REVIEW ARTICLE

Percutaneous left atrial appendage occlusion in the current practice

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ABSTRACT
Oral anticoagulation (OAC) is the standard of care for stroke prevention in atrial fibrillation, but it is associated with a substantial risk of bleeding complications and its effect depends on optimal patient´s compliance. In patients with nonvalvular atrial fibrillation, the left atrial appendage is the source of thrombi that may cause stroke in up to 91% to 95% of cases. Thus, percutaneous left atrial appendage occlusion (LAAO) is being increasingly performed as an alternative to OAC for stroke prophylaxis in patients at increased bleeding risk. The current evidence supporting LAAO derives from 3 randomized controlled trials: 2 on Watchman device use in patients eligible for short-term OAC and a more recent trial comparing LAAO with Amulet and Watchman device use versus long-term OAC with direct oral anticoagulants (DOACs). In addition, numerous real-life registries have reported favorable outcomes with Watchman, ACP, and Amulet devices in patients at higher bleeding risk and / or formal contraindications to short-term OAC, employing less intensive antithrombotic regimens after LAAO. Furthermore, there has been growing evidence on newer devices with distinct features that might be of value to specific subgroups of patients. However, several issues remain unresolved including optimal patient and device selection, individual tailoring of postprocedural antithrombotic therapy, and management of periprocedural complications such as device-related thrombus and residual peridevice leaks. Finally, the relative benefit of LAAO versus DOACs should be further assessed across the spectrum of patient candidacy for DOACs, over extended follow-up periods. In this article, we review the body of evidence supporting LAAO with currently available devices.

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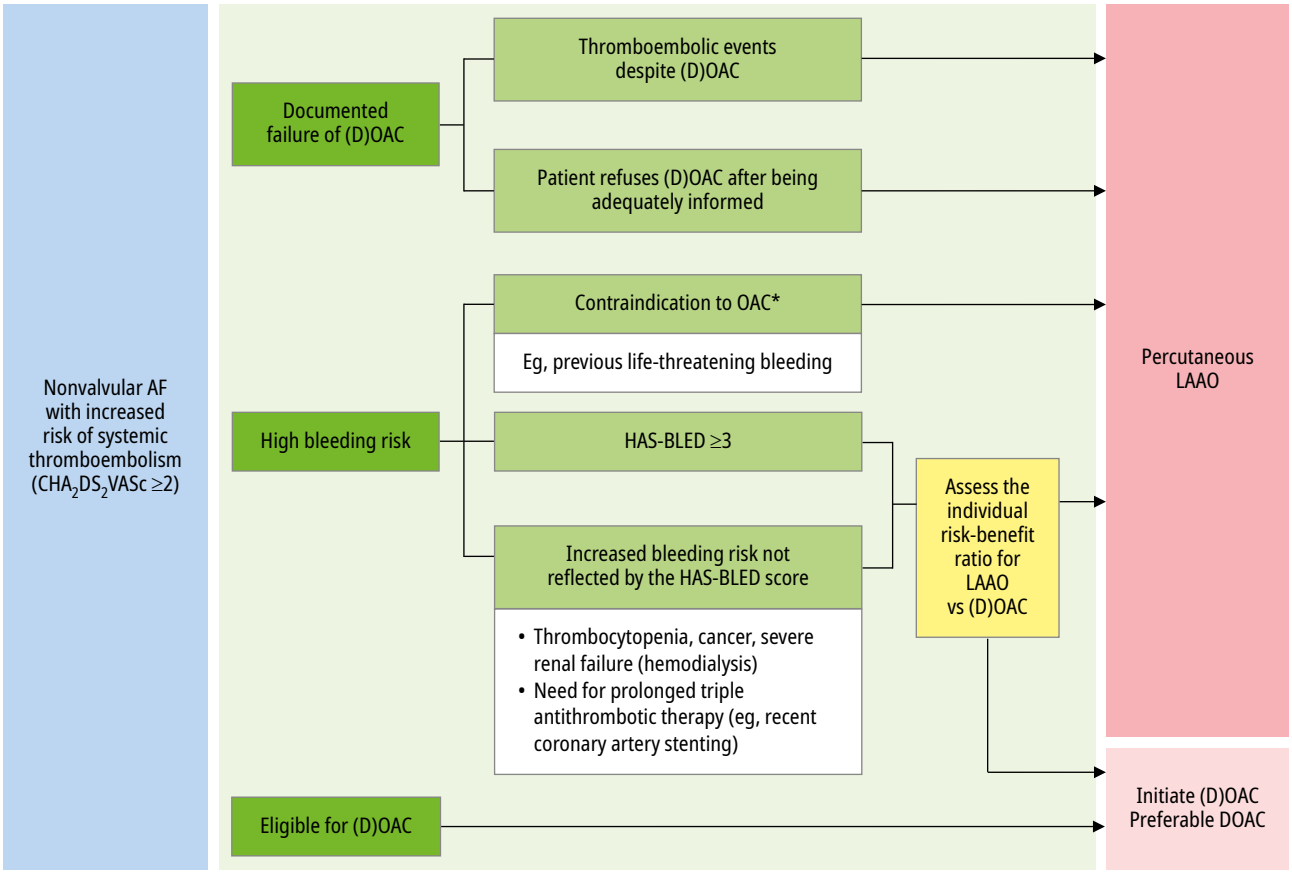
Introduction Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults worldwide, which is associated with a 4- to 5-fold higher risk of cerebrovascular and systemic thromboembolic events if left untreated.[1]

Oral anticoagulation (OAC) is the first-line therapy for stroke prevention in AF, but it entails a substantial risk of hemorrhagic complications that may hinder or pose a formal contraindication to its administration in patients deemed at high-risk of bleeding. Moreover, discontinuation of OAC is not infrequent, leaving patients unprotected.[1]

In this setting, percutaneous left atrial appendage occlusion (LAAO) has emerged as a safe and effective nonpharmacological treatment option for patients with nonvalvular AF (NVAF),[2] in whom 91% to 95% of thrombi that may cause stroke by embolization to the cerebral circulation are located within the LAA.[3] Accordingly, the most recent European and American guidelines on AF[1,4] include a class IIb recommendation, level of evidence B, for LAAO as a means for stroke prevention in NVAF patients with contraindications to long-term OAC. An algorithm to guide LAAO candidate selection in clinical practice, based on the current recommendations from the European Heart Rhythm Association / European Association of Percutaneous Cardiovascular Interventions Expert Consensus Statement on catheter-based LAAO,[3] is depicted in FIGURE 1.

