Percutaneous Transcatheter Closure of the Left Atrial Appendage with Endocardial Implant (CPT Code 33340)

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Key Findings

- Atrial fibrillation is a common condition associated with an increased risk of stroke.
- Current treatment relies on anticoagulation, which carries a small risk of serious bleeding.
- Alternative treatments, including closure of the left atrial appendage (a source of clots), can be performed percutaneously or through open surgery.
- There are data on the efficacy of the WATCHMAN, the only implanted device currently approved by the Food and Drug Administration (FDA) for percutaneous closure of the left atrial appendage, from two randomized controlled trials (RCTs):
    - WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT AF)
    - Prospective Randomized Evaluation of the WATCHMAN Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation (PREVAIL)
- The risk of ischemic strokes appears to be similar for those undergoing WATCHMAN placement or continuing with anticoagulation with warfarin, according to direct comparisons.
- Indirect comparisons through the use of network meta-analysis estimate a similar risk of ischemic stroke with novel oral anticoagulants (e.g., direct thrombin inhibitors, factor Xa inhibitors).
- The first RCT of the WATCHMAN device observed increased risk of serious procedural harms, notably pericardial tamponade necessitating percutaneous drainage or surgery and periprocedural stroke. Subsequent RCTs and clinical registries demonstrate decreased rates of these events compared to the original studies, possibly resulting from increased operator experience.
- Estimates of cost-effectiveness are inconsistent. Recent estimates extrapolated from PROTECT AF and PREVAIL outcomes demonstrated cost savings for the WATCHMAN compared to medical therapy, but not for low-risk groups. However, the estimated cost effects of the WATCHMAN could be at risk of bias.
- Several similar devices are available in Europe, and there are numerous studies in process in Europe and the U.S.

Background

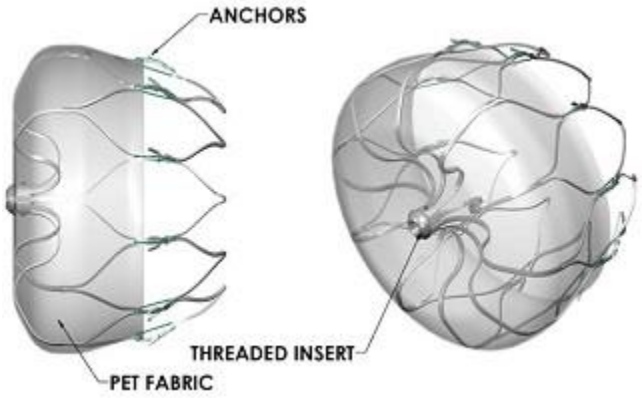
Clinical Overview

- In March 2015, the WATCHMAN, a percutaneously inserted left atrial appendage closure device, received FDA approval for the prevention of stroke in individuals with non-valvular atrial fibrillation who are eligible for anticoagulation with warfarin, a vitamin K antagonist

(VKA) but have an "appropriate reason to seek a non-drug alternative to warfarin" (FDA, 2015). The WATCHMAN is currently the only approved device for this purpose in the U.S.

- Originally presented to the FDA in 2009, the WATCHMAN did not receive approval initially due to high periprocedural complication rates. A subsequent RCT was conducted to address effectiveness of the WATCHMAN for stroke prevention and safety compared to anticoagulation for atrial fibrillation (Masoudi et al., 2015).
- Atrial fibrillation is a heart rhythm disorder in which the rate of the atria (upper chambers of the heart) is different from the ventricular rate (lower chamber of the heart). This causes blood to pool in the atria, resulting in enlargement of the appendage of the left atrium; and pooled blood is at higher risk of forming clots. Blood clots traveling outside the heart may result in thromboembolism. Blood clots traveling to the brain cause thromboembolic strokes, which cut off the blood supply to the affected parts of the brain. These are known as ischemic strokes.
- Anticoagulation, achieved by disruption of the clotting cascade through use of aspirin or VKA, was the mainstay of stroke prevention until recently. Newer agents—factor Xa inhibitors and direct thrombin inhibitors—require less monitoring than VKA and have equal efficacy (Benjamin et al., 2017).
- Valvular disease, particularly requiring valve replacement, is managed with different anticoagulation goals; thus, patients with valvular disease and atrial fibrillation were historically excluded from trials and most of the literature reports on individuals with non-valvular atrial fibrillation.
- Treatment with anticoagulation drugs decreases the risk of ischemic stroke but at an increased risk of major bleeding (e.g., intracranial or gastrointestinal).
- Current procedural terminology (CPT) code 33340 is used to bill for the procedure to place the WATCHMAN device.
- To insert the device, the provider obtains access to the heart through the femoral vein, and a catheter is inserted up the inferior vena cava until it enters the right atrium. The provider then punctures the wall between the right atrium and left atrium with the catheter. Under fluoroscopy, the device is deployed into the left atrial appendage.
- Other devices for left atrial appendage closure are available in Europe and include the AMPLATZER cardiac plug from St. Jude Medical and the WaveCrest from Coherex Medical.
- The left atrial appendage can be closed during surgical procedures (e.g., mitral valve replacement), but intraoperative closure is outside the scope of this report, which focuses on the percutaneous procedure used with the WATCHMAN device.

Figure 1. WATCHMAN Device



Source: U.S. Food and Drug Administration (2015)

Prevalence

- It is estimated that atrial fibrillation will affect nearly 12 million Americans by 2030; recent estimates report that 2.7 to 6.1 million adults currently have the disorder (Benjamin et al., 2017).
- Atrial fibrillation increases an individual's risk of stroke at all ages and portends an increased risk of mortality for individuals with heart failure, diabetes, and kidney failure. Atrial fibrillation causes 23.5% of strokes in adults 80-89 years of age, compared to only 1.5% of strokes in those 50-59 years (Benjamin et al., 2017).

PICO

Population: Adults with non-valvular atrial fibrillation

Intervention: Percutaneous closure of the left atrial appendage with permanent implant (CPT code 33340)

Comparators: Oral anticoagulation (e.g., vitamin K antagonist, direct Factor Xa inhibitors, direct thrombin inhibitors), antiplatelet therapy, or no anticoagulation, with or without other medical therapy (e.g., medications for heart rate control)

Efficacy and Effectiveness Outcomes: Embolic ischemic stroke risk, need for long-term oral anticoagulation therapy, quality of life, cost or cost-effectiveness

Harm Outcomes: Morbidity, major bleeding, procedural complications

Methods

Center researchers searched Center core sources and MEDLINE (Ovid) for systematic reviews (with or without meta-analysis), and technology assessments on left atrial appendage closure devices published within the last 10 years and clinical practice guidelines published within the last five years. To ensure that the most recent data was included, Center researchers also

searched MEDLINE (Ovid) through May 2017 for systematic reviews, individual studies, economic analyses on cost or cost-effectiveness, and clinical practice guidelines on the use of left atrial appendage closure devices for individuals with atrial fibrillation published after the search dates of the most recent, included systematic reviews.

Center researchers evaluated the methodological quality of systematic reviews, individual studies, and clinical practice guidelines included in this report using the quality assessment tools available on the New York State Department of Health website. Center researchers also searched Medicare, several state Medicaid programs, and private payers for coverage policies on the use of left atrial appendage closure devices for the treatment of adults with non-valvular atrial fibrillation. See Appendix A for a full list of payers searched.

Center researchers excluded systematic reviews if all of the included studies were also summarized by a more comprehensive systematic review, a systematic review of a higher methodological quality, and/or a more recently published systematic review. Patient important outcomes that have relevance for New York Department of Health were pre-determined in the topic scope development and studies reporting other outcomes were not included. Exclusion criteria were selected prior to review of the studies, and study methods were assessed prior to review of outcomes to eliminate bias. See Appendix A for a full description of methods.

Evidence Review

Findings

Center researchers identified one recent systematic review (Noelck et al., 2016) and two systematic reviews with network meta-analyses (Bajaj et al., 2016; Sahay et al., 2017) relevant to the effectiveness and/or harms of left atrial appendage closure for the prevention of stroke in non-valvular atrial fibrillation. Figure 2 outlines the number of articles identified by each search and the total number of studies included in this evidence synthesis. Multiple systematic reviews included identical studies; thus, the most up-to-date and highest quality methodological studies are included in this report.

