

Consequences of Oral Anticoagulants for Stroke Risk Reduction in Atrial Fibrillation: Where Do We Go from Here?

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Executive Summary

Atrial fibrillation (AF) is the most common sustained heart arrhythmia, and it increases the risk for stroke about five-fold.¹ As a result, stroke prevention is the most important aspect of managing patients with AF. Stroke prevention is most commonly achieved through the use of oral anticoagulant (OAC) therapy.^{2,3,4} However, patients can find OAC therapy difficult to manage over time, as it escalates the risk for life-threatening bleeds and can have a significant, negative impact on quality of life (QoL), work, and family. The most commonly prescribed OAC therapy, warfarin, includes the additional burdens of regular monitoring and dietary restrictions that can further compromise QoL and lead to noncompliance, undermining the objective of the therapy and leaving the patient at an elevated risk for stroke.

The main source of stroke in non-valvular AF (NVAf) is the formation of thrombi in the left atrial appendage. The use of a left atrial appendage closure (LAAC) device, such as the WATCHMAN™ Left Atrial Appendage Closure Device, may eliminate or reduce the negative consequences associated with OAC therapy by providing a permanent, non-pharmaceutical alternative.* Patients with NVAf who may be considered appropriate candidates for implantation of a WATCHMAN device include those who:⁵

- Have a history of major bleeding with OAC therapy;
- Are unable to maintain a stable therapeutic international normalized ratio (INR) or comply with INR monitoring while on warfarin, and another OAC is not available;
- Have a medical condition, occupation, or lifestyle that puts them at risk for major bleeding.

To review and assess the full spectrum of strategies for stroke risk reduction in patients with NVAf, a literature review was completed and then supplemented with perspectives collected from multi-disciplinary experts via a virtual roundtable discussion. Based on these inputs, the panel concluded that prophylaxis should be based on an individualized approach that takes into account a patient's medical and treatment history, lifestyle, occupation, QoL, and personal preferences. While OACs remain an important therapy, LAAC device implantation can be a better option for some patients based on consideration of these individual factors. Indeed, the increasing, favorable clinical and real-world outcomes with LAAC devices should be reassuring to physicians and may prompt a re-evaluation of their approach to reducing stroke risk in patients with NVAf.

The WATCHMAN™ Left Atrial Appendage Closure Device (Boston Scientific) is currently the only LAAC device approved for use in the United States.

Introduction

Atrial fibrillation is the most common type of cardiac arrhythmia.⁶ According to the American Heart Association, more than 2.7 million people in the United States have AF, although this number may be as high as 6.1 million because people can have AF without obvious symptoms, leaving it undiagnosed.^{1,6,7} The prevalence is predicted to increase to 12.1 million by 2030, due largely to the aging of the population.⁸ In the U.S., AF leads to more than 750,000 hospitalizations each year.⁶ In 2015, it was the underlying cause of death of nearly 24,000 people and was listed as an underlying or possible contributing condition (“any-mention” mortality) on nearly 150,000 death certificates.⁷

AF confers an approximate five-fold increase in the risk of stroke due to the formation of atrial thrombi, more than 90% of which occur in the left atrial appendage.^{1,9} This recorded increased stroke risk may be a substantial underestimate because AF is often asymptomatic and undetected clinically.⁷ To decrease the risk of stroke, physicians managing patients with AF^{2,3,4} often prescribe OACs. However, OAC therapy is associated with significant drawbacks related to clinical outcomes, costs, inconvenience, and adherence (see Box 1).

Figure 1: Left atrial appendage with a large thrombus



Box 1: Potential drawbacks associated with oral anticoagulant therapy for AF

- Increased risk of bleeding, including major, life-threatening bleeds
- High, direct costs for inpatient or outpatient clinical visits related to bleeds, long-term monitoring, treatment of side effects, and pharmacy costs
- Negative impact on quality of life, work, family, dietary restrictions
- Poor adherence, which can lead to a debilitating stroke

Prevention and treatment of AF-related strokes pose challenges for a number of health care specialists, including:

- Cardiologists, who are usually the frontline caregivers making critical decisions about the most appropriate therapy for a given patient;
- Cardio-neurologists, who may make initial treatment decisions but often become involved after a stroke has occurred and focus on treating the neurological impact and preventing recurrent stroke;
- Emergency physicians, who must make rapid, potentially life-saving treatment decisions in the ER for a patient with a major bleed or stroke; and
- Gastroenterologists, who treat AF patients mainly to reduce the risk for recurrent gastrointestinal (GI) bleeds, which can be life-threatening.

