6)	25（38.5）	17（47.2）	

>2.7	59(58.4)	40（61.5）	19（52.8）	
TEE measurement, mm				
LAA ostial diameter				0.029
≤23	67(66.3)	38（58.5）	29（80.6）	
>23	34(33.7)	27（41.5）	7（19.4）	
LAA length				0.677
≤26	48(47.5)	30（46.2）	18（51.4）	
>26	52(51.5)	35（53.8）	17（48.6）	
TTE measurement				
LA size, mm				0.006
≤44	57(56.4)	30（46.2）	27（75）	
>44	44(43.6)	35（53.8）	9（25）	
LVEF, %				0.520
≤60	35(34.7)	21（32.3）	14（38.9）	
>60	66(65.3)	44（67.7）	22（61.1）	
MR, n (%)				0.909
mild	37(36.6)	22（33.8）	15（41.7）	
moderate	16(15.8)	11（16.9）	5（13.9）	

Abbreviation: IDE, incomplete device endothelization; CDE, complete device endothelization; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; CAD, coronary artery disease; CHD, congenital heart disease; Cr, creatinine; FBG, fasting blood-glucose; GFR, glomerular filtration rate; Hb, hemoglobin; $HbA1_C$, glycated hemoglobin $A1_C$; LA, left atrium; LAA, left atrial appendage; LVEF, left ventricular ejection fraction; MR: mitral regurgitation. TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Table 2
Implant procedural data

Variables	Total(N = 101)	IDE(n = 65)	CDE(n = 36)	P
Type and size of occluders used, n (%)				0.239
Watchman™				
21	8(7.9)	5(7.7)	3(8.3)	
24	23(22.8)	11(16.9)	12(33.3)	
27	27(26.7)	16(24.6)	11(30.6)	
30	20(19.8)	16(24.6)	4(11.1)	
33	13(12.9)	9(13.8)	4(11.1)	
Leftear™				
MB02-1923	1(0.9)	1(1.5)	0(0)	
MB02-1527	1(0.9)	0(0)	1(2.8)	
MB02-2125	2(1.9)	2(3.1)	0(0)	
MB02-2529	2(1.9)	2(3.1)	0(0)	
MB02-2327	2(1.9)	2(3.1)	0(0)	
LAmbre™				
LT-LAA-2632	1(0.9)	0(0)	1(2.8)	
LACbes™				
LAA01-24	1(0.9)	1(1.5)	0(0)	
PDL, mm				0.866
0–3	98(97.0)	62(95.4)	36(100)	
> 3	2(1.9)	2(3.1)	0(0)	
Device compression ratio, %				
Maxi	22.33 ± 4.93	22.35 ± 4.87	22.31 ± 5.09	0.971
Mini	16.25 ± 5.44	15.87 ± 5.28	16.90 ± 5.72	0.385
Procedure time, min	121.29 ± 94.41	115.02 ± 95.06	132.94 ± 93.42	0.368
One-stage procedure, n (%)	52(51.5)	32(49.2)	20(55.6)	0.678

Abbreviation: IDE, incomplete device endothelization; CDE, complete device endothelization;LAA, left atrial appendage; PDL, peri-device leak

Variables	Total(N = 101)	IDE(n = 65)	CDE(n = 36)	P
Anticoagulation, n(%)				0.486
Warfarin	22(21.7)	15(23.1)	7(19.4)	
Rivaroxaban	73(72.3)	47(72.3)	26(72.2)	
Dabigatran	6(5.9)	3(4.6)	3(8.3)	
Abbreviation: IDE, incomplete device endothelization; CDE, complete device endothelization;LAA, left atrial appendage; PDL, peri-device leak				

Clinical outcome

No death occurred at 6-month clinical follow-up. In patient with IDE, 3 (4.6%) had HF requiring hospitalization, 1(1.4%) suffered lower limb arterial embolism, and 1(1.4%) experienced intracerebral hemorrhage. In CDE group, 1(2.8%) patient had hospitalized due to HF. The overall rate of MACCE was not significantly higher in IDE group (7.7% vs. 2.8%, p = 0.32) (Table 3). DRT were found in 4 (3.9%) patients who received Watchman device, in whom IDE occurred in 3 patients.

Multivariate analysis found that persistent AF, increased LAA ostial diameter(> 23mm) and LA size(> 44mm) were independently associated with IDE (Table 4).

