LAA closure for stroke prophylaxis in atrial fibrillation

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Is oral anticoagulation the right treatment for stroke prevention in all atrial fibrillation patients?

Internationally renowned expert in atrial fibrillation John Camm (St George’s University of London, UK) discusses current anticoagulation use for stroke prevention in patients with atrial fibrillation and shares his views regarding interventional treatment with left atrial appendage closure.

According to current data, which atrial fibrillation patients benefit the most from oral anticoagulation treatment?

Those patients who are at increased risk for a stroke. Systemic embolism is also a problem, which is helped by anticoagulation in patients with atrial fibrillation, but these events are not as common as strokes.

We can identify patients at risk for stroke by using one of several possible scoring schemes. Essentially, they have to have a risk of at least 0.9% per annum of an ischaemic event in order to justify the use of a non-vitamin K oral anticoagulant (NOAC) and a risk of about 1.7% events per year in order to justify the use of a vitamin K antagonist (VKA) such as warfarin. This difference is because more bleeding events—particularly intracerebral—occur with warfarin than with NOACs.

If we use the scoring schemes, they take into account a series of clinical risk factors, particularly age and a previous history of transient ischaemic attack or stroke. It is also possible to find patients at risk of stroke with hypertension, heart failure, vascular disease, diabetes and renal function. In addition, we know that various biomarkers such as troponin and NT-proBNP are also important for stroke risk assessment.

When prescribing anticoagulation treatment, it is also important to analyse bleeding risks. If bleeding risks are very high we should think carefully whether we can reduce the risk by modifying any of these risk factors. For example, we could reduce blood pressure and, therefore, reduce the likelihood of bleeding. We can also make sure that the patient is not taking other drugs that will encourage bleeding such as antiplatelet drugs. Reduction of alcohol intake is also important to improve bleeding risk scores. These are a few things that we can do to reduce the risk and optimise the environment for the use of anticoagulation therapy.

In the overall atrial fibrillation population, what is the percentage of people who are at risk of stroke?

We know that the risk of stroke is five times more common in patients who have atrial fibrillation. If a patient has mitral valve disease as well as atrial fibrillation, we know that their risk of stroke is about 17 to 20 times greater than a person without these conditions. It is difficult to give an absolute percentage because it all depends on the level of risk that you think is appropriate to justify treatment. But if the risk is around 1% per annum, about 85% or more of the patients with atrial fibrillation could be vulnerable to stroke and have some advantage from anticoagulation. Many believe that the
first thing is to consider anticoagulation and then carefully consider if there are any patients who should not be anticoagulated. Patients who may not need anticoagulation are essentially young people with no underlying cardiovascular or renal disease.

To what degree have the non-vitamin K oral anticoagulants overcome the limitations of warfarin?

The limitations of warfarin are mostly related to its drug-to-drug interactions and food-to-drug interactions. Because of these interactions, the lifestyle for patients may change—they have a restrictive diet, for example. Additionally, the patient has to have regular international normalised ratio (INR) tests to work out his/her anticoagulation levels. These regular tests require the patient to go often to the hospital, perhaps travelling many miles from home, and this is another interference with lifestyle that tends to lead to a reduced quality of life.

The NOACs have overcome some of the limitations with warfarin because they do not have food-to-drug interactions and they have relatively few drug-to-drug interactions. NOACs were designed specifically to be given to patients without the need for monitoring. Some say we ought to be thinking of monitoring patients taking NOACs because there are some drug-to-drug interactions, but most do not believe that this is necessary.

If we look at phase 3 of the major clinical trials in the field, we can conclude that patients should be better off taking NOACs instead of warfarin, as patients are less likely (50% reduction) of having an intracranial bleed, which is the most serious complication of treatment with warfarin and for that matter any anticoagulant. In addition, the total number of strokes or systemic emboli with some of the NOACs seem to be less than with warfarin. Finally, if we look at all our experience with NOACs, people live longer if they are taking them and have a greater net clinical benefit. If you add together all the really serious events—death, life threatening bleeding, intracerebral haemorrhage and disabling stroke—treatment with NOACs beats treatment with VKAs. Additionally, there is no need for monitoring so the quality of life increases.

What limitations exist for the widespread use of NOACs?

There are various limitations. Firstly, NOACs are not yet approved in every country so that process is still ongoing. Secondly, NOAC therapy is more expensive than treatment with warfarin. However, cost-effective analyses have shown that treatment with NOACs reduces healthcare expenditure in the long-term compared with VKA treatment. However, the impact of very high charges to prescribe a NOAC is currently not immediately offset by long-term savings; therefore, some healthcare systems find it difficult to immediately accept the increased cost of NOAC therapy, so for that reason many restrictions have been put on place in various countries to limit the use of NOAC therapy.