While the medical literature addresses many aspects of NVAF treatment and includes many comparative studies of OACs, there has been little focus on the significant clinical and non-clinical costs, both direct and indirect, of lifelong OAC therapy. Recently, a roundtable of multidisciplinary experts (see Box 2) discussed the costs and challenges of preventing AF-related strokes from the vantage point of their respective areas of expertise. This whitepaper captures their perspectives along with findings from the medical literature.

Box 2: Roundtable Participants

- Oussama Wazni, MD, Section Head, Cardiac Electrophysiology and Pacing at the Cleveland Clinic
- Michael Ezekowitz, MD, PhD, Professor, Sidney Kimmell Medical School and Thomas Jefferson University; attending cardiologist at Lankenau, Bryn Mawr, and Paoli Hospitals
- MingMing Ning, MD, MMsc, Co-Director, Cardio-Neurology Division and Director, Clinical Proteomics Research Center at Massachusetts General Hospital, Associate Professor, Harvard Medical School
- Christopher Baugh, MD, MBA, Vice Chair, Emergency Physician, Brigham and Women’s Hospital, Associate Professor, Harvard Medical School

AF-Related Stroke Risk

AF causes 15-20% of ischemic strokes,⁶ though the rate varies by age and gender. For example, AF accounts for 1.5% of strokes in individuals 50 to 59 years of age but rises to 23.5% in those 80 to 89 years of age.⁷ Among adults with AF, females have a significantly higher risk of stroke than males.⁷

AF-related strokes also are likely to be more severe than non-AF-related strokes.⁶ The Framingham study showed that strokes in AF patients compared to non-AF patients had greater 30-day mortality (25% vs 14%, odds ratio 1.84, $p=0.036$) and, after one year of follow-up, a higher rate of recurrence (23% vs. 8%) and of death (63% vs. 34%).¹⁰

Vitamin K Antagonist Therapy and Challenges

Because AF is a powerful risk factor for ischemic stroke, reducing stroke risk is a major priority in managing it.^{2,4,7} A large body of evidence demonstrates that the vitamin K antagonist (VKA), warfarin, reduces the risk of stroke. For example:

- Pooled data from 5 prospective, randomized controlled clinical trials in 2,451 patients with AF showed that warfarin reduces the risk of stroke by 68% compared to control group patients (control group patients received placebo in 4 of the 5 trials; in the fifth trial, control group patients were allowed to take aspirin^{11,12}).
- A study in Medicare patients 65 years and older with AF showed that, from 1992 to 2002, warfarin use increased from 24.5% to 56.3% of patients, and stroke rates decreased from 46.7 to 19.5 per 1,000 patient-years.¹³

While warfarin is effective in reducing the risk of ischemic stroke, it poses significant challenges for patients. The pooled analysis of 5 controlled trials noted above showed that the annual frequency of major hemorrhage (intracranial bleeding or a bleed requiring hospitalization or 2 units of blood) was 1.3% in warfarin-treated patients compared to 1% in control patients.¹² To reduce the risk of major bleeding while still achieving effective anticoagulation, it is usually recommended that a patient's INR be maintained within the therapeutic range of 2.0 to 3.0.² That, however, also can be challenging, since it requires regular monitoring (weekly initially, then monthly if stable); and the INR can be affected by dietary intake of vitamin K (found in abundance in green and leafy vegetables), certain botanicals and supplements, and numerous drugs.¹⁴

Non-VKA Oral Anticoagulants and Challenges

The difficulties with warfarin therapy drove the development of “non-VKA oral anticoagulants,” also referred to as “novel oral anticoagulants” (both abbreviated as NOAC). Whereas VKAs inhibit clotting activity of multiple vitamin K clotting factors (II, VII, IX and X), NOACs have more specific targets in the clotting cascade: either Factor Xa (apixaban, rivaroxaban and edoxaban) or direct thrombin inhibition (dabigatran). They also do not require INR monitoring, nor is their anticoagulation effect altered by vitamin K intake.