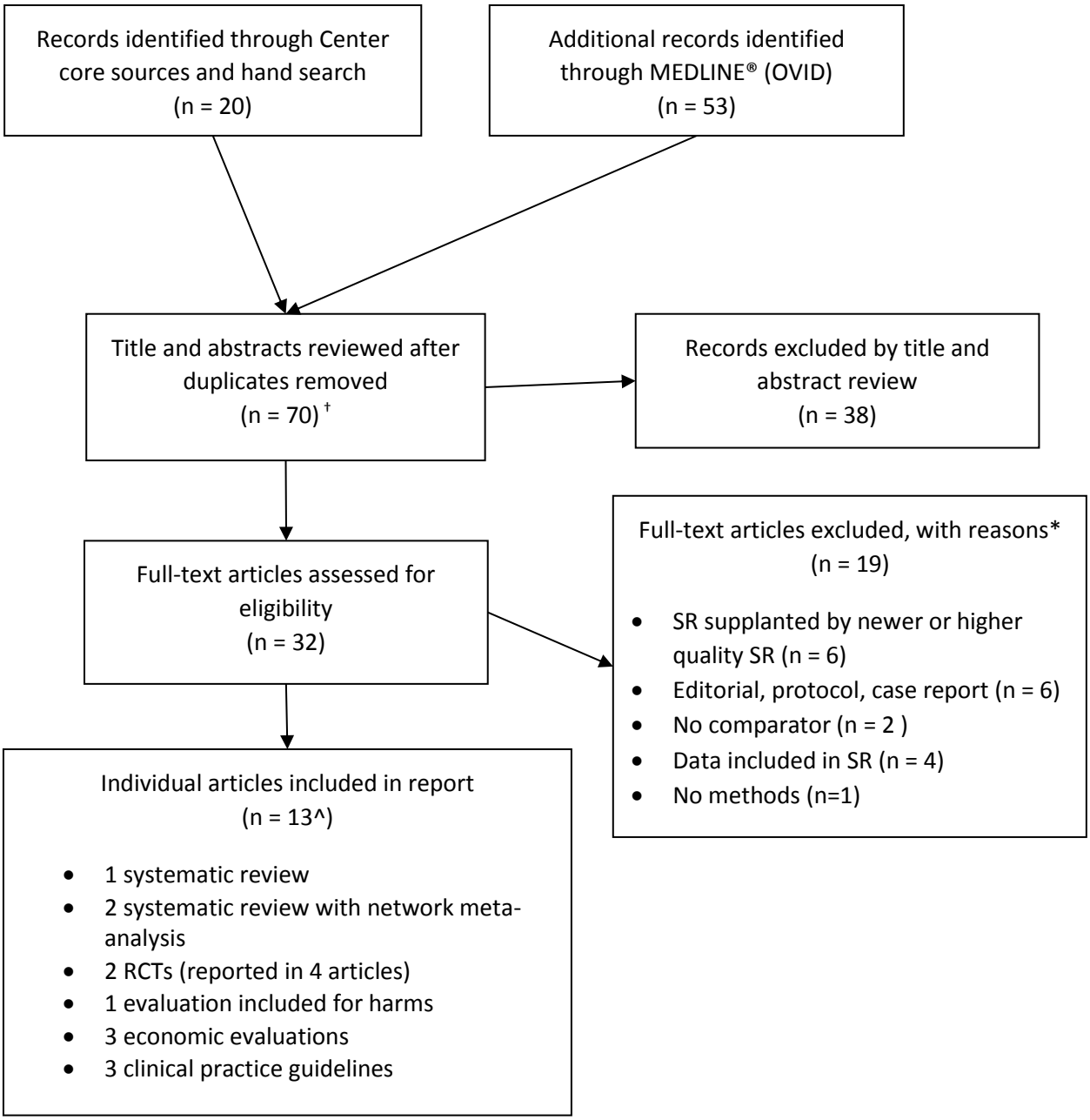
The search strategies and list of studies reviewed in full with reasons for exclusion are in Appendices A and B, respectively.

Overview of Evidence Sources

Center researchers summarized the evidence as reported by the included systematic reviews. There was substantial overlap in study inclusion across the systematic reviews and meta-analyses. Data on the efficacy of the only FDA-approved device, the WATCHMAN, derives from two RCTs: PROTECT AF, as cited in Holmes et al. (2009), Reddy et al. (2013), Reddy et al. (2014); and PREVAIL, as cited in Holmes et al. (2014). Given this high level of overlap, Center researchers

elected to include the original studies and assess their methodological quality. Table 1 provides an overview of findings from the included systematic reviews and individual studies.

Figure 2. Search Results



† Duplication of articles between Center core source search results and MEDLINE (Ovid) search results.
^National Institute for Health and Care Excellence (2014a) is used for both a clinical guideline and a cost-effectiveness review, and not to contribute to the evidence on device effectiveness or harms, because the evidence component was supplanted by more recent reviews.
* Individual study exclusion rationale provided in Appendix B.

Systematic Reviews

Bajaj et al. (2016)

Bajaj et al. (2016) conducted a fair methodological quality systematic review with network meta-analysis evaluating the comparative effectiveness of left atrial appendage compared to VKA therapy (i.e., warfarin) with indirect network comparison to novel oral anticoagulants (i.e., apixaban, dabigatran, edoxaban, rivaroxaban) on stroke risk in the follow-up period (which ranged from a mean of 1.5 to 2.8 years). Secondary outcomes reported were major bleeding and a primary safety composite endpoint. Randomized controlled trials were eligible for inclusion. The review authors used an extensive search strategy (e.g., multiple databases searched, comprehensive search strategy used, few to no limits on study publication date, inclusion of FDA-reported bleeding events) to identify six RCTs (two comparing WATCHMAN to VKA, four comparing novel oral anticoagulants to VKA).

Noelck et al. (2016)

Noelck et al. (2016) conducted a good methodological quality systematic review on the effectiveness of left atrial appendage exclusion procedures compared to VKA anticoagulation to reduce stroke risk. Secondary outcomes reported were mortality, quality of life, need for ongoing anticoagulation, and harms including procedural complications. Randomized controlled trials and cohorts with or without control groups were eligible for inclusion (cohorts needed to include at least 50 individuals). The authors included studies on surgical or percutaneous closure procedures published through January 2015. In addition to the WATCHMAN device, the authors searched for studies investigating the AMPLATZER, PLAATO, WaveCrest, LARIAT, and LAmbre devices. For this report, only outcomes related to percutaneous procedures are reviewed. The review authors used an extensive search strategy (e.g., multiple databases searched, comprehensive search strategy used, few to no limits on study publication date, contacting device companies) to identify 20 primary studies articles that evaluated the comparative efficacy and safety of left atrial appendage closure; 13 studies (two RCTs, 11 observational) were relevant to percutaneous closure and the remaining seven involved surgical interventions. The authors identified four ongoing clinical trials investigating novel percutaneous devices at the time of the their review (Noelck et al., 2016).

Sahay et al. (2017)

Sahay et al. (2017) conducted a fair methodological quality systematic review and network meta-analsysis on the effectiveness of left atrial appendage closure on all-cause mortality, stroke, or systemic embolism compared to medical therapy. Secondary outcomes reported were risk of major bleeding, intracranial bleeding, and gastrointestional bleeding. The authors included RCTs published through November 2015. The authors used a comprehensive search strategy in MEDLINE to identify two RCTs comparing left atrial appendage closure with VKA. An additional 17 studies provided comparisions of novel oral anticoagulants, anti-platelet agents, placebos, and VKA.

Individual Studies

Given the high degree of overlap for included studies in the above systematic reviews, Center researchers also included a detailed analysis of the two RCTs (PREVAIL and PROTECT AF) and their associated publications consistently identified in the reviews.

PROTECT AF, Holmes et al. (2009); Reddy et al. (2014); Reddy et al. (2013)

Holmes, Reddy, and colleagues conducted a fair methodological quality RCT comparing the use of the WATCHMAN device to warfarin. The study investigated two primary outcomes, one for efficacy and one for safety; both outcomes were composites. The primary efficacy outcome was a composite of stroke, systemic embolism, and cardiovascular/unexplained death. The primary safety outcome was a composite of pericardial effusion requiring intervention or prolonged hospitalization, procedure-related stroke, device embolization, and major bleeding. The most recent data from the study provided a mean of 3.8 years of follow-up. Participants were enrolled from 2005 to 2008. The original study protocol is published (Fountain et al., 2006). Participants and clinicians were not blinded to treatment allocation.

PREVAIL, Holmes et al. (2014)

Holmes et al. (2014) conducted a fair methological quality RCT comparing the use of the WATCHMAN device to warfarin. Enrollees were targeted to be at higher risk of stroke (i.e., greater $CHADS_2$ score) than enrollees in the PROTECT AF study. The primary composite endpoint consisted of hemorrhagic or ischemic stroke, systemic embolism, and cardiovascular/unexplained death. Participants were enrolled from 2010 to 2013. Participants and clinicians were not blinded to treatment allocation.

Because PREVAIL sought to include a population at higher risk of stroke, PREVAIL participants were on average older than those in PROTECT AF (74.0 vs. 71.7 years), with a greater proportion of individuals over 75 (52.0% vs. 41.0%), and with more comorbidities (e.g., diabetes, history of stroke/transient ischemic attack (TIA)) that equated to a higher average $CHADS_2$ score (2.6 vs. 2.2) (Holmes et al., 2014).

Post-Approval U.S. Registry Data, Reddy et al. (2017)

Although non-comparative, this publication was included to further assess potential harms from the WATCHMAN device because the authors included procedural outcomes from the post-approval safety registry required by the FDA along with comparisons to original studies and clinical registries in the U.S. and Europe. After FDA approval, all sites performing the procedure were required to collect procedure parameter and complication data using standardized forms devised by staff from Boston Scientific, the manufacturer of the WATCHMAN. On the day of the procedure a clinical specialist from Boston Scientific was present to collect relevant procedural and complication data. Physicians were expected to file a report of complications occuring in subsequent days to the manufacturer. Reddy et al. (2017) is an evaluation report on outcomes from all cases performed after FDA approval in 2015, which consists of 3,822 consecutive cases

and compares outcomes across trials and registries. While day of procedure complications were likely well documented, later complications in the following days may have gone undocumented, as the performing provider was expected to report them to the manufacturer (Saw & Price, 2017).