Another interesting reason is that some patients much prefer to have their INR measured and to know that they have been accurately treated, similarly, some doctors have this preference. Nevertheless, things have improved. If we look at registries that have been tracking the use of NOAC therapy we can see that from 2010, at a global level, there was about 4% use of NOAC therapy in people who were anticoagulated and were at risk of thromboembolism, and in 2015 the percentage went up to 37%. The total number of anticoagulated patients has increased from 51% to 71%.

What is your view regarding alternative methods such as left atrial appendage (LAA) closure for stroke prevention in atrial fibrillation patients?

Anticoagulation is not appropriate in patients who are at risk of recurrent major bleeding—specially intracranial bleeding—because of anticoagulant use. However, these patients may be at very high risk of another ischaemic event if the anticoagulant is removed. These patients may be considered for some interventional approaches to reduce the likelihood of stroke. One of these interventional approaches is the left atrial appendage closure device, which is inserted transvenously into the left atrial appendage. Other techniques involve clipping the atrial appendage via a thoracoscopy, for example, or excising it using minimal thoracotomy. All of these methods are designed to take away the left atrial appendage where approximately 90% of the atrial thrombi forms. We have very extensive studies, both registries and randomised studies with left atrial appendage closure suggesting that there are some definite indications for its use, so it is very important in people who have bleeds with anticoagulants that cannot be managed successfully, otherwise.

There are some other cases in which despite successful anticoagulation people still have systemic strokes. Part of the reason may be poor patient’s adherence to the anticoagulant drug regimen. NOACs have short-half-lives, which means patients have to take the drug everyday according to prescription, otherwise they are at risk of stroke. If they fail to do that or stop the drug because they cannot longer pay for it, then perhaps in those patients an intervention like left atrial appendage closure, excision or clipping may be the best option.
LAA closure with the WATCHMAN™ device:
A clinically proven treatment

Non-vitamin K antagonist oral anticoagulants have overcome some of the limitations associated with vitamin K antagonists (eg, warfarin), such as food-to-drug interactions, but not all. Therefore, alternatives to oral anticoagulation are still needed, and percutaneous closure of the left atrial appendage (LAA) has emerged as a non-pharmacological approach to reducing the risk of stroke for patients with atrial fibrillation. Cardiovascular News reviews the available clinical data for the most well-known and well-studied LAA closure device: WATCHMAN™ (Boston Scientific).

David Holmes (Department of Cardiovascular Diseases, Mayo Clinic College of Medicine, Mayo Clinic and Mayo Foundation, Rochester, USA) says that there are a “large number” of patients with atrial fibrillation who are at increased risk of stroke “who either cannot or choose not to take anticoagulation”. He adds that a recent study indicated that about 50% of patients with the highest risk of stroke (CHA2DS2-VASc score exceeding 4) do not receive oral anticoagulation.

According to Holmes, a high risk of bleeding is a key reason why a patient might not be prescribed oral anticoagulation. For example, he comments, they could have “a history of gastrointestinal bleeding or other problems associated with bleeding”.

A history of non-adherence to drug regimens can also be why a patient may not be a suitable candidate for oral anticoagulation. Holmes notes: “Some patients are just not going to take the drug; no matter what they tell you.” He adds that patients who do not adhere to drug regimens range from those with dementia, who may only remember to “take the drug every other day when they should be taking it every day”, to those who just “get busy doing other things”.

Therefore, for these patients, WATCHMAN™ may be a suitable alternative to oral anticoagulation. The device is CE-mark approved and is the only FDA approved device for the prevention of stroke in patients with non-valvular atrial fibrillation who have an increased risk for stroke and systemic embolism (based on their CHA2DS2-VASc scores) and who are eligible for anticoagulation therapy. It is also used around the world for patients who have a contraindication to anticoagulation therapy.

Reddy et al report that WATCHMAN™ consists of a self-expanding, nitinol frame with fixation barbs and a permeable, polyester fabric covering. They add that transoesophageal echocardiography is used to guide the delivery of the device and that the imaging modality is also, alongside angiography, used to verify the proper position and the stability of the device.

