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Gender Specified in-Hospital Outcome after Left Atrial Appendage Closure with a Dual Occlusive Mechanism Device

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ABSTRACT

Background: Recent studies have suggested an increased rate of adverse events in women following left atrial appendage occlusion (LAAO), particularly with dual occlusive mechanism devices.

Objectives: This study aimed to investigate gender disparities in in-hospital adverse events and short-term device-related outcomes in an experienced center using dual occlusive mechanism devices exclusively.

Methods: In a single-center retrospective study, patients who received dual occlusive mechanism devices (Amplatzer cardiac plug and Amulet) were analyzed. We assessed gender differences in patient characteristics, LAAO indications, procedural data, in-hospital complications, and short-term device-related outcomes in the form of one-month follow-up transesophageal echocardiography.

Results: Among 474 patients, 211 (45%) were women. At device implantation, women were significantly older (77.45±6.98 years vs. 75.89±7.26; p = 0.01), with higher CHA2DS2Vasc scores (5.03±1.46 vs. 4.28±1.51; p < 0.01) and lower HASBLED scores (3.78±1.06 vs. 4.03±1.12; p = 0.01) compared to men. Men had a higher prevalence of coronary artery disease (52% vs. 32%; p < 0.01). LAAO indications did not significantly differ. Device success was 99% in men and 98% in women (p = 0.75). In-hospital complications, including deaths, major bleedings, and pericardial effusion, did not significantly vary by gender. Rates of device-related thrombus and device closure with a residual jet ≤ 5 mm were similar.

Conclusions: In a large cohort of consecutive LAAO patients at an experienced center, gender was not linked to higher in-hospital complications.

KEYWORDS: Follow up, gender, in-hospital outcome, left atrial appendage occlusion, transesophageal echocardiography

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INTRODUCTION

Left atrial appendage occlusion (LAAO) is a valid alternative to oral anticoagulation (OAC) in patients with atrial fibrillation (AF) and contraindications to OAC, effectively reducing the risk of thromboembolism. [1]

Recent large-scale meta-analyses have demonstrated comparable clinical outcomes between the commonly prescribed direct oral anticoagulants (DOAC) and LAAO. [2]

The most commonly used device is the Watchman device [3], representing a lobe-only concept, and the Amplatzer cardiac plug (ACP)/Amulet, a dual occlusive mechanism device with an additional covering disc. [4]

Both device types distinguish themselves with high technical and procedural success rates and low complication rates. [5]

Nevertheless, recent studies have revealed a higher peri-procedural complication rate in women, who are often underrepresented compared to men. [6] These gender differences appear to diminish in long term investigations [7,8], although causally determined correlations remain speculative.

Subgroup analyses of the Amulet IDE Trial by Alkhouli et al. [7] confirmed the recent findings of higher peri-procedural complication rates in women, especially in cases where the Amplatzer Amulet occluder was used. It is important to note that complication rates decreased with the operators' experience, a fact supported by the Amplatzer™ Amulet™ Observational Study [8], which reported no significant gender-specified outcome differences as the operators were highly experienced in implanting the Amplatzer Amulet.

As a center with extensive experience in LAAO using the ACP and Amulet since 2009, we conducted an investigation into gender differences within our patient cohort, focusing on periprocedural adverse events and the short-term echocardiographic follow- up. Our aim was to validate or refute the observations made in the aforementioned studies.

METHODS

Study design

In this retrospective single-center study, we analyzed 474 consecutive patients who underwent LAAO with a dual occlusive mechanism device (ACP or Amulet) due to atrial fibrillation and contraindications to effective OAC between September 2009 and December 2022. The aim was to compare gender differences in terms of baseline characteristics, clinical and laboratory features, pre-LAAO medication, bleeding risk factors, LAAO indications, implantation characteristics, with a particular emphasis on periprocedural adverse events, and echocardiographic follow-up.

