Ann Thorac Cardiovasc Surg 2018; 24: 271–278
Online June 29, 2018
doi: 10.5761/atcs.ra.18-00014

Review Article

The Efficacy and Safety of the WATCHMAN Device in LAA Occlusion in Patients with Non-Valvular Atrial Fibrillation Contraindicated to Oral Anticoagulation: A Focused Review

David Nehemiah Majule, MD,[1] Chang Jing, MD, PhD,[1] Willfredius Mugishagwe Rutahoile, MD,[1] and Felix Samuel Shonyela, MD[2]

The standard treatment for stroke risk patients with non-valvular atrial fibrillation (NVAF) is the use of oral anticoagulants (OACs). However, a substantial number of patients have relative or absolute contraindications to OACs due to concerns of major bleeding risk and other adverse effects while using oral anticoagulation therapy. Recently, occurrences of exclusion of the left atrial appendage (LAA) in patients with contraindication to anticoagulation therapy are widely expanding worldwide, causing major contentious discussions. The LAA is the commonest place of thrombus formation; therefore, the concept of LAA occlusion in reducing stroke and other embolic events in NVAF patients is very important. The current understanding of the available evidence on efficacy and safety of LAA closure (LAAC) with the Watchman device in patients contraindicated to OACs is the major aim of this focused review. After reviewing a significant body of literature, a world experience with no randomized trials, it is suggested that Watchman device implantation is effective and safe in high-risk patients with NVAF contraindicated to OACs therapy.

Keywords: atrial fibrillation, left atrial appendage, oral anticoagulation, watchman device, contraindication

Introduction

Atrial fibrillation (AF) is the most common arrhythmia and occurrences of this are expanding worldwide. Aging population and patients with chronic heart disease are among the factors responsible for a rising prevalence of AF.[1)] Prevention or reduction of the following primary factors can reduce the risk of AF; cigarette smoking, sedentary life style, adverse dietary risk factors (e.g., salt intake, excess calorie consumption), and lowering blood pressure will reduce the incidence of AF.[2)] A total of 1%–2% of the population in North America and Europe is affected with AF.[3)] Among Asian populations, the prevalence of AF increases with age, and there is great variability in different Asian countries. The overall annual incidence of AF in Asian countries is found to be 5.38 per 1000 person-years and the community-based AF prevalence among Asian countries ranges from 0.03% to 3.75%. In China, the prevalence ranges from 0.37% to 3.56%.[4)] In the United States, the prevalence of patients with AF is likely to increase 2.5-fold by the year 2050, and it is estimated that 2.3 million US adults have AF. This is projected to increase by more than 5.6 million by the

[1]*Department of Cardiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China*
[2]*Achbishop James University College, Songea, Tanzania*

Received: January 18, 2018; Accepted: May 8, 2018
Corresponding author: Chang Jing, MD, PhD. Department of Cardiology, The First Affiliated Hospital of Chongqing Medical University, No. 1 Youyi Road, Yuanjiagang, Yuzhong District, Chongqing 400016, China
Emails: 1584105002@qq.com, davidmajule@yahoo.com

Table 1 Contraindication to oral anticoagulation. Part A: contraindication to warfarin; part B: contraindication to new oral anticoagulation[7,8)]

Contraindication to Warfarin therapy, part (A)	Contraindication to new oral anticoagulation therapy, part (B)
Patients with history of hypersensitivity to the drug	Patients with known history of hypersensitivity to the drugs
Patient with history of threatened abortion, eclampsia, and preeclampsia. Unsupervised or independently patients with senility or high fall risk	Patients with history of active significant bleeding, disorder of hemostasis, for example, von Willebrand disease or coagulation factor deficiency, prosthetic heart valve, liver disease with an alanine transaminase (ALT) > 2 times upper limit of normal
Pregnant women except in those pregnant women with mechanical heart valves	Patients with concomitant medication known to affect pharmacokinetics, for example, concomitant warfarin therapy
Patients with history of pathologic condition of the blood (blood dyscrasias)	Patients with history of pregnancy or breast feeding
Patients with history of hemorrhagic tendencies, for example, active peptic ulcers or patients with history of obvious bleeding of the gastrointestinal, genitourinary, or respiratory tract, central nervous system hemorrhage, cerebral aneurisms, dissecting aorta, pericarditis, pericardial effusions, or bacterial endocarditis	Patients with history of poor renal function, for example, dabigatran is contraindicated in severe renal impairment creatinine clearance (CrCL) <30 mL/min, edoxaban is contraindicated in patients with CrCL >95 mL/min, rivaroxaban and apixaban are contraindicated in patients with CrCL <15 mL/min