Quality and Limitations

Center researchers rated two of the systematic reviews with network meta-analysis as having fair methodological quality (Bajaj et al., 2016; Sahay et al., 2017) and the single systematic review without meta-analysis as having good methodological quality (Noelck et al., 2016). There was significant overlap of included studies related to the WATCHMAN device; older systematic reviews and lower methodological quality systematic reviews were excluded after full-text review (Bajaj et al., 2014; Briceno et al., 2015; Hanif et al., 2017; Holmes et al., 2015; Koifman et al., 2016; Munkholm-Larsen, Cao, Yan, Pehrson, & Dixen, 2012; National Institute for Health and Care Excellence, 2014a; Price et al., 2015; Tereshchenko, Henrikson, Cigarroa, & Steinberg, 2016). Full details on reasons for exclusions are available in Appendix B.

Given the high degree of overlap for WATCHMAN data, Center researchers elected to review the individual publications arising from each RCT (i.e., PREVAIL and PROTECT AF) and found them to be of fair methodological quality (Holmes et al., 2014; Holmes et al., 2009). The methodological quality of additional individual studies included in the systematic reviews was assessed by the respective review authors.

There are several common biases across the included studies. Data on the WATCHMAN device derive from two studies, PROTECT AF (Holmes et al., 2009; Reddy et al., 2014; Reddy et al., 2013) and PREVAIL (Holmes et al., 2014), with a total of 1,114 enrollees. Baseline stroke risk (as estimated from $CHADS_2$ score) was intentionally higher for enrollees in the PREVAIL trial. The PROTECT AF trial reported a mean of 3.8 years of follow-up data, compared to a mean of 11.8 months for PREVAIL.

Individuals receiving the device continued to receive warfarin for a minimum of 45 days post-procedure. Device seal (defined as peridevice flow less than 5 mm) was confirmed using a transesophageal echocardiogram at 45 days, 6 months, or 12 months if necessary. For those with device seal noted at 45 days, the protocol was to switch them to clopidogrel 75 mg through six months, and then to 325 mg of aspirin indefinitely. For those without device seal noted at 45 days, VKA was continued through six months and seal reassessed. If there was no seal by six months, individuals were maintained on VKA until device seal was noted (interval of repeat transesophageal echocardiogram unclear). The continued receipt of anticoagulation and antiplatelet therapy through six months limits the ability to estimate the independent impact of left atrial appendage closure during the overlap period.

Both of the original trials reported on the need for ongoing warfarin use at 45 days, 6 months, and 12 months. However, nearly all enrollees were using warfarin prior to study participation, so participants randomized to receive the implant but unable to have it placed and participants lost to follow-up in the device arm might have continued to use warfarin for stroke risk reduction; thus, the requirement for ongoing warfarin therapy could be higher in a real-world setting.

The systematic review by Noelck et al. (2016) included data from observational studies of left atrial appendage closure with more than 50 individuals and differing devices. Included studies used devices not available in the U.S. (e.g., AMPLAZER plug, PLAATO) and often reported on individuals ineligible for long-term anticoagulation. Although an important subgroup, the two RCTs for the WATCHMAN device specifically excluded this population.

Summary of the Evidence

Evidence is summarized in the tables below by comparator and then by outcomes of effectiveness and harms. The overall methodological quality of the systematic reviews and RCTs from PREVAIL (Holmes et al., 2014) and PROTECT AF (Holmes et al., 2009; Reddy et al., 2014; Reddy et al., 2013) are the Center's original assessment of the studies. For systematic reviews, the authors' overall quality assessment of included studies is in the second column. There was significant overlap of included studies across the systematic reviews. Table 1 provides a high-level summary of the evidence listed by systematic review and included studies.

Table 1. Overview of Included Studies

Citation, Study Details	# of Studies (k) Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
Meta-analyses			
Bajaj et al. (2016) Search Dates 1945 to October 2015 Included Study Designs RCTs Methodological Quality Fair	k = 6 (2 for device) total n = 59, 627 (1,114 from device studies) *SR's quality assessment of individual studies:* Good to excellent	Comparators LAAC vs. VKA LAAC vs. NOAC vs. VKA (indirect comparison via network meta-analysis) Outcomes Direct Comparisons *Ischemic Stroke* LAAC vs. VKA: OR 2.26 (95% CI, 0.39 to 12.96) Harms *Major Bleeding* LAAC vs. VKA: OR 1.01 (95% CI, 0.67 to 1.50) *Primary Safety Endpoint* LAAC vs. VKA: OR 1.24 (95% CI, 0.84 to 1.83) Outcomes Indirect Comparisons Apixaban had the highest probability (99%) of being the best strategy for the lowest primary safety endpoint	The authors noted imprecision in estimate of impact of LAAC vs. VKA given small, heterogeneous trials, whereas estimates of NOACs were more precise, given larger populations in studies. The authors reported comparisons to individual NOACs as well, part of "trade-off" analysis. These comparisons are not included in this table for brevity. The authors reported apixaban as best "trade-off" of stroke prevention and lower risk of major bleeding.
Sahay et al. (2017) Search Dates Inception through	k = 19 (2 for device) Total n = 87,831 (1,114 for device)	Comparators LAAC vs. VKA LAAC vs. NOAC vs. VKA vs. APT vs. placebo (indirect comparison via network meta-analysis) Outcomes Direct Comparisons	The authors noted small sample size and low stroke and gastrointestinal bleeding event rate in PREVAIL study as limitations to generalizability.

Citation, Study Details	# of Studies (k) Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
November 2015 Included Study Designs RCTs Methodological Quality Fair	*SR's quality assessment of individual studies:* Not performed	*Stroke or Systemic Embolism:* LAAC vs. VKA: OR 0.84 (95% CI, 0.48 to 1.49) *Mortality Benefit:* LAAC vs. VKA: OR 0.68 (95% CI, 0.45 to 1.02) Harms *Major Bleeding* LAAC vs. VKA: OR 0.63 (95% CI, 0.33 to 1.19) *Intracranial bleeding* LAAC vs. VKA: 0.50 (95% CI, 0.28 to 0.92) *Gastrointestinal bleeding* LAAC vs. VKA: 0.24 (95% CI, 0.11 to 0.51) Outcomes Indirect Comparisons *Overall mortality* • LAAC vs. placebo: HR 0.38 (95% CI, 0.22 to 0.67) • LAAC vs. APT: HR 0.58 (95% CI, 0.37 to 0.91) • LAAC vs. NOAC: HR 0.76 (95% CI, 0.50 to 1.16) *Stroke or systemic embolism* • LAAC vs. placebo: HR 0.24 (95% CI, 0.11 to 0.52) • LAAC vs. APT: HR 0.44 (95% CI, 0.23 to 0.86) • LAAC vs. NOAC: HR 1.01 (95% CI, 0.53 to 1.92) *Major Bleeding* • LAAC vs. placebo: HR 2.33 (95% CI, 0.67 to 8.09) • LAAC vs. APT: HR 0.75 (95% CI, 0.30 to 1.88) • LAAC vs. NOAC: HR 0.44 (95% CI, 0.13 to 1.49)	The authors noted that no direct comparisons of LAAC to placebo nor APT is likely to happen in the near future.

Citation, Study Details	# of Studies (k) Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
Systematic Reviews (without meta-analyses)			
Noelck et al. (2016) Search Dates Inception to June 2013 Included Study Designs Systematic reviews, RCTs, observational studies (harms only) Methodological Quality Good	k = 13 (2 RCTs, 11 observational) n = 2,906 *SR's quality assessment of individual studies:* RCTs at low risk of bias (observational studies not assessed)	Comparators LAAC vs. VKA Outcomes *Ischemic Stroke* PREVAIL: 1.9% vs. 0.7% PROTECT AF: 3% vs. 2.5% *Hemorrhagic Stroke* PREVAIL: 0.4% vs. 0.0% PROTECT AF: 0.2% vs. 2.5% *Quality of Life (Short Form-12)* PROTECT AF: physical health score +0.04 vs. -0.2 (p = 0.0015), mental score 0.0 vs. -0.9 (p = 0.64) *Able To Discontinue VKA* PREVAIL: 92.2% at 45 days, 98.3% at 6 months, 99.3% at 12 months PROTECT AF: 86% at 45 days, 92% at 6 months Harms—no analysis from observational studies *Total Adverse Events* PREVAIL: 11 out of 269 device group (4.1%) (e.g., 1 procedure related stroke, 1 cardiac perforation, 1	Review also includes studies on surgical LAAC, not included for this report. Does not appear to include updated outcomes data from PROTECT AF (Reddy et al., 2014). Because the majority of enrollees were taking warfarin before the study, the patients lost to follow-up may have continued using the medication. If true, then the outcome reported for discontinuation of VKA observed at follow-up would likely be lower. The authors noted quality of life assessed in a subset of PROTECT AF enrollees using the Short-Form 12 (Alli et al., 2013), which observed small but statistically significant changes from baseline to 12 months. In the PROTECT AF study, Reddy et al. (2013) provided follow-up at a mean of 2.3 years, however, one person could only count toward an outcome measure once (e.g., major bleeding requiring transfusion OR pericardial effusion requiring surgery (but was not counted

