Experience of Combined Procedure During Percutaneous Left Atrial Appendage Closure.

Guillaume Domain[1], Nicolas Dognin[1], Gilles O'Hara[1], Josep Rodes-Cabau[1], Jean-Michel Paradis[1], Camille Strubé[1], Mathieu Bernier[1], Kim OConnor[1], Jonathan Beaudoin[1], François Philippon[1], Erwan Salaun[1], and Jean Champagne[1]

[1]IUCPQ

December 1, 2021

Abstract

Introduction: Percutaneous left atrial appendage closure (LAAC) is an alternative to oral anticoagulant (OAC) in patients with non-valvular atrial fibrillation (AF) and contraindication to long-term OAC. Combined strategy with percutaneous LAAC at the same time of other cardiac structural or electrophysiological procedure has emerged as an alternative to staged strategy. Aim: To describe our experience of combined LAAC procedures using Watchman devices. Method: All patients with combined LAAC procedure using Watchman (WN) devices performed from 2016-2021 were included. The primary safety endpoint was a composite of periprocedural complications and adverse events during follow-up. The primary efficacy endpoint included strokes, systemic embolisms, major bleeding, and cardiovascular death. Results: Since 2016, among the 157 patients who underwent LAAC using WN devices, 16 underwent a combined strategy: 6 TEMVR (37%), 6 typical atrial flutter ablation (37%), 2 LP implantation (13%) and 2 atrial fibrillation ablation (13%). The WN device was successfully implanted in 98% and 100% for single and combined LAAC respectively (p = 0.63). Median follow-up was 13 months (IQR 25/75 3/24) in the whole cohort. Device related complications occurred in 6 out of 141 patients (4%) who underwent single LAAC and in no (0/16) patient in the combined LAAC procedure (p=ns). The procedural related complications did not differ significantly between groups (5% vs 12%, respectively in the single and combined group, p=0.1). Conclusion: Combined procedure combining LAAC using the Watchman devices and one other structural or electrophysiological procedure is safe and effective. Larger series are needed to confirm these results.

Introduction

Oral anticoagulation (OAC) is the cornerstone of stroke prevention in non-valvular atrial fibrillation (NVAF) when CHADS-VASC score are high (1,2). However, contraindication for long-term OAC related to comorbidities, personal history of bleeding or persistent risk of bleeding remains a frequent issue in clinical practice (3). In NVAF, thrombi typically occur in the left atrial appendage (4), and over the last years, left atrial appendage closure (LAAC) with an occluder device has emerged as an alternative to OAC in selected patients (5,6).

Different design and generations of devices are available for percutaneous LAA closure: Watchman devices, ACP and Amulet devices, WaveCrest, and LAmbre (7).

Recently, combined strategy of concomitant LAAC for stroke prevention and catheter ablation (CA) for AF was proposed, and an international multicenter registry support the feasibility and safety of this strategy (8,9). The combined strategy of concomitant CA and LAAC procedures in symptomatic AF patients with high risk of stroke and bleeding may be a cost-effective therapeutic option compared with CA and long term standard oral anticoagulation (OAC) (10). Moreover, in patients with both NVAF and patent foramen oval (PFO) or atrial septal defect (ASD), LAAC combined with PFO or ASD closure was previously reported

(11,12). Finally, other percutaneous procedures such as leadless intracardiac transcatheter pacing systems implantation or transcatheter edge-to-edge mitral valve repair (TEMVR) may be combined with LAAC (13-16). Recent publication have shown the possibility to associate safely LAAC using Amplatzer^{TM} devices with structural, coronary, or electrophysiological concomitant procedures (16). Combined approach could thus allow to treat several cardiac conditions in a single intervention.

Here, we report our single center experience of a combined strategy with LAAC procedure using the Watchman^{TM} (WN) devices and other percutaneous procedures.

