

Residual leaks following percutaneous left atrial appendage occlusion: assessment and management implications



Claire E. Raphael^{1*}, MD, PhD; Paul A. Friedman¹, MD; Jacqueline Saw², MD; Sorin V. Pislaru¹, MD; Thomas M. Munger¹, MD; David R. Holmes Jr¹, MD

1. Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA; 2. Division of Cardiology, University of British Columbia, Vancouver, BC, Canada

KEYWORDS

- atrial fibrillation
- left atrial appendage (LAA) closure
- stroke

Abstract

Left atrial appendage (LAA) closure for stroke prevention in the setting of non-valvular atrial fibrillation is an alternative to oral anticoagulation in patients with increased bleeding risk. It allows similar reduction in thromboembolic events, in particular stroke, compared to warfarin. A common clinical dilemma is the management of patients with peri-device leak after LAA occlusion. This has been documented in both percutaneous as well as surgical approaches. The specific definitions of leak severity, and the longer-term clinical implications are poorly understood. Here we review the mechanisms of incomplete occlusion for the different percutaneous closure devices, the data regarding thromboembolic risk in patients with incomplete appendage closure for both percutaneous and surgical strategies, and provide recommendations for management in these patients.

*Corresponding author: Department of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.
E-mail: raphael.claire@mayo.edu

Introduction

Left atrial appendage (LAA) occlusion has been shown to reduce the risk of thromboembolic stroke in patients with atrial fibrillation (AF)¹⁻³. Although oral anticoagulation agents are typically the first-line management for stroke prevention⁴, 30-40% of AF patients who meet criteria for warfarin are not anticoagulated due to the relative or absolute risks of bleeding^{1,5,6}. The majority of left atrial thrombus is thought to form in the LAA in patients with non-valvular AF^{7,8}. LAA occlusion was first performed surgically with the intention of reducing stroke risk⁹. More recently, percutaneous devices have been evaluated and several are now commercially available¹⁰. Following LAA occlusion with the WATCHMAN® device (Boston Scientific, Marlborough, MA, USA), stroke rate was significantly reduced¹¹, and individual trial data have demonstrated non-inferiority to warfarin³.

The LAA shape and size are very variable, and incomplete appendage closure or persistent leaks around the device are common following device placement. Methods of LAA closure vary from occlusion devices such as the WATCHMAN, the AMPLATZER™ Cardiac Plug (ACP) and the AMPLATZER™ Amulet® (St. Jude Medical, St. Paul, MN, USA), which occlude the ostium of the appendage, to external ligation devices such as the LARIAT® (SentreHEART, Redwood City, CA, USA), which exclude the LAA via a suture delivered epicardially. The Amulet is the second generation of the ACP device and has a larger volume in the device lobe, a longer waist, and more stabilising wires. Implantation is usually slightly deeper than with the ACP, also improving device stability. More recently, the WaveCrest device (Biosense Webster, Inc., Irvine, CA, USA) has been developed, which is suitable for short LAAs and can be deployed with minimal catheter manipulation in the LAA¹².

Incomplete LAA occlusion may be identified at the time of the procedure or develop later due to remodelling of the LAA tissue around the device¹³. Whether these peri-device leaks, “perileaks”, are clinically significant is uncertain and there is no consensus at present as to how to manage these patients best. We review the evidence to date regarding the clinical significance and management of incomplete LAA closure.

POTENTIAL RISKS OF INCOMPLETE APPENDAGE CLOSURE

A fibrillating atrium has minimal contraction, leading to local stasis and predisposition to thrombus formation. The blind-ended LAA is particularly prone to thrombus, with low blood flow velocities^{14,15}, and so incomplete LAA closure may increase the risk of thrombus formation and resultant systemic embolisation. For surgical LAA closure, rates of residual communication between the LAA and left atrium have been documented in 20-40% of cases at follow-up imaging^{16,17}. Thrombus was commonly present in patients with a partially closed LAA¹⁶. This was associated with higher rates of stroke or systemic embolisation compared to patients with a completely occluded LAA^{17,18}. Surgical ligation may also be followed by late reconnection of the LAA and the left atrium.

Experience to date suggests that incomplete LAA closure using percutaneous closure devices is not associated with the same elevated stroke risk as incomplete surgical closure. Although there were higher rates of ischaemic stroke post LAA occlusion with the WATCHMAN device compared to the warfarin group², these were predominantly periprocedural events. Theoretically, the presence of perileak may result in turbulent blood flow adjacent to the device, enhancing platelet adhesion and thrombus formation on the device and/or within the LAA. However, small residual leaks are unlikely to have clinical significance as, even if thrombus were to form behind the LAA closure device, it would be difficult for it to embolise through a small perileak into the left atrium¹⁹. On the other hand, a large perileak with a larger diameter aperture may allow such thrombus to escape the LAA into the systemic circulation.