While NOACs reduce the risk of ischemic stroke as much or more than warfarin, and have a lower risk for some types of bleeding compared to warfarin, they introduce other issues. All approved NOACs except apixaban increase the risk for GI bleeding compared to warfarin.^{15,16,17,18} Patients are required to take them once or twice daily, at about the same time each day. If older patients have difficulty adhering to that dosing schedule, the resulting noncompliance may increase their risk of stroke. Unlike warfarin, there is no standard method to monitor maintenance of a therapeutic range with NOACs, making it more difficult for physicians to assess compliance and the patient's degree of protection from stroke risk. Finally, one NOAC (edoxaban) has no approved reversal agent, which can be critical in emergency situations where coagulation is necessary to prevent life-threatening bleeds.

Additional Challenges with OAC Therapy

A major challenge is cost. A comprehensive analysis of the full cost of OACs should include:

- Direct medical costs for inpatient or outpatient visits related to bleeds, long-term monitoring, treatment for side effects and use of reversal agents;
- Direct pharmacy costs;
- Negative impact on QoL, work, family, dietary restrictions; and
- Poor adherence and the resulting increased risk for stroke.

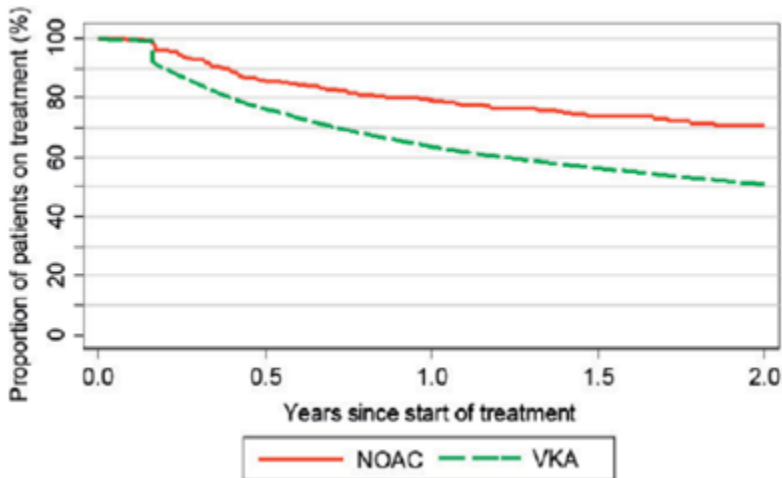
To gain perspective on estimated medical and pharmacy costs for OAC therapy in AF, the experts who participated in the roundtable reviewed findings from seven representative studies based on real-world medical claims databases. Costs were examined per-patient-per-year (PPPY) (a metric commonly used by payers¹⁹) and per-patient-per 10 years (PPP10Y), since treatment is needed for a patient's lifetime. Low-to-high cost ranges are shown in Table 1; findings from each study are in the supplemental tables in the appendix.

Warfarin had lower pharmacy costs than the NOACs, but had the widest range and highest upper value of total costs (\$22,682 to \$58,284 PPPY and \$226,820 to \$582,840 PPP10Y) and medical costs (\$19,815 to \$52,380 PPPY and \$198,150 to \$523,800 PPP10Y), likely due to the additional physician visits for INR monitoring. NOACs were generally similar in their ranges of medical, pharmacy, and total costs. While current guidelines favor NOACs over warfarin for most AF patients to reduce stroke risk,^{2,3} some insurance companies do not cover them, leaving these patients with warfarin as the least expensive option based on out-of-pocket payments.

Dr. Ning pointed out a potential cost often not considered is for the treatment of OAC-related intracranial hemorrhage: OAC reversal agents. The reversal agent for warfarin costs about \$3,000 - \$5,000 per dose, and may need to be given repeatedly. Reversal agents for the various NOACs range from similar cost to about 10 times more per dose.

