Contemporary Cardiology
Series Editor: Christopher P. Cannon

Jacqueline Saw
Saibal Kar
Matthew J. Price *Editors*

Left Atrial Appendage Closure

Mechanical Approaches to Stroke Prevention in Atrial Fibrillation

Humana Press

Contemporary Cardiology

Christopher P. Cannon, MD
Series Editor

More information about this series at
http://www.springer.com/series/7677

Jacqueline Saw • Saibal Kar • Matthew J. Price
Editors

Left Atrial Appendage Closure

Mechanical Approaches to Stroke Prevention in Atrial Fibrillation

Humana Press

Editors
Jacqueline Saw, MD, FRCPC, FACC, FSCAI
Vancouver General Hospital
University of British Columbia
Vancouver, BC, Canada

Saibal Kar, MD, FACC
Cardiovascular Intervention Center Research
Cedars-Sinai Medical Center
Los Angeles, CA, USA

Matthew J. Price, MD, FACC, FSCAI
Division of Cardiovascular Diseases,
Scripps Clinic
Scripps Translational Science Institute
La Jolla, CA, USA

ISSN 2196-8969 ISSN 2196-8977 (electronic)
Contemporary Cardiology
ISBN 978-3-319-16279-9 ISBN 978-3-319-16280-5 (eBook)
DOI 10.1007/978-3-319-16280-5

Library of Congress Control Number: 2015952011

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Humana Press is a brand of Springer
Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Preface

Left atrial appendage (LAA) closure is a rapidly emerging field in stroke prevention for patients with atrial fibrillation. The first surgical procedure to remove the LAA was performed in 1949, and the first percutaneous LAA closure was performed in humans in 2001 with the PLAATO device. Several percutaneous and surgical devices are now approved worldwide, and many more are in clinical development and being evaluated in research trials. The current most widely used endovascular devices worldwide are the WATCHMAN and Amplatzer Cardiac Plug (Amulet, second generation) devices, which received CE Mark in 2005 and 2008, respectively. In addition, the WATCHMAN device recently received FDA approval in March 2015 in the United States for patients at high risk of stroke who are suitable for warfarin, and who have appropriate rationale for non-pharmacologic stroke prevention alternative.

Results from several early preclinical and clinical research studies have ascertained the safety and efficacy of percutaneous LAA closure in stroke prevention, including randomized controlled trials with the WATCHMAN device that showed superiority in comparison to warfarin. Further preclinical and clinical research trials and data are rapidly accumulating with this and other devices. Although these initial randomized trials evaluated patients who are candidates for oral anticoagulation, the current predominant real-world application for this procedure is mostly restricted to patients who have contraindications to anticoagulation. Even this restricted indication has substantial implications on application of this procedure, since over 40 % of patients with atrial fibrillation who have guideline indications for anticoagulation are not on anticoagulation because of contraindications, intolerance, or were felt to be poor candidates for anticoagulation. Broader application to patients without these restrictions is anticipated as this procedure and technology matures, and further clinical trial data becomes available. Thus, LAA closure has evolved to become an important alternative to oral anticoagulation in patients with atrial fibrillation and is expected to remain a dominant technology for stroke prevention with this prevalent arrhythmia.

LAA closure is a technically challenging procedure with both percutaneous and surgical approaches. Advancement in technology and procedural techniques has improved the safety and efficacy of LAA closure. Detailed knowledge of the rationale, anatomy, and technical approach of this procedure guides operators in patient selection and facilitates procedural success. Our textbook provides a comprehensive overview of the current state-of-the-art LAA closure, covering the background epidemiology of atrial fibrillation and stroke, the LAA anatomy, imaging of LAA, and the LAA closure procedure. Modern devices, characteristics, procedural techniques, complications, and contemporary study results on LAA closure are reviewed in detail in dedicated focused chapters according to the different devices. Novel devices in development, procedural complications, post-procedural antithrombotic therapy, and long-term post-closure surveillance are also reviewed.

This textbook is targeted to all medical staffs involved with LAA closure procedures, including those learning to perform the procedure, those who provide imaging guidance for the procedure, and those managing patients during and after the procedure. Thus, interventional cardiologists, electrophysiologists, echocardiographers, radiographers, nurse practitioners, nurses, fellows, and residents should find this textbook to be a useful resource to guide management of patients prior to, during, and following LAA closure.

Vancouver, BC, Canada — Jacqueline Saw, MD, FRCPC, FACC, FSCAI
Los Angeles, CA, USA — Saibal Kar, MD, FACC
La Jolla, CA, USA — Matthew J. Price, MD, FACC, FSCAI

Contents

Contributors

Nitish Badhwar, MD Cardiovascular Division, University of California San Francisco, San Francisco, CA, USA

Sergio Berti, MD, FESC Ospedale del Cuore, Fondazione C.N.R. Reg. Toscana G. Monasterio, Massa, Italy

Stefan Bertog, MD CardioVascular Center Frankfurt, Frankfurt, Germany

Minnesota Veterans Affairs Medical Center, Minneapolis, MN, USA

Hiram G. Bezerra, MD Division of Cardiology, University Hospital, Cleveland, OH, USA

John A. Cairns, MD, FRCPC, FACC GLD Health Care Centre, University of British Columbia, Vancouver, BC, Canada

Ivan P. Casserly, MB BCh Mater Misericordiae Hospital and Mater Private Hospital, Dublin, Ireland

Andrew C. Cook, BSc, PhD University College London, Institute of Cardiovascular Science, London, UK

Creighton W. Don, MD, PhD Department of Medicine, University of Washington, Seattle, WA, USA

Gaetano Fassini, MD Department of Cardiovascular Sciences, Centro Cardiologico Monzino, Cardiac Arrhythmia Research Center, University of Milan, Milan, Italy

Jennifer Franke, MD CardioVascular Center Frankfurt, Frankfurt, Germany

University of Heidelberg, Heidelberg, Germany

Xavier Freixa, MD Department of Cardiology, Thorax Unit, Hospital Clinic of Barcelona, University of Barcelona, Barcelona, Spain

Sameer Gafoor, MD CardioVascular Center Frankfurt, Frankfurt, Germany

Swedish Heart and Vascular, Seattle, WA, USA

Sampath Gunda, MD Department of Cardiology, University of Kansas Hospitals and Medical Center, Kansas City, KS, USA

Hasib Hanif, MD Department of Cardiac Surgery, Hamilton General Hospital, Hamilton, ON, Canada

Luisa Heuer, BA CardioVascular Center Frankfurt, Frankfurt, Germany

Ilona Hofmann, MD CardioVascular Center Frankfurt, Frankfurt, Germany

Julie A. Humphries, MBBS, FRACP, FCSANZ, FASE HeartCare Partners, Ramsay Specialist Centre, Greenslopes Private Hospital, Greenslopes, Brisbane, QLD, Australia

Reda Ibrahim, MD Medical Intensive Care Unit and Structural Heart Program, Department of Medicine, Montreal Heart Institute, Montreal, QC, Canada

Prapa Kanagaratnam, MB BChir, PhD Department of Cardiology, Imperial College Healthcare NHS Trust, London, UK

Arun Kanmanthareddy, MD, MS Cardiovascular Division, Creighton University School of Medicine, Omaha, NE, USA

Saibal Kar, MD, FACC Cardiovascular Intervention Center Research, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Dhanunjaya Lakkireddy, MD, FACC, FHRS Center for Excellence in Atrial Fibrillation & Electrophysiology Research, Bloch Heart Rhythm Center, Mid America Cardiology, KU Cardiovascular Research Institute, University of Kansas Hospital and Medical Center, Kansas City, KS, USA

Randall J. Lee, MD, PhD University of California, San Francisco, San Francisco, CA, USA

Joao Pedro Lopes, MD Division of Cardiology, University Hospital, Cleveland, OH, USA

Louisa Malcolme-Lawes, MB ChB, PhD Department of Cardiology, Imperial College Healthcare NHS Trust, London, UK

David Meerkin, MB BS Structural and Congenital Heart Disease Unit, Shaare Zedek Medical Center, Jerusalem, Israel

Bernhard Meier, MD Department of Cardiology, University Hospital Bern, Bern, Switzerland

Fabian Nietlispach, MD Department of Cardiology, University Hospital Bern, Inselspital, Bern, Switzerland

Department of Cardiology, University Heart Center, Zurich, Switzerland

Umberto Paradossi, MD, FESC Fondazione Toscana G. Monasterio, Pisa, Italy

Karen P. Phillips, MB BS Cardiac Catheterisation Laboratory, Cardiac Electrophysiologist HeartCare Partners, Greenslopes Private Hospital, Brisbane, QLD, Australia

Ramsay Specialist Centre, Greenslopes, Brisbane, QLD, Australia

Matthew J. Price, MD, FACC, FSCAI Division of Cardiovascular Diseases, Scripps Clinic, Scripps Translational Science Institute, La Jolla, CA, USA

Markus Reinartz, MD CardioVascular Center Frankfurt, Frankfurt, Germany

Mark Reisman, MD Department of Medicine, University of Washington, Seattle, WA, USA

University of Washington Medical Center, Seattle, WA, USA

Gennaro Santoro, MD Azienda Ospedaliero Universitaria Careggi, Firenze, Italy

Jacqueline Saw, MD, FRCPC, FACC, FSCAI Vancouver General Hospital, University of British Columbia, Vancouver, BC, Canada

Horst Sievert, MD CardioVascular Center Frankfurt, Frankfurt, Germany

Claudio Tondo, MD, PhD Department of Cardiovascular Sciences, Centro Cardiologico Monzino, Cardiac Arrhythmia Research Center, University of Milan, Milan, Italy

Apostolos Tzikas, MD, PhD Department of Cardiology, AHEPA University Hospital, Thessaloniki, Greece

Miguel Valderrábano, MD, FACC Department of Medicine, Weill College of Medicine, Cornell University, New York, NY, USA

Baylor College of Medicine, Houston, TX, USA

Division of Cardiac Electrophysiology, Department of Cardiology, Houston Methodist Hospital, Houston, TX, USA

Laura Vaskelyte, MD CardioVascular Center Frankfurt, Frankfurt, Germany

Kevin Walsh, MB BCh Mater Misericordiae Hospital and Mater Private Hospital, Dublin, Ireland

Richard Whitlock, MD, PhD Department of Cardiac Surgery, Hamilton General Hospital, Hamilton, ON, Canada

Part I
Rationale for LAA Closure

Chapter 1
Atrial Fibrillation and Stroke Epidemiology

Karen P. Phillips

Abbreviations

AF Atrial fibrillation
TIA Transient ischaemic attack

Atrial Fibrillation Prevalence, Incidence and Global Burden

Atrial fibrillation (AF) is a cardiac arrhythmia characterised by chaotic electrical activity and ineffective contraction of the atrial chambers of the heart, which results in irregularly irregular ventricular contractions [1]. It is strongly associated with structural heart disease and other chronic co-morbid cardiovascular conditions [1, 2] and is an independent risk factor for death [3].

Atrial Fibrillation Incidence and Prevalence

The incidence and prevalence of AF increases substantially with age. Several large population studies have examined the incidence and prevalence of AF worldwide. The Rotterdam Study prospectively followed for a decade over 6800 Northern

K.P. Phillips, M.B.B.S. (✉)
Cardiac Catheterisation Laboratory, Cardiac Electrophysiologist HeartCare Partners, Greenslopes Private Hospital, Newdegate Street, Greenslopes, Brisbane, QLD 4120, Australia

Suite 212, Ramsay Specialist Centre, Newdegate Street, Greenslopes, Brisbane, QLD 4120, Australia
e-mail: kphillips@hearcarepartners.com.au

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_1

European subjects aged 55 years or older between 1990 and 1999 [4]. The overall prevalence was 5.5 % (6.0 % in men and 5.1 % in women). Prevalence increased with each age stratum from 0.7 % in 55–60 year olds to 17.8 % in those aged 85 years or above. A steep increase in incidence was also noted with age from 1.1/1000 person-years at ages 55–60 to 20.7/1000 person-years in age group 80–85 years. The estimated lifetime risk of developing AF at the age of 55 years was 23.8 % for men and 22.2 % for women. The Framingham Heart Study estimated similar lifetime risk for a North American population in 2004—at age 40 years; lifetime risks for AF were 26.0 % for men and 23 % for women [5].

A community study in Iceland found even higher prevalence rates among the advanced age groups sampled between 2006 and 2008 with a prevalence of 27.5 % for men aged 85–99 years and 17.5 % for women [6].

The American population prevalence was assessed in the ATRIA study in 1997 using health insurance data on 1.89 million adults [7]. The prevalence was 0.1 % among age groups younger than 55 years, 0.5 % for ages 50–59 years and increased to 9.1 % for the age group 85 years and older. The overall prevalence for the adult population aged 20 years or older was 0.95 %. The prevalence of AF was lower for African Americans than Caucasians in patients aged 50 years or older (1.5 % vs. 2.2 % $p<0.001$).

A lower prevalence of AF than Western Caucasian populations has been documented for several Asian countries. A Japanese study in 2006 found prevalence rates of 0.2 % for 40–59 year age groups and 2.8 % for those aged 80 years or older [8]. A Korean population study in 2004 found rates of 0.3 % in ages 40–59 years and 4 % in those aged 80 years or more [9].

Consistent differences in prevalence according to gender have been documented in all ethnicities across different population studies with men having a higher prevalence at all age groups [4–9].

Rising Prevalence and Global Burden of AF

Several studies have pointed to a trend in rising prevalence of AF [6, 7, 10, 11]. Population data from the United Kingdom found an increase in the overall prevalence in the adult population over a decade time frame. Between 1994 and 2003, overall prevalence rates for men rose from 0.78 to 1.3 % and in women from 0.79 to 1.15 %. Increasing prevalence was also found in Iceland with age- and sex-standardised prevalence increasing from 1.5 % in 1998 to 1.9 % in 2008 [6]. This is a worldwide phenomenon based on findings from the Global Burden of Disease Study in 2010 [12]. Worldwide AF prevalence rates increased by 5 % for men and 4 % for women between 1990 and 2010, while incidence rates increased by 28 % for men and 35 % for women over the 20-year period. The increases were disproportionately higher for developed countries as compared with developing nations. Proposed factors contributing to the rising prevalence of AF, even after adjusting

for age, include the effect of attributable risk factors such as hypertension and obesity [12].

Based on prevalence modelling estimates, the numbers of individuals with AF are projected to reach 15.9 million in the USA by 2050 [10] and 17.9 million people in the European Union by 2060 [13].

Atrial Fibrillation and the Risk of Stroke

AF is independently associated with an increased risk of ischaemic stroke [14]. Significant differences are apparent between the risk of stroke conferred by rheumatic mitral valve disease and other etiologies of AF in the general population (termed 'nonvalvular AF').

Rheumatic Valvular Heart Disease and the Risk of Stroke

Rheumatic mitral valve disease confers a particularly high lifetime incidence of cardioembolic stroke (approximately 1 in 5) [15, 16]. While the risk of stroke is increased fivefold [14] for nonvalvular AF, the risk of stroke with rheumatic mitral valve disease is increased 17-fold over the general population [17]. As distinct from the general nonvalvular AF population, stroke related to rheumatic valvular disease:

- Commonly occurs in patients from their third or fourth decade of life [16, 18]
- Confers a 31 % risk of stroke when associated with atrial fibrillation [18]
- Confers a 8 % risk of stroke even for patients in sinus rhythm without documented atrial fibrillation [18]
- Is associated with evidence for more generalised left atrial thrombogenicity [19, 20] and intracavitary left atrial thrombus formation [21, 22]

Current guidelines recommend oral anticoagulation for all patients with rheumatic mitral valve disease and AF [23] and recommend that consideration be given to anticoagulation in high-risk patients with severely enlarged left atrium even in the absence of AF [24].

Nonvalvular Atrial Fibrillation and the Risk of Stroke

AF was found to be an independent risk factor for stroke and death in the Framingham Heart Study [14, 25]. However, the risk of stroke is not homogeneous in the general population with stroke rates varying from less than 2 % to more than

18 % in subpopulations [26]. A large number of studies have since examined the attributable risk of various clinical, demographic and echocardiographic patient characteristics.

The strongest predictor of AF-related stroke is a prior history of stroke, transient ischaemic attack (TIA) or systemic embolism with a hazard ratio varying between 1.6 and 4.1 across multiple studies [27–30].

Increasing age over 65 years is also strongly correlated with incremental stroke risk [31]. Multiple studies identified incremental risk with age, with the risk increasing by a factor of approximately 1.4 per decade of life [32]. Age greater than 75 years has been identified as a significant risk factor per se for stroke with a hazard ratio of 1.72 [33].

Female gender has also been identified in multiple studies to increase the risk of AF-related stroke. In the large prospective ATRIA study involving 13,559 patients, female gender was associated with a hazard ratio of 1.6 for stroke [34].

History of hypertension (controlled or uncontrolled) [27, 33] with a hazard ratio of 1.6 and diabetes mellitus [35] have also been identified as an independent risk factors. The presence of vascular disease including peripheral arterial disease, coronary artery disease, myocardial infarction and complex aortic plaque also predicts a higher risk of AF-related stroke [36–38].

Structural heart disease has long been recognised to be associated with an increased risk of stroke in the AF population. Associations have been found with the presence of left ventricular hypertrophy in some smaller studies [29]. Recent congestive cardiac failure episode and/or moderate to severe left ventricular systolic dysfunction have been shown in large population studies to mediate increased stroke risk [29, 39].

Importantly, AF subtype or pattern of arrhythmia has *not* been shown to be a significant independent predictor of stroke. Paroxysmal or spontaneously intermittent occurring patterns of arrhythmia appear to confer similar risk to persistent or chronic patterns of atrial fibrillation [40, 41].

Some echocardiographic predictors of increased stroke risk are also recognised and appear to be indicators of a prothrombotic state in the left atrium. Transesophageal findings of low left atrial appendage ejection velocities $\leq$20 cm/s (hazard ratio of 1.7), spontaneous echo-contrast in the left atrium (hazard ratio 3.7) and the presence of left atrial thrombus (hazard ratio 2.5) are all independent predictors of subsequent stroke and thromboembolism [38].

Clinical Risk Stratification for Stroke Prediction

The heterogeneous risk of ischaemic stroke was recognised in early clinical trials of antithrombotic therapy in AF. Stroke risk classification schemes were proposed by the Atrial Fibrillation Investigators (AFI) [32] and by the Stroke prevention in Atrial Fibrillation (SPAF) Investigators [42].

$CHADS_2$ Index

A new simplified stroke risk index '$CHADS_2$' was developed in 2001 and shown to be an accurate predictor of increasing stroke risk with clinical validation [26]. The index included five documented independent risk factors but assigned a greater importance to prior history of stroke or TIA due to its predictive power. The index assigned 1 point for history of recent congestive heart failure exacerbation (**C**), 1 point for history of hypertension (**H**), 1 point for age ≥75 years (**A**), 1 point for diabetes mellitus (**D**) and 2 points for prior history of stroke or TIA ($\mathbf{S_2}$). The observed stroke rate for patients not taking antithrombotic therapy increased by a factor of 1.5 for each 1 point increase in the $CHADS_2$ score. The adjusted stroke rate per 100 patient-years varied from 1.9 in $CHADS_2$ score 0 to 18.2 in $CHADS_2$ score 6 (see Table 1.1). The $CHADS_2$ score was quickly incorporated into new 2006 Clinical Guidelines for Management of Atrial Fibrillation around the world as a useful tool

Table 1.1 $CHADS_2$ stroke risk index

$CHADS_2$ risk criteria		Score
Prior stroke or TIA		2
Age >75 years		1
Hypertension		1
Diabetes mellitus		1
Heart failure		1
Patients ($N=1733$)	Adjusted stroke rate (%/y)[a] (95% CI)	$CHADS_2$ score
120	1.9 (12–3.0)	0
463	2.8 (2.0–3.8)	1
523	4.0 (3.1–5.1)	2
337	5.9 (4.6–7.3)	3
220	8.5 (6.3–11.1)	4
65	12.5 (8.2–17.5)	5
5	18.2(10.5–27.4)	6

[a]The adjusted stroke rate was derived from multivariate analysis assuming no aspirin usage. Data are from van Walraven WC, Hart RG, Wells GA, et al. A clinical prediction rule to identify patients with atrial fibrillation and a low risk for stroke while taking aspirin. *Arch intern Med* 2003; 163:936–43 [44]; and Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001; 285:2864–70 [45]

AF indicates atrial fibrillation, *$CHADS_2$* Cardiac Failure, Hypertension, Age, Diabetes and Stroke (Doubled), *CI* confidence interval, *TIA* transient ischaemic attack

Reprinted from Eur Heart J, Vol. 27, Fuster V et al, ACC/AHA/ESC 2006 Guidelines 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 European Society of Cardiology Committee for Practice Guidelines, Pages:1979–2030, Copyright (2006), with permission from Oxford University Press

for guiding decision making on stroke prophylaxis therapy [43]. Stroke risk was arbitrarily classified by $CHADS_2$ score as low risk for a score of 0, intermediate or moderate risk for a score of 1 and high risk for a score ≥2. Oral anticoagulation was recommended for patients with 'high risk' factor of previous stroke, TIA or systemic embolism and if more than 1 'moderate risk' factor (including age ≥75 years, hypertension, diabetes, heart failure or LVEF ≤35 %) was present [43].

CHA_2DS_2-VASc Score

Several studies on oral anticoagulation established the clinical benefit of warfarin anticoagulation over aspirin in patients at apparent intermediate risk of AF-related stroke and subsequently set the benchmark that under-treatment with oral anticoagulation was more harmful than overtreatment [44, 45]. In this context, the extended CHA_2DS_2-VASc score stroke risk index was developed by the Euro Heart Survey on AF which appeared to better differentiate truly low risk subjects who may not need antithrombotic therapy [46]. The CHA_2DS_2-VASc schema incorporated other known independent risk factors including the impact of female gender, documented vascular disease and the incremental risk per decade of age from age 65 years. The score allocates 2 points to high-risk factors of prior history of stroke, TIA or systemic embolism and also to age ≥75 years, with 1 point allocated to other risk factors. With clinical validation, the adjusted stroke rate per 100 patient-years ranged from 0 for CHA_2DS_2-VASc score of 0 to 15.2 in CHA_2DS_2-VASc score of 9 (see Table 1.2). The CHA_2DS_2-VASc score was incorporated into revised clinical guidelines for the management of AF from 2010 [47].

HAS-BLED Bleeding Risk Score

Despite evidence from randomised trials for the benefit of oral anticoagulation for at-risk patients with AF, multiple studies have shown that warfarin is prescribed in only about half of appropriate patients [48]. The risk of bleeding due to anticoagulation is cited among the most common concerns of physicians and the reasons for under-prescription [49]. A novel bleeding risk score was developed from multivariate analysis of a large number of European patients studied in the Euro Heart Survey on AF to better quantify bleeding risk in this population. The HAS-BLED score has been shown to have good predictive accuracy with a score of ≥3 associated with a high risk of major bleeding per 100 patient-years [50]. The score allocates 1 point each to risk factors shown to independently increase the 1 year risk of major bleeding events (defined as including intracranial, requiring hospitalisation, haemoglobin decrease >2 g/L and/or transfusion requirement). The risk factors include (**H**) uncontrolled hypertension (systolic >160 mmHg), (**A**) 1 point each allocated for abnormal liver or renal function, (**S**) prior history of stroke, (**B**) previous bleeding history or predisposition to bleeding, (**L**) labile INRs including unstable/high INRs or poor time in the

Table 1.2 CHA_2DS_2-VASc score and stroke risk

(a) Risk factors for stroke and thromboembolism in nonvalvular AF	
'Major' risk factors	'Clinically relevant non-major' risk factors
Previous stroke, TIA or systemic embolism Age ≥75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤ 40%)
	Hypertension—Diabetes mellitus Female sex—Age 65–74 years: Vascular disease[1]

(b) Risk factor-based approach expressed as a point-based scoring; system, with the acronym CHA_1DS_2-VASc (Note: maximum score is 9 since age may contribute 0,1 or 2 points)	
Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	9

(c) Adjusted stroke rate according to CHA_2DS_1-VASc score

CHA_1DS_1-VASc score	Patients ($n = 7329$)	Adjusted stroke rate (%/yr)
0	1	0
1	422	1.3
2	1230	2.2
3	1730	3.2
4	1718	4.0
5	1159	6.7
6	679	9.8
7	294	9.6
8	82	6.7
9	14	15.2

See text for definitions

[a]Prior myocardial infection, peripheral artery disease, a critic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates

[1]Based on Lip et al.

AF artrial fibrillation, *EF* ejection fraction (as documented by echocardiography, radionuclide ventriculography, cardiac catheterization, cardiac magnetic resonance imaging), *LV* left ventricular, *TIA* transient ischaemic attack

therapeutic range, (**E**) elderly (age >65 years) and (**D**) drugs/alcohol concomitantly which allows for 1 point for concomitant use of drugs which increase bleeding risk, e.g. antiplatelet agents or non-steroidal anti-inflammatory drugs and 1 point for alcohol abuse (see Table 1.3). The HAS-BLED score was incorporated into revised clinical guidelines for the management of AF from 2010 [47].

Table 1.3 HAS-BLED bleeding risk score

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

[a]'Hypertension' is defined as systolic blood pressure >160 mmHg. 'Abnormal kidney function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 μmol/L. 'Abnormal liver function' is defined as chronic hepatic disease (e. g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 × upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 × upper limit normal). 'Bleeding' refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia. 'Labile INRs' refer to unstable/high INRs or poor time in therapeutic range (e.g. <60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drug or alcohol abuse.
INR International normalised ratio
Reprinted from Eur Heart J, Vol. 31, Reprinted from The Lancet, Vol. 374, 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). Pages 2369–2429., Copyright (2010), with permission from Oxford University Press
Adapted from Pisters et al. [60]

Severity of AF-Related Stroke

Data from the Framingham Study showed that AF-related stroke was associated with increased stroke severity, poorer survival, greater disability among survivors and a higher recurrence rate of stroke as compared with other etiologies [51]. Other population studies have confirmed these findings.

The North Dublin Population Stroke Study found that AF was associated with a higher frequency of total and partial anterior circulation infarct syndromes and greater acute stroke severity, which mediated poorer functional incomes and greater disability at 90 days than non-AF strokes [52]. The Framingham Study found that by 3 months after stroke, 75 % of AF subjects remained moderately or severely dependent in ADLs (activities of daily living) [51].

AF-related stroke is also associated with higher mortality rates—the Framingham Study found a 30-day mortality of 25 % vs. 14 % for non-AF stroke and 1-year mortality of 63 % compared with 34 % for non-AF subjects. Similar findings were reported by an Italian population-based study with 32.5 % (vs. 16.2 % for non-AF) 30-day mortality and 49.5 % (vs. 27.1 % for non-AF) 1-year case fatality rates [53].

A large Japanese multicentre stroke study (J-MUSIC) published in 2005 which included data on thrombolytic therapy for superacute phase ischaemic stroke

treatment also found a significantly higher 28-day mortality rate for AF-related stroke (11.3 %) than non-AF (3.4 %) [54]. During the study, 7.3 % of the AF group and 1.3 % of the non-AF group received thrombolytic therapy. Longer hospital stays were recorded in AF patients (mean 40.5 days) as compared with non-AF (mean 35.3 days). Stroke severity scores were significantly higher than in the non-AF group. After hospital discharge, 66.4 % of non-AF patients returned to their homes, whereas only 45.1 % of AF patients returned home and 54.9 % were sent to an institution for care.

One-year recurrence rates were also higher for AF-related stroke in The Framingham Study at 23 % vs. 8 % for non-AF [51], and in the Italian Registry 6.9 % vs. 4.7 % for non-AF [53], although the rates of anticoagulation following the initial stroke are not known for the relative studies.

It is also notable that AF is associated with a higher likelihood of presentation with intracerebral or intracranial haemorrhage—including spontaneous as well as associated with prescribed antithrombotic therapy. In the North Dublin Study, 9 % of all AF-associated strokes were hemorrhagic with an equal distribution occurring spontaneously and in patients on oral anticoagulation [52]. This observation was also confirmed by a recent USA Health Insurance Database analysis which found higher rates of intracerebral and intracranial haemorrhage in AF cohorts presenting with stroke [55]. Rates of anticoagulation at the time of stroke were 43.5 % for the AF cohort [55].

The Economic Cost of AF-Related Stroke

The economic implications of AF stroke-related healthcare costs have been assessed in various studies around the world. The results from a 3-year Swedish Stroke Registry found that 3-year inpatient costs (including hospitalisation for index stroke and any stroke-related hospitalisation events including recurrent stroke) was 10,192 € for AF patients who survived the index stroke compared with 9374 € for non-AF subjects based on 2001 prices (exchange rate = US$0.90) [56]. Length of stay for the index event was longer in AF patients 22.4 days vs. 20.9 days for non-AF. A higher re-stroke rate was observed over the 3-year period for AF at 15 % vs. 13 % for non-AF. Patients with AF age <65 years were noted to generate significantly higher hospital costs (on average 4412 € higher) than similarly younger patients without AF—the difference in cost was noted to decrease with advancing age.

The Berlin Acute Stroke Study published data relating to AF—stroke-related use of all medical resources over a 12-month period (inpatient and outpatient) as well as indirect costs which included lost work productivity [57]. The findings showed that AF acute stroke patients consumed more medical resources than non-AF patients over the initial 12-month period 11,799 € vs. 8817 € based on 2005 prices (exchange rate = US$1.32), driven primarily by longer lengths of hospital stay and increased use of home nursing care. Indirect costs due to lost productivity from work absenteeism or early retirement were higher for the non-AF group, which was explained

by the younger average age and higher employment rates 63.9 years of age with 30 % gainfully employed, as compared with the average age of AF patients 73.7 years and only 3 % employment rate.

A more recent retrospective analysis of a large health insurance database in the USA over a 5-year period from 2006 to 2011 found that AF patients had significantly higher rates of not only ischaemic stroke but also intracerebral and intracranial haemorrhage and conversely presented with significantly lower rates of TIA than the non-AF cohort [55]. At index stroke presentation, 43.5 % of the AF patients were on oral anticoagulants. AF patients had longer index hospitalisation for ischaemic stroke than non-AF (8.3 vs. 7.9 days) but the opposite was found for hemorrhagic stroke (10.7 vs. 14.1 days). The mean adjusted 12-month cost of stroke-related healthcare was higher for AF $13,581 vs. non-AF $11,718 and included all inpatient, outpatient, rehabilitation, medical equipment, home healthcare, laboratory and pharmacy costs.

The Impact of Thromboprophylaxis

Meta-analyses have demonstrated that oral anticoagulation with warfarin reduces stroke risk in nonvalvular AF by approximately 60 % [44] but is associated with a small but significant risk of bleeding complications. Reduced stroke severity, improved survival and improved functional outcomes are also documented benefits of therapeutic oral anticoagulation in patients who unfortunately sustain a stroke while prescribed thromboprophylaxis [58]. The cost-effectiveness of warfarin for improving quality-adjusted survival in AF has been previously demonstrated for patients with nonvalvular AF and at least one risk factor for stroke [59].

Overall stroke mortality (AF and non-AF) has been declining since the early twentieth century due to both reduced stroke incidence and lower case-fatality rates [60]. Evidence from observational studies points to the impact of increased warfarin use in reducing incident AF-related stroke rates, especially over the past two decades [11, 60].

Economic Modelling and the Burgeoning AF Burden

The implications of the significantly higher prevalence of AF with advanced age combined with the ageing population phenomenon in most developed countries are clear for healthcare economists. The percentage of the world population aged 65 years and older increased from 6.2 % in 1990 to 6.9 % in 2000 to 7.7 % in 2010 and is expected to reach 16.1 % by 2050 [12]. Population ageing will be associated with a burgeoning number of people living with AF and the challenges of managing the attributable healthcare costs.

Conclusion

AF- related stroke is associated with increased stroke severity, poorer survival, greater disability among survivors and a higher recurrence rate of stroke as compared with other etiologies. The costs associated with stroke-related healthcare are higher for AF than non-AF subjects. The incidence and prevalence of AF increase substantially with age, and the rates are substantially higher in developed nations with populations of European descent. Further, a global trend in rising prevalence of AF has been demonstrated in recent decades. The challenges posed by the growing global burden of AF will need to be met by strategies to better prevent the major associated morbidity and mortality of AF-related stroke.

References

1. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland Jr JC, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 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. Circulation. 2014;130(23):2071–104.
2. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham Study. N Engl J Med. 1982;306(17):1018–22.
3. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med. 2002;113(5):359–64.
4. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, Stijnen T, Lip GY, Witteman JC. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam Study. Eur Heart J. 2006;27(8):949–53.
5. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation. 2004;110(9):1042–6.
6. Stefansdottir H, Aspelund T, Gudnason V, Arnar DO. Trends in the incidence and prevalence of atrial fibrillation in Iceland and future projections. Europace. 2011;13(8):1110–7.
7. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. 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(18):2370–5.
8. Iguchi Y, Kimura K, Aoki J, Kobayashi K, Terasawa Y, Sakai K, Shibazaki K. Prevalence of atrial fibrillation in community-dwelling Japanese aged 40 years or older in Japan: analysis of 41,436 non-employee residents in Kurashiki-city. Circ J. 2008;72(6):909–13.
9. Jeong JH. Prevalence of and risk factors for atrial fibrillation in Korean adults older than 40 years. J Korean Med Sci. 2005;20(1):26–30.
10. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006;114(2):119–25.
11. DeWilde S, Carey IM, Emmas C, Richards N, Cook DG. Trends in the prevalence of diagnosed atrial fibrillation, its treatment with anticoagulation and predictors of such treatment in UK primary care. Heart. 2006;92(8):1064–70.

12. Chugh SS, Roth GA, Gillum RF, Mensah GA. Global burden of atrial fibrillation in developed and developing nations. Glob Heart. 2014;9(1):113–9.
13. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, Witteman JC, Stricker BH, Heeringa J. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. Eur Heart J. 2013;34(35):2746–51.
14. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22:983–8.
15. Salem DN, Stein PD, Al-Ahmad A, Bussey HI, Horstkotte D, Miller N, Pauker SG. Antithrombotic therapy in valvular heart disease—native and prosthetic: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(3 Suppl):457S–82.
16. Szekely P. Systemic embolism and anticoagulant prophylaxis in rheumatic heart disease. Br Med J. 1964;1(5392):1209–12.
17. Wolf PA, Dawber TR, Thomas Jr HE, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham Study. Neurology. 1978;28(10):973–7.
18. Coulshed N, Epstein EJ, McKendrick CS, Galloway RW, Walker E. Systemic embolism in mitral valve disease. Br Heart J. 1970;32(1):26–34.
19. Yamamoto K, Ikeda U, Seino Y, Mito H, Fujikawa H, Sekiguchi H, Shimada K. Coagulation activity is increased in the left atrium of patients with mitral stenosis. J Am Coll Cardiol. 1995;25(1):107–12.
20. Yetkin E, Erbay AR, Turhan H, Ileri M, Ayaz S, Atak R, Senen K, Cehreli S. Decreased platelet activation and endothelial dysfunction after percutaneous mitral balloon valvuloplasty. Int J Cardiol. 2003;91(2–3):221–5.
21. Kaymaz C, Ozdemir N, Kirma C, Sişmanoglu M, Daglar B, Ozkan M. Location, size and morphological characteristics of left atrial thrombi as assessed by echocardiography in patients with rheumatic mitral valve disease. Eur J Echocardiogr. 2001;2(4):270–6.
22. Acar J, Cormier B, Grimberg D, Kawthekar G, Iung B, Scheuer B, Farah E. Diagnosis of left atrial thrombi in mitral stenosis—usefulness of ultrasound techniques compared with other methods. Eur Heart J. 1991;12(Suppl B):70–6.
23. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin 3rd JP, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt 3rd TM, Thomas JD, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Creager MA, Curtis LH, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Stevenson WG, Yancy CW. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(23):2440–692.
24. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MS, Fornage M, Goldstein LB, Greenberg SM, Horvath SE, Iadecola C, Jauch EC, Moore WS, Wilson JA. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the american heart association/american stroke association. Stroke. 2014;45(12):3754–832.
25. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation. 1998;98(10):946–52.
26. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285(22):2864–70.
27. Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. Stroke. 1999;30(6):1223–9.
28. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. J Am Coll Cardiol. 2000;35(1):183–7.
29. Aronow WS, Ahn C, Kronzon I, Gutstein H. Risk factors for new thromboembolic stroke in patients>or=62 years of age with chronic atrial fibrillation. Am J Cardiol. 1998;82(1): 119–21.

30. van Latum JC, Koudstaal PJ, Venables GS, van Gijn J, Kappelle LJ, Algra A. Predictors of major vascular events in patients with a transient ischemic attack or minor ischemic stroke and with nonrheumatic atrial fibrillation. European Atrial Fibrillation Trial (EAFT) Study Group. Stroke. 1995;26(5):801–6.
31. Hughes M, Lip GY. Stroke and thromboembolism in atrial fibrillation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. Thromb Haemost. 2008;99(2):295–304.
32. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med. 1994;154(13):1449–1457.
33. Moulton AW, Singer DE, Haas JS. Risk factors for stroke in patients with nonrheumatic atrial fibrillation: a case-control study. Am J Med. 1991;91(2):156–61.
34. Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG, Go AS. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. Circulation. 2005;112(12):1687–91.
35. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. JAMA. 2003;290(8):1049–56.
36. Schmitt J, Duray G, Gersh BJ, Hohnloser SH. Atrial fibrillation in acute myocardial infarction: a systematic review of the incidence, clinical features and prognostic implications. Eur Heart J. 2009;30(9):1038–45.
37. Conway DS, Lip GY. Comparison of outcomes of patients with symptomatic peripheral artery disease with and without atrial fibrillation (the West Birmingham Atrial Fibrillation Project). Am J Cardiol. 2004;93(11):1422–5.
38. Zabalgoitia M, Halperin JL, Pearce LA, Blackshear JL, Asinger RW, Hart RG. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. Stroke Prevention in Atrial Fibrillation III Investigators. J Am Coll Cardiol. 1998;31(7):1622–6.
39. Predictors of thromboembolism in atrial fibrillation: I. Clinical features of patients at risk. The Stroke prevention in Atrial Fibrillation Investigators. Ann Intern Med. 1992;116(1):1–5.
40. Stöllberger C, Chnupa P, Abzieher C, Länger T, Finsterer J, Klem I, Hartl E, Wehinger C, Schneider B. Mortality and rate of stroke or embolism in atrial fibrillation during long-term follow-up in the embolism in left atrial thrombi (ELAT) study. Clin Cardiol. 2004;27(1):40–6.
41. Cabin HS, Clubb KS, Hall C, Perlmutter RA, Feinstein AR. Risk for systemic embolization of atrial fibrillation without mitral stenosis. Am J Cardiol. 1990;65(16):1112–6.
42. Patients with nonvalvular atrial fibrillation at low risk of stroke during treatment with aspirin: Stroke Prevention in Atrial Fibrillation III Study. The SPAF III Writing Committee for the Stroke Prevention in Atrial Fibrillation Investigators. JAMA. 1998;279(16):1273–1277
43. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith Jr SC, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JLS. ACC/AHA/ESC 2006 Guidelines 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 European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006;114(7):e257–354.
44. 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(12):857–67.
45. Nieuwlaat R, Olsson SB, Lip GY, Camm AJ, Breithardt G, Capucci A, Meeder JG, Prins MH, Lévy S, Crijns HJ, Euro Heart Survey Investigators. Guideline-adherent antithrombotic treatment is associated with improved outcomes compared with undertreatment in high-risk

patients with atrial fibrillation. The Euro Heart Survey on Atrial Fibrillation. Am Heart J. 2007;153(6):1006–112.
46. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263–72.
47. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. 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(19):2369–429.
48. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med. 2010;123(7):638–45.
49. Pugh D, Pugh J, Mead GE. Attitudes of physicians regarding anticoagulation for atrial fibrillation: a systematic review. Age Ageing. 2011;40(6):675–83.
50. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138(5):1093–100.
51. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, D'Agostino RB. Stroke severity in atrial fibrillation. The Framingham Study. Stroke. 1996;27(10):1760–4.
52. Hannon N, Sheehan O, Kelly L, Marnane M, Merwick A, Moore A, Kyne L, Duggan J, Moroney J, McCormack PM, Daly L, Fitz-Simon N, Harris D, Horgan G, Williams EB, Furie KL, Kelly PJ. Stroke associated with atrial fibrillation—incidence and early outcomes in the north Dublin population stroke study. Cerebrovasc Dis. 2010;29(1):43–9.
53. Marini C, De Santis F, Sacco S, Russo T, Olivieri L, Totaro R, Carolei A. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke. 2005;36(6):1115–9.
54. Kimura K, Minematsu K, Yamaguchi T, Japan Multicenter Stroke Investigators' Collaboration (J-MUSIC). Atrial fibrillation as a predictive factor for severe stroke and early death in 15 831 patients with acute ischaemic stroke. J Neurol Neurosurg Psychiatry. 2005;76:679–83.
55. Sussman M, Menzin J, Lin I, Kwong WJ, Munsell M, Friedman M, Selim M. Impact of atrial fibrillation on stroke-related healthcare costs. J Am Heart Assoc. 2013;2(6), e000479.
56. Ghatnekar O, Glader EL. The effect of atrial fibrillation on stroke-related inpatient costs in Sweden: a 3-year analysis of registry incidence data from 2001. Value Health. 2008;11(5): 862–8.
57. Brüggenjürgen B, Rossnagel K, Roll S, Andersson FL, Selim D, Müller-Nordhorn J, Nolte CH, Jungehülsing GJ, Villringer A, Willich SN. The impact of atrial fibrillation on the cost of stroke: the berlin acute stroke study. Value Health. 2007;10(2):137–43.
58. Hannon N, Callaly E, Moore A, Ní Chróinín D, Sheehan O, Marnane M, Merwick A, Kyne L, Duggan J, McCormack PM, Dolan E, Crispino-O'Connell G, Harris D, Horgan G, Williams D, Kelly PJ. Improved late survival and disability after stroke with therapeutic anticoagulation for atrial fibrillation: a population study. Stroke. 2011;42(9):2503–8.
59. Gage BF, Cardinalli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. JAMA. 1995; 274(23):1839–45.
60. Lackland DT, Roccella EJ, Deutsch AF, Fornage M, George MG, Howard G, Kissela BM, Kittner SJ, Lichtman JH, Lisabeth LD, Schwamm LH, Smith EE, Towfighi A. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/ American Stroke Association. Stroke. 2014;45(1):315–53.

Chapter 2
Efficacy and Limitations of Warfarin and Novel Oral Anticoagulants with Atrial Fibrillation

John A. Cairns

Introduction

Atrial fibrillation (AF) is common, with a population prevalence of 1–2 % [1]. Although AF is uncommon in the young, the prevalence rises to 4 % by age 60 and >10 % by age 80. The total number of North Americans with AF is rising steadily as the population ages. Embolic stroke is the most serious complication of AF, reported in the Framingham study to have an annual incidence of 4.5 % [2]. In the United States, the proportion of strokes attributable to AF is 1.5 % in the age group 50–59 years, rising to 23.5 % in the age group 80–89 years and accounting for about 15 % of all strokes [1]. These strokes result in either death or severe neurological deficit in 50–70 % of instances [3]. The Framingham observations on the incidence of stroke were replicated in a meta-analysis of the control groups of the five primary prevention randomized trials of warfarin among patients with nonvalvular AF, who had a mean annual incidence of stroke of 4.5 % and of stroke plus other systemic embolus (SSE) of 5 % [4].

The investigators of the Stroke Prevention in Atrial Fibrillation (SPAF) trial [5] and those who had led the five randomized trials of warfarin each published a series of criteria predictive of stroke among patients with AF [4]. These were combined to create the $CHADS_2$ index, which predicts the annual risk of stroke over a wide range from 1.9 to almost 20 % [6]. The subsequently developed CHA_2DS_2-VASc index [7] incorporating additional risk factors, is only modestly more accurate overall than the $CHADS_2$ index, but is particularly useful to delineate a range of risks among patients with a $CHADS_2 = 0$ [8].

J.A. Cairns, M.D., F.R.C.P.C., F.A.C.C. (✉)
GLD Health Care Centre, University of British Columbia,
2775 Laurel St., Vancouver, BC, Canada, V5Z 1M9
e-mail: john.cairns@ubc.ca

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_2

Warfarin for the Prevention of Stroke and Systemic Embolism

Prior to the conduct of randomized controlled trials (RCTs) of warfarin vs. control, anticoagulation had usually been prescribed for only those AF patients who had mitral stenosis, a prosthetic heart valve, prior arterial embolism or who were to undergo electrical cardioversion. The Framingham study found that the annual risk of stroke for patients with nonvalvular AF was similar to that among patients with rheumatic AF [2]. However, patients with rheumatic AF were much younger, and after adjustment for age, the stroke rate is much higher with rheumatic AF. This insight, along with evidence for the efficacy and increased safety of regimens of lower-intensity warfarin and the advent of the international normalized ratio (INR) for evaluation of the anticoagulant effect of the vitamin K antagonist (VKA) drugs prompted the initiation of five RCTs of warfarin vs. control or placebo for the primary prevention of thromboembolism among patients with nonrheumatic (nonvalvular) AF.

A collaborative meta-analysis of these five RCTs [4] calculated a reduction of the incidence of ischemic stroke from 4.5 to 1.4 %/year (relative risk reduction [RRR] 68 %, 95 % CI 50–79 %, $P<0.001$). The rate of major hemorrhage with VKA was 1.3 %/year vs. 1 %/year in controls. A subsequent meta-analysis of these trials [9], including an additional trial of secondary prevention of stroke found a RRR of 64 % (95 % CI 49–74 %) for the more clinically meaningful outcome of all stroke (ischemic or hemorrhagic). The absolute risk reduction [ARR] for all stroke was 2.7 %/year in the primary prevention trials and 8.4 %/year in the secondary prevention trial. There was an excess of 0.3 %/year ($P=$NS) of major extra cranial hemorrhage with VKA but a statistically significant 1.6 % ARR of mortality.

Adjusted-dose warfarin (INR 2–3) was compared to various regimens of lower dose warfarin plus aspirin [9], to warfarin at lower intensity and to warfarin at low fixed dose [9] but none of these alternative regimens was as effective. An overview [9] reported that among trials of VKA vs. aspirin; the RRR for all stroke was 39 % (95 % CI 19–53 %) in favor of VKA, equivalent to an ARR of about 0.9 %/year for primary prevention and 7 %/year for secondary prevention. There were no significant differences in major extra cranial hemorrhage or mortality.

Adjusted-dose warfarin was also compared to the combination of clopidogrel plus aspirin [10] with the expectation that the combined antiplatelet regimen might be non-inferior to warfarin for the prevention of stroke, while offering the advantages of less bleeding and greater convenience. However, the RR was 1.44 (95 % CI 1.18–1.76, $P=0.0003$) for clopidogrel/aspirin (75 mg and 75–100 mg/day) vs. warfarin (INR 2–3) for the composite outcome of stroke, non-CNS embolus, myocardial infarction (MI), and vascular death, and for major bleeding the RR was 1.10 (95 % CI 0.83–1.45) with the combination.

National guidelines groups now recommend that patients with AF or atrial flutter (AFL) be stratified for stroke risk using a formal schema such as the CHA_2DS_2-VASc or the $CHADS_2$, and that most of these patients receive oral anticoagulant (OAC) therapy, whether the arrhythmia is paroxysmal, persistent, or permanent (Table 2.1). The European Society of Cardiology [11] recommends

Table 2.1 Recommendations of National Guidelines Organizations for antithrombotic therapy for nonvalvular atrial fibrillation

	National Guidelines Organization			
Stroke risk	CCS [12]	ESC [11]	AHA/ACC/HRS [14]	ACCP [13]
High	Age > 65, or any $CHADS_2$ risk factor	CHA_2DS_2-VASc ≥ 1	CHA_2DS_2-VASc ≥ 2	$CHADS_2 \geq 1$
	OAC	*OAC*	*OAC*	*OAC*
Low	Age < 65, no $CHADS_2$ risk factor, but vascular disease	CHA_2DS_2-VASc ≥ 1	CHA_2DS_2-VASc = 1	$CHADS_2 \geq 1$
	ASA	*OAC*	*OAC* or *ASA* or *no antithrombotic*	*OAC*
Very low	Age < 65, no $CHADS_2$ risk factor, no vascular disease	CHA_2DS_2-VASc = 0	CHA_2DS_2-VASc = 0	$CHADS_2 = 0$
	No antithrombotic	*No antithrombotic*	*No antithrombotic*	*No antithrombotic*

*CC*S Canadian Cardiovascular Society, *ESC* European Society of Cardiology, *AHA/ACC/HRS* American Heart Association/American College of Cardiology/Heart Rhythm Society, *ACCP* American College of Chest Physicians, *OAC* oral anticoagulant

OAC for patients with CHA_2DS_2-VASc ≥ 1 and no antithrombotic therapy for those with CHA_2DS_2-VASc = 0. The Canadian Cardiovascular Society [12] recommends: (1) OAC for all patients aged ≥65 years, and all those with any of the $CHADS_2$ risk factors (defined as in the 2012 ESC guidelines [11]), (2) aspirin for patients aged <65 and free of any $CHADS_2$ risk factors but with vascular disease (prior MI, peripheral vascular disease or aortic plaque), and (3) no antithrombotic therapy for those <65 years and free of all the above risk factors. The American College of Chest Physicians [13] recommends OAC for patients with $CHADS_2 \geq 1$, and no antithrombotic therapy for patients with $CHADS_2 = 0$ (with the option of aspirin or the combination of aspirin and clopidogrel if the patient wishes to have antithrombotic therapy. The American Heart Association [14] recommends: (1) OAC for patients with CHA_2DS_2-VASc ≥ 2, (2) a choice of OAC, aspirin or no antithrombotic therapy with CHA_2DS_2-VASc = 1 and (3) no antithrombotic therapy with CHA_2DS_2-VASc = 0.

The efficacy of antithrombotic therapy to prevent ischemic stroke must be balanced against the risk of major hemorrhage. Bleeding risk in a patient receiving anticoagulant therapy may be predicted using the HAS-BLED schema [15]. The score allows clinicians to calculate an individual patient risk of major bleeding ranging from about 1 % (score 0–1) to 12.5 % (score 5). The application of a bleeding-risk schema ensures that important risk factors are systematically considered and allows estimation of the relative risks of stroke vs. major bleeding with various antithrombotic therapies. As many as 70 % of strokes with AF are either fatal or leave severe residual deficits, whereas major bleeding is less often fatal, is less likely to leave significant residual effects in survivors and tends to

be rated by patients as less concerning than stroke. Many of the factors that determine stroke risk are also predictors of bleeding, but stroke risks usually exceed those of major bleeding. Patients at increased risk of major bleeding warrant extra caution and closer monitoring of antithrombotic therapy. Only when the stroke risk is low and the bleeding risk particularly high (e.g., a young patient with AF and few or no stroke-risk factors, but a high risk of major hemorrhage e.g., malignancy, prior major hemorrhage or participation in contact sports) does the risk:benefit ratio favor no antithrombotic therapy. Patient preferences are of great importance in deciding on antithrombotic therapy in relation to benefits and risks.

For the VKAs, bleeding risk depends upon INR, the quality of monitoring, the duration of therapy (higher risk during initial few weeks of therapy) and the stability of dietary and other factors that may alter VKA potency. Bleeding risk is likely higher in clinical practice than in the rigorous setting of a clinical trial or a dedicated, expert anticoagulation service.

Vitamin K Antagonist Pharmacology and Therapeutic Challenges

All VKAs exert their anticoagulant effects by interfering with the hepatic synthesis of the coagulation proteins factors II, VII, IX, and X [16]. Precursors of these proteins are synthesized in the liver and must undergocarboxylation to yield the coagulation factors. The carboxylation is catalyzed by reduced vitamin K, which is converted to oxidized vitamin K in the process and then regenerated by enzymatic reduction of the oxidized vitamin K. The VKAs interfere with the synthesis of coagulation factors by decreasing the regeneration of reduced vitamin K. The ultimate suppression of the coagulation factors resulting from VKA administration is dependent upon this complex series of steps and the effect of a given dose is highly variable from one patient to another and may vary widely within a given patient. Hence, achieving the potential efficacy of VKA for prevention of stroke/systemic embolus with acceptable rates of major bleeding is challenging for both patients and their doctors [16]. Warfarin is the most widely used VKA in North America, but other available VKAs include acenocoumarol, phenprocoumon, and fluindione, each of which has its own intrinsic and extrinsically influenced pharmacodynamics and pharmacokinetic characteristics. Discussions of VKAs in this chapter will henceforth refer only to warfarin unless specifically stated otherwise.

Warfarin is absorbed relatively quickly and completely, but because its action depends upon blocking the synthesis of specific coagulation factors, the onset of the anticoagulant effect depends upon the individual half-lives of these coagulation proteins and up to 5 days is required before a steady-state anticoagulant effect occurs. The return to normal coagulation on stopping warfarin is dependent on both the elimination half-life of warfarin (36–42 h) and the resumed synthesis and steady-state levels of the affected coagulation proteins, which requires about 5 days (Table 2.2).

Table 2.2 Clinical pharmacology of warfarin and the novel oral anticoagulants

Feature	Warfarin [16]	Dabigatran [23]	Rivaroxaban [24]	Apixaban [25]	Edoxaban [26]
Mechanism	Inhibits synthesis II, VII, IX, X	Direct IIa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor
Pro-drug	No	Yes	No	No	No
Dose regimen	Oral	Oral	Oral	Oral	Oral
Administration	od	bid	od	bid	od
AF dose (mg)	INR 2–3	150, 110, 75	20, 15	5, 2.5	60, 30
Food effect	Yes	Delays T_{max}	↑Bioavail	No	No
		No ↓ Bioavail	Take with food	Take with or without food	Take with or without food
		Take with or without food			
Food interaction	Many	No	No	No	No
Bioavailability (%)	98	6.5	100 with food	50	50
T_{max} (hr)	72–120	0.5–2	2–4	3–4	2–3
$T_{1/2}$ (hr)	20–60	11–17	5–13	5–13	9–11
Substrate CYP	2C9, 3A4	No	3A4, 2J2	3A4	3A4
Inhibitor			Ketoconazole	Ketoconazole	Ketoconazole?
Inducer			Ritonavir	Ritonavir	Ritinavir?
			Rifampin	Rifampin	Rifampin
Substrate P-gp	No	Yes	Yes	Yes	Yes
Inhibitor		Ketoconazole	Ketoconazole	Ketoconazole	Ketoconazole
Inducer		Carbamazepine	Ritonavir	Ritonavir	Ritonavir
		Dronedarone	Carbamazepine	Carbamazepine	Carbamazepine
		St J's W	Dronedarone?	Dronedarone?	Dronedarone
			St J's W	St J's W	St J's W
Renal clearance	No	85	33	27	35
Protein bound (%)	99	35	90–95	87–93	54
Monitoring	INR	No	No	No	No

$T_{1/2}$ terminal elimination half-life, *Bioavail* bioavailability, *CYP* cytochrome P450, *P-gp* P-glycoprotein, Drugs listed are strong inhibitors or inducers with clinically important effects on NOAC blood levels, *St J's W* St John's Wort, ? = data not available

The degree of INR prolongation by a given dose of warfarin is unpredictable because of numerous factors affecting the pharmacokinetics and pharmacodynamics of warfarin and resulting in unpredictable and varying INR prolongation by a given dose of warfarin in a given patient [16]. Genetic variations in the enzymes responsible for warfarin metabolism and controlling vitamin K cycling can cause several-fold increased or decreased sensitivity to a given warfarin dose. The hepatic metabolism of warfarin may be slowed by several allelic variations in the CYP-450 enzyme system, reducing warfarin requirement and possibly resulting in bleeding complications at relatively low doses. Mutations of the gene coding for the vitamin K oxide reductase (VCOR) enzyme may result in widely varying sensitivity to the inhibitory effect of warfarin and may cause marked warfarin resistance. These genetic variations in warfarin metabolism and vitamin K cycling are unpredictable and although genetic testing can reveal some of them, the use of these tests has generally not improved the efficacy, safety, and cost-effectiveness of warfarin therapy [17]. Many drugs can influence the absorption, metabolism, or clearance of warfarin and of vitamin K, resulting in increased or decreased sensitivity to a given dose [18]. A variety of foods and dietary supplements may influence warfarin effects, as may dietary vitamin K content and several disease states including hepatic and renal failure. The INR affords an excellent measure of likely efficacy and safety of warfarin. However, even in clinical trials, achieving therapeutic-range INRs >65 % of the time is infrequent and in clinical practice, the figure is commonly 50 % or less [19]. Time in the therapeutic range (TTR) of INR 2–3 is closely related to risk of stroke among patients prescribed warfarin [20] and even following the establishment of a therapeutic dose of warfarin, patients require monthly determination of the INR. Not surprisingly both patients and physicians find warfarin treatment challenging, and registries in Europe and the United States have generally documented rather low rates of initiation and adherence among patients with clear indications for warfarin [21].

The Development and Clinical Evaluation of the New Oral Anticoagulants

The New Oral Anticoagulants (NOACs) were designed to overcome some of the limitations of warfarin. The crystal structure of thrombin was reported in 1989 and of activated factor X in 1992 [22]. Intensive laboratory endeavors culminated in the development and clinical evaluation of the direct thrombin inhibitor dabigatran etexilate and the Xa inhibitors rivaroxaban, apixaban, edoxaban, and betrixaban. All but betrixaban proceeded to phase III studies, initially in venous thromboembolism and then AF. These agents (Table 2.2) [23–26] are all rapidly absorbed following oral intake and reach steady-state anticoagulation quickly because they directly inhibit preformed factor IIa or Xa. After discontinuation, their anticoagulant effects diminish quickly because of short serum and receptor-inhibition half-lives. Their absorption is largely unaffected by food or other medications, and their pharmacokinetics are affected by few agents, although drugs which inhibit or induce

selected CYP enzymes or P-gp can affect concentration levels of the NOACs (Table 2.2). Dabigatran is not metabolized by the hepatic cytochrome P450 system, whereas the Xa inhibitors are and their anticoagulant effects will be enhanced by strong inhibitors and reduced by strong inducers of CYP 3A4. All NOACs are substrates for the P-gp system; accordingly their anticoagulant effects will be enhanced by strong inhibitors and reduced by strong inducers. The active drugs are excreted renally to varying extents; severe renal dysfunction must be taken into account in dose selection, conversion from a NOAC to warfarin and in drug interruptions for invasive procedures. Most of the NOACs are extensively protein bound, although dabigatran is not and is dialyzable. Anticoagulation monitoring is not required and dose recommendations vary little among patients, although lower doses of most NOACs are indicated for patients with reduced renal function, advanced age, or small body mass index. The principal drawbacks to the clinical use of these agents are that there is no readily available assay for assessing anticoagulant effect and no specific antidotes are yet available. Intensive investigation is currently focused on addressing these concerns. Four large RCTs have been conducted, each comparing one of the NOACs to warfarin among patients with nonvalvular AF (Table 2.3).

Dabigatran [23] is approved in Canada, the United States, and Europe for the prevention of SSE in AF and AFL, for the prevention of venous thromboembolic events (VTE) (deep venous thrombosis [DVT] and pulmonary embolism [PE]) among patients undergoing hip or knee replacement and the treatment of VTE and prevention of recurrent DVT and PE. The approvals for AF were based on the results of the RE-LY trial [27], which randomized 18,113 AF patients (mean $CHADS_2$ 2.1) to dabigatran (110 mg vs. 150 mg twice daily, double-blind) or open-label warfarin.

Table 2.3 Selected outcomes from the four major RCTs of a NOAC vs. warfarin among patients with nonvalvular atrial fibrillation

	Dabigatran 110 mg vs Wafarin	Dabigatran 150 mg vs Warfarin	Rivaroxaban vs Warfarin	Apixaban vs Warfarin	Edoxaban 30 mg vs Warfarin	Edoxaban 60 mg vs Warfarin
	HR, 95% CI, P, NNT	HR, 95% CI, P, NNT	HR,95% CI,P,NNT	HR, 95% CI, P, NNT	HR, 95% CI, P, NNT	HR, 95% CI, P, NNT
Stroke/SE	0.91 (0.74-1.11) P=0.34	0.66 (0.53-0.82) P<0.001, NNT=172	0.88 (0.74-1.03) P=0.12	0.79 (0.66-0.95) P<0.01, NNT=303	1.13 (0.96-1.34) P=0.10	0.87 (0.73-1.04) P=0.08
Stroke	0.92 (0.74-1.13) P=0.41	0.64 (0.51 – 0.81) P<0.001, NNT=179	0.85 (0.70-1.03) P=0.09	0.79 (0.65-0.95) P=0.01, NNT=313	1.13 (0.97-1.31) P=0.12	0.88 (0.75-1.03) P=0.11
Ischemic stroke	1.11 (90.89-1.40) P=0.41	0.76 (0.60-0.98) P=0.03, NNT=357	0.94 (0.75-1.17) P=0.581	0.92 (0.74-1.13) P=0.42	1.41 (1.19-1.67) P<0.001, NNH=192	1.0 (0.83-1.19) P=0.97
Hemorrhagic stroke	0.31 (0.17-0.56) P<0.001, NNT=385	0.26 (0.14-0.49) P<0.001, NNT=357	0.59 (0.37-0.93) P=0.024, NNT=556	0.51 (0.35-0.75) P<0.001, NNT=435	0.33 (0.22-0.50) P<0.001, NNT=323	0.54 (0.38-0.77) P<0.001, NNT=476
Major bleed	0.80 ((0.69 – 0.93) P=0.003, NNT=154	0.93 ((0.81 – 1.07) P=0.31	1.04 (0.90-1.20) P=0.58	0.69 (0.60-0.80) P<0.001, NNT=104	0.47 (0.41-0.55) P<0.001, NNT=43	0.80 (0.71-0.91) P<0.001, NNT=147
Major GI bleed	1.10 (0.86-1.41) P=0.43	1.50 (1.19-1.89) P=0.007),NNH=204	1.46 P<0.001, NNH=101	0.89 (0.70-1.15) P=0.37	0.67 (0.53-0.83) P<0.001, NNT=250	1.23 (1.02-1.50) P=0.03, NNH=357
Intracranial bleed	0.31 (0.20-0.47) P<0.001, NNT=196	0.40 (0.27-0.60) P<0.001, NNT=227	0.67 (0.47-0.93) P=0.02, NNT=500	0.42 ((0.30 – 0.58) P<0.001, NNT=213	0.30 (0.21-0.43) P<0.001, NNT=169	0.47 (0.34-0.63) P.001, NNT=227
All –cause mortality	0.91 (0.80 – 1.03) P=0.13	0.88 (0.77-1.00) P=0.051	0.92 (0.82-1.03) P=0.15	0.89 (0.80-0.99) P=0.047, NNT=238	0.87 (0.79-0.96) P=0.006, NNT=181	0.92 (0.83-1.01) P=0.08
Net benefit	0.92 (0.84-1.02) P=0.10	0.91 (0.82-1.00) P=0.04, NNT=137		0.85 (0.78-0.92) P<0.001, NNT=93	0.83 (0.77-0.90) P<0.001, NNT=118	0.89 (0.83-0.96) P=0.003, NNT=76

HR hazard ratio, *NNT* number needed to treat, *NNH* number needed to harm, Net benefit (composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death or major bleeding)
Blue shades statistically significant difference ($P \leq 0.05$)

The principal outcome of SSE occurred at annual rates of 1.69 % (warfarin), 1.53 % (dabigatran 110 mg) (RR vs. warfarin 0.91; 95 % confidence-interval [CI], 0.74–1.11) and 1.11 % (dabigatran 150 mg) (RR vs. warfarin 0.66; CI 0.53–0.82; $P<0.001$) (Table 2.3). The annual rates of major bleeding were 3.36 % (warfarin), 2.71 % (dabigatran 110 mg) (RR vs. warfarin 0.8, $P=0.003$) and 3.11 % (dabigatran 150 mg) (RR vs. warfarin 0.93, $P=0.31$). The rates of major bleeding on warfarin were substantially greater than the mean 1.3 %/year observed in the earlier RCTs of warfarin vs. control [9], perhaps in part because the mean age had risen from 69 [9] to >71 [27] and it is likely that bleeding was more assiduously documented in more recent trials. The phase III trials of the other NOACs also observed higher rates of major bleeding in the warfarin arm than had been documented in the earlier trials of warfarin vs. control [28, 29]. In RE-LY, intracranial bleeding and hemorrhagic stroke were significantly less with dabigatran 110 mg (respective HRs vs. warfarin 0.31 and 0.31) and with dabigatran 150 mg (respective HRs vs. warfarin 0.40 and 0.26) than with warfarin. The annual rates of the outcome of "net clinical benefit" (composite of SSE, pulmonary embolism, MI, death, or major bleeding) were 7.64 % (warfarin), 7.09 % (dabigatran 110 mg) (RR vs. warfarin 0.92; 0.84–1.02) and 6.91 % (dabigatran 150 mg) (RR vs. warfarin 0.91; 0.82–1.00).

Rivaroxaban [24] is approved in Canada, the United States, and Europe for the prevention of SSE in AF/AFL, for the prevention of VTE (DVT and PE among patients undergoing hip or knee replacement and the treatment of VTE and prevention of recurrent DVT and PE. The AF approvals were based on the ROCKET-AF trial [28] which randomized 14,264 AF patients (mean $CHADS_2$ 3.5) to rivaroxaban 20 mg once daily (15 mg once daily when CrCl was 30–49 mL/min) or warfarin. The primary analysis was a per-protocol non-inferiority comparison of warfarin and rivaroxaban for the principal outcome of SSE, which occurred at annual rates of 1.7 % (rivaroxaban) vs. 2.2 % (warfarin) (RR 0.79; 0.66–0.96, $P<0.001$ for non-inferiority) (Table 2.3). In a secondary, intention-to-treat analysis, the respective rates were 2.1 % vs. 2.4 % (RR 0.88; 0.75–1.03; $P=0.12$ for superiority). Major bleeding occurred at annual rates of 3.6 % (rivaroxaban) vs. 3.4 % (warfarin) (RR 1.04). There was significantly less hemorrhagic stroke with rivaroxaban (HR vs. warfarin 0.67). No net clinical benefit data were reported.

Apixaban [25] is approved in Canada, the United States, and Europe for the prevention of SSE in AF/AFL, for the prevention of VTE (DVT and PE among patients undergoing hip or knee replacement and the treatment of VTE and prevention of recurrent DVT and PE. The approvals for AF were based on the results of the ARISTOTLE trial [29], which randomized 18,113 AF patients (mean $CHADS_2$ 2.1) double-blind, to apixaban 5 mg twice daily (2.5 mg twice daily for 2 or more of age ≥80, weight ≤60 kg, or serum creatinine ≥133 μmol/L) or to warfarin. The principal outcome of SSE occurred at annual rates of 1.27 % (apixaban) vs. 1.60 % (warfarin) (RR 0.79; 0.66–0.95; $P<0.01$ for superiority) (Table 2.3). Major bleeding occurred at annual rates of 2.13 % (apixaban) vs. 3.09 % (warfarin) (RR 0.69, $P<0.001$). There were statistically significant reductions in intracranial bleeding (HR vs. warfarin 0.42) and hemorrhagic stroke (HR 0.51). The outcome of net clinical benefit (composite of SSE, major bleeding and all-cause mortality) occurred at annual rates of 3.17 % (apixaban) vs. 4.11 % (warfarin) (RR 0.85; 0.78–0.92, $P<0.001$).

Apixaban was also compared to aspirin in the Apixaban vs. Acetylsalicylic Acid to Prevent Strokes (AVERROES) trial [30]. There were 5590 AF patients (mean $CHADS_2 = 2.0$) unsuitable for warfarin therapy who were randomized double-blind to apixaban 5 mg twice daily (2.5 mg twice daily in selected patients) or to aspirin (81–324 mg/day) and followed for a median of 1.1 year. The trial was stopped early because of marked outcome differences. The rates of the principal outcome (SSE) were 1.6 %/year with apixaban vs. 3.7 %/year with apixaban (RR vs. aspirin 0.45; 0.32–0.62; $P < 0.001$). The rates of major bleeding were 1.4 %/year with apixaban vs. 1.2 % with aspirin (RR 1.13, $P < 0.57$), with no significant differences in intracranial or GI bleeding.

Edoxaban is approved in Japan for the prevention of SSE in AF/AFL, for the prevention of VTE (DVT and PE among patients undergoing hip or knee replacement and the treatment of VTE and prevention of recurrent DVT and PE. The US FDA has voted to approve edoxaban for the prevention of SSE in AF/AFL, and US marketing approval is awaited. Approval requests are under consideration in Europe and Canada. The AF data are available from the Effective Anticoagulation with Factor Xa next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial [31] which randomized 21,105 patients (mean $CHADS_2 = 2.8$) in a double-blind protocol to edoxaban 30 mg once daily, edoxaban 60 mg once daily or warfarin. The principal outcome rates (SSE) were 1.61 %/year with edoxaban 30 mg and 1.50 % with warfarin (HR vs. warfarin 1.07, $P = 0.005$ for non-inferiority) and 1.18 % with edoxaban 60 mg (HR vs. warfarin 0.79, $P < 0.001$ for non-inferiority and HR 0.87, $P = 0.08$ for superiority) (Table 2.3). Annualized major bleeding rates were 3.43 % with warfarin, 1.61 % with low-dose edoxaban (HR vs. warfarin 0.47, $P < 0.001$) and 2.75 % with high-dose edoxaban (HR vs. warfarin 0.80, $P < 0.001$). Intracranial bleeding was significantly less with both low-dose (HR vs. warfarin 0.30) and high-dose edoxaban (HR vs. warfarin 0.47) and hemorrhagic stroke was also significantly less with both low-dose (HR vs. warfarin 0.33) and high-dose edoxaban (HR vs. warfarin 0.54). All-cause mortality was significantly less with low-dose edoxaban (HR vs. warfarin 0.87, $P = 0.006$) and there was a trend to lower all-cause mortality with high-dose edoxaban (HR 0.92, $P = 0.08$). Annualized net clinical benefit rates (composite of SSE, major bleeding or death from any cause) were 8.11 % with warfarin, 6.79 % with low-dose edoxaban (HR vs. warfarin 0.83, $P < 0.001$) and 7.26 % with high-dose edoxaban (HR vs. warfarin 0.89, $P = 0.003$).

Choosing Between a VKA and a NOAC

Patient and Physician Convenience

The NOACs were designed to overcome a number of the patient and physician challenges inherent in the use of warfarin. The starting dose of each of the NOACs is much less variable than that of warfarin. For all of the NOACs, the higher of the doses evaluated in the large RCTs is appropriate as a starting dose in most patients,

whereas the lower dose may be selected for patients with advanced age, low body weight or significant renal failure. Absorption and metabolism of the NOACs is generally not influenced by diet, and alterations of the absorption or metabolism of individual NOACs are caused by relatively few drugs, which are generally not in common usage and are well-described. Coagulation monitoring is not required. The rapid onset and offset of these agents simplifies drug initiation and discontinuation. The comparative simplicity and convenience of the use of a NOAC compared to warfarin appears to result in improved compliance among de novo recipients [32, 33].

Efficacy and Safety (Table 2.3)

In view of the expected greater convenience associated with the NOACs, each of the phase III trials was designed to demonstrate non-inferiority of the new agent compared to warfarin for the efficacy outcome of SSE and the safety outcome of major bleeding. All of the NOACs were found to be non-inferior to warfarin for these outcomes. In addition, dabigatran 150 mg and apixaban were found to be superior to warfarin for the prevention of SSE while dabigatran 110 mg, apixaban and edoxaban both 30 and 60 mg were found to cause significantly less major bleeding than warfarin. All NOACs caused significantly less hemorrhagic stroke and intracranial hemorrhage than warfarin. The net clinical benefits outcome was significantly better with dabigatran 150 mg, apixaban and both doses of edoxaban. Although dabigatran is a thrombin inhibitor and rivaroxaban, apixaban and edoxaban are structurally distinct anti-Xa agents, the overall effects of the NOACs have been estimated in a meta-analysis of the 4 RCTs [34] with the following findings for the higher dose regimens vs. warfarin: SSE (RR 0.81, 95 % CI 0.73, 0.91, $P<0.0001$), major bleeding (RR 0.86, 0.73–1.00, $P=0.06$), intracranial hemorrhage (RR 0.48, 0.39–0.59, $P<0.0001$), gastrointestinal bleeding (RR 1.25, 1.01–1.55, $P=0.04$), all-cause mortality (RR 0.90, 0.85–0.95, $P=0.0003$). Comparison of the lower dose regimens with warfarin showed similar rates of SSE, significantly less intracranial bleeding and significantly less mortality.

These very large trials of a NOAC vs. warfarin have allowed the detection of statistically significant differences which are, however, relatively modest. The primary prevention trials of warfarin compared to control [9] randomized a total of only 2900 patients and yet showed an ARR for stroke of 2.7 %/year (number needed to treat [NNT] 37 for stroke and 56 for death. In RE-LY [27], the ARR for dabigatran 150 mg vs. warfarin was 0.58 %/year, (NNT = 172). In ARISTOTLE [29], the ARR for apixaban vs. warfarin was 0.33 %/year (NNT = 303), and in ROCKET-AF [23] and ENGAGE [31]. There was no significant risk reduction for rivaroxaban or edoxaban. For the outcome of death, the NNT for dabigatran 150 mg was 169 and for apixaban it was 238. The rates of major extra cranial bleeding were significantly lower with dabigatran 110 mg (NNT = 154), apixaban (NNT = 104) and edoxaban (NNT = 43 for 30 mg and NNT = 147 for 60 mg) but not with dabigatran 150 mg bid

or rivaroxaban. For intracranial haemorrhage, the ARRs were: dabigatran 0.44 %/year (NNT = 227); rivaroxaban 0.2 %/year (NNT = 500); apixaban 0.47 %/year (NNT = 213); edoxaban 30 mg 0.26 %/year (NNT = 169), and edoxaban 60 mg 0.39 %/year (NNT = 227). Even though any incremental therapeutic efficacy and safety of the NOACs over warfarin is rather modest, these advantages definitely enhance patient and particularly physician preferences for the NOACs.

Additional Considerations Influencing the Choice of Warfarin vs. a NOAC

There is considerable evidence that the rates of major haemorrhage are higher in the initial months of warfarin therapy than subsequently, and some evidence that efficacy and bleeding risk is better among patients who have been taking warfarin for a period of months and whose INR control is relatively good [34, 35]. Such a patient doing well on warfarin might not be a candidate for switching to a NOAC unless they express strong preference for one of the NOACs. It may be that patients whose warfarin dose remains stable for several months can be managed with less frequent INRs and that attainment of greater TTRs may be facilitated by use of various algorithms for dose adjustment [36].

Compliance with OAC is commonly an issue with AF patients. When a patient is noncompliant with warfarin therapy, the availability of periodic INR testing may serve as a stimulus to compliance, whereas there is no readily-available, reliable measure of anticoagulant effect for any of the NOACs for use in this way. Another consideration with poorly compliant patients is the short half-lives of the NOACs: the reduced anticoagulation associated with a single missed dose would be much more marked than that from a missed dose of warfarin with its much longer half-life.

Renal impairment is increasingly recognized as an independent risk factor for stroke in AF patients. There appears to be a net benefit of warfarin among patients with renal impairment that is moderate (Stage 3 CKD, eGFR 30–59 mL/min/1.73 m^2) or severe (stage 4 CKD, eGFR 15–29 mL/min/1.73 m^2) but the net benefit remains unclear for patients with end stage renal disease (eGFR <15 mL/min/1.73 m^2 or on dialysis) [37]. In the NOAC trials [38–40] the rates of SSE were higher among those patients with reduced CrCl, but the HRs were not different from those observed among patients with normal renal function.

A major advantage of the NOACs is their relatively predictable dose requirements among a wide range of patients with no need for regular assessment of anticoagulation status. However, in settings of urgent surgery or trauma, major bleeding or thrombotic complications, decreasing renal or hepatic function, drug interaction or noncompliance, the accurate assessment of coagulation status may be needed. In contrast to the ready availability of the INR for assessing coagulation status with warfarin therapy, there is no readily-available and quantitative laboratory test for assessment of the anticoagulant effect of the NOACs. The INR does not provide a quantitative assessment of the anticoagulant activities of the NOACs [41].

The aPTT may provide a qualitative assessment of the anticoagulant effect of dabigatran, but the most accurate and quantitative assay is the diluted thrombin time test, commercially available as the Hemoclot® [42]. However, the test is not available in most routine laboratories and correlation of results with suppression of clinical thrombosis is empiric as yet. For the assessment of the anticoagulant effects of the Xa inhibitors, the prothrombin time may provide some information but the aPTT is not useful [41]. Chromogenic assays appear to provide dose-dependent relationships between anti-factor Xa activity and the concentrations of both rivaroxaban [43] and apixaban [44], but are not as yet available in routine hospital laboratories.

The anticoagulant effects of the VKAs may be reversed by the administration of oral or intravenous preparations of vitamin K, and by the administration of preformed coagulation proteins in fresh frozen plasma or as three- or four factor prothrombin complex concentrates or recombinant activated factor VII [17]. No such direct reversal agents are yet available for the NOACs. Guidelines for management of major bleeding are focused on graded responses depending upon the severity of the bleeding (mild, moderate, life-threatening) and suggest that prothrombin complex concentrates or recombinant activated factor VII be considered in severe bleeding. Efforts to develop specific antidotes are active [45].

Despite the absence of coagulation assays specific to the NOACs, and of specific antidotes, the rates of all-cause mortality observed in the large RCTs were significantly less with apixaban and with low-dose edoxaban, and there were favorable trends for the other NOAC regimens. The overview found significantly less all-cause mortality (RR 0.90 vs. warfarin, $P = 0.0003$) [34]. In the RCTs, the outcomes in patients who experienced major bleeding appear to be no worse with the NOACs than with warfarin [46]. The eventual availability of specific coagulation assays and antidotes to the NOACs will no doubt improve the management of selected patients and assuage the anxieties of physicians and patients, but the present non-availabilities should not strongly influence therapeutic choices between warfarin and the NOACs.

There is considerable evidence for the efficacy of OAC for the prevention of SSE among patients undergoing cardioversion [47]. Each of the large RCTs of a NOAC vs. warfarin found comparable efficacy for stroke prevention [48], an important finding because the rapid onset and convenience of these agents particularly favors their use in the setting of the Emergency Department.

The NOACs are substantially more expensive than warfarin, even when consideration is given to costs incurred in obtaining regular INRs. Private and state drug plans are increasingly agreeing to provide coverage, but the costs to an uninsured individual may be an impediment to prescription of a NOAC. Even when coverage is available there are societal costs to be considered. In Canada, dabigatran 150 mg bid is "cost-effective" for patients whose $CHADS_2 < 2$, and both dabigatran 150 mg bid and apixaban 5 mg bid are "cost-effective" for patients whose $CHADS_2 \geq 2$ [49].

The degree of preference for a NOAC over a VKA expressed in national clinical guidelines has been evolving since the introduction of these agents beginning in 2009. The current recommendations in this regard [11–14] are summarized in Table 2.4.

Table 2.4 Recommendations of National Guidelines Organizations for choice of warfarin vs. a NOAC for nonvalvular AF

National Guidelines Organization	Recommendation
CCS	When OAC therapy is indicated for patients with nonvalvular AF, most patients should receive dabigatran, rivaroxaban, apixaban, or edoxaban (when approved) in preference to warfarin. (Strong recommendation, High quality evidence)
ESC	When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either: direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban) should be considered rather than dose-adjusted VKA (INR 2–3) for most patients with nonvalvular AF, based on their net clinical benefit. (Class I, Level A)
	Where OAC is recommended, one of the NOACs, either a direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban) is recommended. (Class IIa, Level A)
AHA/ACC/HRS	With prior stroke, TIA or CHA_2DS_2-VASc score$\geq$2, oral anticoagulants recommended (Class I). Options include warfarin (Level A), dabigatran (Level B), rivaroxaban (Level B), or apixaban (Level B)
ACCP	For patients with AF, including those with paroxysmal AF, for recommendations in favor of oral anticoagulation ($CHADS_2\geq1$), we suggest dabigatran 150 mg twice daily rather than adjusted-dose VKA therapy (target INR range 2.0–3.0). (Grade 2B). (The ACCP chose to recommend only those NOACs which had received regulatory approval for AF at the publication of the 2012 guidelines, i.e., dabigatran)

CCS Canadian Cardiovascular Society, *ESC* European Society of Cardiology, *AHA/ACC/HRS* American Heart Association/American College of Cardiology/Heart Rhythm Society, *ACCP* American College of Chest Physicians

There are several groups of patients with AF for whom warfarin continues to be preferable to the NOACs (Table 2.5). Warfarin has long been used for AF patients who have rheumatic mitral valve disease, based only on case series [50]. There have been no trials comparing a NOAC to warfarin in such patients; accordingly warfarin remains the preferable therapy by default. There are many patients with LV dysfunction, LV aneurysm or LV thrombus who are prescribed warfarin, with varying degrees of support offered by practice guidelines [50]. In the absence of RCTs of NOACs in such patients, warfarin is preferred by default. RE-ALIGN [51], a phase 2 randomized trial of dabigatran vs. warfarin in patients with a prosthetic mechanical valve, was discontinued early by the data and safety monitoring board because of unexpectedly high rates of thromboembolism in the dabigatran group. Warfarin continues to be recommended for prevention of thromboembolism in patients with mechanical valve prosthesis [50]. AF patients with renal failure have an increased risk of thromboembolism; accordingly there is a strong rationale for OAC therapy,

Table 2.5 Definite or relative indications for use of warfarin rather than a NOAC

Definite indication for use of warfarin rather than a NOAC
• Rheumatic AF (mitral stenosis)
• Prosthetic mechanical heart valve
• LV thrombus, aneurysm, dysfunction
• CrCl < 25–30 mL/min
• Severe hepatic dysfunction
• Requirement for a strong inhibitor or inducer of P-gp and/or CYP 3A4
Relative indication for use of warfarin rather than a NOAC
• Stable INRs on warfarin, no strong patient preference for a NOAC
• Poor compliance
• Drug plan not available and/or unacceptable patient financial impact of NOAC choice

LV left ventricular, *CrCl* creatinine clearance, *INR* international normalized ratio

even though the risk of major bleeding is increased [37]. The RCTs of the NOACs all demonstrated no interaction between renal failure and the efficacy of the NOAC compared to warfarin [38–40]. Accordingly the NOACs are preferred over warfarin for patients whose renal function would have made them eligible for the large trials. There were interactions for the outcome of major bleeding: in RE-LY the relatively less major bleeding with dabigatran was less marked with decreasing renal function (not significant) whereas in ARISTOTLE the relatively less bleeding with apixaban was more marked with decreasing renal function. When the CrCl falls below 50 mL/min, the lower doses of the NOACs are recommended. However, patients with CrCl < 30 mL/min (dabigatran, rivaroxaban and edoxaban) and <25 mL/min (apixaban) were excluded from the RCTs. Accordingly, when OAC is indicated in such patients, warfarin is preferred by default, even though the evidence for the efficacy of warfarin is derived only from case series and clinical experience [47]. For patients with CrCl < 15 mL/min or on dialysis, the competing risks of stroke and major bleeding with warfarin are such that the benefit:risk ratio of warfarin is uncertain and must be carefully tailored to each individual patient [47].

Choosing Among the NOACs

There are no published trials directly comparing the various NOACs, and it is unlikely that such trials will be undertaken. The national practice guidelines (Table 2.4) [11–14] which have increasingly recommended a NOAC in preference to or as an alternative to warfarin, have generally not made any formal recommendation for one NOAC over another. Nevertheless, clinicians are required to make choices from among several available agents and doses, so that some discussion as to factors to consider in choosing a NOAC and dose may be useful [41, 52].

Efficacy, Safety and Other Features of Individual NOACs vs. Warfarin in the RCTs

Published indirect comparisons [53, 54] using current statistical methods and acknowledging the limitations of these methods, have concluded (a) for the outcome of SSE, dabigatran 150 mg and apixaban are significantly superior to rivaroxaban but not significantly different from each other, and (b) for the outcome of major bleeding apixaban and dabigatran 110 mg are superior to rivaroxaban and dabigatran 150 mg but not significantly different from each other. Major GI bleeding was significantly greater with dabigatran 150 mg (HR 1.50, $P = 0.003$) and with rivaroxaban 20 mg (HR 1.46, $P < 0.001$) by comparison to warfarin, yet with apixaban and with dabigatran 110 mg GI bleeding was not significantly increased. Postmarketing studies of dabigatran vs. warfarin in "real world" settings confirm the RCT evidence that compared to warfarin, major bleeding rates with dabigatran 150 mg are no higher [55, 56] and with dabigatran 110 mg are lower [56].

The balances of efficacy and safety may influence clinicians to choose dabigatran 150 mg or apixaban when the risk of stroke is high, and might prompt the choice of apixaban, dabigatran 110 mg or edoxaban 30 mg when the risk of major bleeding is high. In a patient at particularly high risk of GI bleeding, apixaban might be the optimal choice among the NOACs.

Among the NOAC vs. warfarin comparisons within various subgroups of RCT subjects in the RE-LY trial of dabigatran, there was no significant interaction between age ≥75 years and allocated therapy for SSE [38]. However, it appears that the benefit to risk ratio of dabigatran 150 mg vs. warfarin was more favorable among patients <75 years, but somewhat less favorable in those ≥75 years, among whom dabigatran 110 mg may be a better choice. For both apixaban and rivaroxaban, the balance of efficacy and safety did not differ between patients ≥75 years vs. those <75 years [28, 29]. Patients ≥75 year have a high risk of stroke and might possibly achieve the best balance of efficacy and safety with apixaban, given its efficacy for prevention of SSE and the preservation of its reduced incidence of major bleeding.

Dabigatran is more dependent on renal clearance so rivaroxaban and apixaban may be preferred for borderline CrCl of 30–50 mL/min, particularly if drug interruptions for invasive procedures are likely to be necessary. Substudy data from ARISTOTLE also suggested greater reduction in bleeding in patients with a CrCl <50 mL/min for apixaban [40].

Among patients with AF, prior stroke or TIA is the strongest single risk factor for subsequent stroke. In none of the three trials of the NOACs vs. warfarin [57–59] was there a statistically significant interaction between the allocated therapy and prior stroke or TIA, for the outcomes of SSE, all stroke or intracranial hemorrhage. Among patients with prior stoke/TIA the ARRs for the outcome of all stroke are greater with dabigatran 150 mg (0.62 %/year) and apixaban (0.91 %/year) than with rivaroxaban (0.05 %/year). Only dabigatran 150 mg was associated with a significant decrease of

ischemic stroke (HR 0.76, CI 0.60–0.98, $P=0.03$). Among patients with prior stroke or TIA, either dabigatran 150 mg or apixaban may be preferable to rivaroxaban when a NOAC is chosen over warfarin.

The initial publication from the RE-LY trial [27] showed an excess of MI with dabigatran over warfarin but the difference was insignificant when additional events were considered [60]. Meta-analyses have consistently shown more MI with dabigatran, although less total mortality [61, 62]. The trials of rivaroxaban and apixaban have shown trends toward less MI with both of these agents [28, 29]. Rivaroxaban or apixaban may be preferable for patients with unstable coronary artery disease. Rivaroxaban is the only NOAC which has been evaluated in a completed phase III trial in acute coronary syndromes (ACS) [63]; 15,526 patients were randomized double-blind to twice daily rivaroxaban 2.5 mg or 5 mg or placebo. The primary efficacy outcome (cardiovascular death, MI or stroke) was reduced from 10.7 to 8.9 % (HR 0.84, CI 0.74–0.96, $P=0.008$). Rivaroxaban increased the rates of non-CABG major bleeding (2.1 % vs. 0.6 %, HR 3.96, $P<0.001$) and intracranial bleeding (0.6 % vs. 0.2 %, HR phase 3.28, $P=0.009$). Although rivaroxaban is approved in Europe for patients with ACS also receiving antiplatelet therapy, the trial does not provide guidance for the use of rivaroxaban for AF patients who also have ACS. Compared to the population of patients with AF studied in ROCKET-AF, the ACS trial cohort was much younger, did not have AF (except by chance) and the doses of rivaroxaban were much lower.

In addition to approval for AF, rivaroxaban is approved in Canada for prevention of DVT and PE in patients undergoing hip or knee replacement and for the treatment and the prevention of recurrent DVT and PE. In addition to AF, dabigatran is approved only for the prevention of DVT and PE following hip or knee replacement, whereas apixaban is also approved for treatment of DVT. In a patient with AF, rivaroxaban might be the best therapy if there is also an indication for DVT/PE treatment or prophylaxis [52].

The new OACs are remarkably free of side effects apart from the increased risk of bleeding. The only substantial difference in non-hemorrhagic side effects occurred with dabigatran, which had significantly more dyspepsia and significantly earlier discontinuation of study therapy [27]. In a patient with prior dyspepsia, rivaroxaban or apixaban might be preferable.

There are patients for whom the possibility of once-daily dosage represents a significant advantage. Also, there is good evidence that compliance with a once daily dose regimen is better than with a twice-daily regimen and accordingly rivaroxaban may be preferable to dabigatran or apixaban in such patients.

The Canadian Agency for Drugs and Technologies in Health (CADTH) performed a detailed economic analysis of dabigatran, rivaroxaban, and apixaban in relation to warfarin as part of the Common Drug Review process [49]. For patients with $CHADS_2<2$, dabigatran 150 mg was most cost-effective, with an incremental cost per QALY gained vs. warfarin of $20,845. For patients with a $CHADS_2\geq 2$, dabigatran 150 mg and apixaban 5 mg were equally cost-effective, with an incremental cost per QALY gained of $17,795. The incremental costs per QALY for rivaroxaban and dabigatran 110 mg were respectively $52,217 and $41,293.