DEFINITIONS OF SUCCESSFUL LAA EXCLUSION

Incomplete closure following surgical LAA occlusion is common^{18,20}, with only 40% complete LAA occlusion at follow-up transoesophageal echocardiography (TEE) in a subset of a surgical cohort following suture/staple exclusion or appendage excision¹⁸. LAA thrombus was present in almost half of the patients with unsuccessful LAA closure¹⁸. Patients with thrombus and incomplete LAA closure had higher rates of stroke or systemic embolisation, particularly if they were not anticoagulated¹⁷. Surgical LAA closure is not routinely recommended at the time of cardiothoracic surgery due to these concerns²¹ as well as the potential to lacerate the LAA during attempts at exclusion.

In contrast, rates of successful appendage closure with percutaneous devices appear higher, although the rates of thromboembolism or stroke appear similar in patients with small residual perileak compared to complete occlusion (**Figure 1**). However, data are again based on a limited number of events and limited follow-up time, and may have been confounded by management of some perileaks with oral anticoagulation or additional closure devices.

LAA occlusion studies have used varying definitions of procedural success. Most have used TEE to assess incomplete appendage closure. Criteria for successful closure have ranged from <1 mm residual flow into the LAA on Doppler colour flow²² to <5 mm²³ (**Table 1**). The only two randomised trials of LAA occlusion using the WATCHMAN device both used <5 mm residual flow into the LAA as the criterion for successful closure^{3,24}, while trials using the ACP and Amulet devices have reported leaks >5 mm as significant and 1-3 mm as moderate^{25,26}. Recent consensus documents have suggested that the <5 mm definition should be used as part of the technical definition for procedural success²⁷.

Small leaks may close spontaneously over time: patients with leaks <2-3 mm after LARIAT LAA exclusion showed complete closure on TEE at one year²². However, more recent registry data for the LARIAT investigators have also demonstrated the potential for new leaks during longer-term follow-up in patients who had appeared to have complete LAA closure at the time of index

Table 1. Criteria for successful LAA closure used in percutaneous device studies.

Paper	Year	Device	Number of patients	Intraprocedural imaging	Post-procedure imaging	Time of follow-up imaging	Definition of complete closure
ACP/Amulet							
Jaguszewski ³⁸	2015	ACP	24	TEE	TEE and CT		Residual peri-device flow ≤5 mm on TEE. CT: presence of early opacification with contrast agent
Santoro ³⁹	2016	ACP	134	TEE	TEE and CT		Residual peri-device flow ≤3 mm
Berti ⁴⁰	2016	ACP/Amulet	110	ICE	CT	6 months	CT: opacification of more than one third of LAA in the arterial phase
Saw ²⁵	2017	ACP	339	TEE, ICE or fluoroscopy	TEE	134 days	Residual peri-device flow ≤3 mm
LARIAT							
Bartus ⁴¹	2016	LARIAT	58	TEE			Residual peri-device flow <1 mm
Gianni ²³	2016	LARIAT	98	TEE			Residual peri-device flow ≤5 mm
Lakkireddy ⁴²	2016	LARIAT	712	TEE			Residual peri-device flow ≤5 mm
WATCHMAN							
Reddy ³¹	2016	WATCHMAN	3,822	TEE			Residual peri-device flow ≤5 mm
Holmes ¹	2014	WATCHMAN	475	TEE	TEE	45 days	Residual peri-device flow ≤5 mm
Reddy ²⁴	2011	WATCHMAN	1,002	TEE			Residual peri-device flow ≤5 mm
Holmes ³	2009	WATCHMAN	463	TEE	TEE	45 days	Residual peri-device flow ≤5 mm

ACP: AMPLATZER Cardiac Plug; CT: computed tomography; ICE: intracardiac echocardiography; TEE: transoesophageal echocardiography

device therapy²³. Non-randomised data have suggested that the LARIAT may be associated with lower rates of thrombus at six months after appendage occlusion compared to the WATCHMAN device²⁸, although whether this relates to anatomic factors or patient selection is unclear.