Method

This study was conducted according to ethical standards of clinical e-research in Canada and in accordance with the Helsinki declaration. This is a retrospective analysis of clinical, biological, and echocardiographic data prospectively collected in a single center registry of all patients (n=157) who underwent percutaneous LAAC using WN devices at our institution from October 2016 to October 2021. Combined strategy was defined as a LAAC closure with WN devices associated with concomitant cardiac structural or electrophysiological interventions using the same femoral venous access.

Definitions and Outcomes Measures

Immediate and delayed procedure related complications were collected according to the Munich Consensus Document (17).

Procedural success was defined as: 1-Technical success and 2-No procedure-related complications.

Technical success was defined as: 1- exclusion of the LAA; 2-No device related complication; and 3-No leak [?] 5mm on color Doppler TEE.

Device related complications included: device related thrombus (DRT), device embolization, erosion, interference with the surrounding structure (circumflex coronary artery, mitral valve, pulmonary artery, or pulmonary vein), fracture, perforation or laceration, infection, or endocarditis.

Based on the Protect AF trial, an adequate sealing of the LAA was characterized by a jet < 5 mm and a jet [?] 5 mm was considered as a significant para-prosthetic leak (18).

The procedure related complications included: stroke (hemorrhage or infarction), transient ischemic attack, systemic embolism, life-threatening or major bleeding, pericardial effusion, vascular complication, pericarditis, myocardial infarction, renal failure, hepatic failure, cardiovascular death, and unknown cause death occurring during the follow-up. Major bleeding was defined as one of the following criteria: 1- fatal bleeding; 2- symptomatic bleeding in a critical organ or area (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, intramuscular with compartment syndrome); 3- a fall in the hemoglobin level of [?] 20 g/L; 4- transfusion of two or more units of whole blood or red cells (19,20). Ischemic stroke was defined as an episode of neurological dysfunction caused by a focal cerebral, spinal, or retinal infarction and could be definitive, transient, or silent (21). Data related to peripheral embolism and hemorrhagic strokes were also collected. The CHA2DS2-VASc and HASBLED score were calculated.

Procedures

The LAAC devices used in this study were the Watchman 2.5^{TM} Devices and the Watchman FLX^{TM}devices (Boston scientific, St. Paul, Minnesota) using the TruSeal access sheath (Boston Scientific, St. Paul, Minnesota). The basic steps of the procedure were similar for the Watchman 2.5^{TM}and FLX^{TM} devices regarding the use of general anesthesia, femoral venous access for the transseptal puncture, use of a guide wire and pigtail for sheath guidance and positioning, and device selection based on transesophageal echocardiography (TEE) and angiography. Implantation of the Watchman 2.5^{TM}devices was performed as recommended (22), and the ball technique was used for the implantation of the Watchman FLX devices (22). After correct TEE assessment of the standard PASS criteria (position, anchor, size/compression, seal), fluoroscopic morphology and angiographic test, a tug-test was performed. The Watchman device was then released, and all material

removed. Patients could receive protamine infusion and venous closure device, or hemostatic suture and a compressive dressing.

Postoperative Care

After the procedure, all patients stayed in the cardiac care unit for 24-h continuous ECG monitoring, and transthoracic echocardiography (TTE) and chest X-ray were performed before discharge. During the first 45 to 60 post-operative days, all patients received, depending on the clinical scenario, oral anticoagulation, dual or single antiplatelets. A TEE was performed between 45 to 60 days post-procedure. The antithrombotic medication was then adapted individually, considering the correct sealing, device related thrombus and outcome occurrence.

Follow-up

All patients were followed in our dedicated LAA clinic, at 6 weeks, 6-months, 1-year, and 2-years after the procedure. During the follow-up visits, clinical status and ECG were recorded. A TEE was performed at 45-60 days post procedure then repeated at 1-year follow-up to assess persistence of correct sealing and PASS criteria and exclude any complication. If a TEE was contraindicated, a standard TTE was performed.

Statistical analysis

Continuous data were expressed as median and interquartile range (IQR) or mean and standard deviation (SD) and compared between groups using ANOVA. Qualitative variables were presented as percentages and compared between groups using Chi2 test or Fisher's exact test.A univariate Cox model was performed to compare the occurrence of events in each group.