Clinical data
Several studies have now shown that the device is non-inferior to warfarin in terms of stroke prevention. In the randomised control trial (RCT) PROTECT AF, after 1,558 patient years of follow up (mean 2.3±1.1 years), the rate of the composite primary efficacy endpoint—including stroke, systemic embolism, and cardiovascular death—was 3% in patients (463) who were randomised to undergo LAA closure with WATCHMAN™ vs. 4.3% for patients (244) randomised to receive warfarin (percent per 100 patient years). Study investigators Reddy et al (including Holmes) report that this finding “met the criteria for non-inferiority (probability of non-inferiority >0.999). Furthermore, after 2,621 patient years of follow-up (3.8 years), the rate of the primary endpoint was 8.4% for patients who received WATCHMAN™ compared with 13.9% for patients who received warfarin—meeting both the criteria for non-inferiority (posterior probability >99.9%) and for superiority (posterior probability 96%). This longer follow-up also showed, Reddy et al report, that “patients in the device group demonstrated lower rates of both cardiovascular mortality (60% lower) and all-cause mortality (34% lower)”.

These data are supported by the PREVAIL RCT, which Holmes says was conducted to further evaluate the safety and efficacy of the LAA closure approach with WATCHMAN™ (for stroke prevention), and the inclusion criteria of PREVAIL was also made stricter than that of PROTECT AF”. In PREVAIL, of which Holmes was the principal investigator, WATCHMAN™ was non-inferior to chronic warfarin for the prevention of stroke and systemic embolism beginning one week after randomisation and the primary efficacy endpoint (composite of stroke, systemic embolism and cardiovascular/unexplained death) of early and late events was similar and did not achieve non-inferiority with the WATCHMAN™ device. Holmes et al
LAA closure for stroke prophylaxis in atrial fibrillation

The **WATCHMAN™** device in clinical practice

Randomised controlled trial data for percutaneous closure of the left atrial appendage (LAA) with **WATCHMAN™** (Boston Scientific) indicate that, in patients with atrial fibrillation at increased risk for stroke, the device is non-inferior to warfarin in terms of stroke prevention. Further data have come from the real-world **EWOLUTION** prospective registry, which found that the rate of serious adverse events within the first seven days of **WATCHMAN™** being implanted was 2.8%—a lower rate than reported in the clinical trials.

The randomised controlled trials—**PROTECT AF**1 and **PREVAIL**2—that assessed the safety and efficacy of **WATCHMAN™** focused on patients who were eligible for treatment with warfarin. But Martin Bergmann (Cardiologicum Hamburg, Hamburg, Germany) believes that the device is a suitable treatment for the “many patients” who cannot take oral anticoagulation (including non-vitamin K antagonist oral anticoagulants or NOACs) because of concomitant medication or comorbidities.

He adds that this is where percutaneous closure of the LAA “belongs”, noting that low doses of NOACs in patients who are unable to tolerate a full dose have been found to be “ineffective”.

According to Bergmann, given that the randomised controlled trials have shown **WATCHMAN™** to be safe and effective for stroke prevention in patients with atrial fibrillation, there is “no reason to believe” more randomised controlled trials will be conducted—particularly for the patients who cannot take oral anticoagulation.

Therefore, he says: “Only real-life studies will show us the risks and benefits of using the device in this population.”

**EWOLUTION**

One such real-life study is the **EWOLUTION** prospective registry,3 of which Bergmann is a contributor.

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**Key points**

- Despite the advent of non-vitamin K antagonist oral anticoagulants, there is still a need for alternative approaches to reducing the risk of stroke in patients with atrial fibrillation.
- **PROTECT AF** found that **WATCHMAN™** is non-inferior to warfarin in terms of preventing stroke.
- Extended follow-up of **PROTECT AF** suggests **WATCHMAN™** is superior to warfarin for the prevention of a composite endpoint of stroke, systemic embolism, and cardiovascular death.
- **PREVAIL** supported the findings of **PROTECT AF** that **WATCHMAN™** is non-inferior to warfarin regarding the prevention of stroke or systemic embolisation (seven days after implantation).
- **WATCHMAN™**, compared with warfarin, may reduce the risk of bleeding (after the procedural period) and is associated with favourable quality of life.

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References

Steering committee member (heading the interventional part). It was started two years ago to provide real-life data for the periprocedural risks associated with implanting WATCHMAN™, looking at if these risks differ between centres experienced at implanting WATCHMAN™ and centres with less experience. Bergmann states that another aim is to compare the periprocedural risks observed in the registry with that seen in the randomised controlled trials.

In this prospective, multicentre registry, more than 1,000 patients were enrolled at 47 centres from 13 countries. Bergmann says enrolment finished in May 2015—“several months earlier than planned”—because the recruitment process was “quite fast”. Boersma et al, reporting on the 30-day outcomes of patients in the registry (in the European Heart Journal), state that 60% of the patients were male, the mean age was 73 years, and the average CHA2DS2VASc score was 4.5±1.6 (ie, a high risk of stroke). They add: “All patients had a sufficiently high risk for stroke to warrant the use oral anticoagulation therapy. However, 62% of patients were deemed unsuitable for oral anticoagulation therapy by their physician, based on factors such as comorbidities, the inability to adhere to oral anticoagulation therapy, bleeding history or high bleeding risk.” Furthermore, “nearly one third” of patients had a history of major bleeding and 40% had a HAS-BLED score of three.