Warfarin therapy may have a negative impact on QoL, work, and family, as well as dietary restrictions—all of which can lead to poor adherence. Indeed, reported rates of discontinuation of warfarin therapy are often greater than for NOACs, though persistence is generally poor for both VKA and non-VKA medications. A retrospective, real-world, U.S. health claims database study in a cohort of 64,661 AF patients newly prescribed OAC therapy found adjusted rates of adherence (defined as >80% of days covered by the prescribed medication) at 1.1 years of 52.1%, 47.6%, 45.9% and 38.7% for apixaban, rivaroxaban, dabigatran and warfarin, respectively.²⁰ Similarly, a UK-based primary care database study in 27,514 OAC-naïve NVAF patients found high rates of discontinuation 2 years following therapy initiation: about 30% of those prescribed a NOAC, and 50% of those prescribed a VKA (Figure 2).²¹ Unfortunately, poor adherence can leave patients at a significant risk of having a stroke.

Figure 2: 30-50% of AF patients initiating OAC therapy discontinue at 2 years (U.K. real-world study)²¹



INR monitoring with warfarin also has a significant negative impact on QoL and inconvenience. Warfarin therapy also demands adherence to dietary restrictions (e.g., limiting consumption of green vegetables because of their vitamin K content) which patients often find difficult to sustain, particularly over the course of years. It can be difficult for many patients to take their NOAC therapy at the same time every day, and if they don't, they may go into a withdrawal phenomenon that can lead to an increased risk for stroke or TIA. People who are traveling long distances may forget to adjust dosing schedule when in a different time zone, resulting in too short or too long an interval between doses.

Dr. Baugh noted that many emergency physicians tend to view treatment from a short-term perspective. But, it can be better for the patient if the physician and emergency pharmacy discuss costs and patient insurance coverage, since those factors can inform a decision on choice of therapy that often must be sustained over the long term. He also noted that it is important emergency physicians become familiar with the decision process for therapies, have educational resources on hand for the patient, and include the emergency nurse and/or pharmacist in educating the patient.

Dr. Ning echoed this, noting the value of shared decision making between patient and physicians across specialties. Active discussion of the advantages and disadvantages of the treatment options is one of the more effective approaches to improve treatment adherence.

Left Atrial Appendage Closure

LAAC is an implanted device that many physicians and patients with AF prefer over lifelong OAC therapy. The rationale for this minimally-invasive procedure is based on the fact that more than 90% of atrial thrombi in AF are generated in the left atrial appendage.⁹ While LAAC has been performed during cardiac surgery and via use of specific percutaneous devices (WATCHMAN, Amplatzer Cardiac Plug, WaveCrest device or Lariat endocardial and epicardial ligation technique), only the WATCHMAN device is currently approved for stroke risk reduction in the United States. It is also the most-studied LAAC device.

The WATCHMAN device is indicated for patients with NVAF who meet all these criteria:⁵

- Have an increased risk for stroke and be recommended for anticoagulation therapy;
- Are suitable for warfarin; and,
- Have an appropriate reason to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

Factors that also may be considered in selecting patients appropriate for the WATCHMAN device include:

- A history of major bleeding with OAC therapy;
- An inability to maintain a stable therapeutic INR or comply with INR monitoring while on warfarin, and another OAC isn't available;
- A medical condition, occupation or lifestyle putting them at risk for major bleeding due to trauma.

The WATCHMAN device is usually implanted under general anesthesia using a standard transeptal technique. The procedure usually lasts about an hour and patients typically stay in the hospital overnight. Following the procedure, patients take aspirin and warfarin for about 45 days or until the device is adequately sealed. This is assessed using trans-esophageal echo. After stopping warfarin, patients take clopidogrel and an increased dose of aspirin for 6 months, followed by ongoing aspirin therapy.²²