Table 3
MACCE at 6-month clinical follow-up

	IDE(n = 65)	CDE(n = 36)	P
All-cause death, n (%)	0	0	NA
HF hospitalization, n (%)	3 (4.6)	1 (2.8)	0.654
AIS, n (%)	0	0	NA
TIA,n (%)	0	0	NA
Peripheral vascular embolism, n (%)	1(1.4)	0	1.0
Major bleeding, n(%)	1(1.4)	0	1.0
Total MACCE, n (%)	**5(7.7)**	**1(2.8)**	**0.32**
Abbreviation: MACCE, major adverse cardio-cerebral events;IDE, incomplete device endothelization; CDE, complete device endothelization; HF, heart failure;AIS, acute ischemic stroke;TIA, transient ischemic attack.			

Table 4
independent predictors of IDE

Variables	OR	95%CI	P
Persistent AF	3.033	1.107–8.314	0.031
LAA ostial diameter	0.279	0.094–0.828	0.021
LA size	0.320	0.121–0.848	0.022

Multivariable logistic regression model was adjusted for body mass index, persistent AF, LAA ostial diameter, LA size and diabetes. AF, atrial fibrillation ;LAA, left atrial appendage; LA, left atrium.

4. Discussion

The results of this prospective study show that IDE was notuncommon within 6 months post LAAC,especially in patients with persistent AF,larger LAA ostial diameter and LA size. IDE confers an increased risk for DRT, but may not be necessarily associated with thromboembolic events and poor clinical outcome on optimal antithrombotic therapy.

Incidence of IDE after LAAC

In canine models, the device surface is often completely endothelialized within3months after implantation[14, 15].By contrast, IDEpost LAAC occurs frequently even well beyond this timeperiodin humans[11, 13, 17, 18].In this study, almost two-thirds of patients had IDE detected by cardiac CT at 6 months post procedure, whichwas similar to most previous reports [22, 24, 25] but somewhat differed from others [26]. In the study of Granier et al,IDE occurred in 14 out of 23 patients(61%) after 10 months of LAAC[29].Lindner et al reported anIDE rate of 56% at median follow-up of 6 months post LAAC procedure[30]. Likewise, in another study including 46 patients undergoing successful LAAC, Sivasambu et alobserved that IDE occurred in 28 patients at 45 days during follow-up.Interestingly, cardiac CT demonstrated that contrast medium entered the left atrial appendage through the fabric rather than around the device in 10 patients [25].Conversely, Zhao and co-workers reported an IDE rate of 8.3% at 6 months in 84 patients who received successful LAAC and ablation of AF[31].The explanation for different occurrence rates of IDE after LAAC is multifactorial, and may be, at least partly, related toheterogenous definitions of IDE, various types of LAA occluder, and different cardiac imaging techniques[14, 30, 32].

Recently, cardiac CT has been shown to be more sensitive to detect device residual leak into the LAAcompared with transesophageal echocardiography, owing to its superior spatial resolution, three-dimensional assessment and largely operator independent nature[24, 33].By cardiac CT, the linear attenuation coefficient within theLAA can be measuredand, residual patent LAA has an attenuation either ≥100HU or ≥25% of that measured in LA could be defined as IDE[24], irrespective of peri-device leak. This may partly account for the higher prevalence of IDE in our study.Similar results have been

demonstrated by Lindner[30, 32],who defined LAA as patent if attenuation of the left atrium exceeded that of the left atrial appendage by 50 HU.

Risk factors for IDE

The potential predisposing factorsofIDE post LAAC remainnot fully clear.Hypercoagulable state, comorbidities, and device size and type may play a role[13, 17].Sharma et al reported a 70-year-old woman with severe mitral regurgitationwho suffered poordevice endothelialization 1.5 years after Watchman procedure. It was considered that an eccentric mitral regurgitation jet may cause shearing force on the device and impede normal endothelialization[13]. Massarenti et al observed IDE 10 months after LAAC in an elderly male with hereditary hemorrhagic teleangectasia, suggesting that IDEcould be due to abnormal vascular smooth muscle development and endothelial remodeling[18].Additionally, Granier et al found that patients with IDEwere more likely to have diabetes, permanent AF and larger devices implanted[29].In the present study, patients with IDE had larger LAA ostialdiameter and LA size.The factors together with persistent AF were independent determinants for IDE by multivariate analysis.Persistent AFmay involve in increased LA size and subsequentIDE[34], although the exact mechanisms remain unknown.