Currently available left atrial appendage occlusion devices As depicted in Supplementary material, *Table S1*, currently available LAAO devices can be classified in 3 categories according to



* Class IIb recommendation according to the 2020 ESC and 2019 AHA Update on AF guidelines

FIGURE 1 Algorithm for stroke prevention in nonvalvular atrial fibrillation

Abbreviations: AF, atrial fibrillation; AHA, American Heart Association; DOAC, direct oral anticoagulation; ESC, European Society of Cardiology; LAAO, left atrial appendage occlusion; OAC, oral anticoagulation

their design and mechanism of action.[3] In the case of single-lobe endocardial devices, the device lobe is deployed in the neck of the LAA, thereby preventing blood flow from entering the LAA (FIGURE 2A–2D). Conversely, lobe and disc endocardial LAAO devices seal the LAA according to the pacifier principle, by which a lobe or an umbrella is delivered in the neck of the LAA, and an additional disc, on the left atrial side of the LAA ostium (FIGURE 3A–3D). Finally, epicardial LAAO devices snare and ligate the body of the LAA by means of a double endocardial and epicardial approach, without additional device deployment (FIGURE 3E).

Evidence on left atrial appendage occlusion: safety and efficacy outcomes To date, evidence on the safety and efficacy of LAAO for the prevention of thromboembolic events in patients with NVAF derives from 3 randomized clinical trials (RCTs), several large multicenter registries, and a number of smaller registries collecting data on the use of newer devices (TABLES 1–3).

Watchman The PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) study[5] was the first noninferiority RCT to assess the safety and efficacy of the Watchman device in patients at high risk of stroke and without contraindications to warfarin treatment. A total of 707 patients were randomized in a 2:1 fashion to LAAO followed by warfarin for 45 days and clopidogrel until the sixth month after the procedure, on top of long-term aspirin versus warfarin treatment. Over an 18-month follow-up period, the device was found noninferior to warfarin regarding the primary efficacy endpoint composed of stroke, systemic embolism (SE), and cardiovascular death. However, the primary endpoint for safety, encompassing major bleeding, device embolization and pericardial effusion, was noted more frequently in the device group than in controls, at the expense of greater periprocedural complications.

After an extended 4-year follow-up, LAAO met the criteria for both noninferiority and superiority compared with warfarin for the prevention of the primary efficacy endpoint and also attained noninferiority for the primary safety endpoint. Interestingly, patients in the device arm displayed lower rates of cardiovascular (hazard ratio [HR], 0.4; $P = 0.005$) and all-cause mortality (HR, 0.66; $P = 0.04$).

Notwithstanding, in light of persistent concerns regarding the periprocedural safety of

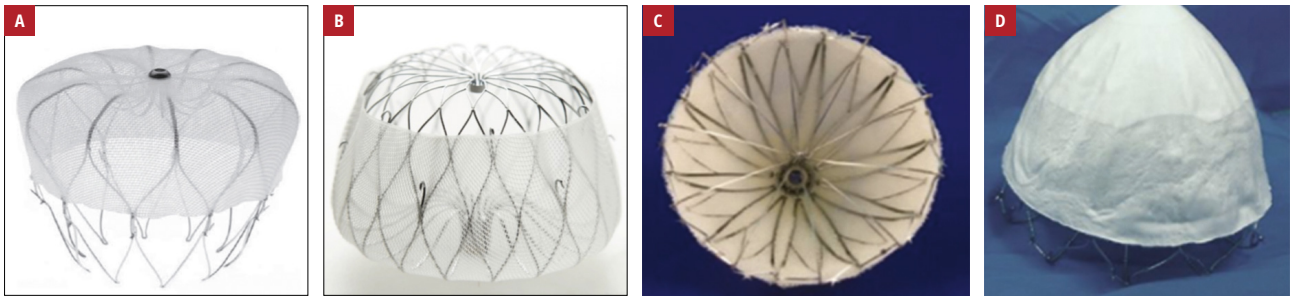


FIGURE 2 Commercially available percutaneous single-lobe endocardial left atrial appendage occlusion devices: **A** – Watchman (Boston Scientific); **B** – Watchman FLX (Boston Scientific); **C**, **D** – WaveCrest (Coherex Medical). Images reprinted with the vendors' permission.

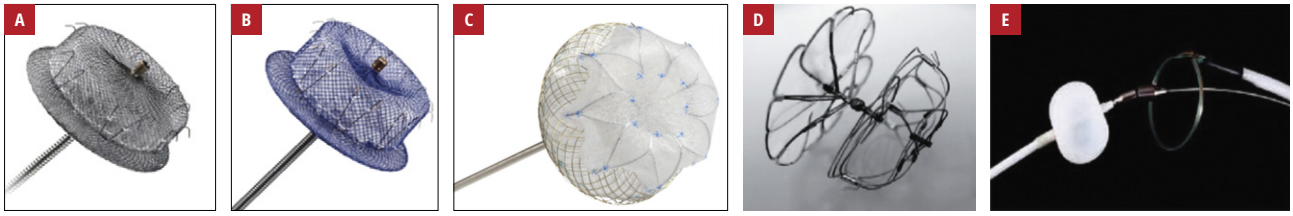


FIGURE 3 Commercially available percutaneous lobe and disc and epicardial left atrial appendage occlusion devices: **A** – Amplatzer cardiac plug (Abbott); **B** – Amplatzer Amulet (Abbott); **C** – LAmbre (Lifetech Scientific); **D** – Ultraseal (Cardia); **E** – Lariat (SentreHEART). Images reprinted with the vendors' permission.

LAAO, a second RCT with the Watchman device was performed. The PREVAIL (Watchman LAA Closure Device in Patients with Atrial Fibrillation Versus Long-Term Warfarin Therapy) study[6] randomized 407 patients to LAAO or warfarin (2:1), employing the same antithrombotic regimen. Only the second coprimary efficacy endpoint of stroke and SE within 7 days after randomization achieved noninferiority, while the first coprimary efficacy endpoint encompassing stroke, SE, and cardiovascular or unexplained death did not, possibly due to lower-than-expected event rates. Of note, that trial reported a significant reduction in early (<7 days) safety events, which occurred only in 2.2% of patients, meeting the noninferiority margin.

A subsequent patient-level meta-analysis including 2406 patients with a 5931 patient-year follow-up from the PROTECT AF and PREVAIL trials and their respective continued access registries[7] reported noninferiority of LAAO for the composite efficacy endpoint of stroke, SE, and cardiovascular death. Although there were more ischemic strokes in the device group (HR, 1.95; P = 0.05), this difference was no longer significant after exclusion of procedure-related strokes. Importantly, in comparison with warfarin, LAAO attained a significant reduction in the number of hemorrhagic strokes (HR, 0.22; P = 0.004), cardiovascular deaths (HR, 0.48; P = 0.006), and nonprocedural bleedings (HR, 0.51; P = 0.006).