Implantation procedure

At least one day before LAAO, all patients underwent transesophageal echocardiography (TEE) to assess LAA eligibility for LAAO and to exclude atrial thrombus. LAAO was performed under general anesthesia with simultaneous contrast angiography and TEE (GE Vivid E9 BT12). Procedure time (minutes) was defined as the time from the beginning of the procedure until patient extubation. Additional parameters, including the amount of contrast medium (ml), fluoroscopy time (minutes), and radiation dose (cGy*cm2), were recorded using the DAVID hemodynamic software (Metek, Germany). Device implantation and device selection were carried out according to the manufacturers' instructions (AMPLATZER Cardiac Plug, AMPLATZER Amulet, Left Atrial Appendage Occluder Instructions for Use, St. Jude Medical, Minnesota, USA).

Definitions

Device success was defined as the successful exclusion of the LAA with the device during the index procedure, with a maximum peri-device leakage of 1 mm in the width of the color jet flow. Periprocedural adverse events encompassed any adverse event listed in our tables from the beginning of the LAAO procedure until patient discharge from the hospital. Major adverse events included all-cause deaths, ischemic strokes, myocardial infarctions, device embolization, and major bleedings, based on the definitions provided in the Munich consensus document.

Transesophageal echocardiographic follow-up

The first TEE follow-up was conducted at least one month after the index LAAO procedure. At this point, the position of the device, device-related thrombus, transseptal shunts, and peri-device leaks (minor leak: < 1 mm, moderate leak: 1-3 mm, major leak: > 3 mm, severe leak: multiple jets or free flow) were evaluated.

Endpoints

As defined in the Amulet IDE trial [12], the primary safety endpoint was a composite endpoint rate of procedure-related complications (requiring invasive surgical or percutaneous intervention), all-cause death or major bleeding until hospital discharge. The mechanism of action primary endpoint was the rate of device closure with a residual jet of ≤ 5 mm around the device in the first follow-up TEE.

Statistical analysis

Continuous variables were presented as mean ± standard deviation and analyzed using the Student's t-test if the distribution was normal. Otherwise, the Mann-Whitney-U test was applied. Categorical variables were reported as absolute numbers and percentages and compared using binary logistic regression analysis. Statistical significance was determined as a two-sided p-value of < 0.05. Statistical analyses were performed with SPSS version 29 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics

Between September 2009 and December 2022, 474 consecutive patients were enrolled.

Of these, 211 (45%) were female, and 263 (55%) were male. Females were significantly older than males (77.45 ± 6.98 years versus 75.89 ± 7.26 years; $p = 0.01$) and had a higher CHA2DS2Vasc score (5.03 ± 1.46 for females versus 4.28 ± 1.51 for males; $p < 0.01$), as the female gender generates an additional point. However, they had a significantly lower HASBLED score (3.78 ± 1.06 for females versus 4.03 ± 1.12 for males; $p = 0.01$).

Males exhibited a significantly higher prevalence of coronary artery disease (138 males (52%) versus 67 females (32%); $p < 0.01$) and a history of three-vessel coronary artery disease (CAD 3) ($p < 0.01$), myocardial infarction (MI) ($p = 0.02$), and coronary artery bypass graft (CABG) ($p < 0.01$). Additionally, more males were smokers (89 males (34%) versus 34 females (16%); $p < 0.01$).

Before LAAO, males had a significantly higher creatinine level (1.46 ± 0.95 mg/dl for males versus 1.20 ± 0.73 mg/dl for females; $p < 0.01$), although the glomerular filtration rate (GFR) was similar (60.85 ± 24.78 ml/min for males versus 57.48 ± 24.52 ml/min for females; $p = 0.14$). Apart from clopidogrel (37 males (14%) versus 11 females (5%); $p < 0.01$), there were no significant differences in coagulation-inhibiting medications before LAAO for males and females. Further details can be found in Table 1.

