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The Effectiveness of Procedures to Remove or Occlude the Left Atrial Appendage: A Systematic Review of the Evidence

October 2015

Prepared for:
Department of Veterans Affairs
Veterans Health Administration
Quality Enhancement Research Initiative
Health Services Research & Development Service
Washington, DC 20420

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PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

Recommended citation: Noelck N, Papak J, Freeman M, Paynter R, Low A, Motu’apuaka M, Kondo K, Kansagara D. The Effectiveness of Procedures to Remove or Occlude the Left Atrial Appendage: A Systematic Review of the Evidence. VA ESP Project #05-225; 2015.

This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the **Portland VA Health Care System, Portland, OR**, funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

EXECUTIVE SUMMARY

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting between 2.7 and 6.1 million people in the United States. The prevalence of AF increases with age and is often associated with structural heart disease and co-morbidities that are common in the Veteran population. AF is the most important cause of cardioembolic stroke, which accounts for 14-36% of all ischemic strokes. While patients at highest risk for AF-related stroke also often have other independent risk factors for stroke secondary to atherosclerotic aortic or carotid disease, most cardiac sources of embolism are thought to be due to thrombus formation from blood stasis in the left atrium. Among patients with non-valvular AF more than 90% of thrombi develop in the left atrial appendage (LAA). Antithrombotic therapy with aspirin, warfarin, or one of several newer oral anticoagulants reduces the risk of stroke due to both atrial fibrillation and atherosclerotic disease but is associated with a risk of serious bleeding. As a potential alternative to long-term anticoagulant therapy, various LAA exclusion procedures have been developed in an attempt to isolate the LAA from circulating blood flow. These procedures, including both surgical occlusion and removal of the LAA and percutaneous catheter-based interventions to occlude the LAA, may be beneficial in reducing risk of cardioembolic stroke originating from the LAA.

The purpose of this report is to systematically review the literature to better understand the balance of benefits and harms of surgical or percutaneous LAA exclusion procedures.

METHODS

The research questions for this systematic review were developed in consultation with key stakeholders and content experts. The key questions (KQs) that this review sought to address were:

KQ1. What is the effectiveness of surgical or percutaneous LAA exclusion compared with usual care?

KQ2. What are the harms associated with surgical or percutaneous LAA exclusion?

KQ3. How do the benefits and harms of LAA exclusion vary in different subgroups?

KQ4. What are the comparative effects of different techniques (surgical and percutaneous) of LAA exclusion on rates of procedural success?

Data Sources and Searches

We developed search strategies in consultation with a research librarian, who conducted database searches in Ovid MEDLINE®, Embase®, the Cochrane databases, the FDA Devices database, ClinicalTrials.gov, the Conference Abstracts database, and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) from database inception through January 7, 2015. We reviewed the bibliographies of systematic reviews and other relevant articles for additional studies, and contacted device manufacturers to inquire for unpublished trial data.

Study Selection

We reviewed titles and abstracts using pre-specified inclusion/exclusion criteria. Potentially relevant full-text articles underwent independent review by at least 2 investigators for final decisions on inclusion/exclusion.

We included controlled clinical trials to assess the effectiveness of percutaneous LAA exclusion procedures. To assess the harms of percutaneous LAA procedures we also included cohort and registry studies with 50 or more patients.

We included cohort studies and controlled clinical trials to review both benefits and harms of surgical LAA procedures. Because LAA exclusion procedures were usually done in the context of heart surgery, and harms related to LAA exclusion are difficult to distinguish from those of the heart surgery itself, we only included cohort studies with a control group of patients who received heart surgery without LAA exclusion.

Data Abstraction and Quality Assessment

One author abstracted data from each study and a second author reviewed the entries for accuracy.

Two reviewers (among NN, DK, JP, and MF) independently assessed the quality of each study using published criteria. We graded the strength of evidence for each outcome using published criteria which consider the consistency, coherence, directness, and applicability of a body of evidence, as well as the internal validity of individual studies. We resolved disagreements through discussion.

Data Synthesis and Analysis

We qualitatively synthesized the evidence on the benefits and harms of LAA exclusion. Clinical heterogeneity and the small number of trials precluded the possibility of combining the findings in meta-analysis.

Peer Review

A draft version of this report was reviewed by 5 individuals with technical expertise and clinical leadership. Their comments and our responses are presented in Appendix E.

SUMMARY OF FINDINGS

We reviewed 2,566 titles and abstracts from the combined searches. We selected 207 articles for full-text review, of which 20 studies contained primary data relevant to the effectiveness and/or harms of LAA interventions. We contacted 7 device companies to request information about unpublished studies but received no response.

Summary of Evidence

There is low-strength evidence that percutaneous LAA exclusion is associated with a similar risk of long-term stroke and mortality as continued oral anticoagulation therapy. This finding is based on trials of one device studied in patients without contraindications to oral anticoagulant therapy. Most patients who received the Watchman device were able to discontinue oral anticoagulant

therapy after undergoing follow-up transesophageal echocardiography (TEE) showing persistent closure of the LAA at 3-6 months. However, there is moderate strength evidence that a substantial proportion of patients undergoing various percutaneous LAA exclusion procedures experienced serious periprocedural harms. For example, patients undergoing placement of a Watchman device experienced 4.1-10.5% periprocedural adverse events. There is insufficient evidence to determine whether factors such as operator experience, patient selection criteria, or choice of device can modify these risks. There is insufficient data to assess the balance of benefits and harms of percutaneous LAA exclusion procedures in patients who are ineligible for long-term oral anticoagulation therapy.