Those findings led to the general conclusion that LAAO was both safe and effective. Next, several observational studies were performed to assess the safety and efficacy of LAAO with the Watchman device, employing less intensive antithrombotic regimens in patients at higher bleeding risk or ineligible for OAC—the most frequently targeted population in real-life practice.

In the ASAP (ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology) registry,[8] 150 patients with a contraindication to OAC underwent LAAO followed by 6 months of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel and aspirin alone thereafter. At 1 year, all-cause stroke and SE occurred in 4 patients (2.3%/year), significantly less frequently than predicted by the $CHADS_2$ estimated event rate of 7.3%/year. The incidence of device-related thrombus (DRT) was 4%, which is similar to 3.7% reported in previous studies employing the Watchman device followed by transition to warfarin.

The larger EWOLUTION (Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the Watchman Left Atrial Appendage Closure Technology) registry[9] included 1025 patients, of whom 73.5% had a contraindication to anticoagulation and were discharged on antiplatelets or without antithrombotic treatment at all. At 1-year follow-up, the rate of ischemic stroke was 1.1%/year, resulting in an 84% relative risk reduction (RRR) compared with the estimated 7.2%/year rate based on CHA_2DS_2VASc. The incidence rates of nonprocedural major bleeding (2.3%) and DRT (3.7%) were overall low and did not vary according to postprocedural antithrombotic regimen.

The ASAP TOO (The Assessment of the Watchman Device in Patients Unsuitable for Oral Anticoagulation) RCT (ClinicalTrials.gov identifier, NCT02928497) that aimed to compare LAAO

TABLE 1 Main studies assessing outcomes with the Watchman device (continued on the next page)

Characteristics	PROTECT AF, 2009[4]	PROTECT AF, 2014[33]	PREVAIL, 2014[5]	Pooled results of PREVAIL, PROTECT, and CAP registries, 2015[6]	CAP and CAP-2 registries, 2019	ASAP, 2013[7]	EWOLUTION, 2017[8]	EWOLUTION, 2019[34]	NCDR LAAO Registry, 2020[35]	PINACLE-FLX, 2020[36]	Watchman FLX, 2020[9]
Design	MRCT 2:1		MRCT 2:1	MRCT 2:1 + MCR data	MCR	MCR	MCR		MCR	MCR	MCR
Device group: control group, n	463:244		269:138	732:382	1144	150	1025		38 158	400	165
Age, y, mean (SD)	72 (9)		74 (4)	73 (8)	74 (8)	73 (7)	73 (9)		76 (8)	74 (9)	75 (9)
$CHADS_2$, mean (SD)	2.2 (1.2)		2.6 (1.1)	2.3 (1.1)	2.6 (1.2)	2.8 (1.2)	NA		NA	NA	NA
CHA_2DS_2-VASc, mean (SD)	NA		3.8 (1.2)	3.6 (1.4)	4.2 (1.5)	4.4 (1.7)	4.5 (1.6)		4.6 (1.5)	4.2 (1.5)	4.4 (1.4)
Follow-up, mo, mean (SD)	18 (10)	47 (20)	12 (6)	48 (20)	50	14 (9)	12	24	In-hospital outcomes	12	1.5
Contraindication to OAC, %	0		0	0	0	100	73.5		NA	0	77.6
Postprocedural antithrombotic therapy	VKA + ASA, 45 days ASA + clopidogrel, 6 months ASA, indefinitely					DAPT, 6 months ASA, indefinitely	DAPT, 60% SAPT, 7% VKA, 16% DOAC, 11% No ATT, 6%		NA	DOAC + ASA, 45 days DAPT, 6 months ASA, indefinitely	DAPT, 64% SAPT, 30% DOAC, 3.6% VKA, 0.6%
Implant success, %	88		95.1	NA	94	94.7	98.5		92.8	98.8	100
Hemorrhagic stroke, %	0.1/100 patient-years	0.6	0.4	0.17/100 patient-years	0.13/100 patient-years	0.6/100 patient-years	0	0.2	NA	0	0
Ischemic stroke/TIA/SE, %	2.5/100 patient-years	1.6/100 patient-years	2.3	1.6/100 patient-years	1.8/100 patient-years	2.3/100 patient-years	1.5/100 patient-years	2/100 patient-years		2.9	0.8
Nonprocedural major bleeding, %	3.5	4.1	NA	1.7/100 patient-years	6.9	NA	2.3/year	2.7/100 patient-years	NA	7.9	3.2
Mortality, %	3/100 patient-years	3.2/100 patient-years	2.6	3.6/100 patient-years	5.4/100 patient-years	5/year	9.8	15.7	NA	6.6	0.8
Total 7-day or in-hospital major adverse events, %	8.7		4.2		4.2	8.7	2.8		2.16	0.5	1.8

TABLE 1 Main studies assessing outcomes with the Watchman device (continued from the previous page)

Characteristics	PROTECT AF, 2009[4]	PROTECT AF, 2014[33]	PREVAIL, 2014[5]	Pooled results of PREVAIL, PROTECT, and CAP registries, 2015[6]	CAP and CAP-2 registries, 2019	ASAP, 2013[7]	EWOLUTION, 2017[8]	EWOLUTION, 2019[34]	NCDR LAAO Registry, 2020[35]	PINACLE-FLX, 2020[36]	Watchman FLX, 2020[9]
Pericardial effusion, %	4.8		1.9		2.2	3.3	0.3		1.39	0	0.6
Device embolization, %	0.6		0.7		0.2	1.3	0.2		0.07	0	0
Procedure-related stroke, %	1.1		0.4		0.2	0	0		0.082	0.5	0
Procedure-related death, %	0		0		0.2	0	0.4		0.19	0	0
Peridevice leak[a], %	8		NA		NA	NA	0.7		0.2	0	0.7
Device-related thrombus, %	4.2		NA	NA	3.3	4	3.7	4.1	NA	1.8	4.7

Empty cells indicate redundant data reported in a particular study.

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Abbreviations: ASA, acetylsalicylic acid; ATT, antithrombotic therapy; DAPT, dual antiplatelet therapy; MCR, multicenter registry; MCRT, multicenter randomized trial; NA, not available; SAPT, single antiplatelet therapy; SE, systemic embolism; TIA, transient ischemic attack; VKA, vitamin-K antagonist; others, see FIGURE 1

with the Watchman device implantation followed by single antiplatelet therapy (SAPT) or DAPT versus conservative medical therapy alone with SAPT or DAPT in patients deemed ineligible for OAC, stopped recruitment early due to low patient enrolment rates, as some investigators considered randomization inappropriate in light of consistent benefits of LAAO followed by antiplatelet agent use.