Fig. 1 LAAC devices. (**A**) Watchman device, (**B**) Amplatzer cardiac plug device, and (**C**) PLAATO device. Adapted from Möbius-Winkler et al.[6)] LAAC: left atrial appendage closure; PLAATO: percutaneous left atrial appendage transcatheter occlusion

year 2050, with most of the increase being the elderly population aged 80 years or older. The prevalence of AF increases from 0.1% in adults younger than 55 years old to 9% in adults aged 80 years or older.[5)]

Transcatheter left atrial appendage closure (LAAC) is used as a primary therapy for AF patients contraindicated to chronic oral anticoagulation to prevent stroke.[6)] Contraindication to warfarin and new oral anticoagulants (NOAC) use had been mentioned elsewhere.[7,8)] **Table 1**, part A and part B, illustrates these contraindications.[7,8)]

Percutaneous Transcatheter Closure of the LAA

The primary source of thromboembolism in nonvalvular atrial fibrillation (NVAF) patients is the LAA, with approximately 90% of thromboembolism occurring in the LAA.[9)] Surgical or percutaneous approaches with devices to close the LAA have been conducted with the aim to reduce the risk of thromboembolic events in NVAF patients. Several devices use a percutaneous approach to close the LAA, including the WATCHMAN LAA system (Atritech, Plymouth, MN, USA) shown in **Fig. 1A**, the Amplatzer Cardiac Plug (AGA Medical, MN, USA) shown in **Fig. 1B**, the PLAATO device shown in **Fig. 1C**[6)] (which is no longer produced and is off the market) and the Lariat system (SentreHEART, Palo Alto, CA, USA). This review will focus on the WATCHMAN device, as it remains the most rigorously examined and studied of all transcatheter-based devices in this space. The WATCHMAN device is the first LAA closure device tested in two randomized studies: the PREVAIL trial[10)] and the PROTECT-AF trial.[11)] These trials did not, however, include subjects contraindicated to OACs therapy. The WATCHMAN device from Boston Scientific was approved on March 13, 2015 by the United States Food and Drug Administration with the aim of reducing the risk of thromboembolic events from the LAA in patients with NVAF.[12)]

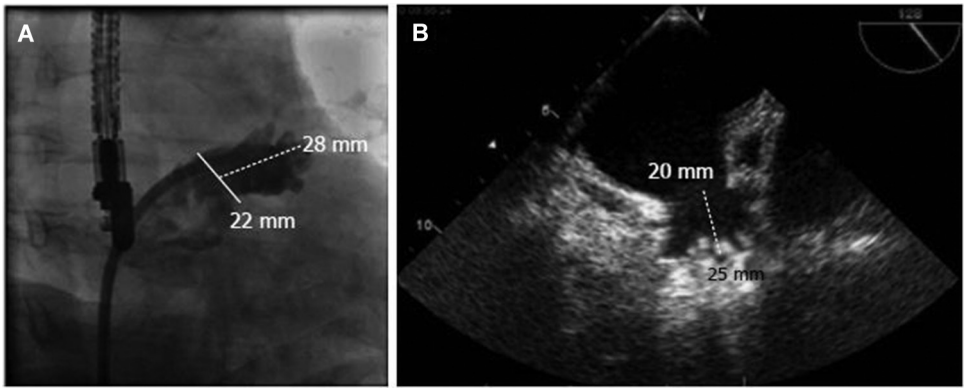

Fig. 2 Measurement of the LAA during implantation of Watchman device. (**A**) After angiography (RAO: 25°, caudal: 20°), ostium size measurement (22 mm) and depth (28 mm); (**B**) measurement using echocardiography at around 135° of ostium size (20 mm) and depth (25 mm). Adapted from Möbius-Winkler et al.[6] LAA: left atrial appendage; RAO: right anterior oblique