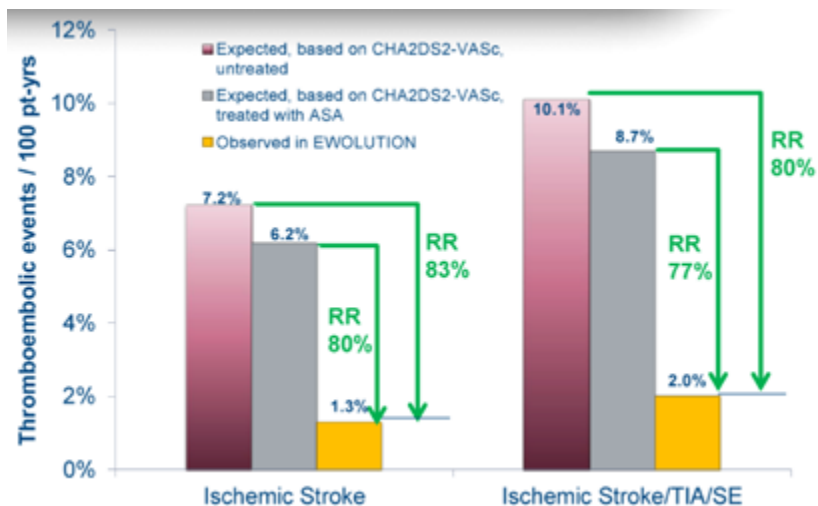
The WATCHMAN device has been implanted in more than 85,000 patients to date, and has been studied in randomized trials and multicenter registries in more than 6,800 patients with more than 11,000 patient-years of follow up.²³ **Data from a number of trials show the WATCHMAN device is a safe alternative to long-term warfarin therapy and enables patients to stop taking warfarin with:**²⁴

- 95% implantation success rate;
- 1.5% procedural complication rate;
- >92% warfarin cessation after 45 days post implantation, >99% after 1 year.

The data also show that, compared to warfarin, use of the WATCHMAN device resulted in:²⁴

- Comparable stroke event reduction of 18% (p=0.27);
- 55% reduction in disabling/fatal stroke (p=0.03), largely driven by an 80% reduction in hemorrhagic stroke (p=0.003);
- 72% reduction in major non-procedure-related bleeding after 6 months (p=0.001);
- 27% reduction in all-cause mortality (p=0.04), largely driven by a 41% reduction in cardiovascular/unexplained mortality (p=0.03).

Real-world findings also have shown a low complication rate with the WATCHMAN device. For example, the EWOLUTION prospective registry showed that, in 1,020 patients, implantation was successful 98.5% of the time. The rate of serious adverse events within 7 days of the procedure was 2.8%, and adequate sealing (no leaks >5mm) was achieved in 99% of patients followed for > 11 months.²⁵

Figure 3: EWOLUTION 2-year follow-up shows low annual stroke rate in full cohort²⁶

Dr. Ezekowitz noted that, in contrast to the ongoing, long-term costs of OAC therapy, implantation of a WATCHMAN device involves an upfront cost, with costs after implantation flat or declining. An analysis found that in patients with a prior ischemic stroke or transient ischemic attack (TIA), LAAC with the WATCHMAN device reached cost-effectiveness relative to warfarin at year 6. It also concluded that the WATCHMAN device procedure resulted in lower costs and more quality-adjusted life years compared to warfarin at 10 years.²⁷

Likewise, complications with the WATCHMAN device are mostly procedural and decrease over time. Procedural complications have been declining as physicians gain more experience with implantation. By contrast, OAC therapy continues to have fairly constant or even increasing bleeding complication rates over time.

Dr. Wazni said that, in his practice, many patients who need an alternative to OAC therapy, and in whom he's performed LAAC, express a great deal of gratitude – not just because their risk of stroke and bleeding is reduced, but because they don't have to deal with problems associated with daily OAC therapy such as going to the emergency room because of blood in their stool or getting a blood transfusion. He noted that, in his experience, patients with the implanted device make fewer demands on the health system (e.g., go to the hospital and emergency department less often).

Dr. Ning also noted that, in addition to the frail older patients with high fall risk, many physically active patients have difficulty adhering with OAC therapy, and are thankful for the improved QoL that LAAC provides.

Dr. Wazni cited data from a retrospective analysis of data on 100 patients with CHADSVASC \geq 5 treated at his center who were at high risk for bleeds. The observed risk of stroke after more than one year of follow-up after implantation of a WATCHMAN device was 2.8%. In this high-risk population, the calculated stroke risk would have been 12.8% with no treatment and 4.4% with warfarin treatment. His center has implanted more than 300 of the devices with no short- or long-term major complications.