Watchman FLX device Recently, a new-generation Watchman FLX device including significant changes in design that allow for a simplified implantation procedure in a wider range of LAA anatomies has received the CE mark approval (Supplementary material, *Table S1*).

Preliminary 1-year data from the PINNACLE FLX (Investigational Device Evaluation of the Watchman FLX LAA Closure Technology) single-arm trial (Doshi SK, 2020; unpublished data) enrolling 400 patients managed with DOAC after LAAO have recently shown high implant success rates at 98.8%, a low incidence of periprocedural complications (0.5%), and complete LAA closure at 1 year in 100% of patients. At 1-year follow-up, 2.6% of patients experienced ischemic stroke and 7.9%, a major bleeding event. Of importance, there were no cases of device embolization, which led to the market retrieval of the previous iteration of the Watchman FLX device in 2016, and only 1.8% of patients developed DRT.

Those results were supported by a recent international multicenter registry including 165 high-risk patients, managed predominantly with antiplatelet agents.[10] Technical success was attained in 100% of cases despite complex anatomy in 24.2% of patients and the rate of periprocedural complications was low at 1.8%. Over a median follow-up of 55 days, only a single patient developed ischemic stroke (0.8%), there were 4 (3.2%) major bleeding events, and DRT occurred in 4.7% of patients.

Lastly, a single-center registry that enrolled 38 patients with high-risk features also reported a 100% technical success rate using this device, with outstanding safety and efficacy outcomes at 3-month follow-up.[11]

Amplatzer devices **ACP device** The largest body of evidence on ACP device implantation derives from a multicenter registry[12] of 1047 patients (1349 patient-years of follow-up), managed mostly with antiplatelet agents. That study reported high procedural success rates at 97.3%, along with a low incidence of periprocedural complications (4.3%) and DRT (0.28%). The annual rates of systemic thromboembolism and major bleeding were 2.3% and 2.1%, respectively, which translates into an RRR of 59% and 61%, respectively, based on estimated event rates. Of note, patients discharged on SAPT after LAAO had fewer bleedings during follow-up.

TABLE 2 Main studies assessing outcomes with the ACP and Amulet Amplatzer devices

Characteristics	Tzikas et al, 2016[12]	López-Mínguez et al, 2015[14]	Berti et al, 2017[15]	Korsholm et al, 2017[25]	Landmesser et al, 2018[13]	Hildick-Smith et al, 2020[37]
Device	ACP	ACP	ACP and Amulet	ACP and Amulet	Amulet	Amulet
Design	MCR	MCR	MCR	SCR	MCR	MCR
Participants, n	1047	167	613	110	1088	
Age, y, mean (SD)	75 (8)	75 (9)	75 (8)	73 (10)	75 (9)	
$CHADS_2$, mean (SD) or median (IQR)	2.8 (1.3)	3 (2–4)	NA	NA	NA	
CHA_2DS_2-VASc, mean (SD) or median (IQR)	4.5 (1.6)	4 (3–6)	4.2 (1.5)	4.4 (1.6)	4.2 (1.6)	
Follow-up, mo, mean, mean (SD), or median (IQR)	13	22 (8)	20 (17)	27 (19–38)	11 (3)	24
Contraindication to OAC, %	73	100	84.5	91	83	
Postprocedural antithrombotic therapy, %	At the last FU: SAPT, 68.9 DAPT, 18.9 DOAC, 1.6 VKA, 2.6 LMWH, 0.2	At discharge: SAPT, 8.9 DAPT, 87.3 OAC, 3.2 No ATT, 0.6	At the last FU: SAPT, 64.4 DAPT, 14.4 OAC, 4.1 LMWH, 4.9 No ATT, 12.2	At discharge: SAPT, 88 DAPT, 12	At discharge: SAPT, 22.5 DAPT, 57.6 OAC, 11.2 LMWH, 6.6 No ATT, 2.1	At 2-year FU: SAPT, 62.8 No ATT, 21.5
Implant success, %	97.3	94.6	95.4	100	99	
Hemorrhagic stroke, %	NA	0.6	0.22/100 patient-years	2.8	0.6/year	0.5/year
Ischemic stroke / TIA / SE, %	2.3/year	2.4/year	2.45/100 patient-years	4.7	3.8/year	3.2/year
Nonprocedural major bleeding, %	2.1/year	3.1/year	2.2/100 patient-years	2.8	10.3/year	7.2/year (4 at 2 years)
Mortality, %	4.2	10.8	4.5/100 patient-years	0.9	8.4	15.2
Total 7-day or in-hospital major adverse events, %	5	5.4	6.2	4.6	4	
Pericardial effusion, %	1.24	1.2	2	0	1.4	
Device embolization, %	0.8	0.6	0.7	0.9	0.2	
Procedure-related stroke, %	0.9	0	NA	0.9	0.4	
Procedure-related death, %	0.8	0	0	0.9	0.3	
Peridevice leak[a], %	1.9	0	0.5	NA	1.6	
Device-related thrombus, %	4.4	8	1.8	1.9	1.7	

Empty cells indicate redundant data reported in a particular study.

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Abbreviations: FU, follow-up; IQR, interquartile range; LMWH, low-molecular-weight heparin; others, see FIGURE 1 and TABLE 1

Amulet device The Prospective Global Amulet Observational Registry[13] was established in 2013, following the CE mark approval of the second-generation Amulet device. A total of 1088 patients were enrolled, of whom 83% had contraindications to anticoagulation and 72% a history of major bleeding. Only 11% of patients were discharged on OAC and nearly 60% were on SAPT or no antithrombotic medication for 1 month to 3 months after LAAO. Procedural success was attained in 99% of cases, with a 3.2% rate of periprocedural complications. At 1-year follow-up, the rate of ischemic stroke was lower than predicted at 2.9%/year (RRR, 57%). The major bleeding rate was 10.3%/year, encompassing a relatively high rate of periprocedural bleedings at 3.2%/year. Device-related thrombus formed in only 1.7% of patients and

TABLE 3 Main studies assessing left atrial appendage occlusion with other devices