WATCHMAN Device Description

The Watchman device consists of three main components:[13] the WATCHMAN LAAC device, the WATCHMAN delivery system, and the WATCHMAN access system. The WATCHMAN LAAC device contains a nitinol (nickel/titanium alloy) frame structure with 10 fixation anchors and a device cap that contains a fabric polyethylene terephthalate which acts as a protective filter. The device is available in five sizes: 21, 24, 27, 30, and 33 mm. The WATCHMAN Transseptal Access system comprises of a single curve or double curve styles. The WATCHMAN device is preloaded within the 12F delivery catheter ready to be released within the LAA after all criteria for device release are met. The measurement of LAA size before implantation is necessary to match with the specific size of the Watchman device as illustrated in **Fig. 2A** and **2B**).[6]

Trials and Studies Looking at Efficacy and Safety of Watchman Device

The EWOLUTION trial[14] was a very large published Watchman registry performed in Europe by Boersma et al. entitled "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." This was a multicenter prospective, nonrandomized cohort study designed to provide data in routine practice from multicenter registry. About 1025 patients were planned for a Watchman LAAC in 47 centers between October 2013 and May 2015. High-risk population included in the registry was mostly contraindicated to OACs with an average $CHADS_2$ score: 2.8 ± 1.3, CHA_2DS_2-VASc: 4.5 ± 1.6, and HAS-BLED score of 2.3 ± 1.2. About 40% of patients had HAS-BLED score ≥3, their mean age was 73.4 ± 8.9 years and 30.5% of patients had prior ischemic stroke/transient ischemic attack (TIA). 15.1% had previously had a hemorrhagic stroke, 31.3% of patients had a history of major bleeding, and 73.3% of patients were deemed ineligible for anticoagulation. According to Boersma et al., the Watchman device implantation was successful in 98.5% with no residual flow in 99.8% of patients. After the procedure, dual antiplatelet therapy (DAPT) was used in 60% of patients for 6 months, vitamin K antagonist (VKA) in 16%, NOAC in 11%, single antiplatelet therapy (SAPT) in 7%, and nothing in 6.4% of patients. This registry reported initial 7 days EWOLUTION report[14,15] on procedural outcomes as follows: procedure- or device-related serious adverse events was 2.8% (which is lower than 8.7% in PROTECT-AF)[16] and the mortality rate was 0.3%. Major adverse cardiac events within 7 days reported one death which occurred due to cerebral air embolism during the procedure, systemic embolism, procedure-related stroke, and myocardial infarction (MI) did not occur. Serious adverse events occurred within 30 days were significantly lower for patient's ineligible to OACs therapy (6.5%) compared to (10.2%) of patients eligible to OACs therapy ($p = 0.042$). The total mortality rate within 30 days was 0.7%. Boersma et al.[14] provided 1-year follow-up results in which the Watchman device was observed to be safe and effective in NVAF patients, of which 73% were deemed ineligible for oral anticoagulation therapy. The registry reported a calculated stroke

rate of 7.2% with no anticoagulation use and a similar CHA_2DS_2-VASc score. The annual ischemic stroke rate was 1.1%, which is very low considering the majority used DAPT medication. This rate translates to an 84% risk reduction. Also there was a 48% risk reduction in major bleeding events, based on an observed small rate of annual major bleeding of 2.6%, and the expected rate based on HAS-BLED score was 5.0%. Authors in this registry compared the annual ischemic stroke rate of 1.1% in the EWOLUTION study with an observed ischemic stroke rate of 1.7% after 2 years and 1.8% after 5 years of follow-up of the ASA plavix feasibility study with watchman left atrial appendage closure technology (ASAP) study[17] a similar pattern was found. The mortality rate in the EWOLUTION registry after 1 year was 9.8%. The possible explanation of this from the authors was that most of patients included in the study had high CHA_2DS_2-VASc and HAS-BLED scores compared to previous large trials on Watchman device and had a higher comorbidity profile with an age more than 75 years. Bergmann et al.[18] also reported Watchman device implantation to be safe in all subjects eligible and ineligible to OACs. After implantation, the following medications were prescribed NOAC, DAPT, or VKA. They report ischemic stroke in subjects who received DAPT (0.5%) and SAPT (1.4%) but no ischemic stroke observed in subjects who received NOAC, VKA, or no medication ($p = 0.5108$). Therefore, in future, randomized trials comparing efficacy and the safety of the Watchman device, implantation without anticoagulation or antiplatelet therapy is needed.