Table 1: Patient Characteristics				
	Overall Cohort n=474 (%)	**Males** n=263 (%)	**Females** n=211 (%)	**p value**
Age (years)	76.47±7.18	75.89±7.26	77.45±6.98	0.01
Age≥75 (years)	299 (63)	153 (58)	146 (69)	0.01
Age≥80 (years)	185 (39)	84 (32)	101 (48)	<0.01
Body mass index (kg/m^2)	28.12±21.04	28.88±27.77	27.17±5.64	0.38
CHA_2DS_2VASC score	4.62±1.53	4.28±1.51	5.03±1.46	<0.01
HASBLED score	3.92±1.10	4.03±1.12	3.78±1.06	0.01
Atrial fibrillation (n)				
Paroxysmal	205 (43)	105 (40)	100 (47)	0.10
Persistent	69 (15)	39 (15)	30 (14)	0.85
Permanent	200 (42)	119 (45)	81 (38)	0.13
Clinical features				
Coronary artery disease (n)	205 (43)	138 (52)	67 (32)	<0.01
CAD 3	54 (11)	47 (18)	7 (3)	<0.01
Myocardial infarction	78 (16)	53 (20)	25 (12)	0.02
CABG	47 (10)	38 (14)	9 (4)	<0.01
Heart failure (n)	139 (29)	79 (30)	60 (28)	0.70
Arterial hypertension (n)	413 (87)	231 (88)	182 (86)	0.61
Pacemaker (n)	97 (20)	63 (24)	34 (16)	0.04
Diabetes mellitus (n)	128 (27)	73 (28)	55 (26)	0.68
COPD (n)	76 (16)	42 (16)	34 (16)	0.97
Hemoglobin (g/dl)	11.89±2.35	12.15±2.57	11.57±1.98	0.01
Creatinine (mg/dl)	1.35±0.87	1.46±0.95	1.20±0.73	<0.01
GFR (ml/min)	59.35±24.69	60.85±24.78	57.48±24.52	0.14
Quick (%)	87.32±24.09	85.11±23.96	90.09±23.91	0.03
INR	1.14±0.30	1.16±0.32	1.11±0.28	0.09
PTT (sec)	27.37±5.73	27.57±5.37	27.12±6.16	0.40
Nicotine (n)	123 (26)	89 (34)	34 (16)	<0.01
Medication before LAA occlusion				
ASA (n)	130 (27)	81 (31)	49 (23)	0.07
Clopidogrel (n)	48 (10)	37 (14)	11 (5)	<0.01
Vitamin K antagonist (n)	39 (8)	26 (10)	13 (6)	0.15
Noval oral anticoagulant (n)	173 (37)	86 (33)	87 (41)	0.06
Low molecular weight heparin (n)	107 (23)	65 (25)	42 (20)	0.21
Risk factors for bleeding				
Previous stroke (ischemic or hemorrhagic) (n)	133 (28)	79 (30)	54 (26)	0.29
TIA (n)	28 (6)	17 (7)	11 (5)	0.57
Prior major bleeding (n)	250 (53)	136 (52)	114 (54)	0.62
Renal disease (n)	188 (40)	106 (40)	82 (39)	0.75
Liver disease (n)	32 (7)	17 (7)	15 (7)	0.78
Labile INR (n)	10 (2)	7 (3)	3 (1)	0.36
Malignant disease (current/previous) (n)	110 (23)	75 (29)	35 (17)	<0.01

CAD: coronary artery disease; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; GFR: glomerular filtration rate; INR: international normalized ratio; PTT: prothrombin time; ASA: acetylsalicylic acid; TIA: transitory ischemic attack

Indications for LAAC

The primary indications for LAAO were previous bleedings, predominantly driven by major bleedings in 250 patients (53%) in the overall cohort. Most of these cases involved major gastrointestinal bleedings, with no significant gender-based differences (73 males (28%) versus 66 females (31%); p = 0.40).

As documented in table 2, further indications did not differ significantly.