Characteristics	LAmbre			Lariat			Ultraseal	WaveCrest
Study	Huang et al, 2017[38]	Park et al, 2018[39]	Ali et al, 2020[17]	Bartus et al, 2013[40]	Price et al, 2014[41]	Lakkireddy et al, 2016[18]	Asmarats et al, 2018[19]	Reddy et al, 2013[42]
Design	MCR	MCR	Meta-analysis	SCR	MCR	MCR	MCR	MCR
Participants, n	153	60	403	89	154	712	126	73
Age, y, mean (SD)	69 (9)	74 (8)	74 (4)	62 (10)	72 (9)	71 (10)	75 (8)	NA
$CHADS_2$	NA	NA	NA	1.9 (0.9)	NA	2.7 (1.3)	5 (2)	2.5
CHA_2DS_2-VASc	4 (1.7)	4 (1.6)	4 (0.9)	2.8 (1.6)	4.1 (1.6)	3.9 (1.8)		
Follow-up, mo, mean, median (IQR), or range	12	12	6–12	12	4	1–3	6 (3–10)	1.5
Contraindication to OAC, %	NA	100	NA	NA	NA	79	92.9	4.9
Postprocedural antithrombotic therapy, %	DAPT, 100 for 3 months	DAPT, 100 for 3 months	DAPT, 96.8	At 1-year FU: warfarin, 55	SAPT, 38 DAPT, 24 VKA, 16 DOAC, 8 No ATT, 19	SAPT, 63 DAPT, 16 OAC, 21	SAPT, 7.4 DAPT, 82.8 DOAC, 4.1 LMWH, 4.9 No ATT, 0.8	NA
Implant success, %	99.4	100	99.7	96	94	96	97	93
Hemorrhagic stroke, %	0.7	NA	NA	1.1	0	NA	0	
Ischemic stroke / TIA / SE, %	1.3	1.6	1.7	1.1	1.3		1.6	
Nonprocedural major bleeding, %	NA	3.3	0	NA	NA		3.2	
Mortality, %	0.7	NA	NA	2.2	1.9			
Total 7-day or in-hospital major adverse events, %	3.3	NA	2.9	3.3	10	5.4	2.4	NA
Pericardial effusion, %	2	3.3	1.7	2.2	10	3.3	0.8	3
Device embolization, %	0	0	0	0	0	0	0.8	0
Procedure-related stroke, %	0.7	NA	0.3	0	0	0	0.8	0
Procedure-related death, %	0	NA	0.3	0	0.6	0.14	0	NA
Peridevice leak[a], %	0.8	5.5	1	0	6	0.2	0	NA
Device-related thrombus, %	1.3	NA	0.7	0	4.8	2.5	5.6	0

Empty cells indicate redundant data reported in a particular study.

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Abbreviations: see FIGURE 1 and TABLES 1 and 2

was not affected by postprocedural antithrombotic regimen.

An extended 2-year follow-up analysis reported sustained efficacy outcomes (ischemic stroke rate, 2.2%/year) with a substantial reduction in major bleeding events in a long-term perspective (4%/year during the second year as compared with 10.3%/year during the first year) and stable DRT rates at 1.6%.

In addition, several multicenter real-life registries encompassing ACP and Amulet devices[14,15] have reported similar efficacy and safety outcomes, with ischemic stroke and major bleeding rates ranging between 1.6% to 2.6% and 3.7% to 3.9% per 100 patient-years, respectively.

Although there has been no head-to-head comparison of different devices, several studies have reported similar safety and efficacy outcomes with Watchman and ACP / Amulet devices. The ongoing Amulet-IDE (Amplatzer Amulet LAA Occluder Trial) (ClinicalTrials.gov identifier, NCT02879448) and SWISS-APERO (Comparison of Amplatzer Amulet and Watchman Device in Patients Undergoing Left Atrial Appendage Closure) (ClinicalTrials.gov identifier, NCT03399851) RCTs will provide more evidence on this matter over the next years.

Furthermore, a recent meta-analysis[16] of 1516 patients that compared the results of the 3 currently available RCTs assessing LAAO versus

TABLE 4 Studies assessing left atrial appendage occlusion in specific populations (continued on the next page)

Characteristics	Intracranial hemorrhage			Resistant stroke		Hemodialysis		LAA thrombus
Study	Nielsen-Kudsk et al, 2017[42]	Cruz-González et al, 2017[44]	Pouru et al, 2020[45]	Freixa et al, 2019[46]	Cruz-González et al, 2020[47]	Cruz-González et al, 2019[48]	Gennovesi et al, 2018[49]	Sharma et al, 2020[50]
Device	ACP and Amulet	ACP, 4.3% Amulet, 44.6% Watchman, 51.1%	ACP, 40% Amulet, 58% Watchman, 2%	ACP / Amulet, 86% Watchman, 9% LAmbre, 5%	ACP, 100%	Amulet, 42.9% Watchman, 50% Ultraseal, 7.1%	ACP / Amulet, 45.7% Watchman, 51% LAmbre, 3.3%	ACP, 26% Amulet, 50% Watchman, 15% LAmbre, 9%
Design	SCR	SCR	SCR	MCR	MCR	SCR	SCR	MCR
Participants, n	151	47	104	22	115	14	92	58
Age, y, mean (SD) or median (IQR)	72 (9)	80 (6)	73 (7)	69 (9)	74 (10)	69 (12)	76 (74–80)	71 (11)
$CHADS_2$, mean (SD)	NA	NA	NA	3.2 (0.9)	3.9 (1)	NA	NA	NA
CHA_2DS_2-VASc, mean (SD), or median (IQR)	3.9 (1.5)	5 (1)	4.7 (1.4)	4.5 (1.3)	5.5 (1.5)	4.5 (1.5)	4 (3–5)	4.4 (1.7)
Follow-up, mo, mean, mean (SD), or median (IQR)	6	28 (15–48)	43	21 (8–34)	16 (12)	20	21 (8–31)	3.4 (7)
Contraindication to OAC, %	100	100	100	0	0	100	100	65
Postprocedural antithrombotic therapy, %	SAPT, 93.2 No ATT, 6.8	SAPT, 12.8 DAPT, 80.8 LMWH, 4.3	DAPT, 20 SAPT, 46 VKA, 1 DOAC, 10 LMWH,22 OAC + antiplatelet, 28	DAPT, 13.6 VKA, 27.3 VKA + aspirin, 18.2 DOAC, 27.3 DOAC + aspirin, 9	SAPT, 76.6 DAPT, 21.6 VKA, 5.4 DOAC, 2.7	DAPT, 85.7	SAPT, 22.8 DAPT, 70.6 No ATT, 2.2	SAPT, 5.7 DAPT, 43.4 OAC, 43.4 OAC + antiplatelet, 5.7 LMWH, 9.4 No ATT, 1.9
Implant success, %	97.7	95.7	100	100	97.3	100	100	100
Hemorrhagic stroke, %	1.3/100 patient-years	1 (2.1)	1.9/100 patient-years	0	0/year	0	NA	0
Ischemic stroke / TIA / SE, % or mean (SD)	2.6/100patient-years	1 (2.1)	3.4/100 patient-years	0.1 (0.3) events / patient-years	2.6/year	0	2.2	1.7
Nonprocedural major bleeding, %	2.6/100 patient-years	NA	0.8/100 patient-years	1 (4.5)	0/year	14.3	8.7	1.7
Mortality, % or mean (SD)	2.6/100 patient-years	NA	5.7/100 patient-years	1 (4.5)	6.9	NA	18.5	0
Total 7-day or in-hospital major adverse events, %	4	4.2	NA	0	7.8	1 (7.1)	4.3	0