The ASAP study was conducted by Reddy et al.[7] between January 2009 and November 2011. It was a multicenter, prospective nonrandomized observational registry assessing the safety and efficacy of LAAC in NVAF patients specifically ineligible for warfarin therapy. A total of 150 patients with NVAF, $CHADS_2$ score ≥1, and who were ineligible for warfarin therapy were included in the study. These patients were managed with 6 months of DAPT and then lifelong aspirin without warfarin therapy after LAAC with Watchman device. The primary efficacy endpoint in this registry consisted of the occurrence of stroke (ischemic or hemorrhagic), cardiovascular or unexplained death and systemic embolism. Watchman device implantation was successful in 94.7% of patients. The mean $CHADS_2$ score and CHA_2DS_2-VASc score were 2.8 and 4.4, respectively, history of hemorrhagic/bleeding was present in 93% of cases and was the commonest reason for warfarin contraindication. The mean duration of follow-up was 14.4 months and the observed stroke/systemic embolism rate was 2.3% per year and the expected rate was 7.3% per year. They concluded implantation using the Watchman device to be safe without Warfarin therapy but rather aspirin and clopidogrel were prescribed after the procedure, as there was an approximate of 64%–77% reduction in risk of stroke based upon their $CHADS_2$ score. There is an ongoing randomized controlled trial, "The Assessment of the Watchman Device in Patients Unsuitable for Oral Anticoagulation (ASAP-TOO)".[19]

The Canadian multicenter experience with Watchman for percutaneous LAAC conducted by Saw et al. reported pooled consecutive series of patients who underwent Watchman LAAC at four major Canadian centers. In this study,[20] they included 106 patients who had the Watchman implant starting from May 2013 up to October 2015. The primary objective of the study was to evaluate the safety and efficacy of the Watchman device. Patients reported in this study were contraindicated or had failure to or intolerance to OACs therapy. Mean follow-up of the study was 210 ± 182 days and the indication for Watchman device implantation was $CHADS_2 \geq 1$ or CHA_2DS_2-VASc ≥ 2 and patients who were ineligible for oral anticoagulation therapy. About 0.9% of patients had history of recurrent strokes on warfarin therapy, and 9.4% of cases had history of bleeding. Meanwhile, 89.6% of cases had prior bleeding history. The mean $CHADS_2$ and CHA_2DS_2-VASc scores were 2.8 ± 1.2 and 4.3 ± 1.5, respectively, with mean age 74.8 ± 7.7, and HAS-BLED scores reported as 3.2 ± 1.2. In this Canadian multicenter study, implantation was successful in 103 cases (97.2%). This aligns with other studies like the EWOLUTION study,[14] of which 98.5% of patients had the Watchman device implanted successfully and the ASAP study[7] which had 94.7% successfully implanted with the device. Procedure experience had been improving with time as a higher rate of successful implantation had been achieved in recent studies compared to previous Watchman studies. After implantation, DAPT was used in 76 patients (73.8%), OACs therapy utilized by 21 patients (20.4%), and aspirin alone in three patients (2.9%). Observed annual thromboembolic events were 3.3% which aligns with the expected thromboembolic events based on $CHADS_2$ score of 9.6% (66% reduction) and CHA_2DS_2-VASc score 8.1% (59% reduction). Therefore, Watchman device implantation for LAAC was concluded to be safe and effective in patients contraindicated to oral anticoagulation, but authors insisted to confirm the results in large registries and randomized trials.

Disadvantages of the percutaneous transcatheter closure of the LAA are as follows: In general, guiding catheters, stiff wires manipulation, the Watchman device itself, and transseptal puncture procedure can cause pericardial effusions/tamponade during occlusion of the LAA.[6,21,22] Air embolism and device embolization are also procedural complications related to transseptal puncture and device implantation. Five out of 449 patients who had Watchman device implantation, as reported by Holmes et al.[21] had periprocedural stroke secondary to air embolism, and about 0.2% of cases had device embolization. Other possible outcomes of the procedure can be cardiac arrest, stroke, hypotension, acute coronary ischemia, and death. Device embolization can occur early or late; however, proper measurements of the LAA morphology and appropriate device sizing can prevent embolization. Routine transthoracic echocardiography on day 1 or 2 after the procedure was used to rule out device embolization and pericardial effusion.[6,23] Proper management and prevention of complications, as well as increased procedure experience with time, all can aid in minimization of the procedural-related complications.