Hence from the perspective of the publically funded Canadian healthcare system, for patients with $CHADS_2 < 2$, dabigatran 150 mg would be the most cost-effective choice whereas for those with $CHADS_2 \geq 2$, dabigatran 150 mg and apixaban are equally cost-effective. Such cost-effective analyses are governed by many assumptions, as detailed in the CADTH report.

Conclusions

Atrial fibrillation is common, the prevalence increase with age and the population prevalence is increasing as the population ages. The most serious complication of AF is embolic stroke, which has an overall annual incidence of 4.5 %, but a wide range depending upon the presence of well-defined risk factors. Oral anticoagulation with a VKA reduces the risk of the outcome of stroke or non-CNS embolism by 64 %. There is a substantial risk of major bleeding with the oral anticoagulants, but the balance of strokes prevented and major bleeds caused favors the use of an oral anticoagulant in most patients. The efficacious and safe use of warfarin, the most commonly used oral anticoagulant in North America, is challenging for both patients and physicians. The novel oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) were developed to overcome many of the challenges of warfarin use. Large randomized trials have compared each of these agents to warfarin and they have all been shown to be non-inferior for the outcomes of stroke or systemic embolism and for major bleeding, while some of the agents have been found to be superior. Dabigatran, rivaroxaban, and apixaban are approved for use in atrial fibrillation in Canada, the United States, and Europe. Some national guidelines indicate a preference for the novel oral anticoagulants over VKAs, whereas others regard them as alternatives. In general, national guidelines do not differentiate among the individual novel oral anticoagulants for the prevention of stroke and non-CNS systemic embolism.

References

1. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation. Chest. 2008;133:546S–92.
2. Wolf PA, Dawber TR, Thomas Jr E, et al. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology. 1978;28:973–7.
3. Cairns JA, Connolly SJ. Nonrheumatic atrial fibrillation: risk of stroke and role of antithrombotic therapy. Circulation. 1991;84:469–81.
4. Investigators AF. Risk factors for stroke and efficiency of antithrombotic therapy in atrial fibrillation analysis of pooled later from five randomized controlled trials. Arch Intern Med. 1994;154:1449–57.
5. Predictors of thromboembolism in atrial fibrillation: I. Clinical features of patients at risk. Stroke prevention in Atrial Fibrillation Investigators. Ann Intern Med. 1992;116:1–5.
6. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285:2864–70.

7. Camm AJ, Kirchof P, Lip GYH, et al. Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Guidelines for the management of atrial fibrillation. Eur Heart J. 2010;31:2369–429.
8. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ. 2011;342:d124.
9. Hart RG, Pearce LA, Aguilare MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146:857–67.
10. ACTIVE Writing Group on behalf of the ACTIVE Investigators, Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of vascular events (ACTIVE W): a randomized controlled trial. Lancet. 2006;367:1903–12.
11. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012;33(21):2719–47.
12. Verma A, Cairns JA, Mitchell B, et al. 2014 focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. Can J Cardiol. 2014;30:1114–30.
13. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 Suppl):e531S–75.
14. January CT, Wann LS, Alpert JS, et al. 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. Circulation. 2014;130:e199–267.
15. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess one-year risk of major bleeding in atrial fibrillation patients: the Euro Heart Survey. Chest. 2010;138:1093–100.
16. Ageno W, Gallus A, Wittkowsky A, Crowther M, Hylek EM, Palatereti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e44S–88.
17. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 suppl):e152S–84.
18. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. Arch Intern Med. 2005;165(10):1095–106.
19. Garcia D, Regan S, Crowther M, Hughes RA, Hylek EM. Warfarin maintenance dosing patterns in clinical practice: implications for safer anticoagulation in the elderly population. Chest. 2005;127:2049–56.
20. Wan Y, Heneghan C, Roberts PR, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. Circ Cardiovasc Qual Outcomes. 2008;1:84–91.
21. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med. 2010;123:638–45.
22. Yeh CH, Fredenburgh JC, Weitz JI. Oral direct factor Xa inhibitors. Circ Res. 2012;111:1069–78.
23. Dabigatran etexilate capsule drug product monograph. http://webprod5.hc-sc.gc.ca/dpd-bdpp/info.do?code=84384&lang=eng. Accessed 29 Dec 2014.
24. Rivaroxaban tablet drug product monograph. http://webprod5.hc-sc.gc.ca/dpd-bdpp/info.do?code=86440&lang=eng. Accessed 16 Dec 2014.
25. Apixaban tablet drug product monograph. http://webprod5.hc-sc.gc.ca/dpd-bdpp/info.do?code=88264&lang=eng. Accessed 16 Dec 2014.

26. Poulsen BK, Grove EL, Husted SE. New oral anticoagulants. A review of the literature with particular emphasis on patients with impaired renal function. Drugs. 2012;72:1739–53.
27. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–51.
28. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91.
29. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–92.
30. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364:806–17.
31. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093–104.
32. Zalesak M, Siu K, Francis K, et al. Higher persistence in newly diagnosed nonvalvular atrial fibrillation patients treated with dabigatran versus warfarin. Circ Cardiovasc Qual Outcomes. 2013;6:567–74.
33. Beyer-Westendorf J, Förster K, Pannach S, et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. Blood. 2014;124:955–62.
34. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major haemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation. 2007;115:2689–96.
35. The ACTIVE Investigators, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, Yusuf S. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med. 2009;360:2066–78.
36. Van Spall HG, Wallentin L, Yusuf S, et al. Variation in warfarin dose adjustment practice is responsible for differences in the quality of anticoagulation control between centres and countries: an analysis of patients receiving warfarin in the randomized evaluation of long-term anticoagulation therapy RE-LY trial. Circulation. 2012;126(19):2309–16.
37. Skanes AC, Healey JS, Cairns JA, et al. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. Can J Cardiol. 2012;28:125–36.
38. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation. An analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation. 2011;123:2363–72.
39. Fox KAA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. Eur Heart J. 2011;32:2387–94.
40. Hohnloser SH, Hijazi Z, Thomas L, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J. 2012;33(22):2821–30.
41. Heidbuchel H, Verhamme P, Alings M, et al. European Heart Rhythm Association practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2013;15:625–51.
42. Gosselin RC, Dwyre DM, Dager WE. Measuring dabigatran concentrations using a chromogenic ecarin clotting time assay. Ann Pharmacother. 2013;47(12):1635–40.
43. Samama MM, Martinoli J-L, LeFlem L, et al. Assessment of laboratory assays to measure rivaroxaban—an oral, direct factor Xa inhibitor. Thromb Haemost. 2010;103(4):815–25.
44. Becker RC, Yang H, Barrett Y, et al. Chromogenic laboratory assays to measure the factor Xa-inhibiting properties of apixaban—an oral, direct and selective factor Xa inhibitor. J Thromb Thrombolysis. 2011;32:183–7.
45. Siegal DM, Cuker A. Reversal of novel oral anticoagulants in patients with major bleeding. J Thromb Thrombolysis. 2013;35:391–8.

46. Majeed A, Hwang H-G, Connolly SJ, et al. Management and outcomes of major bleeding during treatment with dabigatran or warfarin. Circulation. 2013;128:2325–32.
47. Stiell IG, Healey JS, Cairns JA. Safety of urgent cardioversion for patients with recent-onset atrial fibrillation and flutter. Can J Cardiol. 2015;31(3):239–41.
48. Reynolds MR. Cardioversion with novel oral anticoagulants. Reconfirming a 50-year-old standard. J Am Coll Cardiol. 2014;63:1088–9.
49. Canadian Agency for Drugs and Technologies in Health. Antithrombotic agents for the prevention of stroke and systemic embolism in patients with atrial fibrillation. Ottawa: The Agency; 2013. (CADTH Therapeutic Review; vol. 1, no. 1b). http://www.cadth.ca/media/pdf/TR0003_AntithromboticAgents-AF_ScienceReport_e.pdf. Accessed 12 Apr 2013.
50. Whitlock JC, Sun JD, Fremes FE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular heart disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American Collage of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e576S–600.
51. Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American Collage of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e637S–68.
52. Cairns JA. Which oral anticoagulant for which atrial fibrillation patient: recent clinical trials and evidence-based choices. Can J Cardiol. 2013;29(10):1165–72.
53. Lip GYH, Larsen TB, Skjoth F, Rasmussen LH. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. J Am Coll Cardiol. 2012;60:738–46.
54. Mantha S, Ansell J. An indirect comparison of dabigatran, rivaroxaban and apixaban for atrial fibrillation. Thromb Haemost. 2012;108:476–84.
55. Southworth MR, Reichman ME, Unger EF. Dabigatran and postmarketing reports of bleeding. N Engl J Med. 2013;368:1272–4.
56. Larsen TB, Rasmussen LH, Skjoth F, et al. Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation: a prospective nationwide cohort study. J Am Coll Cardiol. 2013;61(22):2264–73.
57. Diener H-C, Connolly SJ, Ezekowitz MD, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. Lancet Neurol. 2010;9:1157–63.
58. Hankey GJ, Patel MR, Stevens SR, et al. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack; a subgroup analysis form ROCKET AF. Lancet. 2012;11:315–22.
59. Easton JD, Lopes RD, Bahit MC, et al. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. Lancet Neurol. 2012;11:503–11.
60. Hohnloser SH, Oldgren J, Yang S, et al. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY (randomized evaluation of long-term anticoagulation therapy) trial. Circulation. 2012;125:669–76.
61. Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. Arch Intern Med. 2012;172(5):397–402.
62. Mak KH. Coronary and mortality risk of novel oral antithrombotic agents: a meta-analysis of large randomized trials. BMJ Open. 2012;2(5).
63. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012;366(1):9–19.
64. Van de Werf F, Brueckmann M, Connolly SJ, et al. A comparison of dabigatran etexilate with warfarin in patients with mechanical heart valves: THE randomized, phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN). Am Heart J. 2012;163:931–7.
65. Herzog CA, Asinger RW, Berger AK, et al. Cardiovascular disease in chronic kidney disease. A clinical update from kidney disease: improving global outcomes (KDIGO). Kidney Int. 2011;80:572–86.

Chapter 3
Mechanistic Rationale for LAA Closure with AF and Stroke Prevention

David Meerkin

Introduction

The high-risk subgroups of atrial fibrillation (AF) patients for ischemic embolic stroke have traditionally been treated with anticoagulation with good, although imperfect results. A narrow therapeutic window, bleeding complications, and multiple contraindications have all limited the use of vitamin K antagonists. The novel oral anticoagulants (NOAC) have been developed as an attractive alternative, but the attraction of a single procedure rather than daily therapy, ongoing bleeding risks, and the remaining large population of patients unable to tolerate anticoagulants have led to the development and broadening penetration of percutaneous left atrial appendage (LAA) occlusion. Understanding the rationale of this localized approach is beneficial in understanding application as well as optimizing patient selection.

Anatomy and Physiology

Although the anatomy of the LAA will be described more extensively in the next chapter, a brief description is necessary in order to consider the rationale for its exclusion from the cardiovascular system as an embolic prevention technique in non-valvular AF.

The atrial appendages have several unique features. The formation of the two appendages differentiates the morphological right and left sides of the primary atrium. They have a different embryonic origin compared to the atria, as they are

D. Meerkin, M.B.B.S. (✉)
Structural and Congenital Heart Disease Unit, Shaare Zedek Medical Center, POB 3235, Jerusalem 91031, Israel
e-mail: meerkin@szmc.org.il

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_3

believed to be remnants of the embryonic left atrium [1]. In distinction to the atria that are smooth walled, the appendages contain numerous trabeculae forming crypts, resembling the ventricles. As such, the LAA is a trabeculated blind pouch with a complex and highly variable anatomy. It is usually long and tubular, often with a multi-lobed body extending over the atrioventricular groove and left ventricular surface [2]. The ostium is most often eccentric, located between the left ventricle and the left upper pulmonary vein [3]. The LAA lies in the left atrioventricular sulcus, overhanging the left circumflex coronary artery and the great cardiac vein; its orifice is typically anterior and inferior to the left superior pulmonary vein, whereas its body is anterior and superior to the left ventricle [4, 5]. Interestingly, the epicardium on the surface of the atrial appendages is significantly thicker than over the ventricles. In addition, the LAA lies in close epicardial contact to the left ventricle within the confines of the pericardium. The physiological properties and anatomical relations of the LAA render it ideally suited to function as a decompression chamber during left ventricular systole and during other instances of elevated left atrial pressure [3, 6]. The atrial appendages also function as storage for atrial natriuretic factor (ANF), and perform an important physiologic function regulating the intravascular volume via release of atrial natriuretic peptide. In normal hearts, 30 % of the ANF is contained in the LAA [2].

Contraction of the LAA is greater than the rest of the left atrium with a distinct pattern of contraction [7]. Although doppler-measured LAA flow in patients in sinus rhythm were initially described as biphasic [8], quadriphasic appendage flow patterns have been described in 40–70 % of the patients due to additional emptying and filling [9]. The cycle commences with forward flow (expulsion from the appendage), occurring soon after the start of transmitral flow in early diastole, followed by a short period of backward flow (back into the appendage). The first forward phase occurring during the start of early diastole, suggests a casual relationship between left ventricular relaxation and early appendage emptying. Coincident with atrial systole is a second phase of forward flow caused by contraction of the appendage, followed by another phase of backward flow, possibly caused by elastic recoil of the appendage. This flow pattern is largely independent of heart rate [2, 6].

The relationship between LAA flow and left ventricular filling also raises the question as to whether the appendage actively contracts or whether it functions passively, being compressed by the left ventricle during ventricular diastole and emptied by the negative pressure caused by ventricular filling [2, 6]. There is evidence to support active LAA contraction during sinus rhythm. This includes the prominent muscle ridges in the LAA that would atrophy if there were no contraction. Furthermore, passive emptying and filling of the appendage would challenge the quadriphasic appendage flow pattern [2, 6].

In humans, clamping of the LAA during cardiac surgery results in an increase in left atrial pressure and dimension as well as increases in the transmitral and pulmonary diastolic flow velocities [10]. Because of its increased distensibility, the LAA may augment hemodynamic function by modulating the left atrial pressure–volume relationship in the setting of left atrial pressure or volume overload [11].

Shirani and Alaeddini [12] reported that patients with AF had significantly greater LAA volumes and a larger LAA luminal surface area compared to those

without AF. Furthermore, in most patients with chronic AF, there is significant endocardial thickening of the LAA with fibrous and elastic tissue (endocardial fibroelastosis). They suggest that because of LAA remodeling, active contraction of the LAA is decreased and the risk of thrombus formation is increased.

Variable Pathology

Clinical studies have demonstrated a significant difference between non-rheumatic AF (NRAF) and rheumatic AF (RAF) [13]. The combination of factors that result in a prothrombotic environment is different in these two situations. In NRAF, passive filling and emptying of the LA in spite of the lack of active contraction maintains adequate flow in the LA body. The LAA however, acting as a blind pouch particularly in the more complex anatomies, is the principal site of stasis and as such, thrombus formation [14]. In distinction, the slow emptying of the LA associated with rheumatic mitral disease, predominantly mitral stenosis, results in marked stasis of blood in the entire LA with an increased risk of thrombus formation in the entire LA, without predilection to the LAA [13, 15].

This seems to be confirmed by an important study reported by Blackshear and Odell [13], where they assessed the incidence of thrombus in patients with AF by TEE, autopsy or surgery. They collected the data from 14 studies with a total of 3504 RAF patients including 446 patients with thrombi [16–29] and found that the LAA was the site of the thrombus in 57 % of these cases (Table 3.1). They also presented data from nine studies with a total of 1288 patients with NRAF and 222 with thrombi [17, 19, 30–36]. In this series, 91 % of the thrombi were located in the LAA (Table 3.2). Although no attempt to control for anticoagulant status was made, and these findings were grouped from retrospective reports, the localization of thrombi to the LAA in NRAF is supportive of the notion that the unique anatomical and physiological features of this site predispose it to this complication.

Approaches to Stroke Prevention in AF

Based upon the increased thrombogenicityas previously described and the stasis that is manifest in the localized region on the LA and particularly the LAA, the approach to intervening to prevent stroke in association with AF could be with either of two potential options. The first approach, which is decades old with clear delineation of its benefits and risks, is to counteract the thrombogenicity resulting in the presence of the stasis by treating with anticoagulants. The range of intravenous, subcutaneous, and oral anticoagulants are all potentially successful avenues to assist in counteracting this effect. An alternative would be to eliminate the local environment where that thrombogenicity is most manifest or to prevent the emergence of thrombi from that local environment (LAA).

Table 3.1 Review of published reports detailing the frequency and site of thrombus location in patients with rheumatic atrial fibrillation (after Blackshear [13])

Setting	No. of patients	Thrombus location		Reference no.
		LA appendage	LA cavity	
Operation	581	26	17	[16]
Autopsy	136	12	11	[17]
Operation	818	20	23	[18]
TEE	50	12	4	[19]
Operation	21	6	0	[20]
Operation	293	11	10	[21]
TEE/operation	110	13	8	[22]
TEE/operation	19	5	0	[23]
TEE	20	1	1	[24]
Operation	581	25	16	[25]
Autopsy	26	13	5	[26]
TEE	260	17	16	[27]
Operation	80	33	13	[28]
Autopsy	509	60	68	[29]
Total	3504	254	192	

LA left atrium, *TEE* transesophageal echocardiography

Table 3.2 Review of published reports detailing the frequency and site of thrombus location in patients with non-rheumatic atrial fibrillation (after Blackshear [13])

Setting	No. of patients	Thrombus location		Reference no.
		LA appendage	LA cavity	
TEE[a]	317	66	1	[30]
TEE	233	34	1	[31]
Autopsy	506	35	12	[17]
TEE	52	2	2	[19]
TEE	48	12	1	[32]
TEE and operation	171	8	3	[33]
SPAF III TEE study	359	19	1	[34]
TEE	272	19	0	[35]
TEE	60	6	0	[36]
Total	1288	201	21	

[a]5 % of this cohort had mitral stenosis or a prosthetic mitral valve
LA left atrium, *SPAF III* stroke prevention in atrial fibrillation trial, *TEE* transesophageal echocardiography

Although appearing simple, there are multiple limitations associated with long-term anticoagulant therapy [37]. These include:

1. Increased risk of bleeding
2. Warfarin's narrow therapeutic window requiring persistent monitoring of coagulation (International Normalized Ratio, INR)
3. Patient noncompliance

4. Physician reluctance to prescribe, especially to elderly patients, associated falls, hypertension, and comorbidities
5. Need for therapy discontinuation for surgery, procedures, and diagnostic tests

Increased bleeding, both major and minor, is inherent to all antithrombotic therapy. In a meta-analysis including 50,578 patients from three randomized trials, Capodanno et al. [38] reported major bleeding rates of 5.0 % and 5.4 % for NOAC and warfarin, respectively. Even minor bleeding may lead to discontinuation of antithrombotic therapy and exposure to stroke risk. A local solution that offers the benefit of embolic protection in the absence of the long-term risks associated with systemic anticoagulation would be an attractive solution.

The potential avenues to remove the local environment would be to excise the LAA, to occlude its ostium therefore separating the thrombogenic environment from the left heart circulation, or to place a filter at the ostium that would prevent the emergence of thrombi that may form distally into the systemic circulation. The challenges of such an approach are multiple, with many potential pitfalls depending upon the approach that is adopted. Almost all the approaches must contend with the issue of: where is the ostium of the appendage? This leads to a number of further issues:

- At what point is the exclusion of the appendage effective at reducing embolic risk?
- Must it all be removed?
- Is a remaining cul de sac thrombogenic?
- Is there a critical size of a residual cul de sac for efficacy?
- Are there residual leaks?
- Is there a critical size of residual leak?
- Does device design play a role in efficacy regarding residual leaks and thrombogenicity?

Based upon the distinct approaches adopted, each will have variable benefits and failures: e.g., surgical excision may leave a cul de sac or miss a proximal lobe, surgical stitching or stapling have the same issues but also residual or recurrent leak [39, 40]. Different devices (e.g., Watchman and ACP) define the ostium differently, which may be distinct to the true anatomical ostium resulting in different depths of deployment [41, 42]. This may result in device-dependent distinctions in depths of residual cul de sac and subsequent efficacy.

The concept of a filter device to prevent migration of thrombi forming in the LAA to the systemic circulation is also appealing, and is the basis of the Watchman device. This could result in embolic protection while allowing the LAA to continue to function as a source for ANF and possibly allowing for increased LA compliance due to its distensibility. In practice it is extremely challenging to prevent endocardial tissue growth and/or fibrin deposition on the filter surface resulting in the filter progressing to an occlusion device over a period of several weeks to months. To date although there is a large combined surgical and percutaneous experience of LAA occlusion or excision, there have been no consistent reports of clinical deterioration (particularly of heart failure) with this approach.

Conclusion

Based upon strong evidence that in NRAF the principal although not exclusive source of intracardiac thrombus formation is in the LAA, two alternative therapeutic avenues have been explored and employed to prevent embolic complications in the patients at risk. A wealth of experience with anticoagulation, predominantly with Vitamin K antagonists, has been built and clearly demonstrated not only its benefits but also its limitations. The NOACs have broadened the scope but most of the critical limitations related to increased bleeding remain. The local approach of excluding the LAA as a source for thrombus formation, from the systemic circulation using a wide range of approaches including surgical, percutaneous, and combined techniques have been developed. These have been increasingly adopted, particularly in the subset of patients where systemic anticoagulation is challenging. However, as experience builds from theoretical rationale to stronger clinical data, it may find a broader application.

References

1. Beeri R. Left atrial appendages from adult hearts contain a reservoir of diverse cardiac progenitor cells. PLoS One. 2013;8:e59228.
2. Sakellaridis T, Argiriou M, Charitos C, Tsakiridis K, Zarogoulidis P, Katsikogiannis N, Kougioumtzi I, Machairiotis N, Tsiouda T, Arikas S, Mpakas A, Beslevis T, Koletas A, Zarogoulidis K. Left atrial appendage exclusion—where do we stand? J Thorac Dis. 2014;6 Suppl 1:S70–7. doi:10.3978/j.issn.2072-1439.2013.10.24.
3. Cruz-Gonzalez I, Yan BP, Lam YY. Left atrial appendage exclusion: state-of the art. Catheter Cardiovasc Interv. 2010;75:806–13.
4. Singh IM, Holmes D. Left atrial appendage closure. Curr Cardiol Rep. 2010;12:413–21.
5. Leal S, Moreno R, de Sousa AM, et al. Evidence-based percutaneous closure of the left atrial appendage in patients with atrial fibrillation. Curr Cardiol Rev. 2012;8:37–42.
6. Al-Saady NM, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. Heart. 1999;82:547–54.
7. Yamaji K, Fujimoto S, Yutani C, Hashimoto T, Nakamura S. Is the site of thrombus formation in the left atrial appendage associated with the risk of cerebral embolism? Cardiology. 2002;97(2):104–10.
8. Pollick C, Taylor D. Assessment of left atrial appendage function by transesophageal echocardiography: implications for the development of thrombus. Circulation. 1991;84:223–31.
9. Mikael Kortz RA, Delemarre BJ, van Dantzig JM, Bot H, Kamp O, Visser CA. Left atrial appendage blood flow determined by transesophageal echocardiography in healthy subjects. Am J Cardiol. 1993;71:976–81.
10. Tabata T, Oki T, Yamada H, Iuchi A, Ito S, Hori T, Kitagawa T, Kato I, Kitahata H, Oshita S. Role of left atrial appendage in left atrial reservoir function as evaluated by left atrial appendage clamping during cardiac surgery. Am J Cardiol. 1998;81:327–32.
11. Davis 3rd CA, Rembert JC, Greenfield Jr JC. Compliance of left atrium with and without left atrium appendage. Am J Physiol. 1990;259:H1006–8.
12. Shirani J, Alaeddini J. Structural remodeling of the left atrial appendage in patients with chronic non-valvular atrial fibrillation: implications for thrombus formation, systemic embolism, and assessment by transesophageal echocardiography. Cardiovasc Pathol. 2000;9:95–101.

13. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg. 1996;61(2):755–9.
14. Kimura T, Takatsuki S, Inagawa K, Katsumata Y, Nishiyama T, Nishiyama N, Fukumoto K, Aizawa Y, Tanimoto Y, Tanimoto K, Jinzaki M, Fukuda K. Anatomical characteristics of the left atrial appendage in cardiogenic stroke with low CHADS2 scores. Heart Rhythm. 2013;10(6):921–5.
15. Nunes MCP, Handschumacher MD, Levine RA, Barbosa MM, Vinicius T, Carvalho VT, Esteves WA, Zeng X, Guerrero JL, Zheng H, Tan TC, Hung J. Role of LA shape in predicting embolic cerebrovascular events in mitral stenosis: mechanistic insights from 3D echocardiography. JACC Cardiovasc Imaging. 2014;7(5):453–61.
16. Acar J, Cormier B, Grimberg D, Kawthekar G, Iung B, Scheuer B, Farah E. Diagnosis of left atrial thrombi in mitral stenosis—usefulness of ultrasound techniques compared with other methods. Eur Heart J. 1991;12(Suppl B):70–6.
17. Aberg H. Atrial fibrillation. I. A study of atrial thrombosis and systemic embolism in a necropsy material. Acta Med Scand. 1969;185:373–9.
18. Beppu S, Park YD, Sakakibara H, Nagata S, Nimura Y. Clinical features of intracardiac thrombosis based on echocardiographic observation. Jpn Circ J. 1984;48:75–82.
19. Tsai LM, Chen JH, Yang YJ. Role of transesophageal echocardiography in detecting left atrial thrombus and spontaneous echo contrast in patients with mitral valve disease and nonrheumatic atrial fibrillation. J Formos Med Assoc. 1990;89:270–4.
20. Aschenberg W, Schlüter M, Kremer P, Schröder E, Siglow V, Bleifeld W. Transesophageal two-dimensional echocardiography for the detection of left atrial appendage thrombus. J Am Coll Cardiol. 1986;7:163–6.
21. Shrestha NK, Moreno FL, Narciso FV, Torres L, Calleja HB. Two-dimensional echocardiographic diagnosis of left-atrial thrombus in rheumatic heart disease. A clinicopathologic study. Circulation. 1983;67:341–7.
22. Lin SL, Hsu TL, Liou JY, Chen CH, Chang MS, Chiang HT, Chen CY. Usefulness of transesophageal echocardiography for the detection of left atrial thrombi in patients with rheumatic heart disease. Echocardiography. 1992;9:161–8.
23. Kronzon I, Tunick PA, Glassman E, Slater J, Schwinger M, Freedberg RS. Transesophageal echocardiography to detect atrial clots in candidates for percutaneous transseptal mitral balloon valvuloplasty. J Am Coll Cardiol. 1990;16:1320–2.
24. Manning WJ, Reis GJ. Douglas PS Use of transoesophageal echocardiography to detect left atrial thrombi before percutaneous balloon dilatation of the mitral valve: a prospective study. Br Heart J. 1992;67:170–3.
25. Cormier B, Serafini D, Grimberg D, Scheuer B, Acar J. Detection of thrombosis of the left atrium in mitral valve stenosis. Particular value of transesophageal echography. Arch Mal Coeur Vaiss. 1991;84:1321–6.
26. Jordan RA, Scheifley CH, Edwards JE. Mural thrombis and arterial embolism in mitral stenosis. Circulation. 1951;3:363–7.
27. Hwang JJ, Kuan P, Lin SC, Chen WJ, Lei MH, Ko YL, Cheng JJ, Lin JL, Chen JJ, Lien WP. Reappraisal by transesophageal echocardiography of the significance of left atrial thrombi in the prediction of systemic arterial embolization in rheumatic mitral valve disease. Am J Cardiol. 1992;70:769–73.
28. Sharma S, Kumar MV, Aggarwal S, Reddy VM, Kaul U, Rajani M, Venugopal P. Chest radiographs are unreliable in predicting thrombi in the left atrium or its appendage in rheumatic mitral stenosis. Clin Radiol. 1991;43:337–40.
29. Wallach JB, Lukash L, Angrist AA. An interpretation of the incidence of mural thrombi in the left auricle and appendage with particular reference to mitral commissurotomy. Am Heart J. 1953;45:252–4.
30. Stoddard MF, Dawkins PR, Prince CR, Ammash NM. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study. J Am Coll Cardiol. 1995;25:452–9.

31. Manning WJ, Silverman DI, Keighley CS, et al. Transesophageal echo (TEE) facilitated early cardioversion for patients with new atrial fibrillation: a 4-year experience. Circulation. 1994;90:1–21a.
32. Brown J, Sadler DB. Left atrial thrombi in non-rheumatic atrial fibrillation: assessment of prevalence by transesophageal echocardiography. Int J Card Imaging. 1993;9:65–72.
33. Manning WJ, Waksmonski CA, Haering JM, et al. Sensitivity and specificity of transesophageal echo for left atrial thrombi: a prospective consecutive surgical study. Circulation. 1994;90:1202a.
34. Klein AL, Grimm RA, Black IW et al. for the ACUTE Investigators. Assessment of cardioversion using transesophageal echocardiography compared to conventional therapy: The ACTE Randomized Pilot Study. Circulation. 1994;90 (Suppl 1):21a
35. Leung DY, Black IW, Cranney GB, Hopkins AP, Walsh WF. Prognostic implications of left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. J Am Coll Cardiol. 1994;24:755–62.
36. Hart RG, Halperin JL. Atrial fibrillation and stroke. Revisiting the dilemmas. Stroke. 1994;25:1337–41.
37. Whitlock R, Healey J, Vincent J, Brady K, Teoh K, Royse A, Shah P, Guo Y, Alings M, Folkeringa RJ, Paparella D, Colli A, Meyer SR, Legare JF, Lamontagne F, Reents W, Böning A, Connolly S. Rationale and design of the left atrial appendage occlusion study (LAAOS) III. Ann Cardiothorac Surg. 2014;3:45–54.
38. Capodanno D, Capranzano P, Giacchi G, Calvi V, Tamburino C. Novel oral anticoagulants versus warfarin in non-valvular atrial fibrillation: a meta-analysis of 50,578 patients. Int J Cardiol. 2013;167:1237–41.
39. Apostolakis E, Papakonstantinou NA, Baikoussis NG, et al. Surgical strategies and devices for surgical exclusion of the left atrial appendage: a word of caution. J Card Surg. 2013;28:199–206.
40. Aryana A, Saad EB, d'avila A. Left atrial appendage occlusion and ligation devices: what is available, how to implement them, and how to manage and avoid complications. Curr Treat Options Cardiovasc Med. 2012;14:503–19.
41. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P, Investigators PROTECTAF. 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.
42. Meerkin D, Butnaru A, Dratva D, Bertrand OF, Tzivoni D. Early safety of the amplatzer cardiac plug™ for left atrial appendage occlusion. Int J Cardiol. 2013;168:3920–5.

Chapter 4
LAA Anatomy

Creighton W. Don, Andrew C. Cook, and Mark Reisman

Introduction

A comprehensive understanding of left atrial anatomy has become essential as transcatheter therapies have emerged for left atrial appendage (LAA) occlusion, atrial fibrillation (AF) ablation, mitral valvular repair and replacement, and atrial septal defect closures. Furthermore, intentional and inadvertent instrumentation of pulmonary veins and LAA during atrial and transseptal procedures requires a fundamental understanding of the anatomy and spatial relationships of these structures, in order to successfully plan and perform these procedures and avoid significant complications.

This chapter describes the anatomy of the LAA, its anatomical variants, and its relationship to other left atrial structures with special regard to transcatheter procedures.

Overall Anatomy of the LAA

Although the LAA is typically the smallest part of the left atrium, it is the most variable anatomically. The LAA is typically characterized as having two components; an ostium or "os," which defines its junction with body of the left atrium, and a lobar

C.W. Don
Department of Medicine, University of Washington, Seattle, WA, USA

A.C. Cook
UCL Institute of Cardiovascular Science, London, UK

M. Reisman, M.D. (✉)
Department of Medicine, University of Washington, Seattle, WA, USA

University of Washington Medical Center, 1959 NE Pacific St.,
Box 356171, Seattle, WA 98195, USA
e-mail: reismanm@uw.edu

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_4

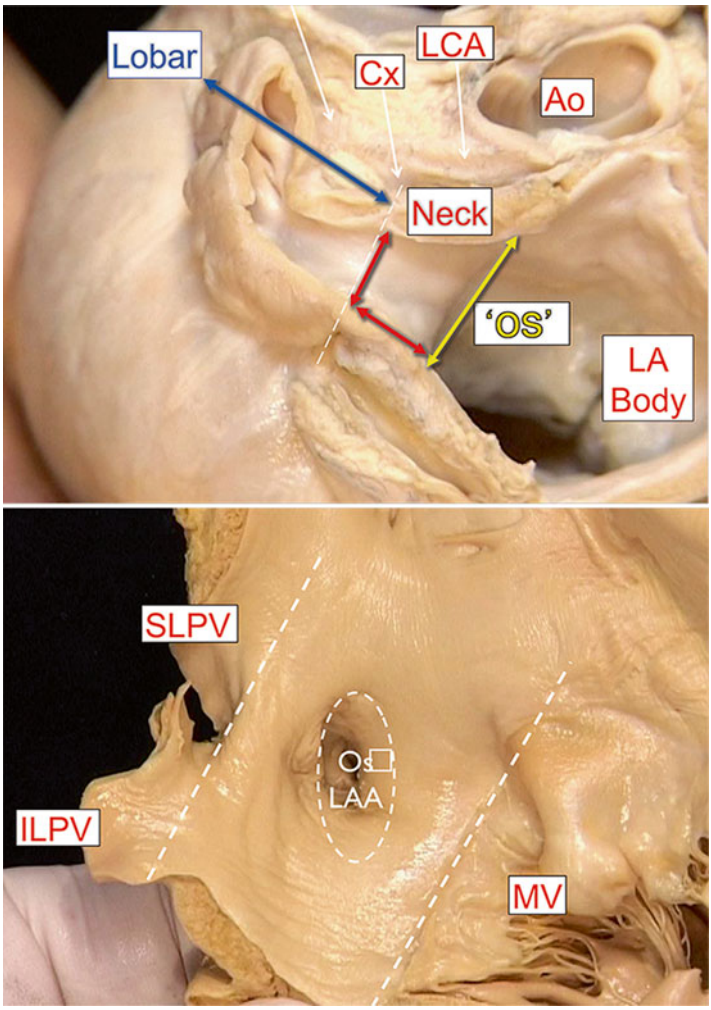


Fig. 4.1 Left atrial appendage structures

region, which is known to be the most variable anatomically [1, 2]. The ostium diameter is defined by the distance from the limbus (the left lateral ridge separating the LAA from the lower pulmonary venous trunk) and the mitral valve annulus. An equally important characteristic is the narrow junction that exists between the lobar region and the ostium. This characteristic "neck" is defined by the course of the circumflex coronary artery (Fig. 4.1), and is the "landing zone" a few mm from the ostium used as a reference for placement of LAA occlusion devices.

Overall, there are reported age- and sex-related variations in the size of the LAA, and changes that can occur in patients known to have had AF [1]. Remodeling of the musculature of the LAA has been noted in patients with both paroxysmal and chronic AF, with smoothing of the pectinate muscles and thereby thinning of the

wall [3]. In addition, patients with AF were shown to have endocardial changes with fibrosis and endocardial fibroelastosis on histologic examination, primarily affecting the proximal part of the LAA close to the os and neck [4, 5].

Left Atrial Structures and the LAA

The LAA is an anterolateral structure within the left atrium that originates anterior to the left pulmonary vein ostia (Fig. 4.2). The body of the atrial appendage typically extends anteriorly toward the right ventricular outflow track, so it may also lay over the left main and left anterior descending coronary artery. In a small number of patients, the LAA is directed laterally and posteriorly or superiorly toward the transverse sinus [6]. The LAA may course behind the pulmonary trunk and thus prohibit use of pericardial snare-type devices. Internally, the os of the LAA is anterior to the pulmonary veins, separated by a left lateral ridge of tissue. This tissue represents an infolding of the left atrial wall, forming a lateral ridge approximately 5 mm in width. In a third of cases, the LAA is either superior or inferior to the pulmonary veins [7]. Inferiorly, a muscular band separates the LAA from the mitral valve (Figs. 4.1 and 4.2). The circumflex coronary artery runs along the mitral annulus, underneath the LAA, near the LAA neck (Fig. 4.1).

The general relationship of these structures to each other is typically preserved but their orientation in space is often displaced due to rotation of the heart or enlargement of the left atrium. There is also significant variation in the distances between these structures. Dilation of the left atrium increases with aging, AF, hypertension, and valvular disease, and such changes may exaggerate these variations [1]. Persistent AF is associated with dilation of the left atrium, pulmonary veins, and LAA [8]. It is also notable that in 25 % of patients, there is a single left pulmonary trunk, instead of separate left superior and inferior pulmonary veins [8]. In such patients, there may be a greater inferior separation between the pulmonary and LAA ostia.

The course of the circumflex and the location of the pulmonary veins are important to recognize given possible trauma to these structures during LAA occlusion procedures. The circumflex and great coronary vein typically run underneath the neck of the LAA and can be compressed during intracardiac LAA occlusion.

While LAA thrombus is often associated with strokes, several components of the left atrium, including the body, pulmonary veins, vestibule, and left side of the atrial septum all play an important role in AF, which may lead to stroke as detailed in prior reviews [7, 9, 10]. These not only described the nonuniform orientation and thickness of the left atrial musculature and its variable extension into the pulmonary veins as sheaths, which is more prominent superiorly, but also related this anatomy to the processes thought to occur in AF [9, 10].

The left phrenic nerve runs anteriorly over the LAA and can be damaged during ablation procedures within the LAA or open surgical procedures, but to date has not been described as a complication of transcatheter LAA occlusion. In one anatomic study, the phrenic nerve ran over the neck of the LAA in 23 % of patients [7]. The esophagus runs posteriorly to the left atrium and pulmonary veins, so is not affected by LAA procedures, but can be damaged during ablation procedures [11].

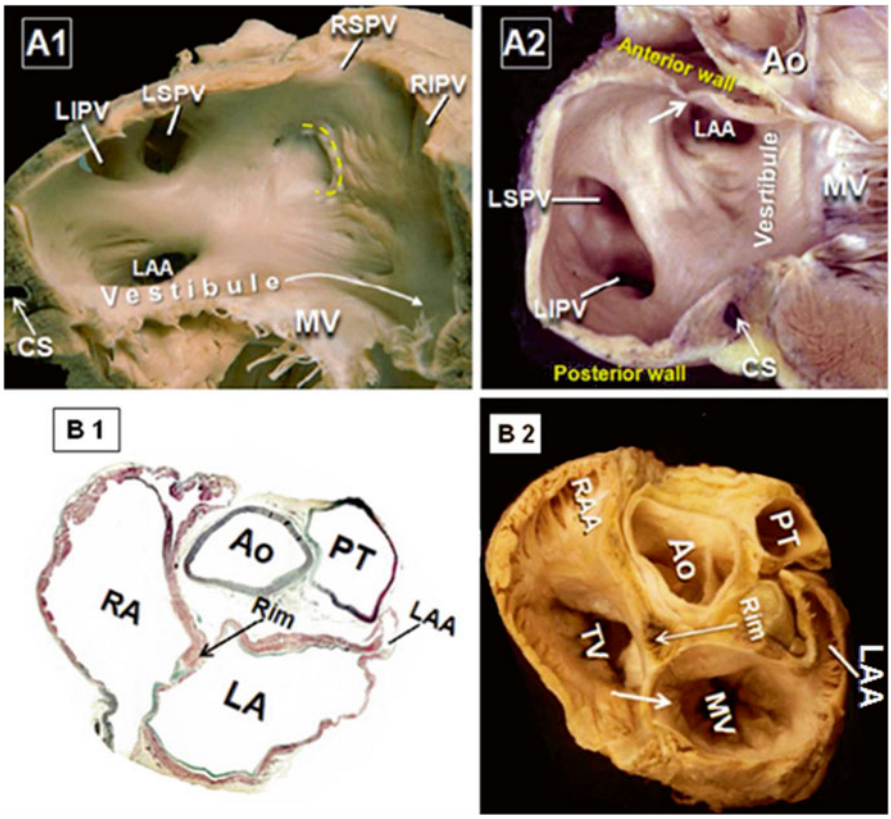


Fig. 4.2 Anatomy of the left atrial appendage and left atrial structures. (**A1**) Dissection of the posterior wall of the left atrium (LA) close to the posterior interatrial groove. The septal aspect of the LA shows the crescentic line of the free edge of the flap valve (*yellow dotted line*) against the rim of the oval fossa. The orifices of the right superior and inferior pulmonary veins (RSPV and RIPV) are adjacent to the plane of the septal aspect of the LA. (**A2**) Sagittal section of the heart showing the anterior wall of the LA behind the ascending aorta can become very thin at the area near the vestibule of the mitral valve (*arrow*). (**B1**) Histological section with Masson trichrome taken through the short axis of the heart to show the thin flap valve and the muscular rim of the fossa. (**B2**) Short axis through the interatrial septum (*arrow*). *Ao* aorta, *CS* coronary sinus, *LAA* left atrial appendage, *LIPV* left inferior pulmonary vein, *LSPV* left superior pulmonary vein, *MV* mitral annulus, *PT* pulmonary trunk, *RA* right atrium, *RAA* right atrial appendage, *TV* tricuspid annulus. (from Cabrera JA, et al. Heart 2014;100:1636–1650)

Atrial Septum and LAA

A complete understanding of the anatomy of the atrial septum and the LAA is crucial to performing both left atrial ablations and LAA occlusion. The intra-atrial septum separates the anteriorly positioned right atrium from the laterally and posteriorly located left atrium. The face of the septum therefore typically points laterally and posteriorly, toward the left pulmonary veins and slightly away from the LAA

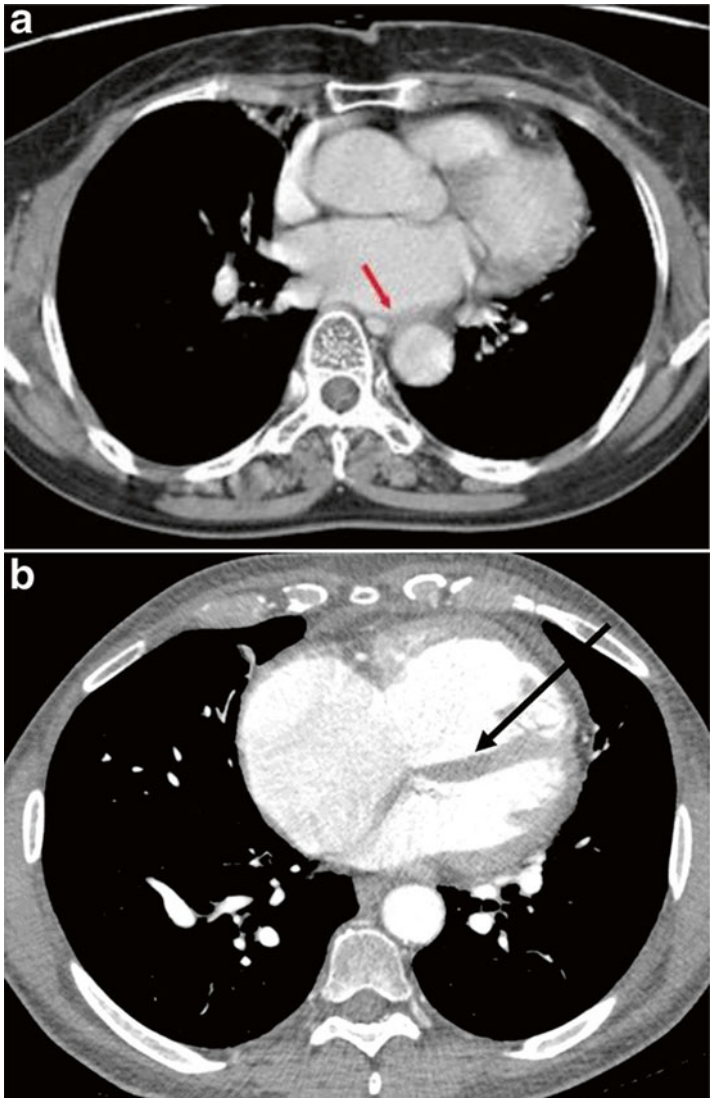


Fig. 4.3 (**a**) Left atrial enlargement with a posterior facing atrial septum. (**b**) Right atrial enlargement with a lateral facing atrial septum [12]

(Fig. 4.2B2). As the left atrium enlarges and the septum bows toward the right atrium, the plane of the intra-atrial septum may be displaced, exaggerating this posterior rotation, and a steeper left angulation of the image intensifier and posterior rotation of the transseptal needle are often needed to achieve perpendicularity to the septal plane (Fig. 4.3a). Conversely, right atrial enlargement requires a more lateral rotation of the transseptal needle (Fig. 4.3b) [12].

In order to engage the LAA from a transseptal approach, a posterior and inferior puncture will allow for the most direct trajectory of wires and delivery sheaths to the

anterior LAA (Fig. 4.2B2). Although a puncture through the center of the fossa or foramen ovalis is the standard technique for transseptal punctures, there is significant variability in the location of the fossa despite its traditional depiction as being in the center of the atrial septum [13]. Additionally, the patent foramen ovale tends to be located superiorly, and catheter crossing from such a high position can make engagement of the LAA challenging.

While endeavoring to perform an inferoposterior septal puncture, it is nevertheless critical to be aware of the surrounding "rims" of the septum, to avoid perforations through the right atrial wall or pulmonary veins, that could lead to pericardial effusion or tamponade [14]. Given the variability in septal anatomy and location of the fossa, real-time echocardiographic imaging is strongly recommended to define the ideal transseptal location, and guide the transseptal puncture.

LAA Ostium

The ostium is typically oval-shaped and obliquely oriented with respect to both the vestibule and annulus of the mitral valve, and the ridge of muscle that separates it from the left pulmonary veins (Figs. 4.1 and 4.2). The average diameter of the short axis is 20 mm and of the long axis is 30 mm, when measuring from the top of the limbus to the muscular band at the mitral valve [15], and tend to increase in size with age, gender, body size [1] and the presence of AF [8]. A more dilated and round profile has been noted in patients with AF [16]. There can be a threefold increase in the dimension of the LAA and its os, a feature that has been shown to recede following successful ablation for AF [5, 17]. There is also significant variation among studies reporting ostial dimensions, however, due to differences in definitions for autopsy versus echocardiographic and imaging landmarks of the ostium [1]. Furthermore, systolic measurements tend to be 15–20 % larger than diastolic ones [15], which is a critical consideration when selecting occlusion device sizes. Importantly, there is anatomic variation in the location (or height) of the ostium with respect to the body of the left atrium, which not only can affect access to the LAA following transseptal puncture, but also the shape of the left lateral ridge itself and proximity of the appendage to the pulmonary trunk or mitral valve. Reconstructions and morphologic studies have shown that the majority of LAA are located in line with the left superior pulmonary vein or just below, sometimes with only narrow separation between the pulmonary vein and the ostium via a narrow left lateral ridge [14, 18–20]. The ostium can also be located above the left superior pulmonary vein making it potentially more difficult to access for device occlusion and more likely that the lobar part of the LAA will run closer to the left side of the pulmonary trunk. Alternatively, an ostium that is adjacent to the body of the left atrium inferiorly, in line with the left inferior pulmonary vein, will be in closer proximity to the mitral valve and its vestibule [14, 18]. All these variations in height of the ostium may alter selection of device type, as well as adjustments in approach to the procedure.

In general the pectinate muscles within the LAA stop at the neck, but sometimes may extend from the neck and ostium along the inferior border of the left atrium.

These extensions are often referred to as "pits or troughs" or by others as the limbus of the LAA. These regions are anatomically identical to the lobar region of the LAA in that they are composed of thin atrial wall interposed between fine pectinate muscle bundles [19, 21]. For endovascular occlusion, these regions are important to recognize prior to the procedure, not only because of the risk of perforation, but also because it may alter device choice and placement.

LAA Neck

The narrowest part of the LAA, appropriately referred to as the "neck," is typically located within the appendage just distal to the ostium (Fig. 4.1). This region is the part of the LAA that usually overlies the course of the circumflex coronary artery. There is wide anatomic variation in the distance between the ostium and the neck of the LAA, which sometimes gives the neck a considerable length that makes it favorable for endovascular closure. Conversely, when the neck is extremely short and is followed by a sharp change in angle within the subsequent lobar region (i.e., chicken-wing configuration), it can prevent the use of longer devices, such as the WATCHMAN that require a depth equivalent to the device diameter, or the Amplatzer Cardiac Plug (ACP, or Amulet) that requires a minimum of 10 mm depth for implantation [7, 22]. The neck width is also highly variable and neck dilation has been associated with an increased risk for stroke [23]. In those cases where the neck has become dilated such that it is of similar size to the ostium, significant device oversizing may be required, given the variation in neck length and diameter, it needs to be carefully imaged and measured when planning for device occlusion.

Lobar Region

Although traditionally depicted as a narrow, finger-like structure, the lobar region demonstrates extreme anatomic variation. This variability has been noted anatomically, by computed tomography angiography (CTA) [24–26], magnetic resonance imaging [27], intracardiac echocardiography [28], and transesophageal echocardiography [15, 29]. A study of 500 human anatomic specimens showed 54 % of LAA having two lobes, 23 % having three lobes, 20 % having only one lobe, and 3 % with four lobes. There is also great heterogeneity within these groupings as each of these lobes can take a different course and are divided internally into successively smaller pockets [1] The endocardial surface is of the LAA is characterized by a network of pectinate muscles (Fig. 4.4). More extensive trabeculations may be associated with increased risk for strokes [30].

There is currently a trend to categorize this variability as seen by CTA and reconstruction into recognizable patterns, i.e., chicken-wing, cactus, windsock, cauliflower [25, 26]. An example of the chicken-wing morphology, which in its extreme form can be a challenge for device implantation for LAA occlusion is

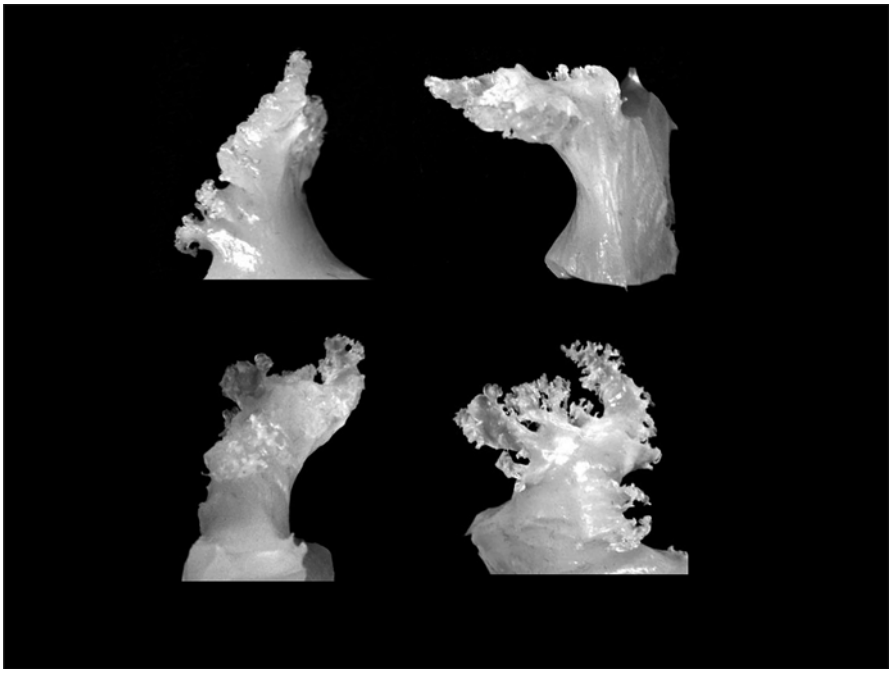


Fig. 4.4 Different left atrial appendage morphology of the same structure seen from different angles

shown in Fig. 4.5. There are contradictory reports as to whether particular morphologies are seen more frequently in patients with thromboembolic events or stroke, or not [8, 25, 31–33]. A series of patients studied by Di Biase et al have found an association between the "cauliflower" morphology and an increased risk for strokes [25], but this finding was not borne out in all studies [31]. It has also been questioned whether such classifications are reproducible between observers. Undoubtedly, numerous other shapes can exist and have been described, reflecting the variable branching pattern of the LAA [34, 35]. The wide variation in LAA anatomy (Fig. 4.6) may not be easily separated into four discrete categories, and the anatomic features relevant to LAA occlusion pertain more to ostium diameter and the implant depth at the neck, rather than the distal LAA shape. The observed morphology also depends on the plane and modality in which the LAA is imaged [2, 36] (Fig. 4.4). An LAA seen as a single lobe in a particular view may be visualized as multilobed in another view, and this would support the concept of pre-implant multidimensional reconstruction [26]. In reality, the lobar region of the LAA is a geometrically complex branching structure, akin to many others found within the heart and many other structures found in nature. Given the vast morphologic variation, it may prove more valid in future studies to describe the complexity of the LAA in numerical terms. Similar analyses, for example using fractal dimensions, have proved useful in analyzing the complex branching pattern of the myocardial trabeculations within the left ventricle [37].

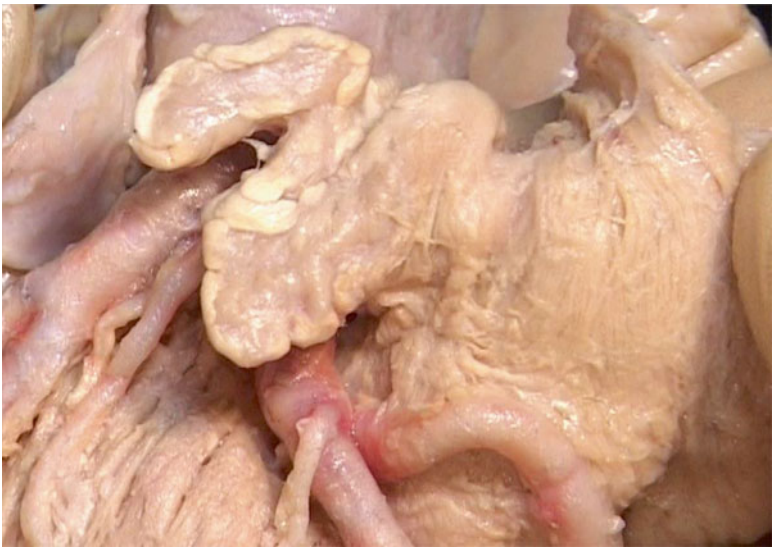


Fig. 4.5 "Chicken-wing" left atrial appendage morphology with a narrow ostium but large "neck" and angulation that may make transcatheter occlusion challenging

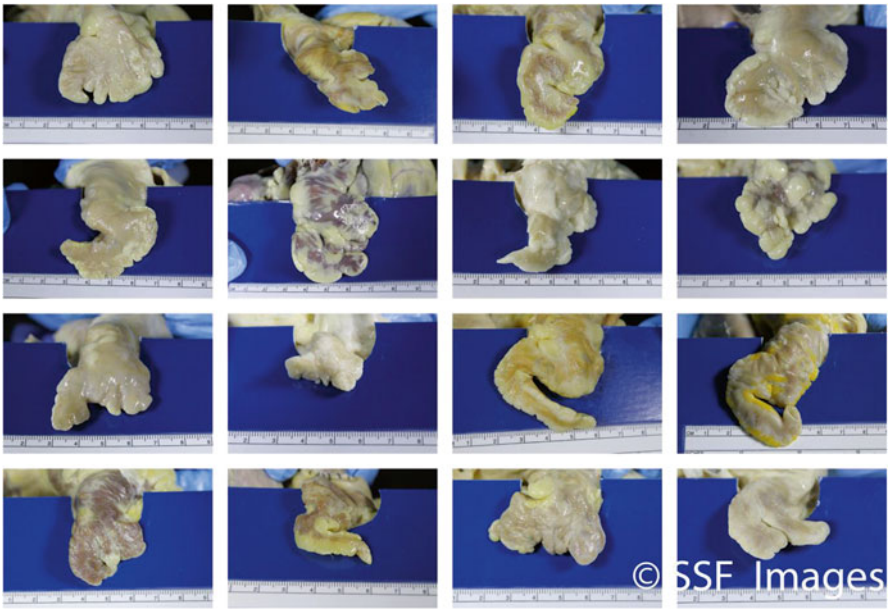


Fig. 4.6 Wide variation in lobar morphologies

Other than the association of the more complex trabeculations with AF and stroke [31], the subtleties of lobar morphology may have little to do with planning for LAA occlusion. The key anatomic features to note for LAA occlusion planning

have more to do with overall lobar size and number of lobes. The SentreHeart Lariat pericardial snare device, for instance, may not be able to encircle a multilobar LAA with a diameter greater than 40 mm. The Boston Scientific WATCHMAN device requires an implant depth equal to the orifice diameter, thus could not be placed in a shallow LAA, or an LAA that has an angled segment or multiple lobes that branch close to the ostium. The St Jude Medical ACP device requires a minimal 10 mm implant depth. Therefore, with regards to LAA occlusion, categorization of LAA morphologies is less important than careful measurement of LAA features pertinent to the device being considered. A summary of the features of the LAA that may affect LAA occlusion procedures is described in Table 4.1.

Table 4.1 Important left atrial and left atrial appendage structures and their implication for transcatheter occlusion (Modified from Cabrera JA, et al. Heart 2014;100:1636–1650) [7]

Anatomic feature	Key features	Significance
Atrial septum	Variable location of the fossa ovalis	A low, posterior puncture is needed to best allow the catheter to be directed anteriorly to the LAA
	Rotation and bowing with atrial enlargement	May change angulation and location of septal puncture
Circumflex artery and cardiac vein	Courses inferiorly along the neck of the LAA	Risk for compression with LAA occlusion
Mitral valve	Inferior and anterior to the LAA	Defines the inferior border of the LAA ostium
Left pulmonary vein	Posterior to the LAA, separated by a left lateral ridge of tissue	Defines the posterior border of the LAA ostium
Phrenic nerve	Courses anteriorly to the LAA	Risk for trauma with surgical resection or pericardial snare occluders
Left atrial appendage		
Ostium	Ovoid orifice defined by left lateral ridge of left pulmonary vein and mitral annulus	Determines sizing of LAA occlude devices • 17–31 mm (Watchman) • 12.6–28.5 mm (ACP)
Neck	The segment of the LAA from its ostium to the mid body	A shallow or very narrow or wide neck may preclude use of certain occlude devices. The Watchman requires an implant depth equivalent to the device diameter. The ACP device requires space for deployment 10 mm from the ostium
Lobes	Multilobed in the majority of cases. May be categorized into "chicken wing," "cactus," "wind sock," or "cauliflower" morphologies that could have implications for stroke risk	Multiple lobes with an LAA greater than 40 mm in diameter may preclude use of the Lariat. Multiple lobes branching close to the ostium may prevent deployment of occlusion devices
Pectinate muscles	A network of trabeculated myocardial bands within the LAA	Very prominent trabeculae may interfere with placement of LAA occlusion devices. Pectinate muscles may be mistaken for thrombus, which would prohibit use of the LAA occlusion device

Conclusions

There is significant variability in the morphology of the LAA itself, but the relatively preserved relationship of the LAA within the left atrium, and to the mitral valve, pulmonary veins, and coronary arteries helps to provide a consistent foundation for performing LAA procedures. Nevertheless, the heterogeneity in LAA morphology requires that careful imaging of the LAA ostial and neck dimensions, and LAA angulation be performed for preprocedural planning, and real-time imaging be used to optimize transseptal approaches to the LAA, verify optimal deployment of occlusion devices within the LAA and avoid compromising surrounding structures. A comprehensive understanding of the multiple anatomic structures surrounding the LAA and of the LAA itself, therefore, is critical in performing any LAA procedures.

References

1. Veinot JP, Harrity PJ, Gentile F, Khandheria BK, Bailey KR, Eickholt JT, Seward JB, Tajik AJ, Edwards WD. Anatomy of the normal left atrial appendage: a quantitative study of age-related changes in 500 autopsy hearts: implications for echocardiographic examination. Circulation. 1997;96:3112–5.
2. Ernst G, Stollberger C, Abzieher F, Veit-Dirscherl W, Bonner E, Bibus B, Schneider B, Slany J. Morphology of the left atrial appendage. Anat Rec. 1995;242:553–61.
3. Imada M, Funabashi N, Asano M, Uehara M, Ueda M, Komuro I. Anatomical remodeling of left atria in subjects with chronic and paroxysmal atrial fibrillation evaluated by multislice computed tomography. Int J Cardiol. 2007;119:384–8.
4. Saito T, Tamura K, Uchida D, Nitta T, Sugisaki Y. Histopathological evaluation of left atrial appendage thrombogenesis removed during surgery for atrial fibrillation. Am Heart J. 2007; 153:704–11.
5. Shirani J, Alaeddini J. Structural remodeling of the left atrial appendage in patients with chronic non-valvular atrial fibrillation: implications for thrombus formation, systemic embolism, and assessment by transesophageal echocardiography. Cardiovasc Pathol. 2000;9:95–101.
6. Beigel R, Wunderlich NC, Ho SY, Arsanjani R, Siegel RJ. The left atrial appendage: anatomy, function, and noninvasive evaluation. JACC Cardiovasc Imaging. 2014;7:1251–65.
7. Cabrera JA, Saremi F, Sanchez-Quintana D. Left atrial appendage: anatomy and imaging landmarks pertinent to percutaneous transcatheter occlusion. Heart. 2014;100:1636–50.
8. Anselmino M, Blandino A, Beninati S, Rovera C, Boffano C, Belletti M, Caponi D, Scaglione M, Cesarani F, Gaita F. Morphologic analysis of left atrial anatomy by magnetic resonance angiography in patients with atrial fibrillation: a large single center experience. J Cardiovasc Electrophysiol. 2011;22:1–7.
9. Cabrera JA, Ho SY, Climent V, Sanchez-Quintana D. The architecture of the left lateral atrial wall: a particular anatomic region with implications for ablation of atrial fibrillation. Eur Heart J. 2008;29:356–62.
10. Ho SY, Sanchez-Quintana D, Cabrera JA, Anderson RH. Anatomy of the left atrium: implications for radiofrequency ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 1999;10: 1525–33.
11. Sanchez-Quintana D, Ho SY, Climent V, Murillo M, Cabrera JA. Anatomic evaluation of the left phrenic nerve relevant to epicardial and endocardial catheter ablation: implications for phrenic nerve injury. Heart Rhythm. 2009;6:764–8.

12. Powell JR, Sproule M. A trainee's guide to imaging pulmonary arterial hypertension. Eur Coll Radiol. 2013. 10.1594/ecr2013/c-1049
13. Ho SY, McCarthy KP, Faletra FF. Anatomy of the left atrium for interventional echocardiography. Eur J Echocardiogr. 2011;12:i11–5.
14. Cabrera JA, Sanchez-Quintana D. Cardiac anatomy: what the electrophysiologist needs to know. Heart. 2013;99:417–31.
15. Nakajima H, Seo Y, Ishizu T, Yamamoto M, Machino T, Harimura Y, Kawamura R, Sekiguchi Y, Tada H, Aonuma K. Analysis of the left atrial appendage by three-dimensional transesophageal echocardiography. Am J Cardiol. 2010;106:885–92.
16. Nucifora G, Faletra FF, Regoli F, Pasotti E, Pedrazzini G, Moccetti T, Auricchio A. Evaluation of the left atrial appendage with real-time 3-dimensional transesophageal echocardiography: implications for catheter-based left atrial appendage closure. Circ Cardiovasc Imaging. 2011;4:514–23.
17. Chang SH, Tsao HM, Wu MH, Tai CT, Chang SL, Wongcharoen W, Lin YJ, Lo LW, Hsieh MH, Sheu MH, Chang CY, Hou CJ, Chen SA. Morphological changes of the left atrial appendage after catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2007;18:47–52.
18. Budge LP, Shaffer KM, Moorman JR, Lake DE, Ferguson JD, Mangrum JM. Analysis of in vivo left atrial appendage morphology in patients with atrial fibrillation: a direct comparison of transesophageal echocardiography, planar cardiac ct, and segmented three-dimensional cardiac ct. J Interv Card Electrophysiol. 2008;23:87–93.
19. Lopez-Minguez JR, Gonzalez-Fernandez R, Fernandez-Vegas C, Millan-Nunez V, Fuentes-Canamero ME, Nogales-Asensio JM, Doncel-Vecino J, Yuste Dominguez M, Garcia Serrano L, Sanchez QD. Comparison of imaging techniques to assess appendage anatomy and measurements for left atrial appendage closure device selection. J Invasive Cardiol. 2014;26:462–7.
20. Wongcharoen W, Tsao HM, Wu MH, Tai CT, Chang SL, Lin YJ, Lo LW, Chen YJ, Sheu MH, Chang CY, Chen SA. Morphologic characteristics of the left atrial appendage, roof, and septum: implications for the ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2006;17:951–6.
21. Su P, McCarthy KP, Ho SY. Occluding the left atrial appendage: anatomical considerations. Heart. 2008;94:1166–70.
22. Freixa X, Tzikas A, Sobrino A, Chan J, Basmadjian AJ, Ibrahim R. Left atrial appendage closure with the amplatzer cardiac plug: impact of shape and device sizing on follow-up leaks. Int J Cardiol. 2013;168:1023–7.
23. Beinart R, Heist EK, Newell JB, Holmvang G, Ruskin JN, Mansour M. Left atrial appendage dimensions predict the risk of stroke/TIA in patients with atrial fibrillation. J Cardiovasc Electrophysiol. 2011;22(1):10–5.
24. Abbara S, Mundo-Sagardia JA, Hoffmann U, Cury RC. Cardiac ct assessment of left atrial accessory appendages and diverticula. AJR Am J Roentgenol. 2009;193:807–12.
25. Di Biase L, Santangeli P, Anselmino M, Mohanty P, Salvetti I, Gili S, Horton R, Sanchez JE, Bai R, Mohanty S, Pump A, Cereceda Brantes M, Gallinghouse GJ, Burkhardt JD, Cesarani F, Scaglione M, Natale A, Gaita F. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. J Am Coll Cardiol. 2012;60:531–8.
26. Wang Y, Di Biase L, Horton RP, Nguyen T, Morhanty P, Natale A. Left atrial appendage studied by computed tomography to help planning for appendage closure device placement. J Cardiovasc Electrophysiol. 2010;21:973–82.
27. Heist EK, Refaat M, Danik SB, Holmvang G, Ruskin JN, Mansour M. Analysis of the left atrial appendage by magnetic resonance angiography in patients with atrial fibrillation. Heart Rhythm. 2006;3:1313–8.
28. Blendea D, Heist EK, Danik SB, Barrett C, Ruskin JN, Mansour M. Analysis of the left atrial appendage morphology by intracardiac echocardiography in patients with atrial fibrillation. J Interv Card Electrophysiol. 2011;31:191–6.
29. Jorgensen J, Palmer S, Kalogeropoulos A, Arita T, Block P, Martin R, Lerakis S. Implantation of left atrial appendage occlusion devices and complex appendage anatomy: the importance of transesophageal echocardiography. Echocardiography. 2007;24:159–61.

30. Anselmino M, Scaglione M, Di Biase L, Gili S, Santangeli P, Corsinovi L, Pianelli M, Cesarani F, Faletti R, Righi D, Natale A, Gaita F. Left atrial appendage morphology and silent cerebral ischemia in patients with atrial fibrillation. Heart Rhythm. 2014;11:2–7.
31. Khurram IM, Dewire J, Mager M, Maqbool F, Zimmerman SL, Zipunnikov V, Beinart R, Marine JE, Spragg DD, Berger RD, Ashikaga H, Nazarian S, Calkins H. Relationship between left atrial appendage morphology and stroke in patients with atrial fibrillation. Heart Rhythm. 2013;10:1843–9.
32. Kimura T, Takatsuki S, Inagawa K, Katsumata Y, Nishiyama T, Nishiyama N, Fukumoto K, Aizawa Y, Tanimoto Y, Tanimoto K, Jinzaki M, Fukuda K. Anatomical characteristics of the left atrial appendage in cardiogenic stroke with low CHADS2 scores. Heart Rhythm. 2013;10: 921–5.
33. Kosiuk J, Nedios S, Kornej J, Koutalas E, Bertagnolli L, Rolf S, Arya A, Sommer P, Husser D, Hindricks G, Bollmann A. Impact of left atrial appendage morphology on peri-interventional thromboembolic risk during catheter ablation of atrial fibrillation. Heart Rhythm. 2014;11:1522–7.
34. Koplay M, Erol C, Paksoy Y, Kivrak AS, Ozbek S. An investigation of the anatomical variations of left atrial appendage by multidetector computed tomographic coronary angiography. Eur J Radiol. 2012;81:1575–80.
35. van Rosendael PJ, Katsanos S, van den Brink OW, Scholte AJ, Trines SA, Bax JJ, Schalij MJ, Marsan NA, Delgado V. Geometry of left atrial appendage assessed with multidetector-row computed tomography: implications for transcatheter closure devices. EuroIntervention. 2014;10:364–71.
36. Kerut EK. Anatomy of the left atrial appendage. Echocardiography. 2008;25:669–73.
37. Captur G, Muthurangu V, Cook C, Flett AS, Wilson R, Barison A, Sado DM, Anderson S, McKenna WJ, Mohun TJ, Elliott PM, Moon JC. Quantification of left ventricular trabeculae using fractal analysis. J Cardiovasc Magn Reson. 2013;15:36.

Part II
Surgical Approaches for LAA Closure

Chapter 5
Conventional Surgery for LAA Closure

Hasib Hanif and Richard Whitlock

Introduction

Atrial fibrillation (AF) is one of the most common rhythm abnormalities affecting 1 % of the general population [1] and the burden increases with age [2]. Patients in AF can exhibit symptoms of palpitations, decreased cardiac output, and thromboembolism [1]. In the Framingham study, AF was shown to increase the risk of stroke fivefold in non-valvular patients and 17-fold in mitral stenosis [2].

Currently, anticoagulation is the first line treatment modality for stroke prevention in AF, along with rate or rhythm control for relief of non-thromboembolic-related symptoms [3]. However, with a high noncompliance rate of anticoagulant use, increased risk of bleeding associated with these drugs [4], and drug and food interactions, patients and physicians both seek alternate methods to decrease the risk of stroke. The majority of the strokes in AF are cardioembolic in nature, the dominant source of which lies within the left atrial appendage (LAA) [5]. Therefore, mechanical occlusion of the LAA, either surgically or percutaneously, is of great interest.

The Left Atrial Appendage

The LAA originates from the embryonic left atrium (LA) proper during the first trimester of gestation [5]. The LAA has been theorized to mediate adaptive responses to circulating blood volume and may function as a reservoir during volume overload [4].

H. Hanif, M.D. (✉) • R. Whitlock, M.D., Ph.D.
Department of Cardiac Surgery, Hamilton General Hospital,
237 Barton Street E, Hamilton, ON, Canada L8L 2X2
e-mail: hasib.hanif@medportal.ca; richard.whitlock@phri.ca

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_5

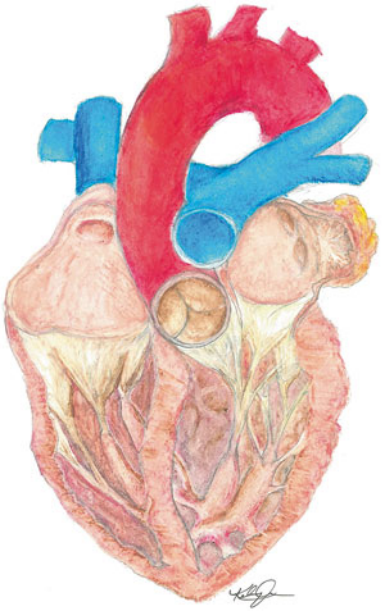


Fig. 5.1 Normal heart anatomy with trabeculated left atrial appendage

In normal cardiac rhythm, the LAA functions in unison with the rest of the atrium (Fig. 5.1). However, during AF, the atria proper and the LAA contract irregularly, leading to dysfunction and stasis [5]. This leads to clot formation, and eventually thromboembolism.

A review of the literature elucidates that 70 % of all strokes in patients with AF are cardioembolic in nature [5]. In a landmark paper by Blackshear and Odell [6], the authors analyzed 23 studies that evaluated the left atrium and LAA in patients with AF. When comparing valvular AF vs. non-valvular AF, 254 of 446 patients (57 %) thrombi in patients with valvular AF were localized to the LAA, while in 201 of 222 patients (91 %) thrombi in non-valvular AF were isolated to, or originated in the LAA ($p<0.0001$) [6]. In another study, researchers evaluated 233 patients with AF who did not undergo anticoagulation [7]. Transesophageal echocardiography showed that 34 patients (15 %) had a left atrial thrombus, and 33 of 34 (97 %) of these thrombi were originating in the LAA. Leung et al. examined a cohort of 272 non-valvular AF patients [8]. In their analysis, the authors found an 8 % incidence of having a left atrial clot, with 100 % of the clots isolated in the LAA [8].

Numerous studies have shown that the LAA is a chief source of thrombus in valvular and non-valvular AF [5]. It is no surprise then, that mechanical occlusion of this LAA, an old idea [9], has received renewed interest in decreasing the risk of stroke in patients with AF.

Excluding the Left Atrial Appendage from Systemic Circulation

In the 1940s [9], the feasibility of resection of the LAA had been studied in dogs, and the operation was suggested as a therapeutic approach to reduce the burden of arterial emboli in patients with AF and rheumatic valve disease. The first report of LAA occlusion in an animal model was by Hellerstein and associates in 1947 [9]. Hellerstein performed atrial appendectomy on 8 canine hearts. Post mortem studies on the canines revealed complete endothelialization at the atrial anastomosis, and the procedure was considered a viable option in patients with rheumatic mitral valve disease and recurrent emboli [9].

The first ever reported resection of the LAA in a human was by John Madden in 1949 [9]. Madden theorized that the "ideal prophylaxis for recurrent arterial emboli should be the removal of the thrombus together with its site of origin [9]." His colleague, Dr. William Dock in 1946 had suggested resection of the LAA in cases of rheumatic heart disease with AF. Madden's first patient was a 38-year-old female, admitted with embolic occlusion of the left iliac artery and rheumatic mitral stenosis. In the days before the heart–lung bypass machine, the operation involved stopping the heart and immediate manual massage of the heart concomitant with artificial respiration. Under these conditions, the LAA was resected. However, postoperatively, the patient was found to have a left hemiparesis, thought to be secondary to a right cerebral embolus. Eight months post surgery, the patient continued to improve from the stroke symptoms, and Madden noted that there was "no recurrence of peripheral arterial emboli [9]." His second patient, a 52-year-old male with rheumatic mitral stenosis and AF, was admitted with an occlusion of the aorta at its bifurcation and underwent LAA resection. Postoperatively, the patient improved until the ninth day, when he suddenly died. Autopsy was not performed, and cause of death was not investigated [9]. In his discussion, Madden admitted at the operation was "not a standard one" and that a satisfactory technique needed to evolve [9]. In conclusion, Madden invited further study and clinical evaluation of patients in order to select those patients that would benefit most from the procedure. However, surgery for AF would first more intensely focus on rhythm control rather than the LAA alone.

Atrial Fibrillation Surgery

The burden of AF arises from both the thromboembolic risk, and the medications used for rate or rhythm control. The first report of corrective surgery for AF was published in 1980 by Dr. Williams in The Journal of Thoracic and Cardiovascular Surgery [10]. The study was designed to develop a technique to isolate the left atrium electrically from the rest of the heart. Ten dogs were subjected to cryoablation of the bundle of His, and initial results indicated that postoperatively all animals maintained normal sinus rhythm [10]. However, longer-term follow up showed that the LA could still fibrillate and continued to pose a thromboembolic threat.

In 1985, Guiraudon and colleagues reported a novel technique, named the "corridor" operation, for patients with disabling AF despite optimal medical therapy [11]. The open-heart procedure involved isolating a "corridor" of atrial tissue from the right and left atrium. The authors reported that the corridor consisted of isolating the left atrium electrically from a corridor containing the sinus node, AV node, and the connecting right atrial mass. They theorized that this corridor would re-route the electrical macro re-entrant circuits in AF and preserve the physiological driving mechanism of the ventricle. However, this technique failed to eliminate AF or reinstate atrial contractility [11]. As such, the risk of thromboembolism remained, and the procedure was soon abandoned.

Cox Maze

In 1987, Cox et al. described a new surgical procedure for the treatment of AF [12]. Cox hypothesized that AF was based on "migrating wavelets of macroreentry" [13] and his Maze operation combated this by compartmentalizing both atria. The Cox Maze procedure has undergone several iterations and has become the cornerstone of AF surgical treatment. In a Cox Maze procedure, the electrical impulse is guided along a surgically determined course, and in theory halts AF. This is done by both incising and sewing in the atria in a "maze like pattern," or through biatrial "lesion sets" via radiofrequency ablation lines (Maze IV). Lastly, the atrial appendages are surgically removed or obliterated. The Cox Maze procedure has been shown to be successful in preventing re-entry AF, and restoration of sinus rhythm [14]. In 1999, Cox published his 11.5-year results of performing the Maze procedure on 306 patients [15]. They reported only 2 perioperative strokes (0.7 %), and in the 265 patients followed for up to 11.5 years, there was only 1 late minor stroke [15]. Cox concluded that the low stroke rate observed in his cohort was secondary to the restoration of sinus rhythm and removal of the LAA, "where most thrombi develop" [15].

However, several criticisms of Cox's results have been presented since publication. The 2012 Heart and Rhythm Society (HRS) recognized that patients in the study did not undergo follow up by present standards [16]. Few patients in the study had any regular monitoring of rhythm and most of the rhythms were documented only via telephone or mailed questionnaire. This may have led to underestimating the number of patients in paroxysmal or persistent AF. A recent systematic review examining the surgical treatment of AF [17] via "cut and sew" Maze or alternative energy sources found the procedures to be successful only 78.3 and 84.9 % ($p = 0.03$) of the time, respectively. The HRS examined the evidence for surgical ablation of AF and concluded that more prospective multicentre trials are needed to better define the safety and efficacy of the surgical techniques [16]. Additionally, there is no robust data that demonstrates that AF ablation decreases stroke risk; the HRS guidelines, thus, do not recommend discontinuation of anticoagulation therapy after ablation. Currently, the guidelines recommend surgical AF ablation only for symptomatic AF patients, who are refractory to antiarrhythmic medications, and undergoing surgery for other indications (Class IIa, Level of Evidence C) [16]. Stand-alone

surgical ablation of AF is even less warranted, and should only be considered in patients who have failed one or more attempts at catheter ablation (Class IIb, Level of Evidence C). The committee, however, did recommend LAA occlusion during surgical AF ablation whenever feasible, as this was thought to decrease stroke risk. Further studies into long-term outcomes and stroke risk were encouraged, but the topic of LAA occlusion was brought to the forefront.

Surgical Techniques for Left Atrial Appendage Occlusion

Over the years, surgeons have proposed several techniques to close the LAA. The principle behind LAA occlusion involves either excluding the LAA from circulation, or excising the LAA altogether. The techniques include (1) Simple neck ligation, (2) Purse-string technique, (3) Endocardial suturing, (4) Envagination and double suture technique, (5) Surgical amputation and closure, (6) Surgical Stapler, and (7) Novel occlusion devices (Table 5.1). Although many of these techniques have been

Table 5.1 Techniques for surgical left atrial appendage occlusion

Surgical technique	Important aspects
• Simple neck ligation	– Most basic of all techniques
	– Challenging when large or irregular LAA base
• Purse-string technique	– May lead to puckered suture line and subsequent thrombus formation endocardially
	– High rate of LAA recanalization
• Endocardial suturing	– Technique for closing the LAA from within the open LA
	– High rate of unsuccessful closure
• Envagination and double suture technique	– Double suture technique requires more time
	– Good postoperative results
• Surgical amputation and closure (cut-and-sew method)	– Important to de-air left heart prior to release to aortic clamp with this method
	– Good postoperative results
• Surgical Stapler	– Stapler more costly than sutures
	– Studies have shown fewer leaks across closure line when using a stapler over ligation technique
• Atriclip surgical device	– Device more costly than sutures
	– Easy to use
	– Can be applied thoracoscopically
• TigerPaw surgical device	– Device more costly than sutures
	– Easy to use
	– Can be applied through small thoracotomy
• Endoloop snare	– Can be applied thoracoscopically
	– Small study ($n=8$) showed increased risk of adverse
	– events (serious bleeding)
• LigaSure TM vessel sealing system	– Bipolar device to weld the LAA shut
	– Small study ($n=12$) showed no adverse events but authors advocated for large-scale studies

practiced for decades, there is little data comparing the approaches. The only paper to whose objective was to directly compare techniques was published by Kanderian in 2008 [18]. In their landmark paper, the authors studied 137 patients who underwent surgical LAA closure. A key finding of the study was that only 40 % of the patients ($n=55$) had successful LAA closure. Unsuccessful closure was defined by the presence of a patent LAA (persistent communication between LAA and left atrium) or LAA stump >1 cm. Out of these patients ($n=55$), successful LAA closure was seen in 38 patients with excision of the LAA (73 %) vs. 17 patients with suture exclusion (20 %) and 0 patients with stapler exclusion (0 %) ($p<0.001$). In analyzing the unsuccessful LAA closures, Kanderian et al. [18] found that of all 12 patients with stapler exclusion, 58 % of them had a persistent LAA stump >1 cm. The authors noted that the presence of a residual LAA stump greater than 1 cm has been classified as unsuccessful closure in literature [18], and this can theoretically pose a risk for harboring thrombus. Out of 73 patients who had suture exclusion of the LAA, 61 % of patients had persistent flow into the appendage via the stump. The implication is that persistent flow into the LAA after exclusion indicates persistent communication [18], and thus thrombi can still develop over time. In these patients the risk of stroke may be even *higher* post surgery because the LAA is more prone to thrombose when partially closed as blood would remain more stagnant [18]. In their series, the prevalence of LAA thrombus in appendages with persistent flow was high (46 % suture exclusion, 67 % stapler exclusion). The study authors therefore concluded that excision of the appendage is the most reliable method of LAA closure, and recommended that anticoagulation not be discontinued without echo investigation post surgery. The common surgical techniques for occlusion are described below.

Simple Neck Ligation

This exclusion technique is perhaps the most basic of all the techniques. Typically the surgeon places a vascular clamp around the neck of the LAA. Following this, a 1-0 or 0 silk tie is placed around the clamp and the suture tied down. Once a knot has been placed, the vascular clamp is removed, and the remaining knots tied down to secure the suture in place. The aim of this technique is to tie off the LAA at the base from the outside of the atrium. Difficulty arises when a large LAA, a wide neck, or an irregular LAA morphology is encountered.

Purse-String Technique

This exclusion technique involves closing the LAA via purse-string from the outside using 4-0 or 3-0 prolene. The suture is placed across the base of the LAA, and usually requires 4 or 5 passes to encircle the base. Surgeons may use Teflon pledgets

to prevent tearing and distribute the tension evenly, as the LAA tissues can be fragile. Although no strong evidence exists, purse-string sutures may lead to a "puckered" suture line [19]. This has been theorized to lead to thrombus formation on the endocardial surface, thus leading to a higher stroke risk [19].

Small cases series have been published using this technique. One such study was by Lynch et al. [20], which reported a high incidence of recanalization of the LAA after purse-string closure of the LAA. On follow up echo, all patients ($n=6$) demonstrated communication between the LAA and the atrium proper, mainly at the superior-lateral border of the appendage. The authors hypothesized that flow into an incompletely ligated LAA could lead to tension along the suture lines, and further breakdown of the LAA inlet, with complete reopening of the closed orifice. The authors recommended that techniques other than purse-string suture be adopted for LAA closure.

Endocardial Suturing

This exclusion technique involves closing the LAA from within the open left atrium. Schneider et al. [21] reported a series of 6 patients who underwent surgical LAA closure at the time of mitral and/or aortic valve surgery. The authors described a technique of endocardial LAA closure. To accomplish this, a double row of 3-0 prolene sutures are placing in a running fashion, sewn from within the left atrium (Fig. 5.2). The authors investigated LAA closure via echo post surgery, and reported that 83 % of patients had unsuccessful closure. No major complication or mortality was reported, but the authors acknowledged that surgical LAA occlusion using endocardial methods may lead to incomplete closures.

Envagination and Double Suture Technique

This exclusion technique was described by Hernandez-Estefania et al. [22]. The authors describe that the LAA is completely invaginated into the LA with forceps. Then a 4-0 prolene purse-string suture is carefully sutured on to the base of the appendage. The author points out that it is important to encircle the oval shape of the inlet orifice. The LAA is then gently pulled outward with forceps, whilst pulling on the two ends of the prolene suture. After this layer is tied up, a second running suture is then placed along the long axis of the LAA. The authors report that in their experience, LAA invagination followed by double suture technique facilitates the exposure of the real LAA rim with subsequent closure and complete occlusion. All patients in their series ($n=8$ patients) had echo post surgery that demonstrated no flow inside the LAA or residual stump. No major complication or mortality was reported.

Fig. 5.2 Excluded left atrium via endocardial suturing (internal view). Note the suture line

Surgical Amputation and Closure (Cut and Sew)

This excision technique involves amputating the LAA once the heart is arrested. Following this the LAA is completely excised until no trabeculated portion remains, and the neck of the LAA is sewn closed (Fig. 5.3). In theory, this would not only remove the trabeculated portions of the LAA where clots may form, but also remove any ability for the LAA to recanalize. Another term for this technique is left atrial appendectomy. It is important to de-air the left cardiac chambers prior to release of the aortic cross-clamp with this approach.

The largest series of appendectomy in published literature was from Johnson et al. [23], who reported 391 patients who underwent the procedure. The authors did not report any major complication, or any mortality owing to appendectomy.

Surgical Stapler

This approach can be an excision or exclusion technique of the LAA. Initial experience with surgical stapling of the LAA demonstrated issues with bleeding from the staple line. To avoid this, Gillinov and associates [24] from the Cleveland Clinic have called for a pericardial buttressing of the LAA staple line.

Fig. 5.3 Epicardial suture line and closure of LAA (external view)

Most commonly after cardioplegic arrest, an Endo GIA II stapler with 4.8 mm staples is used to exclude the LAA [24]. The positioning of the staple is described as being parallel to the base of the LAA, approximately 5 mm from the circumflex coronary artery (Fig. 5.4). On the device itself, the staple line is buttressed with a bovine pericardial strip. In their series of 222 patients, Gillinov et al. [24] report 10 % of patients requiring additional pledget-supported sutures for tears caused by the stapler. Reoperation for bleeding was seen in 7 patients (3 %) but none of these were attributable to the LAA staple line. No mortalities or any other major complications were reported.

Healey et al. [25] examined factors for successful LAA closure in their LAAOS trial. The authors noted that there was a trend for higher occlusion rates when using a stapling device over ligation technique. Use of a stapling device was associated with complete occlusion in 72 % of patients vs. 45 % of patients using ligation alone ($p = 0.14$). Additionally, with the use of a stapler device, all incomplete occlusions were due to residual cul de sac. That is, there was no persistent flow across the staple line from the LA body to the LAA when compared to the ligation technique ($p = 0.0001$).

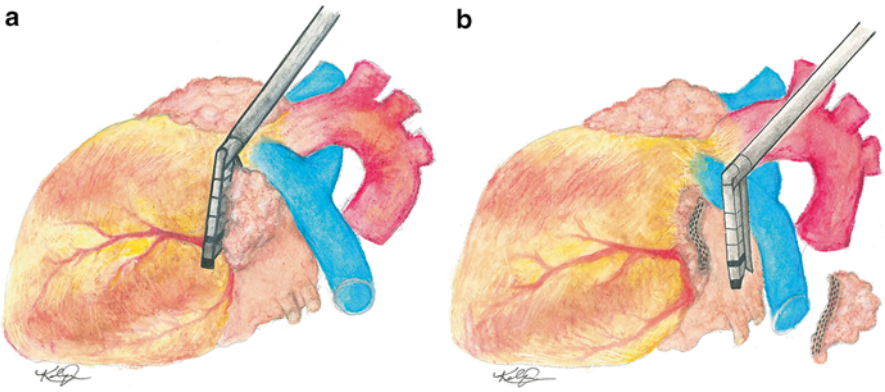


Fig. 5.4 Surgical stapler placed over base of LAA (*left*) and subsequent removal of appendage (*right*). Note the staple line (*right*)

Novel Techniques for LAA Occlusion

In recent years, industry has had increased interest in the field of LAA occlusion and new methods and devices have been developed. These new techniques aim to make surgical LAA occlusion easier, and decrease the risk of incomplete closure.

Atriclip

This novel device recently received FDA approval for occlusion of the LAA under direct visualization, and in conjunction with other open-heart procedures (510(k) K093679). The early results of a multicentre trial (7 centers) have been published [26]. Ailawadi et al. studied a total of 70 patients who underwent elective cardiac surgery and received a concomitant AtriClip (Atricure Inc, Westchester, Ohio) [26]. Efficacy of LAA exclusion was assessed intraoperatively, and at 3 months of follow up. No patients were reported to have any adverse events related to the device, and no perioperative mortality was reported. Out of the 62 patients who had 3-month follow up, 60 patients (98.4 %) had successful LAA exclusion via Atriclip. The authors concluded that safe and atraumatic exclusion of the LAA could be achieved via the Atriclip, but urged for further studies. Additionally, the authors also commented that the device could be used in conjunction with minimally invasive procedures. The device comes in three sizes (35, 40, and 50 mm), can be applied at any point either thoracoscopically or after sternotomy on or off bypass.