Dr. Ezekowitz noted similar, positive anecdotal results with more than 135 implantations of the WATCHMAN device at his center.

Conclusion: A turning point in practice

For the last 60 years, OAC therapy to reduce the risk of stroke has been considered a standard of care for physicians treating patients with AF. But that therapy isn't without its costs and consequences—financial, physical, and emotional.

The increasing success with LAAC device implantation may represent a turning point in medical practice for reducing stroke risk in AF patients. As noted by Dr. Wazni, the success with the WATCHMAN device has prompted his center to rethink its treatment strategy, for example, offering the device to an appropriate patient before they have a major bleed rather than waiting until after a major bleed has occurred. Dr. Ezekowitz noted that the growing technical expertise and success of placing the WATCHMAN device are making it a viable mainstream option.

Patient preference should be a prominent consideration when choosing a stroke risk reduction strategy. When physicians consider the patient's preference along with medical and treatment history, lifestyle, and occupation, they often find that LAAC device implantation can be an alternative option to provide effective stroke risk reduction with fewer emotional and financial consequences.

Indications for use

The WATCHMAN Device is indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on CHADS₂ or CHA₂DS₂-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

The WATCHMAN Access System is intended to provide vascular and transseptal access for all WATCHMAN Left Atrial Appendage Closure Devices with Delivery Systems.

Contraindications

Do not use the WATCHMAN Device if:

- Intracardiac thrombus is visualized by echocardiographic imaging.
- An atrial septal defect repair or closure device or a patent foramen ovale repair or closure device is present.
- The LAA anatomy will not accommodate a device. See Table 46 in the DFU.
- Any of the customary contraindications for other percutaneous catheterization procedures (e.g., patient size too small to accommodate TEE probe or required catheters) or conditions (e.g., active infection, bleeding disorder) are present.
- There are contraindications to the use of warfarin, aspirin, or clopidogrel.
- The patient has a known hypersensitivity to any portion of the device material or the individual components (see Device Description section) such that the use of the WATCHMAN Device is contraindicated.

Warnings

- Device selection should be based on accurate LAA measurements obtained using fluoro and ultrasound guidance (TEE recommended) in multiple angles (e.g., 0°, 45°, 90°, 135°).
- Do not release the WATCHMAN Device from the core wire if the device does not meet all release criteria.
- If thrombus is observed on the device, warfarin therapy is recommended until resolution of thrombus is demonstrated by TEE.
- The potential for device embolization exists with cardioversion <30 days following device implantation. Verify device position post-cardioversion during this period.
- Administer appropriate endocarditis prophylaxis for 6 months following device implantation. The decision to continue endocarditis prophylaxis beyond 6 months is at physician discretion.
- For single use only. Do not reuse, reprocess, or resterilize.

Precautions

- The safety and effectiveness (and benefit-risk profile) of the WATCHMAN Device has not been established in patients for whom long-term anticoagulation is determined to be contraindicated.
- The LAA is a thin-walled structure. Use caution when accessing the LAA and deploying the device.
- Use caution when introducing the WATCHMAN Access System to prevent damage to cardiac structures.
- Use caution when introducing the Delivery System to prevent damage to cardiac structures.
- To prevent damage to the Delivery Catheter or device, do not allow the WATCHMAN Device to protrude beyond the distal tip of the Delivery Catheter when inserting the Delivery System into the Access Sheath.
- If using a power injector, the maximum pressure should not exceed 100 psi.

- In view of the concerns that were raised by the RE-ALIGN study of dabigatran in the presence of prosthetic mechanical heart valves, caution should be used when prescribing oral anticoagulants other than warfarin in patients treated with the WATCHMAN Device. The WATCHMAN Device has only been evaluated with the use of warfarin post-device implantation.