OUTCOMES FOLLOWING INCOMPLETE LAA OCCLUSION

Five studies (three percutaneous closure devices, two surgical) have reported outcomes in patients with incomplete LAA closure (**Figure 1**). Perileak was present in 41% of patients in the PROTECT AF trial using the WATCHMAN device at 45 days,

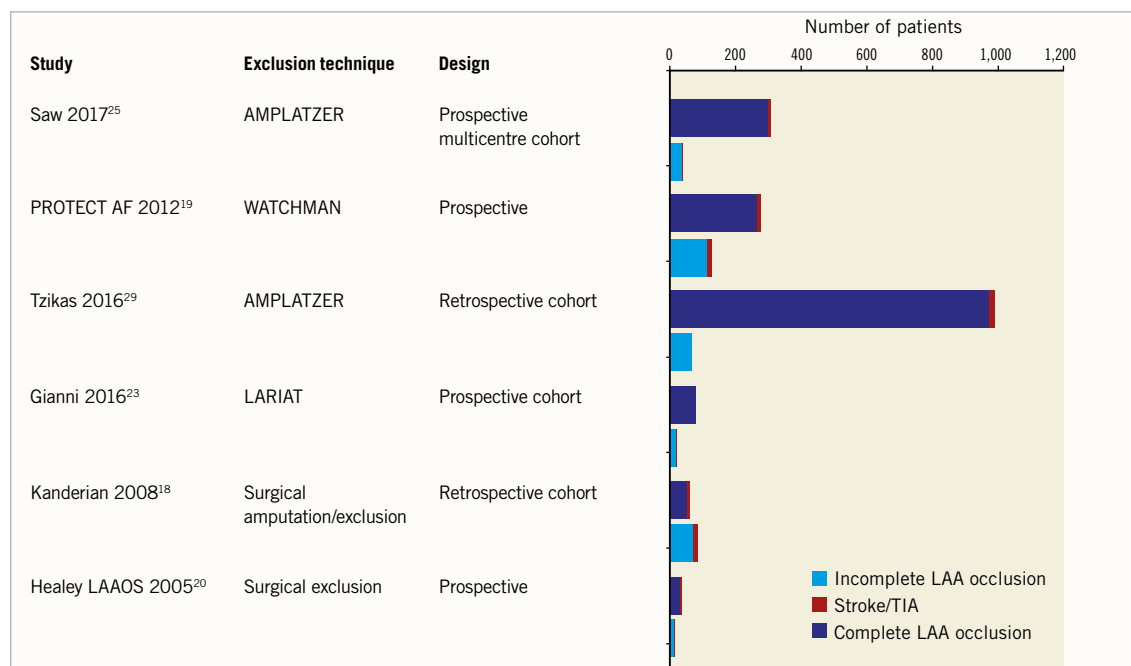


Figure 1. Studies of LAA occlusion reporting clinical outcomes in patients with and without complete occlusion.

34% at six months and 32% at 12 months¹⁹. Approximately one third of patients had a perileak >3 mm in diameter. There was no difference in clinical outcome in patients with a perileak compared to those with complete closure; however, clinicians were aware of the TEE results and many of the patients with a significant perileak remained on warfarin for an extended period of time.

European registry data following ACP insertion in 1,047 consecutive patients across 22 centres reported 73 (7%) patients with a perileak on follow-up (median time to TEE seven months)²⁹. Leak was significant (>3 mm) in 2% and mild (1-3 mm) in 5%. Patients with a major leak were not restarted on warfarin, with the exception of one patient. There were no strokes/transient ischaemic attacks in the patients with incomplete closure at follow-up. In the core lab-adjudicated cohort of this multi-centre series (n=339), the overall incidence of peri-device leak was 12.5% (5.5% minimal leak <1 mm, 5.8% mild leak 1-3 mm, 0.6% moderate leak 3-5 mm, and 0.6% severe leak >5 mm). Presence of any leak was not associated with higher clinical events compared to no leak. In fact there were no stroke, TIA or death events in patients with mild to severe leaks²⁵. However, it is important to emphasise that total patient-years of follow-up and absolute number of events were small in all of these studies and further data are needed to determine whether perileaks are benign or associated with an increased risk of stroke.

MECHANISMS AND DETECTION OF PERILEAK FOLLOWING LAA OCCLUSION

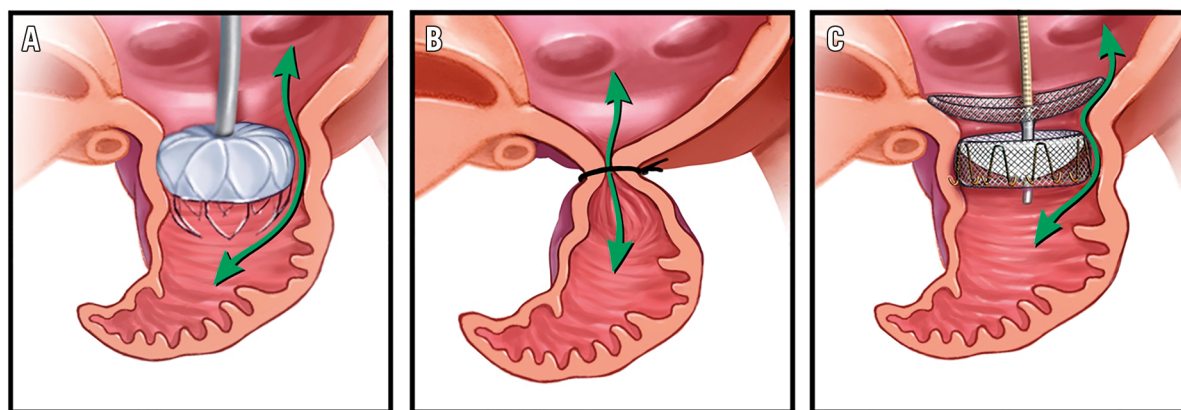
The mechanism of leaks following LAA occlusion appears to vary between devices. For the WATCHMAN device, leaks are typically between the edge of the device and the wall of the LAA. With the LARIAT device, the leaks are described as “gunny