TigerPaw

The TigerPaw is designed with connectors imbedded in a soft silicone fastener to conform to the shape and thickness of the patient's appendage and ensure occlusion. The device has received FDA 501(k) (K101961) approval for occlusion of the LAA, under direct visualization, in conjunction with other open cardiac procedures. A recent study has demonstrated the safety and efficacy of this device [27]. Slater et al. studied 60 patients who had their LAA excluded with this device. Complications included a residual LAA cavity exceeding 6 mm in 5 patients, and 1 patient requiring additional sutures due to a tear caused by device application. Currently, the device offers an alternative to manual suturing or staples.

Endoloop Snare

Blackshear et al. [28] reported on their experience of LAA obliteration in high-risk patients with AF. In 8 patients, an Endoloop snare was fixed as a tie to the tip of the LAA. Then a second Endoloop is passed over the first tie and brought down to the LAA base. This second loop is then clinched to occlude the appendage. The benefits of this novel technique allow for the loops to be placed via minimally invasive methods. The technique was first described in 2003, but has failed adoption into mainstream cardiac surgery. This may be the result of some adverse events noted by the group (including serious bleeding), and the limited data on such a small cohort. It should also be noted that the patient population in Blackshear's cohort underwent thoracoscopic LAA occlusion as a stand-alone procedure, with no concomitant cardiac procedure.

LigaSure TM Vessel Sealing System

A novel technique of occluding the LAA has been described by Jayakar et al. [29]. This technique utilizes a bipolar device and radiofrequency energy to "weld" the LAA shut. Thus far, 12 patients have undergone this off-pump procedure with promising results. This device allows one to fuse the base of the appendage and create a seal. Once isolated, the LAA is removed using surgical scissors. Lastly, a running 4-0 prolene suture is placed on the seal line to ensure haemostasis. On follow up to date, no thromboembolic events or any major adverse complications have been reported. The authors advocated for use of this novel device, but supported the need for more studies in larger patient cohorts.

Complications of LAA Occlusion Surgery

LAA occlusion, just like any surgical intervention, carries with it risks of complications (Table 5.2). However, to date there are no publications that quantify the rate and type of complications seen with LAA occlusion.

The most serious complication of LAA occlusion would be occlusion or injury to the circumflex artery during exclusion or excision. A study by Su et al. [19] looked at the anatomical considerations during LAA occlusion. In their examination of 31 heart specimens, the circumflex artery ran very close to the epicardial aspect of the LAA ostium. Injury via staples or sutures to this artery can lead to myocardial infarction, and lead to increased morbidity and mortality of the procedure.

The LAA is also in close proximity to the left superior pulmonary vein. Although no clinical studies have shown any risk of pulmonary vein stenosis post LAA closure, surgeons should be mindful of this structure. The sinus node artery can also arise from the left coronary system in 40 % of cases, out of which 30 % arise from the circumflex artery [19]. These structures may lie in the myocardium of the LAA ostium, and injury or occlusion may lead to rhythm abnormalities postoperatively.

Another potential complication of LAA surgery is myocardial tears and bleeding. The study by Healey et al. [25] reported that LAA occlusion did not increase perioperative bleeding, and most other studies do not report any reoperation for bleeding from the LAA suture/staple line. Similar conclusions were reached by Whitlock et al. [30] who reported that no patients with LAA occlusion had significant bleeding secondary to the occlusion site ($n=26$). However, given that this is an additional suture line, bleeding can occur from the needle holes, or from the staple line. It is also important to examine the LAA suture line for any tears as the LAA tissue is known to be very fragile. Tears in the atrium may also occur during manipulation of the LAA. Bleeding which may go unnoticed can lead to increased morbidity, and in some cases mortality.

Removal of the LAA may also have physiological consequences. Studies in murine LAA have shown that the LAA plays a role as a reservoir of multiple types of progenitor cells [31]. A growing body of evidence has shown that these progenitor

Table 5.2 Complications of left atrial appendage occlusion

Major complications	Minor complications
• Occlusion or injury to circumflex artery	• Arrthymias
• Left superior pulmonary vein injury	• Decreased ANP production leading to impaired fluid balance
• Myocardial tears	• Minor bleeding from the occlusion site
• Major bleeding from the occlusion site (requiring transfusions and/or surgery)	
• Incomplete LAA occlusion leading to increased risk of thrombus formation	
• Thromboembolism (stroke)	

cells are key components in cardiac regeneration pathways [31]. Currently no link between LAA removal and decreased cardiac regeneration has been investigated, but physicians should be mindful of this theoretical risk. Other authors have reported that once the LAA is removed, the LA becomes less compliant [32]. This leads to changes in left heart filling and overall atrial function. Lastly, 30 % of cardiac atrial natriuretic peptide (ANP) is secreted from atrial appendages [32]. Although no clinical trial has shown any negative impact, theoretically, removal of the LAA can lead to fluid retention and heart failure [33].

Incomplete LAA occlusion can theoretically lead to an *increased* risk of thrombus formation and subsequent stroke. If persistent flow remains across the suture line, it can lead to stagnant blood in the residual LAA. This can then lead to thromboembolism. Occlusion is considered to have failed if a residual stump is left that is >1 cm [18]. This can lead to thrombus formation in the stump, and subsequent embolism. Patients who undergo occlusion may have their anticoagulation stopped, with the physicians thinking that these patients are at lower risk of stroke. However, if these patients have incomplete occlusion, then their risk of thromboembolism would be significant increased. Therefore, all patients who have LAA occlusion should have echo assessment at the time of follow up.

Evidence Regarding Safety and Efficacy of Left Atrial Appendage Occlusion

The LAA has been implicated as the dominant source of thrombus in non-valvular AF, and as such it is theoretically plausible that occlusion of the LAA will decrease a patient's stroke risk [34]. In patients with elevated risk of bleeding or contraindication to anticoagulant use, LAA occlusion could be used to reduce stroke risk [5]. There have been several published reports on LAA occlusion that have investigated its safety and efficacy.

Animal Studies

In 2006, Kamohara and colleagues evaluated an experimental device, called the atrial exclusion device (AED), for LAA exclusion in ten mongrel dogs [35]. The authors reported that the AED enabled reliable and safe exclusion of the LAA and clinical applications in patients with AF was warranted.

In 2008, another group led by Fumoto, studied LAA exclusion on 14 mongrel dogs who underwent median sternotomy and stapling of the LAA [36]. The results showed that the LAA exclusion was safely achievable, ensuring hemodynamic stability with no injury to the circumflex artery. The researchers concluded that LAA exclusion should carry a similar safety profile in patients and advocated for further trials to investigate its therapeutic use in reducing risk of stroke in patients with AF.

Human Studies

The evidence for the efficacy of surgical LAA exclusion in humans for stroke prevention is currently inconclusive [5]. Several studies have been published which show no impact of LAA ligation on stroke risk, while others suggest benefit.

A retrospective study by Almahameed et al. reported on 136 individuals who had LAA amputation during mitral valve surgery [37]. During a mean follow-up period of 3.6 years, the authors noted 14 (12.3 %) thromboembolic events. Six of these events (15 %) were among patients who did not receive warfarin on discharge, and seven (10 %) among patients who did receive warfarin. The authors concluded that based on the results of the study, LAA exclusion did not provide optimal protection against stroke risk, and that warfarin use, not LAA amputation resulted in reduced stroke risk [37]. Limitations of the study included the fact that the level of anticoagulation in the cohort was not documented, and that follow up was not available for all patients. Although the series was small, it provided some insight that perhaps LAA occlusion alone may not be enough to decrease stroke risk.

Another study by Bando et al. ($n=812$) reported on risk factors for stroke in patients undergoing mitral valve surgery [38]. A subset of these patients underwent closure of the LAA ($n=493/812$, 55 %) or LAA plication ($n=148/812$, 18 %) based on the discretion of the surgeon. The authors performed univariate analysis and found that closure of the LAA was not a significant predictor for late stroke ($p=0.69$). Major limitations of the study were that it was not randomized, and the decision to exclude the LAA was based on surgeon preference. This may have lead to preferential LAA closure in larger, easier to reach appendages, or ones with differential clot burdens. Compliance to oral anticoagulation therapy was also not closely tracked and may have led to differences in outcome of thromboembolic events.

The only study to suggest harm was reported by Orszulak et al. [39] who reported on a subset of 92 patients receiving LAA ligation while undergoing valve and CABG, or valve surgery alone. The group found a correlation between postoperative late stroke and LAA ligation in patients undergoing valve and CABG surgery ($p \leq 0.02$), but no correlation with isolated valve surgery ($p=0.81$). This finding resulted from a small subgroup analysis, and was not methodologically designed to investigate LAA ligation and stroke. The authors concluded that based on such a small subset of patients, they could not conclude that LAA ligation either increased or decreased the risk of stroke.

In contrast to the above studies, some investigators have published favorable outcomes after surgical LAA occlusion [5]. In 2000, Johnson et al. [23] reported a series of 437 patients who underwent prophylactic LAA appendectomy during open-heart surgery. The study authors concluded that removal of the LAA was safe as it did not increase risk of bleeding or mortality. As part of the follow up, the group reported that no patients were found to have atrial clots on echocardiographic examination. The authors of the study were some of the first researchers to strongly recommend routine LAA removal during cardiac surgery, although they acknowledged further studies were required.

Healey et al. [25] performed the first randomized controlled trial of 77 patients with risk factors for stroke who underwent coronary artery bypass graft surgery (LAAOS I). Patients were randomized to either LAA occlusion ($n=52$) or no LAA occlusion ($n=25$). Although the study was a pilot trial, the outcomes of completeness of occlusion, postoperative AF, bleeding, and mortality were examined. The occlusion methods used in the study included oversewing or ligating the appendage or a stapling device. Out of the 44 LAA occlusion patients who underwent transesophageal echocardiography, successful LAA occlusion was achieved in only 66 % of patients. As there are no previously established criteria for successful LAA occlusion, the authors used a criterion of no flow past the occlusion line and a residual stump of <1 cm to define successful LAA occlusion. In the 34 % of patients who had LAA occlusion failure, persistent flow across the suture line, or deployment of staples too distally from the base of the LAA was seen. After a mean follow up of 13 months, 2.6 % of patients had thromboembolic events, with no mortalities. There was no increased bleeding observed in the LAA occlusion group. The authors also analyzed the learning curve of LAA closure and determined that after four cases surgeons were more likely to achieve successful LAA occlusion ($p=0.0001$). Although a small study, the results suggested that LAA occlusion was a safe and reliable procedure. The importance of successful LAA closure was also discussed [25], as incomplete closure can lead to recanalization of the LAA and negate any benefits of the procedure.

The importance of complete closure of the LAA was also investigated by Katz et al. [40]. Out of the 50 patients who underwent mitral valve surgery and LAA ligation, incomplete ligation was observed in 36 % of patients (via echocardiography). The study reported that in 50 % of the patients with incomplete ligation, a thrombus was identified, and 22 % of these patients had thromboembolic events. The authors concluded that incompletely ligated appendages are of paramount importance, and further studies are needed to differentiate between different closure techniques and their outcomes.

In 2013, Whitlock et al. published LAAOS II that randomized 51 patients with AF to LAA occlusion or no occlusion in a feasibility pilot study [30]. After a follow up of 1 year, 4 patients in the occlusion arm and 5 patients in the no-occlusion arm met the primary composite efficacy outcome of death, M.I., stroke, noncentral nervous system embolism and major bleeding (Relative Risk [RR], 0.71; 95 % C.I. 0.19–2.66; $p=0.61$). When authors examined the components of the composite outcomes, it was shown that only 1 patient in the occlusion arm vs. 3 patients in the no-occlusion arm had suffered from a stroke ($p=$N.S).

The evidence suggesting greatest benefit for LAA closure comes from Garcia-Fernandez et al. [41]. The authors examined 58 patients who had undergone LAA exclusion during mitral valve surgery vs. 147 patients who did not undergo LAA exclusion. The primary outcome was the occurrence of an embolic event occurring post surgery. In patients who had not received LAA ligation, embolic events were significantly higher than patients who had LAA ligation (17 % vs. 3.4 %; $p=0.01$). Logistic regression analysis revealed that the absence of LAA ligation was an independent predictor of an embolic event (Odds Ratio 6.7, 95 % C.I. 1.5–31.0, $p=0.02$).

Ongoing Trials

Currently, there is a large randomized controlled trial that is recruiting patients to definitively study LAA occlusion at the time of concomitant cardiac surgery. The Left Atrial Appendage Occlusion Study (LAAOS) III aims to recruit 4700 patients across at least 60 centers to determine if removing the LAA can reduce stroke rates in AF patients undergoing heart surgery. The primary outcome of stroke or systemic embolism will be assessed at mean follow up of 4 years, and the secondary outcome of mortality and major bleeding will also be recorded. The investigators believe that the results of this study will change the way heart surgery is performed on patients with AF. The study is expected to complete recruitment in May 2016, while the estimated study completion date is May 2019.

There are also several other studies currently running to investigate surgical LAA occlusion. A search on ClinicalTrials.gov reveals that LAA occlusion is an active area of research, and further trials will promote more definitive evidence behind the intervention (Table 5.3).

Existing Guidelines

To date, no definitive evidence exists for LAA closure. The 2012 HRS guidelines only recommend surgical LAA closure when patients undergo surgical ablation of symptomatic AF (Class IIa, Level of Evidence C) [16]. The task force also recommends that the LAA closure be undertaken only when feasible, and deemed safe by the surgeon. The European Society of Cardiologists (ESC) recommends percutaneous LAA closure be considered in patients with a high stroke risk and contraindications for long-term OACs (Class IIb, Level of Evidence B) [42]. However, the ESC did not publish any indications for surgical LAA closure. The 2014 AHA/ACC guidelines for the Management of patients with Valvular heart disease recommends excision of the LAA during mitral valve surgery for patients who have had recurrent embolic events despite adequate anticoagulation (Class IIb, Level of Evidence C) [43]. Additionally, the 2014 AHA/ACC Atrial Fibrillation guidelines recommend that surgical excision of the LAA may be considered in patients with AF undergoing cardiac surgery (Class IIb, Level of Evidence C) [44].

Conclusion

This chapter has highlighted the surgical aspects of LAA occlusion. From the first time it was described in 1949, the indications and techniques for LAA closure have evolved. From simple ligation methods to novel devices that can have thorascopic application, the field of LAA closure is advancing.

Table 5.3 Studies investigating surgical left atrial appendage occlusion (ClinicalTrials.gov)

Trial name, NCT #	Study population/ intervention	Primary outcomes	Start date	Proposed end date	Estimated enrollment
LAAOS III NCT01561651	Patients with AF and $CHA_2DS_2Vasc \geq 2$ and undergoing cardiac surgery	Stroke or Systemic Arterial embolism over 4 years of follow up	July 2012	May 2016	4700
Stroke Feasibility study NCT01997905	Patients with Non-Valvular AF and contraindication to OAC receiving AtriClip for stroke prophylaxis	Serious injury to cardiac structure, cardiac-related death, MI, Stroke, or Major bleeding (30 days)	January 2014	February 2017	30
		Composite LAAO success: implant success, intraprocedural complete exclusion[a], and complete exclusion at 3 months[b]			
LAACR (not registered on ClinicalTrials.gov)	Surgical Left atrial appendage closure registry	Procedural and durability data on different LAAO modalities, incidence of neurologic complication, rhythm status, and use of anticoagulation over 10 years	Year 2012	Year 2022	Unknown

[a]The complete exclusion of the LAA defined by lack of fluid communication (<3 mm residual communication with LAA and <10 mm residual pocket) between the LA and LAA, assessed intraprocedurally by TEE

[b]The complete exclusion of the LAA defined by lack of fluid communication (<3 mm residual communication with LAA and <10 mm residual pocket) between the LA and LAA at ≥3 month TEE or CTA evaluation

All of the guidelines are based on the consensus opinion of experts (Level of Evidence C), since the strength of evidence for surgical occlusion is currently poor. For any patients who are eligible for surgical LAA occlusion, it is strongly recommended that they enter into current and upcoming surgical clinical trials that are evaluating the safety and efficacy of LAA closure.

References

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, 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(18):2370–5. Epub 2001/05/10.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22(8):983–8. Epub 1991/08/01.
3. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med. 1994;154(13):1449–57. Epub 1994/07/11.
4. Contractor T, Khasnis A. Left atrial appendage closure in atrial fibrillation: a world without anticoagulation? Cardiol Res Pract. 2011;2011:752808. Epub 2011/05/12.
5. Whitlock RP, Hanif H, Danter M. Nonpharmacologic approaches to stroke prevention in atrial fibrillation. Can J Cardiol. 2013;29(7 Suppl):S79–86. Epub 2013/06/29.
6. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg. 1996;61(2):755–9. Epub 1996/02/01.
7. Manning WJ, Weintraub RM, Waksmonski CA, Haering JM, Rooney PS, Maslow AD, et al. Accuracy of transesophageal echocardiography for identifying left atrial thrombi. A prospective, intraoperative study. Ann Intern Med. 1995;123(11):817–22. Epub 1995/12/01.
8. Leung DY, Black IW, Cranney GB, Hopkins AP, Walsh WF. Prognostic implications of left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. J Am Coll Cardiol. 1994;24(3):755–62. Epub 1994/09/01.
9. Madden JL. Resection of the left auricular appendix; a prophylaxis for recurrent arterial emboli. JAMA. 1949;140(9):769–72. Epub 1949/07/02.
10. Williams JM, Ungerleider RM, Lofland GK, Cox JL. Left atrial isolation: new technique for the treatment of supraventricular arrhythmias. J Thorac Cardiovasc Surg. 1980;80(3):373–80. Epub 1980/09/01.
11. Sie HT, Beukema WP, Elvan A, Ramdat Misier AR. New strategies in the surgical treatment of atrial fibrillation. Cardiovasc Res. 2003;58(3):501–9. Epub 2003/06/12.
12. Cox JL, Schuessler RB, Boineau JP. The surgical treatment of atrial fibrillation. I. Summary of the current concepts of the mechanisms of atrial flutter and atrial fibrillation. J Thorac Cardiovasc Surg. 1991;101(3):402–5. Epub 1991/03/01.
13. Cox JL, Canavan TE, Schuessler RB, Cain ME, Lindsay BD, Stone C, et al. The surgical treatment of atrial fibrillation. II. Intraoperative electrophysiologic mapping and description of the electrophysiologic basis of atrial flutter and atrial fibrillation. J Thorac Cardiovasc Surg. 1991;101(3):406–26. Epub 1991/03/01.
14. Cox JL, Ad N, Palazzo T, Fitzpatrick S, Suyderhoud JP, DeGroot KW, et al. Current status of the Maze procedure for the treatment of atrial fibrillation. Semin Thorac Cardiovasc Surg. 2000;12(1):15–9. Epub 2000/04/04.
15. Cox JL, Ad N, Palazzo T. Impact of the maze procedure on the stroke rate in patients with atrial fibrillation. J Thorac Cardiovasc Surg. 1999;118(5):833–40. Epub 1999/10/27.
16. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and

follow-up, definitions, endpoints, and research trial design. Europace. 2012;14(4):528–606. Epub 2012/03/06.
17. Khargi K, Hutten BA, Lemke B, Deneke T. Surgical treatment of atrial fibrillation; a systematic review. Eur J Cardiothorac Surg. 2005;27(2):258–65. Epub 2005/02/05.
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(11):924–9. Epub 2008/09/06.
19. Su P, McCarthy KP, Ho SY. Occluding the left atrial appendage: anatomical considerations. Heart. 2008;94(9):1166–70. Epub 2007/05/10.
20. Lynch M, Shanewise JS, Chang GL, Martin RP, Clements SD. Recanalization of the left atrial appendage demonstrated by transesophageal echocardiography. Ann Thorac Surg. 1997;63(6):1774–5. Epub 1997/06/01.
21. Schneider B, Stollberger C, Sievers HH. Surgical closure of the left atrial appendage—a beneficial procedure? Cardiology. 2005;104(3):127–32. Epub 2005/08/25.
22. Hernandez-Estefania R, Levy Praschker B, Bastarrika G, Rabago G. Left atrial appendage occlusion by invagination and double suture technique. Eur J Cardiothorac Surg. 2012;41(1): 134–6. Epub 2011/06/21.
23. Johnson WD, Ganjoo AK, Stone CD, Srivyas RC, Howard M. The left atrial appendage: our most lethal human attachment! Surgical implications. Eur J Cardiothorac Surg. 2000;17(6): 718–22. Epub 2000/06/17.
24. Gillinov AM, Pettersson G, Cosgrove DM. Stapled excision of the left atrial appendage. J Thorac Cardiovasc Surg. 2005;129(3):679–80. Epub 2005/03/05.
25. Healey JS, Crystal E, Lamy A, Teoh K, Semelhago L, Hohnloser SH, 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(2):288–93. Epub 2005/08/10.
26. Ailawadi G, Gerdisch MW, Harvey RL, Hooker RL, Damiano RJ, Jr., Salamon T, et al. Exclusion of the left atrial appendage with a novel device: early results of a multicenter trial. J Thorac Cardiovasc Surg. 2011;142(5):1002–9, 9 e1: Epub 2011/09/13.
27. Slater AD, Tatooles AJ, Coffey A, Pappas PS, Bresticker M, Greason K, et al. Prospective clinical study of a novel left atrial appendage occlusion device. Ann Thorac Surg. 2012;93(6):2035–8; discussion 8–40. Epub 2012/05/29.
28. Blackshear JL, Johnson WD, Odell JA, Baker VS, Howard M, Pearce L, et al. Thoracoscopic extracardiac obliteration of the left atrial appendage for stroke risk reduction in atrial fibrillation. J Am Coll Cardiol. 2003;42(7):1249–52.
29. Jayakar D, Gozo F, Gomez E, Carlos C. Use of tissue welding technology to obliterate left atrial appendage—novel use of Ligasure. Interact Cardiovasc Thorac Surg. 2005;4(4):372–3. Epub 2007/08/03.
30. Whitlock RP, Vincent J, Blackall MH, Hirsh J, Fremes S, Novick R, et al. Left Atrial Appendage Occlusion Study II (LAAOS II). Can J Cardiol. 2013;29(11):1443–7. Epub 2013/09/24.
31. Leinonen JV, Emanuelov AK, Platt Y, Helman Y, Feinberg Y, Lotan C, et al. Left atrial appendages from adult hearts contain a reservoir of diverse cardiac progenitor cells. PLoS One. 2013;8(3), e59228. Epub 2013/04/05.
32. Sakellaridis T, Argiriou M, Charitos C, Tsakiridis K, Zarogoulidis P, Katsikogiannis N, et al. Left atrial appendage exclusion-Where do we stand? J Thorac Dis. 2014;6 Suppl 1:S70–7. Epub 2014/03/29.
33. Hara H, Virmani R, Holmes Jr DR, Buchbinder M, Lesser JR, Van Tassel RA, et al. Is the left atrial appendage more than a simple appendage? Catheter Cardiovasc Interv. 2009;74(2):234–42. Epub 2009/04/11.
34. Whitlock RP, Healey JS, Connolly SJ. Left atrial appendage occlusion does not eliminate the need for warfarin. Circulation. 2009;120(19):1927–32; discussion 32. Epub 2009/11/11.
35. Kamohara K, Fukamachi K, Ootaki Y, Akiyama M, Cingoz F, Ootaki C, et al. Evaluation of a novel device for left atrial appendage exclusion: the second-generation atrial exclusion device. J Thorac Cardiovasc Surg. 2006;132(2):340–6. Epub 2006/07/29.

36. Fumoto H, Gillinov AM, Ootaki Y, Akiyama M, Saeed D, Horai T, et al. A novel device for left atrial appendage exclusion: the third-generation atrial exclusion device. J Thorac Cardiovasc Surg. 2008;136(4):1019–27. Epub 2008/10/29.
37. Almahameed ST, Khan M, Zuzek RW, Juratli N, Belden WA, Asher CR, et al. Left atrial appendage exclusion and the risk of thromboembolic events following mitral valve surgery. J Cardiovasc Electrophysiol. 2007;18(4):364–6. Epub 2007/02/09.
38. Bando K, Kobayashi J, Hirata M, Satoh T, Niwaya K, Tagusari O, et al. Early and late stroke after mitral valve replacement with a mechanical prosthesis: risk factor analysis of a 24-year experience. J Thorac Cardiovasc Surg. 2003;126(2):358–63.
39. Orszulak TA, Schaff HV, Pluth JR, Danielson GK, Puga FJ, Ilstrup DM, et al. The risk of stroke in the early postoperative period following mitral valve replacement. Eur J Cardiothorac Surg. 1995;9(11):615–9; discussion 20. Epub 1995/01/01.
40. Katz ES, Tsiamtsiouris T, Applebaum RM, Schwartzbard A, Tunick PA, Kronzon I. Surgical left atrial appendage ligation is frequently incomplete: a transesophageal echocardiograhic study. J Am Coll Cardiol. 2000;36(2):468–71. Epub 2000/08/10.
41. Garcia-Fernandez MA, Perez-David E, Quiles J, Peralta J, Garcia-Rojas I, Bermejo 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(7):1253–8. Epub 2003/10/03.
42. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, 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(19):2369–429. Epub 2010/08/31.
43. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin III JP, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2014;63(22):2489.
44. January CT, Wann LS, Alpert JS, Calkins H, Cleveland Jr JC, Cigarroa JE, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary: 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(21):2246–2280.

Part III
Imaging for LAA Closure

Chapter 6
The Use of Transesophageal Echocardiography to Guide Percutaneous LAA Closure

Julie A. Humphries

Periprocedural transesophageal echocardiographic imaging of the left atrial appendage (LAA) is crucial for all steps involved in percutaneous closure of the LAA regardless of the type of device used. Certain devices, specifically the Watchman device, require a coaxial approach and alignment of the delivery system within the LAA to achieve successful deployment of the device and complete closure of the LAA. In order to achieve access to the LAA, it is therefore important to guide the appropriate trans-septal puncture location safely, as well as have an appreciation for the size and location of the appendage in relation to surrounding structures. As LAAs come in many shapes and sizes, as well as having different anterolateral positioning, some operator 3-dimensional (3D) spatial awareness and knowledge of anatomical boundaries is important for guiding percutaneous closure. This chapter will address how best to assess the LAA with transesophageal echocardiography (TEE) for device closure, how to help your proceduralist get the best results for LAA closure, and recommend procedural imaging protocols which can be used to guide LAA closure.

LAA 3D Spatial Anatomical Imaging

The LAA is the most anterolateral structure of the heart, and by definition is therefore the furthest structure from the TEE probe. Correct positioning of the TEE probe in the mid-esophageal region with the probe slightly retroflexed in a 50–70° plane will usually provide the best view of the *long axis* of the LAA (typically

J.A. Humphries (✉)
HeartCare Partners, Ramsay Specialist Centre, Greenslopes Private Hospital, Suite 212 Level 2, Newdegate Street, Greenslopes, Brisbane, QLD, Australia
e-mail: jhumphries@heartcarepartners.com.au

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_6

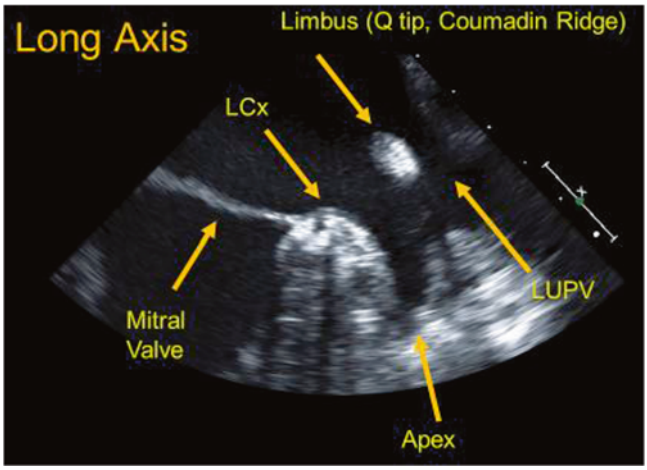


Fig. 6.1 Long axis of the LAA showing medial and lateral anatomical boundaries. *LCx* left circumflex coronary artery, *LUPV* left upper pulmonary vein

longest depth). Other structures on view in this imaging plane will include the mitral annulus and left circumflex coronary artery (LCx) (medial to the LAA), the limbus or Coumadin ridge (lateral and superior), and the left superior pulmonary vein (LSPV) laterally (which shares the LAA limbus) (Fig. 6.1). The LCx and the limbus define the medial and lateral boundaries of the LAA respectively. This plane usually gives the maximum depth measurement for the LAA closure device delivery system.

If the LAA is positioned more anteriorly, the long axis is best viewed closer to the 0–45° TEE view, and in this imaging plane the aortic valve will be on view. If the LAA is positioned more laterally, then the long axis will be best appreciated at 70–90°, with no aortic valve on view, but with the lateral aspect of the mitral valve on view instead (Fig. 6.2).

Next is to determine the *short axis* of the LAA (typically shortest depth), which is usually best appreciated in the 135° imaging plane. This is often a difficult imaging plane to achieve with a 2D imaging probe, and in this case, 3-dimensional (3D) imaging allows for biplane imaging at 45° to achieve the correct orientation. As the LAA is usually elliptical in shape (but not always), the short axis is usually the widest measurement and often dictates the size of a device to be implanted. This plane represents the anterior and posterior aspects of the LAA (Fig. 6.3). It is critical that when assessing the LAA pre-device implantation, that this TEE view and measurement be accurately assessed, as it will usually determine the success of closure at implant, with the posterior aspect being the most common site for post-implant peri-device leaks (Fig. 6.4).

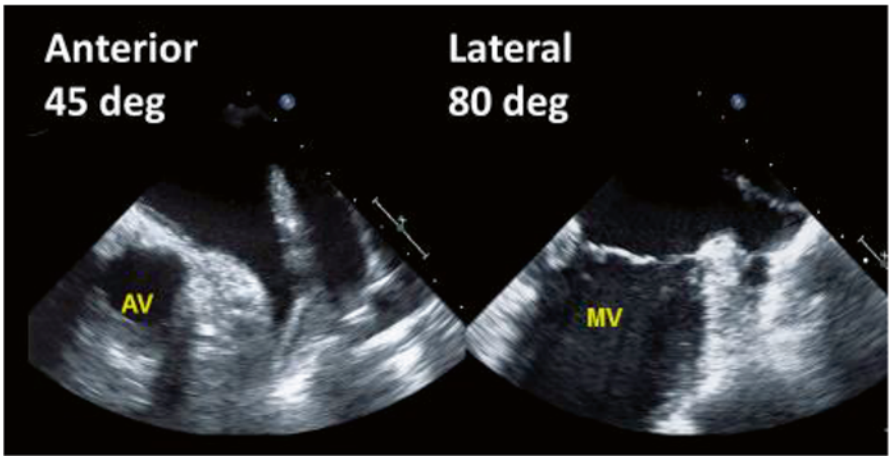


Fig. 6.2 Variability of anterolateral orientation of the LAA. The *left panel* demonstrates a more anterior orientation with Aortic Valve on view in the long axis of the LAA (TEE imaging plane 45°), while the *right panel* demonstrates a more lateral orientation of the long axis of the LAA (TEE imaging plane 80°)

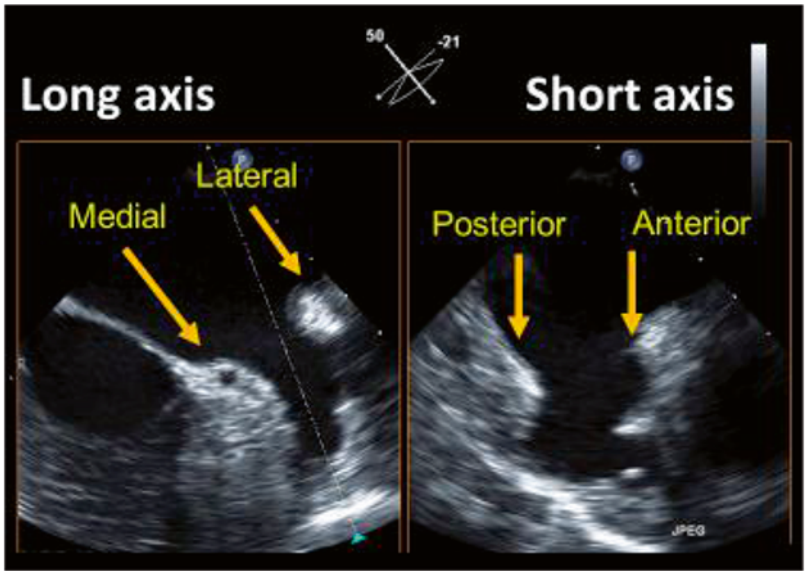


Fig. 6.3 2D biplane imaging of the long axis (*left panel*) provides anteroposterior perspective (*right panel*). The anteroposterior view is usually best appreciated in the 135° view, and provides anatomical information of the anterior and posterior aspects of the LAA (usually the widest dimension when the LAA is elliptical)

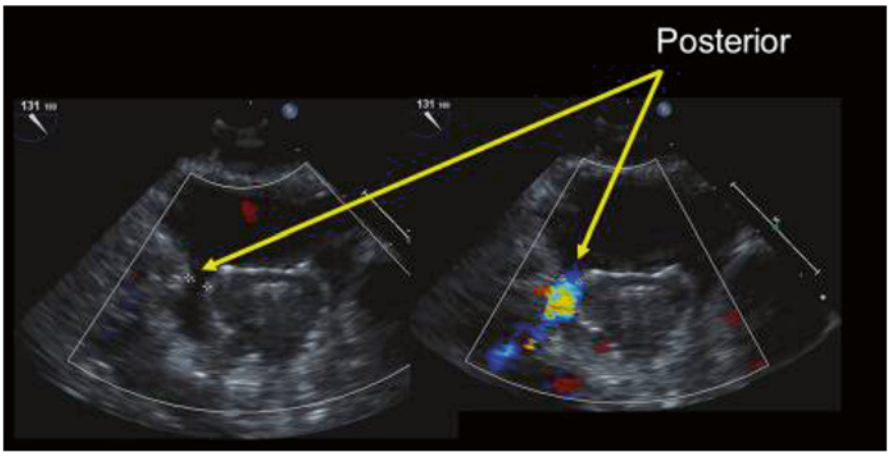


Fig. 6.4 The posterior aspect is the most common site for peri-device leaks at implant or follow-up. This image illustrates a Watchman LAA Occluder with a 3 mm leak at the posterior aspect, seen in both 2D (*left panel*) and colour Doppler (*right panel*)

Once the pre-implant LAA assessment is complete, the operator should have the following information:

1. The size, shape and configuration of the LAA
   - Round vs. elliptical
   - Number of lobes
   - Any shapes or configurations which may make device implantation challenging (accessory lobes, lack of depth, too wide, proximal septae, complex pectination)
   - The measurements at the "landing zone" for the chosen device
2. The anterolateral orientation

This information will assist the proceduralist with choosing the correct transseptal puncture position and device delivery system components to achieve the best LAA closure result for the patient.

What About 3D Imaging of the LAA?

Three-dimensional imaging provides information about the shape of the ostium prior to deployment, and beautiful images of a device in position at the end of the procedure, but due to unreliability of the 3D imaging planes with any 2D measurements and often obstruction of the device landing zone by the limbus of the LSPV, it is not recommended that 3D imaging be used to guide decision making about

device size or positioning during the procedure. A 3D imaging platform, however, is very useful as it allows for 2D biplane imaging which is helpful in guiding sheath position, and manipulation of the imaging planes for "hard to image" LAA angles, particularly 135° view in some patients. Keep in mind that prolonged use of 2D biplane or 3D imaging during a case can cause overheating of the TEE imaging head in the esophagus, and can lead to deterioration in image quality due to esophageal edema as the case progresses. Turning down the power output settings to TI 0–0.1 and MI 0.3–0.4 reduces the amount of heat at the imaging head without significant deterioration of the procedural imaging.

The "Landing Zone"

Successful LAA device closure requires careful measurement of the dimensions where the device will be seated, often referred to as the "landing zone". *For the WATCHMAN LAA occluderdevice*, the landing zone is located between the LCx medially and 1–2 cm inside the limbus laterally. The measurements are taken in four views to determine the widest measurement (most often the 135° view or anteroposterior view), whether the landing zone is round vs. elliptical, and to determine whether there is appropriate depth to accept a delivery system once the size of the device has been determined. The four views are taken at 0, 45, 90 and 135°, and the measurements recorded in millimetres. Examples of measurements obtained in these views are illustrated in Fig. 6.5. Some views may be difficult to achieve with omniplane manipulation of the imaging window, and thus 2D biplane imaging can assist in this regard. For example, imaging at 135° can prove to be difficult in some patients, so getting the best 45° view and bisecting this image with biplane imaging (and sometimes a degree of elevation or subtraction) can better achieve this view.

The WATCHMAN device size selection is based on the largest measurement at the landing zone allowing for 20 % compression. The device sizes are 21, 24, 27, 30 and 33 mm. Each device sizing has the maximum landing zone dimension recommended for that size device, and relies on equal depth for successful positioning and deployment of the device. For example, a maximum LAA landing zone dimension of 19 mm will not be adequately compressed with a 21 mm device, and thus a 24 mm device is chosen. This however, requires at least 24 mm of coaxial depth. Sometimes a compromise is reached such that if there is insufficient depth to deploy a particular sized device, a decision must be made to deploy a smaller device more distally to successfully occlude the LAA distal to the landing zone. Alternatively, choosing a different device may be necessary if there is insufficient depth, such as the Amplatzer Cardiac Plug (ACP) device, which is less reliant on depth for successful device deployment. The Lariat system is another option but has the limitation of LAA size to be captured by the wire loop and requires instrumentation of the pericardium.

In contrast, measurements for the ACP device are made differently. As the ACP device has two components (distal lobe and proximal disc) the measurements need

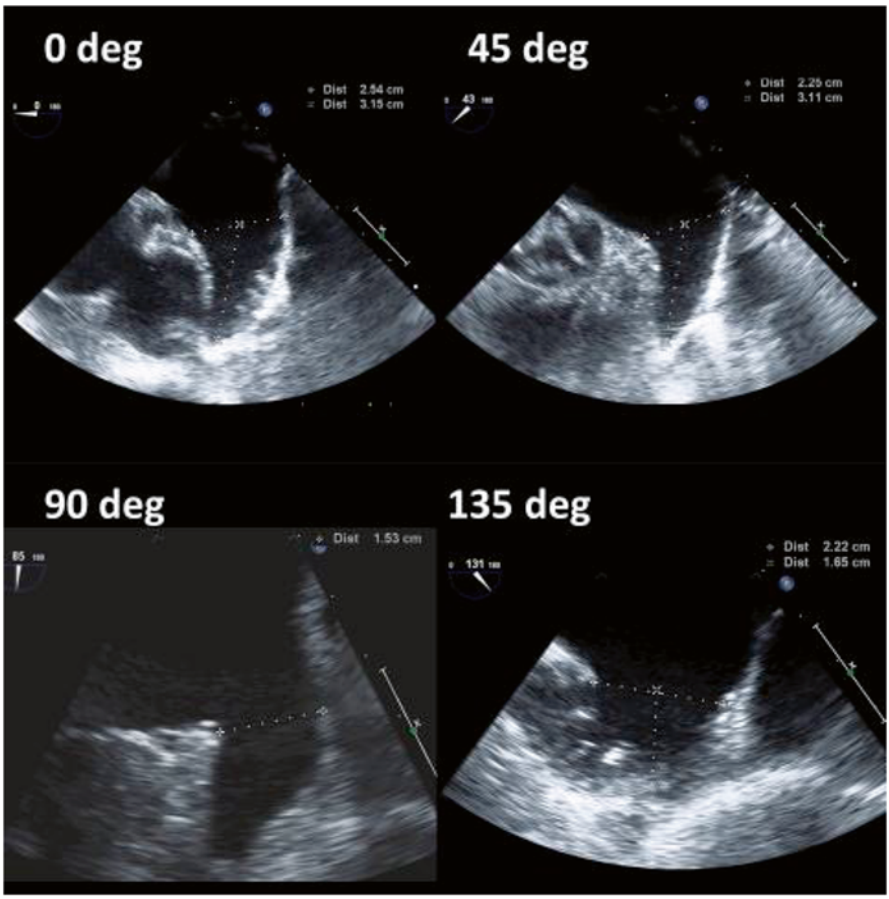


Fig. 6.5 Measurement of the "landing zone". Measurement is taken from the LCx medially to 1–2 cm laterally inside the limbus at the lateral border. All four views (0, 45, 90, 135°) are measured to determine maximum landing zone dimension (most often in 135° view if LAA is elliptical), as well as maximum depth in the long axis (*top two panels*) for the purposes of device sizing

to be made in different positions to the WATCHMAN device. The lobe is deployed approximately 10 mm into the LAA (from the LCx landmark). Measurement for device sizing, which is based on lobe size (16–30 mm), should be made inside the LAA approximately 10 mm distal to the LCx in the long axis view, with matching measurement in the short axis view at the same depth. For disc sizing, the distance between the LCx margin and the LSPV limbus should be made in the long axis view (Fig. 6.6). As the disc will be 4–6 mm bigger than the device measurement as determined by the lobe size, measurement of the ostium will determine whether the device size chosen by lobe measurement will be compatible with a suitable ACP device.

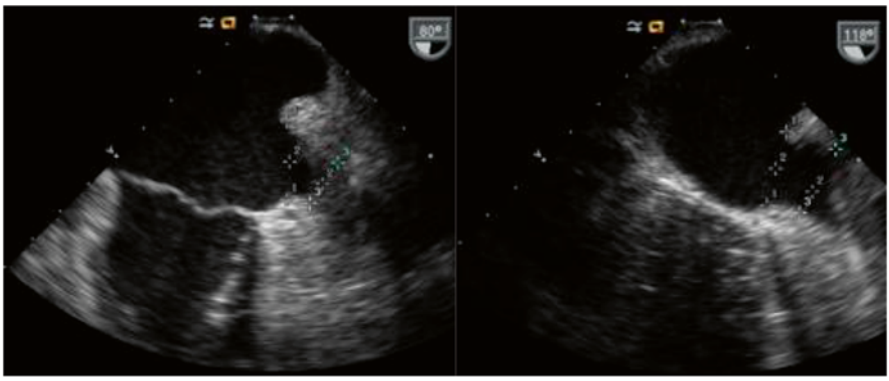


Fig. 6.6 Measurement of the LAA landing zone (approximately 0.5 cm distal to the LCx) and LAA ostium for sizing of ACP device. Images courtesy of Dr J Saw, Vancouver General Hospital

Trans-Septal Puncture

The trans-septal puncture position is probably the most crucial step which will influence the ease of device positioning and deployment. As the LAA is anterior and lateral, the trans-septal puncture position is best achieved at the most posterior location on the fossa ovalis. This usually provides the most coaxial sheath position for accessing the LAA. The craniocaudal position is not quite so critical for LAA access or coaxial alignment, but a mid-to-low fossa position is usually best for puncture with good "run off" into the atrium for the trans-septal puncture needle.

It is best to start with a bicaval view (craniocaudal or superior–inferior view) with the thin membrane of the fossa and the superior vena cava (SVC) on view with the sheath in the SVC. This is best achieved with an imaging plane of 90–110°. The sheath is then drawn down the SVC until it reaches the fossa. It is important to keep the tip of the sheath on view at all times during draw down of the sheath. Once the sheath reaches a suitable position on the fossa (mid to low), the imaging plane should then be focussed on the anteroposterior aspect of the fossa, which is best achieved at the 45° view. This view normally has the aortic valve in short axis, and is usually the plane used to identify any patent foramen ovale or secundum ASD. In this view, the fossa membrane is in an anterior–posterior orientation. For best LAA instrumentation, the most posterior position on the fossa membrane is favourable (Figs. 6.7 and 6.8). Some anterior angulation on the sheath is important so that when the needle punctures across the septum it does not course posteriorly to the back of the left atrium. Improper positioning of this puncture position can have serious consequences such as perforation or tamponade, so care must be taken to guide the needle across the septum safely, keeping the antero-posterior plane on view with care to keep the tip of the needle on view at all times. If the septum is too mobile such that other important structures are at risk of perforation due to excessive tenting of the fossa membrane, advise your proceduralist to pull back the needle to the

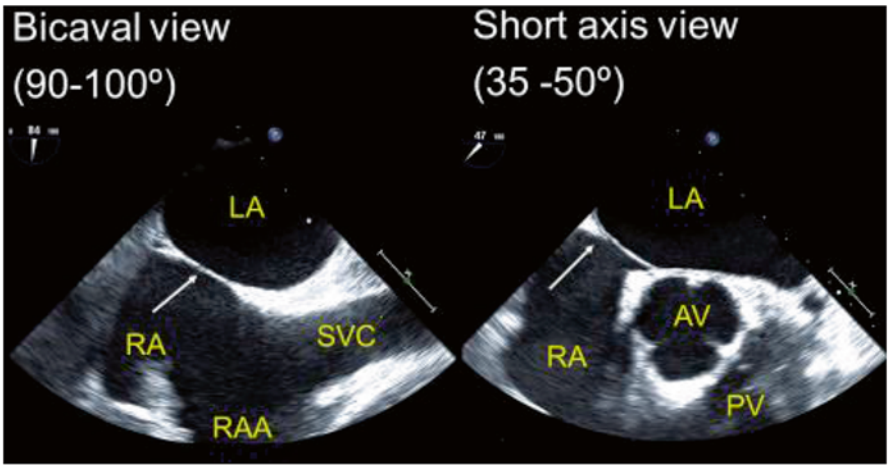


Fig. 6.7 Trans-septal puncture is best performed at the most posterior aspect of the interatrial septum. The *left panel* illustrates the bicaval view (90–100°) which represents the craniocaudal view (or superior–inferior view), while the *right panel* shows the anteroposterior view (45°). This view best shows the most posterior position for IAS puncture, and safety assured by having LA on view in this biplane schema with LA boundaries on view. This will reduce the risk of LA perforation during IAS puncture if done under direct TEE vision

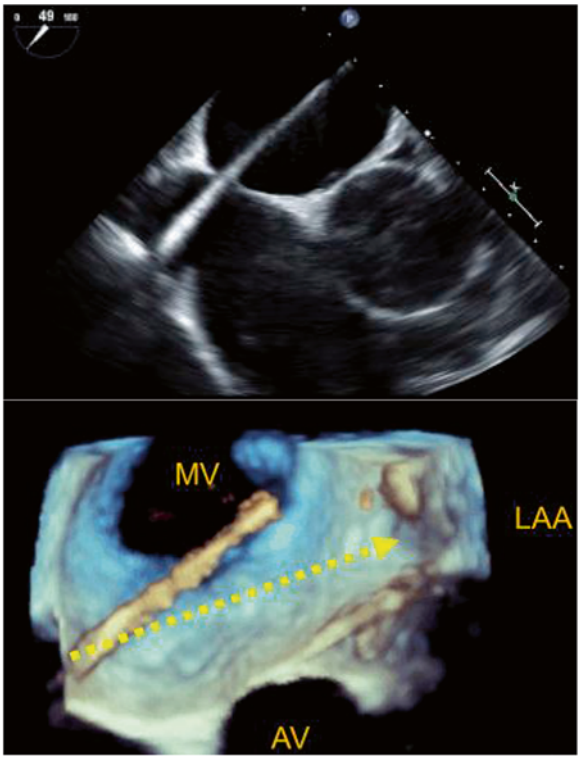


Fig. 6.8 Sheath crossing the IAS. The *top panel* shows the anteroposterior 2D view with a posterior IAS crossing. The *bottom panel* shows the corresponding 3D image showing the position of the sheath as it crosses the IAS and the relative anatomical structures and thus how important a posterior IAS crossing is to access the anterolateral LAA (*arrow*)

tip of the sheath and suggest diathermy to cross the septum. This will provide a safer option for trans-septal puncture and reduce the risk of perforation. *It is common at this juncture of the procedure for the proceduralist to challenge the advised position of the puncture as determined by the TEE, as it often is at an unusual angle to the usual landmarks which are more familiar to the proceduralist for routine trans-septal puncture for other procedures! It is important that there is communication and trust about the position of the needle as determined by TEE given the posterior position of the needle and the surrounding structures at risk of perforation.* Once the needle is across the septum, saline contrast bubbles can be seen in the LA. It is important to notify the proceduralist if air can be seen entering into the LA from the needle or introducer.

The trans-septal puncture can also be achieved using IntraCardiac Echocardiography (ICE), however once across the septum, this imaging technique has several challenges in guiding LAA device positioning or deployment, as it is a non-steerable imaging catheter with limited viewing planes. It is unable to image at the most crucial angle of 135° and some operators use non-standard views (see Chap. 7) and also double trans-septal punctures to gain LA ICE access for better imaging planes.

Once the trans-septal puncture has been achieved, the wire and sheath/delivery systems can be safely guided and confirmed to be "parked" in the LPSV in preparation for device positioning (see Fig. 6.9). This can be achieved by keeping the same imaging plane as the septal puncture (45°) and rotating the imaging probe in a counter-clockwise direction, shifting the image from the septum to the left-sided pulmonary veins to confirm the position of the sheath.

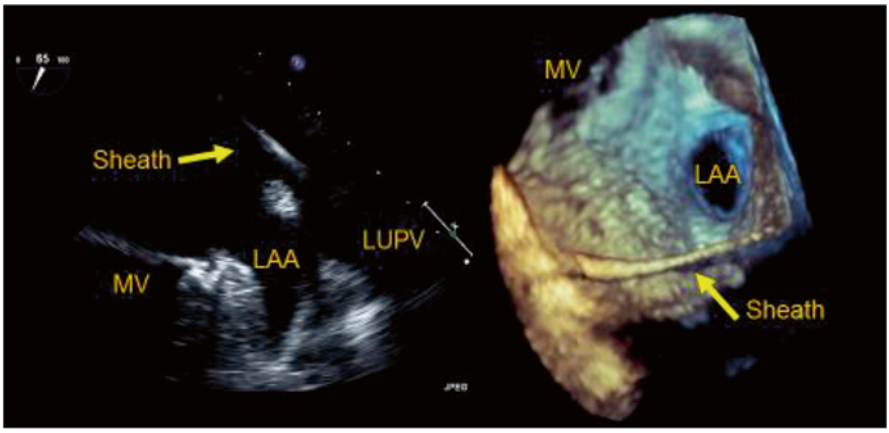


Fig. 6.9 The *left panel* shows in 2D the sheath "parked" in the LUPV after removal of the guide wire and prior to introduction of the pigtail catheter. The *right panel* illustrates the 3D spatial anatomy of the sheath in the LUPV, and its relationship to the LAA ostium and the mitral valve. Parking the delivery system in the LUPV allows direct vision of gentle withdrawal of the pigtail and delivery system over the limbus and into the LAA

If There Is a Patent Foramen Ovale, Can I Use This to Cross the Septum?

A word of caution—if there is a patent foramen ovale (PFO) present it is not recommended to use it for the purposes of accessing the LAA with the intention of LAA closure with *any* closure device. While some devices can be more forgiving with this approach, crossing a PFO directs the delivery sheath in an anterior orientation, hugging the anterior (retroaortic) aspect of the LAA and as a result the sheath enters the LAA with a lateral position (see Fig. 6.10). With the WATCHMAN LAA occluder device in particular, placement of a device with this sheath orientation results in an overly anteriorly angulated device, with a shoulder outside the posterior aspect of the LAA and often the posterior aspect is left uncovered with a significant peridevice leak. Devices left in this position may not fully endothelialize and may have a persistent peridevice leak when followed over time.

TEE Imaging of Instrumentation of the LAA

Once the delivery sheath is parked in the LSPV, with the pigtail catheter on view, it can be drawn back over the limbus and advanced into the LAA under TEE guidance. This is best performed with TEE plane at approximately 70° so that the LAA (long axis view) and the LSPV are both on view**.**

Using the long axis view of the LAA allows for visualisation of the sheath position with the aim being coaxial with the long axis and most anterior within the LAA itself. This is best appreciated with the long axis and short axis on view simultaneously using 2D biplane imaging of the 45–60° view with the 135° view, also known as the "implant view" (see Fig. 6.11).

For the WATCHMAN device, the pigtail is advanced to the most anterior depth within the LAA, then the delivery system is carefully advanced over the pigtail catheter to its final position. The depth of the delivery sheath for the WATCHMAN device is dependent on the size of the device used, and the anatomical features of the LAA to seat the device in the landing zone. There are markers on the delivery system which can be detected on TEE easily if the system is coaxial (Fig. 6.11). This allows for anatomical correlation with the image intensifier during cine acquisition of the sheath in the LAA.

Once the correct sheath positioning has been achieved, the pigtail catheter is withdrawn to allow for the device to be introduced into the delivery system in preparation for deployment. When the pigtail has been removed, care must be taken to ensure the sheath remains in the correct position. Live TEE imaging during pigtail removal allows for monitoring of the position of the sheath and that removal of the pigtail has not caused a change in sheath position which may adversely affect device delivery. Introduction of the device into the delivery system can also cause stiffening or straightening of the sheath and change its position within the LAA, and live

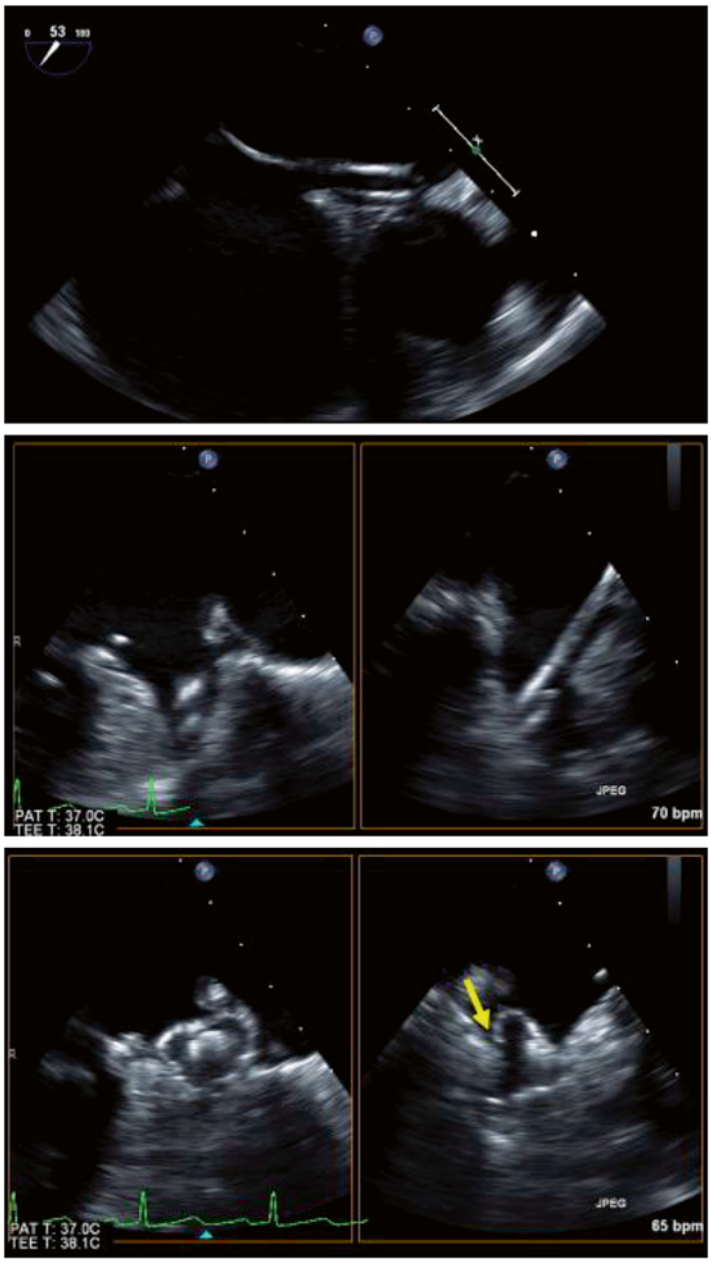


Fig. 6.10 Crossing the interatrial septum using a PFO causes a more anterior septal position, causing the sheath to hug the anterior (retroaortic) aspect of the LA (*top panel*). This approach makes the procedure technically challenging, with a lateral sheath position (*middle panel*) and anterior angulation of the device, often resulting in a significant posterior shoulder (*lower panel*) and peridevice leak (*arrow*)

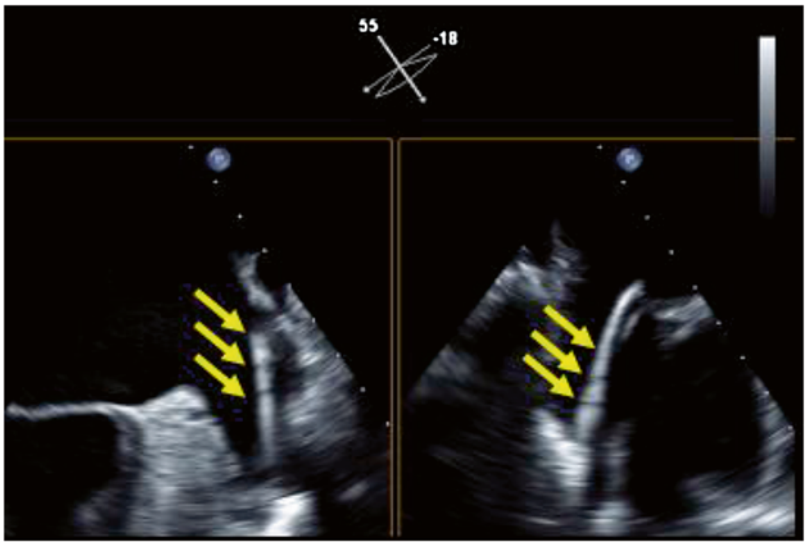


Fig. 6.11 The "implant view" showing the long and short axis views simultaneously. The delivery sheath is in the most favourable position when it is coaxial in both planes as above. In this view, the Watchman device system marker bands can be easily identified (*arrows*)

imaging during this process is again valuable to ensure the sheath has not changed its position as a result.

For the ACP device, the sheath should again be coaxial with the long and short axis of the LAA, however unlike the WATCHMAN device, the depth of the sheath is not required to be at any prescriptive length within the LAA, but be in approximation to the landing zone of the lobe of the device. This is approximately 10 mm beyond the LCx in the long axis view.

For the Lariat device, the endocardial sheath is positioned in the proximal segment of the LAA with TEE guidance. The final position of the sheath is not critical, however the endocardial magnet needs to be advanced into the most distal and anterior aspect of the LAA in order to facilitate epicardial magnet positioning and attachment.

TEE Imaging Planes and Cine Imaging Correlation

The LAA images obtained during TEE assessment can be correlated with cine views. As the image intensifier (II) is external to the chest and anteromedial to the LAA in an RAO orientation, the TEE probe is internal in the chest posteromedial to the LAA. The TEE imaging planes rotate their axis with manipulation of the omniplane imaging angle without changing position, whereas the II image orientation

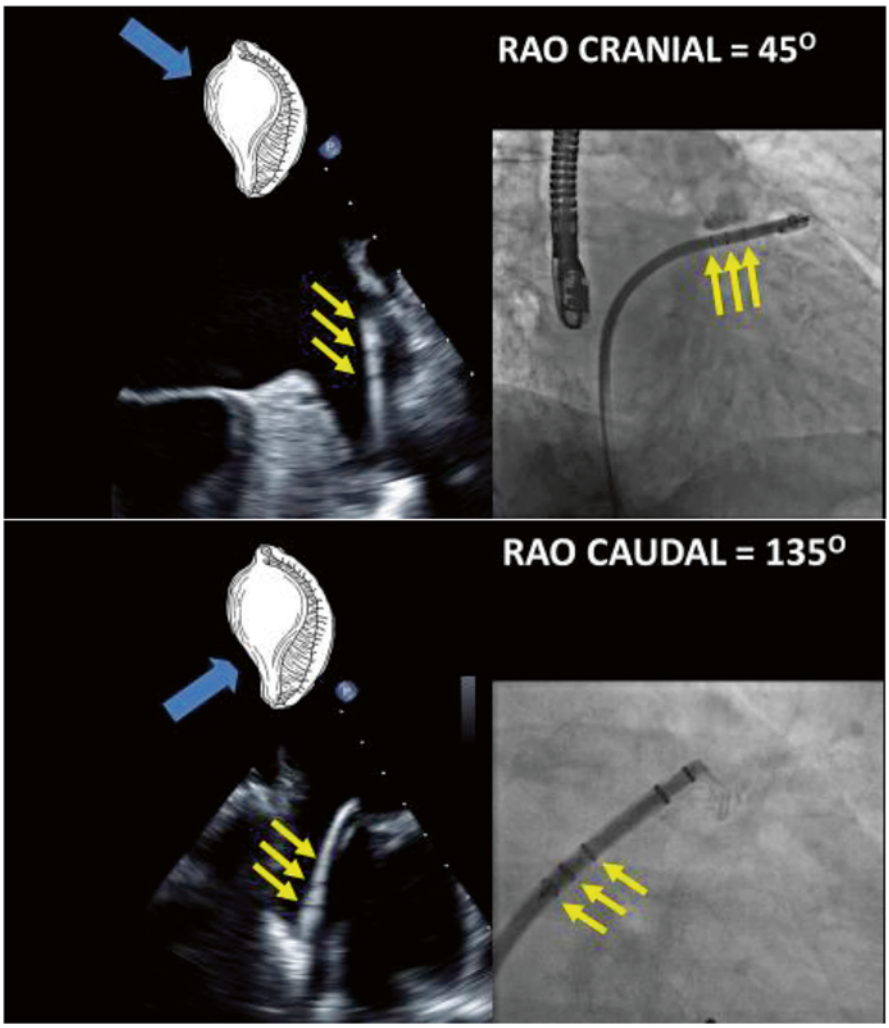


Fig. 6.12 TEE and cine imaging correlations. Visualisation of the marker bands (*arrows*) on the Watchman delivery system allows for more accurate imaging correlation during device positioning prior to deployment. The *top panel* represents the TEE long axis correlating best with RAO Cranial projection, and the *bottom panel* represents the TEE short axis correlating best with the RAO Caudal projection

can only be rotated by moving in a craniocaudal plane. With this in mind, Fig. 6.12 illustrates the imaging correlations for LAA which can be achieved comparing TEE and II. The best view for device deployment which allows for TEE and II comparison is 135° TEE and RAO caudal (approximately RAO 20 caudal 20), especially relevant for WATCHMAN implantation.

Assessment of Device Position and Stability

Once the correct positioning of the sheath has been achieved, and the pigtail catheter has been removed, the device is loaded into the delivery sheath and deployed into position. The device position, degree of compression and presence of any peri-device leaks can then be assessed before determining the final device position.

WATCHMAN device. Device position and measurements are illustrated in Fig. 6.13. In each imaging plane, colour Doppler (using a Nyquist limit of 50 cm/s) should be used to assess for any peri-device leak, and if present, measurement made at the site of the leak. If the leak is less than 5 mm, there will usually be aliasing of the colour Doppler signal at the point of mal-union of the device with the LAA wall, and this can be measured with calipers in mm. If the leak is 5 mm or greater, there will usually be no aliasing of the colour signal with free flow observed between the LA and the body of the LAA.

The device can be recaptured and redeployed if the position is not satisfactory. Occasionally the presence of pectinate muscles within the LAA can cause the device to get caught up and fail to deploy correctly (Fig. 6.14). Once the device is

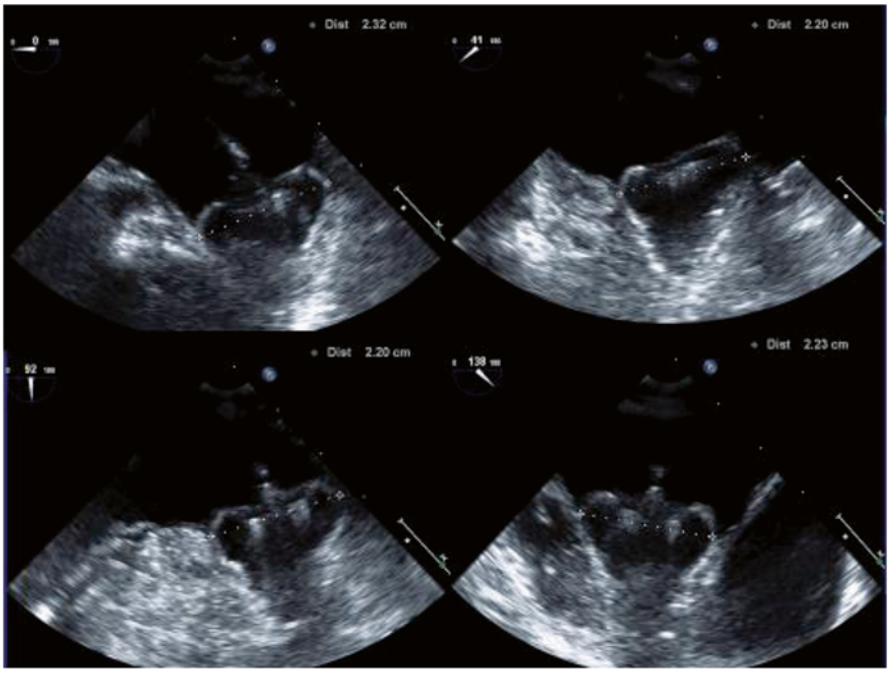


Fig. 6.13 Assessment of position and measurement of the Watchman device. Assessment of position should be made in all four viewing planes and be measured in its widest dimension, with the hub of the device on view, giving the appearance of a crown. If the hub is not visible, the device will be off axis and the measurement will be inaccurate

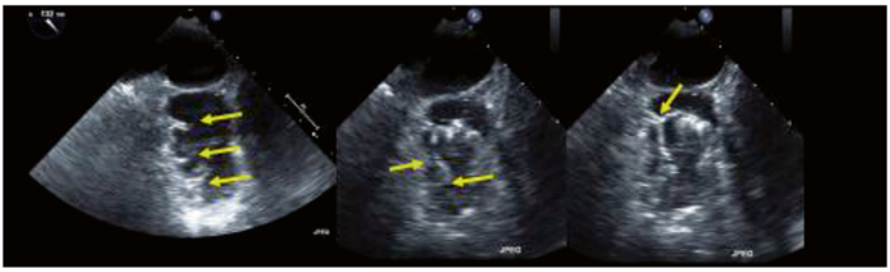


Fig. 6.14 A heavily pectinated LAA can pose technical challenges for device deployment. The *left panel* shows a heavily pectinated LAA (*arrows*) in the anteroposterior view. The *middle panel* shows the first attempted device deployment which gets caught on the pectinates and is therefore too deep and compressed, allowing a leak around the proximal edge of the device. The *right panel* shows the new position after minimal withdrawal of the sheath with appropriate anchoring of the device to the most proximal pectinates and no peridevice leak

determined to be in a satisfactory position, a tug test is performed. The device and the LAA should be observed on TEE to move with the application of tension, and confirm there has been no movement of the device more proximally or extrusion of the device into the LA. Once the tug test has been performed and the position confirmed as satisfactory with no new peri-device leaks or change in device position or stability resulting from the tug test, the device can be released.

ACP device. Biplane imaging or "implant view" is useful for deployment of the ACP lobe to assess alignment, lobe compression and position in relation to the LCx. Two-thirds of the lobe should be distal to the LCx as per the product monograph. Lobe compression is assessed using 2D and colour Doppler, preferably with no flow around the lobe. As the lobe is anchored at the landing zone with sharp barbs, there should be adequate compression best appreciated in the biplane view and measured according to manufacturer's recommendations. The appearances on 2D imaging can best be described as a tyre, with rectangular edges in contact with the wall of the LAA, and indentation at the middle part of the lobe. If the lobe appears rectangular with no indentation, it is likely to be inadequately compressed. If the lobe adopts a strawberry shape, it is also overly compressed. Once correct position and compression have been assessed as adequate, the disc is then deployed proximal to the lobe and covers the ostium of the LAA (Fig. 6.15). The disc should obliterate the ostium of the LAA and there should be no colour flow around the device. Similarly, there should be no impingement on the mitral valve, nor the ostium of the LSPV.

Stability of the ACP device is assessed by gentle but constant back pressure on the disc by the operator. During this time the appearances of the proximal disc will assume a conical shape on TEE and fluoro imaging. Attention should be paid to the appearances and stability of the lobe while the back pressure on the disc is applied to ensure there is no proximal movement or migration, or dislodgement of the lobe. If this occurs, the device is declared unstable, and repositioning and/or re-sizing of the device should be undertaken. If there is no migration or movement of the lobe

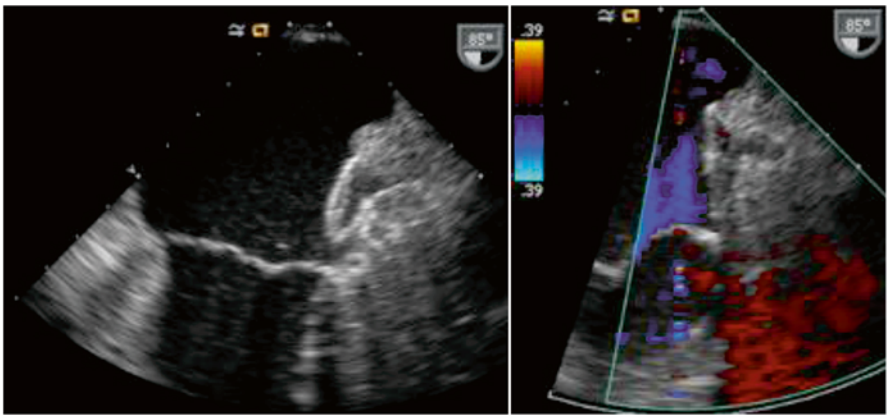


Fig. 6.15 The ACP device deployed in the LAA. The lobe (most distal part of the device) should have 2/3 past the LCx. The disc is then deployed once the position is stable, and colour Doppler is used to assess sealing of the LAA at the ostium. Images courtesy of Dr J Saw, Vancouver General Hospital

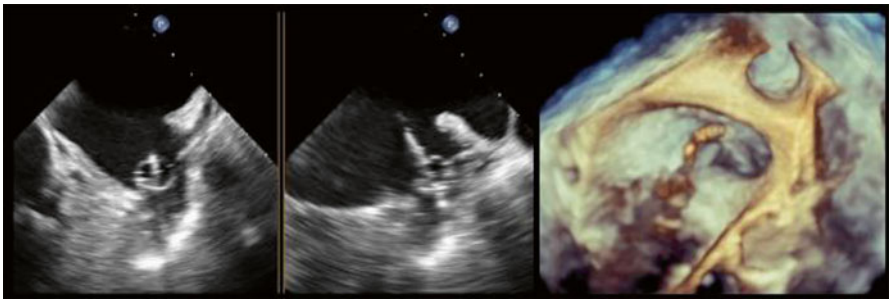


Fig. 6.16 Introduction of the sheath and endocardial balloon of the Lariat device into the LAA. The *left* and *middle panel* shows a biplane image of the endocardial balloon entering the LAA. In this view the balloon can be guided to approximately 1 cm into the ostium. The *right panel* shows the endocardial sheath position within the LAA and the endocardial balloon inflated beyond the ostium. Images courtesy of Dr R. Lee, San Francisco

during disc retraction, and there is no colour flow around the device once tension on the disc is released, assessment should move to adjacent structures to ensure adequate clearance of the mitral valve and LSPV.

The disc and adjacent structures such as mitral annulus, mitral valve, and LSPV can be viewed readily using 3D imaging. There should be adequate clearance of these structures prior to release of the device.

Lariat system. The endocardial balloon is inflated in the proximal LAA but distal to the LCx (approximately 10 mm). This is best viewed in the "implant view" (Fig. 6.16). The position of the balloon needs to be beyond the LCx so that the

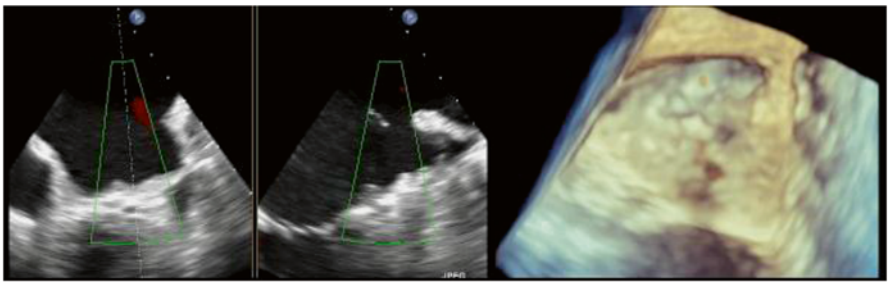


Fig. 6.17 Appearances of the closed ostium of the LAA once Lariat loop has been tightened, prior to release. The occlusion should approximate the ostium, and assessment with colour Doppler should be performed to assess for residual flow. Images courtesy of Dr R. Lee, San Francisco

Lariat device is able to cinch the proximal LAA without causing impingement. Once the Lariat loop has been tightened, and proximal occlusion has been demonstrated without impingement, the balloon is deflated and withdrawn with the sheath into the LAA. Once the endocardial sheath and balloon has been withdrawn, the Lariat loop is tightened to the point of LAA occlusion. Colour Doppler at a Nyquist limit of 50 cm/s should be used in the biplane "implant view" at the site of occlusion to assess for any residual flow into the LAA and whether complete occlusion has been achieved by the Lariat device. If no colour flow is detected, the device can be safely released (Fig. 6.17).

Final TEE Assessment After Device Release

Regardless of the type of device used to close the LAA, once the device has been released and the delivery system has been withdrawn into the right atrium, the interatrial septal puncture should be assessed with colour Doppler to determine the position of the defect (Fig. 6.18), and provide a landmark for future follow-up to assess whether the iatrogenic septal puncture defect has indeed healed. It is also important at this point of the procedure to reassess the pericardial space for any pericardial fluid. Survey should be undertaken of the pericardial space around the entire left ventricle, right ventricle, right atrium, and LAA surrounds, and compared with the pre-procedure imaging if there is any doubt about the presence or extent of any pericardial fluid or echolucent space.

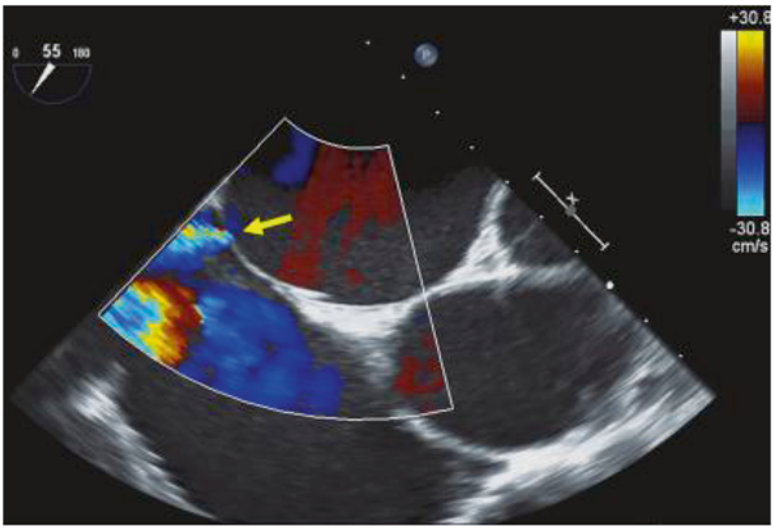


Fig. 6.18 Assessment of the residual interatrial septal defect after sheath removal. For a 14F delivery system the iatrogenic defect will measure approximately 3 mm. Due to atrial pressures, the Nyquist limit should be reduced to approximately 30 cm/s to accurately assess. The size and position of the defect can be compared at follow-up to assess for closure

Conclusion

The use of TEE during LAA occlusion procedures provides an important and useful imaging tool to assist the proceduralist in achieving a successful result. Imaging the LAA with TEE is a skill which requires dedication of an experienced echocardiologist, with attention to detail and thorough knowledge of the procedural steps involved in LAA occlusion procedures.

Chapter 7
The Use of Intracardiac Echocardiography (ICE) to Guide LAA Closure

Sergio Berti, Umberto Paradossi, and Gennaro Santoro

Introduction

Left atrial appendage (LAA) occlusion by percutaneous implantation of an occlusive device has beenshown to have encouraging results as an alternative to OAC therapy [1–18]. The use of imaging techniques is of great importance throughout all phases of the implantation procedure for LAA occlusion, specifically for LAA anatomy evaluation and procedural guidance. Intra-procedural imaging for LAA requires the ability to rule out thrombus, measure the size of the LAA ostium, landing zone, length, number of lobes, and shape, as well as to guide the transseptal puncture, sheath placement, device placement, and assess device stability, post-placement leak, and procedural complications [12, 17, 19].

The use of Intracardiac echocardiography (ICE) allows operators to perform LAA closure without general anesthesia. In some centers, it has replaced transesophageal echocardiography (TEE) to guide all intra-procedural phases of percutaneous LAA occlusion. ICE reduces procedural time and can be performed safely under local anaesthesia [19–22]. ICE is particularly useful for the transseptal puncture since it visualizes the exact area of the fossa ovalis that must be punctured. The ICE catheter, placed within the right atrium, allows for the visualisation of the left atrial anatomy, as well as the ostium and landing zone of the LAA; these measurements, used to select the correct device, can be compared with those previously

S. Berti (✉)
Ospedale del Cuore, Fondazione C.N.R. Reg. Toscana G. Monasterio, Massa, Italy
e-mail: sergio.berti@ftgm.it

U. Paradossi
Fondazione Toscana G. Monasterio, Pisa, Italy
e-mail: umberto.paradossi@ftgm.it

G. Santoro
Azienda Ospedaliero Universitaria Careggi, Firenze, Italy

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_7

obtained by TEE and with those chosen by fluoroscopy. Device placement and the stability assessment during and after a tug test are feasible and safe with ICE guidance and can be confirmed with fluoroscopy [14, 19, 23].

Angiographic injection of contrast is typically used to rule outleaks around the device. Research has shown that small leaks are not associated with increased embolic risk. However, it is imperative to characterize the leak that is present in order to ensure that it is small in nature. For this, an ICE-based Doppler is useful to determine the presence or absence of ICE-based Doppler leak around the device after implantation. We typically perform transthoracic echocardiography (TTE) to rule out pericardial effusion immediately after the procedure, as well as a few hours later. During follow-up, cardiac imaging is usually performed using TEE and/or CT to confirm device position excludes device-related thrombus and assess residual leaks.

In our opinion, ICE is an attractive and increasingly used alternative to TEE, with several potential advantages for LAA closures. We will review the step-by-step approach to ICE-guided LAA closure [19].

Technology Background

In the search for minimally invasive imaging modalities, the main alternative to traditional TEE is ICE. The first and main difference between TEE and ICE is the probe position. The TEE probe is placed in the esophagus and views the anatomical structures of the heart from this position, while ICE images are collected through a catheter inserted directly in the heart (right atrium) via a femoral approach. An important advantage of this technique concerns the possibility of carrying out the procedure without general or deep anesthesia.

There are currently two medical device companies producing ICE catheters: St. Jude Medical (ViewFlex Xtra) and Biosense Webster–Johnson & Johnson Medical (AcuNav) (see Table 7.1 for comparison). The ViewFlex Xtra is a 9 Fr catheter with a working length of 90 cm. It features a quadri-directional deflection (anterior–posterior/left–right) reaching a deflection angle up to 120° in every direction. The probe is compatible with Zonare and Philips echocardiography consoles. The field depth depends on the hardware used; 18 cm on Zonare and 21 cm on Philips machines. The AcuNav is available in 8 and 10 Fr. The working length is 90 cm and the shaft can be deflected in four directions as above with an angle up to 160°. The penetration depth is 16 cm and it is compatible with both Siemens and GE echocardiography consoles.

Step-by-Step Ice Image Orientation for LAA Closure

Anatomical structures can differ greatly from patient to patient, thus a "multi-imaging" methodology is recommended. This section will guide the operator through different structures in the heart in a step-by-step manner, including the main

Table 7.1 Comparison chart between the two commercially available ICE systems

Specs	ViewFlex Xtra	AcuNav
Length	90 cm	90 cm
Diameter	9 Fr	8 or 10 Fr
Shaft material	Pebax	Pebax
Transducer	Phased array 64 elements	Phased array 64 elements
Visualization angle	90°	90°
Field depth	18 cm (Zonare)	16 cm
	21 cm (Philips)	

ICE views utilized for LAA closure procedure. The basic assumptions here are that the projections are taken from a femoral approach, which can be considered standard in percutaneous LAA closure. Although, very few operators prefer to introduce the ICE catheter through the jugular or subclavian veins; both of which can provide good vascular access, but they increase the invasiveness of the procedure. The operator is also standing at the right side of the table, with the patient's head to the left. All ICE catheters currently available on the market will fit in an 8.5–9.5 Fr venous sheath introducer (long or short).

Inserting the Catheter (Liver View)

The catheter should be inserted in a neutral position (straight) and advanced with small movements from the left femoral venous access. It is advisable to advance the catheter into the inferior vena cava under fluoroscopic guidance, which can be achieved by gentle flexion of the catheter at the level of the iliac vein. The catheter is then advanced and the liver images will soon appear (Fig. 7.1). Take the opportunity with small advancement and withdrawal movements to center the image and adjust the depth of the window.

Start View

After visualization of the liver, the catheter is advanced slightly into the right atrium (RA). This long axis image of the RA, tricuspid valve (TV) and right ventricle (RV) is the starting view before any further manipulation of the catheter (Fig. 7.2). Note that the catheter is still in neutral position with no steering on the handle's control knobs. It is useful to return to this "start view" if the operator loses the image bearings during the procedure.

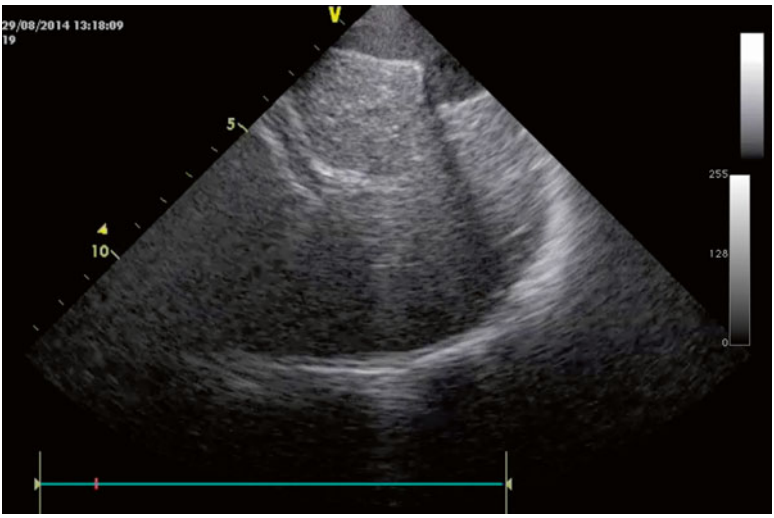


Fig. 7.1 The figure shows the ICE view of the liver parenchyma. The probe is placed in the Inferior Vena Cava, just below the Right Atrium (RA).

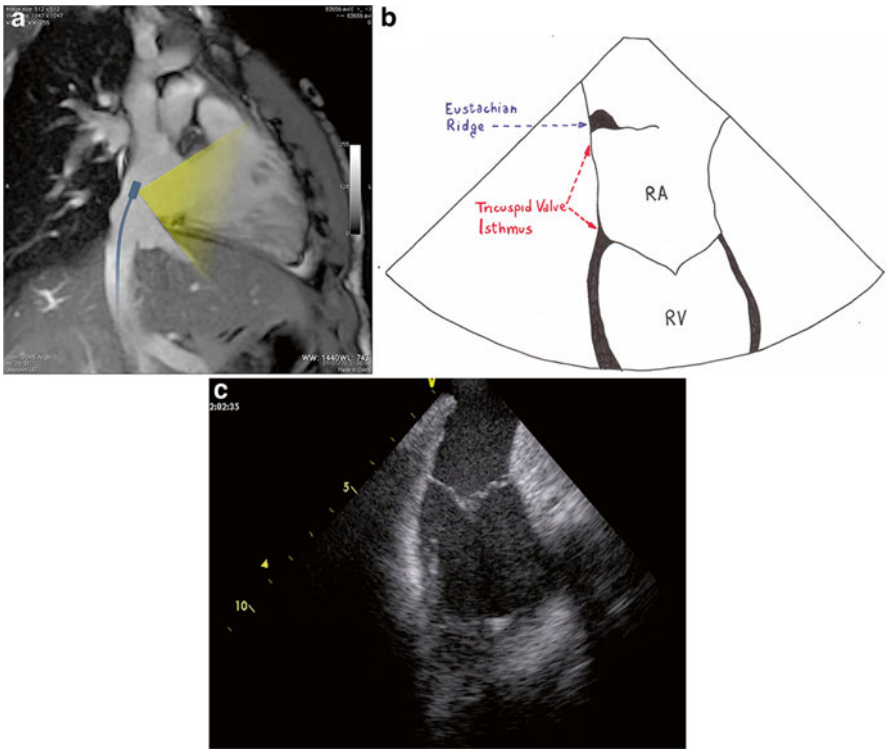


Fig. 7.2 (**a**) In this figure, we use a dedicated MR image to facilitate the comprehension of the ICE probe position and its derived images thanks to the possibility of viewing cardiac 3D anatomy. The ICE field of view is in yellow. (**b**) The drawing provides a global image of the main anatomical structures detected in this view. (**c**) ICE imaging in home view position. We can see the right atrium, tricuspid valve and right ventricle.

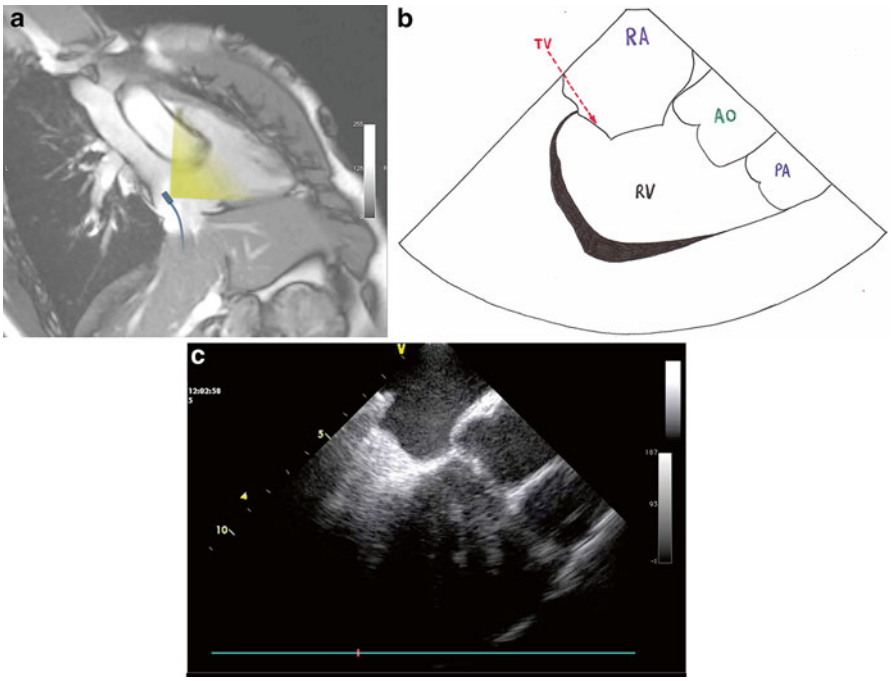


Fig. 7.3 (**a**) In this figure, we use a dedicated MR image to facilitate the comprehension of the ICE probe position and its derived images thanks to the possibility of viewing cardiac 3D anatomy. The ICE field of view is in yellow. (**b**) The drawing provides a global image of the main anatomical structures detected in this view. (**c**) ICE view of the Aorta and pulmonary artery. The ICE image shows: the Aortic Valve, the Aortic Root and the ascending tract, the Pulmonary Valve, RA and RV.

Aorta and Pulmonary Artery

From the "start view" with the catheter still in neutral position, the shaft is then rotated slightly clockwise (towards patient's left). From this view, a long axis image of the aortic valve, aortic root, left ventricular (LV) outflow, pulmonary valve and part of the LA are visualized (Fig. 7.3).

Inter-Atrial Septum and Fossa Ovalis View

From the previous view (aorta and pulmonary artery), a subtle rotation clockwise (towards patient's left) will bring the fossa ovalis into view (Fig. 7.4). Small "back and forth" movements can be made to center the structure. The head of the catheter must be steered back and right, to improve the plane of visualization. Also the depth of field must be adjusted to get a full view of the inter-atrial septum (Fig. 7.5). This view is very useful to monitor and perform a safe and effective transseptal puncture.

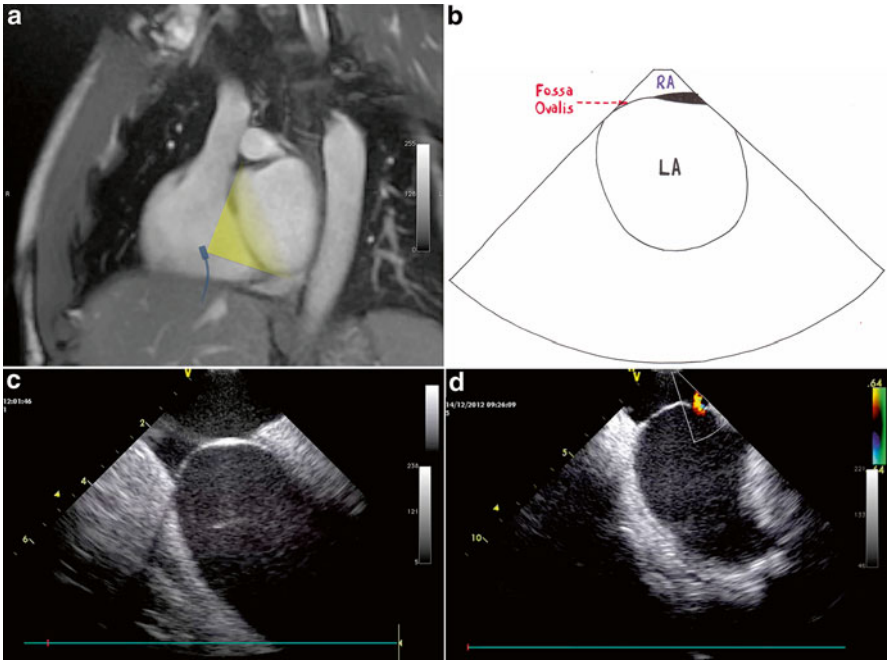


Fig. 7.4 (**a**) In this figure, we use a dedicated MR image to facilitate the comprehension of the ICE probe position and its derived images thanks to the possibility of viewing cardiac 3D anatomy. The ICE field of view is in yellow. (**b**) The drawing provides a global image of the main anatomical structures detected in this view. (**c**) ICE view of the Fossa Ovalis. The figure shows the Fossa Ovalis and LA. The probe is placed in the RA just in front of the Interatrial Septum. (**d**) Fossa Ovalis view with a small Interatrial Septum defect, undetected with the TEE.