All tests were two-sided. A p-value < 0.5 was considered significant for all analysis.

R Studio statistical software (RStudio, Inc. 2019 version, 1.2.5001) was used.

Results

Patient Demographics

From the 157 patients who underwent LAAC using WN devices, 16 (10%) underwent a combined strategy. Overall, the median follow-up was 13 months (IQR 25/75 3/24). The median follow-up was 13 months (IQR 25/75 4/24) for the single group and 5 months (IQR 25/75 1/24) in the combined group (p=0.1). The median age was 76 (IQR 25/75 71/80) and 71 (IQR 25/75 61/73) in the single and combined strategy groups respectively (p<0.01). The CHA2DS2-VASc score (mean ± SD) was 4 (IQR 25/75 3/5) in each group, whereas the HAS-BLED score was 4±1 and 3±1 respectively (p=0.03). Atrial fibrillation was permanent in 47 % of patients in the single procedure group and in 37% in the combined strategy (p=ns). Indications for LAAC are depicted in Table 1.

Device Implantation Outcomes

The LAAC immediate device implantation success rate was not significantly different (p=0.63) in the two groups, 98% in the single procedure group and 100% in the combined strategy group (Table 2). The 2 procedural failures were related to unfavorable anatomy and a high risk of prosthesis embolization after assessment of the PASS criteria. Median procedural time was 69 min (IQR 25/75 53/88) and 115 min (IQR 25/75 76-139), median fluoroscopy time 7 min (IQR 25/75 5-10) and 18 min (IQR 25/75 10-38), median fluoroscopy dose 945 mGy (IQR 25/75 402/2760) and 2500 mGy (IQR 25/75 640/11992) in the single procedure and combined strategy groups, respectively (p<0.01). Recapture or device resizing were required in 42 patients (27%).

The combined strategy included 6 TEMVR (37%), 6 typical atrial flutter ablation (AFL) (37%), 2 LP implantation (13%) and 2 atrial fibrillation ablation (13%). Among the 6 patients undergoing a typical flutter ablation, 3 were in flutter at time of LAAC and sinus rhythm was obtained in all. Procedural time, fluoroscopy duration and fluoroscopy dose was significantly lower for AFL (table 3).

Mid-Term Device Related Complications

Six patients in the single procedure (4%) group had a device related complication during follow-up: Three had a significant para-prosthetic leak (with a jet size > 5 mm) (2%), and 3 a DRT (2%). No device embolization occurred during follow-up in the whole cohort (Table 3). Thus, the mid-term technical success rate was 96% and 100% in the single procedure group and in the combined strategy group respectively (HR=1.1 [0.6-2.0], p=0.6).

Mid-Term Procedural Related Complications

Procedural related complications occurred in 8 and 2 patients in the single procedure group and in the combined strategy group respectively (5% and 12%, HR=3.5 [0.7-17], p=0.1). One patient in each group presented with a major hemorrhage due to recurrent gastrointestinal bleeding on Aspirin (at 2 years in the single group and 7 months in the combined strategy (1 and 6%, HR=12.0 [0.8-201], p=0.07)). Cardiovascular death occurred in 3 patients in the single procedure group due to hemorrhagic stroke in 2 (2%) and end-stage heart failure in 1. There was no systemic embolization over the follow-up period for the whole cohort (Table 4).

Staged Procedures

Among the single procedure group, several patients (n= 66 (42%)) had a structural or electrophysiological intervention before or after the LAAC. Twenty patients underwent atrial flutter ablation (13%) and seven atrial fibrillation ablation (4%), 43 patients received a pacemaker (27%) (17 VVI, 19 DDD and 7 CRT) and TEMVR was performed in one patient. These deferred interventions were performed less than 12 months before or after LAAC in 27 patients (17%).

Discussion

The key findings of our study are that a combined strategy with LAAC using Watchman devices and one other cardiac structural or electrophysiological interventions: 1. is not associated with a lower procedural success; 2. is not associated with higher risk of procedural complications; 3. remains safe and effective at mid-term follow-up.