sack”-like, with incomplete tightening of the suture resulting in a central leak where the residual LAA tissue begins to unfurl²⁸. The ACP device consists of two lobes. When the lobes are well aligned, the left atrial lobe typically is placed to occlude the mouth of the appendage fully. However, when this lobe is off axis, a leak can result around one side of the lobe and disc into the LAA²⁷ (Figure 2).

TEE is considered the gold standard for imaging of the LAA and guiding LAA procedures^{10,12} (Figure 3). Although the majority of data on perileaks have been derived from TEE, cardiac CT may have improved sensitivity in detection of perileak post LAA closure²⁶. No data are available for direct comparison; however, a series of 45 patients who had intraprocedural TEE with a perileak rate of 14% at the end of the procedure demonstrated residual leak on CT in over 60% of cases. Twenty-three of these patients had both follow-up CT and TEE; five had no evidence of perileak on TEE but a residual communication demonstrated on CT²⁶. CT also allows evaluation of the mechanism of residual leak and may provide valuable data for patient-specific device selection as further devices are developed and evaluated. The majority of patients with ACP/Amulet with a perileak had off-axis lobes and a lower mean maximum lobe compression. Two patients had a fabric leak on CT, which subsequently occluded on repeat CT three months later. For the WATCHMAN device, leaks appeared to result from ostial gaps around the device²⁶.

OPTIMISATION OF DEVICE SELECTION AND PROCEDURAL PLANNING TO MINIMISE RISK OF PERILEAK

Recent registry data have suggested high rates of procedural success, with lower rates of acute complications following the early learning curve compared to earlier studies^{29,30}. A strategy of deliberate oversizing of the WATCHMAN device by 20% or more³¹,



©2017 MAYO

Figure 2. Likely mechanisms of perileak for different devices. The WATCHMAN (A) is a nitinol frame coated with polyethylene terephthalate which sits in the mouth of the LAA and is anchored inside the LAA by multiple barbs. Perileaks are typically between the side of the LAA and the device. The LARIAT suture device (B) snares and then ligates the LAA. Leaks are at the site of snare due to incomplete closure and unfurling of the residual LAA tissue. The AMPLATZER Amulet and AMPLATZER Cardiac Plug (C) are composed of self-expanding nitinol mesh; they sit at the mouth of the LAA and attach to an anchoring lobe with stabilising wires which fix into the body of the LAA. Leaks can occur when the lobe is off axis and occur around this edge of the LAA lobe.