TABLE 4 Studies assessing left atrial appendage occlusion in specific populations (continued from the previous page)

Characteristics	Intracranial hemorrhage			Resistant stroke		Hemodialysis		LAA thrombus
Study	Nielsen-Kudsk et al, 2017[42]	Cruz-González et al, 2017[44]	Pouru et al, 2020[45]	Freixa et al, 2019[46]	Cruz-González et al, 2020[47]	Cruz-González et al, 2019[48]	Gennovesi et al, 2018[49]	Sharma et al, 2020[50]
Pericardial effusion, %	0.7	2.1	NA	0	2.6	0	1.1	0
Device embolization, %	0.7	2.1	NA	0	0.9	0	0	0
Procedure-related stroke, %	0		NA	0	2.6	0	0	0
Procedure-related death, %	0		NA	0	0.9	0	0	0
Peridevice leak[a], %	NA		NA	0	NA	NA	0	NA
Device-related thrombus, %	NA		NA	4.5	5.2	NA	0	3.4

Empty cells indicate redundant data reported in a particular study.

Abbreviations: see FIGURE 1 and TABLES 1 and 2

OAC—namely, the PROTECT AF, PREVAIL, and PRAGUE-17 (Left Atrial Appendage Closure Versus Direct Oral Anticoagulants in High-Risk Patients with Atrial Fibrillation) trials—has reinforced the role of LAAO with Watchman (92.7%) and Amulet (7.3%) devices for the prevention of stroke in patients with NVAF at increased bleeding risk. A total of 78% of patients were discharged on short-term OAC and 22% on DAPT. Left atrial appendage occlusion provided a significant reduction in hemorrhagic stroke (RR, 0.22; $P = 0.002$), nonprocedural major bleeding (RR, 0.53; $P < 0.001$), cardiovascular death (RR, 0.65; $P = 0.03$), and all-cause death (RR, 0.78; $P = 0.04$) as compared with OAC, while no differences in ischemic stroke (RR, 1.48; $P = 0.13$) or overall major bleeding (RR, 0.89; $P = 0.46$) were observed.

Other devices Evidence on LAAO with newer devices derives from several multicenter registries (TABLE 3). Briefly, the LAmbre device is characterized by very high procedural success rates at 99% to 100% and a low incidence of periprocedural complications (2.9%), despite being frequently employed in patients with challenging LAA anatomies, such as shallow or multilobe LAA or those with a very wide ostium.[17]

Similar high procedural success rates (96%–100%) have been reported for the Lariat device. Although the initial experience reported a considerable incidence of procedure-related complications, these have declined in later trials, along with increased operator experience.[18] Interestingly, LAA ligation with the Lariat device has been associated with reduced atrial fibrillation (AF) burden and the potential role of that device as an adjunctive therapy to AF ablation is currently being assessed in the aMAZE (LAA Ligation Adjunctive to PVI for Persistent or Longstanding Persistent Atrial Fibrillation) (ClinicalTrials.gov identifier, NCT02513797) RCT.

Regarding the Ultraseal device,[19] its specific feature relies on a multidirectional articulating joint connecting the bulb and sail of the device, which allows for conformation to a wide arrange of variations in LAA shape and angulations. Procedural success rates have been reported to be as high as 97%, with low rates of major periprocedural complications (2.4%) and thromboembolic events (1.6%) at follow-up.

Lastly, favorable short-term outcomes with the WaveCrest device have been reported, and results from the postmarket clinical follow-up study (ClinicalTrials.gov identifier, NCT03204695) of 65 patients are expected in early 2021.

Special populations In addition, several studies have assessed the role of LAAO in particularly high-risk patients, generally excluded from RCTs and larger registries. Currently, there is a growing

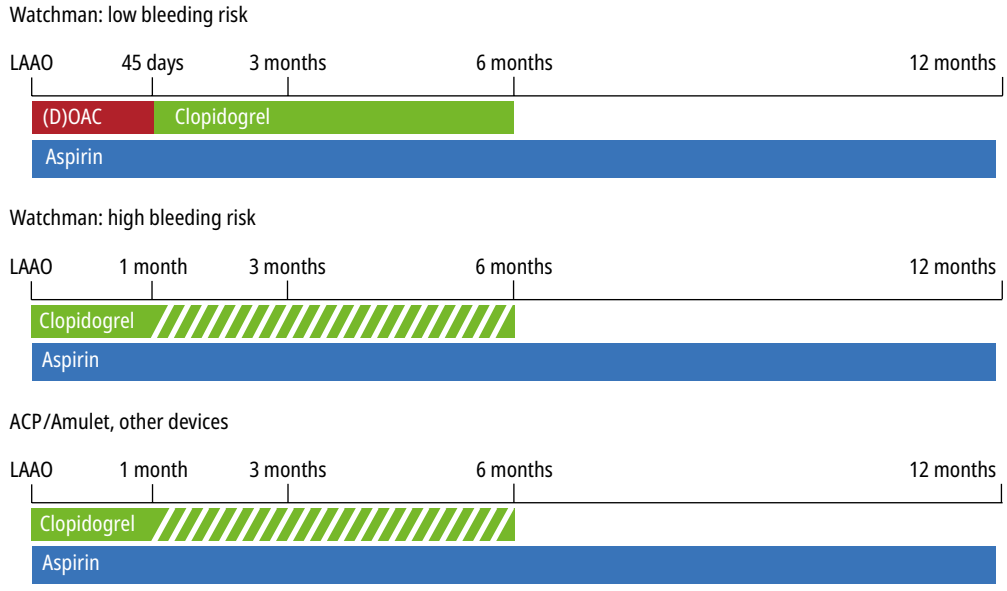

FIGURE 4 Antithrombotic regimens after left atrial appendage occlusion. All treatment schemes include low-dose aspirin for a minimum of 12 months.
Abbreviations: see FIGURE 1

body of evidence supporting the use of LAAO in patients with prior intracranial hemorrhage, resistant stroke despite optimal OAC, end-stage renal failure, or distally located LAA thrombus and in those resistant or not amenable to OAC, given that LAAO is performed by experienced operators with some technical modifications (TABLE 4).