Multiples Interventions and Risk in the Elderly Population

In the frail and elderly population referred for LAAC, patients harbor several cardiac and extracardiac comorbidities (23). This clinical status leads to both: 1. higher risk of requiring multiple cardiac interventions; and 2. higher risk of complications when these cardiac interventions are performed. Moreover, multiple, and repeated hospitalizations and anesthesia in the elderly population can result in periprocedural complications unrelated to the initial clinical condition that prompted the admission or to the procedure itself (24). Thus, a strategy combining LAAC and another cardiac structural or electrophysiological intervention in a single intervention appears attractive. In fact, the combined strategy may decrease hospitalizations and the length of stay and will require only one anesthesia/sedation. On the other hand, due to physiological and pathological changes that occur with age, patients maybe at higher risk of periprocedural morbidity and mortality (25,26). Thus, the combined strategy had to be studied to demonstrate equal or even superior benefits in term of efficacy and safety. In our small cohort, despite similar baseline characteristics, the rates of technical and procedural success and periprocedural complications were not different in patients who underwent the combined strategy compared to those who underwent the single LAAC. These results strengthen the feasibility and safety of the concomitant approach previously described in the Swiss series using the Amplatzer^{TM} devices (16).

Type of Interventions and Procedural Issues

Half of the patients referred for LAAC in our center, had a second cardiac intervention either in a combined strategy or in during a second procedure. These second intervention, whether structural or electrophysiological, were also performed from a venous femoral access. Thus, the combined strategy by using the same

venous femoral access can reduce the cumulative risk of vascular complications. Moreover, the same transeptal puncture when required for AF ablation or TEMVR may be used for the LAAC (16). However, the optimal transeptal position may be different for TEMVR and LAAC, and the use of the optimal TEMVR transeptal puncture position should be preferred and used for the LAAC. In our experience, when AF ablation or TEMVR are combined, LAAC is performed last. However, when the other intervention is a flutter ablation or LP implantation, LAAC is performed first.

LAAC can be combined with other interventions requiring arterial access. The transaortic valve replacement (TAVR) is probably the procedure that could lead to a such combined strategies (16). In this approach, TAVR is first performed from an arterial access and LAAC then performed by a venous femoral access.

However, more procedures are now done using conscious sedation. Most TAVR, AF or flutter ablations, and LP implantations are performed without general anesthesia, while LAAC and TEMVR often require TEE guidance and general anesthesia (27, 28). The use of intracardiac echocardiography may obviate the need for general anesthesia (29).

Perspectives

With the development of percutaneous interventions and therapies, the use of combined strategies will increase. This approach may reduce the overall cost for the health care system reducing hospitalizations and the need for staged interventions (30). Moreover, the Heart Team approach will increase collaboration between different subspecialties such as the electrophysiologists, geriatricians, anesthesiologists, echocardiographists and the structural specialists all oriented towards better patient care and outcome. With this approach, in high volume centers, we may expect a decrease in the complication rates, more efficiency and a decrease in costs (31).

Study limitations and future directions

Multiple limitations arise from a monocentric registry design including variation in implantation modality, post-discharge anticoagulation regimen and the difficulty to extrapolate to other centers or countries. Furthermore, since the registry dataset was primarily focused on LAAC results, other data were not prospectively collected (arrhythmias, rhythm at follow-up, or valvular outcomes) for the combined procedure and were assessed by chart review.

Additionally, since no independent image adjudication was used, all TEE measurements (LAA diameter, device size, compression, peri-device leak, and device thrombosis) are subject to operator interpretation and imaging system variability.

Conclusion

A combined procedure with LAAC using the Watchman^{TM}devices, and another cardiac structural or electrophysiological procedure appears safe and effective. Larger series and prospective and multicentric cohorts are needed to confirm these preliminary results. However, since many patients have a clinical indication for multiple cardiac structural or electrophysiological procedures (TEMVR, atrial flutter ablation, pacemaker implantation), the combined approach may be considered.