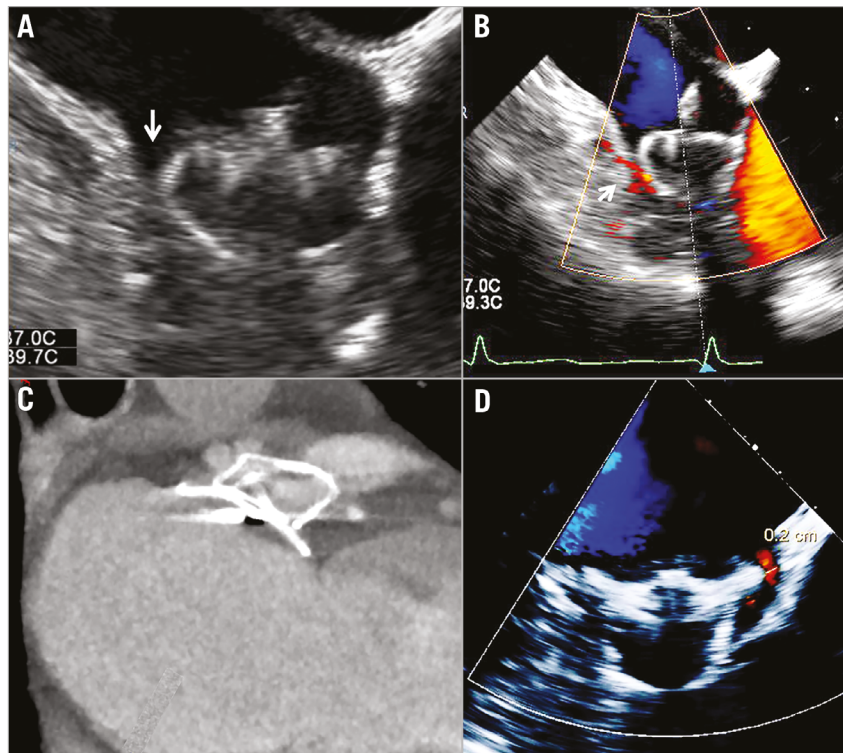


Figure 3. Periprocedural imaging of a 27 mm WATCHMAN using TEE (A) with Doppler colour flow (B). Although the device was adequately compressed, a perileak was evident on 2D TEE (arrowed). C) CT of an Amulet device in situ. D) An Amulet with a 0.2 mm residual perileak evident on TEE.

rather than the initially recommended 10-20%, may have contributed to the lower rates of perileak seen in recent registry studies³⁰. The EWOLUTION prospective multicentre registry reported acute procedural success in 98.5% of patients treated with WATCHMAN. On follow-up TEE, only 1% of patients had a residual perileak of greater than 5 mm³⁰. Similarly, for the Amulet and ACP devices, CT and TEE sizing pre-procedure are useful for sizing, with careful measurement of the maximum and mean LAA neck diameter²⁷. Consecutive case series with the Amulet demonstrated high procedural success (98%) with rates of perileak reported between 0³² and 7%³³, and significantly lower prevalence of perileak compared to ACP³³. For small LAA treated with the Amulet, expert opinion suggests slightly greater oversizing than the manufacturer recommendations to ensure a good seal²⁷.

Preprocedural work-up with CT for device sizing rather than TEE-only measurements may be associated with larger device selection and lower rates of perileak^{27,34} and should be considered prior to LAA occlusion procedures. During the procedure, careful imaging immediately post device insertion should be performed to assess for presence of any perileak before final deployment. Use of multiple views, with a complete sweep of the LAA from 0 to 135 degrees on TEE is recommended for thorough assessment for the presence of any perileak²⁷.

It has yet to be determined whether choice of device will alter rates of perileak. Future trials will perform direct comparison of commercially available devices, including randomisation of

patients to either the Amulet or the WATCHMAN device, with a primary endpoint of procedure-related complications and stroke at 18 months, and a secondary endpoint of residual perileak at 45-day TEE³⁵. However, with contemporary studies reporting low rates of significant perileak with many commercially available devices³⁰ and improved sealing with second-generation devices such as the Amulet, it may be difficult to prove superiority of one device over another. Finally, second-/third-generation and new devices will take into account the mechanisms of perileak that have occurred with the current commercially available devices, and modifications in design, as with the TAVR experience, may further reduce rates of perileak.

UNANSWERED QUESTIONS

Further data will become available in the next few years to allow a better assessment of thromboembolic event rates in patients with persistent perileaks post LAA occlusion. The prevalence of perileaks in the early trials may have been representative of operator learning curves for both device sizing and implantation¹². This appears to have reduced with increased operator experience and further refinement to device design. Going forward, it will be important to accrue greater patient numbers and follow-up duration to determine definitely whether perileaks are associated with an increased risk of stroke or thromboembolism, as this will guide management in these patients. It will be important to collect these data for each of the commercially available devices, since the

mechanism of leak varies between device designs, and the clinical implications of a persistent leak may therefore be device-specific. Such data will guide management of patients with persistent perileaks. The current data lack sufficient numbers and follow-up to determine whether small perileaks may confer an increased risk of stroke or should be intervened upon.

Large leaks (e.g., those >5 mm or uncovered lobes) can potentially be closed with vascular plugs, coils or septal occluder devices. Case series have demonstrated successful closure^{36,37}; alternatively, patients may be managed on oral anticoagulants if tolerated. In a large single-centre retrospective series, 2% of 631 patients who underwent LAA closure required a second LAA closure procedure for peri-device leak >3 mm. These 12 cases of second LAA closure procedure were all successful and none of the patients had a stroke on follow-up³². Thus, a second LAA closure procedure can be feasible; however, current experience is limited and the long-term clinical benefit of this approach should be explored further.

The natural history of perileaks following LAA appendage closure also requires further study. Reports on the LARIAT device have demonstrated increased incidence of leaks at one-year follow-up, suggesting that leaks may develop late after LAA occlusion²³; however, this has not been a consistent finding across studies. Rates of new leaks may vary with different devices. More information is required as to whether patients may require follow-up TEE or CT to check for new perileaks as time since the LAA closure increases.