ADVERSE EVENTS

Potential adverse events (in alphabetical order) which may be associated with the use of a left atrial appendage closure device or implantation procedure include but are not limited to:

Air embolism, Airway trauma, Allergic reaction to contrast media/medications or device materials, Altered mental status, Anemia requiring transfusion, Anesthesia risks, Angina, Anoxic encephalopathy, Arrhythmias, Atrial septal defect, AV fistula, Bruising, hematoma or seroma, Cardiac perforation, Chest pain/discomfort, Confusion post procedure, Congestive heart failure, Contrast related nephropathy, Cranial bleed, Decreased hemoglobin, Deep vein thrombosis, Death, Device embolism, Device fracture, Device thrombosis, Edema, Excessive bleeding, Fever, Groin pain, Groin puncture bleed, Hematuria, Hemoptysis, Hypotension, Hypoxia, Improper wound healing, Inability to reposition, recapture, or retrieve the device, Infection / pneumonia, Interatrial septum thrombus, Intratracheal bleeding, Major bleeding requiring transfusion, Misplacement of the device / improper seal of the appendage / movement of device from appendage wall, Myocardia erosion, Nausea, Oral bleeding, Pericardial effusion / tamponade, Pleural effusion, Prolonged bleeding from a laceration, Pseudoaneurysm, Pulmonary edema, Renal failure, Respiratory insufficiency / failure, Surgical removal of the device, Stroke - Ischemic, Stroke - Hemorrhagic, Systemic embolism, TEE complications (throat pain, bleeding, esophageal trauma), Thrombocytopenia, Thrombosis, Transient ischemic attack (TIA), Valvular damage, Vasovagal reactions

There may be other potential adverse events that are unforeseen at this time.

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CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician. Rx only. Prior to use, please see the complete "Directions for Use" for more information on Indications, Contraindications, Warnings, Precautions, Adverse Events, and Operator's Instructions.

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Table: Representative AF cost ranges from 7 individual reports based on real-world medical claims databases²⁹⁻³⁵**Please note:**

- Since individual studies report different cost categories and subcategories, cost ranges may not add up to subtotals and totals shown
- Cost categories with only one value (not a range) mean only one study was found reporting that cost category

OUTCOMES	COSTS (US DOLLARS)							
	APIXABAN		DABIGATRAM		RIVAROXABAN		WARFARIN	
	Costs PFFY (extrapolated)	10-year Costs (extrapolated)	Costs PFFY (extrapolated)	10-year Costs (extrapolated)	Costs PFFY (extrapolated)	10-year Costs (extrapolated)	Costs PFFY (extrapolated)	10-year Costs (extrapolated)
Total medical cost (inpatient + outpatient)	17,983 - 39,120	179,810 - 391,200	19,195 - 42,648	191,950 - 426,480	38,220 - 47,795	382,200 - 477,960	19,815 - 52,380	198,150 - 523,800
• Inpatient	8,327 - 16,092	83,270 - 160,320	11,128 - 18,060	111,280 - 180,600	14,844 - 22,344	148,440 - 223,440	11,644 - 22,212	116,440 - 222,120
• Outpatient visits	8,655 - 23,376	86,550 - 233,760	4,752 - 24,588	47,520 - 245,880	23,376 - 25,452	233,760 - 254,520	4,344 - 30,168	43,440 - 301,680
o Physician office visits	2,150 -	21,500 -	2,384 - 3,384	23,840 - 33,840			2,358 - 3,468	23,580 - 34,680
o ER visits	854 -	8,640 -	464 - 852	4,640 - 8,520			912 - 1,155	9,120 - 11,550
o Outpatient hospital cost	3,782 -	37,820 -					3,525 -	35,150 -
o Other outpatient cost	2,858 -	28,580 -					4,462 -	44,420 -
Total pharmacy costs	5,159 - 8,304	51,590 - 81,040	4,992 - 8,172	49,920 - 81,720	5,232 - 7,740	52,320 - 77,400	2,867 - 5,904	28,670 - 59,040
• AF - related pharmacy			384 -	3,840 -			240 -	2,400 -
• Other pharmacy			5,076 -	50,760 -			3,696 -	36,960 -
RANGE OF TOTAL COSTS, PFFY	23,140 - 47,424		25,722 - 52,355		44,943 - 57,027		22,682 - 58,284	
RANGE OF TOTAL COSTS, PFFY10Y		231,400 - 474,240		257,224 - 523,554		440,434 - 570,274		226,820 - 582,840

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