Current Evidence Derived from Surgical LAA Occlusion

Until recently, various surgical treatment strategies or percutaneous techniques with different types of devices for LAAC are available.[24,25] Surgical LAAC is divided into two categories: exclusion or excision.[26,27] Epicardial surface exclusion includes running or mattress sutures with or without felt pledgets, purse-string sutures from the epicardial surface, or running sutures or purse-string sutures from the endocardial surface, and single ligation techniques. Excision procedures include a stapled excision, or oversew, and removal techniques. 2016 European Society of cardiology (ESC) guidelines developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)[28] recommended surgical LAAC in patients with AF undergoing cardiac surgery or thoracoscopic AF surgery (class II b, level of evidence B). A study conducted by Kanderian et al.[29] included 137 patients from a cohort study (level IIIb) because follow-up data were available to these patients, and 52 out of these 137 patients had LAA excision (11 patients by the use of an amputating stapling device and 41 patients by using scissors), and 85 (62%) patients had exclusion using the following techniques; 73 (86%) had suture exclusion and 12 (14%) had stapler exclusion leaving LAA attached in place. They reported success rate of LAAC of about only 55 (40%) out of 137 patients. During transesophageal echocardiography (TEE) follow-up examinations after their previous surgery, a total of 55 patients had successful LAAC but among them only six patients (11%) had stroke/TIA compared with 12 patients (15%) of 82 patients with unsuccessful LAAC who also had stroke/TIA ($p = 0.61$). Overall, a total of 18 patients (13%) suffered stroke/TIA; stapler exclusion ($n = 1$) patient, suture exclusion ($n = 11$) patients, and LAA excision ($n = 6$) patients. LAA thrombus occurred in (41%) of unsuccessful LAAC. Excision of the LAA was more successfully achieved (73%) compared to suture exclusion (23%), and stapler exclusion (0%) ($p < 0.001$). Furthermore, their study reported that excision of the LAA using scissors is the most reliable method, and incidence of stroke/TIA decreased in patients with complete LAAC although it was not significant. A study conducted by Healey et al.[30] included 77 patients, out of which 52 patients received LAAC while 25 patients acted as controls. In this study, five out of 11 patients (45%) had complete occlusion of LAA using sutures and also 24 out of 33 patients (72%) had complete LAAC using a stapler without difference observed between the control group and the LAAC side in terms of neurologic events risk reduction, Katz et al.[31] involved 50 patients who underwent mitral valve surgery and LAAC which was performed by endocardial double-row running sutures. A total of 18 patients (36%) had incomplete occlusion with thrombus observed in nine patients (50%) with subsequent thromboembolic events in four patients. They concluded that inadequate LAA may increase the risk of thromboembolism. A study conducted by García-Fernández et al.[32] aims to assess whether ligation of the LAA in patients undergoing mitral valve replacement is associated with the risk of embolism in future. About 58 patients had LAA ligation performed by double suture (a purse-string suture and running suture), among them six patients had an incomplete ligation (10.3%) but only one suffered embolic event and 52 patients had complete ligation (89.7%) of the LAA. During follow-up period from valve replacement surgery to echocardiography study (69.4 months), 27 patients had peripheral arterial embolism (19 suffered an ischemic stroke, 3 suffered TIA, and five patients suffered peripheral embolism). They showed that ligation of the LAA during mitral valve replacement surgery conducted in a population with high-risk can aid in a reduction of the risk of late embolism. However, they insisted

that further randomized trials will validate their results. Starck et al.[33] involved 10 patients with paroxysmal AF who underwent coronary artery bypass grafting (CABG) with bilateral pulmonary vein isolation together with LAA new AtriClip occlusion device (AtriClip, Atricure Inc., West Chester, OH, USA), the clip was successfully applied without any complication, and complete electrical isolation of the LAA achieved in all 10 patients. It was an interesting observation from the AtriClip device, whereby the epicardial LAA clip occlusion leads to the electrical isolation of the LAA which offers more advantage of the device not only offering stroke prevention but also reduce the chance of AF to recur again. The following are the advantages of the AtriClip device enabled epicardial LAAC:[24] after implantation and complete closure of the LAA using AtriClip, it is not necessary to continue short-term or long-term OACs or antiplatelet treatment, therefore for those patients contraindicated to OACs can acquire benefit from this device. Periprocedural safety events, peridevice flow, and operator-dependent learning curve are in favor of surgical LAAC using clipping when compared to interventional approaches, and the AtriClip device implantation is cost-effective than interventional implantation of devices. The only two devices which can be used for minimally invasive stand-alone LAA are the stapler and the newest generation of the AtriClip. The AtriClip is available for video-assisted thoracoscopic surgery while the Stapling has been used as a clinical standard for all thoracosopic approaches.[34,35] A study conducted by Whitlock et al.[36] entitled "Left Atrial Appendage Occlusion Study II (LAAOS II)," randomized 51 patients who had AF and increased stroke risk as follows: LAAC (n = 26) versus no LAAC and no OACs (n = 25), they aim to assess recruitment rate and LAA amputation safety. After a follow-up period of 1 year, only four patients (15.4%) died, experienced MI, stroke, major bleeding, and non-cerebral systemic embolism in the LAAC side compared to five patients (20.0%) in the none occlusion side. They conclude it is safe to perform LAAC during cardiac surgery and call upon for larger trials to validate their clinical efficacy for LAAC during cardiac surgery. A study conducted by Whitlock et al.[37] (LAAOS) III (Clinical Trials.gov NCT01561651) plans to randomize 4700 patients with AF undergoing on-pump cardiac surgical procedures with or without LAAC. It will be the largest trial to provide the efficacy of LAAC for stroke prevention and the safety and efficacy of surgical LAAC will be clearly explored.