Citation, Study Details	# of Studies (k) Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
		pericardial effusion requiring surgery, 1 major bleeding event requiring surgery) PROTECT AF: 49 out of 463 device group (10.5%), 16 major bleeding, 15 pericardial effusions requiring surgery, 6 procedure-related strokes, 3 device embolization; 27 of 49 safety events occurred on day of procedure.	as both if each occurred simultaneously), thus adverse events may be underreported. Additional information in SR from observational studies using devices not currently FDA approved. These studies often included individuals ineligible for oral anticoagulation.
Randomized Controlled Trials (original studies)			
PROTECT AF Relevant publications: (Holmes et al., 2009; Reddy et al., 2014; Reddy et al., 2013) Methodological Quality Fair	n = 707 (463 device, 244 warfarin) Eligible enrollees had persistent or paroxysmal atrial fibrillation, age over 18, $CHADS_2$ of ≥1 Exclusion criteria included contraindicated for warfarin (e.g. history of bleed)	Outcomes at a mean of 3.8 years LAAC vs. VKA *Primary Composite Efficacy Endpoint (stroke, systemic embolism, or cardiovascular/unexplained death)* Risk ratio 0.60 (95% credible interval, 0.41 to 1.05) *Ischemic Stroke* Risk ratio 1.26 (95% credible interval, 0.42 to 1.37) *Hemorrhagic Stroke* Risk ratio 0.15 (95% credible interval, 0.02 to 0.49) *Ability To Discontinue VKA* (ITT analysis by Center staff) At 45 days: 348/463 enrollees (75%) At 6 months: 355/463 enrollees (76%) At 12 months: 345/463 enrollees (75%) *Primary Composite Safety Endpoint (pericardial effusion requiring intervention or prolonged hospitalization,*	Protocol required 5 years of follow-up, but no 5-year evidence reported in literature as of April 2017. A third of patients were at low risk of stroke ($CHADS_2$ = 1) Authors report ability to stop warfarin only in those who received device, not entire group randomized to device arm. 408 of the 463 randomized to device arm received the device (88%); 41 individuals experienced device failure, in 14 no attempt made. As of the latest reporting (Reddy et al., 2014) results from one site (28

Citation, Study Details	# of Studies (k) Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
		procedure-related stroke, device embolization, major bleeding) Risk ratio 1.17 (95% credible interval, 0.78 to 1.95) *Major Bleeding In Both Groups* 9.5% in device vs. 7.4% in warfarin, no statistical analysis provided *Device-Specific Harms* 4.8% experienced serious pericardial effusion 2.6% experienced procedure-related stroke *Enrollees Censored from Data:* (LAAC vs. VKA) no statistical analysis provided Withdrew consent: 3.3% vs. 18.4% Loss to follow-up: 2.8% vs. 4.5% Other: 2.6% vs. 4.1%	individuals) censored due to quality of data concerns. A total of 159 individuals left the PROTECT AF study early. While information on status is provided for 106 individuals (Reddy et al., 2014) information on 53 individuals is missing.
PREVAIL Relevant publications: (Holmes et al., 2014) Methodological Quality Poor	n = 407 (269 device, 138 control) Eligible enrollees had paroxysmal, persistent, or permanent non-valvular atrial fibrillation with a CHADS2 score of ≥2 or CHADS2 ≥ 1 with higher-risk characteristics (female age ≥ 75 years, baseline ejection fraction	Outcomes at 18 months LAAC vs. VKA *Primary Composite Efficacy Endpoint (hemorrhagic or ischemic stroke, systemic embolism, cardiovascular/unexplained death)* Rate ratio 1.07 (95% credible interval 0.57 to 1.89) *Late Ischemic Efficacy (ischemic stroke or systemic embolism >7 days from randomization)* Risk difference: 0.0053 (95% credible interval -0.0190 to 0.0273)	Participants and staff not blinded to treatment group. Primary efficacy endpoint did not meet pre-specified non-inferiority criteria. Data from individuals in PROTECT AF meeting eligibility criteria for PREVAIL, along with clinical registry included in reporting on safety endpoints. All implant recipients received a minimum of 45 days of warfarin

Citation, Study Details	# of Studies (k) Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
	≥30% but <35%, and age ≥ 65 years with congestive heart failure) Exclusion criteria: requirement for long-term anticoagulation therapy for reasons other than AF, contraindication to warfarin or aspirin, previous stroke/transient ischemic attack within 90 days of enrollment, symptomatic carotid disease, patent foramen ovale or atrial septal defect requiring treatment, or patients for whom clopidogrel therapy was indicated	*Stroke Or Systemic Embolism Resulting In Significant Disability, Death, All-Cause Mortality* Not reported *Early Safety Composite (all-cause death, ischemic stroke, systemic embolism, device/procedure complications within 7 days of procedure)* Reported for only those receiving device, but not reported for PREVAIL enrollees alone. *Able To Discontinue VKA* 92.2% at 45 days, 98.3% at 6 months, 99.3% at 12 months	following placement, longer if no seal of device at day 45. Those with device seal on imaging received clopidogrel from day 45 to 6 months, limiting the ability to estimate the impact of LAAC alone on outcomes. Enrolled individuals at higher risk of stroke than PROTECT AF study. 100% of enrollees provided 6-month follow up. Authors report median follow-up but not data specific to each arm (mean follow-up all participants: 11.8 ± 5.8 months)

Citation, Study Details	# of Studies (k) Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
Post-Approval Registry Data (non-comparative)			
Relevant publications: (Reddy et al., 2017) Methodological Quality N/A	n = 3,822 consecutive patients 382 physicians at 169 U.S. centers (71% naïve, 29% clinical trial operators)	95.6% successful implantation Procedural Events within 7 days of procedure *Pericardial Effusion Requiring Intervention* 39 patients (1.02%) 24 percutaneously drained 12 required surgery 3 deaths *Pericardial Effusion Not Requiring Intervention* 11 patients *Periprocedural Stroke* 3 (0.08%): 2 ischemic, 1 hemorrhagic *Death* 3 (0.08%) attributed to left atrial appendage perforation by device 1 attributed to pulmonary embolism not judged to be device related *Device Embolization* 9 (0.24%): 3 required surgical removal, 3 removed percutaneously 8 discovered in hospital (5 in procedure) 1 discovered at 45-day transesophageal echocardiogram	After FDA approval of the WATCHMAN in 2015, all sites were required to use standardized monitoring forms for procedural components and outcomes. Recording of this information was performed by a trained clinical specialist, employed by Boston Scientific. Major procedural complications processed by Boston Scientific "complaint handling system." Events reviewed by two physicians paid by Boston Scientific. Full report includes summary data from multiple registries in U.S. and Europe. No comment on VKA use or peridevice seal. Ischemic strokes outside the 7-day procedural window not assessed by this evaluation.

Abbreviations. APT: antiplatelet therapy; A.fib: atrial fibrillation; $CHADS_2$: scoring system based on history of congestive heart failure, hypertension, age >75 years, diabetes mellitus, and previous stroke/transient ischemic attack); CHF: congestive heart failure; CI: confidence interval; HR: hazard ratio; LAAC: left atrial appendage closure; NOAC: novel oral anticoagulant; OR: odds ratio; RCT: randomized controlled trial; SR: systematic review; VKA: vitamin K antagonist. Note. a indicates assessed by review authors.

Effectiveness Outcome 1: Ischemic stroke

Systematic Reviews

In two fair-quality systematic reviews with meta-analyses (Bajaj et al., 2016; Sahay et al., 2017), rates of ischemic stroke in the follow-up period were not statistically different for participants receiving left atrial appendage closure compared to those receiving warfarin.

Individual Studies

The individual studies were powered to detect a change in a composite primary efficacy outcome as opposed to ischemic stroke alone. In the PROTECT AF study, the reported rate of ischemic stroke did not differ across groups after a mean of 3.8 years of follow-up (Reddy et al., 2014). The PREVAIL study reported no statistically significant difference in stroke or systemic embolism at greater than seven days after randomization (Holmes et al., 2014).

Effectiveness Outcome 2: Proportion able to discontinue warfarin

Systematic Reviews

A single systematic review provided individual study data on the proportion of patients able to discontinue warfarin at 45 days, 6 months, and 12 months (Noelck et al., 2016). Rates across both studies were reported as high, greater than 88%, starting at 45 days. Participants randomized to the WATCHMAN device but lost to follow-up might have continued warfarin therapy.

Effectiveness Outcome 3: Quality of life

Systematic Reviews

A single systematic review reported quality of life outcomes from a subset analysis of PROTECT AF enrollees (Noelck et al., 2016). Quality of life was assessed using the Short-Form 12. The systematic review authors noted that statistically significant improvements were observed at 12 months for those receiving the WATCHMAN device in physical and mental health subcategories, but the clinical impact of this change is unclear.

Harm Outcome 1: Procedural complications

Systematic Reviews

Noelck et al. (2016) reported overall and specific safety events from each study: 4.1% of PREVAIL enrollees experienced a device-related complication compared to 10.6% of PROTECT AF enrollees (Noelck et al., 2016). Specific safety events are also included in the Reddy et al. (2017) evaluation (see Table 2 for comparison).