Appendix

Table 1: Baseline characteristics

		Single procedure (n=141)	Combined strategy (n=16)
Age (years)	Age (years)	76 (71/80)	71 (61/73)
Male	Male	94 (66%)	10 (66%)
AF pattern	AF pattern		
Paroxysmal	Paroxysmal	49 (35%)	7 (44%)
Persistent	Persistent	25 (18%)	3 (19%)
Permanent	Permanent	67 (47%)	6 (37%)

		Single procedure (n=141)	Combined strategy (n=16)
CHA2DS2-VASc Score	CHA2DS2-VASc Score	4 (3/5)	4 (3/5)
HAS-BLED Score	HAS-BLED Score	4 (4/5)	3 (3/4)
Hypertension	Hypertension	118 (84%)	14 (87%)
Diabetes	Diabetes	52 (37%)	8 (50%)
Dyslipidemia	Dyslipidemia	59 (42%)	11 (69%)
History of stroke	History of stroke	35 (25%)	3 (19%)
LV ejection fraction (%)	LV ejection fraction (%)	53 (50/60)	45 (37/56)
Left atrium volume (mL/m2)	Left atrium volume (mL/m2)	44 (35/52)	48 (37/61)
Coronary Heart Disease	Coronary Heart Disease	66 (47%)	10 (62%)
Valvular Heart Disease	Valvular Heart Disease	64 (45%)	7 (43%)
Abnormal renal function	Abnormal renal function	39 (27%)	4 (25%)
Abnormal liver function	Abnormal liver function	9 (7%)	0 (0%)
COPD	COPD	18 (13%)	3 (19%)
Peripheral artery disease	Peripheral artery disease	4 (3%)	0 (0%)
History of major bleeding	History of major bleeding	127 (90%)	12 (75%)
	Gastrointestinal hemorrhage	63 (49%)	9 (56%)
	Intracerebral bleeding	33 (26%)	1 (6%)
	Hematuria	12 (9%)	1 (6%)
	Others	19 (15%)	1 (6%)
Blood Dyscrasia	Blood Dyscrasia	12 (8%)	1 (6%)
Refractory anemia	Refractory anemia	37 (26%)	5 (31%)
Combined procedure	Combined procedure	0 (0%)	16 (100%)
	Atrial flutter ablation	0 (0%)	6 (37%)
	Lead less pacemaker implantation	0 (0%)	2 (13%)
	TEMVR	0 (0%)	6 (37%)
	Atrial fibrillation ablation	0 (0%)	2 (13%)

Continuous data were expressed as median and IQR (25/75). Qualitative variables were presented with number and percentages.

Abbreviations: AF = Atrial Fibrillation; CHA2DS2-VASc score = congestive heart failure, hypertension, 75 years of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, 65 to 74 years of age, female; HAS-BLED score = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; LV = Left ventricle; COPD = chronic obstructive pulmonary disease, TEMVR = Transcatheter Edge-to-Edge mitral valve Repair

Table 2: Left atrial appendage closure procedure

	Single procedure (n=141)	Combined strategy (n=16)	p-value
LAA ostial diameter (mm)	19 (17/21)	20 (18/21)	0.46
No. of device deployment	1 (1/2)	1 (1/1)	0.43
No. device	1 (1/1)	1 (1/1)	0.86
Device compression (%)	20 (15/23)	18 (15/20)	0.49
Procedure time (min)	69 (53/88)	115 (76/139)	<0.01
Fluoroscopy time (min)	7 (5/10)	18 (10/38)	<0.01
Fluoroscopy dose (mGy)	945 (402/2760)	2500 (640/11992)	<0.01
Success	139 (98%)	16 (100%)	0.63

Continuous data were expressed as median and IQR (25/75). Qualitative variables were presented with number and percentages.