Conclusion

Different authors suggested similar conclusions regarding Watchman device implantation for NVAF patients contraindicated to OAC, as this device was suggested to be effective and safe to be implanted in the LAA despite the fact that the majority of patients were prescribed DAPT after implantation. The Watchman device was approved to be used in America, Europe, and some countries in Asia, the Middle East, and North Africa. This device is commercially available in more than 55 countries, with more than 7000 implants performed worldwide. The updated 2016 ESC Guidelines,[28] developed in collaboration with the EACTS, recommended percutaneous LAAC for patients at high stroke risk with contraindications to long-term oral anticoagulation, and surgical LAA occlusion in patients with AF undergoing cardiac surgery or thoracoscopic AF surgery (class II b, level of evidence B). Patients with a contraindication to OACs and those with a high risk of bleeding while on OACs therapy or patients who have had major bleeding while using OACs therapy are likely to benefit most from Watchman device implantation as well as a stand-alone or an adjunct surgical LAA occlusion procedure. Randomized clinical trials comparing Watchman for LAAC versus no anticoagulation therapy postprocedural are needed to balance with the worldwide expansion of Watchman device implantation for LAAC in patients contraindicated to OACs. Furthermore, future larger randomized trials are needed to provide the efficacy and safety of routine surgical LAAC to prevent stroke in patients contraindicated to OACs while undergoing cardiac surgery.

Disclosure Statement

Authors have no conflict of interest.

References

1) Fuster V, Rydén LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American college of cardiology foundation/American heart association task force on practice guidelines developed in partnership with the european society of cardiology and in collaboration with the european heart rhythm association and the heart rhythm society. J Am Coll Cardiol 2011; **57**: e101-98.
2) Huxley RR, Lopez FL, Folsom AR, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the atherosclerosis