Individual Studies

Reddy et al.'s (2017) summary of clinical trials and registries (pre- and post-FDA approval) reported on specific procedural complications, notably pericardial effusion, death,

periprocedural stroke (within seven days), and device embolization. Table 2 summarizes the evidence for the most common procedural complications.

Table 2. Summary of Procedural Complications from WATCHMAN studies

Outcome n (%)	PROTECT AF	PREVAIL	PROTECT AF Registry	PREVAIL Registry	European Registry	Post-FDA Registry
Pericardial tamponade treated percutaneously	13 (2.8)	4 (1.5)	7 (1.2)	11 (1.9%) Data not provided separately	2 (0.2)	24 (0.63)
Pericardial tamponade treated surgically	7 (1.5)	1 (0.4)	1 (0.2)		1 (0.1)	12 (0.31)
Pericardial tamponade resulting in death	0	0	0	0	0	3 (0.078)
Procedure-related Stroke	5 (1.15)	1 (0.37)	0	2(0.35)	1 (0.10)	12 (0.18)
Device Embolization	3 (0.6)	2 (0.7)	1 (0.2)	0	2 (0.20)	9 (0.24)
Death	0	0	0	0	1 (0.1)	3 (0.07)

Source. Adapted from Reddy et al. (2017).

Harm Outcome 2: Major bleeding

Systematic Reviews

Estimates of major bleeding from two meta-analyses did not identify a statistically significant difference in risk of bleeding for left atrial appendage closure compared to warfarin (Bajaj et al., 2016; Sahay et al., 2017).

Harm Outcome 3: Mortality

Systematic Reviews

Sahay and colleagues observed no difference in mortality for participants receiving the WATCHMAN device compared to VKA (Sahay et al., 2017).

Harm Outcome 4: Hemorrhagic stroke

Systematic Reviews

Sahay and colleagues observed no difference in risk of hemorrhagic stroke for participants receiving the WATCHMAN compared to VKA in meta-analysis (2017). Noelck and colleagues reported the proportion of individuals experiencing the outcome in each trial: hemorrhagic strokes were rare in the PREVAIL study and greater for participants on warfarin in PROTECT AF

(PREVAIL: 0.4% vs. 0.0%; PROTECT AF: 0.2% vs. 2.5%) (2016). No statistical analysis was provided in the Noelck et al. (2016) review.

Cost-Effectiveness

Center researchers identified one systematic review (National Institute for Health and Care Excellence, 2014a) that included an economic analysis and two individual studies that conducted cost analysis on the use of the WATCHMAN device for left atrial appendage closure for the treatment of non-valvular atrial fibrillation. The systematic review was rated as having good methodological quality (National Institute for Health and Care Excellence, 2014a) and of the individual economic studies, one was rated as having good methodological quality (Freeman et al., 2016), and one as having fair methodical quality (Reddy et al., 2016) by Center researchers. Table 3 provides study details for the included economic studies.

Systematic Reviews

National Institute for Health and Care Excellence (2014a)

The National Institute for Health and Care Excellence (NICE) 2014 guideline on the management of atrial fibrillation contains a good methodological quality systematic review of available economic analyses on the use of left atrial appendage closure devices. Using a thorough search strategy, the authors identified a single cost-utility analysis meeting inclusion criteria (Singh, Micieli, & Wijeysundera, 2013). The study evaluates the use of the WATCHMAN device compared to dabigatran or warfarin for stroke prevention in adults with non-valvular atrial fibrillation from a Canadian healthcare perspective. The authors of the NICE guideline believed that the study was partially applicable to the U.K. population with minor limitations.

Individual Studies

Freeman et al. (2016)

Freeman et al. (2016) conducted a good methodological cost-effectiveness analysis on the use of left atrial appendage closure with the WATCHMAN compared to warfarin and dabigatran on the prevention of stroke in adults eligible for anticoagulation from a U.S. payer perspective. The hypothetical cohort consists of 10,000 individuals over 70 with a $CHADS_2$ score of at least 1. Estimates of effectiveness were derived from PROTECT AF (average follow-up 3.8 years) and PREVAIL (average follow-up 18 months). Estimates of procedure costs are derived from a recent CMS coverage decision.

Reddy et al. (2016)

Reddy et al. (2016) conducted a fair methodological cost-effectiveness analysis on the use of left atrial appendage closure with the WATCHMAN compared to aspirin and apixaban on the prevention of stroke in adults ineligible for anticoagulation. Estimates of procedure costs are based on German diagnosis-related group reimbursement, and costs could be different in the U.S. health care context.

Table 3. Economic Studies

Citation, Study Details	Population (n)	Study Summary and Findings	Comments
Systematic Reviews			
National Institute for Health and Care Excellence (2014a) p. 175 Search Dates Inception to October 2013 Included Study Designs Economic studies Methodological Quality Good	k = 1 Total n = 707 *SR's quality assessment of individual studies:* Minor limitations	Comparators LAAC vs. VKA Outcomes *Incremental Cost Effectiveness Ratio* £16,595 per QALY gained (not discounted) ($26,248)	Based on single identified economic analysis from Canada (2012 Canadian dollars). Perspective is third-party payer in Canada. Deterministic analysis in original study notes LAAC not cost-effective compared to VKA when odds ratio of stroke >1.56. Authors converted 2012 Canadian dollars to 2012 UK pounds. Center researchers converted to 2012 U.S. dollars provided in parentheses.*
Individual Cost-Effectiveness Analyses			
Freeman et al. (2016) Study Details Cost-effectiveness analysis, U.S. payer perspective Methodological Quality Good	Hypothetical cohort of 10,000 individuals >70, with a CHADS2 score ≥1, eligible for VKA or novel oral agent	Comparators LAAC vs. dabigatran vs. VKA Results *Direct medical cost per QALY gained (ICER)* $20,486 (based on PROTECT AF 3.8 years of follow-up) >$50,000 (based on PREVAIL 18 month follow-up; specific figure not provided)	Hypothetical cohort Uses event rates from PREVENT-AF and PREVAIL. PREVAIL enrolled individuals at higher risk of stroke than PROTECT AF Reimbursement for procedure, post-procedure transesophageal echocardiogram, and physician fee estimate: $24,010

Citation, Study Details	Population (n)	Study Summary and Findings	Comments
Reddy et al. (2016) Study Details Cost-effectiveness analysis, German payer perspective Methodological Quality: Fair	Hypothetical cohort of *Individuals ineligible for VKA*	Comparators LAAC vs. apixaban vs. aspirin Base case: annual stroke risk 8.6%, bleeding risk 3.7% Low risk: annual stroke risk 2.2%, bleeding risk 1.9% Results at 10 years for base case *Total direct medical costs* LAAC $17,722 (cost-saving option) Apixaban $21,115 Aspirin: $23,586 *Incremental QALYs vs. aspirin* LAAC: 0.61 Apixaban: 0.38 *ICER vs. aspirin* LAAC is dominant at 10 years for base case Results at 10 years for low-risk group *Total direct medical costs* LAAC $14,020 Apixaban $11,618 Aspirin: $7,445 *ICER (vs. aspirin)* LAAC: $52,106 Apixaban: $49,252	Study funded by Boston Scientific, authors employees or paid consultants of Boston Scientific. 20-year estimates but no long-term effectiveness data on LAAC; static estimate of efficacy based on PROTECT AF. Estimates based on outcomes observed in studies that didn't include individuals ineligible for warfarin, nor do source studies include estimates of important outcomes (e.g., major bleeding). Estimates for device and procedure: $12,498 2014 euros converted to 2017 U.S. dollars*

*Abbreviations. ICER: incremental cost effectiveness ratio; LAAC: left atrial appendage closure; QALY: quality-adjusted life year; VKA: vitamin K antagonist. Note. *currency calculations performed using www.x-rates.com.*

Clinical Practice Guidelines

Center researchers identified two clinical practice guidelines that address the use of left atrial appendage closure for the treatment of non-valvular atrial fibrillation. One of the guidelines was rated as having good methodological quality (National Institute for Health and Care Excellence, 2014a) and one of the guidelines was rated as having poor methodological quality (Masoudi et al., 2015) by Center researchers. Table 4 provides a summary of recommendations across the included guidelines. The strength of underlying evidence noted in the table for guideline recommendations is an assessment by guideline authors and not Center researchers.

The American College of Cardiology, Hearth Rhythm Society, and Society for Cardiovascular Angiography and Intervention collaborated to produce their 2015 societal overview on left atrial appendage closure. The authors aimed to review the literature and incorporate future devices or approaches for the non-medication management of atrial fibrillation. The authors did not make specific recommendations regarding the use of left atrial appendage closure devices. The authors noted that the most recent guideline on atrial fibrillation management from their respective organizations (January et al., 2014) did not mention this option because data was lacking at that time.

In general, available guidelines on atrial fibrillation management are between three and four years old and might not incorporate much of the recent registry data on the safety or harms of the WATCHMAN. The guideline of the highest methodological quality, National Institute for Health and Care Excellence (2014a), solely relies on outcomes from the original PROTECT AF trial (Holmes et al., 2009), not including data from the higher-risk PREVAIL population (Holmes et al., 2014). Despite this small trial, the guideline authors recommended use in a limited population of individuals ineligible for long-term anticoagulation medication. They cited evidence from a non-comparative study included in Noelck et al. (2016) as providing support for this recommendation.