Animalstudies have demonstrated different processes of endothelialization amongdevices implanted[14, 15]. Watchmanoccluder does not impact left atrial appendage adjacent structures, favoring surface recovery[14]. In comparison, Amplatzer Cardiac Plug (ACP)(St. Jude Medical, Minneapolis, Minnesota)is more likely to trigger IDE because the disk could potentially jeopardize left atrial appendage neighboring structures[14].In this study, IDE was detected in 7 out of 8 patients with implantation of Leftear™, structurally similar to ACP™.However,Lindner et al [30] found no statistically relevant difference in the use of Watchman™ and AMPLATZER™ AMULET™ (St. Jude Medical, St Paul, MN, USA) between patients with IDE and those with CDE.These observations suggest that the effect of different devices on IDE require further investigations.

Clinical implications

Identifying predictive factors of IDE may have clinical implications, especially for the follow-up and postoperative medications for patients after LAAC. Theoretically,IDE leads to residual filling of the LAA with very low velocity and blood turbulence and stagnation, which could trigger thrombus formation behind (and ultimately on) the LAA closure device[29].Several studies have shown that occurrence of IDE later or very late afterLAAC increased the risk ofDRT and subsequentthromboembolic events[7, 11-13]. Therefore, current practice on duration of anticoagulant therapy from animal studies(i.e., 45 days with warfarin or 3 months with direct oral anticoagulants immediately after LAAC) [16]seems to be inadequate for thrombosis prevention. In the current study,4 patients were found with DRT at 6 months post LAAC,and 3 of them had IDEat the same area. Although no thromboembolic events occurred at 6-month clinical follow-up, prolonged antithrombotic treatment were given in these patients.This finding highlights

that standard cardiac CT follow-up and prolonged anticoagulant therapy are encouraged especially for patients with IDE after LAAC procedure.

Study limitations

We recognizelimitations in our study. First, patients number included in the current study is limited, selection bias may exist and the conclusion derived from current study may be underpowered. Second, as a single center study, the treatment regimen of patients included may not reflect the general status of LAAC therapy. Third, 6-month's clinical follow-up duration does not allow us to fully answer the long-term outcomes of patients with IDE, as well as the appropriate antithrombotic regimen in this population. Forth, individual features of baseline echocardiography, such as mitral regurgitation degree, was not analyzed in the current study, which may have adverse influence on IDE.

Conclusion

This study suggests that after successful LAAC procedure,a high proportion of patients develop IDE, particularly for those with persistent AF,larger LAA orifice and left atrial size.IDE confers an increased risk for DRT formation.However, further large-cohort studies are warranted to investigate whether IDE and DRT are associated with embolic stroke and poor outcome, leading to a recommendation for careful monitoring and continued antithrombotic therapy.

Declarations

Acknowledgement

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Competing interests

The authors declare that they have no conflict ofinterest.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by JX, CZC, JX, LW and YRT. The first draft of the manuscript was written by JX and CZC. BY and QZ conducted a critical revision of manuscript.YLS and JQHwas responsible for the

revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethical approval

All procedures performed in studies involving humanparticipants were in accordance with the principles of the declaration of Helsinki and was approved by the hospital ethics committee.

Consent to participate

All patients provided their written informed consents.

Consent for publication

Consent for publication was obtained for everyindividual person's data included in the study.