risk in communities (ARIC) study. Circulation 2011; **123**: 1501-8.
3) European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Camm AJ, et al. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the european society of cardiology (ESC). Eur Heart J 2010; **31**: 2369-429.
4) Bai Y, Wang YL, Shantsila A, et al. The global burden of atrial fibrillation and stroke: a systematic review of the clinical epidemiology of atrial fibrillation in asia. Chest 2017; **152**: 810-20.
5) Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. JAMA 2001; **285**: 2370-5.
6) Möbius-Winkler S, Majunke N, Sandri M, et al. Percutaneous left atrial appendage closure: Technical aspects and prevention of periprocedural complications with the watchman device. World J Cardiol 2015; **7**: 65-75.
7) Reddy VY, Möbius-Winkler S, Miller MA, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA plavix feasibility study with watchman left atrial appendage closure technology). J Am Coll Cardiol 2013; **61**: 2551-6.
8) Tran H, Joseph J, Young L, et al. New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management. australasian society of thrombosis and haemostasis. Intern Med J 2014; **44**: 525-36.
9) Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996; **61**: 755-9.
10) Holmes DR, Kar S, Price MJ, 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; **64**: 1-12.
11) Reddy VY, Sievert H, Halperin J, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. JAMA 2014; **312**: 1988-98.
12) Waksman R, Pendyala LK. Overview of the Food and Drug Administration circulatory system devices panel meetings on WATCHMAN left atrial appendage closure therapy. Am J Cardiol 2015; **115**: 378-84.
13) Möbius-Winkler S, Sandri M, Mangner N, et al. The WATCHMAN left atrial appendage closure device for atrial fibrillation. J Vis Exp 2012; doi: 10.3791/3671.
14) Boersma LV, Ince H, Kische S, et al. 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.
15) Boersma LV, Schmidt B, Betts TR, et al. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. Eur Heart J 2016; **37**: 2465-74.
16) Reddy VY, Holmes D, Doshi SK, et al. 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.
17) Sharma D, Reddy VY, Sandri M, et al. Left atrial appendage closure in patients with contraindications to oral anticoagulation. J Am Coll Cardiol 2016; **67**: 2190-2.
18) Bergmann MW, Betts TR, Sievert H, et al. Safety and efficacy of early anticoagulation drug regimens after WATCHMAN left atrial appendage closure: three-month data from the EWOLUTION prospective, multicentre, monitored international WATCHMAN LAA closure registry. EuroIntervention 2017; **13**: 877-84.
19) Holmes DR, Reddy VY, Buchbinder M, et al. The assessment of the watchman device in patients unsuitable for oral anticoagulation (ASAP-TOO) trial. Am Heart J 2017; **189**: 68-74.
20) Saw J, Fahmy P, Azzalini L, et al. Early canadian multicenter experience with WATCHMAN for percutaneous left atrial appendage closure. J Cardiovasc Electrophysiol 2017; **28**: 396-401.
21) Holmes DR, Reddy VY, Turi ZG, et al. 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.
22) Bayard YL, Omran H, Neuzil P, et al. PLAATO (percutaneous left atrial appendage transcatheter occlusion) for prevention of cardioembolic stroke in-anticoagulation eligible atrial fibrillation patients: results from the European PLAATO study. EuroIntervention 2010; **6**: 220-6.
23) Holmes DR. Left Atrial Appendage Occlusion: Results & Future Predictions. San Francisco, CA: TCT, 2013.
24) Salzberg SP, Emmert MY, Caliskan E. Surgical techniques for left atrial appendage exclusion. Herzschrittmacherther Elektrophysiol 2017; **28**: 360-5.
25) Romero J, Natale A, Engstrom K, et al. Left atrial appendage isolation using percutaneous (endocardial/epicardial) devices: pre-clinical and clinical experience. Trends Cardiovasc Med 2016; **26**: 182-99.
26) Bando K, Hashimoto K. Closure of the left atrial appendage during cardiac surgery–why, when and how? Circ J 2015; **79**: 2541-3.
27) Kato TS, Iwamura T, Endo D, et al. Left atrial appendage closure reduces the incidence of postoperative cerebrovascular accident in patients undergoing cardiac surgery. Circ J 2015; **79**: 2591-7.

28) Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016; **37**: 2893-2962.
29) Kanderian AS, Gillinov AM, Pettersson GB, et al. Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. J Am Coll Cardiol 2008; **52**: 924-9.
30) Healey JS, Crystal E, Lamy A, et al. 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.
31) Katz ES, Tsiamtsiouris T, Applebaum RM, et al. Surgical left atrial appendage ligation is frequently incomplete: a transesophageal echocardiograhic study. J Am Coll Cardiol 2000; **36**: 468-71.
32) García-Fernández MA, Pérez-David E, Quiles J, et al. Role of left atrial appendage obliteration in stroke reduction in patients with mitral valve prosthesis: a transesophageal echocardiographic study. J Am Coll Cardiol 2003; **42**: 1253-8.
33) Starck CT, Steffel J, Emmert MY, et al. Epicardial left atrial appendage clip occlusion also provides the electrical isolation of the left atrial appendage. Interact Cardiovasc Thorac Surg 2012; **15**: 416-8.
34) Krul SP, Driessen AH, Zwinderman AH, et al. Navigating the mini-maze: systematic review of the first results and progress of minimally-invasive surgery in the treatment of atrial fibrillation. Int J Cardiol 2013; **166**: 132-40.
35) La Meir M, Gelsomino S, Lucà F, et al. Minimal invasive surgery for atrial fibrillation: an updated review. Europace 2013; **15**: 170-82.
36) Whitlock RP, Vincent J, Blackall MH, et al. Left atrial appendage occlusion study II (LAAOS II). Can J Cardiol 2013; **29**: 1443-7.
37) Whitlock R, Healey J, Vincent J, et al. Rationale and design of the left atrial appendage occlusion study (LAAOS) III. Ann Cardiothorac Surg 2014; **3**: 45-54.