Table 2: Indications for left atrial appendage occlusion				
	Overall Cohort n=474 (%)	**Males** n=263 (%)	**Females** n=211 (%)	**p value**
Previous major bleeding (n)	250 (53)	136 (52)	114 (54)	0.62
Intracranial bleeding	80 (17)	47 (18)	33 (16)	0.52
Gastrointestinal bleeding	139 (29)	73 (28)	66 (31)	0.40
Other	34 (7)	17 (7)	17 (8)	0.51
Previous minor bleeding (n)	182 (38)	102 (39)	80 (38)	0.85
Gastrointestinal bleeding	89 (19)	56 (21)	33 (16)	0.12
Hematoma	37 (8)	19 (7)	18 (9)	0.60
Other	79 (17)	41 (16)	38 (18)	0.48
Renal disease (n)	57 (12)	29 (11)	28 (13)	0.46
High risk of falls or prior falls (n)	41 (9)	32 (12)	18 (9)	0.93
Physician/patient refusal of oral anticoagulation (n)	4 (8)	3 (1)	1 (0.5)	0.45
For some patients more than 1 indication was reported				

Procedural data

In the overall cohort of 474 patients, the device was successfully implanted in 98% of cases. The device success rate was not influenced by gender (n = 259 (99%) for males versus n = 207 (98%) for females; p = 0.75). In terms of procedure time, use of contrast medium, fluoroscopy time, size of the device finally implanted and the period of hospital stay, there were no significant gender differences (table 3). However, the radiation dose was higher in males (3187 ± 2794.21 cGy*cm2) as compared to females (1945 ± 1955.17 cGy*cm2; p < 0.01).

Table 3: Procedural data				
	Overall Cohort n=474 (%)	**Males** n=263 (%)	**Females** n=211 (%)	**p value**
Device success (n)	466 (98)	259 (99)	207 (98)	0.75
Procedure time (min)	74.01±28.76	74.45±27.20	73.48±30.65	0.72
Contrast medium (ml)	104.11±61.61	110.34±70.67	96.40±47.15	0.28
Fluoroscopy time (min)	12.01±23.28	10.45±6.11	13.96±34.12	0.91
Radiation dose (cGy∗cm2)	2633.17±2529.49	3187.98±2794.21	1945.64±1955.17	<0.01
More than 1 device tried (n)	26 (6)	14 (5)	12 (6)	0.86
Final occluder implanted (mm)	23.37	23.62±3.73	23.06±3.79	0.11
Hospital stay (days)	6.41±4.23	6.23±4.19	6.63±4.26	0.31

Periprocedural adverse events

In the overall cohort, the primary safety endpoint was reached in 22 patients (4.6%), with no gender-based differences (n = 13 (5%) for males versus n = 9 (4.3%) for females; p = 0.73). The rate of overall complications was similar (n = 51 (19%) for males versus n = 37 (18%) for females; p = 0.61). Major adverse events were primarily related to major bleeding, with no gender-specific differences (n = 8 (3%) for males versus n = 7 (3%) for females; p = 0.87). Notably, cardiac tamponades were the leading cause of major bleeding in males, accounting for 5 (2%) cases. In females, no specific major bleeding cause stood out. Although femoro-vascular complications did not differ between the sexes (n = 15 (6%) for males versus n = 17 (8%); p = 0.31), minor hematomas in the groin occurred significantly more often in females (n = 5 (2%) for males versus n = 13 (6%) for females; p = 0.02). Importantly, gender was not a significant factor for pericardial effusion after the intervention (p = 0.42), as reported in Table 4

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Table 4: Periprocedural adverse events				
	Overall Cohort n=474 (%)	**Males** n=263 (%)	**Females** n=211 (%)	**p value**
Major adverse events				
Death (n)	5 (1)	4 (1.5)	1 (0.5)	0.29
Cardiogenic shock (n)	2 (0.4)	1 (0.4)	1 (0.5)	0.88
Septic shock (n)	1 (0.2)	1 (0.4)	0	1