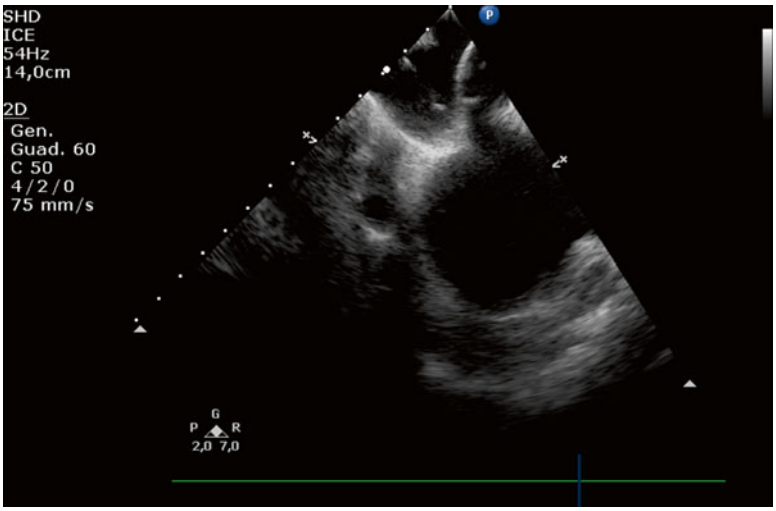


Fig. 7.5 Fossa Ovalis view during Transeptal Puncture. Note the needle and the transseptal apparatus tenting in the inferior part of the Fossa Ovalis.

How to Perform an ICE-Guided Transseptal Puncture

This section is dedicated to the ICE views that are useful for performing transseptal puncture. The aim of this procedural step is to get a safe and effective transseptal puncture in the inferior–posterior portion of the fossa ovalis. Starting with the ICE probe in the center of the RA as described in the section above, a craniocaudal view of the fossa ovalis is seen (Fig. 7.6). We suggest that this view is maintained during the transseptal apparatus withdrawal from the superior vena cava to the right atrium, and then to the fossa ovalis. This ICE view confirms if the transseptal apparatus is tenting on the fossa ovalis and at which level in the vertical direction (see Fig. 7.6 following the vertical blue line across the fossa ovalis, and also Fig. 7.5). From this view, tenting of the fossa ovalis inferiorly is well seen. Following this step, the anteroposterior position of the dilator should be visualized, which can be achieved in two ways: (1) further clockwise rotation which moves the plane of imaging more posteriorly to explore the posterior part of the fossa ovalis, or (2) keeping the dilator stable in this position but move the ICE probe to the "para-coronary sinus view" (see below). These two ICE views reveal if the tenting is in the anterior or posterior fossa ovalis (see Fig. 7.6 following the horizontal red line on the fossa ovalis). To achieve a more posterior position, the catheter should be rotated clockwise. It is suggested that the needle is advanced in the anteroposterior fluoroscopy view and the puncture performed under both fluoroscopic and ICE guidance.

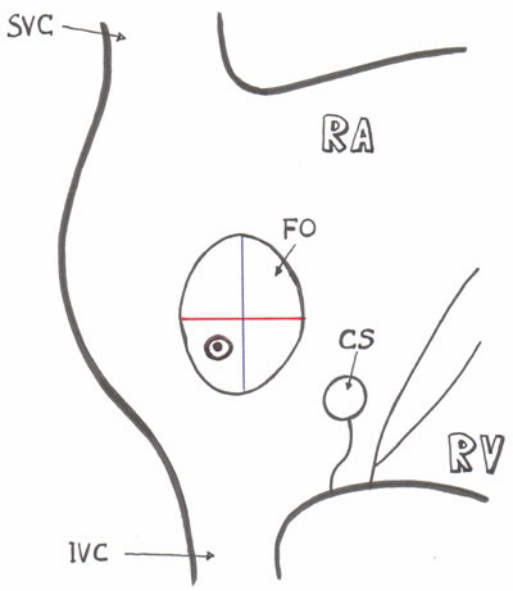


Fig. 7.6 Drawing showing the Fossa Ovalis view for the Transeptal Puncture. The Fossa Ovalis is divided by means of a vertical blue line and an horizontal red line, in four zones: superior anterior, superior posterior, inferior anterior and inferior posterior. The optimal site of puncture should be the inferior posterior zone (defined by a circle).

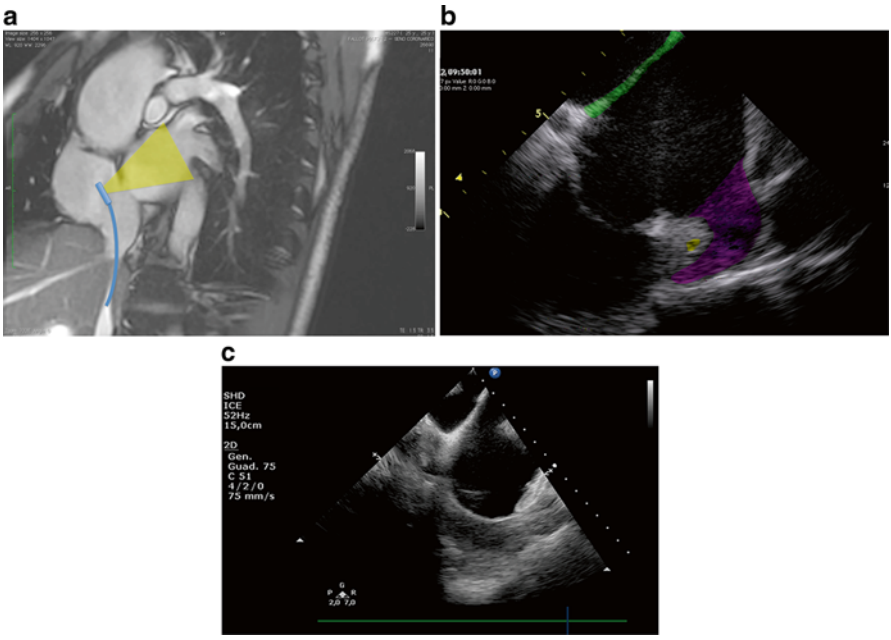


Fig. 7.7 (**a**) In this figure, we use a dedicated MR image to facilitate the comprehension of the ICE probe position and its derived images thanks to the possibility of viewing cardiac 3D anatomy. The ICE field of view is in yellow. (**b**) The figure shows the ICE view of the Interatrial Septum (green), LA, LAA long axis (purple), circumflex artery (yellow) and mitral valve as seen from the RA. (**c**) ICE view of a St. Jude Medical ACP™ device correctly placed in the LAA. View from the RA.

LAA View

From the septum visualization, move the catheter slowly clockwise. An image of the mitral valve (MV) is obtained. At this point, slightly roll the shaft clockwise and then adjust the anterior/posterior knob to get a visualization of the LAA (Fig. 7.7). This view can be used to evaluate LAA morphology and dimensions. It is also of great use to monitor the occluder device placement.

Coronary Sinus (CS) View

Advancing the probe inside the CS usually provides excellent LAA images (Fig. 7.8). Unfortunately, to get to the CS with the ICE catheter can be quite complex, requiring a lot of manipulation and can potentially be dangerous. A recommended safer way would be to advance a sheath into the CS first, before advancing the ICE catheter. For instance, a multipurpose catheter can be used to cannulate the CS cannulation, followed by advancing an exchange length Amplatzer Extrastiff

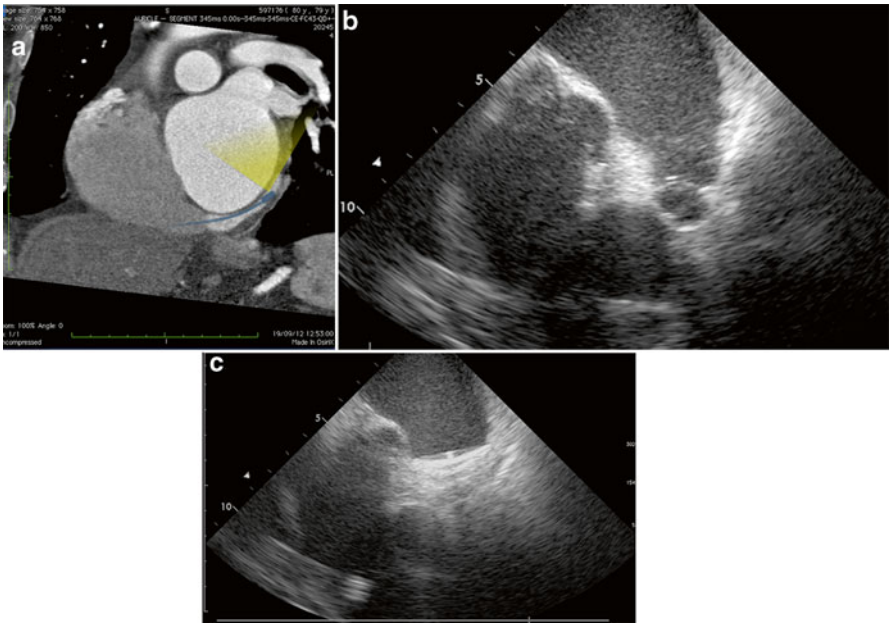


Fig. 7.8 (**a**) In this figure, we use a dedicated CT image to facilitate the comprehension of the ICE probe position and its derived images thanks to the possibility of viewing cardiac 3D anatomy. The ICE field of view is in yellow. (**b**) ICE view of the LAA as seen from the CS. Note the detail of the pectinate muscle. (**c**) ICE view of a St. Jude Medical ACP™ device correctly placed in the LAA. View from the CS.

Wire (AGA Medical Corporation, Plymouth, MN) into the CS. An 11 Fr Mullins sheath can then be advanced into the CS. The ICE catheter can then be advanced through the Mullins sheath into the CS without any steering. The sheath should be carefully flushed with saline before advancing the probe. From this position gently rotate the shaft to center the LAA image. Good images can be obtained by also keeping the ICE probe inside the introducer.

Para-coronary Sinus View (LAA)

This is a previously undescribed view that provides similar images to those obtained by advancing the probe inside the CS, in a simpler and safer way. From the "start view", with the catheter in neutral position, rotate the shaft gently counterclockwise (towards patient's right). Target the typical trabeculated tissue of this structure. Then steer the catheter all the way posteriorly. From this position, a good projection of the LAA can be obtained (Fig. 7.9). Note that the tip of the catheter lies just below the coronary sinus ostium.

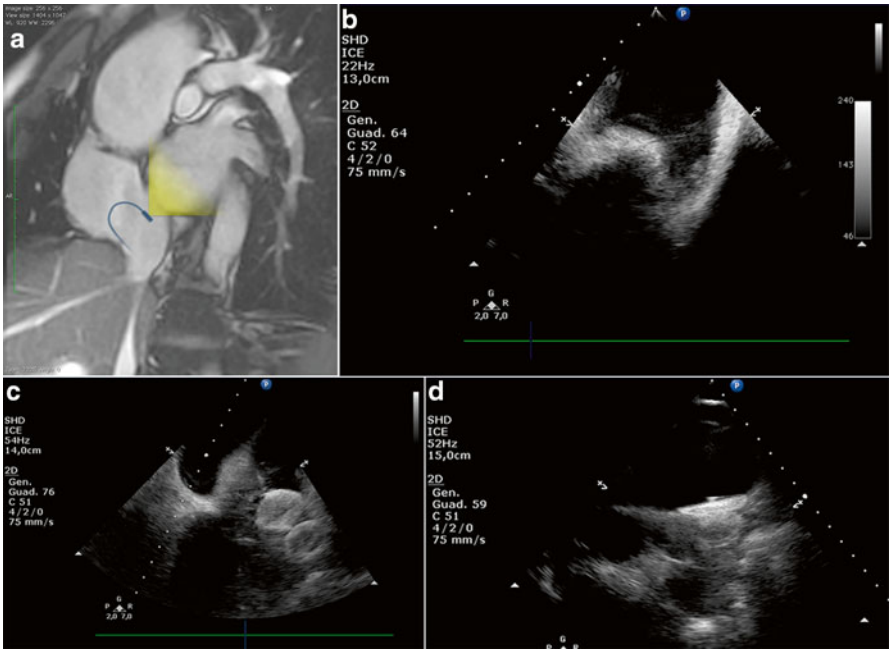


Fig. 7.9 (**a**) In this figure, we use a dedicated MR image to facilitate the comprehension of the ICE probe position and its derived images thanks to the possibility of viewing cardiac 3D anatomy. The ICE field of view is in yellow. (**b**) ICE view of the LAA as seen from the Para-CS. Please note the similarities with the CS view (fig. 8b). (**c**) St. Jude Medical ACP™ Stability test. (**d**) ICE Para-CS view with correctly implanted device.

LAA View from Pulmonary Artery

The pulmonary artery is a good point from which to view the LAA because of the close anatomical relationship between the two. However, advancing the ICE probe into the pulmonary artery (PA) is not easy. Thus, a similar approach to get the ICE probe into position as that described for the CS is recommended [20].

LAA View from the LA and Left Superior Pulmonary Vein (LSPV)

The LA is an ideal point of view to get LAA images, thanks to the proximity of the probe to the appendage. Unfortunately this approach requires another transseptal puncture. In some cases with great catheter manipulation we were able to cross the

patent foramen ovalis. If you decide to use this approach to perform the LAA closure procedure, you need a double transseptal puncture (one for the ICE probe and one for the delivery system). Images from the superior pulmonary vein should also be obtained as it provides good LAA long-axis views. An original technique to cross the septum avoiding a second transseptal puncture has been described [21]. We usually use this approach in patients with very bad acoustic windows from the RA or CS.

RA, CS, para CS, PA, and LA views are excellent to evaluate LAA anatomic findings and dimension (ostium and landing zone). Comparing the LAA measurements obtained from TEE and/or CT in the planning phase and those obtained from the fluoroscopy during the procedure is helpful to select the right device size [19]. For an optimal ICE guidance of the procedure we suggest you get a good view of the LAA and keep the probe.

3D ICE

Until very recently, ICE has been limited to two-dimension (2D) imaging. Three-dimensional (3D) imaging allows a more comprehensive anatomical assessment of complex intra-cardiac structures. The Volume ICE (V ICE) imaging is extremely useful in the peri- and intra-procedural phases, in particular for complex interventional procedures like LAA closure. At present, there is limited experience with this advanced imaging in this setting. The only available device is the ACUSON AcuNav V™ 3D Ultrasound Catheter (Siemens AG, Germany) that works with Siemens ACUSON SC2000 ultrasound system. This system provides simultaneously real-time 2D and 3D images. The volume field of view is 90° by 24° (Azimuth, Elevation respectively). The device also provides a pulse wave (PW) function, as well as real-time 2D and 3D Color Doppler imaging. Table 7.2 reports the main technical features. Figure 7.10 shows images of two cases of V ICE-guided LAA closure procedures [23–26].

Table 7.2 Features of the 3D AcuNav system

Specs	ACUSON AcuNav V
Length	90 cm
Diameter	10 Fr
Shaft material	Pebax
Visualization angle	90° × 24°
Field depth	16 cm

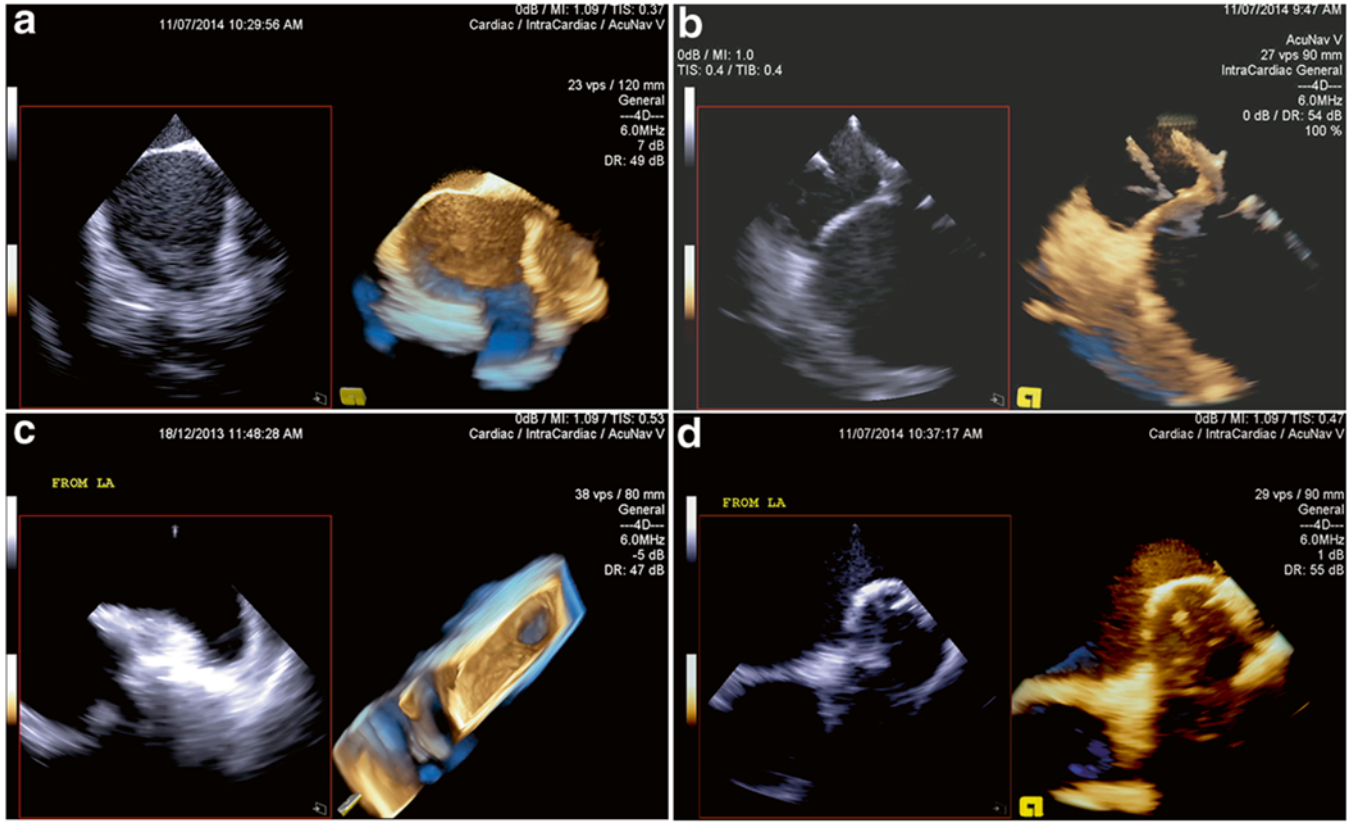


Fig. 7.10 (**a**) 2D and 3D LAA views from the RA. This projection provides a good view of the Fossa Ovalis, LA and LAA. (**b**) 2D and 3D views of the Transeptal Puncture phase. We can see the tenting of the transseptal apparatus on the fossa ovalis. (**c**) 2D and 3D LAA views from the LA. (**d**) 2D and 3D views of a Wavecrest™ device correctly placed in the LAA.

Complications: Recognition and Monitoring

The use of ICE imaging during LAA closure procedures is also invaluable for detecting and monitoring potential procedure-related complications. Pericardial tamponade due to inadvertent cardiac perforation is the most frequent complication in this procedure. Pericardial effusion monitoring is extremely helpful to manage this complication. ICE provides good images of the pericardial structures. From the home view, steering the ICE catheter all the way anteriorly and advancing the probe into the RA, will allow a good view of the RA free wall and pericardium. Moreover, by using this technique the development of thrombus on the catheters and devices can easily be identified.

The Cost–Benefit Ratio

From an economic point of view, the additional costs of the ICE catheter are offset by the savings obtained from shorter procedural times, avoiding general anesthesia and complications [27], and from reduction of clinical team needed for procedure. In fact, if the interventional operator is familiar with echocardiography in general and with ICE in particular, an additional physician reading the images may not be required.

Re-sterilization and reuse of ICE catheters, permitted in Germany, Eastern Europe, and Canada, help lower the costs. A study performed in the United States found that if an interventional cardiologist performs ICE imaging, global hospital and physician charges are similar when using ICE or TEE (US$34.861 ± 43.759 vs. US$32.812 ± 2.656, respectively, $P = 0.107$) [28–30].

The shorter turn-around time resulting from the use of local vs. general anesthesia may add to the relative value of ICE imaging. The main advantages of ICE shown in more than a decade of single-center experiences are unique: safe guidance of percutaneous interventional treatments, avoidance of general anesthesia, and reduction of radiation exposure [30]. These factors provide direct benefits to patients, and the direct clinical impact is more important than any monetary costs or savings [31–34].

Conclusion

ICE has been increasingly used for LAA closure procedures, and in our experience and opinion, it represents a safe and useful ultrasound option for the LAA occlusion guidance. For preventing short- and mid-term complications, ICE has the advantage over TEE of not requiring the support of general anesthesia and anesthesiology. These factors provide direct benefits to patients and reduce the total radiation exposure for patients and operators.

References

1. Santoro G, Meucci F, Stolcova M et al. 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. 2014. doi:10.4244/EIJY14M10_13.
2. Sacco R, Benjamin E, Broderick J, et al. American Heart Association Prevention Conference. IV. Prevention and rehabilitation of stroke. Risk factors. Stroke. 1997;28:1507–17.
3. Wolf P, Abbott R, Kannel W. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22:983–8.
4. Gage B, Waterman A, Shannon W, Boechler M, Rich M, Radford M. Validation of clinical classification schemes for predicting stroke: results from The National Registry of Atrial Fibrillation. JAMA. 2001;285:2864–70.
5. Go A, Hylek E, Phillips K, 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. Blackshear J, Odell J. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg. 1996;61:755–9.
7. Camm A, Kirchhof P, Lip G, et al. Guidelines for the management of atrial fibrillation. Eur Heart J. 2010;31:2369–429.
8. Camm A, Lip G, De Caterina R, et al. 2012 focused update of the ESC guidelines for the management of atrial fibrillation. Eur Heart J. 2012;33:2719–47.
9. Connolly S, Ezekowitz M, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.
10. Granger C, Alexander J, McMurray J, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–92. Published online 28 Aug 2011, Accessed 2 Sept 2011.
11. Patel M, Mahaffey K, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.
12. Holmes D, Reddy V, Turi Z, 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.
13. Park J, Bethencourt A, Sievert H, et al. Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation—initial European experience. Catheter Cardiovasc Interv. 2011;77(5):700–6.
14. Berti S, Santoro G, Palmieri C, Meucci F. Tools and techniques clinical: transcatheter closure of left atrial appendage using the Amplatzer™ cardiac plug. EuroIntervention. 2013;9(4):524–6.
15. Bianchi G, Solinas M, et al. Pulmonary artery perforation by plug anchoring system after percutaneous closure of left appendage. Ann Thorac Surg. 2013;96(1):e3–5. doi:10.1016/j.athoracsur.2012.12.057.
16. Reddy V, Holmes D, Doshi S, 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.
17. Guérios EE, Schmid M, et al. Left atrial appendage closure with the Amplatzer cardiac plug in patients with atrial fibrillation. Arq Bras Cardiol. 2012;98(6):528–36.
18. Meerkin D, Butnaru A, Dratva D, Tzivoni D. Initial experience with Amplatzer Cardiac Plug for left atrial appendage closure. J Am Coll Cardiol. 2011;57 [Abstract]:E1684.
19. Berti S, Paradossi U, Meucci F, et al. Periprocedural intracardiac echocardiography for left atrial appendage closure. J Am Coll Cardiol Intv. 2014;7(9):1036–44.
20. MacDonald ST, Newton JD, Ormerod OJ. Intracardiac echocardiography off piste? Closure of left atrial appendage using ICE and local anesthesia. Catheter Cardiovasc Interv. 2011;77:124–7.

21. Fassini G, Dello Russo A, Conti S, Tondo C. An alternative transseptal intracardiac echocardiography strategy to guide left atrial appendage closure: the first described case. J Cardiovasc Electrophysiol. 2014;24:1269–71.
22. Biermann J, Bode C, Asbach S. Intracardiac echocardiography during catheter-based ablation of atrial fibrillation. Cardiol Res Pract. 2012. doi:10.1155/2012/921746. Article ID 921746.
23. Cunnington C, Hampshaw SA, Mahadevan VS. Utility of real-time three-dimensional intracardiac echocardiography for patent foramen ovale closure. Heart. 2013;99:1789–90.
24. Fontes-Carvalho R, Sampaio F, Ribeiro J, et al. Three-dimensional intracardiac echocardiography: a new promising imaging modality to potentially guide cardiovascular interventions. Eur Heart J Cardiovasc Imaging. 2013;14(10):1028.
25. Ruisi CP, Brysiewicz N, Asnes JD, et al. Use of intracardiac echocardiography during atrial fibrillation ablation. Pacing Clin Electrophysiol. 2013;36(6):781–8.
26. Brysiewicz N, Mitiku T, Haleem K, et al. 3D real-time intracardiac echocardiographic visualization of atrial structures relevant to atrial fibrillation ablation. JACC Cardiovasc Imaging. 2014;7(1):97–100.
27. Ronco F, Pascotto A, Barbierato M, et al. Percutaneous left atrial appendage closure in awake non intubated patient: multimodality intraprocedural imaging. Cardiovasc Revasc Med. 2012;13(6):360–1.
28. Bartel T, Muller S, Biviano A, Hahn R. Why is intracardiac echocardiography helpful? Benefits, costs, and how to learn. Eur Heart J. 2013;35(2):69–76.
29. Alborilas RT, Hijazi ZM. Comparison of costs of intracardiac echocardiography and transesophageal echocardiography in monitoring percutaneous device closure of atrial septal defect in children and adults. Am J Cardiol. 2004;94:690–2.
30. Bartel T, Bonaros N, Edlinger M, Velik-Salchner C, Feuchtner G, Rudnicki M, Muller S. Lower risk of severe acute kidney injury in transcatheter aortic valve replacement: intracardiac echocardiography yields reduction of radio-contrast medium requirements. JACC Cardiovasc Imaging. 2014;7:319–20. doi:10.1016/j.jcmg.2013.07.010.
31. Hijazi Z, Shivkumar K, Sahn D. Intracardiac echocardiography (ICE) during interventional and electrophysiological cardiac catheterization. Circulation. 2009;119:587–96.
32. Ho I, Neuzil P, Mraz T, et al. Use of intracardiac echocardiography to guide implantation of a left atrial appendage occlusion device (PLAATO). Heart Rhythm. 2007;4:567–71.
33. Bartel T, Konorza T, Neudorf U, et al. Intracardiac echocardiography: an ideal guiding tool for device closure of interatrial communications. Eur J Echocardiogr. 2005;6:92–6.
34. Budts W, Troost E, Voigt J, Gewillig M. Intra-cardiac echocardiography in atrial septal interventions: impact on hospitalization costs. Acta Cardiol. 2010;65:147–52.

Chapter 8
CT Imaging for Percutaneous LAA Closure

Jacqueline Saw, Joao Pedro Lopes, Mark Reisman, and Hiram G. Bezerra

Introduction

The success and procedural complexities of percutaneous left atrial appendage (LAA) closure depends largely on the LAA anatomy, and on the anatomic relations between access to the left atrium via the fossa ovalis to the LAA. These anatomic features and three-dimensional cardiac structural relationships are distinctly depicted on cardiac computed tomography angiography (CCTA), especially since the LAA has minimal dynamic role during the cardiac cycle. The spatial resolution and three-dimensional structural depiction of CCTA offers unique imaging planes not appreciated with transesophageal echocardiography (TEE), which has been the conventional pre-imaging modality-of-choice for LAA closure. As with other structural cardiac interventions, the noninvasiveness, superiority in imaging resolution and relational portrayal have progressively established CCTA as instrumental preplanning imaging tool, and is anticipated to overtake TEE as the pre-imaging modality-of-choice for LAA closure. For preplanning imaging, CCTA allows not only anatomic LAA assessment, but also ruling out preexisting thrombus in the LAA that would exclude attempt at LAA closure. In addition, post-surveillance of LAA closure is necessary to rule out device-related thrombus and residual leak, and

J. Saw, M.D., F.R.C.P.C., F.A.C.C., F.S.C.A.I. (✉)
Vancouver General Hospital, University of British Columbia,
2775 Laurel Street, Level 9, Vancouver, BC, Canada, V5Z1M9
e-mail: jsaw@mail.ubc.ca

J.P. Lopes, M.D. • H.G. Bezerra, M.D.
Division of Cardiology, University Hospital, Cleveland, OH, USA

M. Reisman, M.D.
Department of Medicine, University of Washington, Seattle, WA, USA

University of Washington Medical Center, 1959 NE Pacific St.,
Box 356171, Seattle, WA 98195, USA

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_8

CCTA can contribute to this important role. This chapter will review the practical utility of CCTA in preplanning and guiding LAA closure, and post-procedural surveillance.

LAA Anatomy

The ubiquitous structural complexity of the LAA highlights the importance of imaging its morphology and understanding its variations. Despite considerable anatomical variations, in general, the LAA assumes a small, narrow tubular shape, with one or several bends and a final tip (see anatomy chap. 4). Its particular morphology can promote stasis and increase the risk of thrombus formation, especially in patients with atrial fibrillation (AF) [1, 2]. Indeed, more than 90 % of the thrombi in patients with AF are located in the LAA [3]. LAA length ranges, in different series, from 20 to 60 mm, and the width ranges from 16 to 59 mm [2, 4–6]. Its volume ranges from 0.4 to 13 mL and luminal surface area from 2.7 to 21.1 cm^2 [4]. A few studies have shown LAA size to be associated with increased risk for stroke/TIA [5, 7, 8], but other studies showed no correlation [1].

The entrance of the LAA, its border with the left atrium (LA), named the orifice or the ostium, is described as oval-shaped in the majority of the series [4, 5], though data also exists that describes the round-shaped orifices [2], or even other shapes such as foot-like, triangular, and water-drop like [9]. The orifice has a long diameter that ranges from 10 to 24.1 mm and a short diameter that ranges from 5.2 to 19.5 mm [2, 4].

One of the morphological variations of the LAA is the number of lobes, defined as outpouchings from the main tubular body of the LAA, with a lumen of at least 2 mm length, usually demarcated by an external crease [5]. The number of lobes usually ranges from 1 to 4, with the LAA of the majority of the individuals observed in several series consisting of two lobes [1, 5]. One or several lobes can be in a different anatomic plane from the main tubular body, which emphasizes the importance of biplane and, especially, multiplane imaging techniques for correct visualization of the LAA and to avoid mistaking a lobe for a thrombus or missing a thrombus present in one of the lobes located in a different plane [5]. There are also accessory LAA (consisting of pectinate muscles) and atrial diverticular (outpouching consisting only of a muscle layer), which have been reported to occur in 10–27 % of the general population [10].

Gross and histological examination of several heart specimens reveals the presence of areas of the LAA wall deficient in myocardium, with a thickness ranging from 0.4 to 1.5 mm, usually starting between 1.4 and 20.9 mm from the LAA orifice [4].

There are different modes of classification for LAA morphology [1, 4, 9]. The most commonly used one classifies the LAA into four shapes: chicken-wing (LAA with sharp bend), windsock (single dominant lobe), cauliflower (several lobes without dominant lobe) and cactus (dominant central lobe with secondary lobes) (Fig. 8.1). In the series of 932 patients by Di Biase, the prevalence of the shapes was 48 % chicken-wing, 30 % cactus, 19 % windsock, and 3 % cauliflower [1]. Another classification divided the LAA into two types: slender (like a crooked finger), representing the majority of cases, and stump-like [2]. There are other classifications

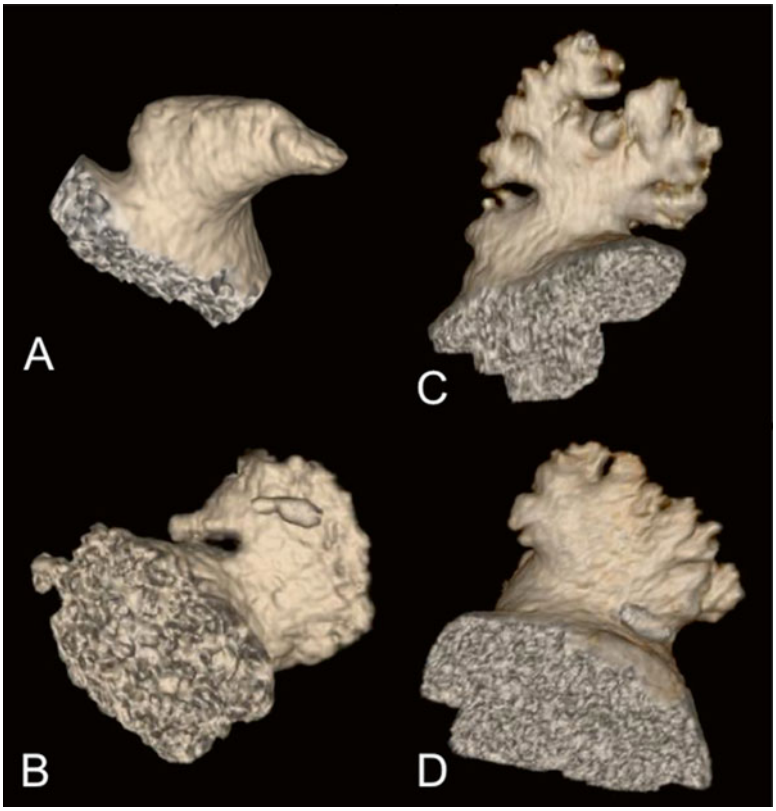


Fig. 8.1 CT images of the four most common shapes of LAA: (**a**) windsock, (**b**) chicken-wing, (**c**) cactus, and (**d**) cauliflower

with different levels of complexity, including an angiographic classification of LAA morphology that considers eight different shapes (tube, claw, sphere-like, tadpole, willow-leaf, sword, duckbill, and irregular) [11].

The shape of the LAA is an important factor to consider, based on the described correlation of different LAA shapes with different incidences of thrombus formation and stroke. In the series by Di Biase, individuals with chicken-wing LAA were less likely to have any history of previous embolic events and high $CHADS_2$ score, when compared with other shapes [1]. Using chicken-wing LAA as a reference group, individuals with cactus were 4.1 times, windsock were 4.5 times, and cauliflower were 8.0 times more likely to have had a stroke/TIA in the past [1]. This association was again shown for cauliflower shape by a different group of researchers, revealing the cauliflower LAA as an independent predictive factor of stroke [12, 13]. Another study, looking at correlation between LAA morphology and silent cerebral ischemia (as assessed by cerebral magnetic resonance imaging) found a stronger correlation between the more complex shapes (windsock and, especially, cauliflower) and the presence of silent cerebral ischemia, while chicken-wing shape had the lowest correlation [14].

Despite several studies showing correlation between particular LAA shapes and incidence of stroke, it is worth mentioning a study of 678 consecutive patients with AF that failed to show the same correlation between LAA morphology and stroke, but rather only the presence of extensive trabeculations and a smaller LAA orifice diameter correlated to stroke [15]. The same study also pointed out that the determination of LAA morphology was not reproducible between trained readers. As well, the prevalence of stroke/TIA history was low in this study (only 9.6 %). A different study also failed to find correlation between LAA morphology and stroke, but in contrast to the study above, correlated positively a larger LAA orifice with a higher incidence of stroke [16].

AF is associated with significant anatomical changes in the LAA, with a volume that on average is more than three times larger than in patients on sinus rhythm [17, 18]. In AF patients the LAA also has a larger luminal surface area, a smoother endocardial surface and higher degree of endocardial fibroelastosis, changes that can contribute to thrombus formation [17, 19].

Baseline CCTA to Rule out LAA Thrombus

Multidetector computed tomography (MDCT) has grown as a three-dimensional modality, increasing its value to evaluate complex multiplanar structures like the LAA. A meta-analysis has shown MDCT as a reliable alternative to TEE (the gold standard technique) [20, 21] for the detection of thrombi in the LAA [22].

In terms of MDCT accuracy for LAA thrombus detection, several studies have shown conflicting results, with sensitivities ranging from 29 to 100 %, specificities from 72 to 98 %, and relatively low positive predictive values from 7 to 31 % [23–30]. Despite such extensive ranges, a recent meta-analysis including 19 studies with 2955 patients identified a mean sensitivity of 96 %, specificity of 92 % and positive predictive value of 41 % [22]. The most consistent finding from several studies has been the negative predictive value of MDCT for thrombus detection, with values ranging from 96 to 100 %, with authors suggesting that patients without filling defects on MDCT do not need a TEE [23–29].

Adaptations to the MDCT protocol have been tried to improve the positive predictive value of this imaging technique for thrombus detection, with delayed imaging (at least 30 s after contrast bolus administration) being one of them, increasing the mean positive predictive value to 92 % or higher [22, 31]. The low positive predictive values were explained in part by the static character of the CT study and the fact that the image capture happens a few seconds after contrast arrives to the left heart (including LAA), which can make it difficult to differentiate thrombus from incomplete contrast mixing due to sluggish flow [equivalent to spontaneous echo contrast] (Fig. 8.2a). Adding delayed imaging improves the ability to differentiate these two situations, since a filling defect persisting 1 min after contrast injection is more likely to represent a thrombus, while the filling defect with sluggish flow should improve with contrast opacification on delayed imaging [22].

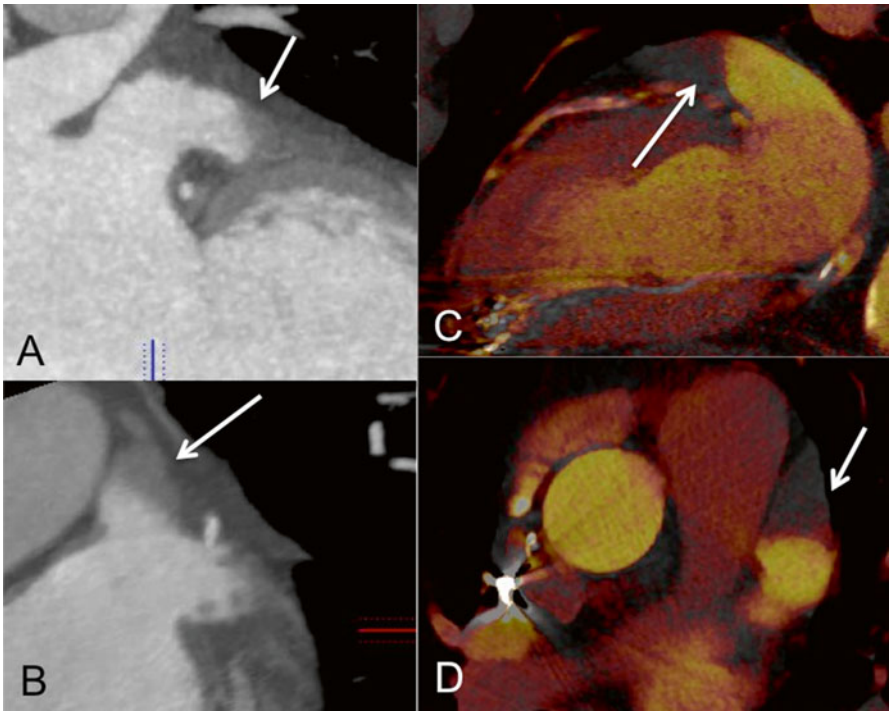


Fig. 8.2 CCTA evaluation of LAA thrombus: (**a**, **b**) filling defects (*arrows*) in different patients due to inadequate contrast mixing, equivalent to spontaneous echo contrast; (**c**, **d**) filling defect (*arrow*) in a patient seen on dual-energy scan in the LAA

However, additional delayed imaging increases radiation exposure, which led to the development of a different protocol, involving only one scan after two separate bolus of contrast, a 50 mL timing bonus first, followed by a 70 mL bolus, with a delay of 180 s between injections [32, 33]. Differentiation between thrombus and sluggish flow is then done by assessing contrast attenuation and shape. Thrombus appears as an oval or round shape, whereas sluggish flow appears more as a triangular shape with homogeneous signal intensity. Despite the lower radiation exposure, the use of a double bolus of contrast is not suited for patients with impaired renal function, and this technique still requires validation. Another approach is obtaining delayed scanning in a prone position, which improves contrast mixing.

Newer CT machines are equipped with dual-energy sources, providing simultaneous acquisition of images from low and high voltage settings, which allows evaluation of tissue characteristics and quantitative analysis of the iodine concentration of LAA filling defects, helping in the differentiation of thrombus from sluggish flow (Fig. 8.2b). A preliminary study showed a positive predictive value of 100 % for thrombus identification with dual-energy [33]. Although encouraging, this technique still needs validation in larger cohorts [33].

Baseline CCTA Protocol for LAA Closure Preplanning

The high spatial resolution and three-dimensional data provided by MDCT allows adequate morphologic characterization of the anatomy of the LAA, a crucial aspect of LAA occluder device selection [34]. In the literature, different CT machines were used for LAA evaluation and device preplanning. A study of 197 patients with AF who went MDCT prior to radiofrequency catheter ablation used either a 64-detector-row CT scanner or a volumetric 320-detector-row CT scanner. For the 64-detector the settings were: rotation time 400 ms, collimation 64×0.5 mm, tube voltage between 100 and 135 kV (depending on body mass index of the patients) and a tube current of 250–400 mA. For the 320-detector, the settings were: rotation time 350 ms, collimation 320×0.5 mm, tube voltages between 100 and 135 kV and currents of 400–580 mA. Patients with heart rates above 65 bpm received beta-blockers. The volume of nonionic contrast media used was dependent on body weight, total scan time, and renal function. For the 64-detector, a flow rate of 5 mL/s and a total amount of 80–110 mL were used. For the 320-detector, a total of 60–100 mL of contrast media was infused in sequential steps: 50–90 mL of contrast media infused at a flow rate of 5.0–6.0 mL/s; 20 mL mixture of 50 % contrast media/saline at the same rate; 25 mL saline at a flow rate of 3.0 mL/s. Automated peak enhancement detection in the left ventricle was used for detection of the contrast bolus, and after achieving +180 HU, craniocaudal scanning was initiated. Image acquisition was acquired during an inspiratory breath-hold of 8–10 s. For the 64-detector, ECG was simultaneously recorded for retrospective gating and images were reconstructed at both 30–35 % and 75–85 % phases of the RR interval for the systole and diastole, respectively. For the 320-detector, prospective ECG-triggered dose modulation was used to visualize one entire cardiac cycle with maximal tube current at 75 %, 65–85 % or 30–80 % of the RR interval in patients with heart rates of <60 bpm, 60–65 bpm or >65 bpm, respectively. The mean effective dose of the 320-detector exams was 3.9 ± 1.8 mSv, and for the 64-detector was 18.1 ± 5.9 mSv. The data was reconstructed with a slice thickness of 0.5 mm and with a reconstruction interval of 0.3 mm (64-detector) and 0.25 mm (320-detector) [34].

As the left atrium is a highly compliant chamber, the patients' volume status will directly impact sizing. For consistency, if hemodynamic status allows, we recommend infusion of at least 500 mL of saline before the scan so the chamber and LAA are close to their maximum dimensions. This is especially important to guide device sizing for LAA closure. Indeed, we have described that volume status can impact LAA dimensions on TEE; patients are often fasting for TEE pre-procedure, and simply administering 500–1000 mL of normal saline during procedure we observed an average increase of 2 mm in the width and depth of the LAA [35].

Digital Post-processing Assessment of LAA

Digital post-processing review of the LAA and surrounding structures is important to guide device selection and implantation strategy for LAA closure. Several different workstations are available for image processing, e.g., VitreaWorkstation™

(Vital, Toshiba Medical Systems Group Company, The Netherlands), Aquarius Workstation (TeraRecon Inc, Foster City, CA), Brilliance Workspace (Philips Healthcare, Andover, MA), and 3mensio (Pie Medical Imaging, Maastricht, The Netherlands). These workstations have similar capability to enable manipulation and reconstruction of the LAA and surrounding structures to guide percutaneous LAA closures.

The use of three-dimensional digital reconstruction offers additional structural relational portrayal to conventional axial images. Multiplanar reconstruction (MPR) creates volume images by stacking the axial slices. Maximum-intensity projection (MIP) is another volume rendering technique that projects the voxel with the highest attenuation value on every view throughout the volume onto a 2-dimensional image. Thin 3–5 mm MIP may be used to select the best rotation to best visualize the LAA, but measurements are typically taken with MPR. Three-dimensional volume rendering is also often used for LAA assessment, which creates a 3-dimension illustration of CT volumetric data for display from any desired perspective, enabling selection of optimal correlative fluoroscopic angles. This technique allows choosing of different tissues based upon Hounsfield range, and the colors, transparency, and shading can be altered to better represent the volume shown on the image.

Of note, measurements should be taken at the cardiac phase with the largest left atrial and LAA dimensions, which is typically at late atrial diastole, corresponding to 30–40 % of the R-R cycle [36]. The left atrium and LAA changes with cardiac cycle in all 3-dimensional directions, but this does not occur in a uniform fashion with medial-lateral expansion less prominent than longitudinal and anteroposterior expansions [37]. Thus, 1-dimensional assessment may be insensitive to evaluate such changes in LA size. Similarly, the pulmonary vein orifice measurements on CCTA had been shown to vary with cardiac cycle, with the largest diameter in late atrial diastole, with mean decrease by ~30 % during atrial systole [38].

Assessment of LAA on CCTA for Endovascular Device Closure

At Vancouver General Hospital, we perform standard pre-procedural and post-surveillance CCTA with the Toshiba 320-detector, see Table 8.1 for protocol. For pre-procedural scans that have to incorporate "rule out" LAA thrombus, the Siemens Dual Source Flash scanner is used, with a different scanning protocol detailed in Table 8.2. We standardly administer 500–1000 normal saline intravenously before imaging.

To assess for suitability for percutaneous LAA closure with the leading devices (i.e., WATCHMAN, ACP/Amulet), evaluation of the LAA shape and dimensions are crucial. The first step is to clearly delineate the orifice/ostium of the LAA and obtain cross-sectional right-angled images of this point. Conventional axial views alone are often inadequate to assess the LAA orifice/ostium, instead, we routinely utilize MPR for this purpose. We identify a view where the circumflex artery, the pulmonary vein (PV) ridge and the LAA orifice/ostium can be clearly seen in one image.

Table 8.1 Protocol to image LAA pre-procedure and post-surveillance

Toshiba 320-detector prospective cardiac-gated	Values
Tube potential	80–120 kV
Tube current	300–500 mA
Scan direction	Cranial to caudal
Scan volume	Heart to diaphragm (14–16 cm)
Size	512 mm
Detector collimation	320 × 0.5
Cardiac phase-reconstruction	30–40 % RR interval or 250 ms after R wave
Contrast bolus tracking	Sure Start
– IV contrast injection (5 cm^3/s)	50–80 cm^3 contrast + 50 cm^3 30 % contrast/saline mixture
– Followed by IV saline injection (5 cm^3/s)	30 cm^3 saline
Heart rate	No restriction
Beta-blocker and nitrates	Not required

Table 8.2 Protocol to image thrombus in LAA pre-procedure

Siemens dual source flash scanner	Values
Prospective ECG tube current modulation	Full RR interval imaged, but full CT dose only in diastole
Functional dual-energy scan	140SnkV:100 kV
Tube current	300–500 mA
Scan direction	Cranial to caudal
Scan volume	Heart (to diaphragm)
Scan type	Flash spiral
Size	512 mm
Detector collimation	128 × 0.6
Cardiac phase-reconstruction	250 ms after R wave
Contrast bolus tracking	"Cardiac Definition" program
– Pre-scan: IV contrast injection (6.5 cm^3/s)	50 cm^3 contrast 5 min before scan
– During scan: IV contrast (6.5 cm^3/s)	65 cm^3 contrast + 55 cm^3 30 % contrast/saline mixture
– Followed by IV saline (6.5 cm^3/s)	30 cm^3 saline
Heart rate	No restriction
Beta-blocker and nitrates	Not required
Scan HEART in 3 min delay with patient prone	CAREKV + CAREDOSE 4D

The orifice for the ACP/Amulet is the line that connects from the PV ridge to the circumflex artery (echocardiographic LAA ostium). The cross-section of this plane is then obtained at right-angle projections, to improve the co-axial measurement of the orifice (Fig. 8.3). Then another diameter measurement is taken at the landing zone, which is 10 mm (for ACP) and 12–15 mm (for Amulet) inside the orifice

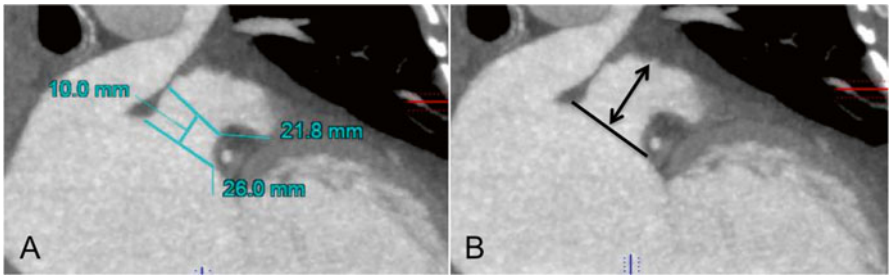


Fig. 8.3 MPR images for LAA measurements for the ACP device: (**a**) measurements at the orifice and landing zone (10 mm) for ACP, (**b**) measurement of the depth of LAA for ACP (*double-sided arrow*)

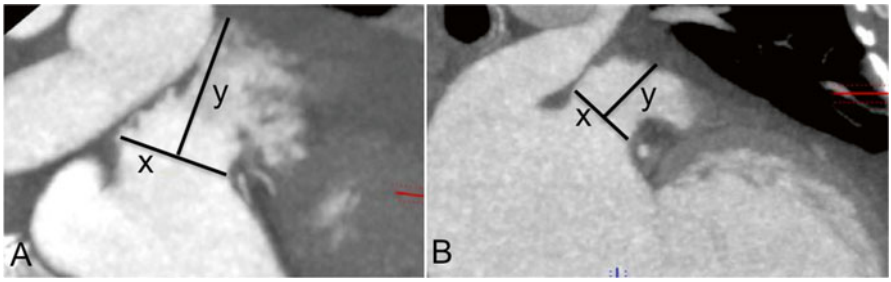


Fig. 8.4 MPR images for LAA measurements for WATCHMAN: (**a**) measurements of the anatomic LAA ostium (x) and the depth (y); (**b**) another example showing measurements of the anatomic LAA ostium (x) and depth (y)

(labeled as the neck of the LAA), making sure that the measurement is co-axial at right-angle projections. For WATCHMAN, the ostium of the LAA is measured from the circumflex artery to 1–2 cm within the PV ridge (anatomic LAA ostium). Again using MPR, right-angles to this plane are viewed and manipulated to obtain the best co-axial plane for measurements (Fig. 8.4). If there are trabeculations at the points of measurements, we err on including the trabeculations for larger measurements. LAA diameters that are suitable for device closures are: 12.6–28.5 mm landing zone for ACP, 12.6–32 mm landing zone for Amulet, and 17–31 mm LAA ostium for WATCHMAN.

The depth of the LAA is then assessed on MPR, sometimes requiring MIP to visualize the entire LAA to its distal tip due to the common angulations/bends of the LAA. For the ACP/Amulet device, a depth of only 10–15 mm from the LAA orifice is required, measured from a line that is perpendicular to the LAA orifice to the back wall of the LAA (Fig. 8.3). For WATCHMAN, the depth is measured from the LAA ostium to the most distal tip of the distal lobe, which has to be as deep as the device size to be used (Fig. 8.4). While evaluating the distal lobes for the depth for WATCHMAN, it's useful to consider where the distal tip of the sheath should be. The superior lobes tend to angle anteriorly, and the inferior lobes posteriorly.

Depending on the depth of these lobes, the operator can select which lobes to park the delivery sheath, and select the appropriate sheath (double-curve, singe-curve, or anterior-curve) for the procedure.

Following assessments of the LAA dimensions, the shape of the LAA is closely evaluated and anatomic structures that may impede device placement are assessed. LAA that are shaped like windsock are typically the simplest appendages for percutaneous closure, as long as the width and depth are suitable for the selected device. Sharp chicken-wing configuration may be challenging especially if the bend is proximal (<10 mm from the orifice) and very sharp-angled (>90° angle), as this may compromise the landing zone of the ACP and WATCHMAN devices. Knowing this challenge pre-procedure can help operators strategize whether the landing zone should be proximal, distal, or at the bend. Alternatively, a different implant strategy may be considered, such as the "sandwich" technique with the ACP device [39], which requires larger ACP lobe size. Cactus and cauliflower shapes may post challenges if the depth is short, or when the tissue ridges of the secondary lobes protrude and impact device placement, or when the diameter is excessively large (>28.5 mm for ACP, >32 mm for Amulet, or >31 mm for WATCHMAN) (Fig. 8.5). Of note, for cases where there are proximal trabeculations, diverticular or lobes, these should be completely covered by the selected devices to avoid recesses that may promote thrombus formation.

Another anatomic characteristic that may pose challenges and should be routinely evaluated is the sphericity of the LAA at the site of device implantation. Marked elliptical shape at the landing zone for ACP/Amulet or the ostium for WATCHMAN can affect device sizing. Although there is no established definition for marked sphericity, in general we have found that if the widest diameter is >6 mm larger than the narrowest diameter, that we could not oversize the devices as much (Fig. 8.6). For ACP, oversizing by the usual 3–5 mm based upon the widest landing zone for markedly elliptical LAA often results in the lobe being extruded (lobe too large); thus, for marked sphericity, we tend to only oversize the ACP by 1–2 mm.

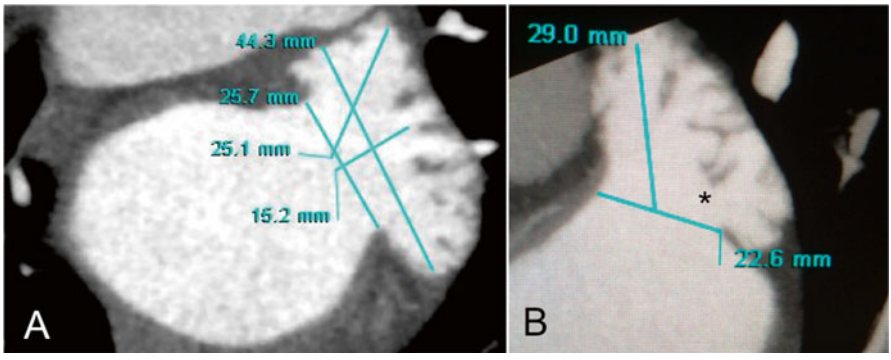


Fig. 8.5 Challenging cactus or cauliflower anatomies: (**a**) short depth and secondary lobes at various planes that are too wide for device closure, (**b**) protruding tissue pectinate muscle ridges (*asterisk*)

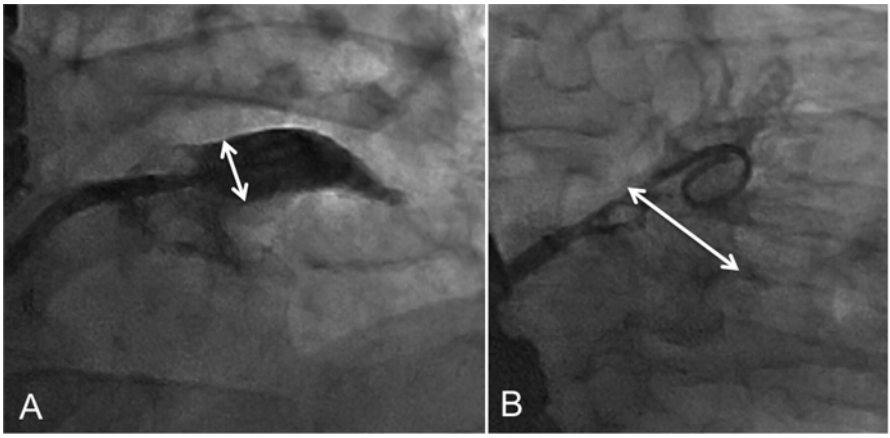


Fig. 8.6 Example of marked sphericity at the landing zone for ACP/Amulet device: (**a**) RAO cranial projection, (**b**) caudal projection

For WATCHMAN, the device appears to be very conformable and accommodates overcompression without compromising stability. Thus, marked sphericity may not pose as much issue for WATCHMAN, although we are still more conservative with oversizing in this scenario.

Volume rendering is then constructed to visualize the LAA in 3-dimension, which allows a more comprehensive appreciation of the complexity of the LAA. This display allows rotation and better characterization of the shape and potential anatomic challenges. These 3-dimensional images are rotated to find the best corresponding fluoroscopic views to guide device placement. For ACP/Amulet, the rotation that shows the orifice and proximal segment of the LAA well is selected, and this typically corresponds to a right anterior oblique and cranial projection (Fig. 8.7a). For WATCHMAN, the rotation that shows the body to distal LAA is required to appreciate where the sheath has to be placed distally, and this typically corresponds to a right anterior oblique and caudal projection (Fig. 8.7b).

There has been increasing interest in using CCTA to guide transseptal puncture for LAA closure. Conventionally, an inferior and posterior puncture at the fossa ovalis is desired, which allows the most direct vector towards the LAA with the preformed guide catheters, since it is situated anterior and superior. Optimizing the alignment of the delivery sheath to the landing zone for the devices is key to orientate the devices properly when deployed. Obtaining the optimal puncture will minimize manipulation of the delivery sheaths. However, using CCTA to guide transseptal puncture can be problematic, as the alignment of the sheath is not only dependent on the distance and angle from the fossa ovalis to the LAA, but also on the distance/angle from the inferior vena cava to the fossa ovalis. In addition, tortuosity in the venous system, or access via the left femoral vein, adds further constraints on catheter manipulation and angulation. An intricate mathematical formula and software will need to be devised to incorporate these variables. At the meantime, operators should rely on procedural TEE for an inferoposterior puncture.

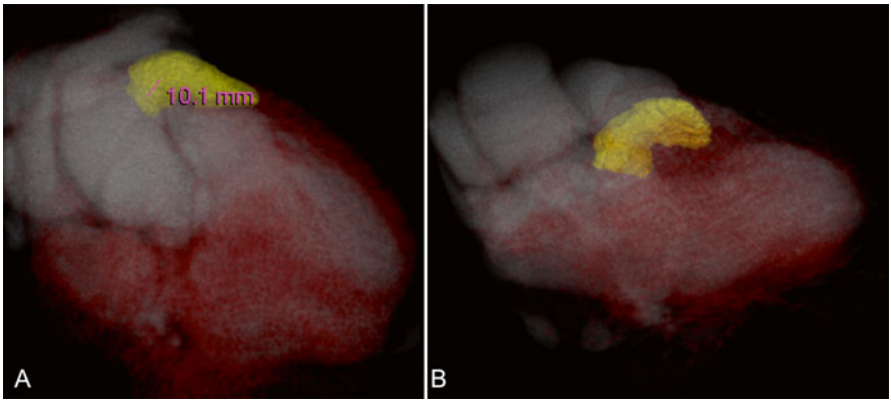


Fig. 8.7 3-D Volume rendering of LAA with fluoroscopic angle optimized for: (**a**) ACP in RAO cranial projection, and (**b**) WATCHMAN in RAO caudal projection

Fig. 8.8 Procedural CT overlay during ACP implantation

The use of procedural CT overlay for LAA closure is also being explored. This technique provides useful procedural guidance, allowing depiction of the LAA in multiple 2-dimensional views while rotating the fluoroscopic angles. This helps with selecting the implant fluoroscopic angle and in guiding device alignment during implantation, which is particularly important for the ACP/Amulet device (Fig. 8.8). For WATCHMAN, CT overlay also helps provide "ghost" images of the distal lobes for sheath placement, and guide device deployment for proper positioning. This technique theoretically lowers contrast usage to gauge proper alignment and positioning, and also may shorten procedural duration.

Pre-procedural CCTA for LARIAT Procedure

A pre-procedural CCTA is necessary to exclude anatomic variants that preclude the use of LARIAT, which may occur in up to 20 % of cases. Exclusions include large (>40 mm) LAA, posteriorly rotated LAA with apex behind the pulmonary artery, multilobed LAA with combined width in different planes >40 mm, pericardial adhesions, and posteriorly rotated heart. Pre-procedural CCTA with volume rendering can also guide pericardial access by visualizing the inferior anterior approach for access of the LARIAT pericardial sheath.

Post-Surveillance with CCTA After LAA Closure

Routine LAA device imaging after percutaneous closure is important to assess for residual leak, device thrombus, device positioning, surrounding structures, and pericardial effusion. CCTA can be used to assess these features noninvasively after LAA closure. We reported the first series of CT follow-up with the ACP device, showing that CCTA provided accurate assessment of the position and function of ACP compared with transthoracic echocardiography [40]. As well, the CT tissue density (Hounsfield) measurement allows the detection of residual flow in the LAA. However, CCTA is much more sensitive than TEE in assessing residual leak after LAA device closure, but the clinical significance of this is unknown. In our series of 21 patients who underwent CCTA imaging after ACP closure, residual leak was identified in 62 % of cases (Fig. 8.9a) [41]. We also found that higher lobe compression and proper alignment was associated with subsequent complete LAA closure with ACP. CCTA is also useful to screen for atrial-side device thrombus

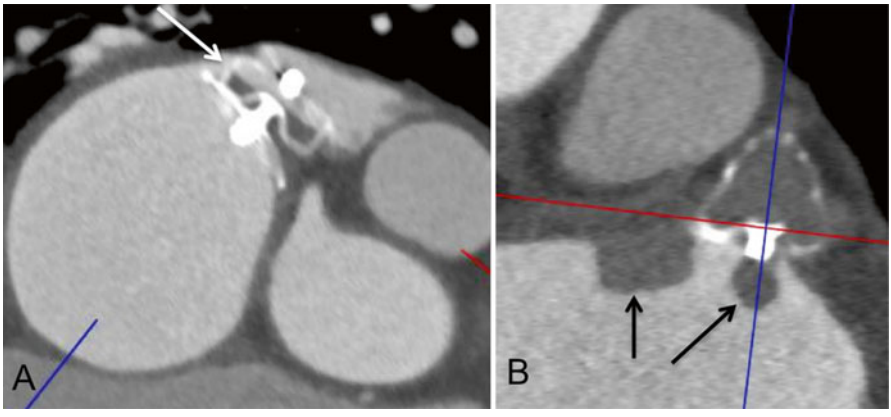


Fig. 8.9 Post-procedural surveillance with CCTA for LAA closure: (**a**) residual leak with an ACP device due to off-axis of lobe (*white arrow*), (**b**) atrial-side device thrombus with a WATCHMAN device (*black arrows*)

after LAA closure. In our series of 45 CCTA post-LAA closure with ACP, Amulet or WATCHMAN devices, we found atrial-side device thrombus in one case (Fig. 8.9b) [42]. With the added advantage of noninvasiveness and the ability to visualize the necessary features post-device closure, CCTA has replaced TEE as our routine post-procedural surveillance modality at 3–6 months post-LAA closure for patients who are not candidates for long-term oral anticoagulation (see Table 8.1 for protocol). The clinical significance of residual leak seen in CCTA and correlation to clinical outcomes still need to be explored.

Conclusions

CCTA provides superior spatial resolution and 3-dimensional structural depiction of the LAA and surrounding structures to facilitate procedural preplanning, rule out LAA thrombus, and post-procedural surveillance with LAA closure. In many centers, like ours, CCTA has become an alternative to TEE as a pre-imaging modality, and has replaced TEE as the routine post-procedural surveillance imaging modality for percutaneous LAA closure.

References

1. Di Biase L, Santangeli P, Anselmino M, et al. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. J Am Coll Cardiol. 2012;60:531–8.
2. Ucerler H, Ikiz ZA, Ozgur T. Human left atrial appendage anatomy and overview of its clinical significance. Anadolu Kardiyol Derg. 2013;13:566–72.
3. Stollberger C, Schneider B, Finsterer J. Is percutaneous left atrial appendage transcatheter occlusion an alternative to oral anticoagulation in patients with atrial fibrillation? Circulation. 2003;107:e11–2; author reply e11–2.
4. Su P, McCarthy KP, Ho SY. Occluding the left atrial appendage: anatomical considerations. Heart. 2008;94:1166–70.
5. Veinot JP, Harrity PJ, Gentile F, et al. Anatomy of the normal left atrial appendage: a quantitative study of age-related changes in 500 autopsy hearts: implications for echocardiographic examination. Circulation. 1997;96:3112–5.
6. Ernst G, Stollberger C, Finsterer J. Determination of left atrial appendage morphology. Circulation. 1998;98:2355.
7. Ernst G, Stollberger C, Abzieher F, et al. Morphology of the left atrial appendage. Anat Rec. 1995;242:553–61.
8. Somerville W, Chambers RJ. Systemic embolism in mitral stenosis: relation to the size of the left atrial appendix. Br Med J. 1964;2:1167–9.
9. Wang Y, Di Biase L, Horton RP, Nguyen T, Morhanty P, Natale A. Left atrial appendage studied by computed tomography to help planning for appendage closure device placement. J Cardiovasc Electrophysiol. 2010;21:973–82.
10. Troupis J, Crossett M, Scneider-Kolsky M, Nandurkar D. Presence of accessory left atrial appendage/diverticula in a population with atrial fibrillation compared with those in sinus rhythm: a retrospective review. Int J Cardiovasc Imaging. 2012;28:375–80.

11. Shi AW, Chen ML, Yang B, Cao KJ, Kong XQ. A morphological study of the left atrial appendage in Chinese patients with atrial fibrillation. J Int Med Res. 2012;40:1560–7.
12. Kimura T, Takatsuki S, Inagawa K, et al. Anatomical characteristics of the left atrial appendage in cardiogenic stroke with low CHADS2 scores. Heart Rhythm. 2013;10:921–5.
13. Verma S. Left atrial appendage and thromboembolism: shape matters. Heart Rhythm. 2013;10:926–7.
14. Anselmino M, Scaglione M, Di Biase L, et al. Left atrial appendage morphology and silent cerebral ischemia in patients with atrial fibrillation. Heart Rhythm. 2014;11:2–7.
15. Khurram IM, Dewire J, Mager M, et al. Relationship between left atrial appendage morphology and stroke in patients with atrial fibrillation. Heart Rhythm. 2013;10:1843–9.
16. Lee JM, Shim J, Uhm JS, et al. Impact of increased orifice size and decreased flow velocity of left atrial appendage on stroke in nonvalvular atrial fibrillation. Am J Cardiol. 2014;113:963–9.
17. Shirani J, Alaeddini J. Structural remodeling of the left atrial appendage in patients with chronic non-valvular atrial fibrillation: implications for thrombus formation, systemic embolism, and assessment by transesophageal echocardiography. Cardiovasc Pathol. 2000;9:95–101.
18. Nedios S, Tang M, Roser M, et al. Characteristic changes of volume and three-dimensional structure of the left atrium in different forms of atrial fibrillation: predictive value after ablative treatment. J Interv Card Electrophysiol. 2011;32:87–94.
19. Ho SY, Cabrera JA, Sanchez-Quintana D. Left atrial anatomy revisited. Circ Arrhythm Electrophysiol. 2012;5:220–8.
20. Manning WJ, Weintraub RM, Waksmonski CA, et al. Accuracy of transesophageal echocardiography for identifying left atrial thrombi. A prospective, intraoperative study. Ann Intern Med. 1995;123:817–22.
21. Hwang JJ, Chen JJ, Lin SC, et al. Diagnostic accuracy of transesophageal echocardiography for detecting left atrial thrombi in patients with rheumatic heart disease having undergone mitral valve operations. Am J Cardiol. 1993;72:677–81.
22. Romero J, Husain SA, Kelesidis I, Sanz J, Medina HM, Garcia MJ. Detection of left atrial appendage thrombus by cardiac computed tomography in patients with atrial fibrillation: a meta-analysis. Circ Cardiovasc Imaging. 2013;6:185–94.
23. Hong SJ, Kim JY, Kim JB, et al. Multidetector computed tomography may be an adequate screening test to reduce periprocedural stroke in atrial fibrillation ablation: a multicenter propensity-matched analysis. Heart Rhythm. 2014;11:763–70.
24. Dorenkamp M, Sohns C, Vollmann D, et al. Detection of left atrial thrombus during routine diagnostic work-up prior to pulmonary vein isolation for atrial fibrillation: role of transesophageal echocardiography and multidetector computed tomography. Int J Cardiol. 2013; 163:26–33.
25. Gottlieb I, Pinheiro A, Brinker JA, et al. Diagnostic accuracy of arterial phase 64-slice multidetector CT angiography for left atrial appendage thrombus in patients undergoing atrial fibrillation ablation. J Cardiovasc Electrophysiol. 2008;19:247–51.
26. Kim YY, Klein AL, Halliburton SS, et al. Left atrial appendage filling defects identified by multidetector computed tomography in patients undergoing radiofrequency pulmonary vein antral isolation: a comparison with transesophageal echocardiography. Am Heart J. 2007;154:1199–205.
27. Martinez MW, Kirsch J, Williamson EE, et al. Utility of nongated multidetector computed tomography for detection of left atrial thrombus in patients undergoing catheter ablation of atrial fibrillation. JACC Cardiovasc Imaging. 2009;2:69–76.
28. Patel A, Au E, Donegan K, et al. Multidetector row computed tomography for identification of left atrial appendage filling defects in patients undergoing pulmonary vein isolation for treatment of atrial fibrillation: comparison with transesophageal echocardiography. Heart Rhythm. 2008;5:253–60.
29. Tang RB, Dong JZ, Zhang ZQ, et al. Comparison of contrast enhanced 64-slice computed tomography and transesophageal echocardiography in detection of left atrial thrombus in patients with atrial fibrillation. J Interv Card Electrophysiol. 2008;22:199–203.

30. Wu X, Wang C, Zhang C, Zhang Y, Ding F, Yan J. Computed tomography for detecting left atrial thrombus: a meta-analysis. Arch Med Sci. 2012;8:943–51.
31. Hur J, Kim YJ, Lee HJ, et al. Left atrial appendage thrombi in stroke patients: detection with two-phase cardiac CT angiography versus transesophageal echocardiography. Radiology. 2009;251:683–90.
32. Hur J, Kim YJ, Lee HJ, et al. Dual-enhanced cardiac CT for detection of left atrial appendage thrombus in patients with stroke: a prospective comparison study with transesophageal echocardiography. Stroke. 2011;42:2471–7.
33. Hur J, Kim YJ, Lee HJ, et al. Cardioembolic stroke: dual-energy cardiac CT for differentiation of left atrial appendage thrombus and circulatory stasis. Radiology. 2012;263:688–95.
34. van Rosendael PJ, Katsanos S, van den Brink OW, et al. Geometry of left atrial appendage assessed with multidetector-row computed tomography: implications for transcatheter closure devices. EuroIntervention. 2013;10(3):364–71.
35. DeJong PM, Lempereur M, Gin K, Jue J, Saw J. Changes in left atrial appendage dimensions following volume loading during percutaneous closure. Can J Cardiol. 2014;10:S218–9.
36. Patel AR, Fatemi O, Norton PT, et al. Cardiac cycle-dependent left atrial dynamics: implications for catheter ablation of atrial fibrillation. Heart Rhythm. 2008;5:787–93.
37. Suh IW, Song JM, Lee EY, et al. Left atrial volume measured by real-time 3-dimensional echocardiography predicts clinical outcomes in patients with severe left ventricular dysfunction and in sinus rhythm. J Am Soc Echocardiogr. 2008;21:439–45.
38. Lickfett L, Dickfeld T, Kato R, et al. Changes of pulmonary vein orifice size and location throughout the cardiac cycle: dynamic analysis using magnetic resonance cine imaging. J Cardiovasc Electrophysiol. 2005;16:582–8.
39. Freixa X, Tzikas A, Basmadjian A, Garceau P, Ibrahim R. The chicken-wing morphology: an anatomical challenge for left atrial appendage occlusion. J Interv Cardiol. 2013;26:509–14.
40. Poulter RS, Tang J, Jue J, et al. Cardiac computed tomography follow-up of left atrial appendage exclusion using the Amplatzer Cardiac Plug device. Can J Cardiol. 2012;28:119; e1–3.
41. Saw J, DeJong PM, Lempereur M, et al. Cardiac CT angiography follow-up of left atrial appendage closure with the Amplatzer Cardiac Plug. Catheter Cardiovasc Interv. 2014;83:S91.
42. Saw J, Fahmy P, DeJong PM et al. Cardiac CT angiography for device surveillance after endovascular left atrial appendage closure. Eur Heart J Cardiovasc Imaging. 2015.

Part IV
Percutaneous LAA Closure Devices and Trial Results

Chapter 9
PLAATO Device

Randall J. Lee

Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia in the United States and is associated with a fivefold increase in cardioembolic events [1–3]. There is a higher mortality and morbidity associated with cardioembolic strokes associated with AF compared to non-AF strokes, emphasizing the need for preventive treatment strategies [4]. The left atrial appendage (LAA) has been long recognized as the primary source of thrombus formation within the cardiovascular system [4–6] and has been termed "the most lethal human attachment" [14]. In surgical patients with AF, left atrial (LA) thrombus was found in 17 % of nonrheumatic AF patients; however, 91 % (201 of 222 patients) of the thrombus was localized to the LAA [7]. These findings were corroborated by transesophageal echocardiography evaluation of patients undergoing cardioversion where LA thrombus is predominantly located in the LAA [8–10]. These observations led to the hypothesis that closure of the LAA would prevent thrombus formation, prevent cardioembolic events, and reduce mortality.

The concept of excluding the LAA during mitral valve surgery existed since the 1930s [5, 6] and has become an integral part of the American College of Cardiology/American Heart Association guidelines for mitral valve surgery to reduce the stroke risk [11, 12]. LAA exclusion is also an essential part of the Maze procedure for both stroke prevention and reduction of AF [13]. Many surgeons now advocate the removal of the LAA during any open-heart procedure [7]. The PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) device was conceived and developed based on the premise that if the appendage could be

R.J. Lee, M.D., Ph.D. (✉)
University of California, San Francisco, 500 Parnassus Ave, San Francisco, CA, 94010, USA
e-mail: Randall.Lee@ucsf.edu

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_9

obliterated by a simple, minimally invasive technique, it would provide an alternative strategy for preventing stroke in patients with nonrheumatic AF [14].

PLAATO Device

Catheter-based left atrial appendage occlusion device was conceived in 1998 with the development of the PLAATO device and delivery system (Appriva Medical, Palo Alto, CA/EV3 Inc., Plymouth, Minnesota). The PLAATO device was the first and prototypical LAA occlusion device. The PLAATO device was developed with the following specifications [14]. The device could not be allowed to: (1) dislodge and embolize, or migrate from its implanted position, (2) erode into the pericardial space or other surrounding structures (such as the circumflex coronary artery), (3) interfere with atrial function or blood flow through the mitral valve or from the pulmonary vein, (4) be the source of emboli. Additionally, the procedure had to be relatively easy to perform; and due to the variability in size and shape of the LAA, even with good criteria for initial device size selection, there had to be a way to collapse and completely remove and replace a given device with another size device.

The PLAATO device consists of a self-expanding nitinol metal cage structure with multiple outwardly bent struts and covered with the occlusive membrane of polytetrafluoroethylene ePTFE (Fig. 9.1). The 14 Fr transseptal delivery system allows for collapse and repositioning or complete removal of the PLAATO device in the event a different size device (15–32 mm) is required to replace the implant with a different size.

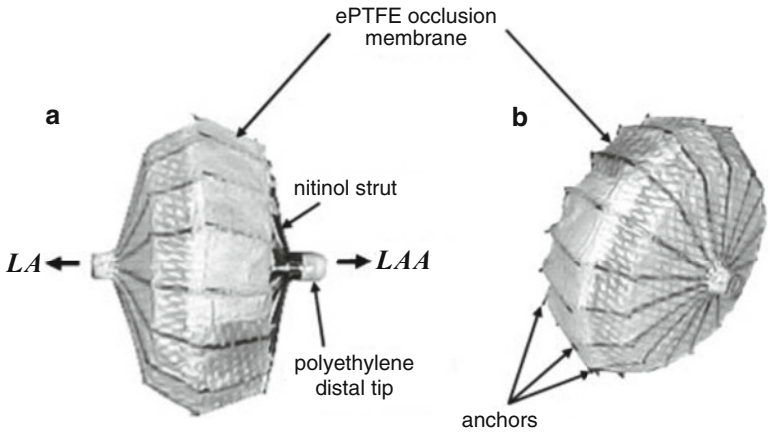


Fig. 9.1 PLAATO device composed of a nitinol collapsible cage structure covered with ePTFE. The device is shown in the lateral view (**a**) and frontal view (**b**). Adapted from Nakai et al. [14] with permission from *Circulation*

Preclinical Studies

The seminal proof of principle study was completed at the University of California, San Francisco [14]. This study was the first demonstration that a LAA occlusion device could be successfully implanted into the LAA with endothelialization of the PLAATO device (Fig. 9.2). The study objectives were to demonstrate feasibility, safety, and healing characteristics of the percutaneous transseptal delivery of the PLAATO device to occlude the LAA.

Twenty-five dogs underwent successful implantation of the PLAATO device into the LAA. Conformation of proper placement of the PLAATO device was confirmed with both LA angiography and intracardiac echocardiography. There were no complications associated with the implant of the device with the exception of a small pericardial effusion that did not need treatment. Animals were sacrificed for histological examination on day 2, 2 weeks, 1 and 3 months. In one animal, there was evidence of a small perforation of the tissue anchor with no other abnormality noted. At 1 and 3 months, there was complete closure of the LAA with demonstration of

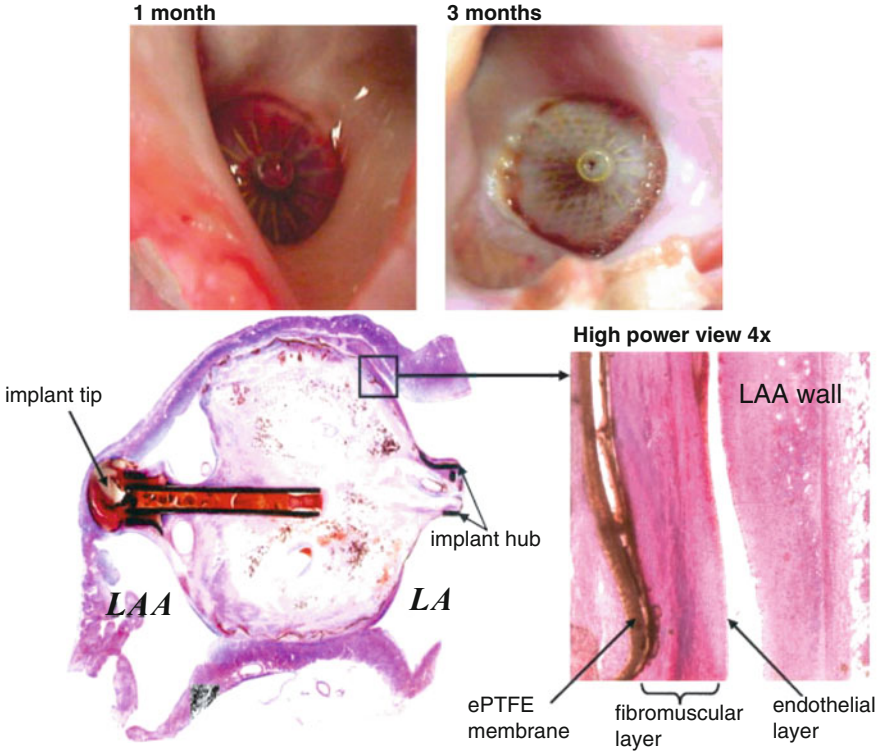


Fig. 9.2 Preclinical postmortem analysis. The *top panel* of figures are the gross anatomy at 1 and 3 months, demonstrating the snug fit of the implant into the LAA orifice. Adapted from Nakai et al. [14] with permission from *Circulation*

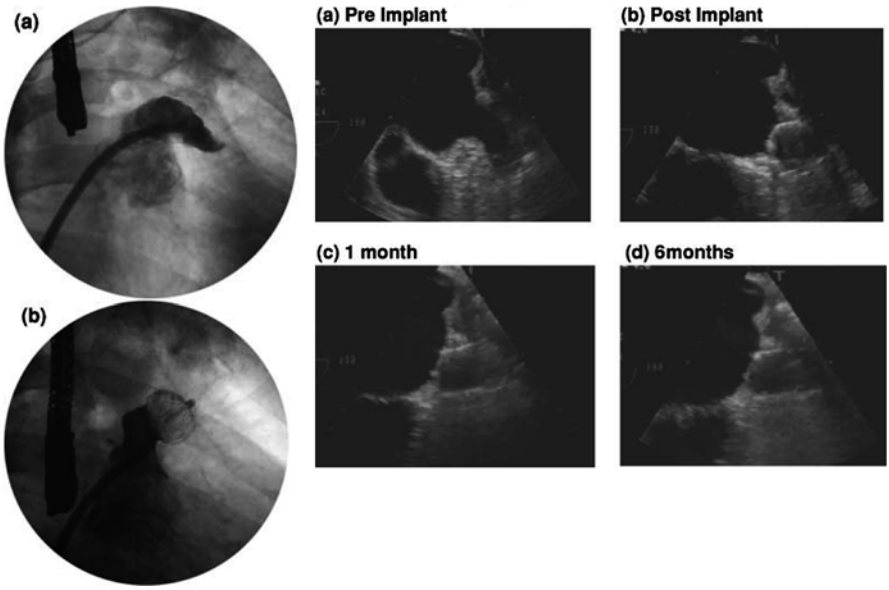


Fig. 9.3 Confirmation of PLAATO positioning within the LAA. Contrast fluoroscopy is shown in the *left* panel. The initial LA angiogram delineating the LAA (**a**) and after the implantation of PLAATO device (**b**) demonstrating complete occlusion of the LAA. Corroboration of the contrast fluoroscopy is provided by TEE imaging. The *top upper left* figure (**c**) is the pre-implant image of the LAA. (**d**) It is the visualization of the PLAATO device seated in the LAA. (**e**, **f**) Shows the same TEE views 1 and 6 months after the implantation. Adapted from Nakai et al. [24] with permission from *Pacing Clin Electrophysiology*

endothelialization of the atrial surface of the implant (Fig. 9.3). It was concluded that the LAA occlusion with the PLAATO device was feasible, safe, and led to complete sealing of the LAA.

Clinical Results

Based on the favorable preclinical studies, Horst Sievert performed the first LAA occlusion intervention in man in August, 2001. The early clinical experience was reported by Sievert and colleagues in 15 patients with chronic AF at high risk for stroke, who were poor candidates for long-term warfarin therapy [15]. The PLAATO device was successfully implanted in all 15 patients with only one non-device complication of hemopericardium resulting from LAA access. LA angiography and TEE were typically used to confirm the PLAATO device sealing the LAA (Fig. 9.4). The authors concluded that the PLAATO was feasible and safe to occlude the LAA.

The initial multicenter observational study was the International Multi-Center Feasibility Trials that assessed the primary end point of incidence of major adverse events (MAEs), a composite of stroke, cardiac or neurological death, myocardial infarction, and requirement for procedure-related cardiovascular surgery within the

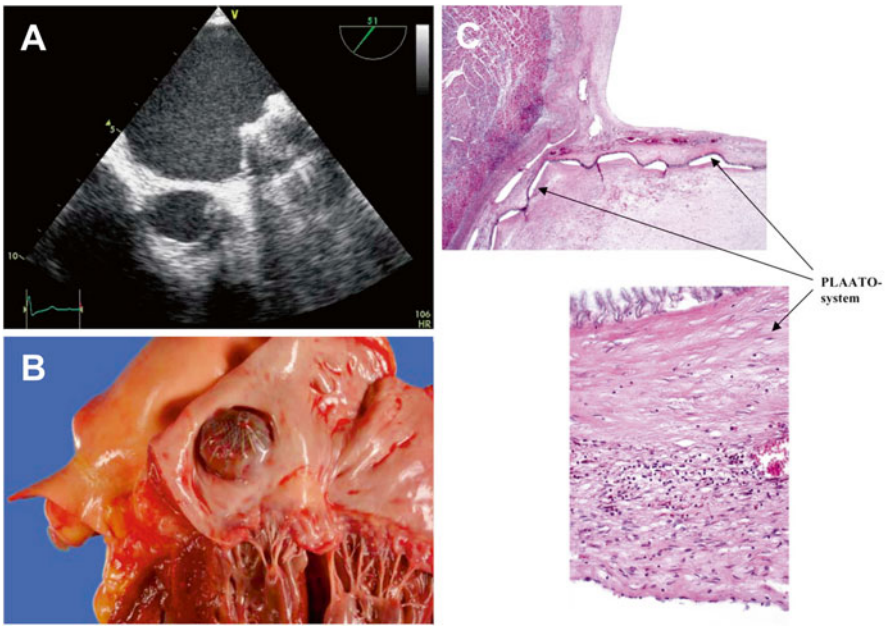


Fig. 9.4 Postmortem analysis from a patient with AF. TEE imaging (**a**) demonstrating a well-seated PLAATO device in the LAA. Gross anatomy dissection showing the PLAATO device occluding the LAA (**b**) covered by endothelium (**c**). Adapted from Omram et al. [21] with permission from *Journal of Interventional Cardiac Electrophysiology*

first month [16]. This study was performed in 111 patients with a contraindication for anticoagulation therapy and at least one additional risk factor for stroke. Following PLAATO implantation into the LAA, patients were treated with ASA or ASA plus clopidogrel. The PLAATO device was successfully implanted in 108 of 111 patients (97 %). During the first 30 days, there were 3 patients with hemopericardium requiring surgery and 1 patient that needed cardiovascular surgery and eventually expired. No thrombi were noted on TEE at 1 and 6 months. However, there were 2 patients sustaining strokes and 3 patients with TIAs. The observed annual stroke rate was 2.2 %, but did not include the TIAs that would have brought the neurological event rate to 5.5 %.

In a subsequent follow-up European PLAATO study, LAA occlusion was successful in 162/180 patients (90 %) [17]. There were 2 procedural deaths (1.1 %), 6 cardiac tamponades with 2 requiring surgical drainage (3.3 %), and 1 device embolization (0.6 %). Three strokes occurred (2.9 %) which was lower than the CHADS2 score predicted 6.6 % per year. The study was stopped prematurely due to financial considerations.

There have been several other small single center or multicenter observational studies suggesting the benefits of LAA occlusion in preventing strokes with acceptable adverse events [18–21]. The annual event rate of stroke ranged from no strokes during a 2-year follow-up of 73 PLAATO implanted patients to 3.8 % annual stroke/

TIA rate after a 5-year follow-up period [18, 19]. All of the studies had small number of patients with no independent adjudication or monitoring. In general, only antiplatelet therapy was used after the LAA implantation of the PLAATO device, supporting the notion that an implant could potentially be used in patients with contraindications to oral anticoagulation therapy.

Postmortem Analysis of the PLAATO Device

Postmortem analysis of the PLAATO device has demonstrated both the desired effect and potential concerns with any LAA occlusion device (Fig. 9.5). The design of the PLAATO device incorporated ePTFE to allow for healing and occlusion of the LAA. A postmortem analysis of the PLAATO device 1 year after implantation

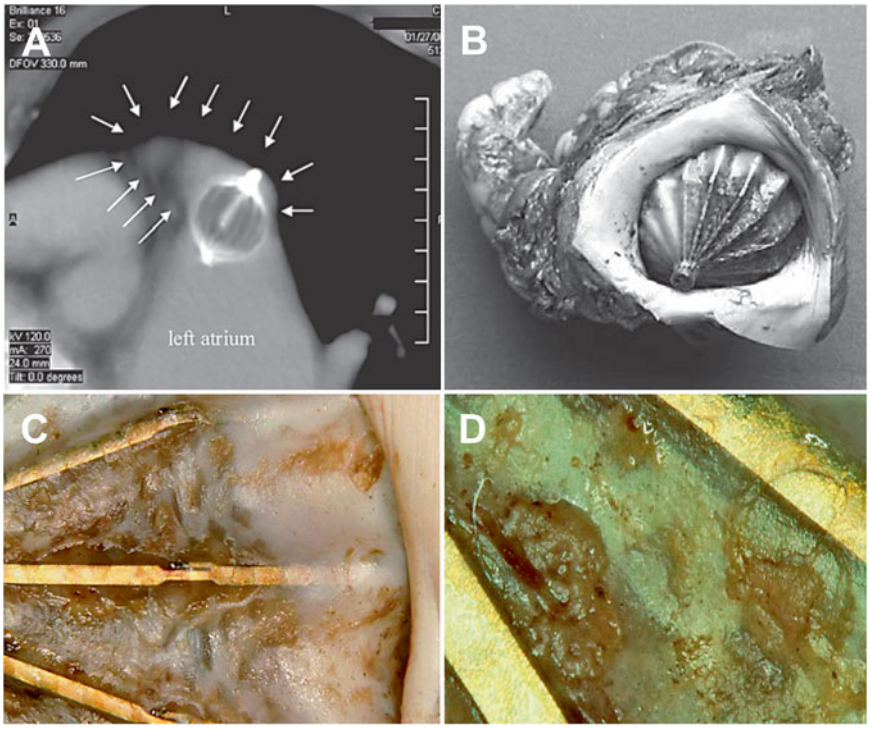


Fig. 9.5 Postmortem analysis of the PLAATO device with thromboembolism. Cardiac CT of the PLAATO device 3 months after implantation (**a**). The *arrows* frame the LAA and demonstrate a partially protruding PLAATO device into the LA. Despite the rotation of the device, the gross examination reveals that the LAA orifice is completely occluded (**b**). Thrombotic deposition is seen on the atrial surface of the PLAATO device at 1:8 magnification (**c**) and 1:18 magnification (**d**). Adapted from Park et al. [23] with permission from *Cardiology*

demonstrated that the atrial surface of the device was completely covered by neo-endothelium and the device occludes the appendage completely [21]. This finding corroborated the preclinical studies that also demonstrated a complete endothelial layer over the device. In contrast, a different postmortem analysis of a PLAATO device implanted for 2 years demonstrated thrombotic deposition on the atrial-side surface of the PLAATO system [22]. The patient did not experience any embolic events, but the detection of thrombotic deposition on the atrial surface of the device presents the potential for future thromboembolic events.