Table 4. Summary of Clinical Practice Guidelines Recommendations for Percutaneous Left Atrial Appendage Closure

Organization (Citation)	Recommendation (Evidence Rating*)
American College of Cardiology, Heart Rhythm Society, and Society for Cardiovascular Angiography and Intervention (Masoudi et al., 2015) Methodological Quality^ Poor	The societies published this overview with the intent of providing a brief literature review on the topic and did not make recommendations for or against use. The authors do recommend the use of a multidisciplinary heart team and suggested appropriate team composition, availability of emergency backup (i.e., cardiothoracic surgeon), and facility needs for sites seeking to place these devices. (No evidence rating was provided by the authors).
National Institute for Health and Care Excellence (2014a) Methodological Quality^ Good	"Consider left atrial appendage occlusion if anticoagulation is contraindicated or not tolerated and discuss the benefits and risks of left atrial appendage occlusion with the person." "Do not offer left atrial appendage occlusion as an alternative to anticoagulation unless anticoagulation is contraindicated or not tolerated." The authors reported the quality of evidence as low to very low based on single study (Holmes et al., 2009).
American College of Chest Physicians (You et al., 2012) Methodological Quality^ Good	No formal recommendations regarding left atrial appendage closure will be issued until additional research has been conducted.

*Notes. ^Determined by Center researchers.*Determined by guideline authors.*

Payer Policies

Center researchers searched for policies on the coverage of percutaneous left atrial appendage closure for the treatment of non-valvular atrial fibrillation from Aetna, Anthem, Blue Shield of Northeastern New York, Capital District Physicians' Health Plan, Centers for Medicare and Medicaid Services, Cigna, Emblem Health, Empire Blue Cross Blue Shield (BCBS), Excellus BCBS, Tufts Health Plan, UnitedHealthcare and nine state Medicaid programs (CA, FL, MA, NJ, NY, OR, PA, TX, WA).

A search of the CMS website identified a national coverage determination (NCD) from Medicare that covers left atrial appendage closure with evidence development. Of the ten private payers searched, six payers (Aetna, Anthem, Cigna, Empire BCBS, Excellus BCBS and United HealthCare) do not cover left atrial appendage closure for their populations; three payers (Blue Shield of Northeastern New York, Emblem Health, Tufts Health Plan) cover closure under certain

conditions described below. Center researchers were not able to identify coverage policies for Capital District Physicians' Health Plan or the nine state Medicaid programs searched.

Medicare National Coverage Determination

On February 8, 2016, CMS issued a final decision memorandum for coverage of percutaneous left atrial appendage closure through Coverage with Evidence Development (CED) (Centers for Medicare & Medicaid Services, 2016). The NCD only covers devices that have received FDA premarket approval (i.e., WATCHMAN) and allows for coverage in two conditions: first, certain patients can be covered if they meet clinical conditions and are enrolled in a national registry for four years after the procedure; second, other patients can be covered if they are enrolled in an FDA-approved randomized controlled trial (CMS, 2016).[1]

Coverage with Patient Registry

Medicare patients who meet the following conditions can receive coverage for left atrial appendage closure (CMS, 2016):

- A $CHADS_2$ score ≥ 2 (congestive heart failure, hypertension, age > 75, diabetes, stroke/transient ischemia attack/thromboembolism) or CHA2DS2-VASc score ≥ 3 (congestive heart failure, hypertension, age ≥ 65, diabetes, stroke/transient ischemia attack/thromboembolism, vascular disease, sex category).
- A formal shared decision making interaction with an independent non-interventional physician using an evidence-based decision tool on oral anticoagulation in patients with non-valvular atrial fibrillation (NVAF) prior to left atrial appendage closure. Additionally, the shared decision making interaction must be documented in the medical record.
- A suitability for short-term warfarin but deemed unable to take long-term oral anticoagulation following the conclusion of shared decision making, as [left atrial appendage closure] is only covered as a second line therapy to oral anticoagulants. The patient (preoperatively and postoperatively) is under the care of a cohesive, multidisciplinary team of medical professionals. The procedure must be furnished in a hospital with an established structural heart disease and/or electrophysiology (EP) program. (CMS, 2016, p. 5)

In addition to the patient requirements, the NCD requires that the provider be either an interventional cardiologist, electrophysiologist, or cardiovascular surgeon who "has received training prescribed by the manufacturer on the safe and effective use of the device prior to performing [left atrial appendage closure]" (CMS, 2016, p. 5) and "has performed ≥ 25

[1] At the time of this report, only the WATCHMAN device manufactured by Boston Scientific has FDA approval. Other devices that do not have FDA approval include the AMPLATZER Cardiac Plug (St. Jude Medical), the Lariat Loop Applicator (SentreHEART), and PLAATO (Appriva Medical) (CMS, 2016).

interventional cardiac procedures that involve transseptal puncture through an intact septum, of which at least 12 are [left atrial appendage closure], over a 2-year period" (CMS, 2016, p. 5).

This coverage option requires providers to enroll their patients in a "prospective, national, audited registry" (CMS, 2016, p. 5) that tracks patient outcomes for four years after the procedure, specifically recording the following:

- Operator-specific complications
- Device-specific complications including device thrombosis
- Stroke, adjudicated, by type
- Transient ischemic attack (TIA)
- Systemic embolism
- Death
- Major bleeding, by site and severity (CMS, 2016, p. 5)

Coverage through Randomized Controlled Trial

The Medicare NCD also allows patients not included in the category described above to be covered if they are enrolled in an FDA-approved RCT (including those using alternative devices to the WATCHMAN) that has been reviewed and approved by CMS and that addresses the following questions:

- As a primary endpoint, what is the true incidence of ischemic stroke and systemic embolism?
- As a secondary endpoint, what is the cardiovascular mortality and all-cause mortality? (CMS, 2016, p. 6)

Private Payer Coverage Policies

Three private payers cover percutaneous left atrial appendage closure under certain conditions. Blue Shield of Northeastern New York (BSNENY) covers the WATCHMAN device for individuals with atrial fibrillation who have an increased risk of stroke and systemic embolism based on $CHADS_2$ or CHA2DS2-VASC scores, although the policy does not specify threshold $CHADS_2$ scores (Blue Shield of Northeastern New York, 2016). The individual must also be considered appropriate for anticoagulation therapy, but the risks of long-term anticoagulation therapy outweigh the risks of the left atrial appendage closure procedure for the patient (BSNENY, 2016). BSHENY also covers left atrial appendage closure for its Medicare Advantage beneficiaries in accordance with the Medicare CED policy (BSNENY, 2016). Prior authorization is required (BSNENY, 2016).

Tufts Health Plan covers percutaneous left atrial appendage closure with the WATCHMAN device for its commercial and public plan beneficiaries with a diagnosis of non-valvular atrial fibrillation (Tufts Health Plan, 2016). Individuals must be at increased risk for stroke and systemic embolism, although the policy does not specify the use of specific risk measures (Tufts Health

Plan, 2016). Patients must also be recommended for anticoagulation therapy and considered suitable for warfarin, but have an "appropriate rationale" for preferring percutaneous left atrial appendage closure to long-term anticoagulation therapy (Tufts Health Plan, 2016, p. 1). Tufts Health Plan does not require prior authorization (Tufts Health Plan, 2016).

Emblem Health covers percutaneous left atrial appendage closure only for its Medicare beneficiaries and cites the CMS NCD in its coverage note (EmblemHealth, 2017). Emblem states that coverage will be decided on a "case by case" basis for patients with non-valvular atrial fibrillation who have increased risk of stroke and systemic embolism and are considered eligible for anticoagulation therapy, but who have an appropriate rationale to choose left atrial appendage closure over long-term anticoagulation treatment (EmblemHealth, 2017, p. 11).

Medicaid Coverage Policies

Center researchers did not identify coverage policies for the nine Medicaid programs searched. However, the Washington Health Technology Assessment program considered reviewing the device in March 2016 and decided not to proceed, based in part on the CMS NCD decision (Washington Health Technology Assessment Program, 2016; Washington State Health Care Authority, 2016).

Policy Summary

Table 5 summarizes the indications for coverage of percutaneous left atrial appendage closure from Medicare and the three private payers that cover the device. Table 6 includes the specific policy language from the six private payers that do not cover percutaneous left atrial appendage closure.

Table 5. Coverage Criteria for the Use of Left Atrial Appendage Closure to Treat Atrial Fibrillation

Payer	Indication Requirements					
	Limited to WATCHMAN device	Diagnosis	Increased risk of stroke and systemic embolism	Use of formal shared decision-making interaction with independent physician	Recommended for anticoagulation therapy (warfarin)	Appropriate rationale to choose LAAC over anticoagulation therapy
Medicare						
NCD (CAG-00445N) *(effective 2/8/2016)* Coverage w/patient registry	Devices that have received FDA premarket approval	NVAF	$CHADS_2$ = 2 or CHA2DS2-VASc = 3	√	√	√
NCD (CAG-00445N) *(effective 2/8/2016)* Coverage through RCT	Devices in FDA-approved RCT	NVAF	---	---	---	---
Private Payers						
BSNENY *(effective 7/1/16)*	√	AF	Based on $CHADS_2$ or CHA2DS2-VASc (no specific scores)	---	√	√
Emblem Health *(effective 12/21/16)* Medicare only	FDA-approved devices	NVAF	√ (no specific criteria)	---	√	√
Tufts Health Plan *(effective 12/14/16)*	√	NVAF	√ (no specific criteria)	---	√	√

Abbreviations. AF: Atrial fibrillation; BSNENY: Blue Shield Northeastern New York; FDA: Food and Drug Administration; LAAC: left atrial appendage closure; NCD: National Coverage Determination; NVAF: Non-valvular atrial fibrillation; RCT: Randomized controlled trial.
Notes. √=requirement for use of WATCHMAN.