Hemorrhagic shock (n)	2 (0.4)	2 (0.8)	0	0.16
Stroke (n)	2 (0.4)	1 (0.4)	1 (0.5)	0.88
Myocardial infarction (n)	1 (0.2)	1 (0.4)	0	1
Major bleeding overall (n)	15 (3)	8 (3)	7 (3)	0.87
Intracranial bleeding (n)	1 (0.2)	1 (0.4)	0	1
Major gastrointestinal bleeding (n)	3 (0.6)	1 (0.4)	2 (0.9)	0.46
Cardiac tamponade (n)	6 (1.3)	5 (2)	1 (0.5)	0.20
Femoral bleeding (n)	3 (0.6)	1 (0.4)	2 (0.9)	0.46
Epistaxis (n)	2 (0.4)	0	2 (0.9)	0.16
Device embolization requiring surgery (n)	1 (0.2)	1 (0.4)	0	1
Device embolization snared (n)	1 (0.2)	1 (0.4)	0	1
Other adverse events				
Pericardial effusion overall (n)	27 (6)	17 (7)	10 (5)	0.42
Femoro-vascular complications (n)	32 (7)	15 (6)	17 (8)	0.31
Femoral artery pseudoaneurysm	8 (1.7)	6 (2.3)	2 (0.9)	0.28
Arteriovenous fistula	3 (0.6)	3 (1.1)	0	1
Hematoma (minor bleeding)	18 (4)	5 (2)	13 (6)	0.02
Air embolism (transient ST elevation and/or chest pain) (n)	2 (0.4)	1 (0.4)	1 (0.5)	0.88
Acute kidney injury (n)	6 (1.3)	4 (1.5)	2 (0.9)	0.58
Fever of unknown origin (n)	6 (1.3)	5 (2)	1 (0.5)	0.20
Overall complications (n)	88 (19)	51 (19)	37 (18)	0.61
Primary Safety Endpoint (n)	22 (4.6)	13 (5)	9 (4.3)	0.73

For some patients more than 1 complication was reported

Primary Safety Endpoint (Amulet IDE trial): Composite Endpoint Rate of Procedure-related Complications (requiring invasive surgical or percutaneous intervention), or All-cause Death or Major Bleeding until hospital discharge

Transesophageal echocardiographic follow-up

Follow-up was completed for 394 of the 474 patients investigated. The prevalence of device-related thrombus did not differ between male and female patients (2 % for each; p = 0.76). Furthermore, transseptal shunts did not show significant differences between the sexes (p = 0.51). As defined in the Amulet IDE trial [12], the *Mechanism of Action Primary Endpoint* was achieved in 218 (100 %) males and 174 (99 %) females, with no significant difference (p = 1).

Table 5: 1. Follow up transesophageal echocardiography

	Overall Cohort n=394 (%)	**Males** n=218 (%)	**Females** n=176 (%)	**p value**
Device-related thrombus (n)	8 (2)	4 (2)	4 (2)	0.76
Transseptal shunt (n)	114 (29)	66 (30)	48 (27)	0.51
Peridevice leakage (n)	54 (14)	28 (13)	26 (15)	0.58
Major leak	1 (0.3)	0	1 (0.6)	0.32
Moderate leak	1 (0.3)	0	1 (0.6)	0.32
Minor leak	52 (13)	28 (13)	24 (14)	0.82

Mechanism of Action Primary Endpoint (n)	392 (99.5)	218 (100)	174 (98.9)	1

Mechanism of Action Primary Endpoint (Amulet IDE trial): Rate of Device Closure (residual jet ≤ 5 mm around the device)

DISCUSSION

Contrary to previous studies showing significantly higher periprocedural complication rates that were driven by bleedings in women after LAAO (Watchman and ACP/Amulet) [7,9,10,11], we did not detect any statistically significant differences between men and women in terms of in-hospital major adverse events (including deaths, strokes, myocardial infarction, major bleedings, and device embolization) and overall complications. Based on the definitions in the Amulet IDE Trial [12] there were no gender-specified differences of the in-hospital primary safety endpoint and the mechanism of action primary endpoint (residual jet ≤ 5 mm). Moreover, in the first follow-up transesophageal echocardiography at least one month after LAAO the occurrence of device-related thrombus (DRT) and transseptal shunts was similar between men and women.