Conclusion

The PLAATO device was the first LAA endocardial occlusion device designed for the prevention of thrombus formation within the LAA and prevention of cardioembolic events. Initial experience demonstrated feasibility, acceptable adverse events, and a decreased stroke rate. Although initial experience with the PLAATO device was encouraging, commercial reasons halted subsequent randomized studies and the withdrawal of the device from the market.

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham study. Arch Intern Med. 1987;147:1561–4.
2. Alpert JS, Petersen P, Godtfredsen J. Atrial fibrillation: natural history, complications, and management. Annu Rev Med. 1988;39:41–52.
3. Area Anticoagulation Trial for Atrial Fibrillation Study; Canadian Atrial Fibrillation Anticoagulation Study; Stroke Prevention in Atrial Fibrillation Study; VeteransAffairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Study. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med. 1994;154:1449–57.
4. Belcher JR, Somerville W. Systemic embolism and left atriatricular thrombosis in relation to mitral stenosis. Br Med J. 1955;2:1000–3.
5. Madden J. Resection of the left auricular appendix. JAMA. 1948;140:769–72.
6. Bailey C, Olsen A, Keown K, et al. Commissurotomy for mitral stenosis technique for prevention of cerebral complications. JAMA. 1952;149:1085–91.
7. Johnson WD, Ganjoo AK, Stone CD, et al. The left atrial appendage: our most lethal human attachment: surgical implications. Eur J Cardiothorac Surg. 2000;17:718–22.
8. Klein AL, Grimm RA, Black IW, et al. Cardioversion guided by transesophageal echocardiography: the ACUTE pilot study: a randomized, controlled trial: assessment of cardioversion using transesophageal echocardiography. Ann Intern Med. 1997;126:200–9.
9. Aschenberg W, Schluter M, Kremer P, et al. Transesophageal two dimensional echocardiography for the detection of left atrial appendage thrombus. J Am Coll Cardiol. 1986;7:163–6.
10. Manning WJ, Weintraub RM, Waksmonski CA, et al. Accuracy of transesophageal echocardiography for identifying left atrial thrombi. A prospective, intraoperative study. Ann Intern Med. 1995;123:817–22.

11. Fuster V, Ryden LE, Cannom DS, et al. 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.
12. Calkins H, Brugada J, Packer DL, et al. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation. Heart Rhythm. 2007;4:816–61.
13. Cox JL. The surgical treatment of atrial fibrillation, IV: surgical technique. J Thorac Cardiovasc Surg. 1991;101:584–92.
14. Nakai T, Lesh MD, Gerstenfeld EP, Virmani R, Jones R, Lee RJ. Percutaneous left atrial appendage occlusion (PLAATO) for preventing cardioembolism: first experience in canine model. Circulation. 2002;105(18):2217–22.
15. Sievert H, Lesh MD, Trepels T, Omran H, Bartorelli A, Della Bella P, Nakai T, Reisman M, DiMario C, Block P, Kramer P, Fleschenberg D, Krumsdorf U, Scherer D. Percutaneous left atrial appendage transcatheter occlusion to prevent stroke in high-risk patients with atrial fibrillation: early clinical experience. Circulation. 2002;105(16):1887–9.
16. Ostermayer SH, Reisman M, Kramer PH, Matthews RV, Gray WA, Block PC, Omran H, Bartorelli AL, Della Bella P, Di Mario C, Pappone C, Casale PN, Moses JW, Poppas A, Williams DO, Meier B, Skanes A, Teirstein PS, Lesh MD, Nakai T, Bayard Y, Billinger K, Trepels T, Krumsdorf U, Sievert H. Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: results from the international multi-center feasibility trials. J Am Coll Cardiol. 2005; 46(1):9–14.
17. Bayard YL, Omran H, Neuzil P, Thuesen L, Pichler M, Rowland E, Ramondo A, Ruzyllo W, Budts W, Montalescot G, Brugada P, Serruys PW, Vahanian A, Piéchaud JF, Bartorelli A, Marco J, Probst P, Kuck KH, Ostermayer SH, Büscheck F, Fischer E, Leetz M, Sievert H. PLAATO (percutaneous left atrial appendage transcatheter occlusion) for prevention of cardioembolic stroke in non-anticoagulation eligible atrial fibrillation patients: results from the European PLAATO study. EuroIntervention. 2010;6(2):220–6.
18. Park JW, Leithäuser B, Gerk U, Vrsansky M, Jung F. Percutaneous left atrial appendage transcatheter occlusion (PLAATO) for stroke prevention in atrial fibrillation: 2-year outcomes. J Invasive Cardiol. 2009;21(9):446–50.
19. Block PC, Burstein S, Casale PN, Kramer PH, Teirstein P, Williams DO, Reisman M. Percutaneous left atrial appendage occlusion for patients in atrial fibrillation suboptimal for warfarin therapy: 5-year results of the PLAATO (percutaneous left atrial appendage transcatheter occlusion) study. JACC Cardiovasc Interv. 2009;2(7):594–600.
20. De Meester P, Thijs V, Van Deyk K, Budts W. Prevention of stroke by percutaneous left atrial appendage closure: short term follow-up. Int J Cardiol. 2010;142(2):195–6.
21. El-Chami MF, Grow P, Eilen D, Lerakis S, Block PC. Clinical outcomes three years after PLAATO implantation. Catheter Cardiovasc Interv. 2007;69(5):704–7.
22. Omran H, Schmidt H, Hardung D, Hammerstingl C, von der Recke G, Haas S, Büttner R, Lüderitz B. Post mortem analysis of a left atrial appendage occlusion device (PLAATO) in a patient with permanent atrial fibrillation. J Interv Card Electrophysiol. 2005;14(1):17–20.
23. Park JW, Gerk U, Franke RP, Jung F. Post-mortem analysis of a left atrial appendage occlusion device (PLAATO) in a patient with permanent atrial fibrillation. Cardiology. 2009; 112(3):205–8.
24. Nakai T, Lesh M, Ostermayer S, Billinger K, Sievert H. An endovascular approach to cardioembolic stroke prevention in atrial fibrillation patients. Pacing Clin Electrophysiol. 2003;26(7 Pt 2):1604–6.

Chapter 10
WATCHMAN Device

Karen P. Phillips and Saibal Kar

Abbreviations

Ao V	Aortic valve
CT	Computed tomography
LAA	Left atrial appendage
LPV	Left pulmonary vein
Mi V	Mitral valve
RPV	Right pulmonary vein
TEE	Transesophageal echocardiography

Historical Background

The WATCHMAN device will remain the landmark advance which demonstrated with randomised control trial data that a local left atrial appendage (LAA)-based therapy could provide effective thromboembolic stroke prevention for patients with atrial fibrillation (AF) [1]. The WATCHMAN device was designed and patented by Atritech Inc (Plymouth, MN) as a filter to prevent harmful-sized thrombi from exiting the LAA in patients with nonvalvular AF (see Fig. 10.1). Following initial animal

K.P. Phillips, M.B.B.S. (✉)
Cardiac Catheterisation Laboratory, Cardiac Electrophysiologist
HeartCare Partners, Greenslopes Private Hospital, Suite 212,
Newdegate Street, Greenslopes, Brisbane, QLD 4120, Australia
e-mail: kphillips@hearcarepartners.com.au

S. Kar, M.D., F.A.C.C.
Cardiovascular Intervention Center Research, Cedars-Sinai
Medical Center, Los Angeles, CA, USA

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_10

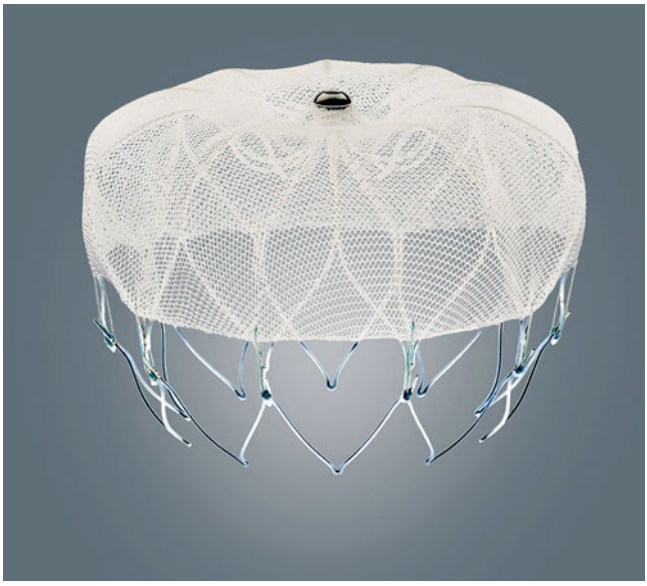


Fig. 10.1 A generation 2 WATCHMAN device.

studies, the device implant was assessed in an open label first-in-man pilot study commenced in 2004. After the initial 16 procedures, a revised second-generation model was developed (with reinforced delivery cable and fixation barbs to prevent embolisation). A shorter device length was also developed as part of the design improvements. The preliminary data on 66 patients suggested feasibility and relative safety of the percutaneous technique [2]. Atritech Inc and the WATCHMAN device technology was subsequently acquired by Boston Scientific (Natick, MA) in 2011. The next-generation 'WATCHMAN FLX' device was in development by Boston Scientific at the time of publication and planned for commercialisation in 2015.

WATCHMAN Clinical Trials and Evidence Base

PROTECT AF

The prospective randomised trial of the device therapy compared with warfarin (PROTECT AF trial) commenced in 2005 across sites in Europe and the USA. Patients with nonvalvular (i.e., excluding patients with rheumatic valvular disease) AF with a $CHADS_2$ score of 1 or more were randomised in a 2:1 ratio to WATCHMAN implant or continuation of warfarin (target INR 2.0–3.0). In patients receiving a device implant, warfarin therapy was discontinued after a 45-day follow-up

transesophageal echocardiogram (TEE) if satisfactory criteria for LAA closure were demonstrated (residual peri-device flow <5 mm). The primary endpoints were of (a) efficacy—a composite occurrence of all-cause stroke (ischemic and hemorrhagic), systemic embolism, cardiovascular, and unexplained death; and (b) safety—a composite occurrence of excessive bleeding and procedure-related complications. A total of 707 patients were enrolled with a follow-up duration of 5 years. Clinical characteristics of the PROTECT AF subjects are shown in Table 10.1.

After a mean follow-up of 18 ± 10 months (1065 patient years), the WATCHMAN intervention group met non-inferiority criteria for the primary efficacy endpoint. The primary efficacy event rate was 3.0 per 100 patient years (95 % CI 1.9–4.5) in the WATCHMAN group and 4.9 per 100 patient years (95 % CI 2.8–7.1) in the warfarin group. The primary safety event rate was however significantly higher in the intervention group at 2 years, 10.2 % (95 % CI 7.4–13.0) than the warfarin control group 6.8 % (95 % CI 3.0–10.6). Expanded details of results are shown in Table 10.2.

Subsequent follow-up data on the cohorts was published for 2.3 years and 4.0 years [3, 4]. The primary efficacy event rate at 4 years of follow-up for the WATCHMAN group was 2.3 per 100 patient years (95 % CI 1.7–3.2) and 3.8 per 100 patient years (95 % CI 2.5–4.9) in the warfarin group. This suggested a 40 % relative risk reduction for all-cause stroke, systemic embolism, cardiovascular, and unexplained death in the WATCHMAN group with superiority over warfarin therapy demonstrated.

The safety event rate proved to be a significant hurdle in pursuing Food and Drug Administration (FDA) approval in the USA. However, regulatory approvals were followed in other regions of the world including Europe and Australasia, with commercialisation of the WATCHMAN device by Atritech Inc in 2009. Atritech Inc and the WATCHMAN device technology was subsequently acquired by Boston Scientific (Natick, Massachusetts) in 2011.

CAP Registry

In the USA, the FDA permitted a Continued Access Program (CAP) nonrandomised registry for a subset of PROTECT AF investigators to continue implanting the WATCHMAN device according to study protocol to gain further safety and efficacy data on the device. The rate of procedure or device-related safety events within 7 days of the procedure declined from 7.7 % in PROTECT AF to 3.7 % in the CAP registry [5].

PREVAIL Study

A further randomised control trial was still mandated by the FDA with a similar protocol, but requiring a minimum of 25 % enrolment by new operators to re-examine the safety issues. The PREVAIL study included a further 407 patients with a mean

Table 10.1 Baseline characteristics and risk factors of PROTECT AF trial participants

Characteristics	Intervention group (*n*=463)	Control group (*n*=244)
Age (years)	71.7 (8.8;46-0–95.0)	72.7 (9.2;41-0–95.0)
Male	326 (70.4 %)	171 (70.1 %)
Race/ethnicity		
Asian	4 (0.9 %)	1 (0.4 %)
Black/African-American	6 (1.3 %)	5 (2.0 %)
White	425 (91.8 %)	222 (91.0 %)
Hispanic/Latin American	25 (5.4 %)	15 (6.1 %)
Hawaiian/Pacific Islander	1 (0.2 %)	1 (0.4 %)
Other	2 (0.4 %)	0
Risk factors		
CHADS2 score[a]		
1	157 (33.9 %)	66 (27.0 %)
2	158 (34.1 %)	88 (36.1 %)
3	88 (19.0 %)	51 (20.9 %)
4	37 (8.0 %)	24 (9.8 %)
5	19 (4.1 %)	10 (4.1 %)
6	4(0.9%)	5(2.0%)
Congestive heart failure	124 (26.8 %)	66 (27.0 %)
History of hypertension	413 (89.2 %)	220 (90.2 %)
Age 75 years or more	190 (41.0 %)	115 (47.1 %)
Diabetes	113 (24.4 %)	72 (29.5 %)
Previous transient ischaemic attack/ ischaemic stroke	82 (17.7 %)	49 (20.1 %)
Previous warfarin use		
Less than 1 year	254 (54.9 %)	145 (59.4 %)
1 Year or more	203 (43.8 %)	96 (39.3 %)
No estimate	6 (1.3 %)	3 (1.2 %)
Atrial fibrillation pattern		
Paroxysmal	200 (43.2 %)	99 (40.6 %)
Persistent	97 (21.0 %)	50 (20.5 %)
Permanent	160 (34.6 %)	93 (38.1 %)
Unknown	6 (1.3 %)	2 (0.8 %)
Atrial fibrillation onset		
Less than 1 year	69 (14.9 %)	50 (20.5 %)
1 Year or more	360 (77.8 %)	182 (74.6 %)
No estimate	34 (7.3 %)	12 (4.9 %)
Left ventricular ejection fraction (%)	57.3 % (9.7; 30.0–82.0)	56.7 % (10.1; 30.0–86.0)

Reprinted from The Lancet, vol. 374, Holmes DR 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. Pages 534–42, Copyright (2009), with permission from Elsevier
Data are mean (SD; range) or *n* (%)

[a]At least one of the following: previous stroke or transient ischaemic attack, congestive heart failure, diabetes mellitus, hypertension, or were 75 years or older

Table 10.2 Clinical outcomes of PROTECT AF trial participants

	Intervention group		Control group			Posterior probabilities	
	Events/ patient-years	Observed rate (events per 100 patient-years [95 % CrI])	Events/ patient-years	Observed rate (events per 100 patient-years [195 % CrI])	Rate ratio (intervention/ control [95% CrI])	Non-inferiority (%)	Superiority (%)
ITT population[a]							
Primaiy efficacy[b]	11/694.1	3.0 (1.9–4.5)	18/370.8	4.9 (2.8–7.1)	0.62 (0.35–1.25)	>99.9	90.0
Ischaemic stroke	15/694.6	2.2 (1.2–3.5)	6/372.3	1.6 (0.6–3.0)	1.34 (0.60–4.29)	71.8	20.1
Cardiovascular/ unexplained death	5/708.4	0.7 (0.2–1.5)	10/374.9	2.7 (1.2–4.4)	0.26 (0.08–0.77)	>99.9	99.3
Haemorrhagic stroke	1/708.4	0.1 (0.0–0-5)	6/373.4	1.6 (0.6–3.1)	0.09 (0.00–0.45)	>99.9	99.8
Systemic embolism	2/707.8	0.3 (0.0–0.8)	0/374.9	0	…	…	…
All stroke	16/694.6	2.3 (1.3–3.6)	12/370.8	3.2 (1.6–5.2)	0.71 (0.35–1.64)	99.3	76.9
All-cause mortality	21/708.4	3.0 (1.9–4.5)	18/374.9	4.8 (2.8–7.1)	0.62 (0.34–1.24)	>99.9	90.7
Primary safety[c]	49/658.8	7.4 (5.5–9.7)	16/364.2	4.4 (2.5–6.7)	1.69 (1.01–3.19)	…	…
Successfully treated population[d]							
Primary efficacy	11/593.6	1.9 (1.0–3.2)	17/370.2	4.6 (2.6–6.8)	0.40 (0.19–0.91)	>99.9	98.6
Primary safety	9/592.1	1.5 (0.7–2.8)	16/363.6	4.4 (2.5–6.7)	0.35 (0.15–0.80)	…	…

Reprinted from The Lancet, vol. 374, Holmes DR 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. Pages 534–42, Copyright (2009), with permission from Elsevier

CrI credible interval, *ITT* intention-to-treat—not applicable. Different events have different numbers of patient years because patients without an event or lost to follow-up were censored at the time of the last known event status. Posterior probabilities of non-inferiority are based on a twofold non-inferiority margin. Posterior probabilities and CrIs are based on a Bayesian model stratified by CHADS2 score

[a]The ITT population consists of all randomised patients (intervention, $n=463$; control = 244)

[b]The primary composite endpoint for efficacy was the occurrence of stroke (including ischaemic or haemorrhagic stroke), cardiovascular or unexplained death, or systemic embolism

[c]The primary composite endpoint for safety consisted of events related to excessive bleeding (e.g., intracranial or gastrointestinal bleeding) or procedure-related complications (e.g., serious pericardial effusion, device embolisation, procedure-related stroke)

[d]Successful treatment was defined in the intervention group as device implantation followed by discontinuation of warfarin and in the control group as the start of warfarin treatment (intervention, $n=389$; control = 241)

$CHADS_2$ score of 2.6 and was commenced in 2011. The required safety endpoint was reached with a 7-day safety event rate of 2.2 % (95 % upper CI 2.61) in the WATCHMAN group [6]. The primary efficacy composite endpoint, however, did not meet prespecified criteria for non-inferiority at the 18-month follow-up. The event rate was 1.07 per 100 patient years (95 % CI 0.57–1.88) in the WATCHMAN group and 0.7 per 100 patient years (95 % CI 0.1–5.1) in the warfarin group. Comparative event rates for warfarin control groups were significantly higher in other anticoagulation trials: PROTECT AF 1.6 % [1], RELY 1.7 % [7], ROCKET AF 2.2 % [8], and ARISTOTLE 1.6 % [9]. FDA approval of the WATCHMAN device in the USA was subsequently granted in March 2015 for use in patients with nonvalvular AF at high stroke risk who are suitable for warfarin, but who have an appropriate rationale to seek a non-pharmacologic alternative.

ASAP Study

Additional data on the safety and efficacy of WATCHMAN LAA device closure on warfarin-ineligible patients came from the ASAP Study published in 2013 [10]. One hundred and fifty patients with contraindications to warfarin therapy were included in the prospective nonrandomised study. Following device implantation, patients were administered 6 months of clopidogrel or ticlopidine antiplatelet therapy in addition to lifelong low-dose aspirin. The primary efficacy (all-cause stroke, systemic embolism, cardiovascular, and all-cause death) event rate was 4.6 per 100 patient years. The ischemic stroke annual event rate was 1.7 %. Comparison was made with the expected annual ischemic stroke rate predicted by $CHADS_2$ score (mean score 2.8) while taking aspirin of 7.3 %, suggesting that WATCHMAN device therapy conferred a 77 % reduction in ischemic stroke rate.

Implant Success Rates

Technical success of the implant procedure has a demonstrated learning curve over the WATCHMAN clinical studies. Implant success rates were 91 % in PROTECT AF, 94.7 % in ASAP, 95 % in CAP registry, and 95.1 % in PREVAIL studies.

WATCHMAN Device Characteristics

Device

The WATCHMAN device was designed and patented as a filter to prevent harmful-sized thrombi from exiting the LAA in patients with nonvalvular AF. Subsequent animal studies and post-mortem analysis have confirmed that full endothelialisation

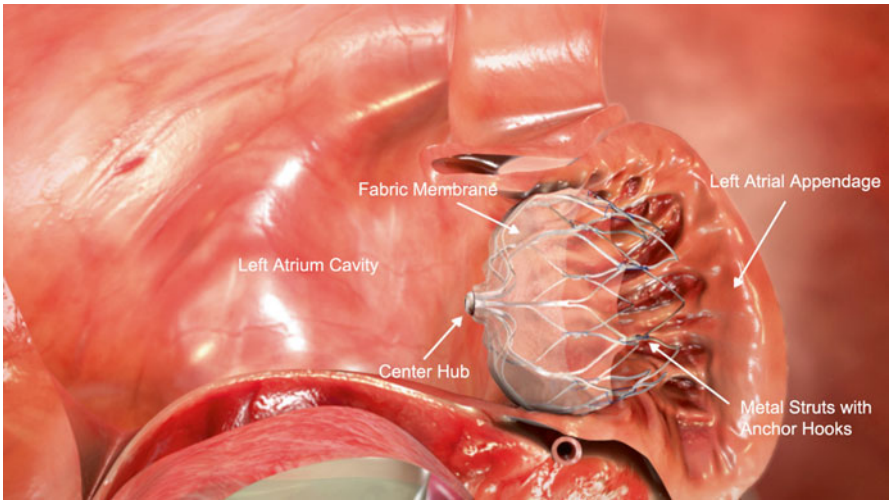


Fig. 10.2 Design features of the WATCHMAN device seated in the ostium of the left atrial appendage. ©2014 Boston Scientific Corporation or its affiliates. All rights reserved. Used with permission of Boston Scientific Corporation

Fig. 10.3 The WATCHMAN device is available in 21, 24, 27, 30, and 33 mm diameters. ©2014 Boston Scientific Corporation or its affiliates. All rights reserved. Used with permission of Boston Scientific Corporation

of the device atrial surface occurs generally over a 6-month period. The device is a self-expanding nitinol frame with a 160 μm permeable PET (polyethylene terephthalate) membrane cap. Ten active fixation anchors positioned at the distal third of the nitinol frame (composed of ten struts) help to achieve fixation and stability in the LAA tissue. The device is designed to be oversized for the LAA ostium so that radial force imparts stability and apposition with the LAA walls (Fig. 10.2). The device is available in 21, 24, 27, 30, and 33 mm diameters to accommodate individual variations in anatomy (Fig. 10.3). The device length shortens as it is deployed from the delivery catheter. The fully constrained device within the delivery catheter measures a similar length to the deployed maximum device diameter. The device is classified as magnetic resonance conditional according to the American Society for Testing and Materials. A patient with a WATCHMAN device can be safely scanned with magnetic resonance imaging immediately after implant with a static magnetic field of 3-T or less.

Fig. 10.4 The WATCHMAN device is attached via a central screw insert to a core wire during delivery. ©2014 Boston Scientific Corporation or its affiliates. All rights reserved. Used with permission of Boston Scientific Corporation

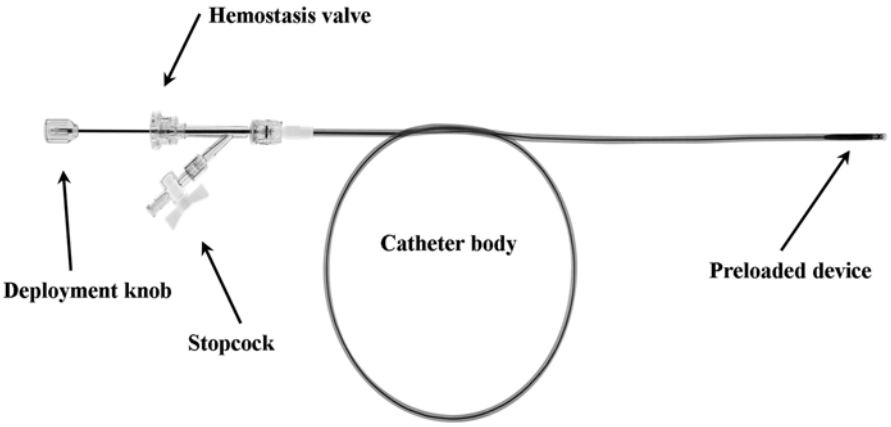


Fig. 10.5 The preloaded WATCHMAN device inside the 12 Fr delivery catheter. ©2014 Boston Scientific Corporation or its affiliates. All rights reserved. Used with permission of Boston Scientific Corporation

Delivery Catheter

The WATCHMAN device is preloaded into a delivery catheter for deployment. It is attached to a core wire via its central screw insert (Fig. 10.4), and the core wire exits the proximal end of the delivery catheter as a rigid control handle and knob. The delivery catheter has a 12 Fr outer diameter, haemostasis Touhy valve, and injection side port with stopcock. The catheter is transparent except for a distal radio-opaque marker band 3 mm proximal to the soft tip end of the catheter (Fig. 10.5).

WATCHMAN Access Sheath

The WATCHMAN access sheath is the platform for instrumenting the LAA and for unsheathing the device into its final deployed position. The access sheath has a 12 Fr inner and 14 Fr outer diameter with a Touhy haemostasis valve and sideport with stopcock. Additional features include distal side vent holes at the catheter tip for contrast injection and a soft atraumatic tip. A distal radio-opaque marker band is used for identifying the sheath during fluoroscopic manipulation and for aligning with the radio-opaque marker on the delivery catheter during loading. Three proximal-grouped radio-opaque marker bands correspond to the approximate level of the device face following deployment for 21, 27, and 33 mm device sizes, respectively (in order of distal to most proximal markers) (Fig. 10.6). The access system consists of the sheath and a tapered rigid vessel dilator. The access sheath has a 75 cm working length and is available in two fixed curves: a 'single curve' with 90° curvature, and a 'double curve' with a secondary terminal superior curvature (Fig. 10.7). There is also an anterior curve access sheath available for challenging anterior-tilt (or retroflex) LAA anatomy.

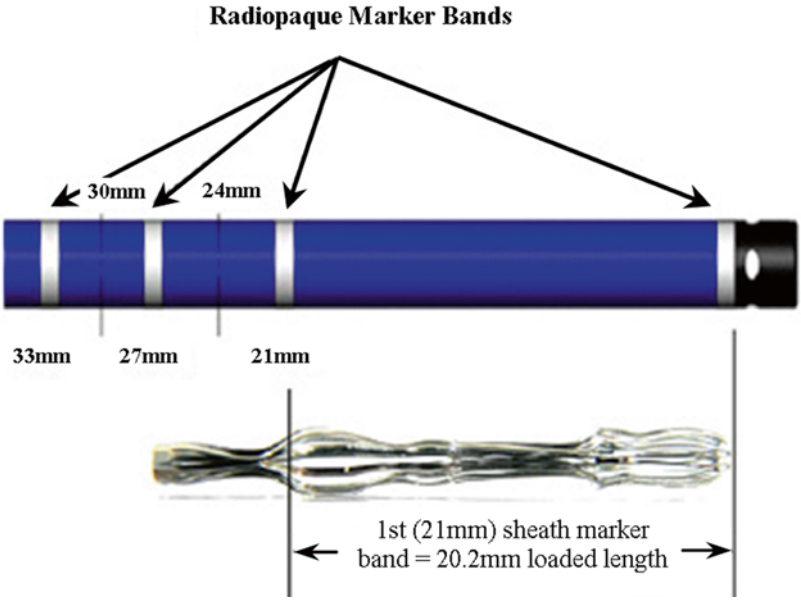


Fig. 10.6 Radiopaque marker bands on the access sheath are *arrowed* at the sheath tip (*right*) and grouped more proximally (*left*). The proximal markers correspond to the approximate level of deployment of the face of the device for each of the device sizes 21 mm, 27 mm, and 33 mm, respectively (from distal to proximal).

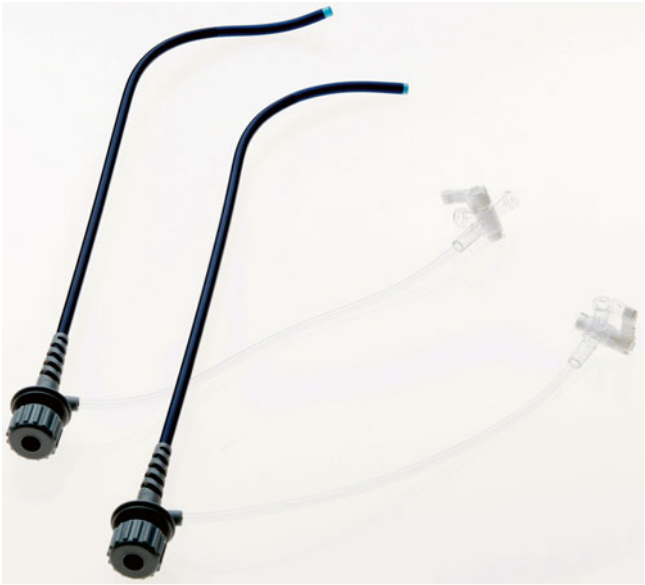


Fig. 10.7 The WATCHMAN access sheath in the two available fixed curves—double and single curves (from *left* to *right*).

Next-Generation 'WATCHMAN FLX' Device

The subsequent generation WATCHMAN device is in development by Boston Scientific at the time of publication. This WATCHMAN FLX device (Fig. 10.8) will incorporate a number of design changes—most significantly the current open exposed distal struts of the device will terminate in a closed design, meeting at a distal nexus. An increased number of struts (18) aims to improve conformability of the device and 12 anchors staggered in two rows at mid and distal locations on the device aim to improve tissue fixation. The device will have a shorter profile (10–20 % depending on device diameter) with the majority of the nitinol frame now covered by the PET fabric. An extended sizing range will be available—20, 24, 27, 31, and 35 mm. Commercialisation of the WATCHMAN FLX device is being proposed for 2015.

Procedural Technique

Pre-procedural Planning

Prerequisite imaging including TEE and also cardiac CT angiography three-dimensional reconstructions are valuable for conceptualising the approach and technique for WATCHMAN device closure in individual patients. This information

Fig. 10.8 The next generation 'WATCHMAN FLX' device in development by Boston Scientific. The distal struts of the device will terminate in a closed design, meeting at a distal nexus. The device has 18 struts, a staggered configuration of fixation anchors, a shorter profile, and increased fabric coverage.

helps to account for variation in interatrial septum, left atrial, and LAA anatomy. A key concept in successful WATCHMAN device implantation is the ability to unsheath the device from a position of sufficient depth within the LAA and that is relatively coaxial with the ostium location.

Because the LAA is typically a structure which arises from the anterior/anterolateral and superior aspect of the left atrium, an optimal sheath trajectory will be achieved by crossing the interatrial septum from a mid to inferior level and generally posterior location (see Fig. 10.9). Anatomical variations of the LAA include a retroflexed chicken wing where the LAA courses posteriorly over the left atrial roof (Fig. 10.10) and are an example of the requirement for significantly more anterior transseptal puncture position. Absolute contraindications to WATCHMAN implantation that must be identified on pre-procedural TEE imaging include LAA thrombus and a maximal LAA ostial diameter of >31 mm.

Device Sizing

Appropriate device sizing is determined by the maximum LAA ostium diameter at the implant zone. The LAA ostium should be imaged in multiple TEE or fluoroscopic planes to determine the maximal dimension. Recommended TEE views are 0, 45, 90, and 135° (see Fig. 10.11). A device larger than the maximal LAA dimension must be selected: the recommended device sizing chart is shown in Table 10.3.

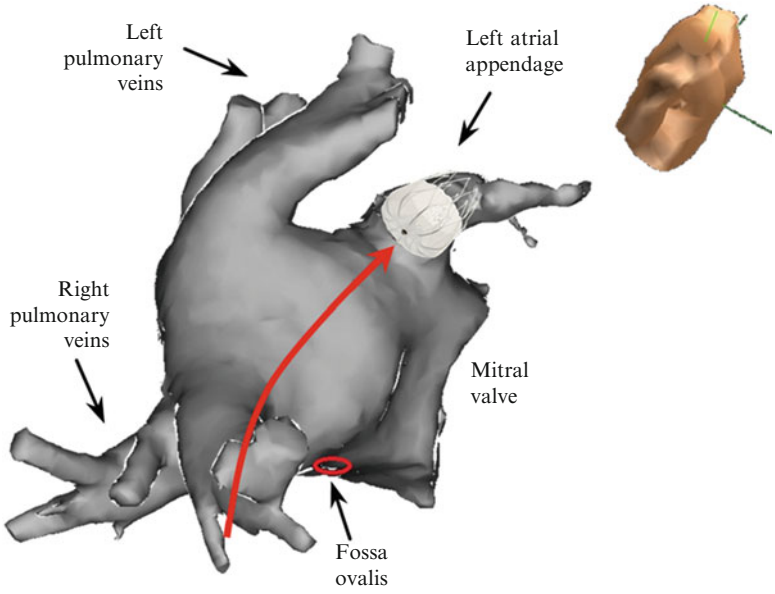


Fig. 10.9 Superior view of left atrium and left atrial appendage from CT reconstruction. *Red arrow* shows preferred sheath trajectory to instrument the long axis of the left atrial appendage. Note this approach begins more posteriorly than mid fossa ovalis location (*red circle*)

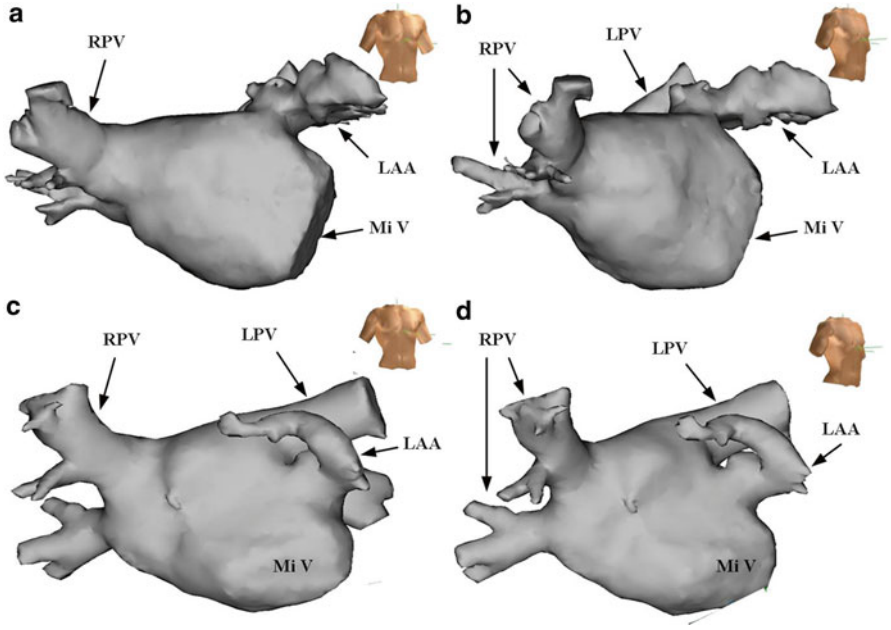


Fig. 10.10 CT reconstructions of two different left atria and appendages. The *upper panel* shows a single-lobed LAA coursing in an anterior direction in (**a**) AP view and, (**b**) RAO view. The *lower panel* shows a single-lobed 'retroflexed' LAA coursing posterior back over the left atrial roof in (**c**) AP view and, (**d**) RAO view. *RPV* right pulmonary vein, *LPV* left pulmonary vein, *LAA* left atrial appendage, *Mi V* mitral valve

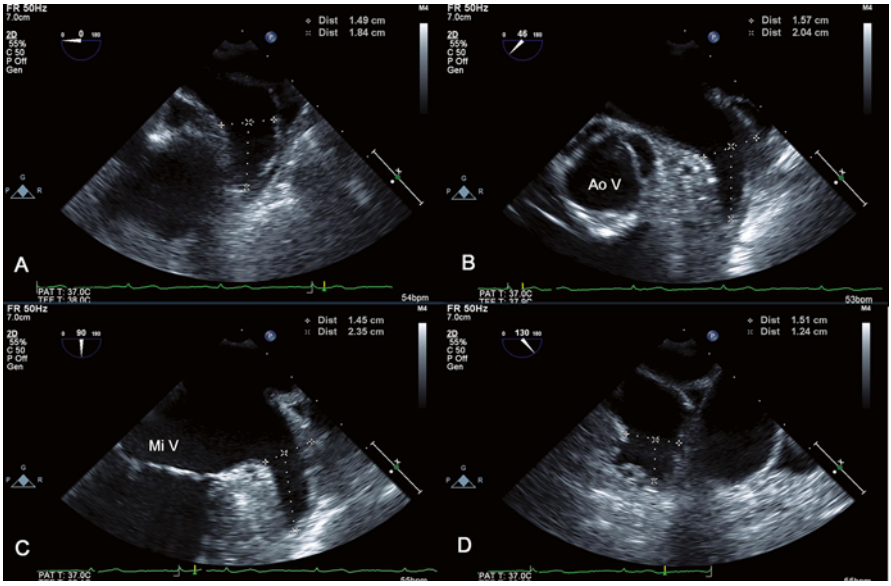


Fig. 10.11 TEE measurements of the LAA ostium performed at recommended angles of 0° (**a**), 45° (**b**), 90° (**c**), and 135° (**d**) for WATCHMAN device sizing. The ostium diameter and LAA depth are measured for each view. (*AoV* aortic valve, *Mi V* mitral valve)

Table 10.3 WATCHMAN® LAA closure-recommended device sizing

Max LAA ostium (mm)	Device diameter (mm)
17–19	21
20–22	24
23–25	27
26–28	30
29–31	33

Vascular Access and Transseptal Catheterisation

Single right femoral vein access is performed by Seldinger technique. Interatrial transseptal puncture is then performed using a transseptal access system (sheath, dilator, and transseptal needle) under fluoroscopic and TEE guidance to achieve an optimal puncture position (Fig. 10.12). Systemic anticoagulation to achieve an activated clotting time of around 250 s may be administered before or immediately after transseptal access.

WATCHMAN Access Sheath Positioning

An exchange length extra support guidewire is advanced through the transseptal sheath and positioned at the left superior pulmonary vein to enable railroading of the larger 14 Fr WATCHMAN access sheath. The transseptal sheath is removed and

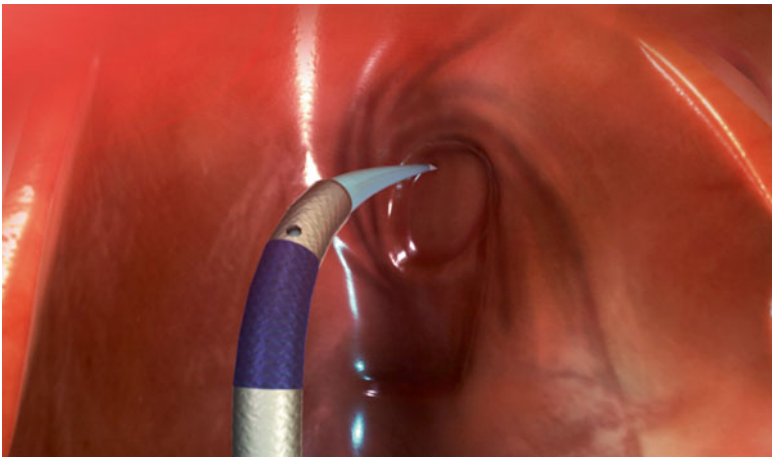


Fig. 10.12 WATCHMAN implant procedure step by step. Transseptal puncture aiming towards posterior aspect of interatrial septum.

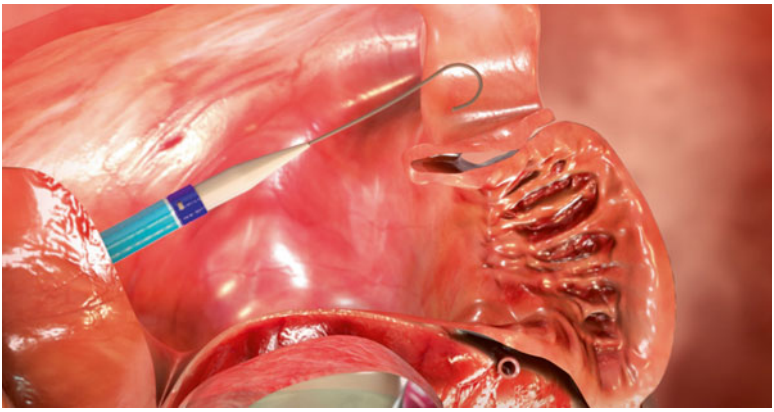


Fig. 10.13 The transseptal sheath is exchanged for the WATCHMAN access sheath over a long, stiff wire positioned out the left pulmonary vein.

exchanged for the WATCHMAN Access sheath (single or double curve) (Fig. 10.13). Caution is required after crossing the atrial septum with the dilator so that it is not advanced past mid-atrial level to avoid damaging other cardiac structures. The soft tip sheath is unlocked from the dilator and advanced further over the support guidewire into the left pulmonary vein ostium. The dilator and guidewire can be removed and the sheath de-aired and flushed. A pigtail catheter is advanced via the access sheath into the left pulmonary vein, de-aired and connected to the catheterisation manifold (contrast/saline/pressure transducer).

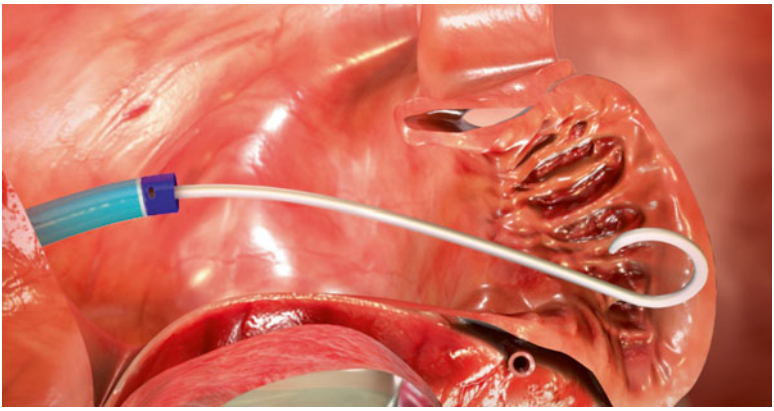


Fig. 10.14 A pigtail catheter is recommended to atraumatically instrument the LAA ahead of the access sheath and to assist with contrast injections.

Left Atrial Pressure Measurement
A mean left atrial pressure of 10 mmHg or greater is recommended prior to proceeding with device implantation to prevent inadvertent undersizing if the LAA is 'underfilled'. Repeat TEE imaging should be performed following intravenous volume loading to re-determine the largest LAA dimension before continuing with the implant procedure.

Using fluoroscopic and TEE guidance, the access sheath and pigtail catheter are repositioned into the LAA (see Fig. 10.14). The pigtail catheter is advanced into the distal LAA and rotated into the desired position using contrast injections and TEE imaging. The access sheath is advanced carefully into the LAA up to the curve of the pigtail, or until the proximal marker band corresponding to the device diameter is at or just distal to the 'landing zone' at the LAA ostium. Further positioning of the pigtail catheter and sheath may be required to achieve the desired sheath depth and angulation compared with the LAA ostium (see Fig. 10.15).

Fluoroscopic Views
RAO views (e.g. 20°) help to 'open out' the long axis of the LAA, while cranial through caudal angulation gives views of the ostium that usually correspond with TEE angles (cranial 20° corresponds with TEE 45°, 0° corresponds with TEE 90°, and caudal 20° corresponds with TEE 135°).

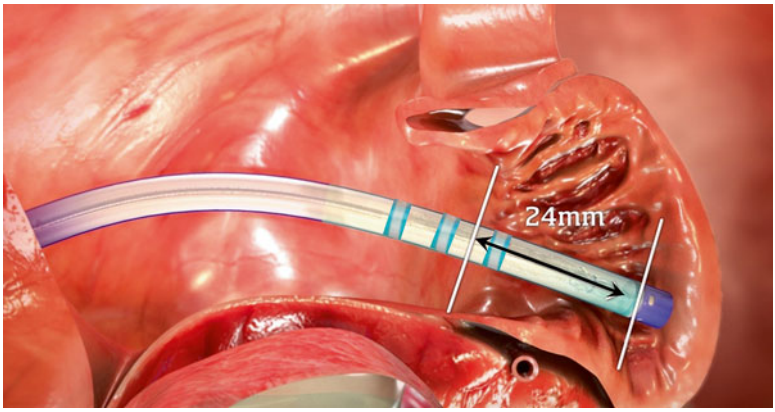


Fig. 10.15 The access sheath must be advanced into the LAA to a depth corresponding to the proposed device size, in this example 24 mm. The *halfway mark* between the distal (21 mm) and mid (27 mm) radio-opaque marker bands should be aligned with the ostium landing zone for the 24 mm device.

Introducing the WATCHMAN Delivery Catheter

Preparation of the WATCHMAN Delivery Catheter (with preloaded device) requires an initial inspection of device integrity and appropriate movement of the device attached to the core wire. The proximal haemostasis valve is loosened and the core wire knob retracted and then advanced again until the device extremity is realigned with the distal marker band on the catheter. The delivery catheter is flushed until all bubbles have been removed. The pigtail catheter is then removed from the access sheath and care taken not to manipulate the sheath while 'unprotected' in the distal LAA. The syringe manifold is then connected to the delivery catheter and pressurised saline flush delivered while the catheter is initially inserted to avoid air entrainment. The delivery catheter is advanced under fluoroscopic visualisation until the distal marker bands of the catheter and the access sheath align. The access sheath is then *retracted* until it snaps onto the connection with the delivery catheter. The appropriate locking of the access sheath and delivery catheter ensures the required support and concurrent action of the outer sheath during 'unsheathing' and 'resheathing' of the device.

WATCHMAN Device Deployment

The device is deployed with an 'unsheathing' action. The haemostasis valve around the core wire knob is loosened. The knob is held fixed while the locked access sheath/delivery catheter is withdrawn steadily to expose the device (Fig. 10.16). Care is taken

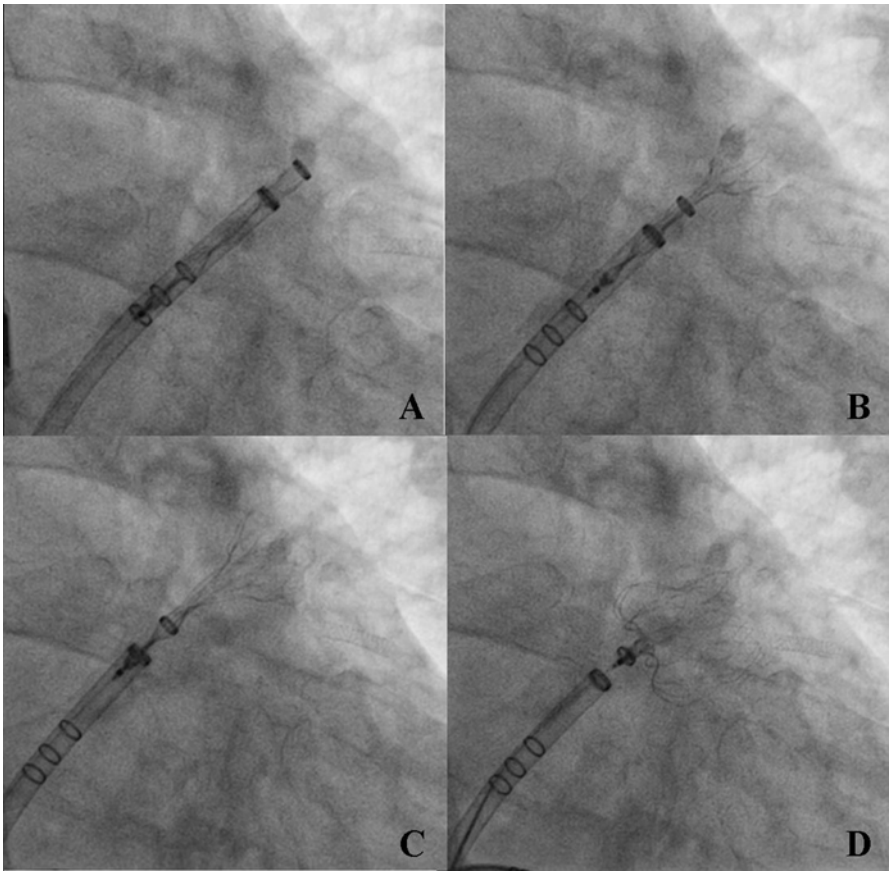


Fig. 10.16 A consecutive series of fluoroscopic images (**a**–**d**) showing progressive unsheathing of the WATCHMAN device during deployment

to withdraw the sheath around 1 cm proximal to the face of the device and to adjust any angulation of the sheath while still attached to the core wire (Fig. 10.17). Device position, stability, and seal are systematically assessed using TEE imaging and fluoroscopy (Fig. 10.18). When optimally positioned, the device should span the entire LAA ostium sitting at or just distal to the ostium and should be covering all lobes. Device protrusion may be acceptable in some angles if the criteria in Table 10.4 are met. The maximum diameter of the implanted device must also meet minimum 'compression' requirements or instability of the implant may result. When properly sized, the device should be compressed 80–92 % of its original size (see Table 10.4.). In practice, greater device compression can also be accepted with satisfactory results. Device seal is assessed in all appropriate TEE and fluoroscopic views with measurement of any residual jet flows around the margin of the device, noting that contrast passage through the permeable PET membrane will be observed (Fig. 10.19). A peridevice leak of ≥5 mm is not considered an appropriate endpoint for the implant procedure. Stability of the implant is

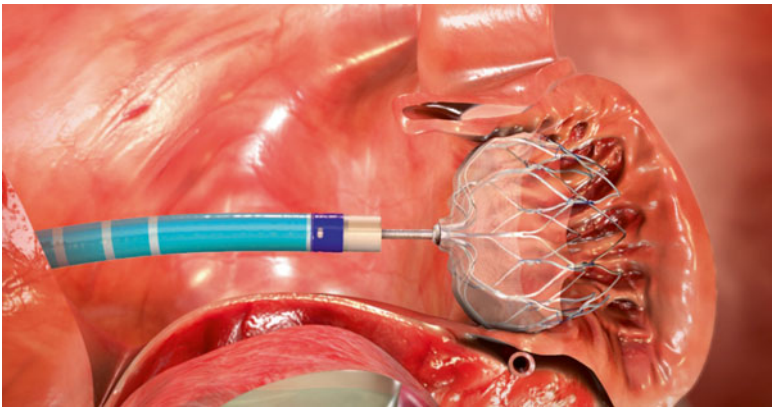


Fig. 10.17 The WATCHMAN device (with core wire still attached) seated in the ostium of the LAA immediately following deployment. ©2014 Boston Scientific Corporation or its affiliates. All rights reserved. Used with permission of Boston Scientific Corporation

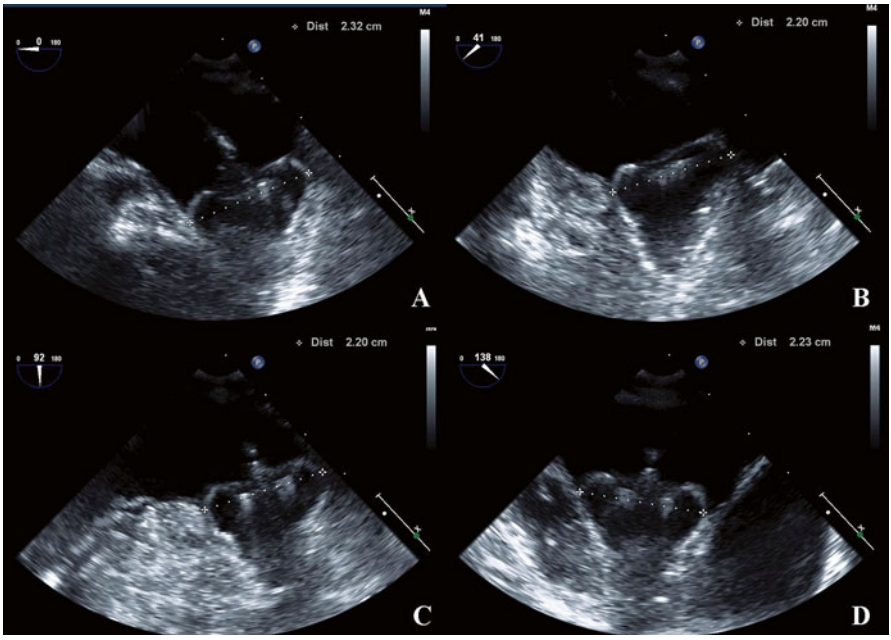


Fig. 10.18 TEE measurements of the maximum deployed device diameter at recommended angles of approximately 0° (**a**), 45° (**b**), 90° (**c**), and 135° (**d**). This 27 mm device has been compressed to between 22.0 and 23.2 mm

further assessed by a 'tug test'. With the haemostasis valve loosened, the core wire is gently retracted and released while the implant stability is assessed on TEE and fluoroscopy. If all of the above device release criteria are not met, the device should be repositioned or removed.

Table 10.4 Deployed WATCHMAN device acceptable parameters

Device size (mm)	Deployed diameter (80–92 % original) (mm)	Acceptable protrusion (mm)
21	16.8–19.3	≤4.2
24	19.2–22.1	≤4.8
27	21.6–24.8	≤5.4
30	24.0–27.6	≤6.0
33	26.4–30.4	≤6.6

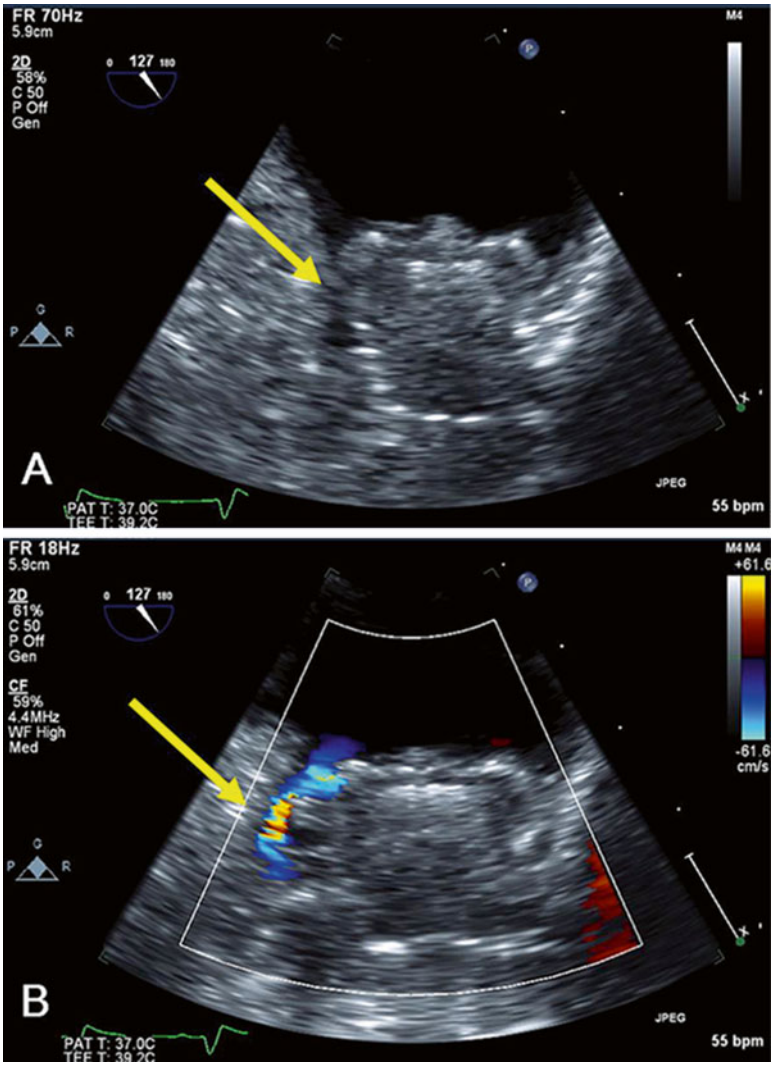


Fig. 10.19 TEE images of a peridevice gap and leak (*arrowed*) as demonstrated on (**a**) 2D, and (**b**) color flow imaging

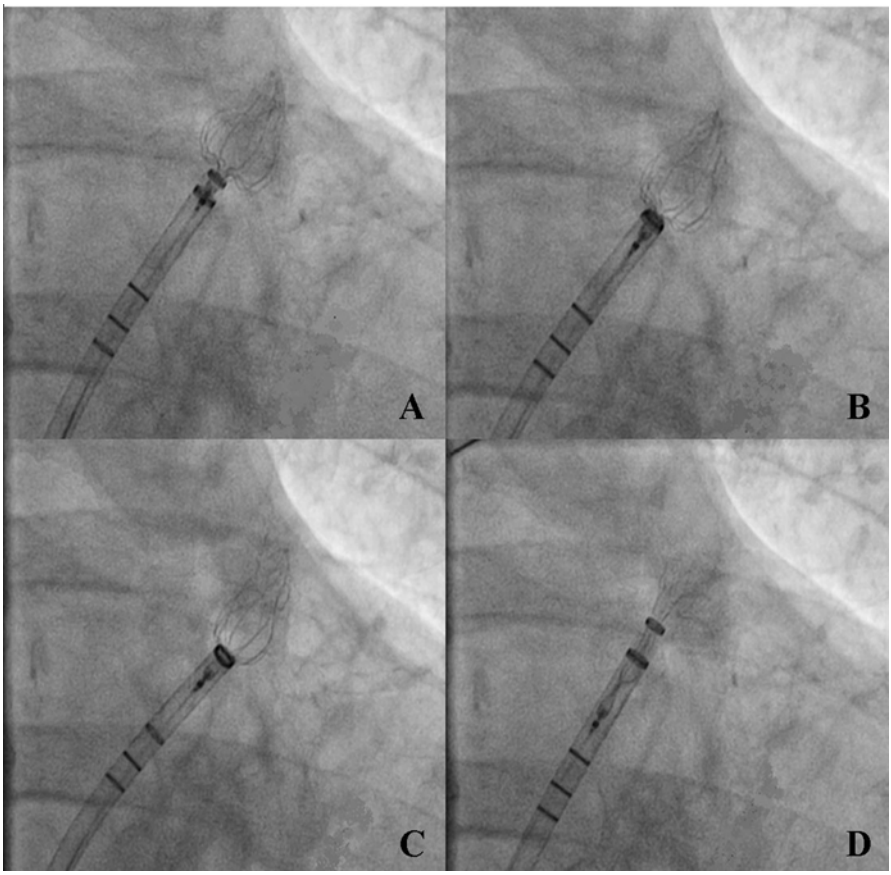


Fig. 10.20 A consecutive series of fluoroscopic images (**a**–**d**) showing progressive resheathing of the WATCHMAN device during 'partial recapture.' Note that the distal struts of the device remain exposed beyond the delivery catheter/access sheath ensemble following a partial recapture

Repositioning the WATCHMAN Device

Resheathing the WATCHMAN device occurs in two stages termed 'partial recapture' and 'full recapture.' With a partial recapture, the widest portion of the device is collapsed down within the access sheath/delivery catheter, but the fixation barbs and distal struts still protrude (Fig. 10.20). A full recapture resheaths the remainder of the exposed device including the barbs and struts. Recapture requires the reverse manoeuvres to deployment. The haemostasis valve is loosened, the core wire knob held fixed while the locked access sheath/delivery catheter ensemble is advanced back over the opened device. Resistance is felt when the device collapses with the partial recapture. Further resistance is felt during advancement of the sheath when the barbs re-enter the delivery catheter during a full recapture.

Repeat deployment of a partially recaptured device can be performed if minor angle correction or withdrawal of the device is required to achieve a more proximal position. A WATCHMAN device deployed too proximally requires full recapture and removal of the delivery catheter, followed by repositioning of the access sheath again using the pigtail catheter. Due to the possibility that the fixation barbs could be damaged during device full recapture, a new device delivery catheter should be selected for further device deployment attempts.

WATCHMAN Device Release

Once a satisfactory position and all device release criteria have been satisfied [i.e., PASS criteria: Position, Anchor (stability, tug testing), Size (device compression 8–20 %), and Seal (residual leak assessment)], the device may be released from the core wire. The haemostasis valve is loosened, the sheath position and angulation adjusted if required, and the core wire knob rotated counterclockwise 3–5 full turns until the core wire separates from the device on fluoroscopy. The core wire is retracted inside the delivery catheter and haemostasis valve closed. Final fluoroscopic images of the implanted device may be taken using contrast injections.

Periprocedural Patient Care

Periprocedural oral anticoagulation or antiplatelet therapy should be individualised at the discretion of the implanting physician. Dual antiplatelet therapy is recommended for up to 6 months post-implant in patients not receiving oral anticoagulation. Intraprocedural anticoagulation should aim for a target activated clotting time of 250 s. Pre-procedural antibiotic prophylaxis should be administered, with endocarditis prophylaxis measures observed for 6 months post-implant. Overnight observation in a cardiac unit is recommended post-implant. Pre-discharge check should include attention to vascular access site and exclusion of pericardial effusion.

Patient Follow-up

A 6-week follow-up TEE study is required to reassess the device position, to identify and measure any residual LAA flow, to assess for device thrombus, and to reassess left atrial structures and residual shunt across the interatrial septum. Device-associated thrombus or a leak around the margin of the device $\geq$5 mm should prompt initiation or continuation of oral anticoagulation. Further follow-up TEE studies at 6, 12 months or beyond may be based on clinical need and documentation of outcome for device thrombus or leaks.

Procedural Complications

The published WATCHMAN clinical trials to-date point to complications being clustered in the early periprocedural period. The most serious recognised complications related to WATCHMAN device implantation include procedure-related stroke, pericardial effusions, device embolization, and device-associated thrombus. Other procedure or device-related complications include vascular access complications (bleeding, hematoma, pseudoaneurysm, arteriovenous fistula), arrhythmia, complications related to general anaesthesia and TEE (airway trauma, esophageal injury, and post-procedure respiratory failure), and intravenous contrast reactions including allergy and nephrotoxicity. Late complications from WATCHMAN implantation remain rare and include a reported death at 16 days from erosion of a distal strut through the LAA wall, resulting in laceration of the left main pulmonary artery [11].

Procedure-Related Stroke

Intraprocedural ischemic stroke was reported in 0.9 % (5/542) of implant procedures in the PROTECT AF randomised trial. Two of the 5 patients sustained long-term disabling neurological deficits. No procedure-related strokes were observed in the subsequent CAP registry and 0.4 % (1/269) rate in the PREVAIL randomised trial. The mechanism of the strokes in PROTECT AF was adjudicated to be due most likely to large volume air embolism from the transseptal access sheath. Procedure-related stroke has been reported in other percutaneous catheter-based left atrial procedures, notably catheter ablation for AF. The factors implicated in intraprocedural thrombus formation and thromboembolic risk have included transseptal sheath management (flushing techniques) [12] and timing and intensity of intraprocedural anticoagulation [13].

Pericardial Effusions

The rate of periprocedural pericardial effusion is approximately 2 % during later experience with WATCHMAN device implantation [5]. A significant reduction in pericardial effusion rates from early PROTECT AF (6.3 %) to later enrolled patients in PROTECT AF (3.7 %) to the CAP registry (2.2 %) and PREVAIL study (1.5 %) has been attributed to operator experience and the procedure 'learning curve' [5].

Eighty-nine percentage of pericardial effusions in the combined PROTECT AF and CAP population were detected within 24 h of the procedure; 76 % (26/34) were drained percutaneously and the remaining 24 % (8/34) underwent surgical intervention (6 of the 8 following attempted pericardiocentesis). A good functional recovery was reported for all cases. A root cause analysis of the pericardial effusions was published for the PROTECT AF trial and included the following factors: initial transseptal puncture

(9 %), from adjunctive device to enter the LAA such as a guidewire or catheter (18 %), manipulating delivery system within the LAA (14 %), protruding delivery sheath from the transseptal access sheath (9 %), WATCHMAN deployment process (18 %), and no definitive cause in 32 % [5]. The depth and calibre of sheath instrumentation into the LAA required during device implantation will continue to pose a risk for intra-procedural cardiac perforation with the WATCHMAN device design.

Device Embolization

Device embolization was first documented in 2 of the 13 initial implants in the pilot feasibility study commenced in 2004 [2]. This led to a design change to include the fixation barbs at the device perimeter. The embolization rate has remained very low with subsequent experience with the current second-generation device—0.6 % in PROTECT AF, 0 % in CAP registry, and 0.8 % in PREVAIL. Device dislodgement has generally been asymptomatic and recognised during the index procedure or detected at subsequent routine TEE follow-up. Percutaneous arterial removal with snare or surgical interventions are all described as removal techniques [5].

Device-Associated Thrombus

Evidence to-date points to WATCHMAN device-associated thrombus being a predominantly asymptomatic finding detected at routine TEE follow-up. The majority of cases have resolved on anticoagulation without clinical sequelae. Device-associated thrombus was subsequently observed in 4.2 % of PROTECT AF patients (20/478 patients), but in only 3 of the 20 patients (15 %) was an ischemic stroke associated. Device-associated thrombus has been reported at similar rates in un-anticoagulated patients—4 % (6/150) in the ASAP study [10] and 5 % (3/59) in a single center registry [12]. Asymptomatic device thrombus was detected at a mean follow-up time of 164 ± 135 days in the ASAP study and at either 42 or 72 days in the single center registry. One associated ischemic stroke was detected at 341 days post-implant in the ASAP study. A European implant registry reported a 7.9 % (3/38) device thrombus rate at 6-week follow-up TEE in a mixed group of patients taking either oral anticoagulation or dual antiplatelet therapy post-procedure [14–15]. All thrombi had resolved by the 12-week follow-up TEE on intensified antithrombotic therapy (Fig. 10.21).

Thrombus characteristics have not been shown to correlate with clinical events—mobile thrombus (laminar or pedunculated) was noted in at least 20 % of asymptomatic PROTECT AF cases detected at follow-up. Device thrombus detected in patients investigated following a stroke in the PROTECT AF follow-up was mobile in 1 and non-mobile in 2.

Clinical management of asymptomatic device thrombus has generally been continuation or initiation of anticoagulation until thrombus resolution; however, one patient in the ASAP study received no treatment without adverse sequelae.

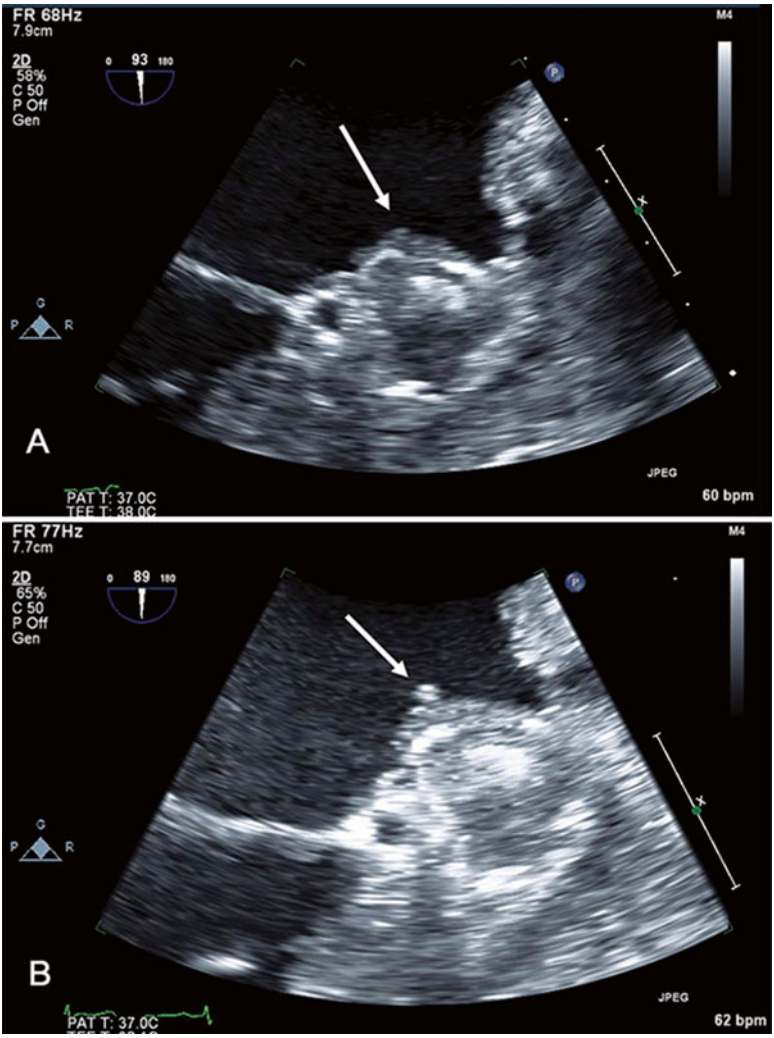


Fig. 10.21 TEE images of (**a**) sessile and (**b**) pedunculated thrombus (*arrowed*) on the atrial surface of implanted WATCHMAN device as detected incidentally at 6-week follow-up study

Clinical Significance of Peri-Device Leaks

Because of the geometric variability of the LAA ostium, a complete seal with the device may not be possible. Frequently, this arises because of an elliptical rather than round shape to the ostium. All LAA device occlusion studies have accepted small peri-device leaks as a successful implant endpoint for 'successful closure' of the LAA [16]. The PROTECT AF study discontinued warfarin at the 45-day

follow-up TEE if a peri-device leak of ≤5 mm was detected. A substudy evaluating the clinical significance of residual peri-device leaks on a composite endpoint of stroke, systemic embolism, and cardiovascular/unexplained death found no association between the presence or size of a leak and adverse outcome [17]. Patients with no peri-device leak who had discontinued warfarin had an event rate of 2.8 per 100 patient years, and for patients with any peri-device leak who had ceased warfarin, the event rate was 2.1. The rates of persistent peri-device leak detected at serial TEE follow-up in the PROTECT AF study appeared to reduce over time—from 40.9 % at 45 days to 32.1 % by 12 months.

Conclusions

A step-by-step approach to LAA closure with the WATCHMAN device is detailed in this chapter. In summary, the WATCHMAN device is the most well-studied LAA occlusion device. Occlusion of the LAA using the WATCHMAN device is a safe and effective alternative to long-term anticoagulation therapy. Attention to detail and proper use of fluoroscopy and transesophageal echocardiography during the procedure minimizes the complications and improves the success of the procedure.

References

1. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P. 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.
2. Sick PB, Schuler G, Hauptmann KE, Grube E, Yakubov S, Turi ZG, Mishkel G, Almany S, Holmes DR. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. J Am Coll Cardiol. 2007;49:1490–5.
3. Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, Halperin JL, Holmes DR. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation 2.3-year follow-up of the PROTECT AF (Watchman left atrial appendage system for embolic protection in patients with atrial fibrillation) trial. Circulation. 2013;127:720–9.
4. Reddy VY, Doshi SK, Sievert H, et al. Long term results of PROTECT AF: the mortality effects of left atrial appendage closure versus warfarin for stroke prophylaxis in AF. In: Proceedings of heart rhythm scientific meeting, Denver; 8–11 May 2013.
5. Reddy VY, Holmes DR, 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.
6. Holmes DR, Doshi S, Kar S, et al. Results of randomized trial of LAA closure vs. warfarin for stroke/thromboembolic prevention in patients with non-valvular atrial fibrillation (PREVAIL). In: Proceedings of China interventional therapeutics conference, Shanghai; 20–23 March 2013.
7. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H,

Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.
8. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.
9. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.
10. Reddy VY, Mobius-Winkler S, Miller MA, Neuzil P, Schuler G, Wiebe J, Sick P, Sievert H. 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.
11. Sepahpour A, Ng MK, Storey P, McGuire MA. Death from pulmonary artery erosion complicating implantation of percutaneous left atrial appendage occlusion device. Heart Rhythm. 2013;10:1810–1.
12. Meincke F, Schmidt-Salzmann M, Kreidel F, Kuck KH, Bergmann MW. New technical and anticoagulation aspects for left atrial appendage closure using the WATCHMAN® device in patients not taking warfarin. EuroIntervention. 2013;9:463–8.
13. Maleki K, Mohammadi R, Hart D, Cotiga D, Farhat N, Steinberg JS. Intracardiac ultrasound detection of thrombus on transseptal sheath: incidence, treatment, and prevention. J Cardiovasc Electrophysiol. 2005;16:561–5.
14. Ren JF, Marchlinski FE, Callans DJ, Gerstenfeld EP, Dixit S, Lin D, Nayak HM, Hsia HH. Increased intensity of anticoagulation may reduce risk of thrombus during atrial fibrillation ablation procedures in patients with spontaneous echo contrast. J Cardiovasc Electrophysiol. 2005;16:474–7.
15. Chun J, Bordignon S, Urban V, Perrotta L, Dugo D, Furnkranz A, Nowak B, Schmidt B. Left atrial appendage closure followed by 6 weeks of antithrombotic therapy: a prospective single-center experience. Heart Rhythm. 2013;10:1792–9.
16. Ostermayer SH, Reisman M, Kramer PH, Matthews RV, Gray WA, Block PC, Omran H, Bartorelli AL, Della Bella P, Di Mario C, Pappone C, Casale PN, Moses JW, Poppas A, Williams DO, Meier B, Skanes A, Teirstein PS, Lesh MD, Nakai T, Bayard Y, Billinger K, Trepels T, Krumsdorf U, Sievert H. Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: results from the international multi-center feasibility trials. J Am Coll Cardiol. 2005;46:9–14.
17. 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.

Chapter 11
WATCHMAN: Trials and Registries Results

Jacqueline Saw, Saibal Kar, and Matthew J. Price

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults, affecting 1–2 % of the general population and over 10 % of individuals over age 80 [1, 2]. With aging of the population, the prevalence of AF and its impact on global healthcare system is projected to increase substantially. The true prevalence of AF may also be underestimated since it may be challenging to detect paroxysmal AF or occult asymptomatic AF. AF is associated with considerable morbidity and mortality, especially being an independent risk factor for stroke, increasing the risk of ischemic stroke by 4–5 fold after adjusting for other risk factors [3]. In fact, AF is detected in up to 19 % of stroke patients over the age of 70 [3]. Furthermore, cardioembolic strokes related to AF are more severe than other types of ischemic stroke and are associated with higher 30-day and 1-year mortality [4, 5]. Annually, 800,000 strokes occur in the U.S., with 1.5 % of these attributed to AF for those under 59 and 23 % of those >80 years of age [3]. Stroke is the third leading cause of death and the number one cause of major morbidity in the U.S. and is estimated to cost the healthcare system ~30 billion dollars annually.

Anticoagulation is the mainstay treatment for reducing the risk of stroke with AF; however, this comes with considerable risks of bleeding with annual major

J. Saw, M.D., F.R.C.P.C., F.A.C.C., F.S.C.A.I. (✉)
Vancouver General Hospital, University of British Columbia,
2775 Laurel Street, Level 9, Vancouver, BC, Canada, V5Z1M9
e-mail: jsaw@mail.ubc.ca

S. Kar, M.D., F.A.C.C.
Cardiovascular Intervention Center Research, Cedars-Sinai Medical Center,
Los Angeles, CA, USA

M.J. Price, M.D., F.A.C.C., F.S.C.A.I.
Division of Cardiovascular Diseases, Scripps Clinic, Scripps Translational
Science Institute, La Jolla, CA, USA

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_11

bleeding of 3–4 % despite the use of novel oral anticoagulants [6–9]. Moreover, 30–50 % of eligible patients do not receive oral anticoagulation due to absolute contraindications or perceived risks of bleeding [10]. Therefore, mechanical strategies to exclude the left atrial appendage (LAA) have been pursued as an alternative for stroke prevention with AF. Numerous devices have been or are being developed for percutaneous LAA closure. The most advanced device in development and clinical studies is the WATCHMAN device (Boston Scientific, Natick, MA). This chapter will focus on the clinical trials that evaluated the WATCHMAN device.

WATCHMAN Regulatory Approvals

The WATCHMAN device was originally developed by Atritech Inc. (Plymouth, MN) and was acquired by Boston Scientific in 2011. This device was first implanted in humans in 2002 and received CE mark in 2005. After three panel deliberations, the WATCHMAN finally received FDA approval on March 13/2015 with relatively broad indications: patients with non-valvular AF at high stroke risk who are suitable for warfarin, and who have appropriate rationale for non-pharmacologic alternative. From a global perspective, WATCHMAN is available in over 50 countries, and >10,000 devices have been implanted to-date.

Fig. 11.1 WATCHMAN clinical trial program

WATCHMAN Clinical Trial Program

The safety and clinical efficacy of the WATCHMAN device has been rigorously evaluated in several registries and randomized controlled trials (Fig. 11.1). Both subsets of patients who are eligible for anticoagulation, or who have contraindications to anticoagulation, were evaluated in these studies. The first pilot feasibility study was approved in 2003 and published in 2007. Since then, two randomized controlled trials and two multi-center registries have been published. Several multi-center registries are ongoing, and further randomized studies and registries will be embarked upon given the recent FDA approval of the device.

Pilot Feasibility Study

This was the first initial worldwide experience with the WATCHMAN device, which consisted of 75 patients enrolled in three European and four US centers [11]. In this open-label non-randomized pilot study, patients >18 years of age with a life expectancy of at least 2 years, with documented chronic or paroxysmal non-valvular AF, who had CHADS2 score of $\geq$1, and who were eligible for warfarin therapy were included. In this initial experience, a few complications occurred with the first-generation device ($n=16$) with 3 device failures (2 embolizations, 1 delivery system failure). The device and the delivery system were altered with the second-generation device, and no further embolization occurred with the updated device/system ($n=59$). Of the 75 patients, 66 (88 %) had successful implantation (7 had unsuitable anatomy, 1 core wire malfunction, and 1 unsuccessful transseptal sheath placement in LAA). Pericardial effusions occurred in 2 patients (2.6 %); one was related to an overly vigorous "tug test," and the tug technique had since been modified as the LAA is thin. At 45 days, 93 % (54/58) devices showed successful sealing of LAA on TEE (LAA completely sealed with absence of flow or with minimal flow around the device with jet of <3 mm). At a mean follow-up of 24 months, no ischemic stroke or systemic embolism occurred. There were two transient ischemic attacks (TIA): 1 at 4 months without thrombus visible on the device, and 1 at 6 months who had a smooth layer of thrombus on device surface. There were two deaths that were not device-related, and there were four device-associated thrombus (5.3 %). Overall, this pilot study provided preliminary data suggesting that LAA occlusion with WATCHMAN was safe and feasible, setting the stage for randomized studies.

PROTECT AF Study

Following the pilot feasibility study, the WATCHMAN device was studied in the multi-centre PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) [12] study. This prospective, randomized controlled trial involved Bayesian sequential design and was conducted at 59 sites in the U.S. and Europe from February 2005 to June 2008. There were 707 patients with non-valvular AF and ≥1 risk factor (age >75 years, hypertension, heart failure, diabetes, or prior stroke/TIA) who were randomized to WATCHMAN ($n=463$) or continued warfarin ($n=244$) in a 2:1 ratio. The mean CHADS2 score was 2.2 and mean age was 72 years. WATCHMAN was successfully implanted in 90.9 %. Warfarin was continued for 45 days with WATCHMAN and switched to clopidogrel for 4.5 months (if there was no peri-device leak, or leak was <5 mm on TEE at 45 days), with aspirin lifelong after implant. The composite primary efficacy event-rates (stroke, systemic embolism, and cardiovascular death) were 3.0 and 4.9 % (per 100 patient-years; relative risk 0.62) at 1065 patient-years follow-up with WATCHMAN and warfarin, respectively, meeting the criteria for non-inferiority (Table 11.1) [13]. However, the primary adverse outcome (procedure-related events and major bleeding) was higher with WATCHMAN (5.5 %/year) compared to warfarin (3.6 %/year; RR, 1.53; 95 % CI, 0.95–2.70). The incidence of serious pericardial effusion was 4.8 %, procedure-related stroke 1.3 % (majority related to procedural air embolism), and device embolization 0.6 %. Warfarin was discontinued in 86 % of patients at 45 days and 92 % at 6 months. At follow-up TEE, device-associated thrombus was seen in 4.2 %; however, device thrombus-associated stroke rate was only 0.3 % per 100 patient-years [14].

With longer follow-up at 1588 patient-years (mean 2.3 years), the primary efficacy event-rates were 3.0 % and 4.3 % in the WATCHMAN and warfarin groups, respectively (RR 0.71; 95 % CI 0.44–1.30 %), still meeting the non-inferiority criteria [15].

At 2621 patient-years (3.8 years) follow-up, the primary efficacy event-rates were 2.3 per 100 patient-years (95 % CI 1.7–3.2) with WATCHMAN and 3.8 per 100 patient-years (95 % CI 2.5–4.9) with warfarin (Table 11.2) [16]. This met both the superiority and non-inferiority criteria, demonstrating a 40 % risk reduction (rate ratio 0.6, 95 % CI 0.41–1.05) of all-cause stroke, systemic embolism, cardiovascular, and unexplained death with WATCHMAN. There was also statistically significant 85 % reduction in hemorrhagic stroke (RR 0.15, 95 % CI 0.03–0.49), 63 % reduction in disabling stroke (RR 0.37, 95 % CI 0.15–1.00), 60 % reduction in cardiovascular death (RR 0.4, 95 % CI 0.23–0.82), and 34 % reduction in all-cause mortality (RR 0.66, 95 % CI 0.45–0.98). The longer-term safety events of procedural safety events and subsequent major bleeding were not significantly different (RR 1.21, $p=0.41$). Major bleeding occurred in 4.8 % with WATCHMAN versus 7.7 % with warfarin. In terms of ischemic stroke, beyond the peri-procedural period, the ischemic stroke events that accrued during follow-up were similar in both groups.

The 5-year (2717 patient-years) results were presented at TCT 2014, and the primary efficacy event-rates were 2.2 per 100 patient-years with WATCHMAN and

Table 11.1 Summary of major published WATCHMAN clinical studies. Adapted from reference [13]

Study	Design	CHADS2	Procedural success	F/U duration	Efficacy events	Safety events
PROTECT-AF [12, 14–16]	*N* = 707 RCT 2 WM: 1 warfarin	2.2 ± 1.2	90.9 %	1065 pt-year (mean 1.8 years)	Primary endpoint: stroke, systemic embolism, CV death: 3.0 % WM, 4.9 % warfarin per 100 pt-year; RR 0.62. Met non-inferiority criteria	Serious pericardial effusion 4.8 %, procedural stroke 1.3 %, device embolization 0.6 %, major bleed 3.5 % (4.1 % warfarin), hemorrhagic stroke 0.2 % (2.5 % warfarin), device-thrombus 4.2 % (with 0.6 % causing stroke)
				1588 pt-year (mean 2.3 years)	Primary endpoint: 3.0 % WM, 4.3 % warfarin per 100 pt-year; RR 0.71. Met non-inferiority	
				2621 pt-year (45 months)	Primary endpoint: 2.3 % WM, 3.8 % warfarin per 100 pt-year; RR 0.6. Met non-inferiority and superiority criteria	Major bleeding 4.8 % (7.4 % warfarin), hemorrhagic stroke 0.6 % (3.7 % warfarin)
PREVAIL [17]	*N* = 407 RCT 2 WM: 1 warfarin	2.6 ± 1.0	95.1 %	18 months	Stroke, systemic embolism, CV and unexplained death at 18 months: 0.064 both groups, RR 1.07. Did not meet non-inferiority (<90 pt 18 months F/U). Ischemic stroke or systemic embolism >7 days met non-inferiority: 0.0253 WM, 0.0201 warfarin	7 days death, ischemic stroke, systemic embolism and procedure complications met non-inferiority criteria (2.2 % WM). Pericardial effusion needing drainage or window 1.5 %. Cardiac perforation 0.4 %. Procedure stroke 0.4 %. Device embolization 0.7 %
CAP [14]	*N* = 460 Registry	2.4 ± 1.2	95.0 %	Median 0.4 year		Procedural stroke 0 %, serious pericardial effusion 2.2 %
ASAP [19]	*N* = 150 Registry	2.8 ± 1.2	94.7 %	14 months	All-cause stroke and systemic embolism 2.3 %/year. Observed ischemic stroke rate was 77 % lower than expected	Serious procedure-related events 8.7 %. Pericardial effusion with tamponade 1.3 %, device embolism 1.3 %, device thrombus 4.0 % (with 0.7 % causing stroke)

RCT randomized controlled trial, *WM* WATCHMAN

Table 11.2 Intention-to-treat primary efficacy and safety events according to treatment group by Bayesian model in the PROTECT AF study (3.8 year follow-up). Adapted from reference [16]

Event	WATCHMAN (*n*=463) observed rate %	Warfarin (*n*=244) observed rate %	WATCHMAN/warfarin rate ratio (95 % Crl)	Non-inferiority posterior probabilities %	Superiority posterior probabilities %
Primary efficacy endpoints	2.30 (1.7–3.2)	3.8 (2.5–4.9)	0.6 (0.41–1.05)	>99	96
– Stroke	1.5 (1.0–2.2)	2.2 (1.3–3.1)	0.68 (0.42–1.37)	>99	83
Ischemic	1.4 (0.9–2.1)	1.1 (0.5–1.7)	1.26 (0.72–3.28)	78	15
Hemorrhagic	0.2 (0.0–0.4)	1.1 (0.5–1.8)	0.15 (0.03–0.49)	>99	99
Disabling	0.5 (0.2–0.8)	1.2 (0.6–1.9)	0.37 (0.15–1.00)	>99	98
Non-disabling	1.0 (0.7–1.7)	1.0 (0.4–1.7)	1.05 (0.54–2.80)	89	34
– Systemic embolization	0.2 (0.0–0.4)	0	NA		
– Cardiovascular or unexplained death	1.0 (0.6–1.5)	2.4 (1.4–3.4)	0.40 (0.23–0.82)	>99	99
Primary safety endpoints	3.6 (2.8–4.6)	3.1 (2.0–4.3)	1.17 (0.78–1.95)	98	20

Table 11.3 Learning curve shown in the early-half of PROTECT AF, compared to the later-half and to CAP registry. Adapted from reference [14]

	PROTECT AF overall study	PROTECT AF early-half study	PROTECT AF later-half study	CAP	P*	P+
Procedure time: min (mean ± SD)	62 ± 34	67 ± 36	58 ± 33	50 ± 21	<0.001	<0.001
Implant success %	89.5	88.2	90.8	95.0	0.001	0.001
Procedural safety events 7d %	7.7	10.0	5.5	3.7	0.007	0.006
Serious pericardial effusion %	5.0	6.3	3.7	2.2	0.019	0.018
Procedural stroke %	0.9	1.1	0.7	0	0.039	0.039

3.7 per 100 patient-years with warfarin (RR 0.61, 95 % CI 0.42–1.07), again meeting both superiority and non-inferiority criteria. There remained a significant 85 % reduction in hemorrhagic stroke (RR 0.15, 95 % CI 0.03–0.49) and 56 % reduction in cardiovascular death (RR 0.4, 95 % CI 0.26–0.9).

CAP Registry

Following completion of the PROTECT AF study, the FDA permitted a Continued Access Program (CAP) non-randomized registry for a subset of PROTECT AF investigators in the U.S. to continue implanting WATCHMAN according to study protocol to gain further safety and efficacy data. This CAP registry showed lower procedural-related events compared to the *early-half* of the PROTECT AF study, with a definite learning curve demonstrated with this complex procedure (Table 11.3) [14]: implant success improved from 88.2 to 95.0 %, procedural duration improved from 67 to 50 min, procedural safety events reduced from 10.0 to 3.7 %, serious pericardial effusion decreased from 6.3 to 2.2 %, and procedural-related stroke decreased from 1.1 to 0 %. The subsequent CAP2 registry enrolled 579 patients and was discontinued in Feb 2014; results have not been reported.