Table 6. Policy Language for Payers not Covering Left Atrial Appendage Closure

Payer	Policy Language
Private Payers	
Aetna (*last review 2/22/17)*	"Experimental and investigational for the prevention of stroke and all other indications because their effectiveness for these indications has not been established"
Anthem (*last review 2/2/17)*	"Investigational and not medically necessary for all indications"
Capital District Physicians' Health Plan	*Coverage policy not publicly available*
Cigna (*effective 4/15/2017*)	"Experimental/investigational/unproven/not covered"
Empire BCBS (*effective 3/29/17*)	"Investigational and not medically necessary"
Excellus BCBS (*last review 11/10/16*)	"Has not been proven to be medically effective and is therefore considered investigational"
UnitedHealthcare (*effective 3/1/2017)*	"Unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in the published peer reviewed medical literature"
State Medicaid	
California	*No coverage criteria identified*
Florida	*No coverage criteria identified*
Massachusetts	*No coverage criteria identified*
New Jersey	*No coverage criteria identified*
New York	*No coverage criteria identified*
Oregon	*No coverage criteria identified*
Pennsylvania	*No coverage criteria identified*
Texas	*No coverage criteria identified*
Washington	*No coverage criteria identified*

Conclusion

Estimates of the effect of the WATCHMAN device for percutaneous left atrial appendage closure demonstrate non-inferiority to warfarin therapy for ischemic stroke, mortality, and major bleeding. Current studies have not been designed to provide information of superiority for any of these outcomes. The data providing the estimates from meta-analyses arise from two RCTs with a total of 1,114 individuals. The older study, PROTECT AF, found increased rates of procedure-related complications that appeared to improve in the more recent PREVAIL study, but still include potential for significant morbidity and mortality from complications such as procedure-related stroke and pericardial effusion/tamponade requiring surgery or prolonged hospitalization. Procedure-related risks are balanced by the potential for major bleeding events caused by warfarin or other novel oral anticoagulants. Direct comparisons between the WATCHMAN, warfarin, and newer agents do not exist in the literature, but several network meta-analyses estimated similar risk of major bleeding for WATCHMAN, warfarin, and novel oral anticoagulant agents.

The original studies on the WATCHMAN device required enrollees to be eligible for warfarin therapy. The available comparative data do not address the efficacy or safety for patients ineligible for warfarin therapy, an important subgroup. Older guidelines recommend the use of left atrial appendage closure devices for patients ineligible for long-term anticoagulation based on observational studies.

A recent Medicare coverage determination lays out a coverage with evidence approach for a specific population of individuals with non-valvular atrial fibrillation.

Strength of Evidence

The Center uses the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group approach to enhance consistency in grading the strength of evidence. RCTs are initially categorized as having high strength of evidence and observational studies are categorized as having low strength of evidence. The strength rating is downgraded based on limitations including inconsistency of results, uncertainty of directness of measurement or population, imprecise or sparse data, and high probability of reporting bias. The grade is increased from low for evidence from observational studies if there is a strong association,[2] a very strong association,[3] or a dose-response gradient. The grade is also increased if all plausible confounders would have reduced the effect (GRADE Working Group, 2004). Table 7 provides an

[2] Significant relative risk of >2 or <0.5 with no plausible confounders in two or more observational studies.

[3] Significant relative risk of >5 or <0.2 based on direct evidence with no major threats to validity.

overview of the strength of evidence by outcome and associated rationale for the strength of evidence rating.

Table 7. Strength of Evidence for Percutaneous Left Atrial Appendage Closure: Effectiveness, Harms, and Cost-Effectiveness

Outcome	Strength of Evidence Assessment	Rationale
Effectiveness		
Ischemic stroke	Moderate	Estimates in meta-analysis based on two RCTs with differing populations demonstrate consistent non-inferiority of LAAC compared to VKA. Neither of the original studies powered to detect a change in this outcome. • Downgraded for imprecision
Quality of life	Low	Estimate of impact of left atrial appendage closure on quality of life based on subset of enrollees from single RCT. • Downgraded for inconsistency
Ability to discontinue Warfarin	Low	Estimates are reported from 2 RCTs. • Downgraded for risk of bias
Harms		
Major bleeding	Moderate	Estimates in meta-analysis demonstrate similar rates of major bleeding.
Procedural complications	Low	Procedural complications were high in the original PROTECT AF study; lower quality, non-comparative evidence from registries suggests lower rates than the original RCT.
Mortality	Moderate	Estimates in meta-analysis based on 2 RCTs demonstrate no statistically significant difference in mortality for patients undergoing closure compared to oral therapy.
Cost-Effectiveness		
ICER	Low	Estimates of cost-effectiveness are at risk for bias based on estimates of effectiveness and harms as well as payer perspective.

Abbreviations. ICER: incremental cost effectiveness ratio; LAAC: left atrial appendage closure; RCT: randomized controlled trial; VKA: vitamin K antagonist.

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Appendix A. Methods

General Search Strategy

Evidence

A full search of Center's core clinical evidence primary sources was conducted to identify systematic reviews and meta-analyses and technology assessments using the search terms *left atrial appendage* and *watchman*. Searches of core sources were limited to citations published after 2007. Center researchers also searched the MEDLINE (Ovid) database for relevant systematic reviews and meta-analyses or technology assessments, clinical practice guidelines, individual studies published after the search dates of the identified systematic reviews, and cost-effectiveness studies published through May 2017.

The following are the core sources searched:

Agency for Healthcare Research and Quality (AHRQ)

BMJ Clinical Evidence

Cochrane Library (Wiley Interscience)

National Institute for Health and Care Excellence (NICE)

PubMed Health

Tufts Cost-Effectiveness Analysis Registry

Veterans Administration Evidence-based Synthesis Program (ESP)

Washington State Health Technology Assessment Program

Clinical Practice Guidelines

Center researchers conducted a full search of Center clinical practice guidelines primary sources to identify clinical practice guidelines using the terms *left atrial appendage* and *watchman* Searches were limited to citations published within the last five years.

The following are the guideline sources:

Australian Government National Health and Medical Research Council (NHMRC)

Centers for Disease Control and Prevention (CDC) – Community Preventive Services

Institute for Clinical Systems Improvement (ICSI)

National Guidelines Clearinghouse

National Institute for Health and Care Excellence (NICE)

New Zealand Guidelines Group

Scottish Intercollegiate Guidelines Network (SIGN)

United States Preventive Services Task Force (USPSTF)

Veterans Administration/Department of Defense (VA/DOD)

Coverage Policies

Center researchers searched for policies on the coverage of percutaneous left atrial appendage closure for the treatment of non-valvular atrial fibrillation from Aetna, Anthem, Blue Shield of Northeastern New York, Capital District Physicians' Health Plan, Centers for Medicare and Medicaid Services, Cigna, Emblem Health, Empire BCBS, Excellus BCBS, Tufts Health Plan, UnitedHealthcare, and nine state Medicaid programs (CA, FL, MA, NJ, NY, OR, PA, TX, WA).

General Exclusion Criteria

Staff members excluded studies that were not systematic reviews, meta-analyses, or technology assessments, or individual studies (as applicable by topic) that were published before 2007, or were published in a language other than English.

Quality Assessment

Staff members assessed the methodological quality of the included studies using standard instruments developed and adapted by the Center that are modifications of the systems in use by the Campbell Collaboration, Cochrane, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), the National Institute for Health and Care Excellence (NICE), and the Scottish Intercollegiate Guidelines Network (SIGN) (Campbell Collaboration, 2015; Cochrane Collaboration, 2011; Guyatt et al., 2008; Moher, Liberati, Tetzlaff, & Altman, 2009; National Institute for Health and Care Excellence, 2014b; Scottish Intercollegiate Guidelines Network, 2015a, 2015b). Two Center researchers independently rated all studies. In cases where there was not agreement about the quality of a study, consensus was reached through discussion.

Each rater assigned the study a rating of good, fair, or poor, based on its adherence to recommended methods and potential for biases. In brief, good-quality systematic reviews include a clearly-focused question, a literature search sufficiently rigorous to identify all relevant studies, criteria used to select studies for inclusion (e.g., RCTs) and assess study quality, and assessments of heterogeneity to determine if a meta-analysis would be appropriate. Good-quality RCTs include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Good-quality systematic reviews and RCTs also have low potential for bias from conflicts of interest and funding source(s). Fair-quality systematic reviews and RCTs have incomplete information about methods that might mask important limitations. Poor-quality systematic reviews and RCTs have clear flaws that could introduce significant bias.