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Figures

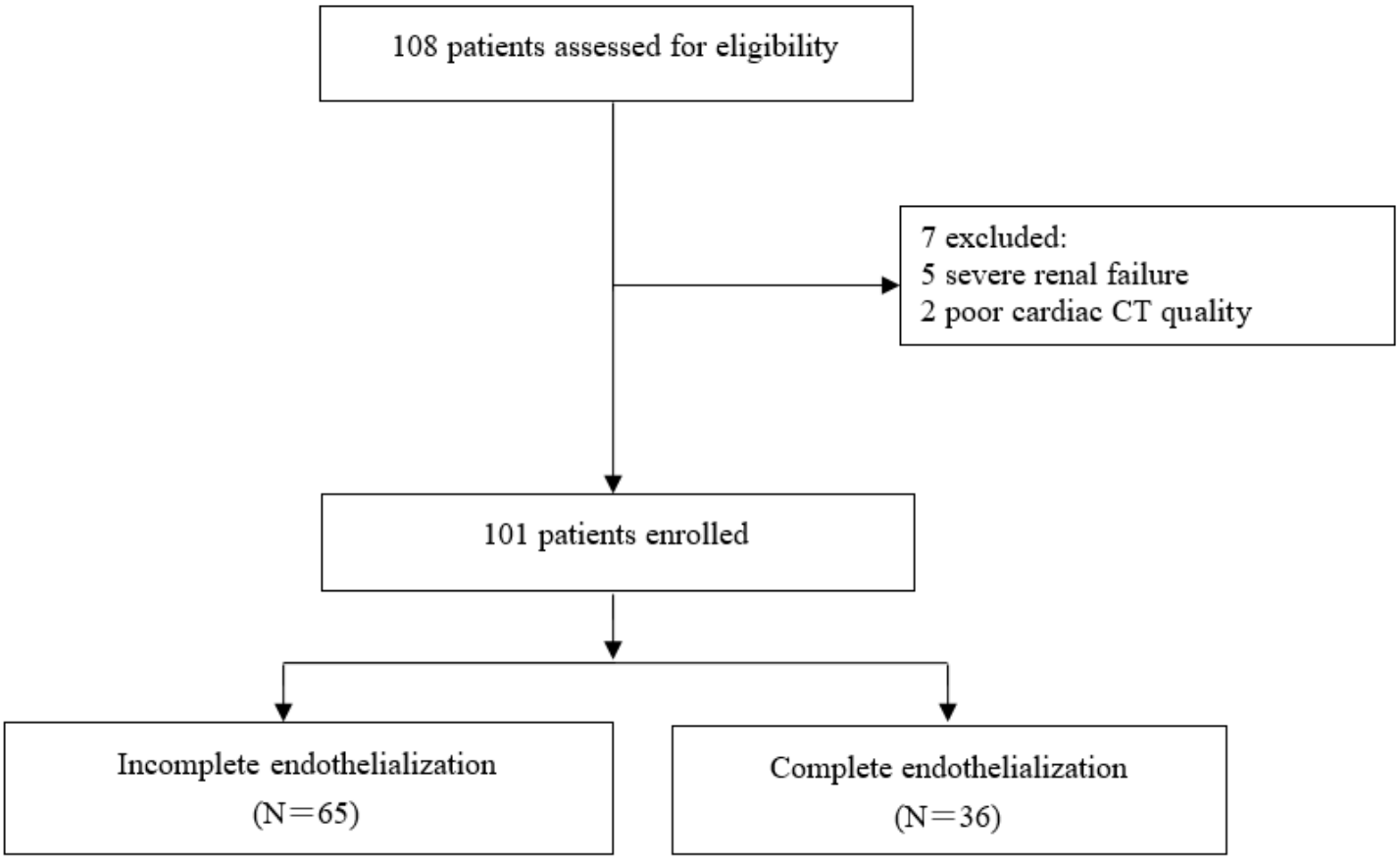

Figure 1

Patient selection flowchart.

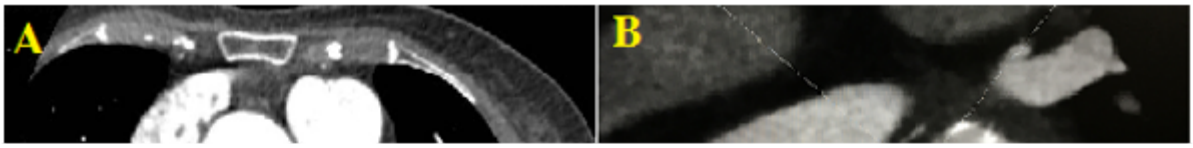

Figure 2

Device endothelialization assessed by cardiac CT. (A) complete endothelial coverage of the Watchman device, no trans-fabric leak with LAA HU<100 and LA/LAA<0.25. (B) incomplete endothelial coverage of the Watchman device, trans-fabric leak with LAA HU>100. (C) incomplete endothelial coverage of the Leftear device, trans-fabric leak with LAA HU>100. (D) poor DE at the same area as DRT(arrow).