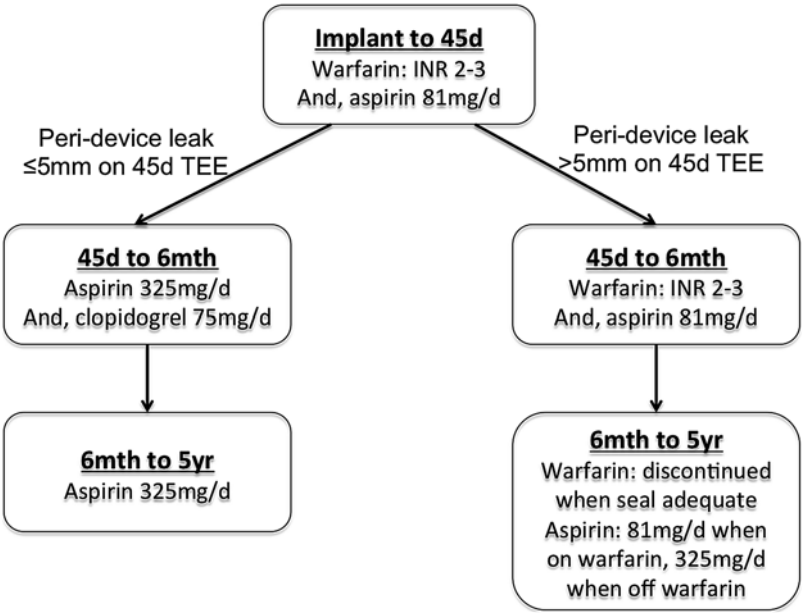


Fig. 11.2 Antithrombotic regimen following WATCHMAN implantation in the PROTECT AF and PREVAIL studies. Adapted from reference [17]

PREVAIL Study

Due to the initial early safety concerns in the PROTECT AF study, the FDA mandated a second randomized trial to confirm the late PROTECT AF and CAP (Continued Access Protocol) registry safety results for regulatory approval. There were also a few potential confounding factors in PROTECT AF, such as the low $CHADS_2$ score threshold for enrolment, the ongoing use of warfarin in the device group, and the discretionary use of antiplatelet agents. Also, there were concerns if study results can be extended to new sites and operators. Thus, the PREVAIL (Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation vs. Long-Term Warfarin Therapy) trial was designed to address these concerns and again utilized Bayesian statistics requiring smaller study size. The PREVAIL study began in 2011, and randomized 407 patients in a 2:1 ratio to WATCHMAN or warfarin [17]. There was a roll-in phase allowing new centers to implant 2 patients prior to the randomization phase. Inclusion criteria was CHADS2 ≥ 2, or CHADS2 $= 1$ if ≥ 1 of the following was present: female ≥ 75 years-old, left ventricular ejection fraction 30–34.9 %, age 65–74 with diabetes or coronary artery disease, or age ≥ 65 with documented congestive heart failure. A minimum of 25 % of cases had to be performed by new operators, and a minimum

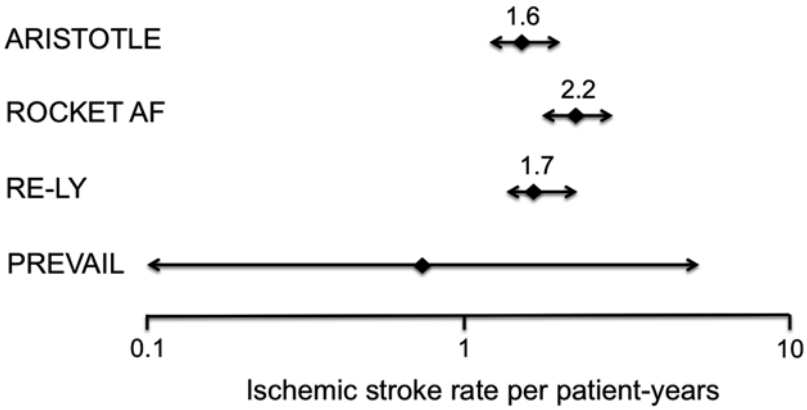


Fig. 11.3 Ischemic stroke rates in warfarin control groups in contemporary AF stroke prevention trials. Adapted from reference [17]

Table 11.4 Comparison of outcomes with WATCHMAN in PROTECT AF, CAP, and PREVAIL studies. Adapted from reference [17]

	PROTECT AF (%)	CAP (%)	PREVAIL (%)	*P* value
Device implant success	90.9	94.3	95.1	0.04
7-day procedural complications	8.7	4.2	4.5	0.004
– Pericardial effusion requiring surgery	1.6	0.2	0.4	0.03
– Pericardial effusion requiring pericardiocentesis	2.4	1.2	1.5	0.318
– Procedure-related Strokes	1.1	0	0.7	0.02
– Device embolization	0.4	0.2	0.7	0.368

of 20 % of cases had to be performed at new sites. Antithrombotic regimen post-device implantation was similar to PROTECT AF (Fig. 11.2).

The mean $CHADS_2$ score was 2.6, and implant success was 95.1 %. The 7-day safety endpoint was 2.2 % with WATCHMAN, which was significantly lower than PROTECT AF, meeting the non-inferiority criteria. Peri-procedural stroke occurred in 0.4 %, device embolization in 0.7 %, and pericardial effusion requiring drainage or window in 1.5 %. At 18-month follow-up, the first coprimary efficacy endpoint (composite of stroke, systemic embolism, and cardiovascular/unexplained death) was 0.064 with WATCHMAN versus 0.063 with warfarin [RR 1.07, 95 % credible interval (CrI): 0.57–1.89] and did not achieve the prespecified non-inferiority criteria (upper boundary of 95 % CrI ≥1.75). The second coprimary efficacy endpoint (stroke or systemic embolism >7 days' post-randomization) was 0.0253 versus 0.0200 [risk difference 0.0053 (95 % CrI: −0.0190 to 0.0273)], achieving non-inferiority. There was no difference in implant success comparing new implanters (93.2 %) to experienced implanters (96.3 %), $p = 0.256$.

The 24-month follow-up results of PREVAIL were presented at TCT 2014, and both coprimary endpoints did not meet non-inferiority criteria. Of note, despite a higher baseline CHADS2 score of 2.6, the observed ischemic stroke rate in the warfarin group in PREVAIL was only 0.7 % per 100 patient-years, which was much lower than contemporary AF stroke-prevention trials (Fig. 11.3). There were also wide confidence bounds due to the small number of patients enrolled. Nevertheless, the key primary safety endpoint was met in this study, and complications and procedural success improved compared to PROTECT AF (Table 11.4).

Meta-Analysis of PROTECT AF and PREVAIL

Recently, a meta-analysis of PROTECT AF and PREVAIL was presented at TCT 2014 by Holmes et al. [18]. The analysis ($n = 1114$) showed comparable efficacy for WATCHMAN and warfarin, with a hazard ratio of 0.79 ($p = 0.22$). Similarly, there was no difference in all-cause stroke or systemic embolization, major bleeding, or all-cause death. Although there appeared to be more ischemic strokes with WATCHMAN (HR = 1.95, $p = 0.05$), there was significant reduction in hemorrhagic stroke (HR = 0.22), which resulted in reduction in disabling stroke by half with WATCHMAN. Moreover, the WATCHMAN device fared better with regard to major bleeding beyond 7 days (HR 0.51; $p = 0.002$) and cardiovascular mortality (HR 0.48; $p = 0.006$).

ASAP Study

The global experience with percutaneous LAA closure involves predominantly patients who are ineligible for oral anticoagulation. To-date, there is no randomized trial in this patient population. The largest registry experience with the WATCHMAN device in this patient cohort is the ASAP (ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology) study. This study enrolled 150 patients with non-valvular AF and CHADS2 ≥ 1 who were ineligible for warfarin [19]. All patients underwent WATCHMAN implantation and were treated with thienopyridine for 6 months and lifelong low-dose aspirin after the procedure. The majority of patients (93 %) had prior bleeding events/tendencies. Mean duration of follow-up was 14-months, and all-cause stroke and systemic embolism was 2.3 % per year. Ischemic stroke occurred in 3 patients (1.7 % per year) and hemorrhagic stroke in 1 patient (0.6 % per year). The observed ischemic stroke rate was 77 % lower than expected based on the CHADS2 of 2.8 in this cohort. Device embolization occurred in 1.3 %, pericardial effusion requiring drainage in 1.3 %, and device-associated thrombus in 4.0 %.

Ongoing Registries

There are several ongoing observational, prospective, multi-center registries outside the U.S. The EWOLUTION study is an international 16 country registries intending to enrol approximately 1000 real-world patients in 50-sites and is near completion. The WASP study is an Asian-Pacific registry intending to enrol 300 patients and is about half-way to completion. The Canadian WATCHMAN Registry is a multi-center Canadian study that recently commenced and is intending to enrol 100 high-risk AF patients with contraindications to anticoagulation.

Future Directions

Given the recent FDA approval of WATCHMAN, it is anticipated that future trials will be launched to evaluate WATCHMAN in the context of different subsets of patient population and geography. It is anticipated that a randomized trial comparing WATCHMAN to a "no device" arm in patients who have contraindications to anticoagulation (ASAP 2) will be conducted. Post-marking registries in the U.S. with WATCHMAN and similar studies in other countries are also anticipated.

Conclusions

Clinical studies have shown LAA closure with the WATCHMAN device to be a safe and efficacious alternative to warfarin in patients with non-valvular AF. Currently, the worldwide practice for WATCHMAN implantation involves predominantly patients with contraindications to anticoagulation. However, this pattern of practice is expected to shift towards patients who are eligible for warfarin, but who have reasons to have non-pharmacologic intervention, according to FDA approval. Ongoing prospective studies, both registries and randomized studies, will likely further establish the efficacy of this device technology in the real-world and other subsets of patient populations with AF.

References

1. 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.
2. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med. 1995;155:469–73.

3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. Stroke. 1991;22:983–8.
4. Marini C, De Santis F, Sacco S, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke. 2005;36:1115–9.
5. McGrath ER, Kapral MK, Fang J, et al. Association of atrial fibrillation with mortality and disability after ischemic stroke. Neurology. 2013;81:825–32.
6. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.
7. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.
8. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.
9. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093–104.
10. Nieuwlaat R, Capucci A, Camm AJ, et al. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on atrial fibrillation. Eur Heart J. 2005;26:2422–34.
11. Sick PB, Schuler G, Hauptmann KE, et al. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. J Am Coll Cardiol. 2007;49:1490–5.
12. 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.
13. Saw J, Lempereur M. Percutaneous left atrial appendage closure: procedural techniques and outcomes. JACC Cardiovasc Interv. 2014;7:1205–20.
14. 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.
15. Reddy VY, Doshi SK, Sievert H, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-year follow-up of the PROTECT AF (Watchman left atrial appendage system for embolic protection in patients with atrial fibrillation) trial. Circulation. 2013;127:720–9.
16. 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.
17. Holmes Jr 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.
18. WATCHMAN II: PROTECT-AF/PREVAIL. Meta-analysis and implications. Dr. David Holmes. TCT 2014, Washington, DC; 2014.
19. Reddy VY, Mobius-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.

Chapter 12
Amplatzer Cardiac Plug and Amulet

Jacqueline Saw

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with current prevalence in the developed world estimated at 1.5–2 % of the general population, and the prevalence is projected to more than double to 15.9 million by 2050 [1]. AF is a major cause of stroke, responsible for 15 % of strokes in persons of all ages and 30 % of strokes in patients age >80 [2]. Strokes associated with AF are more severe with higher mortality and morbidity [3]; AF-related stroke victims have 50 % greater likelihood to become disabled or handicapped, and >50 % likelihood of death, compared to non-AF-related stroke victims [4, 5]. Therefore, stroke prevention with oral anticoagulation (OAC) is one of the main pillars of AF management. Unfortunately, ~50 % of patients eligible for OAC are not receiving OAC in the community [6, 7]. Thus, percutaneous left atrial appendage (LAA) closure as a local stroke-prevention strategy is increasingly being performed worldwide and is expected to increasingly play a dominant role for patients with nonvalvular AF. This is supported by guidelines from the European Society of Cardiology, which recently implemented a class IIB recommendation for LAA closure in AF patients with high stroke-risk and contraindications to long-term OAC [8]. The majority of procedures currently performed in Europe adhere to this guideline as reported by Tzikis of ~1000 patients who underwent LAA closure with the Amplatze Cardiac Plug (ACP) (St Jude Medical, Maple Grove, MN) [9]: 74 % were performed in patients with major bleeding or at high bleeding risk, 23 % in patients with coronary stenting requiring dual antiplatelet therapy, 18 % for drug interaction, 16 % for stroke while on warfarin, 13 % for renal or hepatic disease, 7 % for labile INR, and 7 % for high

J. Saw, M.D., F.R.C.P.C., F.A.C.C., F.S.C.A.I. (✉)
Vancouver General Hospital, University of British Columbia,
2775 Laurel Street, Level 9, Vancouver, BC, Canada, V5Z1M9
e-mail: jsaw@mail.ubc.ca

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_12

risk of falls. In Canada, LAA closure may be performed under the special access program for patients with CHADS2 ≥ 1 and contraindications to long-term OAC. In the United States, the WATCHMAN (Boston Scientific Corporation, Natick, MA) device received FDA approval in March 2015 for patients who are eligible for OAC.

Amplatzer Cardiac Plug and Amulet Device Characteristics

The Amplatzer double-disc devices have been used widely for percutaneous closures of atrial septal defects and patent foramen ovale. Early adopters of percutaneous LAA closure in Europe used non-dedicated Amplatzer devices for LAA closures in a small series of patients [10, 11]; however, the incidence of embolization was high (12 % in the series of 32 patients in Bern) with these non-dedicated devices and they are no longer used for this indication. The dedicated ACP device was specifically designed to occlude the proximal segment of the LAA and is the third LAA device to be manufactured after the PLAATO (Appriva Medical Inc., Sunnyvale, CA) and WATCHMAN devices.

This device is constructed of a self-expanding nitinol mesh that forms a lobe and a larger disc connected by a central waist (Fig. 12.1). Both the lobe and disc have a polyester mesh that is sewn in by hand. The lobe is intended to be implanted at 10 mm within the orifice of the LAA (proximal/neck segment of LAA) and serves as the key anchoring mechanism together with six pairs of stabilizing wires at the distal aspect of the lobe. The disc is intended to be deployed in the left atrium and completely covers the LAA orifice and also pulled in under traction by the central

Fig. 12.1 ACP device

waist that connects to the lobe to give additional seal. This traction pull of the disc against the LAA orifice gives it the appearance of concavity, with separation between the lobe and the disc. The multi-prong mechanisms of occlusion by the lobe and disk, together with the polyester mesh, provide superior seal of the LAA.

The ACP comes in eight different sizes according to the lobe dimension (accommodating diameters 12.6–28.5 mm) (Table 12.1). The second-generation ACP device, Amulet, is similar in design, but has a wider lobe, longer waist, recessed proximal endscrew, and more stabilizing wires (Fig. 12.2). These features improve device stability and theoretically reduce the risk of thrombus formation on the atrial

Table 12.1 Characteristics and differences between Amulet and ACP

Feature	AMPLATZER™ Amulet™								AMPLATZER™ Cardiac Plug							
Size /lobe diameter (mm)	16	18	20	22	25	28	31	34	16	18	20	22	24	26	28	30
Disc diameter	Lobe + 6 mm				Lobe +7 mm				Lobe +4 mm				Lobe + 6 mm			
Lobe length (mm)	7.5				10				6.5							
Waist length (mm)	5.5				8				4							
Stabilizing wires (pairs)	6		8				10		6							
Sheath diameter	12 Fr						14F		9 Fr		10 Fr				13 Fr	
	14 Fr (with adaptor)															

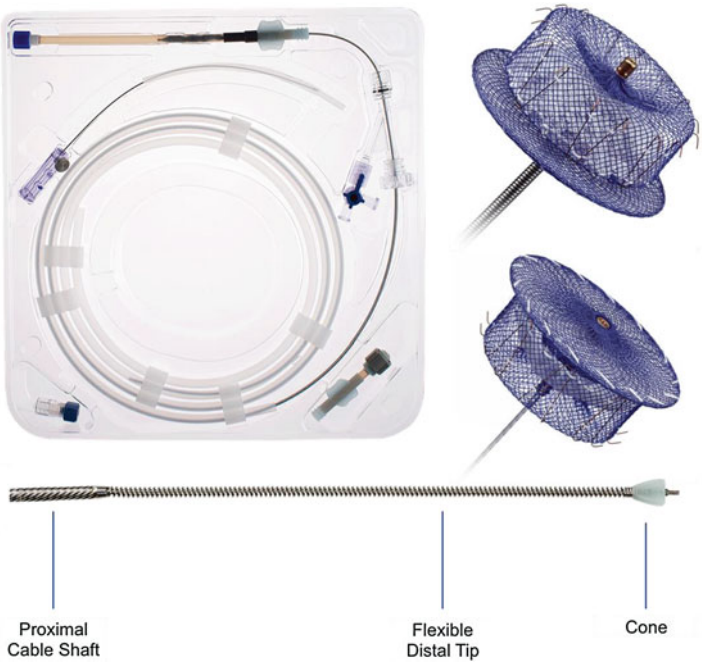


Fig. 12.2 Amulet device, delivery cable, and packaging

side of the device. The Amulet also comes in eight different sizes (Table 12.1) and can accommodate LAA up to 32 mm in diameter (12.6–32 mm). The ACP is implanted through 9–13 Fr sheaths and the Amulet through 12–14 Fr sheaths according to device size. Currently, only the TorqueVue 45 × 45 delivery sheath (100 cm) is being manufactured for ACP and Amulet (Fig. 12.3). This sheath has a third-dimensional distal tip that allows anterior and superior angulation of the sheath tip, enabling coaxial position at the landing zone. The TVLA 1 and TVLA 2 sheaths are no longer being manufactured since they were not found to be useful or adopted by operators.

The ACP device has to be manually loaded onto the delivery cable, and readers are directed to the manufacturer's instruction for use for device preparation. The Amulet device comes preloaded on the delivery cable for ease of setup. Following initial release, the Amulet was subsequently temporarily removed from the market to re-design the delivery system for ease of use. The Amulet was re-launched in October 2014 with the delivery system simplified to remove the core-wire dissociation feature and now consists of a single-component delivery cable (the actual Amulet device was unchanged) (Fig. 12.2). The ACP received CE Mark approval in December 2008 and the Amulet in January 2013. The first human implant of Amulet was performed in July 2012 in Montreal [12].

Implantation Technique

Preprocedural Imaging

Baseline transesophageal echocardiogram (TEE)or cardiac computed tomography angiography (CCTA) is important to exclude pre-existing LAA thrombus and assess for suitability for LAA closure, especially for sizing and device selection. TEE is the conventional standard pre-procedural imaging and multiple views should be evaluated, including a complete sweep from 0 to 180° for complete evaluation of the LAA, and with multiple measurements taken at 30° intervals. In particular, baseline measurements at both short-axis (30–60°) and long-axis (120–150°) of the landing zone and orifice are important. The LAA measurements are usually wider at the long-axis (which corresponds to the caudal projection on fluoroscopy), compared to the short-axis (corresponds to the RAO cranial view). For ACP, the LAA orifice represents the line from the pulmonary vein ridge to the atrial-side of the circumflex artery (echocardiographic LAA ostium) (Fig. 12.4). The landing zone is measured at 10 mm within the orifice at an angle that is perpendicular to the axis of the neck (proximal segment of the LAA). The depth of the LAA is measured from the orifice to the back wall of the appendage along the axis of the neck. For the Amulet device, the landing zone is ~12 mm (12–15 mm) from the orifice, due to the wider lobe dimensions (Table 12.1).

Best used if the angle of the LAA neck ≤40°			Best used if the angle of the LAA neck >40° and ≤70°			Best used if the angle of the LAA neck >70°		
Sheath Size (French)	Tip Angle	Usable Length (cm)	Sheath Size (French)	Tip Angle	Usable Length (cm)	Sheath Size (French)	Tip Angle	Usable Length (cm)
9	45°x45°	100	9	45°	80	9	45°x20°	80
10	45°x45°	100	10	45°	80	10	45°x20°	80
13	45°x45°	100	13	45°	80	13	45°x20°	80

Fig. 12.3 Delivery sheaths for ACP/Amulet: TorqueVue (TV) 45×45, TVLA1, and TVLA 2

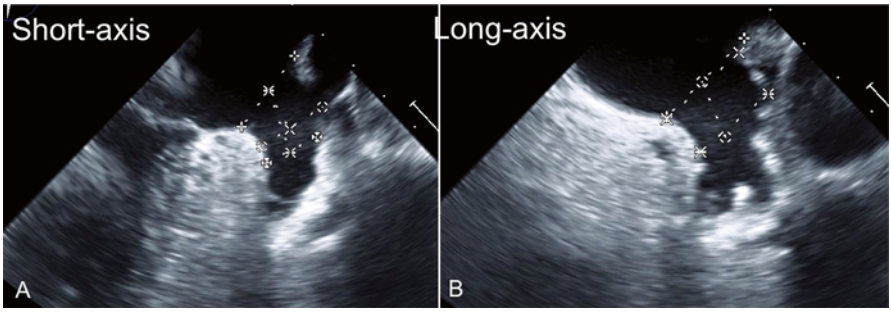


Fig. 12.4 TEE measurements for ACP/Amulet in the short-axis (**a**) and long-axis (**b**) views, of both the echocardiographic LAA ostium and the landing zone (10 or 15 mm inside of the ostium for the ACP and Amulet, respectively)

Pre-procedural cardiac CT angiography (CCTA) is also useful to examine LAA anatomy and dimension, given the superior spatial resolution and three-dimensional portrayal of cardiac structures. Moreover, CCTA is good for ruling out LAA thrombi, especially when double-contrast injection, delayed imaging, dual-energy, and prone positioning are employed (negative predictive value 100 %) [13]. Patients also need not be fasting prior to CCTA and saline infusion is typically administered before scans, which provides more accurate measurements at euvolemic states. Thus, CCTA may be a non-invasive alternative to TEE in experienced CCTA centers and is increasingly routinely performed prior to LAA closures. We routinely perform baseline CCTA for all LAA cases, which help strategize device selection and approach to closure (see Chap. 8).

Procedural Imaging

Procedural TEE is the routine standard in the majority of centers and is usually accompanied by general anaesthesia. There are a few centers adept with and use procedural intracardiac echocardiography (ICE) to guide LAA closure, avoiding the need for general anaesthesia. However, obtaining adequate ICE LAA images can be challenging, and operators may overcome this problem by advancing the ICE probe into the left atrium through another transseptal puncture (see Chap. 7). Although very limited centers rely on fluoroscopy alone during LAA closure, this approach is not generally advised.

Transseptal Puncture

Venous access is preferred through the right femoral vein for easier and more direct transseptal access. The subcutaneous tissue at the access site should be well-separated and dilated with scalpel and forcep to ease advancement of large 13–14 Fr sheaths. Manual compression, "figure-of-8" suture, and pre-closing with 6 Fr Perclose are various approaches used for venous hemostasis.

The optimal location for transseptal puncture for LAA closure is inferior and posterior at the fossa ovalis. This position is well-visualized with the bicaval and short-axis TEE view, respectively (Fig. 12.5). ICE is a good alternative to guide transseptal puncture. The patent foramen ovale should not be used for sheath access as the resulting transseptal angle is not optimal for co-axial approach to the LAA. Instead, it is advised to perform a separate transseptal puncture inferoposteriorly to provide a more direct vector orientation to access the LAA, which arises anteriorly and superiorly. Intravenous heparin is administered before or immediately following transseptal puncture to maintain ACT >250 s. Adequate mean left atrial pressure (>12 mmHg) should be attained with fluid bolus for accurate LAA measurements.

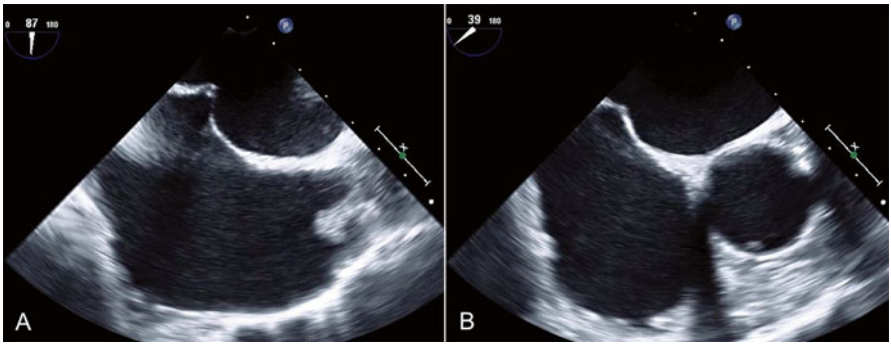


Fig. 12.5 Transseptal puncture inferoposteriorly with TEE guidance: (**a**) bicaval view aiming for inferior position, and (**b**) short-axis view aiming for posterior puncture

Fluoroscopic LAA Measurements

Following transseptal access, a 5F marker pigtail is advanced into the LAA and cineangiograms are taken in multiple projections to ascertain the LAA anatomy and measurements (Fig. 12.6). Baseline CCTA can help predict the best fluoroscopic angles during the procedure. For ACP, we usually start with right anterior oblique (RAO) 30° cranial 10°, RAO 30° cranial 30°, and anteroposterior (PA) caudal 20–30° projections. Both fluoroscopic landing zone and orifice diameters are measured as per the TEE described above. The typical implant view used for the ACP device is RAO 30° cranial 10°, which is best to visualize the proximal LAA and orifice.

Access Sheath Advancement

To cross the interatrial septum with the delivery sheath safely, we typically advance a long (260 cm) J-tipped stiff 0.035″ wire (e.g. Amplatz Super Stiff™ J-tip 3 mm curve) into the left upper pulmonary vein (LUPV) as a rail support.

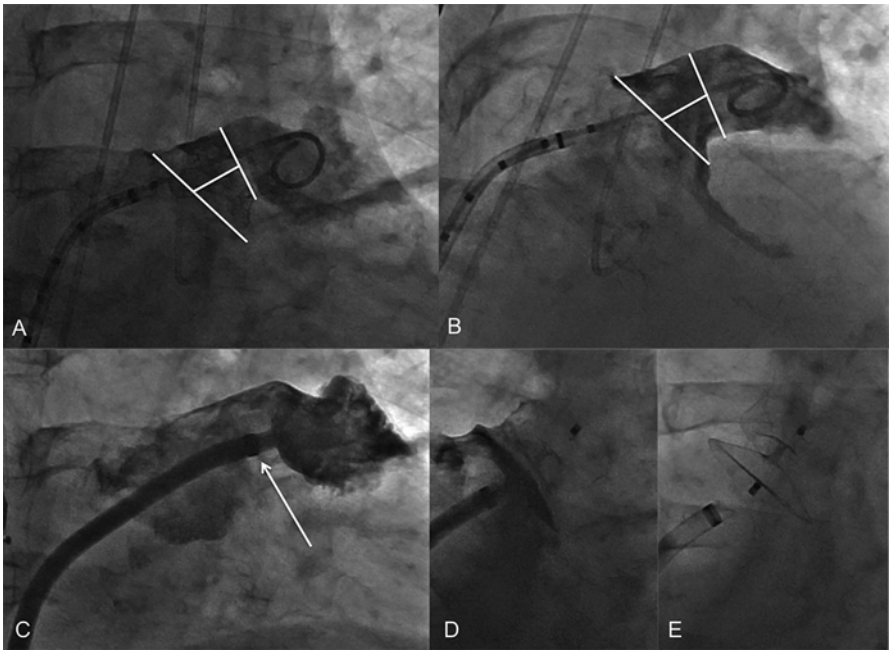


Fig. 12.6 Fluoroscopic measurements for ACP/Amulet: (**a**) RAO 30° cranial 10° view (*lines* representing where measurements of the orifice and the landing zones were taken), (**b**) RAO 30° cranial 30° view, (**c**) placement of the delivery sheath (tip pointed by the *arrow*) at the landing zone before device deployment, (**d**) assessment of ACP device positioning before release, (**e**) released ACP device

The appropriately sized TorqueVue 45×45 delivery sheath is then advanced to the LUPV ostium over the stiff wire. The delivery sheath should be gently rotated during advancement to achieve coaxial approach when crossing the interatrial septum. The TorqueVue sheath tip is advanced to the LUPV orifice over the stiff J-wire, and the dilator and wire are removed and de-aired carefully. The sheath is then withdrawn slightly and counterclocked to fall into the LAA ostium. Alternatively, a J-wire or pigtail may be used to engage the LAA to minimize traumatizing the thin left atrium.

ACP/Amulet Sizing and Implantation Steps

ACP/Amulet sizing is based on the widest diameter of the landing zone measured on fluoroscopy or TEE. An accepted recommendation is to upsize the device by 3–5 mm for ACP and 2–4 mm for Amulet according to the widest landing zone diameter (Table 12.2). This degree of oversizing improves stability of the device. In addition, oversizing and achieving adequate lobe compression may improve the seal of the device and potentially lower the chance of residual leak into the LAA as we have shown on CCTA follow-up [14]. However, dramatic oversizing should probably be avoided, especially in the case of very elliptical landing zones (where the widest diameter is >6 mm larger than the narrowest diameter) where the tendency is to upsize according to the widest diameter. This may lead to dramatic oversizing of the narrowest dimension, which often results in the lobe being extruded out of the LAA.

The selected prepped device is then advanced to the tip of the delivery sheath, which is positioned at the landing zone of the LAA (10 mm from the orifice for ACP, and 12–15 mm for Amulet) (Fig. 12.6). The first step of ACP/Amulet deployment is unsheathing by withdrawal of the delivery sheath to deploy the "ball" (Fig. 12.7). Once the "ball" is formed, the system can be advanced or withdrawn relatively safely within the LAA to achieve optimal position. The remainder of the lobe is then deployed by a "push-pull" manoeuvre, which often requires

Table 12.2 Recommended landing zone measurements and Amulet sizing

Maximum landing zone width (mm)	Amulet™ device size	Lobe length (mm)	Minimum LAA depth (mm)	Disc diameter (mm)	Sheath diameter
11.0–13.0	16	7.5	>10	22	12 or 14 Fr (with adaptor)
13.0–15.0	18	7.5	>10	24	
15.0–17.0	20	7.5	>10	26	
17.0–19.0	22	7.5	>10	28	
19.0–22.0	25	10	>12	32	
22.0–25.0	28	10	>12	35	14F
25.0–28.0	31	10	>12	38	
28.0–31.0	34	10	>12	41	

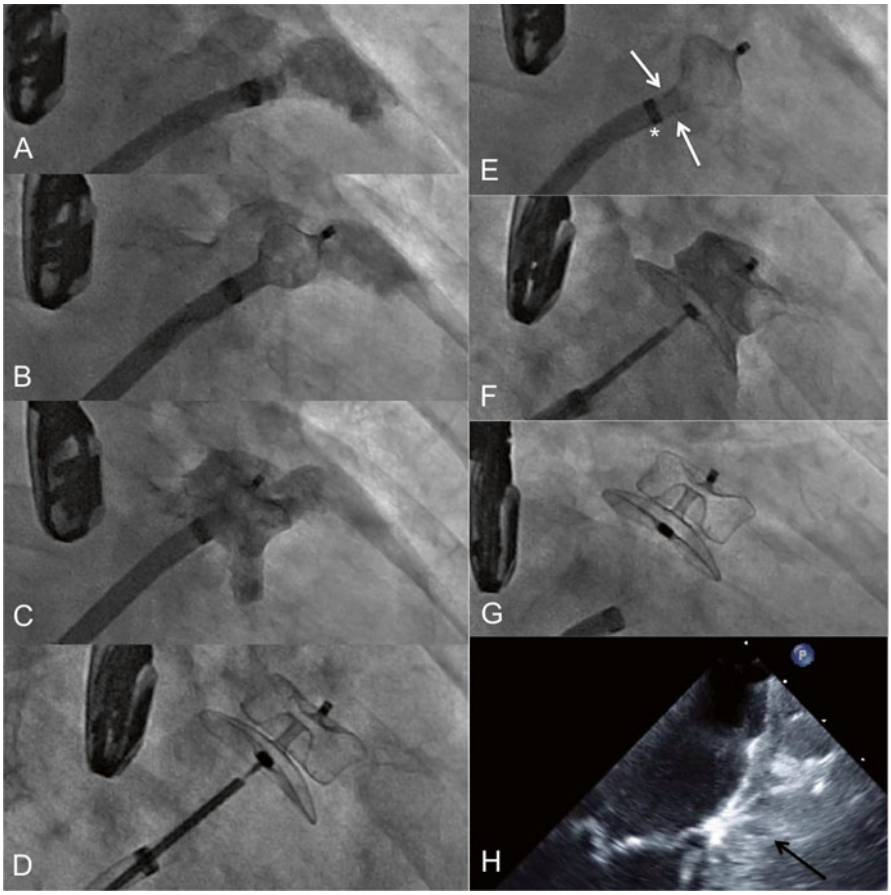


Fig. 12.7 Procedural steps for ACP/Amulet implantation: (**a**) TorqueVue 45×45 sheath tip at the landing zone of the LAA, (**b**) deployment to the ball-shape configuration, (**c**) deployment of the entire lobe, (**d**) deployment of the disc in the left atrium, (**e**) partial recapture of the device, making sure that the two dots (*arrows*) do not enter the radio-opaque marker band of the sheath (*asterisk*), (**f**) redeployment of the lobe and disc in the proper position, (**g**) release of the ACP/Amulet device, and (**h**) TEE showing that the lobe of the device is inside of the circumflex artery (*arrow*)

concomitant counterclock rotation of the sheath to allow co-axial positioning of the lobe for full contact against the LAA neck. The lobe is then assessed for good positioning on cineangiogram and TEE. The disc is then deployed in the left atrium to cover the LAA orifice, and this step requires slight traction of the delivery cable during unsheathing of the disc to separate the lobe from the disc. If device positioning is unsatisfactory at any point prior to release, the disc and lobe can be re-sheathed into the "ball" configuration, as long as the two platinum markers on the lobe do not enter the radio-opaque band on the sheath (which marks the location of the stabilizing wires at the tip of the sheath) (Fig. 12.7). If a different device size is required,

the device may be completely withdrawn, but it is recommended that the sheath should be replaced before introducing the new device.

There are five criteria for good deployment that should be met before releasing the ACP/Amulet device: (1) tire-shaped lobe (ensures adequate compression of the lobe and engagement of stabilizing wires), (2) separation of the lobe and disc (ensures that the disc is pulled in against the LAA orifice with good seal), (3) concavity of the disc (indicating traction of the disc against the lobe with good seal), (4) axis of the lobe perpendicular to the neck axis at the landing zone (ensures proper contact of lobe and stabilizing wires against the LAA), and (5) lobe is ≥2/3 within the circumflex artery TEE (ensures that device is deep enough) (Fig. 12.7). If there is uncertainty about device stability, a gentle tug test may be performed by slight pulling of the disc but vigorous wiggle testing should be avoided. The device may also be observed for several minutes to ensure stability without any device movement prior to release. The presence of residual leak is assessed on TEE with the Nyquist limit lowered to 50 cm/s, and contrast injection is performed through the delivery sheath to assess for optimal positioning and appendage opacification. If satisfactory position is achieved, the device is released with counterclock rotation of the delivery cable.

Procedural and Late Complications

Since the launch of the ACP device in 2008, over 10,000 devices have been implanted worldwide to-date for LAA closures. ACP was evaluated in several small retrospectively registries mostly involving single center experience in Europe, Canada, Asia, and Latin America [11, 15–23]. In aggregate, over 1100 patients were included in these separate registries, showing good safety profile, with serious pericardial effusion ~1.7 %, device embolization ~1.1 %, ischemic stroke ~0.4 %, and procedural success ~96.4 %. The first European experience (pre-CE mark) in 143 patients was published in 2011 [15], and the follow-up European post-CE mark approval registry was presented at EuroPCR in 2012 ($n = 204$) [23]. In this more recent study, the procedural success was 96.6 %, and in 89.2 % of cases the first device selected was implanted successfully. Procedural stroke was 0 %, serious pericardial effusion 1.5 %, and device embolization 1.5 %. Device thrombus was seen in 2.4 % at follow-up TEE. The observed annual stroke rate was 1.98 % with ACP, which was 65 % lower than expected based on the CHADS2 score.

More recently, Tzikas et al. presented a pooled analysis of 969 patients who underwent ACP implantation mostly in Europe [9]. The implantation success rate was 97.2 %, and in 93.2 % of cases the first device selected was implanted. With follow-up TEE, the closure rate (<3 mm residual flow) was 97.6 %. The rate of 7-day peri-procedural major adverse events (death, ischemic stroke, systemic embolism, and procedure or device-related complications requiring major cardiovascular or endovascular intervention) was 4.13 %, with mortality 0.6 %, pericardial tamponade 1.2 %, device embolization 0.2 % (that required surgical retrieval), and

stroke 0.7 %. The observed annual stroke rate was 2.1 %, which was 63 % lower than the estimated 5.62 % stroke rate based on the CHA2DS2-VASc Score.

The US pivotal randomized-controlled trial of ACP versus OAC (warfarin or dabigatran) was discontinued in December 2013 after ~80 patients were enrolled due to slow enrolment and imminent FDA approval of the WATCHMAN device. A new re-designed randomized study is anticipated to involve non-inferiority comparison to WATCHMAN.

Overall with increased operator experience, ACP/Amulet implantation can be performed with low peri-procedural ischemic stroke-risk of <0.5 %, serious pericardial effusion 1–2 %, and device embolization 0.5–1 %. Ischemic strokes may occur due to air-embolism from inadequate device preparation or poor technique, or from thrombus in the LAA or developing on equipment. Baseline imaging to exclude pre-existing LAA thrombus, adequate procedural anticoagulation with ACT >250 s, and meticulous techniques are important to minimize thromboembolism. Pericardial effusion risk can be minimized by careful wire, sheath, and device manipulations in the left atrium and LAA. Using a pigtail to guide sheath advancement into the LAA can minimize such risks. Pericardial tamponade requires emergent pericardiocentesis, sometimes requiring pericardial window or surgical intervention for cardiac perforation. Device embolization with the ACP/Amulet device can usually be managed by percutaneous retrieval (see Chap. 18). A large arterial sheath that is at least 2 Fr larger than the implanting delivery sheath is required to retrieve the embolized device, in conjunction with loop-snares and sometimes bioptomes. Embolized ACP trapped in the left ventricle, left atrium, and aorta had been successfully retrieved. However, surgical removal may be required if the device is trapped by tissues (such as papillary muscles or trabeculations), or if the device cannot be fully retracted into the large sheath, or if the operator is unable to percutaneously capture the device.

Longer-term potential issues include thrombus on device and residual leak, thus follow-up TEE or CCTA at ~3–6 months post-procedure should be routinely performed, and preferably with repeat at 1 year. For ACP, no leak >5 mm has been documented, leak 3–5 mm was reported in 0–1 % of cases [23], and leak <3 mm was reported in 0–16 % of cases. This is lower than what was reported for WATCHMAN, where some degree of leak was seen in 32 % of cases in the PROTECT-AF study at 12-month follow-up, but this was not associated with increased risk of thromboembolism [24]. The apparent superior closure with ACP is presumably related to the double-disc design. With follow-up CCTA, we identified residual leak into the LAA (patency) in over 60 % of cases [14], which is much higher than reported with TEE presumably due to the much higher sensitivity of CCTA to diagnose even small leaks. However, the consequence of residual leaks with ACP/Amulet has not been explored.

Device thrombus formation may occur in 2–5 % of cases with ACP, which tended to occur on non-endothelized device protrusions of the proximal endscrew, especially with deep implants. Thus, deep implantations, especially those causing uncovered trabeculations and recesses, should be avoided. The newer design of Amulet with recessed proximal endscrew theoretically allows faster and more complete endothelialization. Although there is no consensus, atrial-side device

thrombus is usually managed with anticoagulation (OAC or low-molecular-weight heparin) for 8–12 weeks, with repeat imaging (TEE or CCTA) to assess for thrombus resolution before discontinuing anticoagulation. Reported thromboembolic stroke event-rate related to device-thrombus is low at 0.3–0.7 % [25, 26].

Conclusions

In summary, there has been a large real-world experience with the ACP device in the past 5 years, and a recent large multicenter registry involving almost 1000 patients revealed a good safety profile. A randomized trial comparing Amulet to WATCHMAN is anticipated in the near future. At the meantime, the current worldwide experience with the ACP device predominantly involves patients who are not candidates for long-term anticoagulation (or perceived poor candidates). The Amulet device was re-launched recently, and real world experience is awaited from post-marketing registry, with regards to the expected improvement in device stability, lower device thrombus, and clinical efficacy.

References

1. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006;114:119–25.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham study. Arch Intern Med. 1987;147:1561–4.
3. Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham study. Stroke. 1996;27:1760–4.
4. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham study. Stroke. 1991;22:312–8.
5. Lamassa M, Di Carlo A, Pracucci G, et al. Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (The European Community Stroke Project). Stroke. 2001;32:392–8.
6. Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Ann Intern Med. 1999;131:927–34.
7. Kakkar AK, Mueller I, Bassand JP, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. PLoS One. 2013;8:e63479.
8. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012;33:2719–47.
9. Tzikas A. LAAO for stroke prevention in AF: multicenter experience with the Amplatzer cardiac plug. Transcatheter cardiovascular therapeutics—San Francisco; 2013.
10. Meier B, Palacios I, Windecker S, et al. Transcatheter left atrial appendage occlusion with Amplatzer devices to obviate anticoagulation in patients with atrial fibrillation. Catheter Cardiovasc Interv. 2003;60:417–22.

11. Nietlispach F, Gloekler S, Krause R, et al. Amplatzer left atrial appendage occlusion: single center 10-year experience. Catheter Cardiovasc Interv. 2013;82:283–9.
12. Freixa X, Chan JL, Tzikas A, Garceau P, Basmadjian A, Ibrahim R. The Amplatzer cardiac plug 2 for left atrial appendage occlusion: novel features and first-in-man experience. EuroIntervention. 2013;8:1094–8.
13. Romero J, Husain SA, Kelesidis I, Sanz J, Medina HM, Garcia MJ. Detection of left atrial appendage thrombus by cardiac computed tomography in patients with atrial fibrillation: a meta-analysis. Circ Cardiovasc Imaging. 2013;6:185–94.
14. Saw J, DeJong PM, Lempereur M, et al. Cardiac CT angiography follow-up of left atrial appendage closure with the Amplatzer cardiac plug. Catheter Cardiovasc Interv. 2014;83:S91.
15. Park JW, Bethencourt A, Sievert H, et al. Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience. Catheter Cardiovasc Interv. 2011;77:700–6.
16. Lam YY, Yip GW, Yu CM, et al. Left atrial appendage closure with AMPLATZER cardiac plug for stroke prevention in atrial fibrillation: initial Asia-Pacific experience. Catheter Cardiovasc Interv. 2012;79:794–800.
17. Damonte A, Costantini C, Pedra C, et al. Percutaneous closure of the left atrial appendage: initial experience in Latin America. J Am Coll Cardiol. 2013;62:B211.
18. Lopez-Minguez JR, Eldoayen-Gragera J, Gonzalez-Fernandez R, et al. Immediate and one-year results in 35 consecutive patients after closure of left atrial appendage with the Amplatzer cardiac plug. Rev Esp Cardiol. 2013;66:90–7.
19. Streb W, Szymala M, Kukulski T, et al. Percutaneous closure of the left atrial appendage using the Amplatzer cardiac plug in patients with atrial fibrillation: evaluation of safety and feasibility. Kardiol Pol. 2013;71:8–16.
20. Guerios EE, Schmid M, Gloekler S, et al. Left atrial appendage closure with the Amplatzer cardiac plug in patients with atrial fibrillation. Arq Bras Cardiol. 2012;98:528–36.
21. Urena M, Rodes-Cabau J, Freixa X, et al. Percutaneous left atrial appendage closure with the AMPLATZER cardiac plug device in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy. J Am Coll Cardiol. 2013;62:96–102.
22. Meerkin D, Butnaru A, Dratva D, Bertrand OF, Tzivoni D. Early safety of the Amplatzer cardiac plug for left atrial appendage occlusion. Int J Cardiol. 2013;168:3920–5.
23. Park JW, Sievert H, Schillinger W, et al. Results of the Amplatzer cardiac plug European multicenter prospective observational study. J Am Coll Cardiol. 2012;60.
24. Viles-Gonzalez JF, Kar S, Douglas P, et al. 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.
25. 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.
26. Reddy VY, Mobius-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.

Chapter 13
ACP and Amulet: Trials and Registries Results

Xavier Freixa, Apostolos Tzikas, and Réda Ibrahim

Introduction

The left atrial appendage (LAA) is the main source of thrombus in non-valvular atrial fibrillation (NVAF) [1]. Percutaneous left atrial appendage (LAA) closure is considered an alternative to anticoagulation in patients with NVAF at risk of stroke or peripheral embolization [2]. Despite the relatively recent introduction of the technique, percutaneous LAA occlusion is growing rapidly in reference centers all over the world. Currently, the Amplatzer™ Cardiac Plug (AGA-St. Jude, Minneapolis, MN, USA) and the WATCHMAN™ (Atritech-Boston Scientific, Natick, MA, USA) are the two devices with most published data.

The Amplatzer Cardiac Plug (ACP) is a first-generation device with a particular design consisting of a distal lobe and a proximal disc specifically conceived to be deployed in the body and to seal the ostium of the LAA, respectively (pacifier effect). Indeed, the ACP seats in the proximal part of the LAA, avoiding the highly heterogeneous anatomy of the distal portion of the appendage [3]. Besides the potential device's versatility to adapt to variable anatomies, the double-sealing system with lobe and disc enhances the occlusion of the LAA, avoiding at the same time the formation of LAA recesses proximally to the lobe.

X. Freixa, M.D.
Department of Cardiology, Thorax Unit, Hospital Clinic of Barcelona, University of Barcelona, Barcelona, Spain

A. Tzikas, M.D., Ph.D. (✉)
Department of Cardiology, AHEPA University Hospital, Thessaloniki, Greece
e-mail: aptzikas@yahoo.com

R. Ibrahim, M.D.
Medical Intensive Care Unit and Structural Heart Program, Department of Medicine, Montreal Heart Institute, Université de Montréal, Montreal, QC, Canada

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_13

A second generation of the ACP device called Amplatzer Amulet™ (Amulet) has been recently released (CE mark since January 2013) [4]. The Amulet has been designed to facilitate the implantation process and minimize the occurrence of complications. A few important modifications were implemented without changing considerably the main design of the ACP. The new design covers the technical needs expressed by several operators with the increased experience with the ACP. The following chapter describes the technical features of both devices and provides the current data on registries and trials.

Summary of Technical Features: Amplatzer Cardiac Plug Versus Amplatzer Amulet

The ACP and Amulet are the first- and second-generation devices for LAA occlusion, respectively. Both are self-expanding dedicated devices made of a nitinol mesh with two polyester patches sewn onto a distal lobe and a proximal disc connected by a short articulated waist. The distal lobe conforms to the inner LAA wall in a depth of approximately 10–15 mm, the articulated waist allows a proper orientation of the device into the LAA, and the proximal disc seals the LAA ostium [5]. Both devices are retrievable and repositionable and are implanted through the atrial septum using a 9–14 French delivery system from the femoral vein.

The main modifications of the Amulet with respect to the ACP are the following [4] (Fig. 13.1): (1) no need to prepare and load the device as it comes pre-loaded, (2) longer lobe length (1–3.5 mm longer than the ACP) that improves the stability and sealing, (3) the stabilizing wires are stiffer and its number has been increased (from 6 pairs in the ACP to up to 10 pairs) to provide more stability and reduce the risk of embolization, (4) larger proximal disc (6–7 mm bigger than the distal lobe diameter compared to 4–6 mm in the ACP) to achieve a complete LAA ostial sealing, (5) longer articulated waist (from 4 mm in the ACP to 5.5 or 8 mm depending on the size of the device) to provide more position forgiveness, (6) recessed proximal endscrew to reduce the risk of thrombus formation, (7) larger available sizes (31 and 34 mm), and (8) delivery cable with an inner 0.014″ wire to reduce the tension before releasing the device (initial iteration of Amulet). Of note, after subsequent redesign of Amulet, the ultimate delivery cable will remain similar to the ACP following several cases of early detachment of the device within the delivery sheath and few cases of entrapment of the tip of the wire within the device after release.

Amplatzer Cardiac Plug Registries and Trials

Procedural and In-Hospital Outcomes

The first ACP was implanted by Dr. Kevin Walsh in December 2008. Since then, the number of procedures using this device has rapidly grown worldwide. Currently, several registries support the efficacy and safety of the device at both short- and

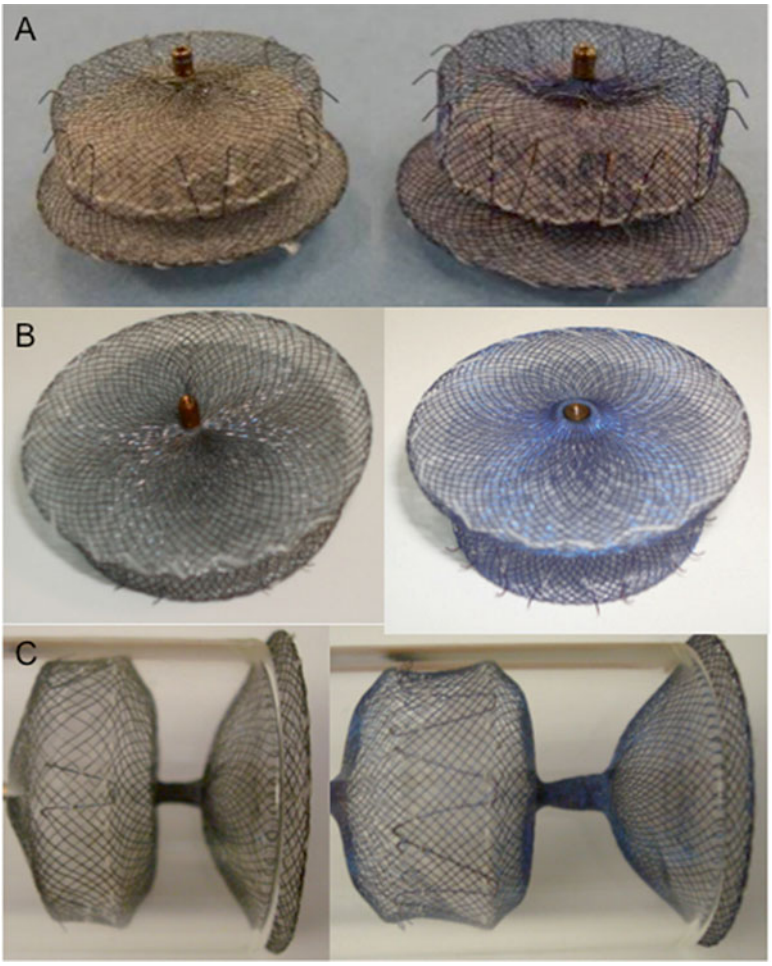


Fig. 13.1 Comparison between the Amplatzer Cardiac Plug and the Amulet. Comparison between the ACP (*left*) and the Amulet (*right*) highlighting the increased number of stabilizing wires (**a**), the inversion of the disc end-screw (**b**), and the greater diameter of the Amulet distal lobe (**a** and **c**) and waist (**c**)

long-term follow-up [6–16]. However, in contrast with the Watchman device [17], there are no randomized studies comparing the use of ACP and oral anticoagulation (OAC) in patients with NVAF. Park et al. [6] published the first ACP registry in 2011 reporting the results of 143 patients who underwent LAA occlusion in different centers across Europe. Although this first registry showed the very initial experience of several operators with the device, the percentage of procedural success reached 96 % and the rate of complications was relatively low with no intraprocedural deaths, cardiac tamponade in 3.5 %, device embolization in 1.4 %, and procedural stroke in 2.1 %. In 2011, Lam et al. [7] also reported the initial Asia-Pacific experience. Similar to the European registry, the procedural success rate

reached 95 % and none of the patients presented any intra-procedural complication. Even though these two initial registries showed a high success rate and relatively low number of complications, the procedural outcomes have kept improving over the last few years with the increased experience of operators. As shown in Table 13.1, procedural success ranges between 95 and 100 % according to different series. In addition, the number of complications seems to be decreasing in most of the series as depicted by the reduction of the percentage of cardiac tamponade (0–2 %), device embolization (<1 %), and procedural stroke (0 %). This finding was also observed in the CAP registry [18], a non-randomized continued access program of the Watchman™ system in 460 patients following PROTECT AF [17]. Indeed, the CAP registry revealed a significant improvement of outcomes with the increasing experience of operators, showing a higher successful implantation rate (from 89 to 95 %), shorter procedural times, lower rates of pericardial effusions requiring drainage (from 4.4 to 2.2 %), and lower procedural-related strokes (from 0.5 to 0 %) [18]. Tzikas et al. [19] have recently published the largest registry (1047 patients) on LAA occlusion with the ACP. This large registry is probably the one that reflects better the current overall status of LAA occlusion with the ACP after collecting the initial and subsequent experience of 22 European and Canadian centers. As shown in Table 13.1, procedural success reached 97.3 % and the overall incidence of procedural complications was reduced as compared to the initial registries: procedural stroke (0.9 %), device embolization (0.7 %), cardiac tamponade (1.2 %), and peri-procedural death (0.8 %). Another relevant finding of the study were the indications for LAA occlusion, which reflected the current international practice: previous major bleeding as main indication (47 %), followed by high risk for bleeding (35 %), coronary stenting mandating dual-antiplatelet therapy (DAPT) plus anticoagulation (22 %), and stroke despite warfarin treatment (16 %). This registry also showed the average profile of a patient undergoing LAA occlusion: mean age of 75 ± 8 years with 55 % >75 years old, mean $CHADS_2$ score of 2.8 ± 1.3, mean CHA_2DS_2-VASc score of 4.5 ± 1.6, and mean HAS-BLED score of 3.1 ± 1.2.

Long-Term Follow-up

As shown in Table 13.1, the annual rate of stroke after LAA occlusion with the ACP ranged between 0 and 2.2 % [6–16]. In PROTECT-AF, the annual rate of stroke (ischemic or hemorrhagic) with the Watchman device and warfarin was 2.3 % and 3.2 %, respectively [17]. Similarly, the recent randomized trials comparing warfarin versus new OAC showed comparable rates of stroke/peripheral embolism: 1.6–2.4 % with warfarin [20–22], 1.5 % with dabigatran at low dose (110 mg BID) [20], 1.1 % with dabigatran at high dose (150 mg BID) [20], 2.1 % with rivaroxaban [22], and 1.2 % with apixaban [21]. Although not truly comparable because of the different design (randomized versus observational studies), baseline characteristics, and event adjudication, the similar rates among studies are worth

Table 13.1 In-hospital and follow-up outcomes of different series of patients treated with the Amplatzer™ cardiac plug

		In-hospital outcomes					Follow-up outcomes		
	n	Procedural success (%)	Stroke (%)	Device embolism (%)	Cardiac tamponade (%)	Death (%)	Mean follow-up (months)	Stroke/ TIA (%)	Device thrombosis (%)
Park et al. (2011)—Europe [6]	143	96	2.1	1.4	3.5	0	0	–	–
Walsh et al. (2012)—Europe [10]	204	96	0	1.5	1.5	0	6	0.9	2.4
Lam et al. (2011)—Asia-Pacific [7]	20	95	0	0	0	0	13	0	0
Italian Registry (2011)—Italy [11]	100	99	0	0	2	0	0	–	–
Guérios et al. (2012)—Brazil [8]	85	99	2.3	2.3	1.1	1.1	12	0	0
López-Minguez et al. (2012)—Spain [9]	35	97	0	0	0	0	21	2.8	14
Ureña et al. (2013)—Canada [12]	52	98	0	1.9	1.9	0	20	1.9	1.9
Meerkin et al. (2013)—International [13]	100	100	0	0	1	0	NA	NA	NA
Kefer et al. (2013)—Belgium [14]	90	98	0	0	3.3	1.1	12	2.2	0
Streb et al. (2013)—Poland [15]	25	95	4.7	0	0	0	NA	NA	NA
Wiebe et al. (2014)—Germany [16]	60	95	0	3.3	1.6	0	21	0	3.5
Tzikas et al. (2014)—International [19]	1047	97.3	0.9	0.7	1.2	0.8	13	1.8	4.4

mentioning. Additionally, it is also important to highlight the differences in the $CHADS_2$ score between the ACP registries (2.8 ± 1.3) [19], PROTECT AF [17] (2.2 ± 1.2), and the randomized trials with novel OAC: dabigatran 110 mg [20] (2.1 ± 1.1), dabigatran 150 mg [20] (2.2 ± 1.2), rivaroxaban [22] (3.4 ± 0.9), and apixaban [21] (2.0 ± 1.1).

In the largest ACP registry [19], the annual rate of systemic thromboembolism (peri-procedural and follow-up) was 2.3 %, which translated into a 59.1 % risk reduction compared to the estimated risk according to the CHA_2DS_2VASc score of the study population. Moreover, the annual rate of major bleeding in the study (peri-procedural and follow-up) was 2.1 %, which also translated into a 61.0 % risk reduction compared to the estimated risk according to the HASBLED score of the study population.

The device thrombosis at follow-up is another relevant point of discussion. According to registries, the detection of thrombus at follow-up varies between 0 and 14 % [6–16]. These differences probably reflect variable antithrombotic therapies after LAA occlusion and especially different TEE follow-up protocols among series. Currently, the most followed antithrombotic regimen post-ACP implantation is DAPT for 3–6 months followed by a single antiplatelet agent [19]. Lopez-Minguez et al. [9] found a very high rate of ACP thrombosis (14 %) after an intensive follow-up with TEEs at 24 h, 1, 3, 6, and 12 months post-procedure. The number of TEEs probably explains the fact that they found the largest number of thrombus in comparison with most of the other centers that performed only one TEE at follow-up (usually 1–3 months after the procedure). In any case, although the clinical impact and predictors of device thrombosis are not very well-known yet, vast majority of device thromboses did not seem to be associated with additional clinical events and usually respond to anticoagulation therapy [6–16].

The incidence of peri-device residual leaks after LAA occlusion is another matter of controversy. The incidence of significant leaks (>3 mm) with the largest ACP registry was 1.9 %, and accordingly to a PROTECT-AF sub-study [23], residual leaks did not correlate with any adverse event at follow-up [19]. A higher rate of device oversizing might be associated with a lower incidence of residual leaks at follow-up [5].

The ACP Trial, a US trial using the ACP system, halted enrollment in December 2013 prior to completion. Stroke management landscape had changed significantly from when the protocol was first written, with the introduction of several novel anticoagulants to the US market and the launch of a competitive LAA occlusion device. Then, decision was made by the manufacturer to modify the protocol to better align with the anticipated indications of approved LAA occlusions devices. Therefore, stopping enrollment was not a consequence of a safety or efficacy issue with the device or the study. Follow-up of patients enrolled in the ACP trial is ongoing per the original protocol. St. Jude Medical is currently in discussions with the Food and Drug Administration (FDA) on a new trial design and protocol to bring Amplatzer Amulet to the US market.

Amplatzer Amulet Data

The first Amulet device was implanted at the Montreal Heart Institute by Dr. Ibrahim in July 2012 [4]. Between mid 2012 and 2013, the device was implanted in selected centers over the world. As mentioned in a previous section of this chapter and following the suggestions from experienced operators, the initial release of the Amulet was stopped in mid 2013 in order to modify the delivery cable (with the inner wire). A novel version of the Amulet with a conventional delivery cable (similar to ACP) has been released in the second half of 2014.

Since Amulet utilization was limited in time and centers, the available data is also limited. Freixa et al. published the first Amulet series in 25 patients who underwent percutaneous LAA occlusion [24]. In this initial registry, Amulet showed a remarkable acute and short-term performance in terms of feasibility and safety as depicted by the high successful implantation rate (96 %) and the low incidence of major complications (0 %). In addition, other publications with single cases or small series showed the higher versatility of the device with complex LAA anatomies. The two larger Amulet sizes (31 and 34 mm) allowed the closure of very large appendages that were not approachable with the previous version of the device [25]. In addition, the novel design of the device was found to be very useful in treating LAAs with early and severe bends (chicken-wing) as the longer articulated waist and larger lobe/disc eased unconventional device positioning like the "sandwich" technique [26]. The Amulet device has also been used to fully seal the LAA after incomplete occlusion with a previous Watchman device [27]. A recent publication compared 50 patients with ACP and 50 with Amulet. Using only fluoroscopy as guidance for the procedure, a similar success rate and combined safety endpoint (surgical bailout, stroke, cardiac tamponade, and periprocedural death) was observed among devices [28]. Further data will be necessary to extract more conclusions about the performance of the device.

Conclusions

Although no randomized data is available, a 5-year experience with the ACP and several published registries have shown a remarkable performance of the device in terms of feasibility and safety at short-term as well as efficacy for stroke/peripheral embolism prevention and hemorrhagic risk reduction at long-term follow-up. A second-generation device, the Amplatzer Amulet, has recently been released. Although similar in design, several important modifications have been added to facilitate the implantation process and reduce the number of complications. Despite some promising initial data, further studies will be necessary to show if the novel design is linked to a better performance.

References

1. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg. 1996;61:755–9.
2. Camm AJ, Lip GY, De Caterina R, et al. 2012 Focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012;33:2719–47.
3. Di Biase L, Santangeli P, Anselmino M, et al. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. J Am Coll Cardiol. 2012;60:531–8.
4. Freixa X, Chan JL, Tzikas A, Garceau P, Basmadjian A, Ibrahim R. The Amplatzer cardiac plug 2 for left atrial appendage occlusion: novel features and first-in-man experience. EuroIntervention. 2013;8:1094–8.
5. Freixa X, Tzikas A, Sobrino A, Chan J, Basmadjian AJ, Ibrahim R. Left atrial appendage closure with the Amplatzer cardiac plug: impact of shape and device sizing on follow-up leaks. Int J Cardiol. 2013;168:1023–7.
6. Park JW, Bethencourt A, Sievert H, et al. Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience. Catheter Cardiovasc Interv. 2011;77:700–6.
7. Lam YY, Yip GW, Yu CM, et al. Left atrial appendage closure with AMPLATZER cardiac plug for stroke prevention in atrial fibrillation: initial Asia-Pacific experience. Catheter Cardiovasc Interv. 2012;79:794–800.
8. Guerios EE, Schmid M, Gloekler S, et al. Left atrial appendage closure with the Amplatzer cardiac plug in patients with atrial fibrillation. Arq Bras Cardiol. 2012;98:528–36.
9. Lopez-Minguez JR, Eldoayen-Gragera J, Gonzalez-Fernandez R, et al. Immediate and one-year results in 35 consecutive patients after closure of left atrial appendage with the Amplatzer cardiac plug. Rev Esp Cardiol. 2013;66:90–7.
10. Walsh K. Left atrial appendage closure with the amplatzer cardiac plug: results of the European prospective observational study. In: EuroPCR 2012; 2012.
11. Santoro G. Amplatzer cardiac plug: Italian registry. In: Progress in clinical pacing, Rome; 2010.
12. Urena M, Rodes-Cabau J, Freixa X, et al. Percutaneous left atrial appendage closure with the AMPLATZER cardiac plug device in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy. J Am Coll Cardiol. 2013;62:96–102.
13. Meerkin D, Butnaru A, Dratva D, Bertrand OF, Tzivoni D. Early safety of the Amplatzer cardiac plug for left atrial appendage occlusion. Int J Cardiol. 2013;168:3920–5.
14. Kefer J, Vermeersch P, Budts W, et al. Transcatheter left atrial appendage closure for stroke prevention in atrial fibrillation with Amplatzer cardiac plug: the Belgian Registry. Acta Cardiol. 2013;68:551–8.
15. Streb W, Szymala M, Kukulski T, et al. Percutaneous closure of the left atrial appendage using the Amplatzer cardiac plug in patients with atrial fibrillation: evaluation of safety and feasibility. Kardiol Pol. 2013;71:8–16.
16. Wiebe J, Bertog S, Franke J, et al. Safety of percutaneous left atrial appendage closure with the amplatzer cardiac plug in patients with atrial fibrillation and contraindications to anticoagulation. Catheter Cardiovasc Interv. 2014;83:796–802.
17. 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.
18. 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.

19. Tzikas A, Shakir S, Gafoor S et al. Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicentre experience with the Amplatzer cardiac plug. Eurointerventions 2015. Jan 22; 10(10)
20. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.
21. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364:806–17.
22. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.
23. Viles-Gonzalez JF, Kar S, Douglas P, et al. 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.
24. Freixa X, Abualsaud A, Chan J, et al. Left atrial appendage occlusion: initial experience with the Amplatzer Amulet. Int J Cardiol. 2014;174(3):492–6.
25. Freixa X, Kwai Chan JL, Tzikas A, Garceau P, Basmadjian A, Ibrahim R. Percutaneous closure of a very large left atrial appendage using the Amplatzer Amulet. Can J Cardiol. 2013;29(10):1329.e9–11.
26. Freixa X, Tzikas A, Basmadjian A, Garceau P, Ibrahim R. The chicken-wing morphology: an anatomical challenge for left atrial appendage occlusion. J Interv Cardiol. 2013;26:509–14.
27. Lam SC, Bertog S, Sievert H. Incomplete left atrial appendage occlusion and thrombus formation after Watchman implantation treated with anticoagulation followed by further transcatheter closure with a second-generation Amplatzer cardiac plug (Amulet device). Catheter Cardiovasc Interv. 2015;85(2):321–7.
28. Gloekler S, Shakir S, Doblies J, et al. Early results of first versus second generation Amplatzer occluders for left atrial appendage closure in patients with atrial fibrillation. Clin Res Cardiol 2015 Mar 4.

Chapter 14
LARIAT: The Endo-Epicardial Technique for Left Atrial Appendage Exclusion

Arun Kanmanthareddy, Sampath Gunda, Nitish Badhwar, Randall J. Lee, and Dhanunjaya Lakkireddy

Introduction

Atrial fibrillation (AF) is a cardiac rhythm disorder and is associated with increased risk of stroke [1]. The prevalence of AF is rapidly increasing and current projections indicate a prevalence of 6.7 million AF patients in the U.S. in the year 2010 and this is projected to increase to 12.1–15.9 million by the year 2050 [2]. Annual healthcare bill for managing AF patients is estimated to be in the range of $6–$26 billion [3]. Oral anticoagulation with warfarin and novel oral anticoagulants (Apixaban, Dabigatran, Rivaroxaban, Edoxaban) are effective for preventing thromboembolic events in AF [4–8]. Complications such as bleeding and need for frequent testing (warfarin) to maintain therapeutic anticoagulation levels are the barriers for using these agents and are therefore not suitable for all patients. Several different percutaneous left atrial appendage (LAA) exclusion devices (PLAATO, WATCHMAN, Amplatzer Cardiac Plug, Coherex Wavecrest) have been developed for use in AF patients who are at increased risk of stroke and also have contraindications to

A. Kanmanthareddy, M.D., M.S.
Cardiovascular Division, Creighton University School of Medicine, Omaha, NE, USA

S. Gunda, M.D.
Department of Cardiology, University of Kansas Hospitals and Medical Center, Kansas City, KS USA

N. Badhwar, M.D.
Cardiovascular Division, University of California San Francisco, San Francisco, CA, USA

R.J. Lee, M.D., Ph.D.
University of California, San Francisco, 500 Parnassus Ave, San Francisco, CA 94010, USA

D. Lakkireddy, M.D., F.A.C.C., F.H.R.S. (✉)
Center for Excellence in Atrial Fibrillation and Electrophysiology Research, Bloch Heart Rhythm Center, Mid America Cardiology, KU Cardiovascular Research Institute, University of Kansas Hospital and Medical Center, 3901 Rainbow Blvd, Kansas City, KS 66160, USA
e-mail: dlakkireddy@kumc.edu

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_14

anticoagulation with promising results [9–12]. These devices have been shown to have comparable efficacy to warfarin in preventing thromboembolism [13]. However, all the above devices need to be implanted within the LAA and run the risk of embolization and infection. The LARIAT is a novel percutaneous endo-epicardial LAA exclusion device that leaves behind just an epicardially placed suture around the ostium of the LAA without the need for any endovascular device. Below we discuss the LARIAT device, method of implantation, the efficacy, and its role in rhythm management in detail.

The LARIAT Device

(a) The LARIAT is a suture made from Teflon-coated braided polyester (Fig. 14.1). The thickness of the suture is USP 0 and the maximum width of the suture is 40×20×70 mm. The suture comes in a pre-packaged delivery device and this device has a length of 40 cm. The distal end of the delivery device has a Tensure™ Suture Tightener for easy deployment once the suture is positioned at the right location. This suture has a Meltzer one-way slip knot and this knot can be controlled from the suture tightener.

(b) FindrWIRZ Guidewire system: The guidewires consist of endocardial and epicardial guidewires that have magnet tips at their distal ends. The endocardial guidewire is 0.025″ thick and the length is 220 cm with a magnet tip that is 2.57 mm thick. The epicardial guidewire is 0.035″ thick and is 150 cm long and the magnet diameter is 3.5 mm thick. The epicardial and endocardial guidewires require introducers of 8F and 11F, respectively. When deployed, both the endocardial and epicardial guidewires form a railing on which the LARIAT suture can be guided over the epicardial surface of the LAA.

(c) SOFTIP Guide Cannula: This cannula helps deliver the LARIAT suture from the epicardial surface of the LAA. This soft-tipped cannula helps prevent traumatic injury to the heart while delivering the catheter. This catheter has a diameter of 12.9F and has a working length of 22.5 cm and overall length of 25 cm.

(d) SURECUT SUTURE CUTTER: This device helps cut the LARIAT suture just proximal to the LARIAT suture.

(e) TENSURE SUTURE TIGHTENER: This device helps deliver constant and consistent tension while deploying the LARIAT suture. The device has an indicator that indicates the tension applied at the distal LARIAT suture to minimize variability in the amount of tension applied by different operators. Use of this device facilitates grip on the suture and helps deliver a uniform tension on the suture.

(f) ENDOCATH occlusion balloon: This balloon requires a 9F introducer and has a length of 90 cm. The balloon dimensions are 12×15 mm, and when fully inflated, has a maximal volume of 1.5 cm^3. This balloon has a distal port through which contrast can be delivered. This balloon is used as a marker for the neck of the LAA.

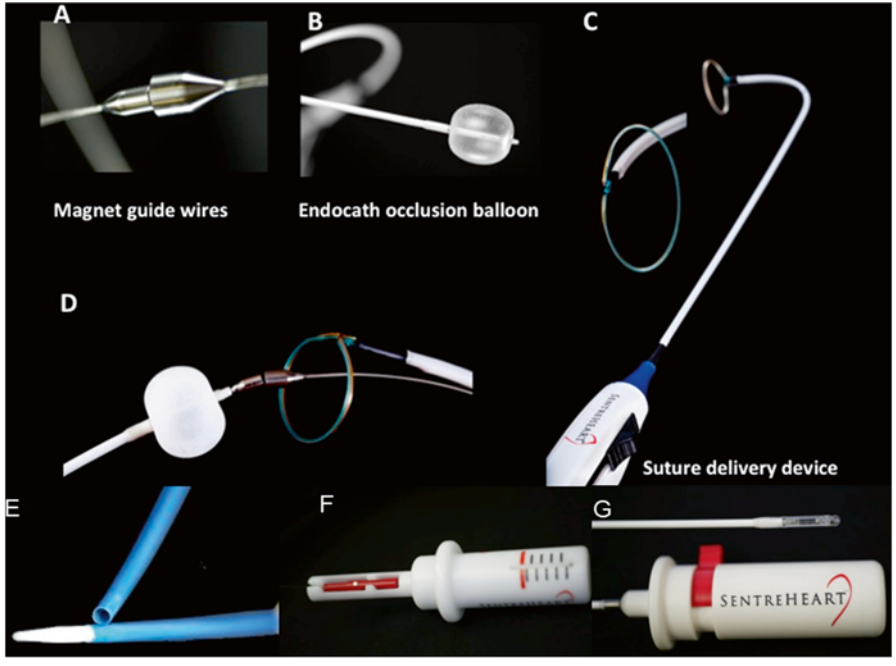


Fig. 14.1 Components of the LARIAT™ system. The components of the percutaneous LAA ligation procedure include: (panel **a**) A 0.025-in. endocardial magnet-tipped and 0.035-in. epicardial magnet-tipped guidewire, each with a magnet of opposite polarity enabling an end-to-end alignment, (panel **b**) A 15 mm compliant occlusion balloon catheter to identify the LAA OS with TEE, (panel **c**) The LARIAT™ suture delivery device. The higher power inset demonstrates the pre-tied size 0 Teflon-coated, braided polyester suture (*blue*) mounted within a radiopaque adjustable snare. Panel (**d**) demonstrates the use of the components as a system to ligate the LAA. Panel (**e**) is the soft-tipped, 4.3 mm guide cannula for placement and direction of the LARIAT Suture Delivery Device. Panel (**f**) is the TenSURE™ that eliminates operator variability in suture tightening and assures consistency in closure outcomes. Panel (**g**) is the SureCUT™ remote suture cutter with easy-load threader designed to terminate remnant suture without risk to the knot (Adapted from Bartus et al. [15] with permission)

Indications and Contraindications for LARIAT Procedure

Indications

1. Nonvalvular AF patients with high risk of stroke ($CHADS_2$ score$\geq$2 or CHA_2DS_2VASc score$\geq$3) and contraindications to oral anticoagulation due to history of internal or external bleeding (neurological, intraocular, gastrointestinal, urological, pulmonary).
2. Intolerance to oral anticoagulants (adverse effects, bleeding).
3. Oral anticoagulation is ineffective (unable to achieve therapeutic INR or thromboembolic events while on therapeutic oral anticoagulation).
4. AF patients who are perceived to be at increased risk for bleeding (recurrent syncope and traumatic falls, high risk occupations like firefighters, intracranial aneurysms).

Contraindications

1. LAA diameter >40 mm, because the maximum diameter of the LARIAT suture is only 40 mm and therefore this device cannot be used in patients with LAA diameter >40 mm.
2. Prior cardiac surgery: In case of previous cardiac surgery, the LARIAT device cannot be used because of fibrotic changes in the pericardium following the surgery. In the presence of these fibrotic changes, it is difficult to position and deliver the catheters and the LARIAT suture accurately and therefore it is recommended not to perform this procedure in patients with prior cardiac surgery.
3. Pectus excavatum: In this situation, the posteriorly directed sternum poses a challenge for the epicardial access and may result in direct cardiac perforation while attempting this. In addition, the working angle will be extremely difficult to accurately position the LARIAT suture delivery catheter at the tip of the LAA and therefore the LAA cannot be engaged in this situation.
4. Posteriorly directed LAA: the posteriorly directed LAA cannot be engaged by means of the LARIAT suture from the anterior epicardial approach.
5. Multi-lobed LAA: In the case of multi-lobed LAA, the LARIAT suture cannot be positioned accurately at the neck of the appendage and some of the lobes of the LAA may be missed leading to incomplete sealing of the LAA.
6. Comorbidities such as severe heart failure, metastatic malignancy, and/or life expectancy less than 1 year.

Preoperative Assessment

Highly skilled operator and suitable cardiac anatomy are the key requisites for performing the LARIAT procedure. The patients therefore need to be worked up appropriately to determine their suitability for this procedure. Multimodality cardiac imaging (CT scan, TEE, and LAA contrast angiography) helps in the preoperative assessment and successful completion of the procedure (Fig. 14.2). All patients undergo a cardiac CT scan with contrast to assess the anatomy of the thorax, heart, and the LAA. All CT scan are then converted to a 3D reconstruction model to visualize the anatomy of the LAA and its surrounding structures. The LAA size and morphology are assessed to determine their eligibility for this procedure. A preoperative TEE is also recommended to confirm the size of the LAA and also to rule out left atrial and LAA thrombus. Comorbidities are assessed to see if the patient can tolerate this procedure with general anesthesia. General anesthesia allows stability of the patient for epicardial puncture and continuous TEE for visualization and closure of the LAA. It is recommended to perform this procedure at a high volume

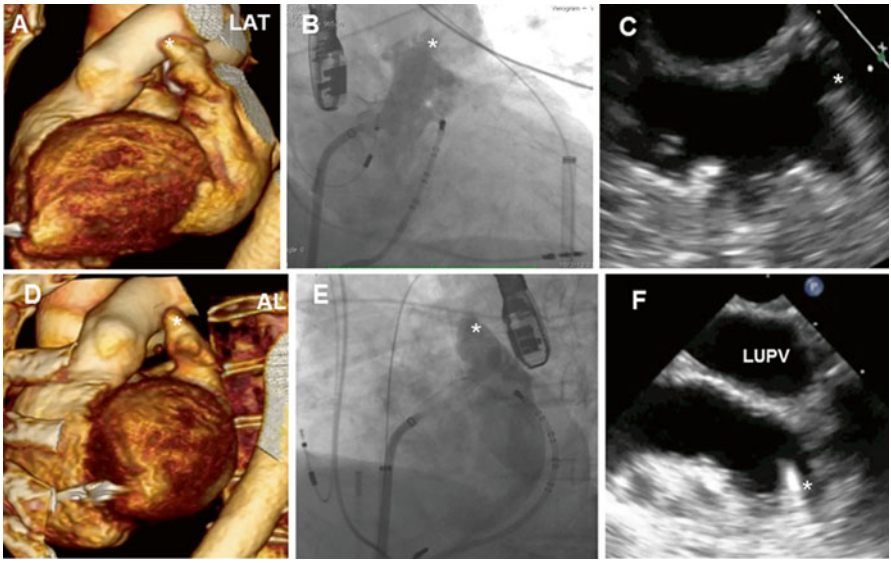


Fig. 14.2 Imaging. The lateral view of the CT (panel **a**), RAO caudal fluoroscopic view (panel **b**) and the 120–135° TEE view (panel **c**) are complimentary views that can provide information regarding LAA size and morphology. The most anterior aspect of the LAA can be seen in the lateral view of the CT that is analogous to a true left lateral view. The anterior lateral view of the CT (panel **d**) is analogous to a shallow, 30° LAO fluoroscopic view (panel **e**). Panel (**f**) demonstrates a 60° TEE view with the magnet tip in the anterior lobe. The *white asterisk* represents the anterior aspect of the LAA. *LAT* lateral, *AL* anterior-lateral, *LUPV* left upper pulmonary vein (Reproduced from Koneru et al. [14] with permission)

center where considerable expertise is available. The use of cardiac anesthesiologist is recommended for the procedure. Once the eligibility for the procedure is determined, all patients who can tolerate anticoagulation for a limited time are continued on oral anticoagulation. If the patient has absolute contraindication to oral anticoagulation, anticoagulation is not recommended for these patients. Oral anticoagulants are stopped 24–48 h prior to the procedure and patients are bridged with unfractionated heparin.

LARIAT Procedure

Directionally and anatomically accurate pericardial access and appropriate placement of the endocardial magnet wire within the LAA are the two most critical steps to assure a successful procedure.

Epicardial Access

Accessing the anterior pericardial space is one of the key steps for positioning the LARIAT suture over the LAA (Fig. 14.3). Standard pericardiocentesis needle or micro-puncture needle can be used for accessing the anterior pericardial space. The goal is to enter the pericardial space anteriorly and the needle should be directed laterally [14]. This orientation will help access the LAA from the anterior surface of the right ventricle and will ensnare the LAA tip lateral to the pulmonary vasculature anteriorly [14]. As the LARIAT suture device is advanced further, the suture will move across from the tip of the LAA to the neck and base of the LAA in an anterio-posterior direction. Posterior pericardial access will preclude accessing the LAA from its most anterior aspect [14]. Similarly, positioning of the needle more medially will present the challenge of manipulating the LARIAT suture laterally towards the tip of the LAA [14]. Preoperative assessment of cardiac anatomy using 3D-reconstructed CT scan will therefore help plan this procedure more efficiently. The lateral view of the CT demonstrates the space between the sternum and the anterior surface of the heart and allows for estimation of the steepness of the pericardial needle. The CT also delineates the most inferior aspect of the sternum in relationship to the inferior aspect of the myocardium. This allows for a pre-procedure assessment of how far the pericardial needle needs to be advanced in order to obtain pericardial access. In our center, we always keep the reconstructed cardiac CT scan readily available during the procedure to review and reposition the pericardial access.

After cleaning and prepping the sub-xiphoid area, the xiphoid process is palpated and an area 2–3-finger breadth below the xiphoid process is infiltrated with local anesthetic. After this, the pericardiocentesis needle is directed superior-laterally towards the left shoulder under fluoroscopic guidance in the AP view. In this view, the needle should be directed between 1 and 2:30° clock position [15]. Orientation

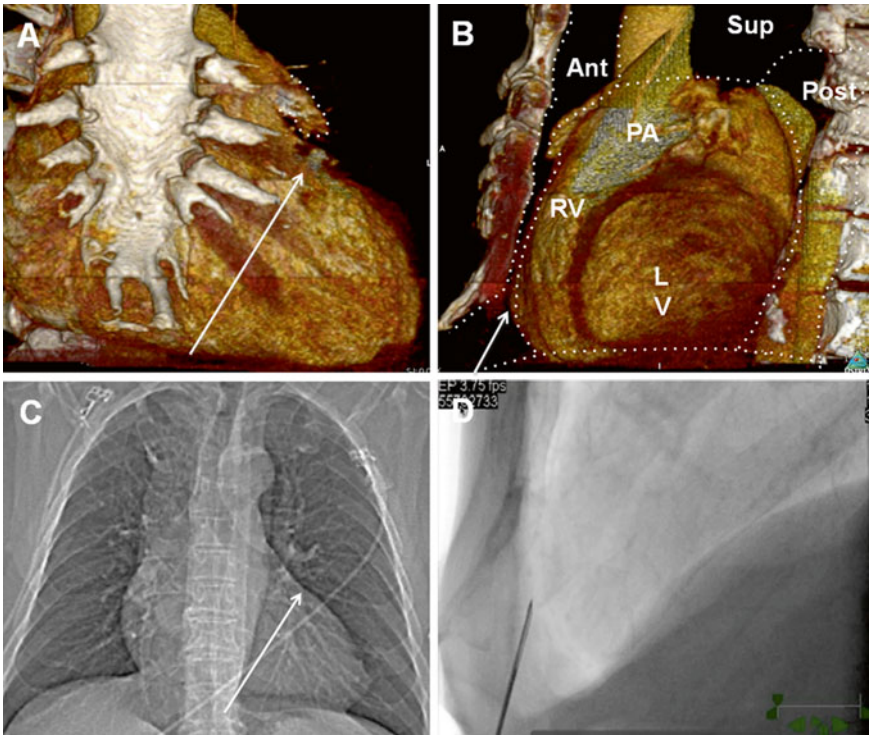


Fig. 14.3 Utility of Cardiac CT angiography (CTA) for estimation of the direction and depth of the pericardial needle. Pericardial access for LAA ligation utilizing the LARIAT™ suture delivery device requires an anterior access approach into the pericardial space. As seen in the anteroposterior view (AP) of the 3D reconstruction of the CT angiogram (panel **a**), the LAA (delineated by the *dashed line*) is lateral to the pulmonary artery (PA) and appears to be in front of the hilum. The needle is directed (direction of the *arrow*) just lateral to the LAA that is generally toward the left shoulder. In the fluoroscopic image, the needle (*arrow*) would be directed just lateral to the hilum (panel **c**). The lateral view of the 3D reconstruction of the CT angiogram (panel **b**) demonstrates the virtual space of the anterior mediastinal space (Ant). The needle (*arrow*) is directed through the sternocostal triangle that allows for the needle to pass under the xyphoid process and above the diaphragm into the anterior mediastinal space, thus avoiding damage to the diaphragm and avoiding abdominal organs. The 90° left lateral fluoroscopic view allows for the needle to be advanced to the myocardial border (panel **d**). *Ant* anterior mediastinal space, *Sup* Superior mediastinal space, *Post* posterior mediastinal space, *RV* right ventricle, *PA* pulmonary artery, *LV* left ventricle (Reproduced from Koneru et al. [14] with permission)

in this position increases the chance of successful pericardial access [15]. The needle is also directed posteriorly by about 10–15° or between 3:30 and 4:30 clock position for successful pericardial access [15]. This posterior positioning of the pericardiocentesis needle is evaluated in left lateral view on fluoroscopy. The use of AP and the left lateral perpendicular fluoroscopic views help accurate localization of the needle and lead to successful pericardial access with one single attempt in >97 % of the patients undergoing LARIAT procedure.

The entry into the pericardial space is made 1–2 cm above the apex of the heart. This ensures that the guidewire will traverse anteriorly. If the pericardial access is at or near the apex, despite anterior pericardial access, the wire could traverse along the lateral border of the heart and slip posteriorly. Entry into the pericardial space can be confirmed by one of the two methods: "Contrast dye technique" or "Guidewire technique" [14]. In the contrast dye technique, small amounts of contrast are injected through the pericardial access needle. This allows visualization of the tenting of the pericardium, and once the needle enters the pericardial space, the contrast dye will track along the cardiac silhouette confirming the entry into the pericardial space. Subsequently, the guidewire can be introduced and the needle can be withdrawn. In the guidewire technique, the operator perceives the tactile pulsations of the heart and the pericardiocentesis needle is advanced slowly by about an mm at a time [14]. Once the parietal pericardium is approached, the operator can feel the heart pulsations and gentle advancement will result in a popping sensation. Then the guidewire can be slowly introduced through the pericardial access needle and the guidewire should hug the lateral heart border and cross the midline in LAO view to confirm placement in pericardium [14]. The needle is then withdrawn and serial dilators are used to dilate the tract from the skin surface to the pericardium. Dilators should be advanced carefully to avoid compression of the RV or kinking of the guidewire. RV compression can be seen by TEE examination and prevented by mild depression of the abdomen to alleviate the acute angle of the entry of the dilator into the pericardial space. After the dilation of the tract, the epicardial SOFTIP guide cannula is inserted into this tract and held in place.

Transseptal Access

The femoral vein is accessed using the Seldinger technique and a sheath is left in place. At this time the ACT is measured and additional heparin boluses are given to keep the ACT >300 s. The Brockenbrough needle is then introduced towards the interatrial septum. The interatrial septum is then visualized by means of TEE and atrial septal puncture is done with the help of the Brockenbrough needle. The interatrial septal puncture is done in the mid-portion of the septum and the angle is directed postero-superiorly to facilitate a more direct access to the LAA (Fig. 14.4). Once the interatrial septum is punctured, additional 2000 Units of heparin bolus is given.

Next, the ENDOCATH balloon occlusion catheter is introduced across the atrial septal puncture to gain access to the left atrium. A pigtail catheter is then introduced into the left atrium and is positioned in the LAA. Contrast is injected through this pigtail catheter to visualize the LAA in multiple planes and the size and lobes of the LAA are reassessed during this step (Fig. 14.5a). After verifying the size of the LAA and its suitability for LARIAT procedure, the endocardial FindrWIRZ magnet-tipped guidewire is introduced into the LAA and positioned at the distal most tip of the LAA (Fig. 14.5b).