Specific Search Details

The search terms left atrial appendage and *watchman* were used in the remaining core source searches. Archived government reports were not included.

Inclusion Criteria

Population: Adults with non-valvular atrial fibrillation

Intervention: Percutaneous closure of the left atrial appendage with permanent implant (CPT code 33340)

Comparators: Oral anticoagulation (e.g., vitamin K antagonist, direct Factor Xa inhibitors, direct thrombin inhibitors), antiplatelet therapy, or no anticoagulation; with or without other medical therapy (e.g., medications for heart rate control)

Efficacy and Effectiveness Outcomes: Embolic ischemic stroke risk, need for long-term oral anticoagulation therapy, quality of life, cost or cost-effectiveness

Harm Outcomes: Morbidity, major bleeding, procedural complications

Exclusion Criteria

Study exclusion criteria included:

- Duplicate information from a research study published in more than one source (only the highest quality, most recent publication with outcome of interest was included)
- Systematic reviews that included only studies that were summarized by more comprehensive SRs or SRs of higher quality and/or that were more recently published
- Studies identified that were included in a summarized SR or technology assessment
- Non-comparative studies included for evidence on harms, not efficacy.

MEDLINE (Ovid) Search

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 03, 2017>

Search Strategy:

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1 "left atrial appendage closure".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

2 limit 1 to (controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or systematic reviews)

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Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 03, 2017>

Search Strategy:

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1 watchman.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

2 atrial fibrillation.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3 1 and 2

Appendix B. Articles Excluded After Full Text Review with Rationale

Table B1. Articles Excluded by Full Text Review

Citation	Exclusion Rationale
Bajaj et al. (2014)	Supplanted by newer SR
Belgaid, Khan, Zaidi, and Hobbs (2016)	Review
Briceno et al. (2015)	Supplanted by newer SR
Chun et al. (2013)	Included in Noelck et al, 2016
Fender, Kiani, and Holmes (2016)	Narrative review, no methods.
Fountain et al. (2006)	Protocol
Hanif et al. (2017)	Supplanted by newer SR (Bajaj et al., 2016). Actual search date of Hanif et al. 2017, was through December 2014, whereas Bajaj was through October 2015. Combines surgical and percutaneous outcomes together (not primary exclusion reason).
Holmes et al. (2015)	Data included in Reddy et al, 2017
Koifman et al. (2016)	Supplanted by higher quality SR
Munkholm-Larsen et al. (2012)	Supplanted by newer SR
New Zealand National Health Committee (NHC) (2015)	No methods provided.
Price et al. (2015)	Data included in Reddy et al, 2017
Reddy, Holmes, Doshi, Neuzil, and Kar (2011)	Data included in Noelck et al, 2016
Romero, Perez, Krumerman, Garcia, and Lucariello (2014)	Review article
Saw and Price (2017)	Editorial
Sohaib and Fox (2015)	Editorial
Tereshchenko et al. (2016)	Supplanted by newer SR
Wei et al. (2016)	No comparison
Xu, Xie, Wang, Ma, and Wang (2016)	No comparison

Abbreviations. SR: systematic review.

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Chun, K. R. J., Bordignon, S., Urban, V., Perrotta, L., Dugo, D., Furnkranz, A., . . . Schmidt, B. (2013). Left atrial appendage closure followed by 6 weeks of antithrombotic therapy: A prospective single-center experience. *Heart Rhythm, 10*(12), 1792-1799. doi: https://dx.doi.org/10.1016/j.hrthm.2013.08.025

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Appendix C. List of Ongoing Trials

Trial	Status	Intervention
The Evaluation of Thrombogenicity in Patients Undergoing WATCHMAN Left Atrial Appendage Closure Trial	Recruiting	Device: WATCHMAN Left Atrial Appendage Closure
A Pilot Study of Edoxaban in Patients With Non-Valvular Atrial Fibrillation and Left Atrial Appendage Closure	Not yet recruiting	Drug: Edoxaban Device: WATCHMAN LAA Closure Drug: Aspirin and Clopidogrel Drug: Aspirin and Warfarin
Left Atrial Appendage Closure with the LAmbre	Completed	Device: LAA closure with LAmbre
China Registry of WATCHMAN	Recruiting	Device: left atrial appendage closure device implantation
Atrial Appendage Closure Prospective Observational Study	Withdrawn	Device: Lariat
Canadian Left Atrial Appendage Closure Study	Recruiting	Device: Ultrasept LAA Closure System
Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation	Recruiting	Drug: NOAC Device: Left atrial appendage closure
Left Atrial Appendage Closure With SentreHeart Lariat Device	Recruiting	Procedure: Left atrial appendage closure Device: SentreHeart Lariat
French Database of Left Atrial Appendage Closure	Active, not recruiting	Other: Percutaneous Left Atrial Appendage Closure in routine care
ELIGIBLE (Efficacy of Left Atrial Appendage Closure After GastroIntestinal Bleeding)	Unknown status	Device: Left atrial appendage occlusion
Watchman FLX Left Atrial Appendage Closure Device Post Approval Study	Not yet recruiting	Device: Watchman FLX
Left Atrial Appendage Closure Compared to Standard Antiplatelet Therapy in Patients With AF Who Underwent PCI	Unknown status	Device: Left Atrial Appendage Closure Device (Watchman) Drug: Warfarin
Impact of Left Atrial Appendage Closure on Physical Capacity	Recruiting	Not specified
ASA Plavix Feasibility Study With WATCHMAN Left Atrial Appendage Closure Technology	Completed, no results posted yet	Device: WATCHMAN
Prevention of Stroke by Left Atrial Appendage Closure in Atrial Fibrillation Patients After Intracerebral Hemorrhage	Recruiting	Device: LAAO Drug: Medical Therapy

Trial	Status	Intervention
Clinical Investigation of the LAmbre Left Atrial Appendage Closure System	Completed, no results posted yet	Device: LAA closure system
Feasibility Study of a Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation	Recruiting	Device: Aegis Sierra Ligation System
Comparison of Outcomes After Left Atrial Appendage Closure or Oral Anticoagulation in Patients With Atrial Fibrillation	Completed, no results posted yet	Other: Questionnaire
A Study to Evaluate the Safety and Effectiveness of the Left Atrial Appendage Closure Therapy Using BSJ003W	Recruiting	Device: BSJ003W
Study of Left Atrial Appendage Closure in Patients With Atrial Fibrillation - III	Withdrawn	Device: LARIAT Suture Delivery Device and Accessories
Left Atrial Appendage Closure During Open Heart Surgery	Unknown status	Procedure: Surgical closure of the left atrial appendage
Left Atrial Appendage CLOSURE for the Prevention of Thromboembolisms in Patients Undergoing Aortic Bioprosthesis Surgery	Recruiting	Procedure: Surgical closure of left atrial appendage Procedure: No closure of left atrial appendage
Safety and Efficacy of Left Atrial Appendage Closure Versus Antithrombotic Therapy in Patients With Atrial Fibrillation Undergoing Drug-Eluting Stent Implantation Due to Complex Coronary Artery Disease	Not yet recruiting	Drug: Dabigatran plus aspirin, Dabigatran plus clopidogrel Device: AMPLATZER Cardiac Plug (ACP)
PLUG Dementia Trial	Recruiting	Other: Questionnaire
Evaluation of the Cardioblate Closure Device in Facilitating Occlusion of the Left Atrial Appendage	Terminated	Device: Medtronic LAA Occlusion Device
Atrial and Brain Natriuretic Peptide Secretion After Percutaneous Closure of the Left Atrial Appendage	Unknown status	Device: WATCHMAN LAA system (Percutaneous left atrial appendage closure)
Canadian WATCHMAN Registry	Recruiting	Device: WATCHMAN
Combined Transcatheter Aortic Valve Implantation and Percutaneous Closure of the Left Atrial Appendage	Recruiting	
Study of Safety and Efficacy of a Left Atrial Appendage Occluder	Not yet recruiting	Device: The Left Atrial Appendage Occluder of Shanghai Push Medical Device Technology CO.td

Trial	Status	Intervention
Interventional Strategies in Treatment of Atrial Fibrillation: Percutaneous Closure of the Left Atrial Appendage Versus Catheter Ablation	Completed, no studies posted yet	Procedure: Percutaneous closure of LAA Procedure: Catheter ablation of AF
Continued Access to PREVAIL (CAP2) - WATCHMAN Left Atrial Appendage (LAA) Closure Technology	Active, not recruiting	Device: WATCHMAN LAA Closure Technology
Prospective, Non-randomized, Safety and Efficacy Study of a New Occluder Design for Minimally Invasive Closure of the Left Atrial Appendage (LAA) in Patients With Atrial Fibrillation	Active, not recruiting	Device: Implantation of LAA closure device
Safety and Efficacy Study of LAmbre LAA Closure Device for Treating AF Patients Who Cannot Take Warfarin	Unknown status	Device: LAA closure system
WAVECREST Post Market Clinical Follow-Up (PMCF) Study	Recruiting	Device: Coherex WaveCrest Left Atrial Appendage Occlusion System
Medical and Surgical Hybrid Treatment of Atrial Fibrillation	Recruiting	Device: The AtriCure Synergy Ablation System

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