Abbreviations: LAA = left atrial appendage

Table 3: Atrial flutter ablation procedure

	Atrial flutter ablation (n=6)	Others combined procedure (n=10)	p-value
LAA ostial diameter (mm)	20 (18/21)	19 (18/21)	0.55
No. of device deployment	1 (1/1)	1 (1/2)	0.18
No. device	1 (1/1)	1 (1/1)	0.46
Device compression (%)	17 (15/19)	20 (15/21)	0.56
Procedure time (min)	75 (64/80)	133 (123/148)	<0.01
Fluoroscopy time (min)	8 (4/11)	36 (22/56)	<0.01
Fluoroscopy dose (mGy)	512 (336/769)	7820 (3134/15300)	0.01

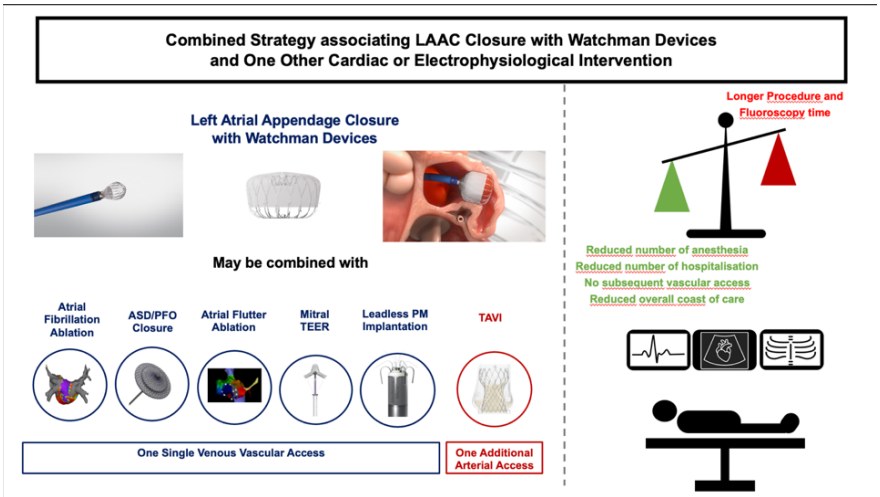
Table 4: Mid-term outcomes in single LAAC procedure and combined strategy

		Single LAAAC (n=141)	Single LAAAC (n=141)
		No. of patients	Rate (%)
Device related complication	Device related complication	6	4
	Thrombosis	3	2
	Device embolization	0	0
	Leak (> 5mm)	3	2
Technical success	Technical success	135	96
Procedural related complications	Procedural related complications	8	5
	Ischemic stroke	1	1
	SE	0	0
	Hemorrhagic stroke	3	2
	Bleeding	1	1
	CV/unknow death	3	2
	Pericardial effusion	2	1
	Vascular complication	0	0
	Pericarditis	0	0
Procedural success	Procedural success	129	91
All death	All death	8	5

Qualitative variables were presented with number and percentages.