We found insufficient evidence to determine the efficacy of surgical LAA exclusion in reducing stroke. We found low-strength evidence that surgical LAA exclusion in the context of heart surgery done for another indication is unlikely to be associated with significant incremental harm. In 2 studies, successful closure of the LAA was demonstrated in follow-up in only 40-66% of patients.

Table 1 summarizes the evidence on percutaneous and surgical LAA exclusion interventions.

Research Gaps/Future Research

Trials of percutaneous LAA interventions were limited to studies of the Watchman device in patients who were eligible for long-term warfarin therapy. Trials of surgical LAA interventions were few and limited by sample size. Several studies that should add substantively to this body of evidence are underway, including a large RCT of surgical interventions with an estimated sample size of 4,700 patients, studies of recently developed percutaneous devices (LAmbre and Occlutech), and a trial comparing Watchman with Apixaban in patients ineligible for warfarin therapy.

Conclusions

Overall, there is limited evidence that percutaneous LAA exclusion using the Watchman device may be an effective alternative to long-term oral anticoagulation in selected patients who are closely followed and in whom procedural success is sustained. However, in many studies, percutaneous LAA exclusion has been associated with high rates of serious procedure-related harms. There is insufficient evidence to assess the benefits of surgical LAA exclusion. While surgical LAA exclusion does not appear to be associated with a significant increase in harms over the heart surgery during which the procedures are typically performed, rates of procedural success may be low. Overall, there is insufficient evidence to support the routine use of surgical LAA exclusion to reduce stroke risk or future need for anticoagulant therapy.

Table 1. Summary of evidence on the effectiveness of procedures to remove or occlude the left atrial appendage

Outcome	Device or procedure N studies (N=combined participants)	Findings	Strength of Evidence*	Comments
Percutaneous interventions				
Mortality	Watchman 2 RCTs (N=1,114)	No significant difference in mortality. RR (95% CI) in 2 RCTs: 1.20 (0.31 to 4.56) 0.62 (0.34 to 1.24)	Low	Limited applicability: only one device has been studied in 2 RCTs. Patients were eligible to receive LT-OAC. Low precision (wide confidence intervals).
Stroke	Watchman 2 RCTs (N=1,114)	No significant difference in risk of stroke. RR (95% CI): in 2 RCTs: 0.71 (0.35 to 1.64) 3.28 (0.37 to 25.31)		
Harms	ACP: 3 registries (N=147) Coherex: 1 registry (N=4) Lariat: 2 registries (N=93) PLAATO: 5 registries (n=441) Watchman: 2 RCTs + 4 registries (N=742) Device not specified: 2 registries (N=211)	Serious procedure- or device-related safety events (% of patients): 1.6 to 13.6. Overall, rate of serious adverse events within 7 days of device implantation was 6.5% (98/1506).	Moderate	A range of devices were examined among 2 trials and 11 observational studies. Strength of finding limited by wide range of event rates across studies, relatively small number of patients treated in each observational study.
Surgical interventions				
Mortality	Sutures or stapler in 3 RCTs (N=171) Various excision and exclusion techniques in 4 Cohort studies (N=1695)	No significant difference in mortality, among studies in which at least one event occurred in both groups: In 1 RCT: 7.7 vs 12% ($P > .05$) RR (95% CI) 0.64 (0.12, 3.52) In 1 cohort: 5.0 vs 8.4% ($P > .05$) RR (95% CI) 0.60 (0.22 to 1.60)	Insufficient	Trials too small and event rates too low to determine effectiveness of procedure.
Stroke	3 RCTs (N=171) 2 cohort studies (N=1500)	No significant difference in risk of stroke, among studies in which at least one event occurred in both groups: In 1 RCT: 3.8 vs 12% ($P > .05$); RR (95% CI) 0.32 (0.03 to 2.88) In 2 cohorts: 1.0 vs 1.4% ($P = .44$) 0.84 vs 1.7% ($P > .05$)	Insufficient	
Harms	3 RCTs (N=171) 1 cohort study (N=238)	Serious safety events: 6.9-32.0% of patients No significant differences in most major harms between cardiac surgery groups with and without LAA exclusion	Low	Limited number of studies and limited number of patients included.

Abbreviations: ACP = Amplatzer cardiac plug; CI = confidence interval; LT-OAC = long term oral anticoagulation; RCT = randomized controlled trial; PLAATO = percutaneous left atrial appendage transcatheter occlusion; RR = relative risk

ABBREVIATIONS

ACP	Amplatzer cardiac plug
AF	Atrial fibrillation
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CHADS2	Stroke risk score in AF (congestive heart failure, hypertension, age 75+, diabetes mellitus, and stroke/TIA)
CHA2DS2-VASc	Stroke risk score in AF that includes CHADS2 with age in 2 categories and vascular disease
CHF	Congestive heart failure
CI	Confidence interval
CT	Computerized tomography
DM	Diabetes mellitus
HAS-BLED	Score that estimates risk of major bleeding for patients on anticoagulation for atrial fibrillation
HR	Hazard ratio
HTN	Hypertension
Hx	History (of)
INR	International normalized ratio
LAA	Left atrial appendage
LT-OAC	Long-term oral anticoagulation therapy
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MRI	Magnetic resonance imaging
PICOTS	Population, Intervention, Comparator, Outcome, Timing, Study Design
PLAATO	Percutaneous Left Atrial Appendage Transcatheter Occlusion
PSM	Propensity score matching
QoL	Quality of life
RCT	Randomized controlled trial
RR	Relative risk
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
VATS	Video assisted thoracoscopy
WHO ICTRP	World Health Organization International Clinical Trials Registry Platform