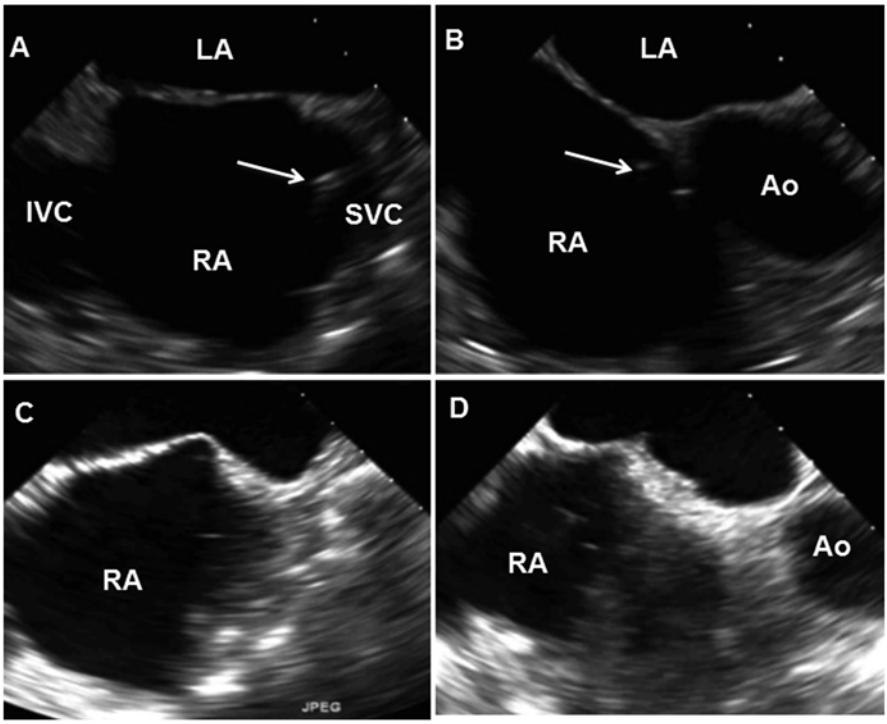


Fig. 14.4 Transesophageal echocardiography for transseptal catherization. Bicaval and short-axis views of the intra-atrial septum are useful for an inferior–posterior transseptal puncture. The bicaval views (panels **a** and **c**) allow for superior (closer to the SVC) to posterior (closer to the IVC) orientation, while the short-axis view allows for anterior (near the Ao) position. The *arrows* in panels (**a**) and (**b**) indicate the transeptal sheath in the SVC. Panels (**c**) and (**d**) demonstrate "tenting" of the transeptal needle on the foramen ovale. *LA* left atrium, *RA* right atrium, *SVC* superior vena cava, *IVC* inferior vena cava, *Ao* aorta (Reproduced from Koneru et al. [14] with permission)

Following the positioning of the endocardial magnet-tipped guidewire, the epicardial magnet-tipped guidewire is introduced through the epicardial soft-tipped guide cannula and is carefully guided through the pericardial space towards the endocardial magnet. Once the magnet tips are aligned, they attach to each other and form a continuous railing (Fig. 14.5f, g). Next, the LARIAT snare device catheter is introduced through the epicardial guide catheter over the epicardial magnet guidewire. The LARIAT suture is carefully guided on top of this guidewire until the LARIAT suture reaches the ostium of the LAA (Fig. 14.5j). Disengagement of the magnet tips is frequent during this step. When the magnet tips disengage, the LARIAT suture has to be withdrawn and the magnet tips are realigned and then the LARIAT suture is moved over the LAA. To identify the neck of the LAA, the balloon of the ENDOCATH balloon occlusion device is inflated and this acts as a

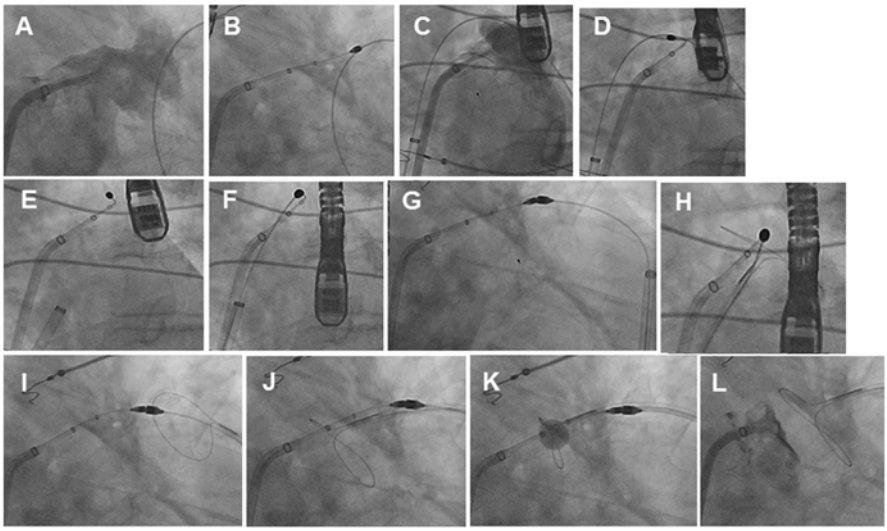


Fig. 14.5 Overview of LAA ligation with the LARIAT device. Percutaneous LAA ligation with the LARIAT suture delivery device requires an anterior pericardial access and a transseptal puncture. After transseptal puncture, a LA angiogram is performed in the RAO caudal (panel **a**) and LAO (panel **c**) fluoroscopic views to allow placement of the endocardial magnet-tipped guidewire into the most anterior lobe of the LAA (panels **b** and **d**). Connection of the epicardial magnet-tipped guidewire to the endocardial magnet is facilitated by rotating the epicardial sheath in the LAO view, so that the tip of the sheath is directed toward the endocardial magnet-tipped guidewire (panel **e**). Connection of the magnet-tipped guidewires should result in symmetrical alignment of the guidewires in both the LAO (panel **f**) and RAO caudal (panel **g**) fluoroscopic views. The LARIAT snare is then advanced over the epicardial magnet-tipped guidewire through the epicardial sheath. Alignment of the LARIAT snare is performed in the LAO fluoroscopic view to assure that the snare is positioned to move freely over the posterior aspect of the LAA (panel **h**). This should also result in the LARIAT snare being aligned in the RAO fluoroscopic view (panel **i**). Connection of the magnet-tipped guidewires stabilizes the LAA and allows positioning of the LARIAT suture delivery device over the LAA in an "over-the-wire" approach (panel **j**). Proper positioning of the snare over the LAA is guided by TEE-guided placement of the inflated balloon catheter at the mouth of the LAA and closure of the snare over the balloon (panel **k**). Confirmation of complete capture of the LAA is obtained with TEE and contrast LA angiography prior to release of the suture. If the snare closure does not result in complete capture of the entire LAA, the snare can be opened and repositioned to ensure complete LAA capture. Complete closure of the LAA is seen by the lack of color flow Doppler and LA angiography (L) (Reproduced from Koneru et al. [14] with permission)

guide to identify the neck of the LAA. Fluoroscopy and TEE guidance are used to accurately position the LARIAT suture at the neck of the LAA. The LAA is again imaged in multiple planes to ensure all the lobes of the LAA are proximal to the LARIAT suture. The LARIAT suture is then deployed and tightened (Fig. 14.5k). Next contrast is injected to verify complete sealing of the LAA (Fig. 14.5l). This is verified further on TEE with color Doppler. If there is flow into the LAA, then the

LARIAT suture is released and repositioned until complete sealing of the LAA can be demonstrated. Once it is confirmed on both fluoroscopy and TEE that the LAA is sealed off, then the LARIAT suture is tightened and tension applied by means of TENSURE suture tightener for about 3–5 min. Again the sealing of the LAA is confirmed on fluoroscopy and TEE. Complete sealing of the LAA is defined as absence of flow across the neck of the LAA on TEE color Doppler and no leakage of the dye into the LAA. Further, there should not be any leftover stump of the LAA. However, leaks <5 mm and stump size less than 5 mm have been considered as acceptable results. The goal of the procedure should be to secure complete sealing of the LAA. After tension has been applied to the LARIAT suture, the LARIAT suture is cut by means of SURECUT suture cutter. After the suture is cut, all the magnet guidewires are withdrawn.

Due to extensive manipulation of the heart and pericardial space during this procedure, significant amount of pericardial effusion can be expected. Therefore, a pericardial drain is introduced and left in place for 24–48 h. Once the pericardial effusion decreases to <50 cm^3/day, the pericardial drain is withdrawn and the skin opening is sealed off.

Anticoagulation Management

There have been several instances of thrombus formation at the site of the LAA stump following the LARIAT procedure [16–20]. The timings of detection of these thrombi have varied between different reports. However, the vast majority of these clots have been detected during the first 45–90 days. This could be likely due to inflammatory activity at the site of the LAA stump from the traumatic soft tissue occlusion by the LARIAT suture. The endothelial injury and likely release of inflammatory mediators at this site promote pro-coagulant activity at this site and result in thrombus formation. It is therefore recommended that these patients be continued on oral anticoagulation for a duration of at least 90 days, in those patients without absolute contraindication to anticoagulation. However, this approach is not without controversy and is intensely debated. At our center in those patients without absolute contraindication to oral anticoagulation, we continue oral anticoagulation with vigorous follow-up for a period of 90 days. Utilizing this approach, we did not have any thromboembolic events in our experience of 100 patients who have undergone LARIAT procedure. In those patients with absolute contraindication to oral anticoagulation, we recommend continuing antiplatelet agents for the duration of 90 days. Earlier discontinuation of oral anticoagulants or antiplatelet agents can be done if complete sealing of the LAA can be demonstrated by means of TEE. This area still requires further exploration. There is no perfect anticoagulation strategy that can be recommended at this point. If the LAA ligation is done for anticoagulation contraindication, long-term antiplatelet therapy should be considered after the initial short-term OAC. If the LAA exclusion is offered for arrhythmia-related reasons, continuation of OAC is recommended.

Follow-Up

The patients usually remain in the hospital for 2–3 days following LARIAT procedure. The patients are then followed up at 30, 60, and 90 days in the clinic. A follow-up TEE is recommended between 45 and 90 days to verify complete sealing of the LAA. If complete sealing of the LAA is confirmed, then the patients can discontinue the anticoagulant agents. Leaks <5 mm are considered non-significant and the patients can still discontinue the oral anticoagulation. Since there is limited data on the evolution of the remnant LAA leaks following the LAA exclusion procedures, further imaging follow-up can be performed at the discretion of the treating physician. In case of leaks >5 mm, we recommend closer follow-up with TEE every 3–6 months. If complete sealing of the LAA can be demonstrated, then the frequency of follow-up can be decreased based on the discretion of the physician. In our experience, an annual TEE is a reasonable strategy to assess for late thrombus formation at the ligation site and possible late leaks that have been reported by a few operators. Again this is an area that requires further research in figuring out the optimal imaging follow-up strategy.

Complications

Perioperative Complications

Pericarditis: This is one of the most common complications following the LARIAT procedure. The incidence of pericarditis following LARIAT procedure has reported to be in the range of 2–22 % in various studies [21–25] (Table 14.1). Pericardial access and manipulation of the LAA during the procedure by means of the magnetic guidewire and other catheters may cause irritation and cause inflammation of the pericardium resulting in pericarditis. Besides this, deployment of the LARIAT suture around the neck of the LAA may result in pericarditis. Bartus et al. also observed that subjects undergoing LARIAT procedure developed chest pain without evidence of pericarditis [25]. In their study, 20 patients developed chest pain following LARIAT procedure, but only 2 of these patients had evidence of pericarditis [25]. Pericarditis can be managed with NSAIDS and/or colchicine. In our experience, colchicine is very effective for post-LARIAT pericarditis.

Pericardial effusion: Pericardial effusion has also been noted commonly following the LARIAT procedure. There is wide variability in the reported incidence of pericardial effusion. The reported incidence varies between 1 and 44 % (Table 14.1). This wide variability in the incidence of pericardial effusion is due to the different criteria of evaluation for pericardial effusion [21–25]. Pericardial inflammation following the LARIAT procedure may result in pericardial effusions. In addition, the ischemic changes in the LAA due to application of the LARIAT suture may contribute to the pericardial inflammation and effusion. In our center, we routinely leave a

Table 14.1 Summary of reported efficacy and complications of LARIAT procedure

	Miller et al. [23]	Price et al. [22]	Stone et al. [21]	Massumi et al. [24]	Bartus et al. [15]
Efficacy	41	154	27	21	89
Initial success	38 (93 %)	132 (86 %)	25 (92.6 %)	20 (100 %)	85 (95.5 %)
Immediate leaks <1 mm	38 (93 %)	58 (92 %)	25 (92.6 %)	20 (100 %)	85 (95.5 %)
90 Days leaks <1 mm	31 (76 %)	50 (79 %)	22 (100 %)	17 (100 %)	77 (95 %)
1 Year leaks <1 mm	NR	NR	NR	NR	64 (98 %)
Leak <5 mm	41/41 (100 %)	59/63	22/22 (100 %)	17/17 (100 %)	81/81 (100 %)
TIA/stroke	1 (2 %)	NR	1 (3.7 %)	1 (4.7 %)	2 (2.2 %)
Complications					
Pericardial access complications	NR	NR	NR	NR	2 (2.2 %)
Transseptal access complications	NR	NR	NR	NR	1 (1.1 %)
Major bleeding	2 (5 %)	14 (9.1 %)	1 (3.7 %)	NR	3
Pericardial effusion	18 (44 %)	16 (10 %)	1 (3.7 %)	2 (9.5 %)	1 (1.1 %)
Pleural effusion	6 (15 %)	4 (3 %)	1 (3.7 %)	NR	0
Cardiac perforation	4 (9 %)	3 (2 %)	1 (3.7 %)	1 (4.7 %)	2 (2.2 %)
Thrombus formation	0	4 (3 %)	0	0	0
Pericarditis	9 (22 %)	NR	3 (11.1 %)	3 (14.3 %)	2 (2.2 %)
Death	0 %	0 %	0 %	0 %	2 (2.2 %)
Tamponade	2 (4 %)	7 (4.5 %)	0	2 (9.5 %)	0

NR not reported

pericardial drain for 24–48 h following the LARIAT procedure and the drain is removed once the drainage is <50 cm^3/day. Clinically significant pericardial effusions with tamponade physiology requiring pericardiocentesis have also been reported [22–24]. Tamponade due to cardiac perforations have also been reported in a few studies [22–24].

Cardiac perforation: This is a potentially fatal complication that can occur during the LARIAT procedure. Perforation of the heart can occur during epicardial access from the pericardiocentesis needle or with the epicardial guidewires and catheters. Cardiac perforation can also occur during trans-septal puncture; the endocardial magnetic guidewire can perforate the LAA while being positioned there. Further, perforation can also occur during the deployment of the suture. In the study by Miller et al., 9 % of the patients had cardiac perforation, while in the study by Bartus et al. the incidence of cardiac perforation was reported to be 2.2 % [23, 25]. Operator inexperience may also contribute to the perforations. Appropriate precautions should be taken during pericardial access and it should always be done under fluoroscopic guidance. Due to the high risk of perforation during the LARIAT procedure, it is recommended to perform the procedure in a hybrid suite with surgical back up.

Thromboembolism: multiple catheters are used for this procedure and also there is intense manipulation within the heart by means of the guidewires and catheters and therefore thromboembolic events may occur. Therefore, adequate periprocedural anticoagulation with heparin is recommended to avoid adverse thromboembolic events during the procedure.

Others: Besides the above complications, access site complications such as bleeding, hematoma, and pseudoaneurysm formation can occur. Pleural effusion has also been noted in some patients undergoing LARIAT procedure [23].

Late Complications

Thrombus formation: There have been several reports of thrombus formation at the site of the LAA stump. In our survey of LARIAT operators across the United States, there were a total of 19 (2 %) cases of LAA thrombus formation out of a total of 964 LARIAT procedures. After the LARIAT procedure, the stump of the LAA undergoes ischemic remodeling following the application of the LARIAT suture and this remodeling is likely to cause this surface to become thrombogenic. Although several reports of thrombus have been reported, so far there have been no reports of embolism from these thrombi [16–20]. We believe that the highest risk of thrombus formation at the site of the LAA is during the first 45 days when there is ischemic necrosis of the LAA and endothelialization of the stump site. Therefore, during this period these patients should be anticoagulated, if feasible, to prevent thrombus formation.

LAAleaks: Application of the LARIAT suture is expected to completely seal off the LAA and results in its involution due to ischemic necrosis of the LAA. However, leaks into the LAA with blood flow are not uncommon after the LARIAT procedure. The estimated prevalence of the leaks varies based on follow-up duration and across multiple studies. This is due to dynamic evolution of the leaks due to remodeling process in the left atrium and the LAA after the application of LARIAT suture. Spontaneous sealing of the LAA leak has been reported in a few patients; however, in a few patients the leaks also increased in size [15]. At 90 days follow-up TEE, 76–95 % of the patients had leaks <1 mm in size (Table 14.1). One-year follow-up was reported by Bartus et al., and in their study, 98 % of their patients had leaks <1 mm [15]. TEE is therefore recommended for follow-up of patients with persistent LAA leaks to monitor the size of the leak, and if the leak continues to increase in size, closure of the LAA leaks can be considered with the atrial septal occluder devices.

Efficacy of LARIAT Procedure

The LARIAT procedure when successfully performed completely eliminates the LAA and therefore mitigates stroke risk in AF. The efficacy of this procedure in mitigating stroke risk in AF patients therefore depends on complete elimination of the LAA. The incidence of TIA/Stroke following LARIAT procedure has been reported to be in the range of 2–4.7 % (Table 14.1). Thromboembolic events as reported from these observational studies are similar to those reported with other percutaneous LAA exclusion devices. In the PROTECT-AF trial, after WATCHMAN device implantation, ischemic stroke event rate was 1.9 per 100 patient years [13]. Systemic embolism and hemorrhagic stroke event rate was 0.3 per 100 patient years for both these outcomes [13]. Santoro et al. evaluated the long-term thromboembolic event rate with Amplatzer Cardiac Plug and this was estimated to be 2.5 % per year [11]. There are no randomized controlled studies reporting the efficacy of LARIAT in stroke prevention. Published observational studies vary in their follow-up durations and therefore the outcomes are variable across these studies.

Management of Post-LARIAT Leaks

Following the LARIAT procedure, there is remodeling of the stump of the LAA and the leaks in the LAA continue to evolve over a period of time. There has been no consensus on the acceptable leak size in patients undergoing percutaneous LAA exclusion devices. However, leaks <5 mm are considered to be acceptable [26]. Persistent LAA leaks if deemed to increase the risk of thromboembolism can be sealed off using several percutaneous techniques. In our series of 6 patients, we had reported successful closure of the persistent LAA leaks following LARIAT

procedure by means of percutaneous techniques [27]. These patients were deemed to have high risk of thromboembolism as evidenced by their high CHADS2 score and these patients also had bidirectional flow into the LAA with complete filling of the LAA [27]. The above patients obviously had high bleeding risk and therefore underwent LARIAT procedure in the first place. Considering their high risk for thromboembolism, attempt was made to seal off this leak. Leaks in the LAA tend to be concentric after the LARIAT procedure unlike WATCHMAN device, wherein the leaks tend to be eccentric [27]. In 5 of these patients, we used Amplatzer septal occluder device (St. Jude Medical) to seal off the remnant leaks [27]. In another patient, the LARIAT procedure was repeated successfully and the remnant leak was sealed off [27]. Yeow et al. reported the use of Gore Helex septal occluder device to seal the LAA leak after LARIAT procedure [28]. These procedures led to complete sealing of the LAA. The above approaches may not be suitable in all patients and are recommended only for patients with a significant leak in the LAA who are deemed to be at high risk for thromboembolism.

Role of LARIAT in Rhythm Management

Di Biase et al. demonstrated the importance of LAA as a source of triggers for AF [29]. In their study, they observed that LAA was capable of independent firing in 27 % of the patients who had recurrence of AF following catheter ablation [29]. Further in 8.7 % of the subjects, the LAA was the only trigger for AF [29]. Based on these observations, our group had hypothesized that LAA exclusion with LARIAT procedure will decrease the AF burden. This hypothesis was tested in multiple studies. Han et al. demonstrated that the electrical activity in LAA as measured by endocardial and epicardial surface voltage decreased significantly following the application of LARIAT suture [30]. In their study on 68 patients, 94 % had decrease in LAA voltage after successful application of the LARIAT suture [30]. The bipolar LAA voltage decreased from 4.7 ± 2.83 to 0.6 ± 0.27 mV [30]. Further, 90 % of the patients lost pacing capture of the left atrium when paced from the LAA after the LARIAT procedure.

We further tested this hypothesis in patients with AF and an implanted cardiac electronic device (CIED). In this study, 50 patients with AF and an implanted CIED underwent LARIAT procedure and were followed up for 12 months [31]. The CIED device was interrogated to assess the AF burden [31]. The baseline AF burden was 76 ± 33 %, and at 3 months, the AF burden had decreased to 42 ± 34 % ($p < 0.0001$) [31]. At 12 months, the AF burden was 59 ± 26 %; this was significantly lower than baseline ($p < 0.001$) [31]. We have shown the feasibility and efficacy of sequential LAA ligation and pulmonary vein isolation in patients with persistent AF [32]. Seventy-five percentage of the patients were in sinus rhythm at 6 months with significant decrease in *P* wave duration and dispersion [32]. This added benefit is unique to LAA ligation as compared to WATCHMAN occlusion device for LAA as the WATCHMAN device does not lead to ischemic necrosis of LAA. Our prospective

study—the left atrial appendage ligation and ablation for persistent atrial fibrillation (LAALA-AF registry) —has assessed the adjunctive benefit of LARIAT procedure to AF ablation. In this study, prospective patients undergoing AF ablation were compared to patients undergoing both AF ablation and LARIAT. The AF recurrence rates were 32.5 % in the LARIAT with AF ablation group compared to 57.5 % in the AF ablation only group ($p=0.025$) [33]. The number of repeat ablations was also lower in the LARIAT with AF ablation group (15 vs. 35 %, $p=0.04$) [33]. Although these studies were observational in nature, they are uniform in their observation that LARIAT procedure helps decrease AF burden as well as recurrence of AF.

The decrease in AF triggers following LARIAT procedure is due to ischemic necrosis and atrophy of the LAA, which contains triggers and the substrate for the AF. This procedure therefore has additional advantage of decreasing AF burden unlike other LAA exclusion procedure. In spite of the above evidence of decreased AF burden with LARIAT procedure, it is our opinion that this procedure should not be performed solely for the purpose of decreasing AF burden and primarily be performed for LAA exclusion in patients with stroke risk and contraindications to oral anticoagulation.

Role of LARIAT in Homeostasis

The LAA plays a role in systemic homeostasis. There was a minor decrease in serum sodium levels after the LARIAT procedure. In this study of 54 patients, immediately after the LARIAT procedure, the serum sodium decreased to 135 ± 3.9 mmol/L from a baseline of 139 ± 3.2 mmol/L ($p<0.0001$) [34]. However, the serum sodium levels returned back to near baseline during follow-up. There was a remarkable decrease in both systolic and diastolic blood pressures after the LARIAT procedure. The mean systolic blood pressure decreased from 137 ± 17 to 117 ± 18 mmHg ($p<0.0001$) [33]. Similarly, the mean diastolic blood pressure decreased from 77 ± 13 to 67 ± 13 mmHg ($p<0.0001$) [34]. The acute changes in serum sodium and blood pressures are likely due to degranulation and release of ANP from the ischemic cardiomyocytes in the LAA. Further validation of these observations is ongoing in the LAA-Homeostasis study.

Conclusion

LARIAT procedure is a minimally invasive technique for LAA exclusion that has been shown to have reasonably good safety and efficacy in observational studies. This procedure requires suitable cardiac anatomy and highly skilled operators to achieve good results. Multimodality cardiac imaging helps in the preoperative planning and intraoperative positioning and placement of the LARIAT suture at the ostium of the LAA. In addition to minimizing stroke risk, LARIAT procedure also

helps in decreasing AF burden. As operators gain more experience with this technique, it is likely to become a favorable strategy of LAA exclusion in AF patients given the added benefit of decreasing AF burden.

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. Stroke. 1991;22:983–8.
2. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted county, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006;114:119–25.
3. Chamberlain AM, Gersh BJ, Alonso A, et al. Decade-long trends in atrial fibrillation incidence and survival: a community study. Am J Med. 2015;128(3):260–7.
4. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: stroke prevention in atrial fibrillation II study. Lancet 1994;343:687–91.
5. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.
6. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.
7. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093–104.
8. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.
9. Ostermayer SH, Reisman M, Kramer PH, et al. Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: results from the international multi-center feasibility trials. J Am Coll Cardiol. 2005;46:9–14.
10. 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.
11. Santoro G, Meucci F, Stolcova M, et al. Percutaneous left atrial appendage occlusion in patients with nonvalvular atrial fibrillation: implantation and up to four years follow-up of the AMPLATZER Cardiac Plug. EuroIntervention. 2014. Accessed online on 08/03/2015 at http://www.pcronline.com/eurointervention/ahead_of_print/201410-13/.
12. Bergmann MW, Landmesser U. Left atrial appendage closure for stroke prevention in nonvalvular atrial fibrillation: rationale, devices in clinical development and insights into implantation techniques. EuroIntervention. 2014;10:497–504.
13. Reddy VY, Doshi SK, Sievert H, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-year follow-up of the PROTECT AF (Watchman left atrial appendage system for embolic protection in patients with atrial fibrillation) trial. Circulation. 2013;127:720–9.
14. Koneru JN, Badhwar N, Ellenbogen KA, Lee RJ. LAA ligation using the LARIAT suture delivery device: tips and tricks for a successful procedure. Heart Rhythm. 2014;11:911–21.
15. Bartus K, Han FT, Bednarek J, et al. 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.
16. Truesdell AG, Patel CP, Maini BS. Late-occurring left atrial appendage thrombus after ligation using LARIAT. J Interv Card Electrophysiol. 2014;41:101.
17. Koranne KP, Fernando RR, Laing ST. Left atrial thrombus after complete left atrial appendage exclusion with LARIAT device. Catheter Cardiovasc Interv. 2015;85(2):E54–7.

18. Giedrimas E, Lin AC, Knight BP. Left atrial thrombus after appendage closure using LARIAT. Circ Arrhythm Electrophysiol. 2013;6:e52–3.
19. Briceno DF, Fernando RR, Laing ST. Left atrial appendage thrombus post LARIAT closure device. Heart Rhythm. 2014;11:1600–1.
20. Baker MS, Paul Mounsey J, Gehi AK, Chung EH. Left atrial thrombus after appendage ligation with LARIAT. Heart Rhythm. 2014;11:1489.
21. Stone D, Byrne T, Pershad A. Early results with the LARIAT device for left atrial appendage exclusion in patients with atrial fibrillation at high risk for stroke and anticoagulation. Catheter Cardiovasc Interv. 2015;86(1):121–7.
22. Price MJ, Gibson DN, Yakubov SJ, et al. Early safety and efficacy of percutaneous left atrial appendage suture ligation: results from the U.S. transcatheter LAA ligation consortium. J Am Coll Cardiol. 2014;64:565–72.
23. Miller MA, Gangireddy SR, Doshi SK, et al. Multicenter study on acute and long-term safety and efficacy of percutaneous left atrial appendage closure using an epicardial suture snaring device. Heart Rhythm. 2014;11(11):1853–9.
24. Massumi A, Chelu MG, Nazeri A, et al. Initial experience with a novel percutaneous left atrial appendage exclusion device in patients with atrial fibrillation, increased stroke risk, and contraindications to anticoagulation. Am J Cardiol. 2013;111:869–73.
25. Bartus K, Bednarek J, Myc J, et al. Feasibility of closed-chest ligation of the left atrial appendage in humans. Heart Rhythm. 2011;8:188–93.
26. Viles-Gonzalez JF, Kar S, Douglas P, et al. 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.
27. Pillai AM, Kanmanthareddy A, Earnest M, et al. Initial experience with post LARIAT left atrial appendage leak closure with Amplatzer septal occluder device and repeat LARIAT application. Heart Rhythm. 2014;11:1877–83.
28. Yeow WL, Matsumoto T, Kar S. Successful closure of residual leak following LARIAT procedure in a patient with high risk of stroke and hemorrhage. Catheter Cardiovasc Interv. 2014;83:661–3.
29. Di Biase L, Burkhardt JD, Mohanty P, et al. Left atrial appendage: an underrecognized trigger site of atrial fibrillation. Circulation. 2010;122:109–18.
30. Han FT, Bartus K, Lakkireddy D, et al. The effects of LAA ligation on LAA electrical activity. Heart Rhythm. 2014;11:864–70.
31. Afzal MR, Kanmanthareddy A, Earnest M, et al. Impact of left atrial appendage exclusion using an epicardial ligation system (LARIAT) on atrial fibrillation burden in patients with cardiac implantable electronic devices. Heart Rhythm. 2015;12(1):52–9.
32. Badhwar N, Lakkireddy DR, Kawamura M, et al. Sequential percutaneous LAA ligation and pulmonary vein isolation in patients with persistent atrial fibrillation: initial results of feasibility study. J Cardiovasc Electrophysiol. 2015;26(6):608–14.
33. Lakkireddy DR, Reddy M, Sridhar ARM, et al. Left atrial appendage ligation and ablation for persistent atrial fibrillation (LAALA-AF registry). J Am Coll Cardiol. 2014;63 (abstract).
34. Maybrook R, Pillarisetti J, Yarlagadda V, et al. Hyponatremia and hemodynamic changes following percutaneous left atrial appendage ligation with the LARIAT device. J Am Coll Cardiol. 2014;63 (abstract).

Chapter 15
LARIAT: Trials and Registries Results

Miguel Valderrábano

Since its commercialization in the United States in 2011, the Lariat® suture device for left atrial appendage (LAA) occlusion has experienced widespread utilization. It has been released into the market in the United States under FDA 510 (K) approval as a tool for "suture placement and knot-tying for use in surgical applications where soft tissues are (sic) being approximated." However, the device conception, design, and implementation are entirely and exclusively aimed at delivering a suture ligature to the LAA for the purpose of its exclusion from the circulation and stroke prevention in atrial fibrillation. This commercialization outside the scope of a clinical trial has led to a large collective experience in unselected patient populations. Significant heterogeneity exists in regard to patient characteristics, operator experience, and quality and extent of data collection. Nevertheless, the accumulated evidence provides valuable, "real-life" insights into its clinical application. Sources of information about the clinical outcomes of the Lariat® procedure include single-center reports, multicenter registries of voluntarily collected data, and reports to the FDA's MAUDE database. Undoubtedly, the available data are subject to publication and other biases, but do offer a glimpse of the Lariat's clinical performance. Table 15.1 summarizes the clinical data available to date.

M. Valderrábano, M.D., F.A.C.C. (✉)
Department of Medicine, Weill College of Medicine, Cornell University, New York, NY, USA

Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030, USA

Division of Cardiac Electrophysiology, Department of Cardiology, Houston Methodist Hospital, 6550 Fannin St, Suite 1901, Houston, TX 77030, USA
e-mail: Mvalderrabano@houstonmethodist.org

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_15

First-in-Man Experience

Bartus et al. [1] first reported the use of Lariat® appendage occlusion in 13 patients. Two of these patients were undergoing cardiac surgery and the procedure was open-chested. The closed-chest procedure was attempted in 11 patients out of 14 patients screened. Percutaneous subxyphoid pericardial access was used in 9 patients and a minithoracotomy (<20 mm) was used in two. Success at ligation of the LAA was achieved in 10/11 patients. In one of them, a thoracotomy was required to extract the Lariat® snare after an otherwise successful LAA ligation. One procedure failed due to inadequate visualization of the LAA on transesophageal echocardiogram (TEE). Six patients returned for a 60-day follow-up TEE. Four of six patients had complete LAA closure, while two patients had a less than 2-mm opening by color flow Doppler. This pioneering work demonstrated the feasibility and acute success of the approach for the human anatomy, since the prior experience had only been in canines [2].

Initial Outcomes Data

Bartus et al., in a single-center series from Poland, reported on 103 consecutive patients undergoing Lariat® LAA ligation [3]. An additional group of 16 patients had been previously excluded due to unsuitable LAA anatomies as assessed on pre-procedure cardiac CT scan. Of the 103 patients taken to the procedure, 14 were excluded intraprocedurally due to pericardial adhesions (3) or mobile thrombus (11). Thus, overall, the Lariat® LAA ligation was attempted in 89 out of 119 potential candidates, and the suture was successfully deployed in 85 (95.5 %). However, complete LAA closure without flow leaks 1 mm or greater was achieved in 82. Thus, the success of complete acute LAA ligation was 92 % (82/89). On follow-up, TEE was performed on 85 patients at 30 days post-procedure and showed complete closure on 81 patients. This represents 95 % of the patients in whom the Lariat® suture was successfully delivered (81/85), but only 91 % of the patients the procedure was attempted (81/89) and 78 % of the patients taken to the procedure (81/103). At 1 year, TEE was performed on 65 patients, 64 of which had complete LAA closure (98 %).

Intraprocedural adverse events included hemopericardium (2 treated with percutaneous pericardial drainage, one due to right ventricular perforation and another due to a complicated transseptal puncture), epigastric vessel laceration requiring cauterization. There were 2 deaths and 2 strokes on follow-up. One patient developed a thrombus on the LAA stump. Overall, the data was interpreted as confirmation that the procedure can effectively lead to enduring LAA ligation in the vast majority of patients in which it is attempted. Doubts remain as to the long-term efficacy at stroke prevention. Deaths occurring after the procedure appeared unrelated.

Table 15.1 Outcomes of reported Lariat® studies

	Attempted/ total screened		Acute LAA closure		Persistent LAA closure		Stroke		Bleeding		Pericardial bleeding drained		Emergency surgery		Pericarditis		Late pericardial effusion		Death		LAA stump thrombus		Pleural effusion	
Study	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Bartus 2011	11/14	79	10/14	91	4/6	67	N/A	N/A	N/A	N/A	1/11	9	1/11	9	N/A	N/A	0	0	0	0	0	0	0	0
Bartus 2013	89/119	75	82/89	92	81/89	91	2/89	2	3/89	3	2/89	2	0	0	2/89	2	1/89	1	2/89	2	1/85	1	0	0
Massumi 2013	20	N/A	20/20	100	20/20	100	0	0	0	0	2/20	10	1/20	5	3/20	15	1/20	5	0	0	0	0	0	0
Stone 2013	27	N/A	5/27	93	22/27	81	2/27	7	0	0	0	0	1/27	4	3/27	11	0	0	0	0	0	0	1/27	4
Price 2014	154	N/A	133/154	86	50/63	79	3/154	2	14/154	9	16/154	10	3/154	2	N/A	N/A	3/154	2	4/154	3	4/145	3	3/154	2
Lee 2014	140	N/A	135/140	96	112/122	92	4/140	3	0	0	0		2/140	1	8/140	6	0	0	4/140	3	0/140	0	0	0
Miller 2014	41	N/A	38/41	93	31/41	76	1/41	2	0	0	8/41	20	2/41	5	9/41	22	5/41	12	0	0	0	0	3/41	7

US Single-Center Experiences

Since its initial commercialization, selected centers have accumulated substantial experience and have reported it in the literature. Massumi et al. [4] reported a series of 20 patients, in which successful LAA ligation was achieved in all and complete ligation persisted on follow-up TEE. One patient required emergency surgery to repair a right ventricular perforation that occurred during pericardial access. Three patients developed significant pericarditis post-procedure. Two patients required pericardiocentesis. Stone et al. [5] reported outcomes of 27 patients undergoing Lariat® LAA ligation. Acute procedural success was achieved in 25 patients. There was one LAA perforation that required surgical LAA closure. On follow-up TEE, complete LAA ligation was present in 22/25 patients. Post-procedural events included two strokes, three cases of pericarditis, and one pleural effusion.

Multi-Center Registries

Additional collective experiences have been reported. Price et al. [6] compiled retrospectively collected data from eight sites in the United States and a total of 154 unselected patients. In nine patients, the Lariat® device was not deployed due to access or delivery issues. Of the remainder 145, successful LAA ligation was achieved acutely in 92 %, which was 86 % of the attempted patients. Follow-up post-discharge imaging of the LAA was available in 63 patients, of whom 79 % had persistent complete LAA ligation, thus resulting in a long-term incomplete closure rate of 21 % of the imaged patients. Significant procedural complications occurred, including major bleeding (9 %), right ventricular perforations (2) and LAA perforation (1) requiring emergency surgery (3). There was one in-hospital death related to pneumonia and sepsis. On post-discharge follow-up, strokes occurred in 2 patients, and pericardial (3) and pleural effusions (3) also occurred. A total of four deaths occurred post-procedure. These data highlight that, despite comparable rates of acute success at LAA ligation, the Lariat® device, when applied to an unselected population of patients, deemed to be at high risk of stroke and bleeding (the standard clinical indications) can be associated with higher rates of complications than in the original series. Of particular concern, in the absence of efficacy studies showing stroke protection, is the occurrence of LAA stump thrombi (four cases) and the significant rate of incomplete LAA closure (up to 21 %). The incomplete, inconsistent follow-up imaging of these patients casts doubt as to the accuracy of the reported rates of these complications and highlights the need for prospective, controlled data.

Miller et al. [7] reported a series of 41 patients from four centers. Despite achieving an acute success (complete LAA closure) in 38 patients (93 %), incomplete closure was detected on follow-up imaging in 24 % of the patients. Two patients required surgical repair of an LAA perforation. One patient (2 %) had a transient

ischemic attack, and 8 (20 %) developed pericardial effusions requiring pericardiocentesis. Similarly, despite the high acute technical success, the incidence of complications and significant LAA leaks raise concerns about its safety when applied to unselected populations.

Finally, a multicenter registry was reported in abstract form as a late-breaking clinical trial in the Heart Rhythm Society meeting in San Francisco in 2014 [8]. It reported data from five centers and a total of 140 patients in whom the Lariat® procedure was attempted. It was successful at achieving complete LAA closure in 135 (96 %). One patient had incomplete closure and in four patients the suture could not be delivered due to pericardial adhesions. Follow-up TEE was completed in 122 patients and showed persistent closure in 112 (92 %). The average follow-up was 22 months. There were a total of 4 deaths (one periprocedural due to pulmonary embolism, 3 on follow-up deemed to be unrelated to the procedure). Four patients developed strokes (2 not deemed to be embolic in nature).

Other Reported Data

LAA Stump Thrombus

Development of endocardial thrombus on the left atrial side of the Lariat® ligature is a most concerning complication of the procedure, because it implies an iatrogenic creation of the very problem the Lariat® aims to prevent. Thus far there have been multiple single-center reports of individual cases [9–13]. The real incidence remains unknown in the absence of prospective data collection. Bartus et al. [3] reported one case of LAA stump thrombus out of 89 patients attempted. Price et al. [14] reported 4 cases out of 145 patients in whom the device suture was deployed. Thus far all reported cases of stump thrombi were incidentally discovered on routine imaging post-procedure, in the absence of signs or symptoms of systemic embolization. Thrombi have consistently resolved after treatment with oral anticoagulation.

Leakage Occlusion

Incomplete ligation of the LAA has been reported to occur with variable incidences, ranging from 0 [4] to 24 % [7]. In all reported cases, flow "leaks" into the LAA have been detected as an incidental finding demonstrated by Doppler flow into the LAA on post-procedure TEE, without attributable clinical consequences. Despite the uncertain clinical significance, concerns about potential risk of stroke arising from an incompletely ligated LAA have led to the implementation of leakage closure strategies [14–17]. Successful closure of residual leaks has been routinely achieved with septal occlusion devices or repeat Lariat® suture delivery. Outcomes data are necessary to establish the clinical validity of these approaches.

FDA Maude Database

Given the absence of systematically collected outcomes data in the context of controlled clinical trial, and the possibility of significant biases plaguing the available data (publication and otherwise), it is helpful to consult the FDA Maude database. However, these anecdotal reports should be interpreted with extreme caution, given the lack of a denominator and the self-reported nature of the data. Self-reported adverse events entered by operators and the manufacturer included a total of 35 events between 2011 and September 2014 (data available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm). Of these, there were 25 patients requiring emergency surgery (19 for LAA perforations, 3 for complete LAA avulsion, 2 for RV perforation, and 1 for LA perforation). Five patients died (3 after LAA avulsion, 2 after LAA perforation). There were nine additional LAA perforations that resolved with Lariat® deployment or pericardiocentesis. Finally, there was one case of ventricular tachycardia attributed to the pericardial access.

Future Studies

The accumulated experience in the United States thus far has not clarified the role Lariat® occupies in the prevention of stroke in atrial fibrillation and has led to the surfacing of significant complications, despite a high rate of technical success. It should be clear that the relevant goal is a clinical one to prevent stroke, not an anatomical one—to simply ligate the LAA. The manufacturer and the FDA are currently in the process of designing a study to specifically address stroke prevention. Additionally, anecdotal data suggests that LAA ligation may improve restoration of sinus rhythm in AF ablation, and studies to determine the antiarrhythmic role of Lariat® LAA ligation are also being planned.

Conclusions

The Lariat® commercialization in the United States was a staged process whereby individual centers initiated their experiences with the procedure, under some degree of guidance and proctoring by the manufacturing company. Such centers were selected based on their prior experience in pericardial access and trans-septal puncture, and data collection for reporting was not planned. Centers were rapidly expanded, and operators received a brief training. Certain details of periprocedural management were unstandardized, including the optimal analgesic or anti-inflammatory regimen, or the need for transient anti-thrombotic or anticoagulant treatment. It is clear from this experience that a high degree of procedural success at ligating the LAA can be achieved. However, there has been also a disorderly

surfacing of data on procedural complications, whose incidence must be clarified. In order to ascertain the ultimate role of the Lariat® LAA ligation in the prevention of stroke in AF, a randomized, controlled trial must be conducted.

References

1. Bartus K, Bednarek J, Myc J, Kapelak B, Sadowski J, Lelakowski J, Yakubov SJ, Lee RJ. Feasibility of closed-chest ligation of the left atrial appendage in humans. Heart Rhythm. 2011;8:188–93.
2. Lee RJ, Bartus K, Yakubov SJ. Catheter-based left atrial appendage (LAA) ligation for the prevention of embolic events arising from the LAA: initial experience in a canine model. Circ Cardiovasc Interv. 2010;3:224–9.
3. 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.
4. Massumi A, Chelu MG, Nazeri A, May SA, Afshar-Kharaghan H, Saeed M, Razavi M, Rasekh A. Initial experience with a novel percutaneous left atrial appendage exclusion device in patients with atrial fibrillation, increased stroke risk, and contraindications to anticoagulation. Am J Cardiol. 2013;111:869–73.
5. Stone D, Byrne T, Pershad A. Early results with the Lariat® device for left atrial appendage exclusion in patients with atrial fibrillation at high risk for stroke and anticoagulation. Catheter Cardiovasc Interv. 2015;86(1):121–7.
6. Price MJ, Gibson DN, Yakubov SJ, Schultz JC, Di Biase L, Natale A, Burkhardt JD, Pershad A, Byrne TJ, Gidney B, Aragon JR, Goldstein J, Moulton K, Patel T, Knight B, Lin AC, Valderrabano M. Early safety and efficacy of percutaneous left atrial appendage suture ligation: results from the U.S. transcatheter LAA ligation consortium. J Am Coll Cardiol. 2014;64:565–72.
7. Miller MA, Gangireddy SR, Doshi SK, Aryana A, Koruth JS, Sennhauser S, d'Avila A, Dukkipati SR, Neuzil P, Reddy VY. Multicenter study on acute and long-term safety and efficacy of percutaneous left atrial appendage closure using an epicardial suture snaring device. Heart Rhythm. 2014;11(11):1853–9.
8. Lee RJ, Bartus K, Morelli R, Massumi A, Badhwar N, Sievert H. Atrial fibrillation patients with contraindications to oral anticoagulation therapy treated with LAA ligation: initial long-term clinical outcomes. Heart Rhythm. 2014;11:LB02–3.
9. Giedrimas E, Lin AC, Knight BP. Left atrial thrombus after appendage closure using lariat. Circ Arrhythm Electrophysiol. 2013;6:e52–3.
10. Briceno DF, Fernando RR, Laing ST. Left atrial appendage thrombus post Lariat® closure device. Heart Rhythm. 2014;11:1600–1.
11. Baker MS, Paul Mounsey J, Gehi AK, Chung EH. Left atrial thrombus after appendage ligation with lariat. Heart Rhythm. 2014;11:1489.
12. Koranne KP, Fernando RR, Laing ST. Left atrial thrombus after complete left atrial appendage exclusion with Lariat® device. Catheter Cardiovasc Interv. 2015;85(2):E54–7.
13. Truesdell AG, Patel CP, Maini BS. Late-occurring left atrial appendage thrombus after ligation using lariat. J Interv Card Electrophysiol. 2014;41(1):101.
14. Mosley II WJ, 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.

15. Yeow WL, Matsumoto T, Kar S. Successful closure of residual leak following Lariat® procedure in a patient with high risk of stroke and hemorrhage. Catheter Cardiovasc Interv. 2014;83(4):661–3.
16. Pillai AM, Kanmanthareddy A, Earnest M, et al. Initial experience with post Lariat® left atrial appendage leak closure with amplatzer septal occluder device and repeat Lariat® application. Heart Rhythm. 2014;11(11):1877–83.
17. Guerrero M, Greenbaum A, O'Neill W. First-in-man late partial recanalisation after Lariat® suturing of the left atrial appendage successfully treated with an amplatzer septal occluder device. EuroIntervention. 2015;10(9):1126.

Chapter 16
Novel Percutaneous LAA Closure Devices in Clinical or Preclinical Trials

Sameer Gafoor, Luisa Heuer, Jennifer Franke, Markus Reinartz, Stefan Bertog, Laura Vaskelyte, Ilona Hofmann, and Horst Sievert

Abbreviations

CE mark	Conformité Européenne mark
LAA	Left atrial appendage
mm	Millimeter
PET	Polyethylene terephthalate
PTFE	Polytetrafluoroethylene
PVA	Polyvinylacetate
TEE	Transesophageal echocardiogram

S. Gafoor, M.D.
CardioVascular Center Frankfurt, Seckbacher Landstrasse 65, Frankfurt 60389, Germany

Swedish Heart and Vascular, Seattle, WA, USA

L. Heuer • M. Reinartz, M.D. • L. Vaskelyte, M.D. • I. Hofmann, M.D.
H. Sievert, M.D. (✉)
CardioVascular Center Frankfurt, Seckbacher Landstrasse 65, Frankfurt 60389, Germany
e-mail: info@cvcfrankfurt.de

J. Franke, M.D.
CardioVascular Center Frankfurt, Seckbacher Landstrasse 65, Frankfurt 60389, Germany

University of Heidelberg, Heidelberg, Germany

S. Bertog
CardioVascular Center Frankfurt, Seckbacher Landstrasse 65, Frankfurt 60389, Germany

Minnesota Veterans Affairs Medical Center, Minneapolis, MN, USA

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_16

Introduction

There are multiple devices already developed for left atrial appendage (LAA) closure. Each device provides a slightly different approach to address the issues of access, device delivery, and closure. This chapter will discuss novel devices and their preclinical or clinical studies that have been performed to-date.

Coherex

The Coherex WaveCrest LAA Occlusion system (Salt Lake City, Utah, USA) is made of three parts: occluder, anchors, and delivery system. The occluder is an expanded polytetrafluoroethylene (PTFE) membrane that is anchored with 20 microtines attached to the border of the device (Fig. 16.1a, b). In contrast to other

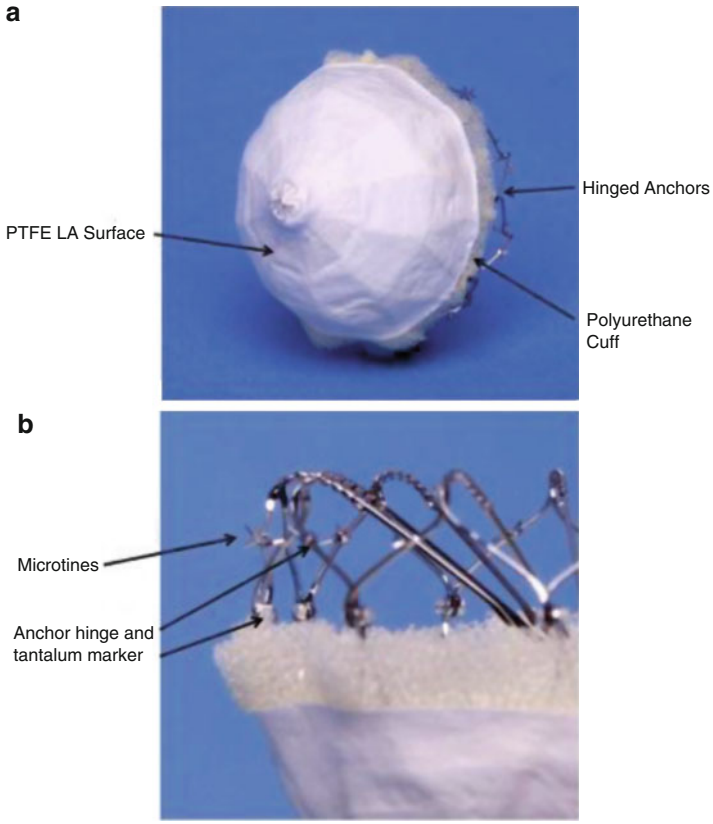


Fig. 16.1 (**a**) Coherex WaveCrest LAA Occluder (proximal side). This shows the PTFE surface on the LA with a polyurethane cuff. (**b**) Coherex WaveCrest LAA Occluder (anchors). Each anchor is connected with a hinge and marked with a tantalum marker. Each of the ten anchors has a single and double-pronged microtine for 20 microtines in total

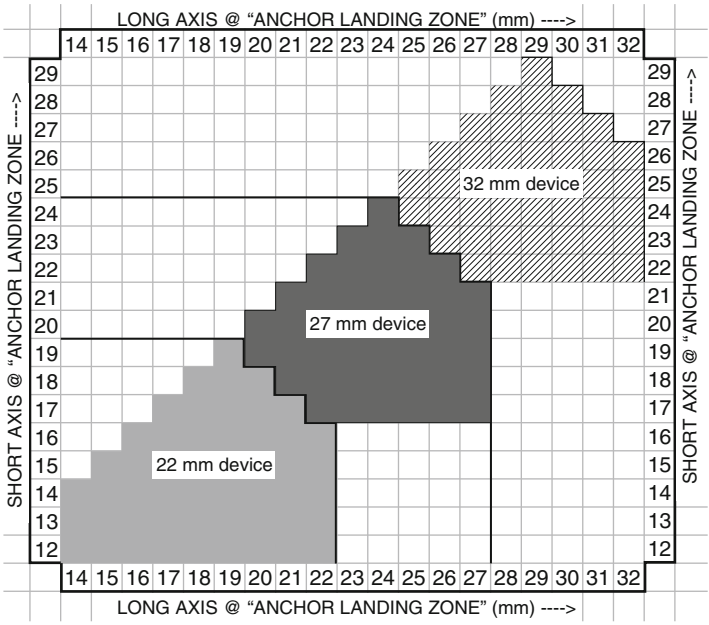


Fig. 16.2 Coherex WaveCrest LAA Closure sizing algorithm. This incorporates both short and long axis diameter of the LAA landing zone

devices, the occluder and anchoring system can be operated independently, allowing repositioning before anchoring. In addition, the operator has the option of injecting contrast through the delivery sheath (proximally) or on the appendage side of the occluder (distally) to evaluate stability and assess occlusion.

The occluder comes in three sizes (22, 27, and 32 mm). As with other devices, size selection is based upon measurements performed at 0, 45, 90, and 135° on transesophageal echocardiogram (TEE). The smallest device size is chosen so that the longest measured diameter does not exceed the nominal device size and the average of the longest and shortest diameters is at least 3 mm below the nominal device size. The sizing table is included in the instructions for use and is unique to other LAA occluder devices in that it incorporates both the short and long axis of the LAA in the sizing strategy (Fig. 16.2).

Implantation of the Coherex WaveCrest LAA Occluder is shown in Fig. 16.3. The optimal landing zone is determined by the line of widest measurement of the ostium, using the circumflex artery medially and a point at least 10–15 mm into the LAA from the tip of the lateral edge for reference, leaving room distally for the anchors to deploy. The landing zone is generally more proximal than other devices, which is meant to allow treatment of proximal lobe bifurcations and acutely angulated appendages. Distal injection is a unique feature of this device that allows visualization of contrast extravasation to assess leak.

The device was first implanted in June 2012. The first results of the device were presented by Dr. Vivek Reddy at Congenital and Structural Interventions (CSI) 2013, with successful deployment in 96 % of patients ($n=73$); 45-day data showed primary efficacy of 92 and 97 % with an intention-to-treat and as-treated protocol, respectively.

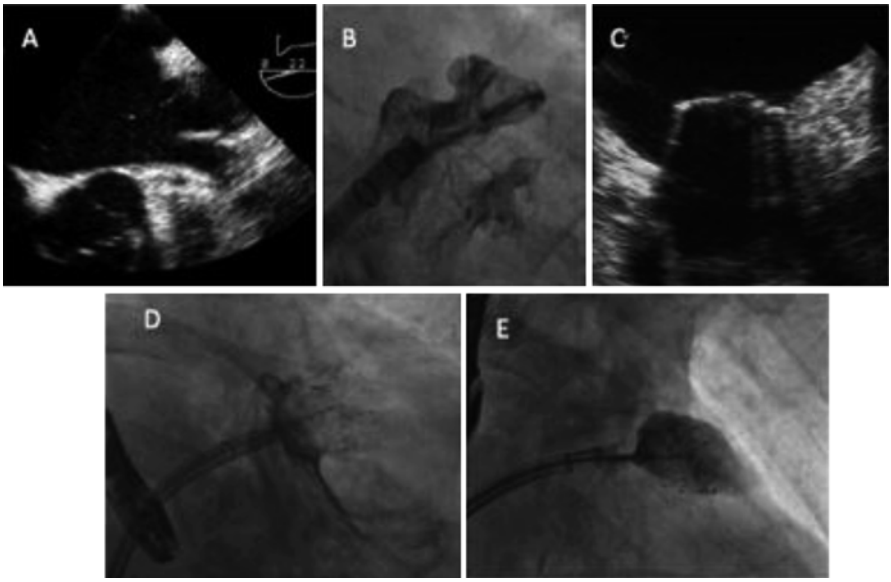


Fig. 16.3 Coherex implantation. LAA with proximal bifurcation seen on echocardiography (**a**) and angiography (**b**). Implanted Coherex device is seen on echocardiography (**c**) and fluoroscopy (**d**). Distal injection within the LAA showed no evidence of leak into the left atrium (**e**)

The total major adverse event rate was 2.7 %, consisting of two pericardial effusions treated by percutaneous drainage. There were no reports of stroke, device embolization, or associated thrombus. One-year follow-up will conclude in August 2014.

CE Mark was obtained in 2013. Next steps include a US investigational device exemption (IDE) trial with plans for start of enrollment in the end of 2014.

Occlutech LAA Occluder

The Occlutech LAA Occluder (Occlutech International AB, Helsingborg, Sweden) is a self-expanding nitinol wire mesh that uses distal closed loops for anchoring. The device has a sprayed polyurethane layer cover that is meant to seal off the LAA and allow fast cell adhesion and implant ingrowth. Of note, the occluder is conical in shape and tapers distally from the ostium. The connection to the delivery system is via a ball-shaped hub that allows full pivoting capability. The implant is flexible and self-adjusting (Fig. 16.4).

Deployment of the device is similar to other endocardial LAA devices. An example of deployment is seen in Fig. 16.5. Device sizing is performed using the height and landing zone of the LAA. Sheath size ranges from 12 to 14 Fr. The delivery pusher comes in three colors (yellow, purple, and blue), depending on device and sheath size (Fig. 16.6).

The device is undergoing CE mark study and cases are ongoing. Approval is expected in the second half of 2014.

Fig. 16.4 Occlutech LAA Occluder with a nitinol wire mesh and distal closed loops for anchoring, as well as a *ball-shaped* hub for full pivoting capability

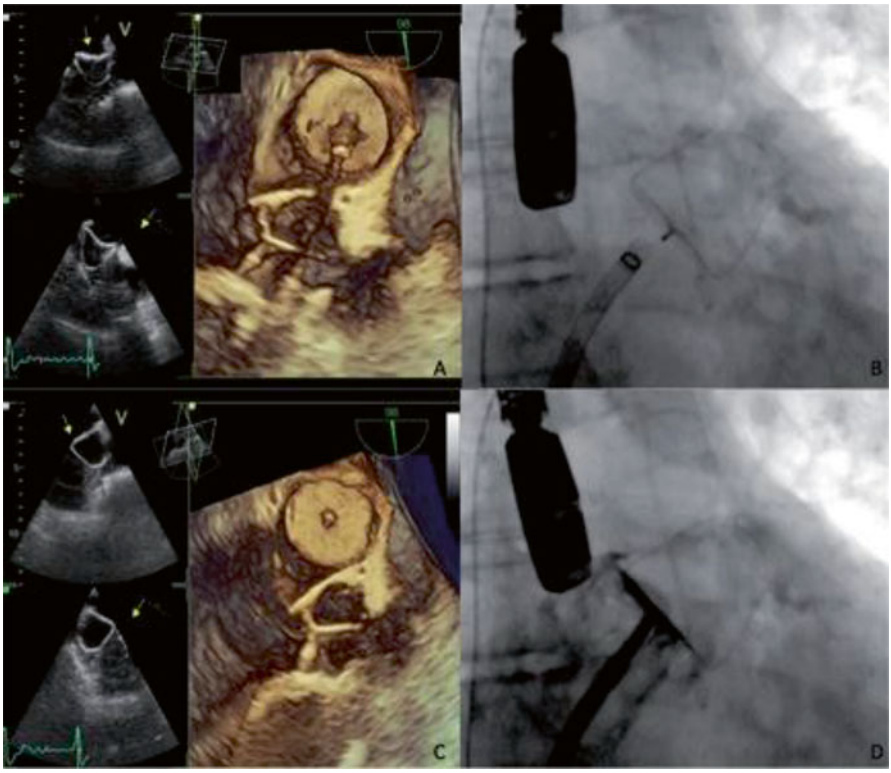
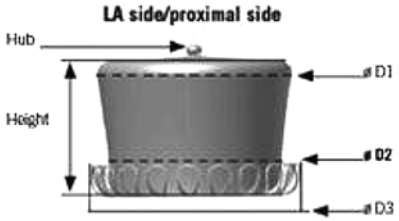


Fig. 16.5 Occlutech LAA occluder implantation. The device is placed in the LAA before being released from the pusher and seen on echocardiography (**a**). The device is then released and seen on fluoroscopy (**b**) and echocardiography (**c**). Left atrial angiography shows no leak around the device on fluoroscopic evaluation (**d**)



Size	D1	D2	D3	Height	Landing Zone	Sheath	Pusher
LAA 15	15	12	18	8	7-9	12F	51FP120 (yellow)
LAA 18	18	15	25	9	10-12	12F	51FP120 (yellow)
LAA 21	21	18	27	13	13-15	12F	51FP120 (yellow)
LAA 24	24	21	29	16	16-18	14F	51FP120 (yellow)
LAA 27	27	23	31	18	18-20	14F	51FP120 (yellow)
LAA 30	30	25	34	20	20-22	14F	51FP120 (yellow)
LAA 33	33	28	37	22	23-25	14F	51FP150 (purple)
LAA 36	36	30	40	24	25-28	14F	51FP150 (purple)
LAA 39	39	33	43	26	28-30	14F	51FP160 (blue)

Fig. 16.6 Occlutech device sizing chart. Measurements of the height and landing zone of the LAA are used to find the appropriate device size

Lifetech LAmbre LAA Closure System

LifeTech LAmbre LAA occluder (Lifetech Scientific, Sczenzhen, China) has two components: (1) a left atrial cover and (2) distal umbrella connected with a short central waist. The cover is a nitinol elastic mesh on a flat disc with a recessed hub at the center for connection to the delivery cable. The umbrella is a nitinol elastic framework with hooks to secure the device to the LAA wall. The hooks are recessed within the umbrella until deployment. Both umbrella and cover are sewn with polyethylene terephthalate (PET) membrane to prevent blood entry. One unique characteristic of this device is the articulating waist that allows the cover and umbrella to be at different angles to each other, which may have an advantage in very angulated LAA takeoffs. The delivery system consists of a sheath, dilator, delivery cable, loader, and hemostatic valve. The system can be a double curve (45 and 30°) or single curve (45°) system and ranges in size from 8 to 10 Fr (Fig. 16.7). Stages of deployment are seen in Fig. 16.8.

Unlike other devices, the Lifetech LAmbre occluder offers the ability to have a sizing chart to address both single and double lobe anatomies. Sizing of the device is based on distance from the orifice of the LAA and landing zone (Ls), size of the landing zone (Ds), and distance from the orifice of the LAA and the bifurcation for double lobes (Lo). The sizing chart can be seen in Figs. 16.9 (for single lobe anatomy) and 16.10 (for double lobe anatomy).

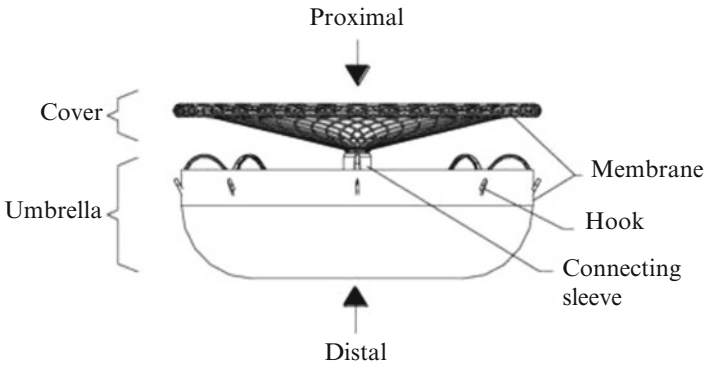


Fig. 16.7 LifeTech LAmbre LAA Occluder consists of a cover and umbrella. The umbrella has hooks that are recessed until deployment

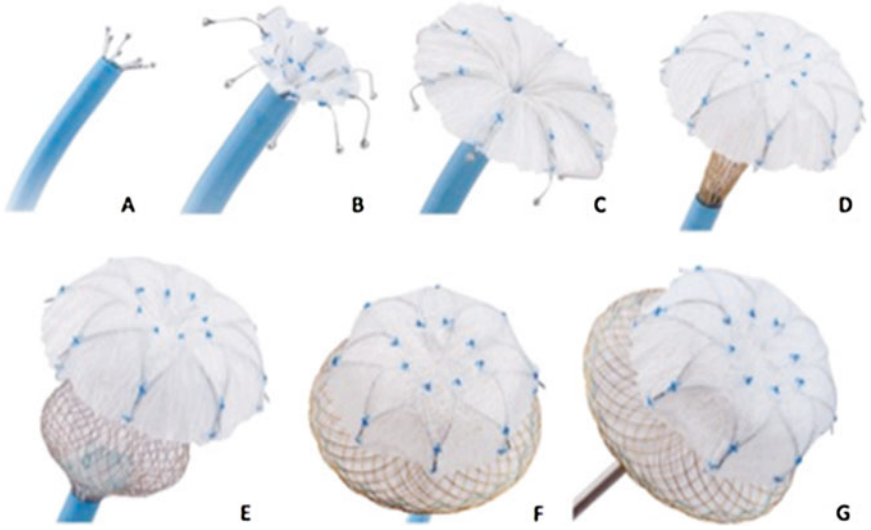
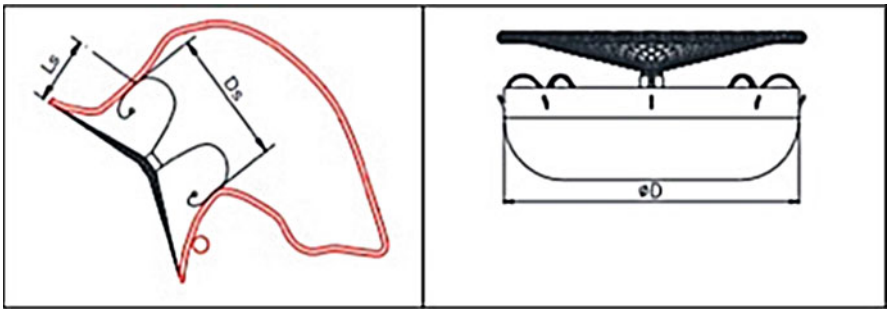


Fig. 16.8 Deployment of the LifeTech LAmbre LAA Occluder. The distal umbrella is deployed first, with hooks recessed in umbrella until deployment to minimize risk of tear (**a**–**d**). The proximal cover is then released (**e**–**g**)

The device was first described in 2013 by Lam [1]. Unlike the deep delivery sheath placement with few other devices, the delivery sheath of the LAmbre device is positioned at the proximal part of the LAA. The umbrella is then pushed out with the sheath in place; next the whole system is pushed forward to the desired landing zone to allow flowering of the umbrella and grasping of the LAA retention hooks. Finally, the delivery sheath is then withdrawn to expose the disc [1]. Preclinical work with 22 healthy canine subjects showed 100 % implantation success in all



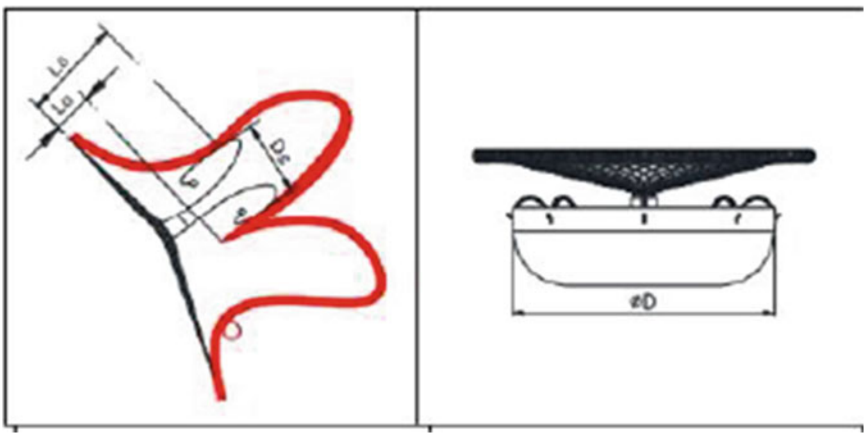
Measure		Device	
Ds	Ls	D	Specification
11.0~12.0	≥10	16	LT-LAA-1622
12.0~14.0	≥10	18	LT-LAA-1824
14.0~16.0	≥10	20	LT-LAA-2026
16.0~18.0	≥10	22	LT-LAA-2228
16.0~18.0	≥10	24	LT-LAA-2430
18.0~20.0	≥10	26	LT-LAA-2632
20.0~22.0	≥10	28	LT-LAA-2834
21.0~24.0	≥10	30	LT-LAA-3036
23.0~26.0	≥10	32	LT-LAA-3236
24.0~26.0	≥10	34	LT-LAA-3438
26.0~28.0	≥10	36	LT-LAA-3640

Fig. 16.9 LifeTech LAA LAmbre Occluder sizing chart for single lobe anatomy. This is based on distance from orifice of LAA and landing zone (Ls), size of the landing zone (Ds), and distance from the orifice of the LAA. Device spec. refers to specific device size that will be used; e.g., LT-LAA-1622 is umbrella size 16 mm and cover 22 mm

dogs. Ten dogs were sacrificed at ≥3 months to show complete healing on the atrial surface with optimal LAA obliteration [2]. In 2013, a 19-patient Asian registry was completed. This was followed by a CE Mark study; cases are ongoing.

Cardia Ultrasept Closure Device

The Cardia Ultrasept LAA Closure Device is a fully retrievable, repositionable occluder for the LAA. This is composed of two parts: a distal section (bulb), which anchors to the appendage and a proximal section (sail) that occludes the appendage (Fig. 16.11). A polyvinylacetate foam (PVA) covers the proximal sail. This device is connected to the delivery system with a dual articulating joint and has an integral locking delivery and retrieval mechanism.



Measure			Device	
Ds	Lo	Ls	D	Spec.
11.0~12.0	<10	≥10	16	LT-LAA-1630
12.0~14.0	<10	≥10	18	LT-LAA-1832
14.0~16.0	<10	≥10	20	LT-LAA-2032
16.0~18.0	<10	≥10	22	LT-LAA-2234
16.0~18.0	<10	≥10	24	LT-LAA-2436
18.0~20.0	<10	≥10	26	LT-LAA-2638

Fig. 16.10 LifeTech LAA LAmbre Occluder sizing chart for single lobe anatomy. This is based on distance from orifice of LAA and landing zone (Ls), size of the landing zone (Ds), distance from the orifice of the LAA, and bifurcation for double lobes (Lo)

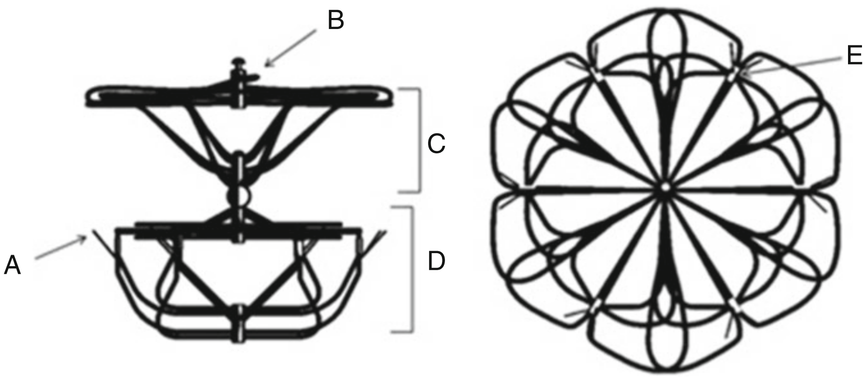


Fig. 16.11 The Cardia Ultrasept closure device consists of a proximal sail section and a distal bulb. Marked parts include (**a**) hook, (**b**) knob, (**c**) proximal sail, (**d**) distal bulb, and (**e**) proximal sail marker bands

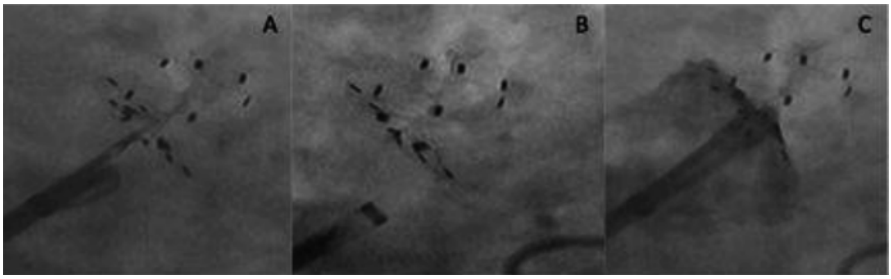


Fig. 16.12 Cardia Ultrasept device deployment. In (**a**), we see the device still attached to the delivery system. The device is then deployed (**b**) and checked for leak with an injection of contrast into the left atrium (**c**)

Maximum Measured LAA Orifice Diameter	Ultrasept LAA Device	Minimum LAA Depth	Cardia Delivery System	Depth of Sheath
11 mm – 13 mm	LAA-16	16 mm	10 Fr	12 mm
13 mm – 15 mm	LAA-18	16 mm	10 Fr	13 mm
15 mm – 17 mm	LAA-20	16 mm	11 Fr	14 mm
17 mm – 19 mm	LAA-22	17 mm	11 Fr	15 mm
19 mm – 21 mm	LAA-24	18 mm	11 Fr	16 mm
11 mm – 23 mm	LAA-26	19 mm	11 Fr	17 mm
23 mm – 25 mm	LAA-28	20 mm	12 Fr	18 mm
25 mm – 27 mm	LAA-30	21 mm	12 Fr	19 mm
27 mm – 31 mm	LAA-32	22 mm	12 Fr	20 mm

Fig. 16.13 Cardia Ultrasept sizing chart. The diameter of the LAA is used to determine the LAA device size

The device is sized based on echocardiographic views in 0, 45, 90, and 135°. The device is delivered into the LAA (Fig. 16.12). The device can be partially/fully retrieved a total of five times, according to the instructions for use.

Sizing of the device is performed by using the maximum measured LAA orifice diameter. The LAA depth should be checked before device implantation. Sheath size ranges from 10 to 12 Fr (Fig. 16.13). Unlike other devices, depth of sheath implantation is also predetermined according to device used.

Preclinical and clinical data are available. Five devices were implanted in animals as part of in vivo evaluation. There were no safety issues with device deployment. At 30 days, animals were sacrificed and found to be clinically healthy, with complete appendage closure, and no thrombi were present on the atrial surface of the device (Personal communication with Michael Corcoran, May 19, 2014). Devices were submitted for histopathological analysis, which showed that devices were fully deployed in the appendage, received full occlusion, and there was complete neointimal coverage and pannus formation on all devices. First-in-human

study (Ultra-Close study) was successfully completed by Dr. Alejandro Martinez in Santiago, Chile. Preliminary results show minimal incidence of device-related adverse events and successful closure of device at 1-month post-implant (Personal communication with Michael Corcoran, May 19, 2014). A second clinical trial was performed to collect additional data on the device. The trial will include use of additional sizes, which were not available during the first clinical trial. CE Mark application is pending based on results from these studies.

Conclusion

There are many devices in preclinical and clinical trials that should become available in the future. The characteristics of the ideal device should include being repositionable, redeployable, and easy to deliver. The device should fit a variety of LAA anatomies and sizes. There should be a good track record of procedural safety and long-term efficacy, without leak or thrombus. As seen above, the upcoming different devices address these goals through various methods. Device selection in the future may require not only trials comparing devices to medications, but also comparing devices to other devices.

References

1. Lam YY. A new left atrial appendage occluder (Lifetech LAmbre device) for stroke prevention in atrial fibrillation. Cardiovasc Revasc Med. 2013;14:134–6.
2. Lam YY, Yan BP, Doshi SK, et al. Preclinical evaluation of a new left atrial appendage occluder (Lifetech LAmbre device) in a canine model. Int J Cardiol. 2013;168:3996–4001.

Chapter 17
Concomitant Left Atrial Appendage Closure and Catheter Ablation of Atrial Fibrillation

Claudio Tondo and Gaetano Fassini

Introduction

Electrical disconnection of pulmonary veins (PV) is regarded as the cornerstone to treat atrial fibrillation (AF) by means of transcatheter ablation [1–4]. This target can be achieved by conventional point-to-point radiofrequency current delivery with an irrigated tip electrode catheter or, more recently, by using cryoenergy through a specific balloon designed platform. Furthermore, AF is probably the most challenging arrhythmia to treat in the general population, due to the unsatisfactory efficacy provided by drug treatment in the long term and the high risk of thromboembolic event [5–8]. It is reported that the overall annual risk of stroke is 5 % in patients suffering from AF and, increasing up to 15 % in very high-risk patients [9]. The left atrial appendage (LAA) is undoubtedly the main source of thrombus formation in patients with non-valvular AF, as autopsies and echocardiography studies have revealed [10]. According to international guidelines, anticoagulation treatment needs to be prescribed to patients with CHA_2DS_2-VASc score ≥ 1 to prevent embolic events [11]. In clinical practice, the administration of vitamin K antagonists (VKA) or novel oral anticoagulants (NOACs) can carry some critical disadvantages, such as profuse and frequent bleeding, noncompliance, difficulty keeping in a therapeutic range and frequent interactions with some dietary components and medications [12–14]. All these reasons can lead to undertreatment of patients, especially elderly patients who have high propensity to major hemorrhage [15, 16] associated with thromboembolic risk.

Due to the role of LAA in harboring thrombi, an effective alternative to anticoagulation treatment is its mechanical occlusion. Furthermore, since catheter ablation

C. Tondo, M.D., Ph.D. (✉) • G. Fassini, M.D.
Department of Cardiovascular Sciences, Centro Cardiologico Monzino, Cardiac Arrhythmia Research Center, University of Milan, 4 Via Carlo Parea, Milan 20138, Italy
e-mail: claudio.tondo@ccfm.it; claudio.tondo@unimi.it

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_17

has become an attractive option of treatment for AF and, multiple randomized studies have shown its superiority in the maintenance of cardiac rhythm than antiarrhythmic drugs [1, 2, 17, 18], the combination of catheter ablation and LAA mechanical closure may be offered as an effective therapy in those patients with drug-resistant AF and a high thromboembolic and bleeding risks. Either cryoenergy or radiofrequency current (RF) can be chosen as the preferred energy source to accomplish the ablation procedure.

The rationale of this approach is to offer an effective treatment of AF, avoiding the need for VKA or NOACs treatment in a very selected population at high risk of bleeding or with prior history of thromboembolic or major bleeding events during therapeutic anticoagulation.

Due to the lack of robust data in the literature, the chapter will describe the rationale of the approach, how to properly select the candidates, advantages and disadvantages of the procedure and the first clinical data available, which comprises our personal experience.

Rationale for a Combined Procedure

A combined approach is potentially better than performing two separate procedures. First of all, if one considers the composite primary efficacy endpoint of the PROTECT-AF study [15] (i.e., freedom from all stroke, cardiovascular death, and systemic embolization) the event-free probability was better in the device group (3.0 % vs. 4.9 % per 100 patient-years; relative risk 0.62) and met non-inferiority criteria. The event-rate of all ischemic and hemorrhagic stroke was lower in the intervention group than in controls (2.3 % vs. 3.2 % per 100 patient-years; relative risk 0.71), and all-cause mortality rate was lower in the intervention group (3.0 % vs. 4.8 % per 100 patient-years; relative risk 0.62). Therefore, in terms of stroke prevention, the mechanical closure of LAA is, at least, non-inferior to VKA therapy. Furthermore, the somehow disappointing long-term efficacy of AF catheter ablation, with success rate around 50 % [19], might be an additional advantage to combine ablation and LAA closure. This could be beneficial for those patients with non-valvular AF and prior ischemic stroke or high stroke risk and, for patients with contraindication to VKA therapy, prior intracranial hemorrhage, or a high bleeding risk. In this regard, patients with inherited bleeding disorders (e.g., haemophilia, von Willebrand disease with different subtypes) and AF are at particular risk. Also, a combined approach may be considered in those patients with an anticipated reduced efficacy of catheter ablation alone. From the practical standpoint, the combination of PVI with LAA mechanical closure in a single procedure reduces the need for (and consequently the risk of) a second transseptal puncture and repeated left atrial maneuvers should LAA occlusion become indicated during the follow-up.

On the other hand, even the NOAC drugs may bear the same bleeding risk in these categories of patients, even though these drugs are at least non-inferior to VKA, with a lower rate of intracranial bleeding as the most significant benefit. Also,

we need to highlight the concept that patients with severe prior bleeding complications during VKA or a high-bleeding risk do not represent an attractive population to be treated with long-term NOACs.

The association of AF ablation and LAA closure clearly prolongs the procedural time and requires longer time for deep sedation or general anesthesia. This should be taken into consideration whenever a patient is evaluated for the combined approach.

Patient Selection

In our center only patients with documented, drug-resistant, non-valvular paroxysmal or short-lasting AF (≤6 months), and ≥18 years of age are considered eligible for a combined approach if they already had a clinical history of thromboembolic events and/or major bleeding on therapeutic anticoagulation. A separate category of patients is those with inherited bleeding disorders and AF, in whom anticoagulation treatment can increase the risk of major bleeding. In our experience, these patients are the ideal candidates for the simultaneous AF ablation and LAA occlusion. To rule out the presence of left atrial (LA) and LAA thrombi, all patients undergo two-dimensional (2D) transesophageal echocardiogragphy (TEE) before the procedure, along with a transthoracic echocardiogram (TTE) for the assessment of LA dimension, left ventricular and valvular function. For additional clinical information, a pre-procedural LA anatomy and LAA dimension and morphology can be determined by computed tomography (CT) or magnetic resonance imaging (MRI). Exclusion criteria comprise the occurrence of LA thrombus, ejection fraction (EF) ≤30 %, contraindications to general anesthesia (GE), and very large LA dimension (≥55 mm or volume ≥30 mL). LA dimension (area and volume) assessment is critical for catheter ablation only and not for LAA occlusion, as a very large LA anticipates poor clinical outcome for catheter ablation. Since the concomitant AF catheter ablation and mechanical closure of LAA is not discussed in international guidelines [11], each patient needs to be fully informed of the procedure and a written consent obtained. In particular, in our institution, the study protocol was approved by the local ethics committee and this approach has become regular practice.

Ablation Procedure

Cryoenergy

The choice of ablating patients with cryoenergy is based on the preference of our center to use the cryoballoon in this clinical context to provide PV isolation [20–22] and on the concept that by ablating the anatomic ridge between the left superior PV and the LAA via radiofrequency current might cause injury to the ostium of LAA and, then potentially precluding a safe positioning of an occluder device.

Through a single transseptal puncture a 23 or 28 mm Cryoballoon (Arctic Front, Advance, Medtronic, Mn, USA) is inserted through a steerable 15F sheath (FlexCath, Medtronic) in the LA. In any circumstance, the cryoballoon is used in conjunction with the Achieve catheter, which is an inner lumen circular catheter for mapping PV electrograms at baseline, during and, after cryoenergy application. The Achieve catheter also has the purpose to serve as supporting guidewire in the positioning maneuver of the cryoballoon. Once the balloon is inflated and wedged in the PV ostium, contrast dye is injected and vein occlusion is judged visually by the operator as to achieve a perfect occlusion. For cryoenergy applications at the septal veins, pacing of the ipsilateral phrenic nerve at maximum output is provided as to avoid phrenic nerve injury. During the entire procedure, activated clotting time is maintained between 300 and 350 s.

Complete PV isolation is provided by recordings from the Achieve catheter and pacing maneuvers to assess bidirectional block. Isoproterenol infusion (up to 20 μg/min) is provided to investigate the potential occurrence of extrapulmonary foci and PV electrical activity is checked at least 30–40 min following ablation in each vein.

Radiofrequency Current

PV isolation can be achieved through point-by-point radiofrequency (RF) current delivery by using a conventional irrigated tip electrode catheter. Only a few patients in our laboratory are treated with RF current ablation prior to LAA mechanical closure. Even though it is not proven, we suspect that cryoenergy may reduce the risk of inadvertent injury to LAA ostium as compared to RF current. Swaans et al. [23] have recently reported their own experience in combined AF ablation and LAA closure in 30 patients by achieving PV isolation via RF current using the PVAC catheter (Medtronic/Ablation Frontiers, Inc, Carlsbad, CA, USA) which is a 9F, over-the-wire, circular, decapolar, ablation catheter, that (as Cryoballoon) does not need additional 3D nonfluoroscopic guiding system to carry out the procedure. These authors did not report any complication in the closing of LAA following RF current delivering thus, suggesting the safety of both energy sources for PV isolation in conjunction with mechanical closure of LAA.

LAA Closure

In our laboratory, the Amplatz Cardiac Plug (ACP) (St. Jude Medical, USA) or the WATCHMAN device (WATCHMAN LAA Occlusion Device, Boston Scientific, USA) are usually implanted right after the ablation procedure is completed, while the patient is still under general anesthesia. The implant is performed under monoplane fluoroscopy and 2 and 3-dimensional TEE guidance. If cryoenergy is used, the 11F Flexcath sheath previously used for positioning the Cryoballoon is replaced by a 13F long sheath for the ACP and 14F sheath for the WATCHMAN device and

maneuvered towards the mouth of the LAA. Through these sheaths, a pigtail catheter is then positioned within the LAA in the majority of patients to perform angiograms to determine size and shape of the LAA. In a minority of patients LAA angiogram is performed through the sheath itself. The remainder of the LAA closure procedural steps for either the ACP or WATCHMAN devices have been previously described in preceding chapters.

Post-procedural Management

In our institution, after combined AF ablation and LAA closure, patients are discharged 48 h later, provided a TTE and a chest X-ray confirm the position of the occlusive devices and the lack of any sign of pericardial effusion. In the majority of patients, except those with inherited bleeding disorders, they are started on warfarin or NOACs (dabigatran, rivaroxaban or apixaban) 24 h after the procedure, preceded by low molecular weight heparin (LMWH) bridging therapy started on the same day of the procedure. Therefore, LMWH therapy is discontinued as soon as the target international normalized ratio of 2–3 was reached in those patients in whom warfarin is chosen. In some patients, known to be at a very high risk of bleeding, dual antiplatelet therapy is started after the procedure. Between the first and third month of follow-up, each patient undergo TEE to evaluate the position of the occlusive LAA devices, thrombus formation and residual flow. If the sealing criteria are confirmed, that means no residual or minimal flow (<5 mm), anticoagulation treatment is discontinued and, aspirin and clopidogrel started. Dual antiplatelet therapy is then maintained till the sixth month and then switched to a single antiplatelet agent. Moreover, all patients undergo 7-day Holter monitoring at the first month after the procedure and every 3 months for the first 12 months. Antiarrhythmic drug therapy is allowed for the first 3 months (blanking period) and, then discontinued if sinus rhythm is confirmed.

Results of Our Experience with Combined AF Ablation and LAA Closure

Patient Population Characteristics (Table 17.1)

Thirty-five consecutive patients (mean age 72 ± 4 male 28) were included in our prospective, feasibility study. Cryoenergy was chosen as the ablative approach to use. The clinical characteristics are reported in Table 17.1. Twenty-eight patients (80 %) had paroxysmal AF and 7 patients (20 %) early persistent AF (≤6 months duration). The median CHA_2DS_2-VASc score was 3 and HAS-BLED score was 3. Seven patients (2 %) had well-established inherited bleeding disorders (3 patients with von Willebrand type two disorder and the remaining 4 patients with Haemophilia type B).

Table 17.1 Baseline demographic of the study population

	Patients ($n=35$)
Age (years)	72 ± 4
Male subjects	28/35 (79 %)
AF history (months)	66 ± 36
Paroxysmal AF (%)/Persistent AF (%)	28 (80 %)/7 (20 %)
LV ejection fraction, %	54 ± 7
Hypertension, %	21/35 (60 %)
Genetic bleeding disorders	7(20 %); 3 von Willebrandt; 4 Haemophilia
Previous stroke/TIA	30/35 (86 %) (26 during OAT)
Diabetes	15/35 (43 %)
Contraindication to VKA, due to:	6/35 (17 %)
– Intracranial bleeding	2
– Profuse intestinal bleeding	4
CHA_2DS_2-VASc > 2	35 (100 %)
HAS-BLED ≥ 2	13 (37 %)

All data are presented as mean ± standard deviation

Thirty patients (86 %) had a previous stroke (26 patients while on oral anticoagulation treatment). Besides the 7 patients with inherited bleeding disorders, contraindication to a continuous vitamin K antagonist (VKA) therapy was ascertained in additional 6 patients. In these patients, intracranial bleeding (2 patients) or profuse intestinal hemorrhage (4 patients) prevented reestablishing anticoagulation. Furthermore, 8 patients (23 %) (3 patients among those with bleeding disorders and 5 among those major gastrointestinal bleeding) had both major bleeding and cerebral ischemic events (transient ischemic attack).

Procedural Parameters (Table 17.2)

The mean procedural time was 174 ± 32 min for Cryoablation and 44 ± 12 min for LAA occlusion. Therefore, the overall procedural time was 218 ± 34 min. The fluoroscopic time for the ablation procedure was 36 ± 11 and 9 ± 3 min for LAA occlusion. The entire procedure was performed under general anesthesia.

Cryoballoon Pulmonary Vein Isolation

In 35 patients, a total number of 132 PVs were identified, including a left common PV in 8 patients. In the majority of cases, the 28 mm size balloon was used. The endpoint of the procedure, i.e., the complete isolation of all PVs was achieved in 34 out of 35 patients (97 %). In one patient, treated with the first Cryoballoon generation, the right inferior PV was not successfully occluded and, therefore, PV isolation was then

Table 17.2 Procedural and periprocedural parameters

Procedure (%)	
Cryoisolation PV	34/35 (97 %)
RF	1 (3 %)
Device (%)	25 (71 %)
Amplatz	10 (29 %)
Watchman	
Size mm (%)	
Amplatz :	11 (44 %)
24	12 (48 %)
26	2 (8 %)
30	
Watchman:	6 (60 %)
24	3 (30 %)
27	1 (10 %)
30	218 ± 34
Procedure time, min	45 ± 10
Fluoroscopy time, min	174 ± 32
Cryoablation time, min	44 ± 12
LAA closure time, min	
TEE *n* (%)	35 (100 %)
Successful occlusion	5 (14 %)
Residual leakage (≤3 mm)	3 (8 %)
Slight pericardial effusion	
Complications *n* (%)	0 (0 %)
Pericardial effusion required drainage	0 (0 %)
Device embolization	0 (0 %)
Stroke	3 (8 %)
Vascular events (bleedings, groin haematoma, pseudoaneurism, …)	

All data are presented as mean ± standard deviation

achieved through two pulses of radiofrequency applications. Specific Cryoballoon procedure-related complications occurred in 2 patients with transient phrenic nerve palsy, while ablating at the right superior PV; this did not prevent from completing the procedure with the closure of LAA. The complete resolution of the phrenic nerve injury was demonstrated in both patients by day 24 and 60, respectively.

LAA Occlusion

Occluder devices for LAA were implanted under fluoroscopy and TEE guidance right after the PV cryoisolation was concluded. Once the size and shape of the LAA were determined by performing selected angiograms and TEE measurements, the

chosen device, ACP or WATCHMAN was implanted. Successful implantation occurred for each device without major adverse event. The mean size of LAA device was 24 mm; in 5 patients a minimal residual flow (between 3 and 5 mm: two ACP and three WATCHMAN devices, respectively) was confirmed at the end of the procedure. Only in 3 patients, small pericardial effusion was detected at the end of the procedure, with no need of drainage. In additional 3 patients, a groin hematoma developed and in 1 patient arteriovenous fistula developed 24 h later, requiring surgical repair in the following days.

Follow-up (Table 17.3)

Arrhythmia Recurrence

During follow-up (14 ± 8 months), atrial arrhythmias (AF or atrial flutter/tachycardia) occurred in 10 (28 %) of the patients. In half of them a redo procedure was then successfully performed, while 3 patients developed persistent AF and refused to undergo an additional ablation. The redo-ablation procedure was performed by using Cryoenergy, revealing PV-LA re-conduction in all patients. The presence of the occluding device did not affect the redo-ablation. The remaining 2 patients remained on antiarrhythmic drugs with still paroxysmal atrial arrhythmias.

Table 17.3 Follow-up

	Patients ($n = 35$)
Months	14 ± 8
Arrhythmia recurrence	10/35 (28 %)
Redo-ablation	5/35 (14 %)
TEE evaluation	
3 months, complete sealing	30/35 (86 %)
3 months, minimal leaking (<5 mm)	5/35 (14 %)
12 months, complete sealing	32/35 (91 %)
Stroke/TIA	0/35 (0 %)
Device embolization/device thrombus	0/35 (0 %)
VKA off	30/35 (86 %)
Death	0/35 (0 %)

All data are presented as mean ± standard deviation and/or percentage

LAA Mechanical Closure

In each patient, TEE evaluation was established at 1, 3, and 12 months. Thirty patients (86 %) had perfect sealing at 90 days and the remaining 5 patients (14 %) had a persistent minimal residual flow (<5 mm) at 90 days, and 2 of them had successful sealing at 1 year while the remaining 3 patients still had residual flow. In 13 patients (37 %) (those who were known to have inherited disorders and previous cerebral and gastrointestinal hemorrhage) VKA therapy was immediately discontinued and antiplatelet therapy started at 90 days. In additional 6 patients (17 %), due to patients' cardiologist's preference, NOACs treatment (dabigatran in 4 and rivaroxaban in 2 patients, respectively) was started after the procedure and then discontinued within 3 months. At 1 year, 30 patients (85 %) were off of VKA treatment. In no instances, was device embolization or thrombus formation on surface device detected. More importantly, at 1-year follow-up no thromboembolic events had occurred.

Procedural Outcome

Our data showed that successful PV isolation with cryoballoon was achieved in all patients but one, confirming the high success rate of the approach in achieving the goal [20]. During the follow-up, redo cryoablation was performed in 5 patients among the 10 patients who had arrhythmia recurrences. In all of these 5 patients, resumption of LA-PV conduction was demonstrated as primary driver of the arrhythmia. Therefore, based on every 3-month 7-day Holter recordings, the success rate of a single procedure was 71 %; while with the redo-ablation included 85 %.

Successful implantation of LAA occluder device was achieved in all patients, regardless the device used. This confirms the high success rate of the procedure already reported in previous study [15, 16, 24–26]. Complete sealing was completed in a high percentage of patients at 90 days; in 2 patients successful sealing was reached at 1 year and only in 3 patients remained a residual flow (<5 mm). Even the persistence of minimal, residual flow is not considered predictor of potential thromboembolic events [27], and longer TEE follow-up may be considered in patients who present this finding.

The absence of thromboembolic events over the entire follow-up, suggests that the sealing of LAA and reduced probability to have arrhythmia recurrences after ablation, may constitute a valid option of treatment for some categories of patients at particular risk of embolic events or with high predisposition to bleeding. One could argue that combining ablation with LAA mechanical occlusion may bear some disadvantages, such as the need to keep the patient on anticoagulation for at least 2–3 months after the procedure. In those patients presenting with hemorrhagic tendency due to inherited bleeding disorders, we prescribed subcutaneous LWMH for 2 months after the procedure and, then the patients are treated only with antiplatelet therapy.