With increased data on outcomes and natural history of perileaks, evidence-based management recommendations will emerge. The major unanswered questions at present are whether patients with a persistent perileak require long-term anticoagulation or antiplatelet therapy, and whether additional mechanical perileak closure should be attempted. Imaging of perileaks is also a developing field. When and if repeat imaging should be performed to check for development of new perileaks is still uncertain.

Based on the available evidence, it would seem reasonable to observe perileaks less than 5 mm serially for patients post WATCHMAN or Amulet/ACP device. For leaks of 5 mm and greater, management with continued oral anticoagulation would be reasonable if clinically safe, while perileak closure may be considered on an individualised basis. For patients with incomplete surgical appendage closure, ongoing anticoagulation or consideration of percutaneous closure would be recommended. The data for the LARIAT device are less clear but a similar strategy to surgery may be reasonable.

Summary

Prospective analysis of contemporary percutaneous therapies has not revealed an increased event rate with persistent perileaks, although data are limited. Different devices appear to be associated with different mechanisms of device leak post LAA closure. Further work is required to assess the thromboembolic risks associated with persistent perileak and to guide management recommendations in these patients.

Impact on daily practice

Persistent leaks (perileaks) following left atrial appendage closure occur in up to 30% of patients. Use of preprocedural imaging and improved decision making regarding device size appear to have reduced contemporary perileak rates. Limited data from early trials did not suggest a higher rate of stroke in patients with persistent perileaks; however, the number of events was small and further data are needed. In patients with perileaks of 5 mm or greater, clinicians should consider continued oral anticoagulation if tolerated or percutaneous closure of the perileak.

Conflict of interest statement

D. Holmes (along with the Mayo Clinic) would like to declare a financial interest in the WATCHMAN device. The other authors have no conflicts of interest to declare.

References

- Holmes DR Jr, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, Huber K, Reddy VY. 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;64:1-12.
- Holmes DR Jr, Doshi SK, Kar S, Price MJ, Sanchez JM, Sievert H, Valderrabano M, Reddy VY. Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation: A Patient-Level Meta-Analysis. *J Am Coll Cardiol.* 2015;65:2614-23.
- Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P; 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;374:534-42.
- Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med.* 2007;146:857-67.
- Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, Cobbe S, Breithardt G, Le Heuzey JY, Prins MH, Lévy S, Crijns HJ; European Heart Survey Investigators. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J.* 2005;26:2422-34.
- Camm AJ, Accetta G, Ambrosio G, Atar D, Bassand JP, Berge E, Cools F, Fitzmaurice DA, Goldhaber SZ, Goto S, Haas S, Kayani G, Koretsune Y, Mantovani LG, Misselwitz F, Oh S, Turpie AG, Verheugt FW, Kakkar AK; GARFIELD-AF Investigators. Evolving antithrombotic treatment patterns for patients with newly diagnosed atrial fibrillation. *Heart.* 2017;103:307-14.
- Manning WJ, Silverman DI, Gordon S, Krumholz HM, Douglas PS. Cardioversion from atrial fibrillation without prolonged anticoagulation with use of transesophageal echocardiography to exclude the presence of atrial thrombi. *N Engl J Med.* 1993;328:750-5.

8. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg*. 1996;61:755-9.
9. MADDEN JL. Resection of the left auricular appendix; a prophylaxis for recurrent arterial emboli. *J Am Med Assoc*. 1949;140:769-72.
10. Saw J, Lempereur M. Percutaneous left atrial appendage closure: procedural techniques and outcomes. *JACC Cardiovasc Interv*. 2014;7:1205-20.
11. Holmes DR Jr, Reddy VY. Left Atrial Appendage and Closure: Who, When, and How. *Circ Cardiovasc Interv*. 2016;9:e002942.
12. Meier B, Blaauw Y, Khattab AA, Lewalter T, Sievert H, Tondo C, Glikson M; Document Reviewers. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. *Europace*. 2014;16:1397-416.
13. Holmes DR Jr, Lakkireddy DR, Whitlock RP, Waksman R, Mack MJ. Left atrial appendage occlusion: opportunities and challenges. *J Am Coll Cardiol*. 2014;63:291-8.
14. Mügge A, Kühn H, Nikutta P, Grote J, Lopez JA, Daniel WG. Assessment of left atrial appendage function by biplane transesophageal echocardiography in patients with nonrheumatic atrial fibrillation: identification of a subgroup of patients at increased embolic risk. *J Am Coll Cardiol*. 1994;23:599-607.
15. Pollick C, Taylor D. Assessment of left atrial appendage function by transesophageal echocardiography. Implications for the development of thrombus. *Circulation*. 1991;84:223-31.
16. Cullen MW, Stulak JM, Li Z, Powell BD, White RD, Ammash NM, Nkomo VT. Left Atrial Appendage Patency at Cardioversion After Surgical Left Atrial Appendage Intervention. *Ann Thorac Surg*. 2016;101:675-81.
17. Aryana A, Singh SK, Singh SM, O'Neill PG, Bowers MR, Allen SL, Lewandowski SL, Vierra EC, d'Avila A. Association between incomplete surgical ligation of left atrial appendage and stroke and systemic embolization. *Heart Rhythm*. 2015;12:1431-7.
18. Kanderian AS, Gillinov AM, Pettersson GB, Blackstone E, Klein AL. Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. *J Am Coll Cardiol*. 2008;52:924-9.
19. Viles-Gonzalez JF, Kar S, Douglas P, Dukkipati S, Feldman T, Horton R, Holmes D, Reddy VY. The clinical impact of incomplete left atrial appendage closure with the Watchman Device in patients with atrial fibrillation: a PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) substudy. *J Am Coll Cardiol*. 2012;59:923-9.
20. Healey JS, Crystal E, Lamy A, Teoh K, Semelhago L, Hohnloser SH, Cybulsky I, Abouzahr L, Sawchuck C, Carroll S, Morillo C, Kleine P, Chu V, Lonn E, Connolly SJ. Left Atrial Appendage Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke. *Am Heart J*. 2005;150:288-93.
21. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64:e1-76.
22. Bartus K, Han FT, Bednarek J, Myc J, Kapelak B, Sadowski J, Lelakowski J, Bartus S, Yakubov SJ, Lee RJ. Percutaneous left atrial appendage suture ligation using the LARIAT device in patients with atrial fibrillation: initial clinical experience. *J Am Coll Cardiol*. 2013;62:108-18.
23. Gianni C, Di Biase L, Trivedi C, Mohanty S, Gökoğlan Y, Güneş MF, Bai R, Al-Ahmad A, Burkhardt JD, Horton RP, Krumer AK, Palma EC, Valderrábano M, Gibson D, Price MJ, Natale A. Clinical Implications of Leaks Following Left Atrial Appendage Ligation With the LARIAT Device. *JACC Cardiovasc Interv*. 2016;9:1051-7.
24. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF (PROTECT AF) clinical trial and the Continued Access Registry. *Circulation*. 2011;123:417-24.
25. Saw J, Tzikas A, Shakir S, Gafoor S, Omran H, Nielsen-Kudsk JE, Kefer J, Aminian A, Berti S, Santoro G, Nietlispach F, Moschovitis A, Cruz-Gonzalez I, Stammen F, Tichelbäcker T, Freixa X, Ibrahim R, Schillinger W, Meier B, Sievert H, Gloekler S. Incidence and Clinical Impact of Device-Associated Thrombus and Peri-Device Leak Following Left Atrial Appendage Closure With the Amplatzer Cardiac Plug. *JACC Cardiovasc Interv*. 2017;10:391-9.
26. Saw J, Fahmy P, DeJong P, Lempereur M, Spencer R, Tsang M, Gin K, Jue J, Mayo J, McLaughlin P, Nicolaou S. Cardiac CT angiography for device surveillance after endovascular left atrial appendage closure. *Eur Heart J Cardiovasc Imaging*. 2015;16:1198-206.
27. Tzikas A, Gafoor S, Meerkin D, Freixa X, Cruz-Gonzalez I, Lewalter T, Saw J, Berti S, Nielsen-Kudsk JE, Ibrahim R, Lakkireddy D, Paul V, Arzamendi D, Nietlispach F, Worthley SG, Hildick-Smith D, Thambo JB, Tondo C, Aminian A, Kalarus Z, Schmidt B, Sondergaard L, Kefer J, Meier B, Park JW, Sievert H, Omran H. Left atrial appendage occlusion with the AMPLATZER Amulet device: an expert consensus step-by-step approach. *EuroIntervention*. 2016;11:1512-21.
28. Pillarisetti J, Reddy YM, Gunda S, Swarup V, Lee R, Rasekh A, Horton R, Massumi A, Cheng J, Bartus K, Badhwar N, Han F, Atkins D, Bommana S, Earnest M, Nath J, Ferrell R, Bormann S, Dawn B, Di Biase L, Mansour M, Natale A, Lakkireddy D. Endocardial (Watchman) vs epicardial (Lariat) left atrial appendage exclusion devices: Understanding the differences in the location and type of leaks and their clinical implications. *Heart Rhythm*. 2015;12:1501-7.