Abbreviations: SE = systemic embolism; CV = cardiovascular

Figure 1: Benefits and limitations of the combined strategy during LAAC



Bibliography

1. Robert G et al. "Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have. Nonvalvular Atrial Fibrillation" J Am Coll Cardiol 2017;70,2964-75
2. Ruff CT et al. "Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials" Lancet 2014;338:955-62
3. Bungard TJ et al. "Why do patients with atrial fibrillation not receive warfarin?" Arch intern Med 2000;160:41-6
4. Marcus F et al. "Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: A transesophageal echocardiographic study" JACC 1995:452-9
5. Reddy VY et al. "5-Years outcomes after left atrial appendage closure forme the PREVAIL and PROTECT AF trials" JACC 2017;70(24):2964-2975
6. Saw J et al. "Early Canadian Multicenter Experience With Watchamn for Percutaneous Left Atrial Appendage Closure" J Cardiovasc Electrophysiol 2017 Apr;28(4):396-401
7. Gianni C et al. "Closure of the left atrial appendage using percutaneous transcatheter occlusion devices" J Cardiovasc Electrophysiol 2020 Aug;31(8):2179-2186
8. Gasperetti A et al. "A left atrial appendage closure combined procedure review: Past, present and future perspectives" J Cardiovasc Electrophysiol 2019;30(8):1345-1351
9. Phillips KP et al. "Combining Watchman left atrial appendage closure and catheter ablation for atrial fibrillation: multicentre registry results of feasibility and safety during implant and 30 days follow-up" Europace 2018;20(6):949-955
10. Kawakami H et al. "Cost-effectiveness of combined catheter ablation and left atrial appendage closure for symptomatic atrial fibrillation in patients with high stroke and bleeding risk" Am Heart J 2021;231:110-120
11. Jiantao Y et al. "Long-term safety and efficacy of combined percutaneous LAA and PFO/ASD closure: a single-center experience" Expert Rev Devices 2019;16(5):429-435
12. Zhang ZH et al. "One-stop shop: Safety and efficacy of combining atrial septal defect occlusion and left atrial appendage closure for patients with atrial septal defect and atrial fibrillation" BMC Cardiovasc Disord. 2020;20(1):444
13. Reynolds D et al. "Micra Transcatheter Pacing Study Group. A leadless intra- cardiac transcatheter pacing system" N Engl J Med 2016;374:533-541.
14. Regoli F. et al. "Combined left atrial appendage closure and pacemaker implant through a single right femoral vein access" Pacing Clin Electrophysiol 2016;39:900-902.
15. Regoli F et al. "Potential Clinical Utility and Feasibility of Combined Left Atrial Appendage Closure and Positioning of Miniaturized Pacemaker Through a Single Right Femoral Vein Access" Am J Cardiol

2017;120:236-242
16. Kleinecke C et al. "Amplatzer left atrial appendage closure: Single versus combined procedures" Catheter cardiovasc interv. 2020 10.1002/ccd.29271
17. Tzikas A et al. "Percutaneous left atrial appendage occlusion: the Munich consensus document on definitions, endpoints, and collection requirements for clinical studies" Europace 2017;(19)4-15:10.1093
18. Holmes DR et al., for the PROTECT AF Investigators. "Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial" Lancet 2009;374: 534–4
19. Schulman, S. et al. "Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients" Journal of Thrombosis and Haemostasis 3(4), 692–694.
20. Mehran, R. et al. "Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium" Circulation, 123(23), 2736–2747.
21. Sacco, R. L. et al. "Council on Nutrition, Physical Activity and Metabolism. (2013). An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association" Stroke, 44(7), 2064–2089.
22. Michael Glikson et al. "EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion – an update" EuroIntervention. 2020 Jan 17;15(13):1133-1180
23. Holmes Jr DR et al. "Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial" J Am Coll Cardiol 2014 16;64(11):1186
24. Alison Cooper et al. "Sources of unsafe primary care for older adults: a mixed-methods analysis of patient safety incident reports" Age Ageing. 2017 Sep 1;46(5):833-839.
25. John E. Morley, MB et al. "Frailty Consensus: A Call to Action" J Am Med Dir Assoc. 2013 Jun; 14(6): 392–397.
26. Jeremy Walston et al. "Frailty Screening and Interventions: Considerations for Clinical Practice" Clin Geriatr Med. 2018 Feb;34(1):25-38
27. Louis Labrousse et al. "Guidance of the MitraClip ® procedure by 2D and 3D imaging" Arch Cardiovasc Dis. Jun-Jul 2018;111(6-7):432-440.
28. Turagam MK et al. "Intracardiac echocardiography-guided implantation of the Watchman FLX left atrial appendage closure device" J Cardiovasc Electrophysiol. 2021 Mar;32(3):717-725.
29. Gianni C at al. "Intracardiac echocardiography- versus transesophageal echocardiography-guided left atrial appendage occlusion with Watchman FLX" J Cardiovasc Electrophysiol. 2021 Oct;32(10):2781-2784.
30. John Fanourgiakis et al. "Cost-of-illness study of patients subjected to cardiac rhythm management devices implantation: results from a single tertiary centre" Europace. 2013 Mar;15(3):366-75.
31. Clifford J. Kavinsky et al. "SCAI/ACC/HRS Institutional and Operator Requirements for Left Atrial Appendage Occlusion" J Am Coll Cardiol. 2016 May 17;67(19):2295-2305.