Previous Studies

Swaans et al. [23] first published clinical results on LAA occlusion in combination with AF ablation in a single procedure. The study included 30 patients, in whom catheter ablation was performed by using multielectrode catheters with phased radiofrequency energy. LAA was occluded only with the WATCHMAN device. All patients had high CHA_2DS_2-VASc score (median 3) or HAS-BLED score (median 2) and no periprocedural major complications were reported. During follow-up, successful sealing of the LAA was demonstrated in all patients and 70 % of patients were free of atrial arrhythmias thus, indicating the safety and feasibility of the combined procedure. Even if the two studies draw the same conclusion on safety and feasibility of the combined procedure, there are differences between the two approaches. First, in our study cryoablation was elected as privileged energy source to achieve PV isolation in order to limit the potential injury of the tissue at the LAA's ostium that theoretically can be promoted by the use of a conventional radiofrequency catheter ablation. This may happen by attempting to ablate the ridge between the left superior PV and the LAA by surfing the ablation catheter at that anatomic location. Second, in our population, only a minority of patients presented with persistent AF (early, i.e., <6 month duration) and, therefore requiring only PV isolation and not extensive ablative strategy. Third, two different types of LAA occluder were used in our study, providing the effectiveness of the procedure regardless the design of the device.

An additional advantage highlighted by the two clinical studies is that adding LAA closure to AF catheter ablation permits avoiding the need to perform a second transseptal puncture, should the closure of LAA is deemed beneficial for the patient. Even the hypothesis to use the NOACs to overcome bleeding complications due to VKA therapy is still to be proven and, in patients with prior profuse bleeding on VKA therapy or high bleeding propensity, the NOACs therapy might not be completely safe.

Nonetheless, since combining LAA mechanical closure with AF catheter ablation prolongs the procedural time and, theoretically increases the potential complications, experienced operators in left atrial interventions are highly recommended.

Conclusion

Combined isolation of PV (through RF current or cryoenergy) and LAA mechanical closure appears to be safe and feasible in patients with non-valvular AF associated with high risk of stroke or specific contraindication to antithrombotic treatment (VKA and/or NOACs). For the time being, this approach needs to be limited to well-selected populations with non-valvular AF (high risk of thromboembolic events despite therapeutic VKA therapy or high propensity to major bleedings or

with inherited bleeding disorders) while randomized clinical trials are warranted to define the benefit and cost-effectiveness of this interventional strategy. In order to ensure high success rate of the approach and minimize potential complications, experienced operators in left atrial procedures are required.

Combined cryoablation or RF ablation of AF and LAA mechanical closure could be considered an effective treatment in a population of patients with non-valvular AF and a high risk of stroke or strong contraindication to anticoagulant regime. The clinical findings of our study (under revision at the time of this chapter) and of other authors confirm the feasibility of such an approach and indicate that it can be proposed as an effective alternative to a very selected category of patients.

References

1. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert R, Brachmann J, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R, Raviele A, Themistoclakis S, Rossillo A, Bonso A, Natale A. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. JAMA. 2005;293:2634–40.
2. Stabile G, Bertaglia E, Senatore G, De Simone A, Zoppo F, Donnici G, Turco P, Pascotto P, Fazzari M, Vitale DF. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation for the Cure of Atrial Fibrillation Study). Eur Heart J. 2006;27:216–21.
3. Jaïs P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, Hocini M, Extramiana F, Sacher F, Bordachar P, Klein G, Weerasooriya R, Clémenty J, Haïssaguerre M. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. Circulation. 2008;118:2498–505.
4. Mohanty S, Mohanty P, Di Biase L, Bai R, Santangeli P, Casella M, Dello Russo A, Tondo C, Themistoclakis S, Raviele A, Rossillo A, Corrado A, Pelargonio G, Forleo G, Natale A. Results from a single-blind, randomized study comparing the impact of different ablation approaches on long-term procedure outcome in coexistent atrial fibrillation and flutter (APPROVAL). Circulation. 2013;127(18):1853–60.
5. Capucci A, Santini M, Padeletti L, Gulizia M, Botto G, Boriani G, et al. Monitored atrial fibrillation duration predicts arterial embolic events in patients suffering from bradycardia and atrial fibrillation implanted with antitachycardia pacemakers. J Am Coll Cardiol. 2005;46:1913–20.
6. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk. The TRENDS Study. Circ Arrhythm Electrophysiol. 2009;2:474–80.
7. Botto GL, Padeletti L, Santini M, Capucci A, Gulizia M, Zolezzi F, et al. Presence and duration of atrial fibrillation detected by continuous monitoring: crucial implications for the risk of thromboembolic events. J Cardiovasc Electrophysiol. 2009;20:241–8.
8. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH, ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012;366(2):120–9.
9. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation. 2004;110:1042–6.

10. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg. 1996;61:755–9.
11. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder I, Al-Attar N, Hindicks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey IY, Ponikowski P, Rutten FH, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas PE, Widimski P, Agladze V, Aliot E, Balabanski T, Blomstrom-Lundqvist C, Capucci A, Crjins H, Dahlos B, Folliguet T, Glikson M, Goethals M, Gulba DC, Ho SY, Klautz RJ, Kose S, McMurray J, Perrone FP, Raatikainen P, Salvador MJ, Schalij MJ, Shpector A, Souse J, Stepinska J, Uuetoa H, Zamorano JL, Zupan I. Guidelines for the management of atrial fibrillation: the Task force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace. 2010;12:1360–420.
12. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, Yang S, Alings M, Kaatz S, Hohnloser SH, Diener HC, Franzosi MG, Huber K, Reilly P, Varrone J, Yusuf S. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation. 2011;123:2363–72.
13. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation. 2007;115:2689–96.
14. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, Pais P, Dans A, Eikelboom J, Oldgren J, Pogue J, Reilly PA, Yang S, Connolly SJ. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet. 2010; 376:975–83.
15. Fountain RB, Holmes DR, Chandrasekaran K, Packer D, Asirvatham S, Van Tassel TR, Turi Z. The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients with Atrial Fibrillation) trial. Am Heart J. 2006;151:956–61.
16. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P. 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.
17. Oral H, Pappone C, Chugh A, Good E, Bogun F, Pelosi Jr F, Bates ER, Lehmann MH, Vicedomini G, Augello G, Agricola E, Sala S, Santinelli V, Morady F. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. N Engl J Med. 2006;354:934–41.
18. Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, Paglino G, Mazzone P, Sora N, Greiss I, Santagostino A, LiVolsi L, Pappone N, Radinovic A, Manguso F, Santinelli V. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. J Am Coll Cardiol. 2006;48: 2340–7.
19. Weerasooriya R, Khairy P, Litalien J, Macle L, Hocini M, Sacher F, Lellouche N, Knecht S, Wright M, Nault I, Miyazaki S, Scavee C, Clementy J, Haissaguerre M, Jais P. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? J Am Coll Cardiol. 2011;57:160–6.
20. Neumann T, Vogt J, Schumacher B, Dorszewski A, Kuniss M, Neuser H, Kurzidim K, Berkowitsch A, Koller M, Heintze J, Scholz U, Wetzel U, Schneider MA, Horstkotte D, Hamm CW, Pitschner HF. Circumferential pulmonary vein isolation with the cryoballoon technique result from a prospective 3-center study. J Am Coll Cardiol. 2008;52:273–8.
21. Furnkranz A, Bordignon S, Schmidt B, Gunawardene M, Schulte-Hahn B, Urban V, Bode F, Nowak B, Chun JKR. Improved procedural efficacy of pulmonary vein isolation using the novel second-generation cryoballoon. J Cardiovasc Eectrophysiol. 2013;24(5):492–7.

22. Moltrasio M, Al-Nono O, Fassini G, Dello Russo A, Riva S, Casella M, Tundo F, Majocchi B, Zucchetti M, Marino V, Carbucicchio C, Cattaneo F, Innocenti E, Colombo D, Bologna F, Tondo C. Cryoablation of pulmonary veins for paroxysmal atrial fibrillation: comparison of acute and mid-term outcome between first and second generation balloon. J Cardiol. 2013;9(16):1713–23.
23. Swaans MJ, Post MC, Rensing BJWM, Boersma LVA. Ablation for atrial fibrillation in combination with left atrial appendage closure: first results of a feasibility study. J Am Heart Assoc. 2012;1:e002212. doi:10.1161/JAHA.112.002212.
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. Urena M, Rodes-Cabau J, Freixa X, Saw J, Webb JG, Freeman M, et al. Percutaneous left atrial appendage closure with the AMPLATZER cardiac plug device in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy. J Am Coll Cardiol. 2013;62:96–102.
26. Meier B, Blauw Y, Khattad AA, Lewalter T, Sievert H, Tondo C, Glikson M. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. Europace. 2014;16:1397–416.
27. 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.

Part V
Post-procedural Management and Issues

Chapter 18
Procedural Complications and Management

Ivan P. Casserly, Kevin Walsh, and Jacqueline Saw

Introduction

The vast majority (>90 %) of complications related to left atrial appendage (LAA) closure are procedure-related, occurring within 7 days of the index procedure [1]. These complications attenuate the overall clinical benefit of this strategy for stroke prophylaxis in patients with non-valvular atrial fibrillation and highlight the importance of the safe execution of the procedure to maximize the overall clinical benefits of LAA occlusion in this patient cohort [2]. The current chapter will outline the major procedural complications of LAA closure and discuss their management. Although a large number of LAA occlusion devices have now been developed [3], the majority of the discussion will center around second generation devices for which there is reasonable registry or randomized trial data available (i.e., WATCHMAN, Boston Scientific, and Amplatzer Cardiac Plug (ACP), St Jude Medical).

Pericardial Effusion/Perforation

Significant pericardial effusion following LAA closure, defined as an effusion requiring intervention or that prolongs hospitalization, remains the most frequent major complication of this procedure. The frequency of this complication in the

I.P. Casserly, M.B., B.Ch. (✉) • K. Walsh, M.B., B.Ch.
Mater Misericordiae Hospital and Mater Private Hospital, Eccles St., Dublin, Ireland
e-mail: stentman@gmail.com

J. Saw, M.D., F.R.C.P.C., F.A.C.C., F.S.C.A.I.
Vancouver General Hospital, University of British Columbia, 2775 Laurel Street, Level 9, Vancouver, BC, Canada, V5Z1M9
e-mail: jsaw@mail.ubc.ca

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_18

landmark PROTECT-AF trial was 4.8 % [4]. With improved operator experience, this figure has steadily declined with a frequency of 2.2 % in the Continued Access Protocol (CAP) Registry [1], and 1.5 % in the most recently completed PREVAIL trial [5]. In smaller registry studies with the ACP device, the frequency of significant pericardial effusion has ranged between 0 and 3.5 % [6, 7]. The vast majority (>90 %) of pericardial effusions occur within 24 h of the procedure [1]. However, late significant effusions occurring several months following device implantation have been reported [8].

The mechanism of pericardial effusion in the setting of LAA closure procedures is varied. Early effusions are primarily caused by procedure-related misadventures. For the WATCHMAN and ACP devices, trauma to the wall of the LAA, or less commonly the left atrial wall, from guidewires, catheters, and delivery sheaths, in addition to manipulation of the LAA closure device in the left atrium and appendage is the most likely explanation in most cases. The stabilizing barbs on the WATCHMAN or ACP devices may also cause trauma to the wall of the LAA or adjacent structures (e.g., the pulmonary artery [9, 10]), and explain both early and late cases of pericardial effusion. Trauma during the transseptal puncture is an uncommon cause, accounting for up to 10 % of pericardial effusions [1]. The dry pericardial tap required for delivery of the LARIAT snare device (SentreHeart) introduces the unique risk of perforation of cardiac chambers such as the right atrium and right ventricle.

Regardless of the cause of pericardial effusion following LAA closure, most of the fundamentals of management are similar. Hemodynamic resuscitation and drainage of the pericardial effusion is required in most cases. Central venous access for volume resuscitation and the administration of vasopressor agents, if required, is essential.

Emergency pericardiocentesis will be required in >90 % of cases. Most operators in the catheterization laboratory will use a subxiphoid approach (Fig. 18.1). However, alternative access sites such as the parasternal and apical areas may be required, particularly in larger patients (Fig. 18.2). The authors' preference is to use a stiffened micropuncture access kit to minimize the risk of trauma while gaining access to the pericardial space, particularly if not using a subxiphoid approach (Fig. 18.3). In these kits, there is a 21 gauge 7 cm long needle which allows delivery of a stiff 40 cm long 0.018″ wire. Confirmation that the wire is in the pericardial space prior to delivery of any dilators or sheath is essential. The fluoroscopic appearance of the wire is the most reassuring sign that the wire is in the pericardial space and not in a cardiac chamber. The needle is then exchanged for a 4/5Fr 10 cm long locking sheath/stiffened dilator combination. Removal of the wire and dilator then allows recording of the pericardial pressure before insertion of any larger dilators or sheaths. This serves as the second level of confirmation before delivery of a stiff 0.035″ wire to the pericardial space and delivery of the pericardial drain. If the needle on the micropuncture kit is not long enough, then an 18G spinal needle that is 11 cm long works well (e.g., Portex Extra Length Tuohy Needle, Smiths Medical ASD Inc., Kent, UK) (Fig. 18.3). This needle is still significantly smaller in caliber than the usual needle provided in most conventional pericardiocentesis kits. Once

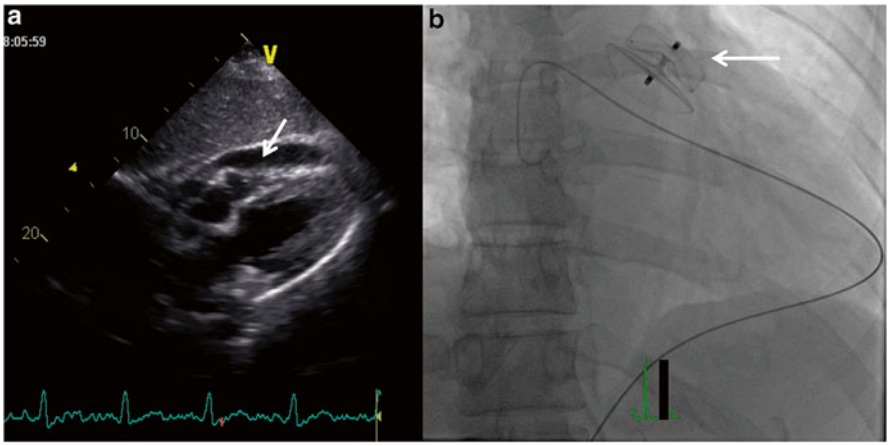


Fig. 18.1 Delayed presentation with pericardial effusion in a 45 year-old female, 1 month following combined atrial fibrillation ablation procedure and left atrial appendage closure using ACP device. (**a**) Subxiphoid transthoracic echocardiographic window showing circumferential effusion (*arrow*) that is amenable to a subxiphoid approach to pericardiocentesis. (**b**) Flouroscopic image showing typical appearance of 0.035″ wire in pericardial space. ACP device indicated by *white arrow*

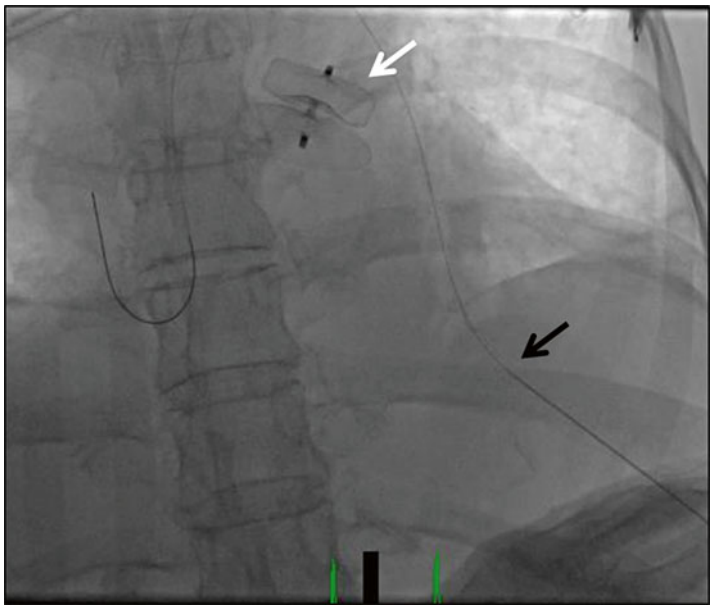


Fig. 18.2 Acute pericardial effusion in 74 year-old female with clinical tamponade within 12 h of LAA closure with ACP device. Patients body habitus and location of the effusion necessitated a parasternal approach to pericardiocentesis. Tip of micropuncture needle indicated by *black arrow*. ACP device indicated by *black arrow*

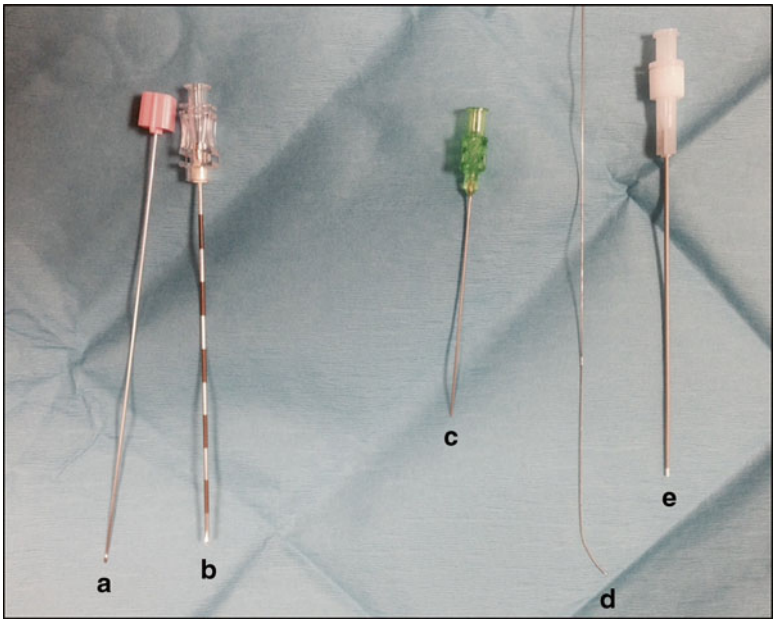


Fig. 18.3 Portex 11 cm length 18G tuohy spinal needle (**b**) and trochar (**a**). Micropuncture kit with 7 cm 21G Needle (**c**), 0.018 in. stiff wire (**d**), and stiffened dilator (**e**)

the needle and trochar of the spinal needle have been introduced beyond the skin, the trochar is removed and the needle advanced with aspiration on a syringe attached to the needle. Once the pericardial space has been accessed, the authors use the micropuncture wire and sheath/dilator to facilitate the delivery of the stiff 0.035″ wire to the pericardial space.

Frank cardiac perforation during LAA occlusion procedures is a rare event, with individual cases reported in most large series [5, 6], suggesting a frequency of <0.5 % (Fig. 18.4). Perforation will typically lead to an immediate pericardial effusion and clinical tamponade. Blood loss can be large and life-threatening. Following pericardiocentesis, it is recommended that the blood drawn from the pericardial space be immediately administered into the central venous access to try to minimize blood loss and subsequent need for transfusions. The standard approach for dealing with a cardiac perforation is surgical repair, particularly if the patient is a reasonable operative candidate. Based on a single case experience of the authors (IC and KW) and anecdotal reports, we would recommend that reversal of anticoagulation and administration of clotting factors should not be performed until the operative team is in place and emergency sternotomy is possible. The latter agents may result in formation of large amounts of clot in the pericardial which can occlude the pericardial drain but without sealing of the perforation site. This can lead to tamponade that cannot be rescued with manipulation of the pericardial drain.

Rare instances of percutaneous management of a LAA perforation have been reported using an Amplatzer PFO or ASD closure devices [11]. In such cases, the

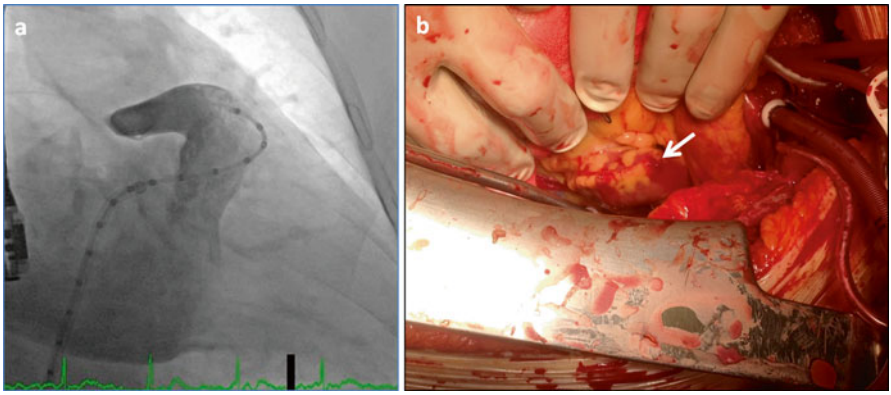


Fig. 18.4 LAA perforation during LAA occlusion procedure to seal chicken wing shaped appendage. (**a**) LAA angiography shown at baseline. (**b**) Photograph taken at the time of emergency sternotomy to deal with perforation of the LAA (indicated by *white arrow*) caused by a wire perforation

perforation was likely caused by the delivery sheath, and the perforation was recognized with the sheath in the pericardial space, allowing delivery of the device through the sheath with deployment of the traditional left atrial disk in the pericardial space and the right atrial disk in the LAA. It would be prudent to recommend that such attempts should only be made by experienced operators and with the availability of the cardiothoracic surgical team in case these maneuvers are not successful.

Device Embolization

Device embolization is one of the most feared complications of LAA closure procedures. The device embolizes initially to the left atrium, and will typically make its way across the mitral valve into the left ventricle. For small and medium-sized devices in the absence of significant aortic valve disease, the device may subsequently embolize to the thoracic or abdominal aorta. If lodged in the left ventricle, the device may become entrapped in the left ventricular outflow tract (LVOT) or the mitral valve apparatus.

Although the frequency of device embolization is low, it has remained a stubbornly consistent event in most clinical trials and registries of LAA occlusive devices. A meta-analysis by Bajaj et al. reported an overall embolization rate of 3.9 % [12], but more contemporary trials and registries with second generation devices report a rate between 0 and 2 % [4–7]. Clinical presentation with device embolization may either occur acutely in close temporal relationship to the index procedure or be delayed several months. Variation in the recognition of this complication beyond the time of the index procedure is likely a function of the ultimate site to which the device embolizes. Embolization to the thoracic or abdominal aorta may

Table 18.1 Sample of studies reporting device embolization following LAA closure

Study	Device	Timing	Embolization	Outcome
Aminian et al. (Aminian, 2014 #2)	ACP	1 month	LVOT/mitral apparatus	Death
Case report				
Reddy et al. (Reddy, 2011 #10)	WATCHMAN	Procedure	LVOT	Perc removal[a]
PROTECT-AF Trial		45-day follow-up	Thoracic aorta	Perc removal
CAP registry		45-day follow-up	Abdominal aorta	Surgical removal
Gupta P et al. (Gupta, 2013 #1)	ACP	1 day	LVOT	Surgical retrieval
Case report				
Pisani P et al. (Pisani, 2014 #3)	ACP	6 months	LVOT/mitral apparatus	Surgical retrieval
Case report				

[a]complicated by trauma to aortic valve requiring surgical AVR
LAA left atrial appendage, *ACP* Amplatzer cardiac plug, *LVOT* left ventricular outflow tract, *Perc* percutaneous

be clinically silent, whereas embolization to the left ventricle with the subsequent risk of LVOT obstruction or disturbance of the mitral valve apparatus is more likely to present acutely with symptoms.

LAA device embolization is a highly morbid complication (Table 18.1) [1, 13–15]. Percutaneous retrieval of the device is technically very challenging due to the presence of barbs on the devices that are used to secure the device in the LAA. These can cause the device to become embedded in adjacent tissue in the heart or aorta. In addition, they complicate percutaneous retrieval in that the device has to be optimally snared to collapse the barbs before removal into a sheath, reducing the risk of injury to adjacent structures and the vascular access site. Collapsing the barbs into the retrieval sheath appears to be more difficult with the WATCHMAN device compared to the ACP device. As a result, surgical removal has been required for many of the cases reported in the literature, particularly when the site of embolization is the left ventricle and a WATCHMAN device has been used.

Despite the challenges of percutaneous retrieval, a number of successful retrievals have been performed, including two cases by one of the authors (JS). The ACP device appears easier to retrieve percutaneously compared to the WATCHMAN device, likely related to the fact that the device can be fully collapsed and completely withdrawn into a large arterial sheath, regardless of which endscrew of the device is grasped. We have been successful in retrieving embolized ACP devices from the left atrium and the left ventricle, both of which were observed to have embolized on transthoracic echocardiogram the day after procedure. In the case where an embolized 24 mm ACP device was lodged in the left atrium (Fig. 18.5), a large 16F Checkflo 80 cm sheath was advanced into the left atrium across the transseptal puncture from the procedure the day before. A 5F EBU guide was telescoped

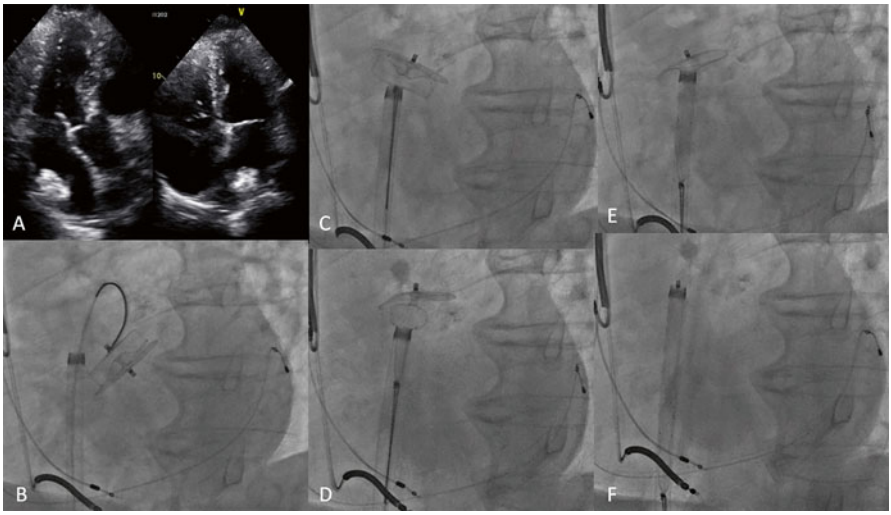


Fig. 18.5 Percutaneous retrieval of embolized 24 mm ACP device lodged in the left atrium. (**a**) Transthoracic echocardiogram images showing the embolized device (*arrows*). (**b**) Flouroscopic image showing a 25 mm gooseneck snare, which had been delivered through a 5F EBU guide within a 16F 80 cm Checkflo sheath, grabbing the distal endscrew of the ACP device. (**c**) The device was pulled in against the 16F sheath in a coaxial manner. (**d**) The device was then pulled in firmly, with the lobe partially retrieved. (**e**) The lobe was entirely retrieved. (**f**) The disk was entirely retrieved

through the sheath and to help direct a 25 mm gooseneck snare onto the embolized device. The snare was cinched on the distal endscrew of the device, which was completely pulled into the 16F sheath before removing the sheath from the left atrium and body.

In the case where an embolized 28 mm ACP device was lodged in the left ventricular outflow tract (Fig. 18.6), we advanced a 14F 80 cm sheath into the ascending aorta from common femoral arterial access. A 5F JR4 guide was delivered into the left ventricle over a wire, and a 10 mm gooseneck snare was placed through the JR4 guide to direct the snare to the distal endscrew. Once captured, the device was pulled across the aortic valve in a vertical position (to avoid the hooks from disrupting the valve leaflets and adjacent tissue, as the hooks point from the lobe towards the disk). A transvenous pacer for temporary pacing of the patient was required for this case as there was transient heart block during the short time that the device was pulled across the aortic valve. The device was partially recaptured into the 14F sheath with the snare, but subsequently came off the snare. A bioptome was then used to grab the distal endscrew within the arterial sheath, and completely withdraw the device into the sheath, before removing the arterial sheath completely. In both cases, the patients tolerated the procedures well without any complications.

The general guidelines and tools (Fig. 18.6) for percutaneous retrieval of devices are as follows: A large sheath at least 1–3F size larger than the initial delivery sheath

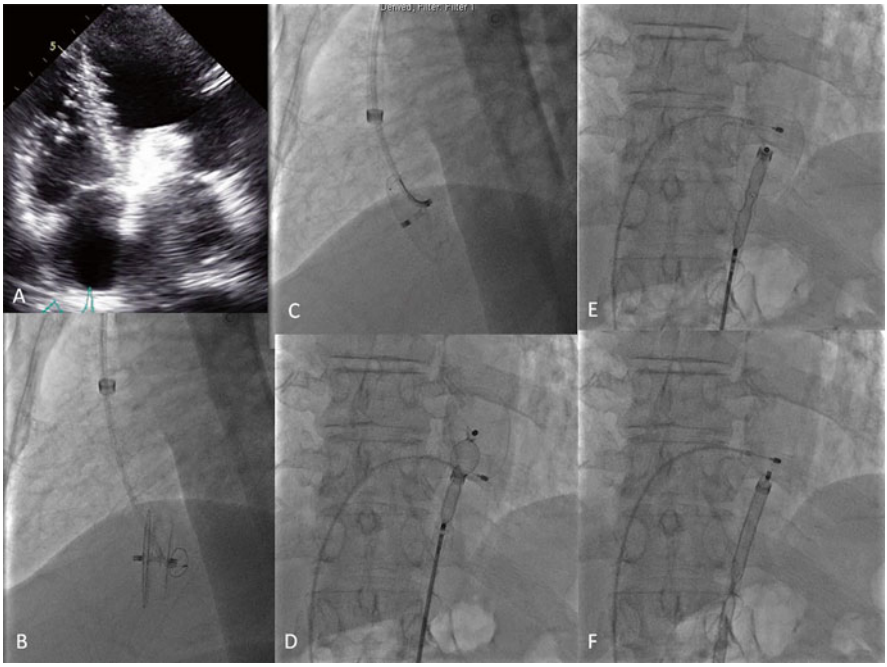


Fig. 18.6 Percutaneous retrieval of embolized 28 mm ACP device lodged in the left ventricular outflow tract. (**a**) Transthoracic echocardiogram image of the embolized device (*arrow*) in the left ventricle. (**b**) A 14F 80 cm sheath was delivered from the femoral artery to the ascending thoracic aorta. A 5Fr JR4 guide was then delivered through the sheath into the left ventricle. A 10 mm gooseneck snare was delivered through a 5F JR4 guide into the left ventricle. (**c**) The gooseneck snare was cinched onto the distal endscrew and the device was pulled up vertically against the aortic valve. (**d**) The partially recaptured device was pulled into the descending thoracic aorta, but the snare came loose and a bioptome (*arrow*) was used to grab onto the endscrew within the sheath. (**e**) With firm grasp of the bioptome, the lobe of the device was entirely retrieved. (**f**) With further firm pulling, the entire device was retrieved into the 14F sheath

size should be used. For most cases, this will mean using a 14–16F sheath size. These sheaths will typically come in an 80 cm length. The operator may consider cutting the tip of the sheath to create a bevel-shape for ease of retrieving the embolized device, although we have not found that to be necessary (Fig. 18.7). In general, the gooseneck snares (length of 120 cm) work much better than other types of snares (e.g., Ensnare), and the size of the snare loop can range from 10 to 25 mm. The diameter of gooseneck snare chosen will depend on the specific anatomy encountered. However, for retrieval in the aorta, using a snare that is 70–80 % of the diameter of the aorta will typically work well. Snaring in the left atrium will require a larger snare (20–30 mm). For devices in the LVOT, choosing a snare diameter 50–80 % of the LVOT diameter is reasonable. The snare should be placed through a 5–6F guiding catheter (e.g., JR4, EBU, Voda left, length 100 cm) to help direct the snare onto the desired location on the device (i.e., the endscrews). For the ACP

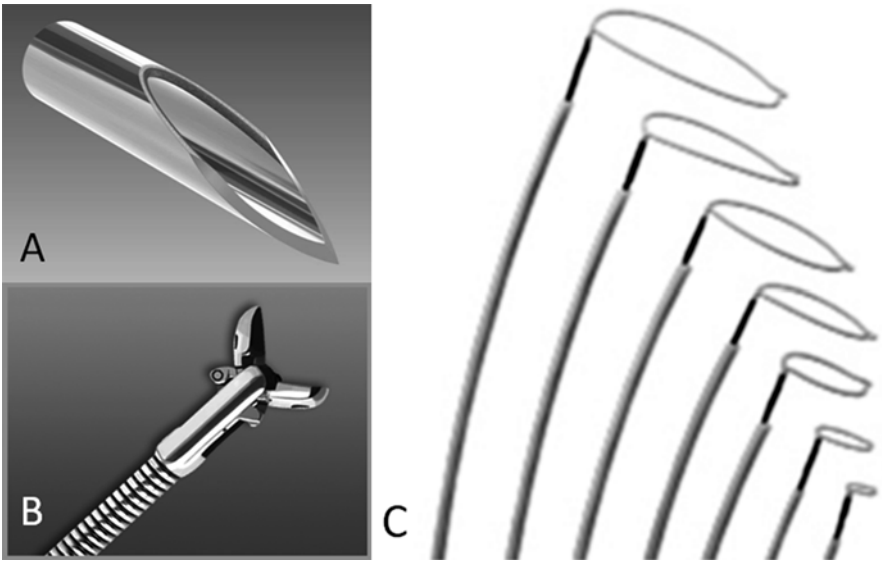


Fig. 18.7 Examples of tools for percutaneous retrieval of embolized devices. (**a**) The sheath may be cut to create a bevel-shape for easier retrieval of large devices. (**b**) A bioptome is especially helpful if the device is partially recaptured within the sheath. (**c**) Various sizes of gooseneck snares

device, either the proximal or distal endscrews can be snared. For the Amulet device, only the distal endscrew is available for snaring. In both the ACP and Amulet devices, both embolized devices should be pulled entirely within the sheath before removal of the sheath from the access site. For the WATCHMAN device, the aim would be to snare the foot pedal and attempt to pull-in and compress the device as fully as possible within the sheath, before removing the sheath from the access site. Patients should be anticoagulated with heparin throughout the procedure, aiming for ACT >250 s as per standard LAA procedures.

Stroke

Based on differing etiologies, stroke related to LAA occlusion may be broadly divided into those related to the immediate procedure, and those occurring beyond the index hospitalization. Procedure-related strokes are most commonly due to air-embolism, occurring with a frequency of approximately 0.5–1 % [1, 5–7], and will usually manifest clinically immediately following the procedure (assuming general anesthetic used) or less commonly later on the day of the procedure. A clinical clue that air embolization may have occurred during the procedure is the observation of transient ST-segment elevation intraprocedurally, typically located in the inferior leads due to the predilection for embolization of air to the right coronary artery.

The risk of air-embolism during LAA occlusion procedures is likely related to the transseptal access where the tip of the sheath is located in the low pressure left atrial chamber. Strategies to reduce this risk include: (1) pre-procedural hydration to keep the LAA pressure >15 mmHg, (2) having delivered any transseptal sheath, remove the wire first, open the stop-cock on the side arm of the sheath, then slowly remove the dilator while keeping the tip of the sheath below the level of the heart. After ensuring an airless blood-fluid connection, carefully flush the sheath. If the sheath has a valve and side arm, flush through the side arm keeping a finger over the valved entrance on the sheath, (3) follow the instructions for device preparation to ensure all air is removed from the device before insertion into the sheath, (4) maintain continuous irrigation to the side arm of the large caliber delivery sheath during introduction of the LAA occlusion device into the sheath and advancement of the device through the sheath to the LAA. Some operators fill the sheath with contrast prior to introduction of the LAA occlusion device as this will facilitate the visualization of any air bubbles during device delivery.

Other potential etiologies for procedure-related stroke include dislodgement of preexisting LAA thrombus not recognized at the time of the procedure, or new thrombosis on interventional wires, catheters, sheaths, or devices in the left atrium or appendage due to suboptimal periprocedural anticoagulation. Careful assessment with transesophageal echo (TEE) of the LAA prior to transseptal puncture to exclude the presence of thrombus, and administration of unfractionated heparin to achieve an activated clotting time >250 s, will help to minimize these potential mechanisms for stroke.

Cerebrovascular ischemic events beyond 7 days post-LAA device implant provides an estimated measure of the performance of the device in stroke prevention. In this time period, the major concerns are of device-associated thrombus formation (Fig. 18.8) or failure of the device to achieve occlusion of the LAA with resultant LAA thrombus formation and subsequent embolization. Device-associated thrombus formation was observed in 4.2 % of patients in the PROTECT-AF trial using the WATCHMAN device [1], but in most patients, this was clinically asymptomatic (3 of 20 patients with device-associated thrombus had an ischemic stroke). The reported incidence of device-associated thrombus with the ACP device has varied significantly. A small single-center study among patients receiving the ACP device reported device-associated thrombus in 6 of 34 patients (17.6 %), with half of these diagnosed prior to discharge, and the remainder at 3-month follow-up TEE [16]. None of these patients had an ischemic event, and all thrombi resolved following treatment with heparin and vitamin K antagonist treatment. However, this frequency of device-associated thrombosis for the ACP device has not been reported in other larger registry studies [6, 7]. In the largest ACP series reported by Tzikis et al. (EuroPCR 2014), 632 of 1001 patients had follow-up TEE post-LAA closure, and device-associated thrombus was observed in 4.4 % of cases. These reports of ACP-associated thrombosis [8, 17] have led to modification of the next generation ACP device (i.e., Amulet) where the connector pin on the disk of the device is recessed in an attempt to eliminate a nidus for thrombus formation [18].

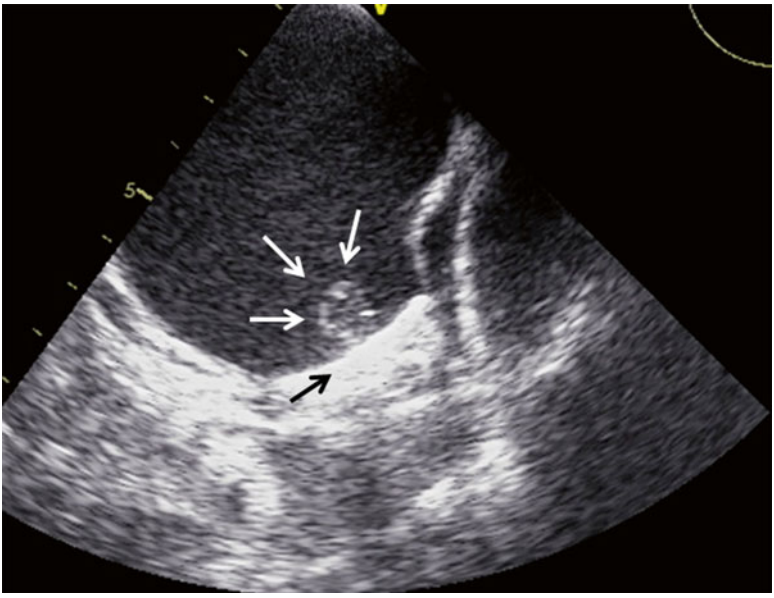


Fig. 18.8 Mobile thrombus (*white arrows*) adherent to the connector pin of an ACP device (*black arrow*). This resolved with prolonged treatment (i.e., 3 months) with oral anticoagulation following initial treatment with intravenous unfractionated heparin

The issue of residual leaks around LAA occlusion devices or residual recesses near the ostium of the LAA as a mechanism for recurrent stroke following LAA occlusion is a contentious one. While it makes intuitive sense that such findings might be associated with an increased risk, analysis from a substudy of the PROTECT-AF trial showed no relationship between the presence of residual peridevice flow and the composite endpoint of ischemic stroke/systemic embolism [19]. The management of significant residual peridevice leaks (i.e., >3–5 mm) is uncertain, although such leaks led to the recommendation to continue anticoagulation in the PROTECT-AF trial in patients who were eligible for that therapy.

Miscellaneous Complications

A long list of other potential complications can occur during LAA closure procedures. Vascular access complications including bleeding, hematoma, arteriovenous fistula, and pseudoaneurysm formation are frequent. Because arterial access is not typically required for LAA closure procedures, the vascular access morbidity is typically caused during attempts to gain venous access or as a result of the large caliber venous sheaths required for device delivery. In the meta-analysis by Bajaj et al., the cumulative frequency of these complications was 8.6 % (95 % CI 6.3–11.7) [12].

Management of these complications is similar to that for other interventional procedures and is summarized in several interventional textbooks [20]. The authors are aware of an unusual access site complication following LAA closure where thrombosis at the venous access site caused by prolonged compression with a FemoStop™ device was associated with subsequent stroke due to embolism across the residual atrial septal defect created by the transseptal puncture and large caliber delivery sheath.

Other complications may occur as a result of general anesthesia (tongue trauma, airway trauma, respiratory failure) or use of the TEE probe (esophageal trauma). Arrhythmia (typically supraventricular tachycardias) may also occur as a result of manipulations in the atria.

Conclusion

Despite significant advances in operator experience, procedural technique, and device technology, major procedural complications from LAA closure remain a significant challenge. The broader application of this strategy for stroke prophylaxis in patients with non-valvular atrial fibrillation beyond those who are ineligible for anticoagulation will be highly dependent on further improvements to achieve improved complication rates.

References

1. 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(4):417–24.
2. Holmes Jr DR, Lakkireddy DR, Whitlock RP, Waksman R, Mack MJ. Left atrial appendage occlusion: opportunities and challenges. J Am Coll Cardiol. 2014;63(4):291–8.
3. Bergmann MW, Landmesser U. Left atrial appendage closure for stroke prevention in non-valvular atrial fibrillation: rationale, devices in clinical development and insights into implantation techniques. EuroIntervention. 2014;10(4):497–504.
4. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, 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(9689):534–42.
5. Holmes Jr DR, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, 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):1–12.
6. Park JW, Bethencourt A, Sievert H, Santoro G, Meier B, Walsh K, et al. Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience. Catheter Cardiovasc Interv. 2011;77(5):700–6.

7. Urena M, Rodes-Cabau J, Freixa X, Saw J, Webb JG, Freeman M, et al. Percutaneous left atrial appendage closure with the AMPLATZER cardiac plug device in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy. J Am Coll Cardiol. 2013;62(2):96–102.
8. Schroeter MR, Danner BC, Hunlich M, Schillinger W. Uncommon delayed and late complications after percutaneous left atrial appendage closure with Amplatzer((R)) Cardiac Plug. Clin Res Cardiol. 2014;103(4):285–90.
9. Bianchi G, Solinas M, Gasbarri T, Bevilacqua S, Tiwari KK, Berti S, et al. Pulmonary artery perforation by plug anchoring system after percutaneous closure of left appendage. Ann Thorac Surg. 2013;96(1):e3–5.
10. Hanazawa K, Brunelli M, Saenger J, Grosse A, Raffa S, Lauer B, et al. Close proximity between pulmonary artery and left atrial appendage leading to perforation of the artery, tamponade and death after appendage closure using cardiac plug device. Int J Cardiol. 2014;175(2):e35–6.
11. Meier B, Tarbine SG, Costantini CR. Percutaneous management of left atrial appendage perforation during device closure. Catheter Cardiovasc Interv. 2014;83(2):305–7.
12. Bajaj NS, Parashar A, Agarwal S, Sodhi N, Poddar KL, Garg A, et al. Percutaneous left atrial appendage occlusion for stroke prophylaxis in nonvalvular atrial fibrillation: a systematic review and analysis of observational studies. JACC Cardiovasc Interv. 2014;7(3):296–304.
13. Aminian A, Chouchane I, Compagnie M, Decubber M, Lalmand J. Delayed and fatal embolization of a left atrial appendage closure device. Circ Cardiovasc Interv. 2014;7(4):628–30.
14. Gupta P, Szczeklik M, Selvaraj A, Lall KS. Emergency surgical retrieval of a migrated left atrial appendage occlusion device. J Card Surg. 2013;28(1):26–8.
15. Pisani P, Sandrelli L, Fabbrocini M, Tesler UF, Medici D. Left-atrial-appendage occluder migrates in an asymptomatic patient. Tex Heart Inst J. 2014;41(4):443–4.
16. Plicht B, Konorza TF, Kahlert P, Al-Rashid F, Kaelsch H, Janosi RA, et al. Risk factors for thrombus formation on the Amplatzer Cardiac Plug after left atrial appendage occlusion. JACC Cardiovasc Interv. 2013;6(6):606–13.
17. Fernandez-Rodriguez D, Vannini L, Martin-Yuste V, Brugaletta S, Robles R, Regueiro A, et al. Medical management of connector pin thrombosis with the Amplatzer cardiac plug left atrial closure device. World J Cardiol. 2013;5(10):391–3.
18. Freixa X, Chan JL, Tzikas A, Garceau P, Basmadjian A, Ibrahim R. The Amplatzer Cardiac Plug 2 for left atrial appendage occlusion: novel features and first-in-man experience. EuroIntervention. 2013;8(9):1094–8.
19. Viles-Gonzalez JF, Kar S, Douglas P, Dukkipati S, Feldman T, Horton R, et al. 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(10):923–9.
20. Casserly IP. Vascular access and closure issues in structural heart disease interventions. In: Carroll JD, Webb JG, editors. Structural heart disease interventions. Philadelphia: Lippincott Williams & Wilkins; 2012.

Chapter 19
Antiplatelet and Anticoagulant Strategies Following Left Atrial Appendage Closure

Louisa Malcolme-Lawes and Prapa Kanagaratnam

The thrombogenicity of implanted cardiac devices relates largely to the material and the position of the device within the cardiovascular system. Mechanical mitral valves require the highest levels of systemic anticoagulation with vitamin K antagonists aiming for an INR of 3.0, whilst bio-prosthetic and aortic valve replacements require only short periods of antiplatelet therapy with a lower target INR [1, 2]. Recent studies using dabigatran as the anticoagulant for valve replacements were terminated early due to thromboembolic events [3], illustrating the idiosyncratic nature of the relationship between thromboprophylaxis and implants when using drugs acting on different locations in the coagulation cascade. Conversely, intracoronary stent deployment was initially protected with warfarin anticoagulation but stent thrombosis was largely platelet-driven and was later shown to be significantly reduced by 3–6 months of dual antiplatelet therapy (DAPT), with drug-eluting stents requiring up to 1 year of DAPT due to intentionally delayed endothelialisation [4, 5]. Atrial septal defect (ASD) and patent foramen orifice (PFO) closure devices initially have a non-endothelialised wall on the left atrial (LA) aspect but DAPT for 6 months and subsequent aspirin for 2 years have been shown to be safe in most patients [6]. However, thrombus can form on PFO/ASD closure devices, the occurrence of which appears to be more frequent in patients with atrial fibrillation (AF) [7]. This additional prothrombotic risk in patients with AF and LA devices appears to be multifactorial. Endothelial dysfunction, coagulation activation, platelet activation and increased fibrinolytic activity are all thought to contribute. Elevated levels of inflammatory markers have also been noted in AF patients. These include Von Willebrand factor, Interleukin 6 and CRP [8]. Stasis in areas of low blood flow, due to LA chamber enlargement and reduced LA transport, is likely to further contribute to the development of atrial thrombus.

L. Malcolme-Lawes, M.B. Ch.B., Ph.D. • P. Kanagaratnam, M.B. B.Chir., Ph.D. (✉)
Department of Cardiology, Imperial College Healthcare NHS Trust, 150 Du Cane Road, London W12 0HS, UK
e-mail: l.malcolme-lawes@imperial.ac.uk; p.kanagaratnam@imperial.ac.uk

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_19

Some studies have shown that activation of the coagulation cascade may play a more significant role in thrombus formation in patients with AF than that of platelet aggregation [9], which may explain why anticoagulants such as warfarin have been found to be more effective than antiplatelet agents (aspirin or clopidogrel) in preventing thromboembolic events [10]. It is on this background that our approaches to LAAO device-related thromboprophylaxis need to be developed.

The PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) study demonstrated that left atrial appendage occlusion (LAAO) with the Watchman device (Boston Scientific Corporation, Natick, MA) was a viable method for stroke prevention comparable to anticoagulation with warfarin. Importantly, the efficacy of LAAO was driven by the reduction of intracranial bleeds rather than embolic events indicating that further improvement in thromboprophylaxis when using LAAO may be necessary. The study was designed and conducted in the era of anticoagulation with warfarin, but results were reported at a time when pharmacological alternatives to warfarin (dabigatran, rivaroxaban and apixaban) had also been shown to be highly effective with similar protection from thromboembolic events but with improved intracranial bleed risk without the need for drug level monitoring. Furthermore, since the description of the Watchman, alternative devices such as the Amplatzer Cardiac Plug (St. Jude Medical) and the Lariat suture (SentreHeart) devices have also been shown to be feasible in non-randomised series. This has led to a debate about the appropriate indications for LAAO. Many clinicians favour their use only in patients who have a bleeding risk or contraindication to anticoagulation which may restrict the choice and approach for peri-procedural thromboprophylaxis.

LAAO Device-Related Thrombus

The formation of LAAO device-related thrombus has been documented with post-procedural transesophageal echocardiography (TEE) imaging in all of the approved devices for LAAO (see Chap. 10) and can also be visualised on CT (see Fig. 19.1).

As the only randomised study in the field to date, detailed analysis of the data from PROTECT-AF helps reveal some important features of thrombotic risk of LAAO. All patients receiving the Watchman device were given warfarin (target INR = 2–3) for the first 45 days. A TEE was then performed to assess for any residual flow leaks around the device or any device-related thrombus. In successfully occluded patients (86 %), defined as a residual peri-device flow of <5 mm, warfarin was stopped and patients were switched to aspirin 75 mg and clopidogrel 75 mg for 6 months and subsequently life-long aspirin 75 mg. Those patients found to have greater than 5 mm residual flow around the device on TEE continued to take warfarin until a further TEE was performed at 6 months and again at 1 year.

The additional period of DAPT in patients who stopped warfarin therapy after 45 days was introduced following a pilot study of 60 patients in 2007. They noted four cases (6.7 %) of device-related thrombus in this cohort on the 6-month TEE, one of whom had a transient ischaemic attack.

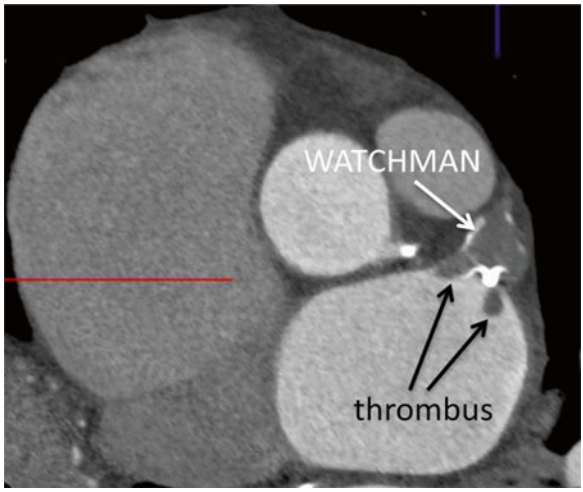


Fig. 19.1 Thrombus seen on CT image of Watchman device (Courtesy of J. Saw)

Despite careful management of anticoagulation, the investigators of PROTECT-AF reported 15 peri-procedural ischaemic strokes. One was pre-procedural and reported as an intention-to-treat outcome. Five were intra-procedural and thought to be related to air embolization during sheath manipulation, though thrombus formation within the sheath cannot be ruled out. Nine were post-procedural, and in all patients in whom an INR was available, it was found to be sub-therapeutic at the time of the stroke. Device-related thrombus was identified in 15 of 389 (3.8 %) patients with TEEs at 6 and 12 months. Two of these 15 patients had ischaemic strokes (13 %) indicating that device-related thrombus was not a benign finding.

LAAO Device Implantation Without Anticoagulation

There is evidence that PFO and ASD closure devices can be implanted without anticoagulation despite foreign material in the left atrium. The Amplatzer Cardiac Plug (St. Jude Medical) was a modification of the septal closure devices, and as a second-generation device, the instruction for use followed the same thromboprophylactic regime as the septal closure devices with only aspirin and clopidogrel advised at time of implantation. Several centres have reported that there were minimal or no thromboembolic events following this approach; however, the data were collected retrospectively, and the follow-up period was relatively short. The ASAP (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology) study was a multi-centre, prospective non-randomised trial designed to assess the WATCHMAN device with 6 months of aspirin and clopidogrel followed by life-long aspirin in patients with a relative contraindication to anticoagulation [11]. The majority (93 %) of patients who were entered into the trial had a history of haemorrhagic/bleeding tendencies, which made them ineligible for warfarin. Six (4 %) of the 150 patients who had a Watchman device implanted in the ASAP study

were found to have device-related thrombus on TEE. One of these patients had a stroke, and the others had thrombus detected on routine TEE screening at 3 or 12 months. This is very similar to the 3.8 % device-related thrombus rate in the PROTECT-AF study in which warfarin was continued post-procedure. Patients in the ASAP study who had thrombus were treated with 4–8 weeks of low molecular weight heparin. In terms of the primary efficacy outcomes, the ASAP study reported a rate of all-cause stroke or systemic embolism of 2.3 %, ischaemic stroke 1.7 % and haemorrhagic stroke 0.6 %. These compare favourably to the 3 %, 1.9 % and 0.3 % rates, respectively, for the PROTECT-AF trial although these were not done at similar training levels or on an intention-to-treat basis.

These studies suggest that DAPT for LAAO implantation is safe and feasible but does not establish whether it is superior to an initial period of anticoagulation. Furthermore, it is not known whether anticoagulation with warfarin, novel anticoagulants or DAPT is the safest in patients with risk factors or a history of bleeding. In the ACTIVE-W study, there was an unexpected finding that DAPT was not as effective as warfarin for stroke prevention and yet it caused significantly more minor bleeding events. Long-term aspirin use is associated with a two- to threefold increase in the risk of both peptic ulcer and non-ulcer upper and lower gastrointestinal (GI) bleeding events [12–14]. However, in patients receiving aspirin for secondary prevention of cardiovascular events, continuation of aspirin following an episode of serious upper GI bleed has been shown to be beneficial, i.e. the risk of recurrent GI bleed is still lower than the risk of cardiovascular events [15]. Similarly, patients with a GI bleed whilst on warfarin therapy for AF have a lower mortality risk if warfarin is restarted within a week without a significant increase in the rate of recurrent GI bleeds. Warfarin appears to be specifically linked to an increase in the risk of intracranial haemorrhage (ICH) [16]. Unfortunately, there is no consensus about restarting warfarin in patients who have suffered a haemorrhagic stroke whilst on warfarin for AF, although the risk of thromboembolic stroke and the location of the ICH are usually taken into account [17, 18]. When all types of bleeding are taken into account, there is no significant difference between the risk of bleeding with aspirin or warfarin therapy [16]; however, clopidogrel alone appears to carry a higher risk for non-fatal or fatal bleeds, as does DAPT and triple therapy, as would be expected [19]. Ideally, the uncertainties regarding anticoagulant and antiplatelet strategies in patients with a history of bleeding tendencies should be resolved by randomised studies; however, history of bleeding may be from a range of underlying pathology for both GI and ICH and may need to be taken into account when deciding on patient-specific therapies.

Thromboembolic Risk from Residual Peri-Device Flow

Incomplete closure is a potential outcome in any form of LAAO. Surgically closed LAA was shown to have residual flow of 60 % at TEE although surgical excision has a lower rate of incomplete LAA closure at 27 % compared to other forms of

surgical LAA closure [20]. Intracardiac devices are circular in shape and the LAA is often oval leading to a leak along the side of the device. If a device is implanted deep in the appendage rather than at the ostium, then an 'ante-chamber' can be present and some of the device-related thrombi detected have been in devices implanted too deeply within the LAA. External ties such as the Lariat device can also result in a central channel with remnant flow. There is a concern that incomplete sealing of the LAA orifice may lead to the creation of a small pouch of stagnant blood, which could lead to thrombus formation and increase the risk of stroke post-device implant. On the other hand, these leaks may be too small to allow any large thrombi that develop to pass around the device, and thereby pose minimal risk of stroke. The PROTECT-AF investigators deemed a residual gap of $<3 \pm 2$ mm, an acceptable amount of peri-device flow; however, the clinical implications of this cut-off were unknown.

A sub-study of PROTECT-AF investigated the frequency and clinical impact of incomplete left atrial appendage sealing and residual peri-device blood flow following implantation of the Watchman device (see Fig. 19.2). Peri-device flow was defined as minor (<1 mm), moderate (1–3 mm) or major (>3 mm), and its effect on the primary efficacy outcome of stroke, systemic embolism or cardiovascular death was assessed. The prevalence of any residual flow was 41 % at the 45-day TEE, 34 % at 6 months and 32 % at 12 months [21].

There was no significant difference in the rate of stroke, systemic embolism or cardiovascular death between patients with or without residual peri-device flow, nor between patients with minor, moderate or major peri-device flow [21]. In addition, there was no increase in primary efficacy events seen in those patients with residual

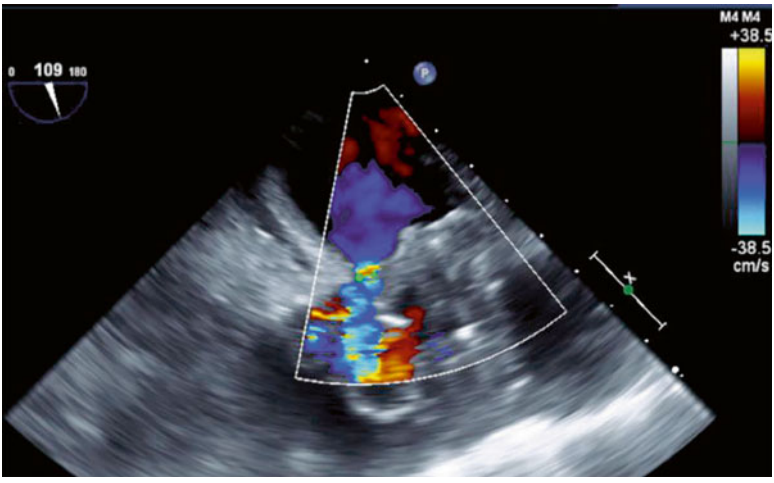


Fig. 19.2 Residual peri-device leak after LAA occlusion by Watchman device seen with TEE imaging. (Courtesy of J. Saw)

peri-device flow who discontinued warfarin compared to those with no residual flow. Although these results suggest that it may be safe to stop warfarin at 45 days regardless of the presence of peri-device flow, they should be interpreted with caution since it is a retrospective analysis and may be confounded by continued anticoagulation therapy in some patients with residual flow.

The results of the PROTECT-AF sub-study and ASAP registry combined suggest that post-procedural warfarin may not be required unless device-related thrombus is present and even this does not invariably always cause stroke but certainly increases the risk.

Use of Novel Oral Anticoagulants

Direct thrombin inhibition with dabigatran is approved for stroke prevention in patients with non-valvular AF and is superior (high-dose 150 mg bid) to warfarin in preventing thromboembolic events and associated with less ICH. Factor Xa inhibitors, rivaroxaban and apixaban, are another class of novel anticoagulants that have been shown to be non-inferior to warfarin for thromboprophylaxis and with lower ICH. These novel oral anticoagulants are increasingly being used to prevent stroke in patients with non-valvular AF in preference to warfarin given its multiple limitations of a narrow therapeutic window, many drug–drug and drug–food interactions and requirement for regular INR monitoring. Of note, all patients from the PROTECT-AF study who had a stroke or TIA, in whom there was an INR available, it was found to be sub-therapeutic. Theoretically, NOACs would maintain more stable anticoagulation and potentially limit these strokes in the early phase of endothelialisation over the device. However, NOACs come with a significant lifetime risk of major bleeding ranging from 1.4 to 3.0 % per year in clinical trials [22–26], and their use in patients with previous bleeds in particular would have to be undertaken with caution. The AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) study did investigate patients who had problems with warfarin, including inability to maintain the INR in the therapeutic range and medication compliance issues, but only a minority of these patients had a prior bleeding event. Furthermore, patients who had a recent serious GI bleeding event or active peptic ulcer disease were excluded from the trial [27]. The rates of bleeding were found to be similar in patients treated with aspirin or apixaban [28]. There is currently no study data for the use of NOACs in conjunction with LAAO devices; however, given the significant advantages of these agents over warfarin, a randomised study of the safety and efficacy of their use in the immediate post-procedural period following Watchman device implantation offers clear advantages over DAPT or warfarin thromboprophylaxis. The published series for the ACP device have used DAPT, and it is possible that short-term anticoagulation may not offer any advantage for this device and could possibly be used in those patients where device-related thrombus is identified.

No Long-Term Therapy

There is a particular attraction in not using any agents after endothelialisation. Long-term aspirin does have some associated risks, particularly in those with GI bleeding, and the prospect of avoiding all medications is sought by many patients. This has not been formally published but many centres anecdotally report small number of patients on no long-term treatment. For those patients with bleeding risk, this would be the most desirable approach but again robust registry or randomised data would be needed before advocating this.

Summary

LAAO with the Watchman device with short-term warfarin followed by aspirin and clopidogrel and then remaining on life-long aspirin is the only adjuvant pharmacotherapy that has been tested in a randomised study. However, it is more than likely that there are alternative device-specific pharmacological approaches that are superior to this that may never get tested in randomised controlled studies due to the large number of patients that would be needed to be recruited to have sufficient events to draw a conclusion. Prospective registry data with robust follow-up may be the only method by which such data will be acquired, and consensus statements will be developed based on such information. At present, it would seem reasonable to use the PROTECT-AF data as a benchmark and for centres to adopt local policy, but ensuring close follow-up to confirm that outcomes are in keeping with this standard.

References

1. Whitlock RP, et al. Antithrombotic and thrombolytic therapy for valvular disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e576S–600.
2. Puskas J, et al. Reduced anticoagulation after mechanical aortic valve replacement: interim results from the prospective randomized on-X valve anticoagulation clinical trial randomized Food and Drug Administration investigational device exemption trial. J Thorac Cardiovasc Surg. 2014;147(4):1202–10; discussion 1210–1.
3. Eikelboom JW, Brueckmann M, Van de Werf F. Dabigatran in patients with mechanical heart valves. N Engl J Med. 2014;370(4):383–4.
4. Asencio LA, Huang JJ, Alpert JS. Combining antiplatelet and antithrombotic therapy (triple therapy): what are the risks and benefits? Am J Med. 2014;127(7):579–85.
5. Levine MJ, et al. Clinical and angiographic results of balloon-expandable intracoronary stents in right coronary artery stenoses. J Am Coll Cardiol. 1990;16(2):332–9.
6. Anzai H, et al. Incidence of thrombus formation on the CardioSEAL and the Amplatzer interatrial closure devices. Am J Cardiol. 2004;93(4):426–31.
7. Krumsdorf U, et al. Incidence and clinical course of thrombus formation on atrial septal defect and patient foramen ovale closure devices in 1,000 consecutive patients. J Am Coll Cardiol. 2004;43(2):302–9.

8. Guo Y, Lip GY, Apostolakis S. Inflammatory biomarkers and atrial fibrillation: potential role of inflammatory pathways in the pathogenesis of atrial fibrillation-induced thromboembolism. Curr Vasc Pharmacol. 2015;13(2):192–201.
9. Kamath S, et al. A study of platelet activation in atrial fibrillation and the effects of antithrombotic therapy. Eur Heart J. 2002;23(22):1788–95.
10. Connolly S, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet. 2006;367(9526):1903–12.
11. Reddy VY, 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(25): 2551–6.
12. Spinler SA. Safety and tolerability of antiplatelet therapies for the secondary prevention of atherothrombotic disease. Pharmacotherapy. 2009;29(7):812–21.
13. Lanas A, Sekar MC, Hirschowitz BI. Objective evidence of aspirin use in both ulcer and nonulcer upper and lower gastrointestinal bleeding. Gastroenterology. 1992;103(3):862–9.
14. Hallas J, et al. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study. BMJ. 2006;333(7571):726.
15. Sung JJ, et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. Ann Intern Med. 2010;152(1):1–9.
16. Warkentin AE, et al. Bleeding risk in randomized controlled trials comparing warfarin and aspirin: a systematic review and meta-analysis. J Thromb Haemost. 2012;10(4):512–20.
17. Eckman MH, et al. Can patients be anticoagulated after intracerebral hemorrhage? A decision analysis. Stroke. 2003;34(7):1710–6.
18. Paciaroni M, Agnelli G. Should oral anticoagulants be restarted after warfarin-associated cerebral haemorrhage in patients with atrial fibrillation? Thromb Haemost. 2014;111(1):14–8.
19. Hansen ML, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Arch Intern Med. 2010;170(16):1433–41.
20. Kanderian AS, et al. Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. J Am Coll Cardiol. 2008;52(11):924–9.
21. Viles-Gonzalez JF, et al. 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(10):923–9.
22. Connolly SJ, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–51.
23. van Walraven C, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. JAMA. 2002;288(19):2441–8.
24. Connolly SJ, et al. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364(9): 806–17.
25. Cleland JG, et al. Clinical trials update from the American Heart Association meeting 2010: EMPHASIS-HF, RAFT, TIM-HF, Tele-HF, ASCEND-HF, ROCKET-AF, and PROTECT. Eur J Heart Fail. 2011;13(4):460–5.
26. Eikelboom JW, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation. 2011;123(21):2363–72.
27. Eikelboom JW, et al. Rationale and design of AVERROES: apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment. Am Heart J. 2010;159(3):348–53. e1.
28. Flaker GC, et al. Bleeding during treatment with aspirin versus apixaban in patients with atrial fibrillation unsuitable for warfarin: the apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment (AVERROES) trial. Stroke. 2012;43(12):3291–7.

Chapter 20
Device-Related Thrombi, Residual Leaks, and Consequences

Fabian Nietlispach and Bernhard Meier

Introduction

Most operators and patients fear peri-procedural complications and these occur in approximately 4–9 % with left atrial appendage (LAA) closure procedures. Development of dedicated LAA occlusion devices together with operator experience play key roles in improving procedural outcome [1–3].

On the other hand, the most common long-term complications with LAA closure comprise residual leaks and device-related thrombi. Data on these two complications are scarce, but diagnosis is important. Residual leaks occur in approximately 5 % of patients after implantation of the Amplatzer Cardiac Plug (ACP) device, with the vast majority of these leaks being small (<5 mm). The incidence of relevant leaks (>5 mm) is 1 % (own unpublished data). The clinical impact of residual leaks is therefore usually negligible. Device-related thrombi occur in approximately 6 % of patients (own unpublished data) and warrant treatment. We therefore recommend performing a follow-up transesophageal echocardiogram (TEE) 3–6 months after device implantation (Fig. 20.1a). In patients where TEE cannot be performed, a computed tomography (CT) scan can be done instead (Fig. 20.1b).

Correct interpretation of these follow-up investigations is warranted and if needed, initiation of appropriate measures is crucial.

F. Nietlispach, M.D. (✉)
Department of Cardiology, University Hospital Bern, Inselspital, Bern 3010, Switzerland

Department of Cardiology, University Heart Center,
Raemistrasse 100, Zurich 8091, Switzerland
e-mail: fabian.nietlispach@usz.ch

B. Meier, M.D.
Department of Cardiology, University Hospital Bern, Inselspital, Bern 3010, Switzerland
e-mail: Bernhard.meier@insel.ch

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5_20

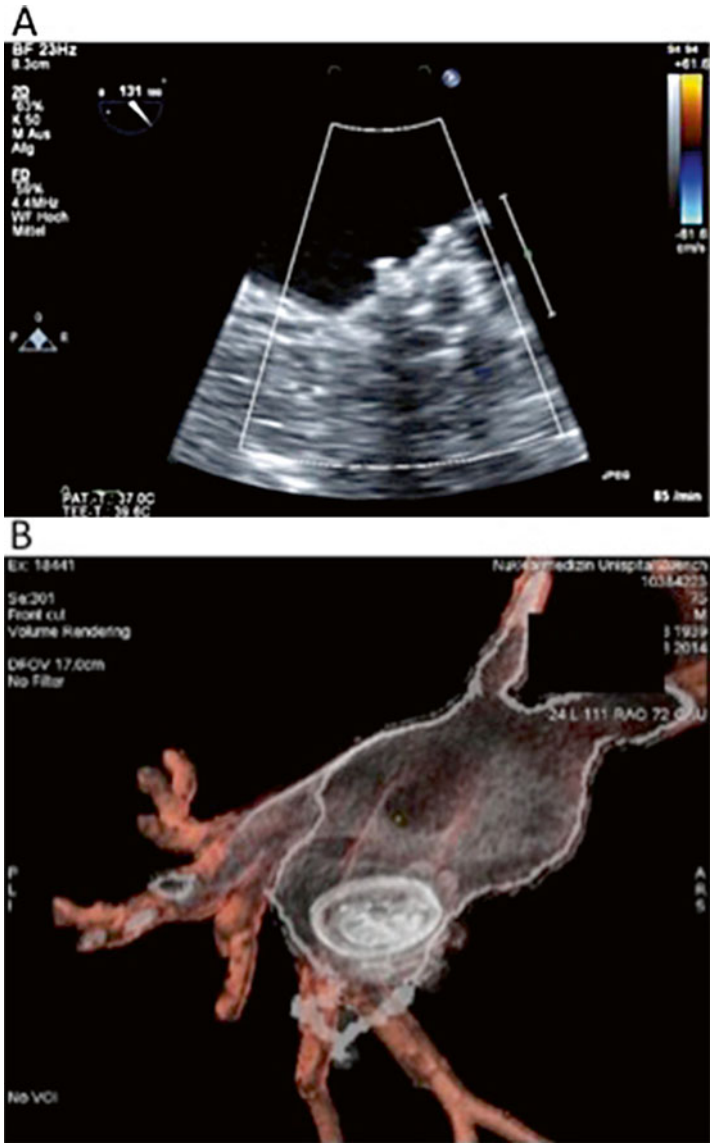


Fig. 20.1 (**A**) Follow-up TEE at 3 months after Implantation of an Amplatzer Cardiac Plug showing no thrombus formation. (**B**) Follow-up CT showing no device thrombus

Current Data

Surgical LAA Ligation

Incomplete exclusion of the LAA from blood flow is quite common after surgical LAA ligation and is associated with a higher risk of thromboembolic events. Two studies reported successful surgical LAA ligation/closure in only 40–70 %

of patients [4, 5]. Incomplete closure was associated with spontaneous echo contrast or thrombus formation and went along with a higher rate of thromboembolic events during follow-up. Evidence of LAA thrombus was found in one-third of patients with incomplete surgical LAA exclusion.

A routine practice to ligate the LAA during open-heart surgery is supported by another study [6]; however, the absence of LAA ligation during mitral valve surgery was a predictor of future thromboembolic events. After a mean follow-up of 69 months, 17 % of patients without LAA ligation suffered a thromboembolic event as opposed to 3.4 % in patients who underwent LAA ligation (odds ratio 6.7). This was true despite the fact that >10 % of LAA ligations were incomplete. If only complete LAA ligations were included in the analysis, the odds ratio for a thromboembolic event without LAA ligation was as high as 11.9, indirectly suggesting a higher risk for thromboembolic events if the LAA ligation is not complete.

Current American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) atrial fibrillation (AF) guidelines state that surgical excision of the LAA may be considered in patients undergoing cardiac surgery (Class IIB, Level of evidence C). In our opinion, routine LAA closure during open-heart surgery makes sense and is supported by the published data. However, incomplete surgical LAA closure is a very common finding and goes along with a higher thromboembolic risk. Furthermore, data suggest an association of residual leaks with the occurrence of LAA thrombus.

Percutaneous LAA Closure

Our "Bern single-center experience" with dedicated Amplatzer LAA devices Amplatzer Cardiac Plug (ACP) and Amulet in 210 patients (own unpublished data) found residual leaks in 5 % of patients. Three quarters of these leaks were minor (<5 mm). Device-related thrombus was found in 6 % of patients whereof 1 % were mobile thrombi. Interestingly, the incidence of residual leaks was much higher (25 %) in patients with device-related thrombi. Such leaks were >5 mm in most patients.

The large European multicenter registry of LAA occlusion with the ACP [7] found comparable rates of peri-device leaks (11.6 %, with relevant leaks >3 mm in 1.9 % of patients) and device-related thrombus (4.4 %). In this large registry, neither peri-device leaks nor the presence of device-related thrombus translated into adverse outcomes.

A slightly higher incidence of device-thrombus was found in a smaller TEE study (17.6 %) [8]. Patients who developed device-related thrombus had a significantly higher $CHADS_2$-score, CHA_2DS_2-Vasc-score, platelet count, and lower ejection fraction as compared to patients without device thrombus.

In a substudy of the PROTECT-AF trial [9], a much higher rate of peri-device leak is reported (32 %), comparable to that of surgical results. The presence of such a peri-device leak was, as opposed to surgical data, not associated with

worse clinical outcome. Furthermore, there was no difference in outcome if patients with a peri-device leak continued oral anticoagulation with Vitamin K antagonists (VKA) or not, suggesting that the presence of a peri-device leak does not warrant continued oral anticoagulation. In this study, device thrombus was found in 3.4 %.

Data on the epicardial/endocardial LARIAT technique indicate a high closure rate of 95 % at 3 months [10]. No patient was left with a leak >3 mm. No thrombus formation at the ligation site was detected. Of note, of the 119 patients, 30 were excluded due to anatomical reasons; therefore only 75 % of patients could be treated with this device.

Several case reports also documented the presence of stump thrombus after the Lariat procedure, but the absolute incidence is not known.

In summary, the rate of incomplete LAA closure seems lower with percutaneous LAA closure as compared to surgical ligation. Data on percutaneous closure suggest that peri-device leaks (unless large) have no clinical consequences. Large leaks appear to be linked to a higher risk for thrombus formation and may need to be addressed.

Definition and Diagnosis of Device-Related Thrombi Formation and Residual Leaks

Device-Related Thrombi

Fibrin deposition is an important step during device endothelialization and occurs in all patients after device implantation (Fig. 20.2). Thrombus formation is usually followed by organization of the thrombus, some inflammation, formation of granulation tissue, and finally endothelialization. Therefore, thrombus formation is an important part during endothelialization.

During follow-up TEE, it is therefore important to differentiate “physiologic” thrombus formation/fibrin deposition of the occluder and “tissue-filling” of niches from “pathologic” thrombus formation.

Device-related thrombi that protrude into the left atrium and show mobile components have to be considered “high-risk thrombi” (Fig. 20.3). Differentiation from endothelialization is unambiguous. Predilection sites are niches around the device and protruding device structures such as screws. Intentions to minimize these predilection sites therefore make sense (e.g., internalization of the disc-screw with the Amulet second-generation ACP device).

Tissue-filling starts at the same predilection sites and progressively covers the entire device. It consists of a thin tissue layer without protruding components and needs no further measures.

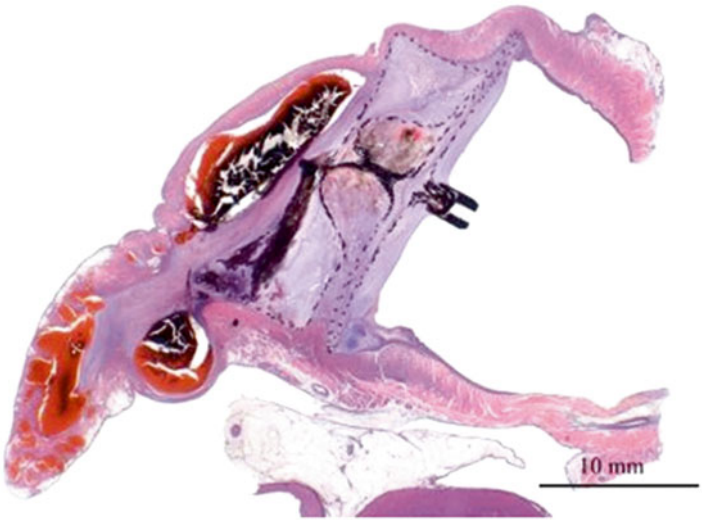


Fig. 20.2 Fibrin deposition on atrial side of the device

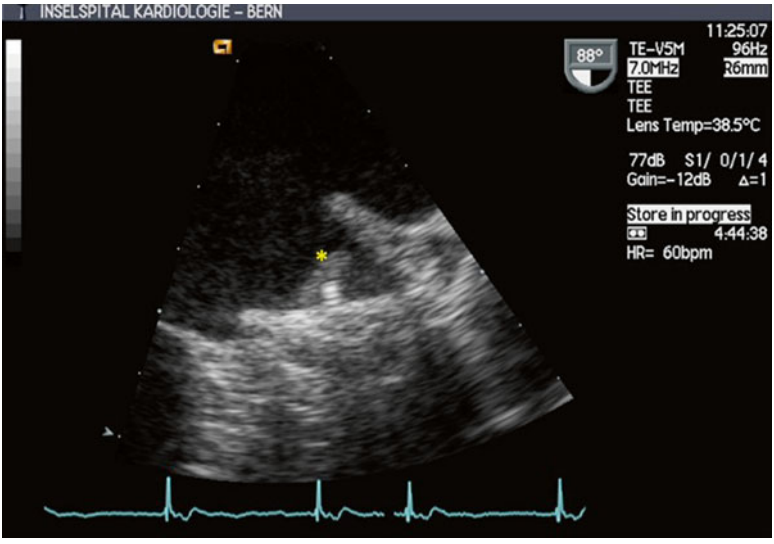


Fig. 20.3 Mobile thrombus on atrial-side of device

Residual Leaks

A residual leak is defined as residual flow into the LAA after LAA closure. In the aforementioned substudy of the PROTECT-AF trial [9], peri-device leaks were classified as none, minor (<1 mm), moderate (1–3 mm), and severe (>3 mm).

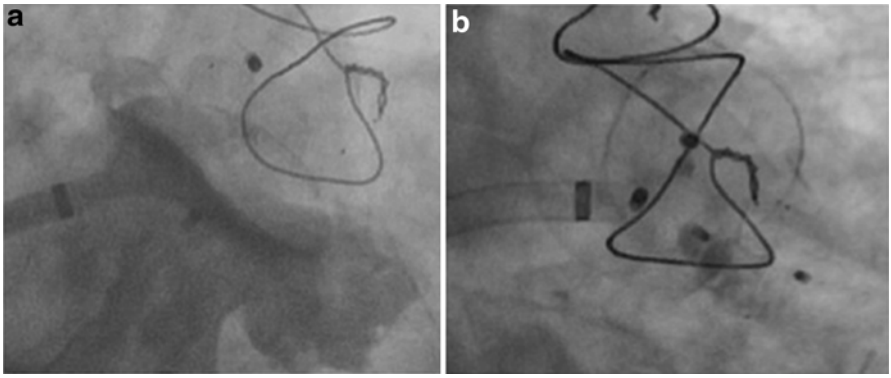


Fig. 20.4 (**a**) Large residual peri-device flow following ACP implantation (**b**) Second ACP device implantation for residual peri-device leak

No difference in thromboembolic events was found during follow-up between the four subgroups.

From our own data on 210 patients using Amplatzer devices, the incidence of peri-device leak was 5 %, with small leaks (<5 mm) being responsible for the vast majority of the leaks (73 %) (Bern LAA registry, unpublished data).

A large residual flow into the LAA (e.g., entire LAA lobes that are not excluded, Fig. 20.4a) most likely results in immediate intra-procedural treatment measures (e.g., implantation of a second device, Fig. 20.4b). Peri-device leaks diagnosed during follow-up are therefore most likely smaller. Classification according to the size is somewhat arbitrary, with >3 mm being considered a relevant leak in the Watchman trials (while warfarin was continued post-device implantation if the leak exceeded 5 mm) and >5 mm being considered significant for Amplatzer devices.

Exact quantification of the size of the leak can be difficult. Therefore, another aspect to consider on TEE is the differentiation of leaks according to continuous bi-directional flow (indicating a more relevant leak) versus noncontinuous color-flow signals.

Technical difficulties in properly assessing the size of the leak may arise, and inter-observer differences can be expected to be high. In our own experience, multiple angles should be used (30°, 60°, 90°, and 120°) in order to screen the entire circumference of the device. This should be done using a low Nyquist limit (e.g., 30 cm/s) to increase sensitivity.

Etiology and Causes of Device-Related Thrombi Formation and Residual Leaks

Factors that can be influenced by the operators are device position and device sizing. Besides, patient-specific factors may play a role, such as undiagnosed coagulopathies enhancing the risk of thrombus formation. It is also likely that permanent AF is more thrombus-prone than paroxysmal AF [11].

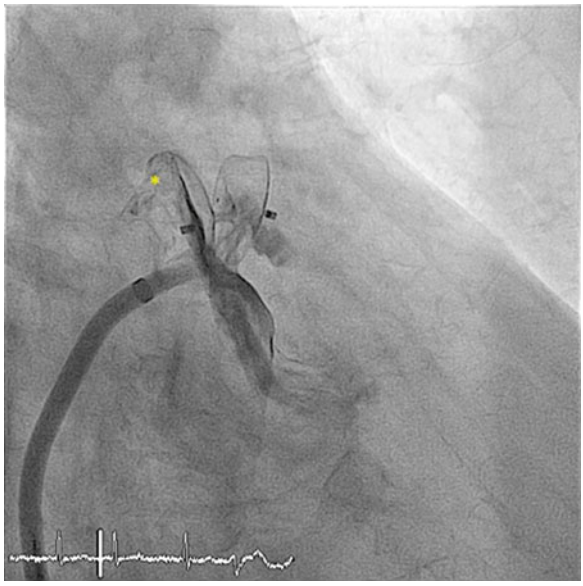


Fig. 20.5 Prolapse of the ACP disc into the LAA neck (*)

Ideally, the lobe of either LAA occluder sits at the entrance of the LAA, while with the ACP, the disc provides additional sealing of the entire LAA entrance (pacifier principle). In case of a less-than-ideal position of the device after first deployment (Fig. 20.5; e.g., too distal implantation of the lobe with partial prolapse of the disc into the LAA neck in the case of ACP), operators are confronted with a dilemma: should the device be recaptured, repositioned, or even exchanged for another device, or should the result be accepted? Should the added procedural risk by the abovementioned measures or the potentially slightly higher risk for intermediate-term complications (e.g., leaks or device thrombus within the first 1–6 months) be valued more important?

From our own experience (Wolfrum M. et al., submitted), we tend to accept a retracted disc of the ACP into the neck of the LAA (Fig. 20.5; comparable outcome after a mean follow-up of 11 months) and a rather deeply seated Watchman device that leaves part of the neck uncovered. If, however, entire lobes with their crypts remain uncovered, measures should be taken (e.g., exchange for a larger device or implantation of a second device; Fig. 20.4b).

Prioritizing a more frugal procedure with as little repositioning of the device as needed enables a reduction of procedural complications, knowing that residual leaks most likely do not have any clinical consequences and that the occurrence of device-related thrombi is an infrequent complication that can be managed successfully in most patients.

Different Devices

The incidence of device thrombus was 3.4 % in the PROTECT-AF trial [9], as compared to 4–6 % with Amplatzer devices [7] [own unpublished data]. Peri-device leaks seem to be more common with the Watchman device as compared to the ACP probably due to the pacifier principle of the latter. With regard to the LARIAT device, we do not have sufficient data yet to make a definite statement regarding the incidence of leaks and thrombus, but it seems that they are not exceeding the other devices.

The Amulet has more hooks on the lobe to improve stability and anchoring. The larger size devices also come with a larger disc, to improve sealing at the LAA entrance. It can be speculated that better sealing with the larger discs and better anchoring could result in less peri-device leaks, perhaps at the price of higher risk of device thrombus given the larger disc. In fact, in a series of 100 patients undergoing Amplatzer LAA occlusion (50 ACP and 50 Amulet), no peri-device leaks were found in the Amulet group, whereas the ACP group showed 3 patients with a small peri-device leak. On the other hand, 2 patients in the Amulet group developed device-related thrombus found on routine follow-up TEE (as compared to none in the ACP group). All these differences, however, did not meet statistical significance [12].

LAA Closure: Outcomes with the Frugal Bern Approach

At Bern, our routine is to perform LAA occlusion in the catheterization laboratory in an awake patient under local anesthesia, using fluoroscopic guidance alone [3]. This approach also allows for ad hoc LAA occlusion [13]. In case a PFO is present, we use it for left atrial access, thereby omitting transseptal puncture [14]. We recently showed feasibility, efficacy, and safety of our approach in the largest single-center experience with the longest follow-up [3]. Our routine is to perform a baseline TEE before the procedure to exclude thrombus. In case of ad hoc LAA occlusion, no baseline TEE is performed, but contrast medium is injected to the LAA from distance to exclude the presence of thrombus. The LAA is then depicted in at least two different views, right anterior oblique (RAO) cranial and RAO caudal, and device-sizing depends on fluoroscopic measurements. Our incidence of device thrombus or peri-device leak appears comparable to other centers' approach. For cases done through PFO access, our peri-device leaks (2 %) and device thrombus (5.8 %) also appeared comparable.

Therapy

Device-Related Thrombus

If true device-related thrombus is present, an additional course of oral anticoagulation or low-molecular weight heparin is warranted [1, 15]. We recommend 3 months of oral anticoagulation with VKA or a non-VKA oral anticoagulant (NOAC), after which time another TEE should be performed. In the vast majority of patients, the thrombus resolves without sequelae.

A true clinical challenge is patients with absolute contraindications for oral anticoagulation that show a device-related thrombus. A course of low-molecular weight heparin (with the advantage of a shorter half-life than VKA) might be an option, balancing the risks and potential benefits of such a therapy. A suboptimal solution in such a patient would be low-dose NOAC or prolonged dual antiplatelet therapy.

Peri-Device Leak

We have learnt that small leaks do not warrant any measures. A large peri-device leak with entire lobes and crypts being uncovered should be closed with a second device. As a second device, another dedicated LAA occluder can be used. Vascular plugs or small atrial septal defect occluders are valid possibilities [16]. As a less optimal alternative, oral anticoagulation with VKA or NOAC can be re-initiated.

Summary

Device thrombus and peri-device leaks are rare complications. True device-related thrombus requires short-term (8–12 weeks) anticoagulation, but sometimes may be difficult to differentiate from "tissue-filling" (which represents physiological thrombus formation during endothelialization). Peri-device leaks rarely require measures unless large, in which case implantation of a second device should be considered.

References

1. 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.
2. Reddy VY, Mobius-Winkler S, Miller MA, Neuzil P, Schuler G, Wiebe J, Sick P, Sievert H. 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.
3. Nietlispach F, Gloekler S, Krause R, Shakir S, Schmid M, Khattab AA, Wenaweser P, Windecker S, Meier B. Amplatzer left atrial appendage occlusion: single center 10-year experience. Catheter Cardiovasc Interv. 2013;82:283–9.
4. Katz ES, Tsiamtsiouris T, Applebaum RM, Schwartzbard A, Tunick PA, Kronzon I. Surgical left atrial appendage ligation is frequently incomplete: a transesophageal echocardiograhic study. J Am Coll Cardiol. 2000;36:468–71.
5. 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.
6. Garcia-Fernandez MA, Perez-David E, Quiles J, Peralta J, Garcia-Rojas I, Bermejo J, Moreno M, Silva J. 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.
7. Tzikas A, Shakir S, Sievert H, Omran H, Berti S, Santoro G, Kefer J, Landmesser U, Nielsen-Kudsk JE, Cruz-Gonzalez I, Gafoor S, Tichelbacker 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: multicenter experience with the Amplatzer Cardiac Plug. Euro Interv. 2015;10:10.
8. Plicht B, Konorza TF, Kahlert P, Al-Rashid F, Kaelsch H, Janosi RA, Buck T, Bachmann HS, Siffert W, Heusch G, Erbel R. Risk factors for thrombus formation on the Amplatzer Cardiac Plug after left atrial appendage occlusion. JACC Cardiovasc Interv. 2013;6:606–13.
9. 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.
10. 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.
11. Al-Khatib SM, Thomas L, Wallentin L, Lopes RD, Gersh B, Garcia D, Ezekowitz J, Alings M, Yang H, Alexander JH, Flaker G, Hanna M, Granger CB. Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial. Eur Heart J. 2013;34:2464–71.
12. Gloekler S, Shakir S, Doblies J, Khattab AA, Praz F, Guerios Ê, Koermendy D, Stortecky S, Pilgrim T, Buellesfeld L, Wenaweser P, Windecker S, Moschovitis A, Jaguszewski M, Landmesser U, Nietlispach F, Meier B. Early results of first versus second generation Amplatzer occluders for left atrial appendage closure in patients with atrial fibrillation. Clin Res Cardiol. 2015 Mar 4. [Epub ahead of print].
13. Nietlispach F, Krause R, Khattab A, Gloekler S, Schmid M, Wenaweser P, Windecker S, Meier B. Ad hoc percutaneous left atrial appendage closure. J Invasive Cardiol. 2013;25:683–6.
14. Koermendy D, Nietlispach F, Shakir S, Gloekler S, Wenaweser P, Windecker S, Khattab AA, Meier B. Amplatzer left atrial appendage occlusion through a patent foramen ovale. Catheter Cardiovasc Interv. 2014;84(7):1190–6.
15. Cruz-Gonzalez I, Martin Moreiras J, Garcia E. Thrombus formation after left atrial appendage exclusion using an Amplatzer cardiac plug device. Catheter Cardiovasc Interv. 2011;78:970–3.
16. Guerios EE, Gloekler S, Schmid M, Khattab A, Nietlispach F, Meier B. Double device left atrial appendage closure. EuroIntervention. 2014. Jul 10. pii: 20130311-05. doi:10.4244/EIJY14M07_03. [Epub ahead of print].

Index

J. Saw et al. (eds.), *Left Atrial Appendage Closure*, Contemporary Cardiology,
DOI 10.1007/978-3-319-16280-5