29. Tzikas A, Shakir S, Gafoor S, Omran H, Berti S, Santoro G, Kefer J, Landmesser U, Nielsen-Kudsk JE, Cruz-Gonzalez I, Sievert H, Tichelbäcker T, Kanagaratnam P, Nietlispach F, Aminian A, Kasch F, Freixa X, Danna P, Rezzaghi M, Vermeersch P, Stock F, Stolcova M, Costa M, Ibrahim R, Schillinger W, Meier B, Park JW. Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicentre experience with the AMPLATZER Cardiac Plug. *EuroIntervention*. 2016;11:1170-9.
30. Boersma LV, Ince H, Kische S, Pokushalov E, Schmitz T, Schmidt B, Gori T, Meincke F, Protopopov AV, Betts T, Foley D, Sievert H, Mazzone P, De Potter T, Vireca E, Stein K, Bergmann MW; EWOLUTION investigators. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-Year follow-up outcome data of the EWOLUTION trial. *Heart Rhythm*. 2017;14:1302-8.
31. Reddy VY, Gibson DN, Kar S, O'Neill W, Doshi SK, Horton RP, Buchbinder M, Gordon NT, Holmes DR. Post-FDA Approval, Initial US Clinical Experience with Watchman Left Atrial Appendage Closure for Stroke Prevention in Atrial Fibrillation. *J Am Coll Cardiol*. 2017;69:253-61.
32. Kleinecke C, Park JW, Gödde M, Zintl K, Schnupp S, Brachmann J. Twelve-month follow-up of left atrial appendage occlusion with Amplatzer Amulet. *Cardiol J*. 2017;24:131-138.
33. Abualsaud A, Freixa X, Tzikas A, Chan J, Garceau P, Basmadjian A, Ibrahim R. Side-by-Side Comparison of LAA Occlusion Performance With the Amplatzer Cardiac Plug and Amplatzer Amulet. *J Invasive Cardiol*. 2016;28:34-8.
34. Rajwani A, Nelson AJ, Shirazi MG, Disney PJ, Teo KS, Wong DT, Young GD, Worthley SG. CT sizing for left atrial appendage closure is associated with favourable outcomes for procedural safety. *Eur Heart J Cardiovasc Imaging*. 2016 Dec 24. [Epub ahead of print].
35. AMPLATZER™ Amulet™ LAA Occluder Trial (Amulet IDE). Available from: <https://clinicaltrials.gov/ct2/show/NCT02879448>
36. Mosley WJ 2nd, Smith MR, Price MJ. Percutaneous management of late leak after lariat transcatheter ligation of the left atrial appendage in patients with atrial fibrillation at high risk for stroke. *Catheter Cardiovasc Interv*. 2014;83:664-9.
37. Hornung M, Gafoor S, Id D, Vaskelyte L, Hofmann I, Franke J, Sievert H, Bertog SC. Catheter-based closure of residual leaks after percutaneous occlusion of the left atrial appendage. *Catheter Cardiovasc Interv*. 2016;87:1324-30.
38. Jaguszewski M, Manes C, Puipe G, Salzberg S, Müller M, Falk V, Lüscher T, Luft A, Alkadhi H, Landmesser U. Cardiac CT and echocardiographic evaluation of peri-device flow after percutaneous left atrial appendage closure using the AMPLATZER cardiac plug device. *Catheter Cardiovasc Interv*. 2015;85:306-12.
39. Santoro G, Meucci F, Stolcova M, Rezzaghi M, Mori F, Palmieri C, Paradossi U, Pastormerlo LE, Rosso G, Berti S. Percutaneous left atrial appendage occlusion in patients with non-valvular atrial fibrillation: implantation and up to four years follow-up of the AMPLATZER Cardiac Plug. *EuroIntervention*. 2016;11:1188-94.
40. Berti S, Paradossi U, Meucci F, Trianni G, Tzikas A, Rezzaghi M, Stolkova M, Palmieri C, Mori F, Santoro G. Periprocedural intracardiac echocardiography for left atrial appendage closure: a dual-center experience. *JACC Cardiovasc Interv*. 2014;7:1036-44.
41. Bartus K, Gafoor S, Tschopp D, Foran JP, Tilz R, Wong T, Lakkireddy D, Sievert H, Lee RJ. Left atrial appendage ligation with the next generation LARIAT(+) suture delivery device: Early clinical experience. *Int J Cardiol*. 2016;215:244-7.
42. Lakkireddy D, Afzal MR, Lee RJ, Nagaraj H, Tschopp D, Gidney B, Ellis C, Altman E, Lee B, Kar S, Bhadwar N, Sanchez M, Gadiyaram V, Evonich R, Rasekh A, Cheng J, Cuoco F, Chandhok S, Gunda S, Reddy M, Atkins D, Bommana S, Cuculich P, Gibson D, Nath J, Ferrell R, Matthew E, Wilber D. Short and long-term outcomes of percutaneous left atrial appendage suture ligation: Results from a US multicenter evaluation. *Heart Rhythm*. 2016;13:1030-6.