Antithrombotic therapy after left atrial appendage occlusion The optimal choice and duration of the postprocedural antithrombotic regimen after LAAO remains controversial to date and should be tailored individually, according to the patient's bleeding risk. The current recommendations from the European Heart Rhythm Association / European Association of Percutaneous Cardiovascular Interventions Expert Consensus Statement on catheter-based LAAO[3] and the 2020 European Society of Cardiology Guidelines on AF[1] are summarized in FIGURE 4.

Patients without contraindications to short-term oral anticoagulation In the pivotal PROTECT AF and PREVAIL RCTs,[5,6] patients were managed with a short-term warfarin transition as illustrated in FIGURE 4A. The long-term incidence of bleeding complications after LAAO with this antithrombotic regimen was relatively high, as depicted in the patient-level analysis of both studies including 1114 patients at moderate bleeding risk (HAS-BLED ≤2 in 73.5% of patients).[20] Over a median follow-up of 3.1 years, the overall major bleeding rate was similar between both study groups (3.5 vs 3.6 events per 100 patient-years), whereas non-procedural (>7 days after LAAO) bleeding complications were significantly less frequent in the device-arm (1.8 vs 3.6 events per 100 patient-years; RR, 0.49; P = 0.001). The greatest reduction in bleeding events emerged 6 months after LAAO (1 event vs 3.5 events per 100 patient-years; RR, 0.28; P <0.001), when adjunctive antithrombotic therapy was discontinued.

Numerous recent studies have assessed the role of short-term DOAC regimens following LAAO and demonstrated favorable outcomes. The study by Enomoto et al[21] included 214 patients treated with a 6-week DOAC regimen after Watchman device implantation, who were compared with controls receiving uninterrupted warfarin. Despite the inclusion of patients at moderate-to-high bleeding risk (HAS-BLED ≥3 in approximately 50% of patients), the incidence of early postprocedural bleeding at 1.5 to 4 months was overall low (0.7%), without differences between DOAC and warfarin.

In addition, a 3-month analysis of 109 patients (16%) from the EWOLUTION trial who were managed with DOACs reported a lower incidence of postprocedural bleeding with DOACs (1.9%) in comparison with the remaining antithrombotic strategies.

In conclusion, although a post-LAAO warfarin-based regimen is feasible in patients without contraindications to short-term anticoagulation, it is associated with a substantial risk of hemorrhagic events. Accordingly, the European LAAO device labeling now allows for a 3-month DAPT or DOAC scheme following Watchman implantation in patients deemed at higher risk of bleeding.[22]

The ongoing ANDES (Short-Term Anticoagulation Versus Antiplatelet Therapy for Preventing Device Thrombosis Following Left Atrial

Appendage Closure) (ClinicalTrials.gov identifier, NCT03568890) and ADALA (Antithrombotic Therapy after Left Atrial Appendage Occlusion: Double Antiplatelet Therapy vs Apixaban) (EudraCT Number, 2018-001013-32) RCTs will compare the safety and efficacy of short-term DOAC versus short-term DAPT after LAAO.

Patients ineligible for transient oral anticoagulation Numerous observational studies performed with the Watchman, Amulet, and newer LAAO-dedicated devices support the use of an initial DAPT transition for 1 to 6 months following LAAO (FIGURE 4B–4C). Regarding bleeding events, several single-arm studies, as well as a recent meta-analysis of 11 071 patients,[23] have reported substantial reductions in the observed bleeding rates versus those predicted according to HAS-BLED, employing a short-term DAPT scheme.

Of importance, the majority of bleeding events in patients managed with antiplatelet agents after LAAO occur during the initial DAPT transition.[22] This led to a debate on the optimal length of DAPT that adequately prevents thromboembolic events, especially DRT, until full device endothelization, while minimizing the risk of bleeding.

The value of a shortened 6-week DAPT regimen followed by SAPT was assessed in a single-center study[24] including 298 patients at high risk of bleeding (HAS-BLED, 3.5 ± 1). A total of 8.4% of patients developed non–procedure related major bleedings, of whom 4.4% experienced them during the initial 6 weeks while on DAPT and 4% over an extended follow-up period longer than 2 years, thus resulting in a significant lower rate of hemorrhagic complications in the long-term perspective. Of note, early DAPT cessation did not lead to a higher incidence of thromboembolic events, as illustrated by low annual rates of stroke and SE (1.7%) and DRT (2%).

The ongoing SAFE-LAAC (Optimal Antiplatelet Therapy Following Left Atrial Appendage Closure) (ClinicalTrials.gov identifier, NCT03445949) randomized trial, comparing 1 versus 6 months of DAPT, will add to our knowledge on the safety of early aspirin discontinuation. In addition, that trial will assess the outcomes of patients in whom all antithrombotic medications are discontinued at 6 months versus those managed with long-term SAPT.

On the other hand, starting SAPT directly after LAAO remains controversial, as it has been assessed in fewer studies, with conflicting results. A single-center study by Korsholm et al,[25] including 110 patients at high risk of bleeding (HAS-BLED, 4.4 ± 1.1) who were managed predominantly with SAPT, reported a relatively low annual major bleeding rate at 3.8%, depicting a 57% reduction as compared with the predicted rate. Importantly, there was no increase in the incidence of DRT (1.9%) or stroke (2.3%) at 1 year (TABLE 2). Similarly favorable results were reported in a recent multicenter registry including 600 patients allocated to SAPT (n = 280) or DAPT (n = 330) at the operator's discretion.[26] The use of SAPT was associated with a significant reduction in Bleeding Academic Research Consortium type 3 to 5 bleedings (2.9% vs 6.7%, P = 0.04), without differences in major adverse cardiovascular events (7.6%) or DRT (0.8%) at 1 year.

However, other studies have reported an association between the use of SAPT directly after LAAO and DRT. This was the case of a multicenter registry of 469 patients,[27] of whom 36.2% received SAPT and 7.5% no antithrombotic therapy after LAAO. More patients with DRT were not receiving any antithrombotic therapy compared with those without DRT (15.4% vs 4.5%; P = 0.02), and OAC and DAPT administered after the procedure, yet not SAPT, acted as protective factors against DRT in multivariate analysis. Importantly, the incidence of DRT in that study was particularly high at 7.2%.

Finally, the lack of any antithrombotic medication following LAAO has been poorly studied and may only be used in patients at extremely high risk who cannot tolerate short-term SAPT, following a thorough assessment by an expert team.[3] Alternatively, the possibility of epicardial LAA closure, either surgically or by means of the Lariat device, should be considered.