The only procedure related difference in complications was a significantly higher rate of hematoma (minor bleedings) in the femoro-vascular access site in women than in men. This finding corresponds with previous studies in catheter ablations for AF. [13] In the latter study the lower body size of women was identified as a predicting factor. However, in our study BMI did not differ significantly between men and women.

In a Watchman device registry, Hana et al. [14] reported an increased risk for access site bleeding and hematoma in women as compared to men (10.3 % versus 6.8 % and 6.6 % versus 4.1 %, respectively).

Remarkably, the HASBLED score in our cohort was significantly higher in men than in women (4.03 ± 1.12 versus 3.78 ± 1.06; p = 0.01) whereas the occurrence of previous major and minor bleedings (> 50 % overall), as the main indication for LAAO, did not differ between the sexes.

Concordant with previous studies [7,9,10,14], men of our cohort showed a significantly higher cardiovascular risk profile than women, whereas women were significantly older (48 % of all women ≥ 80 years versus 32 % of men; p < 0.01).

We found significantly higher radiation doses in men than in women. Kleinecke et al. [10] found similar increased radiation doses in men as compared to women (3187 ± 2794.21 cGy*cm2 versus 1945 ± 1955.17 cGy*cm2; p < 0.01).

Previously De Caterina et al. [8] (98.9 % for males versus 99.5 % for females; p = 0.51) and Alkhouli et al. [7] (98.7 % for males versus 97.9 % for females; p = 0.48) showed very high success rates for both men and women. Our study confirmed those findings.

The subgroup analysis of the Amulet IDE trial [7] raised concerns that periprocedural complications may depend on gender. The latter authors reported a significantly higher rate of major bleeding events and any in-hospital major adverse event with the Amplatzer Amulet (0.4 % for males versus 5.0 % for females; p = 0.01 and 1.3 % for males versus 23 % for females; p = 0.01, respectively). Whereas, De Caterina et al. [8] reporting the results of the Amplatzer™ Amulet™ Observational Study, didn´t detect any difference in major bleedings (2.6 % for males versus 3.1 % for females; p = 0.70) or any procedure related serious adverse event (SAE) ≤ 7 days (5.4 % for males versus 6.5 % for females; p = 0.50). The results of De Caterina et al. [8] coincide with our investigations as our major bleeding rates (3.0 % for males versus 3.3 % for females; p = 0.87) were similar. A potential explanation of this finding is that both the operators of the Amplatzer™ Amulet™ Observational Study [8] and the operators in our center are very experienced in the implantation of the ACP/Amulet. In this respect it is important that the Amulet IDE trial was performed in frequently inexperienced operators with the Amulet device. This is supported by the finding that most of the bleeding events in the Amulet IDE trial occurred in the first 10 cases after implantation of the Amplatzer Amulet.

Nonetheless, although the operators of Amulet IDE trial [12] were less experienced in the implantation of the Amplatzer Amulet, the Watchman device showed higher rates of peridevice leakage in the first follow-up echocardiography after 45 days. The primary mechanism of action end point was 98.9 % for the Amplatzer Amulet and 96.8 % for the Watchman device, which corresponds with the 99.5 % in our study with no statistical difference between the sexes.

CONCLUSION

In a large cohort of consecutive patients undergoing LAAO in an experienced center, gender was not associated with higher in-hospital complications.

Strength and limitations

The main weakness of this study is its retrospective design. However, all consecutive patients were reported and reporting of in hospital complications was complete.

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