Comparison with direct oral anticoagulation Since the initial RCTs supporting LAAO were performed and following the introduction of DOACs, the number of pharmacological options for stroke prevention in AF have substantially increased. The noninferiority of LAAO versus warfarin in those early studies was largely driven by an approximately 80% reduction in intracranial hemorrhage and an approximately 50% decrease in cardiovascular mortality. However, DOACs also provide a considerable reduction in hemorrhagic stroke (approximately 50%) and mortality (approximately 10%) in comparison with warfarin.[3,21] Therefore, the question as to whether LAAO or DOAC therapy might be more appropriate in a given patient might be raised.

This issue was recently addressed in the noninferiority PRAGUE-17[28] RCT that enrolled 402 patients at moderate-to-high risk of stroke (CHA_2DS_2VASc, 4.7 ± 1.5; HAS-BLED, 3 ± 0.9). The indications for LAAO included a history of clinically relevant bleeding in 47.7% of patients and prior cardioembolic event while on OAC in 35.3%. Upon discharge, 81.8% of patients randomized to LAAO received DAPT and 18.2%, apixaban, while 95.5% of patients in the DOAC group received apixaban. Over a median 19.9-month follow-up, LAAO met the prespecified criteria for noninferiority in comparison with DOAC (HR, 0.84; P = 0.44; P = 0.004

for noninferiority) for the primary outcome encompassing stroke, transient ischemic attack, SE, cardiovascular death, clinically relevant major and nonmajor bleeding, and procedure- and device-related complications. Interestingly, the number of nonprocedural bleedings was lower in the device arm (HR, 0.53; P = 0.07), although no significant differences in the individual components of the composite endpoint were observed.

Indeed, longer follow-up periods and the use of a more restrictive antithrombotic regimen after LAAO could make differences in bleeding events between both strategies more remarkable. Notwithstanding, that trial highlighted the importance of further refinements in both operator technique and device technology to reduce LAAO procedure- and device-related events and compete with the more favorable safety and efficacy profile of DOACs, as compared with warfarin. However, several caveats should be considered when assessing the relative benefit of LAAO versus DOACs. First, the pivotal trials leading to DOAC approval excluded patients deemed at high bleeding risk, who constitute the target population for LAAO. Besides, except apixaban, the rest of full-dose DOACs failed to reduce the risk of gastrointestinal bleeding, which is a frequent indication for LAAO. On the other hand, LAAO entails a certain risk of procedure- and device-related complications, which might not be limited to the acute phase as illustrated by DRT. However, the benefit of LAAO appears greater as follow-up periods expand. Accordingly, further larger studies powered to detect ischemic and bleeding endpoints separately across the spectrum of patient candidacy for DOAC therapy, over extended follow-up periods, are warranted to establish firm conclusions on the relative safety and efficacy of both strategies.

Device-related complications

Peridevice leaks

A consensus as to which peridevice leaks should be considered relevant is currently lacking. In the PROTECT AF trial, a significant peridevice leak was defined as a color Doppler jet by transesophageal echocardiography (TEE) exceeding 5 mm, based on results from surgical LAA exclusion. However, other studies have employed a stricter definition that categorizes 3 to 5 mm and larger than 3 mm jets as moderate and mild leaks, respectively. The 2017 Munich Consensus Document[29] advocated for a more detailed assessment of leaks including its size, location, and the imaging modality employed for diagnosis. The latter appears particularly relevant, as cardiac computed tomography has proven significantly more sensitive than TEE in detecting LAA patency, with any degree of peridevice leak being identified in up to 50% to 60% of patients.[29,30]

The current reports on the incidence of any peridevice leak assessed by TEE are as follows: 12% to 41% for Watchman, 1.8% to 13% for ACP / Amulet, 0.8% to 6% for LAmbre, below 1% to 14% with Lariat, below 1% to 12% with Ultraseal, and 4% with WaveCrest devices.[30]

Proposed mechanisms and predictors include a lower degree of oversizing, a low device compression ratio below 10%, and off-axis device implantation, among others.[3,30] Of importance, the currently available data have failed to establish a link between the existence of peridevice leak or its size and thromboembolic events.[29,30]

Device-related thrombus

Device-related thrombosis is another relevant, albeit infrequent, complication that can develop following LAAO. Its reported incidence varies between 2% and 4% in most studies,[3,7-18,23,31,32] although higher rates of up to 7% to 8% have been described in several real-life registries.[27] Of note, DRT rates appear similar for Watchman and ACP / Amulet devices.[31]

Device-related thrombosis is independently associated with a 4- to 5-fold increase in the risk of ischemic events[31,32] and warrants the intensification of antithrombotic therapy with vitamin K antagonists, DOACs, or low-molecular-weight heparin for 4 to 12 weeks.[3] Notwithstanding, the majority of patients presenting with DRT do not develop any thromboembolic complications.[23,32]

For its diagnosis, it is recommended that at least a single TEE or cardiac computed tomography examination should be performed at 6 to 12 weeks after LAAO. However, timing of DRT is unpredictable and it can be developed in over half of cases after the first 3 months.[3,31] Moreover, several studies have observed a correlation between the frequency of follow-up imaging and reported DRT rates, highlighting the need for standardized follow-up imaging protocols after LAAO.[32]

The predictors of DRT include left ventricular ejection fraction below 40%, a prior thromboembolic event, or a larger LAA orifice.[3,23,31,32] Also, deep device implantation that might leave a larger volume of uncovered appendage ("neo-appendage") and the lack of coverage of the left upper pulmonary vein ridge creating a "cul-de-sac" have been linked with increased DRT rates. Finally, while DRT has been related with less intensive antithrombotic regimens in some studies,[27] this association has not been corroborated in other trials, including several large meta-analyses.[23,31,32]

Conclusions

Percutaneous LAAO represents an attractive treatment alternative for stroke prophylaxis in NVAF patients with contraindications to long-term OAC. Randomized controlled trial data supporting the safety and efficacy of this technique was limited to patients suitable for short-term OAC with warfarin for many years. Just recently, a further RCT has reported the noninferior outcomes of LAAO versus

DOAC in patients at higher bleeding risk. In addition, a large body of evidence encompassing several large multicenter registries with Watchman, ACP, Amulet, and newer devices supports the role of LAAO in patients ineligible for short--term OAC, employing less intensive postprocedural antithrombotic regimens. However, further studies in this field are necessary to refine patient and device selection, optimize antithrombotic management after LAAO, and determine the long-term benefits of LAAO versus DOAC in a wider spectrum of patients.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

CONFLICT OF INTEREST IC-G is a proctor and consultant for Abbott, Boston Scientific, Lifetech, Qatnamedical, and IHT.

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