Boersma et al comment that the device was “successfully deployed” in 1,004 of 1,018 patients (98.5%) enrolled in the registry “comparing favourably with previously reported rates in other WATCHMAN™ trials”. The rate of device-related serious adverse events (SAE) within the first seven days of the implantation procedure was 2.8%, which the authors note “is lower than in any of the prior WATCHMAN™ LAA closure trials”. Of 31 SAEs that occurred within one day of the procedure, all but one were “managed effectively with complete recovery of the patient”. At 30 days, the rate of total SAEs was 7.9% with the rate of procedure and/or device-related events being 3.6%.

“The incidence of serious adverse events through seven or 30 days (whether or not related to the procedure) did not appear to be related to CHADS, or CHA2DS2VASc scores, nor was it generally different for patients on oral anticoagulation therapy after implant vs. patients not on oral anticoagulation after implant,” Boersma et al write. However, they add that the rate of serious adverse events was “significantly lower” for patients ineligible for oral anticoagulation therapy compared with those eligible for such therapy (6.5% vs. 10.2%, respectively; p=0.042). They conclude: “The WATCHMAN™ device has a high success rate of LAA closure with low periprocedural risk, even in patients with more comorbidities and higher risk for stroke and bleeding.”

Bergmann says these periprocedural data “are very important” because in the randomised controlled trials, “the periprocedural risk was a little bit high, so we wondered if all of the training that has taken place and the experience of some of the centres would mean that this risk would come down. Indeed, we did find the risk to be much lower than previously shown.” Boersma et al do state in the EWOLUTION registry, “all implanting physicians underwent thorough training and certification programme to ensure an appropriate level of experience in order to minimise patient risk.”

### Three-month data

Presenting the three-month outcome data from EWOLUTION at the 2016 EuroPCR meeting (17–20 May, Paris, France), Bergmann reported that successful procedural closure of the LAA with no or minimal residual flow (≤5 mm assessed via periprocedural transoesophageal echo, TEE) was achieved in 98.9% at first follow-up and that the rate of device/procedure-related SAE was 4.4%. He also noted that 4.1% of patients with device/procedure-related SAE or unknown “fully recovered”. Only 0.5% of the device/procedure related events or unknown proved to be fatal (compared with 2.7% of the unrelated events): “There was a low rate of periprocedural events despite the high-risk, mostly ineligible for oral anticoagulation patient population. Centres with less experience had similar high success rates with low complications compared to more experienced centres,” Bergmann commented. He added: “Most importantly, EWOLUTION found that dual antiplatelet therapy was safe after WATCHMAN™ implantation. There was no increase in stroke or thrombus at the device after three months with >80% of patients having documented TEE follow-up. No late gaps!”

Additionally, NOAC therapy for the first three months “appears to be an option”, with Bergmann noting that there was a very low rate of bleeding and stroke, and no thrombus on the device, in patients who received NOACs. After three months, all patients were switched to aspirin.

### Key points

- According to the 30-day outcome data from EWOLUTION, the WATCHMAN™ device is associated with a high success rate of LAA closure with low periprocedural risk, even in patients with more comorbidities and higher risk for stroke and bleeding.
- The three-month data show that centres with less experience had similar high success rates with low complications compared to more experienced centres and that DAPT therapy and NOACs are feasible and safe.

### Implications for the future

Bergmann says that the available data from EWOLUTION “will and should have a huge impact” on clinical practice, explaining that there were uncertainties about the use of WATCHMAN™ in patients who have “relative contraindications to anticoagulation”. He adds that the European Society of Cardiology (ESC) gives percutaneous LAA occlusion in patients with contraindications for long-term oral anticoagulation a Class Ib Level of Evidence B recommendation (ie, may be considered). Therefore, data from EWOLUTION may help to strengthen this recommendation in future versions of the guidelines—the ESC is due to revise its guidelines for the management of atrial fibrillation later this year. “With the EWOLUTION registry, we can confirm to all those that have been sceptical about WATCHMAN™ that, at three months, it is very safe and it is not associated with major bleeding issues. So, WATCHMAN™ can be considered for all patients who are not eligible for full-dose oral anticoagulation therapy,” Bergmann states.

Further data from EWOLUTION, he says, will explore the rate of stroke with WATCHMAN™ as compared with the rate observed in the studies. “We also hope to have country-specific analysis to determine if they have similar outcome data to the overall findings. There is a vast array of questions in the field that needs addressing. For example, is it safe to combine WATCHMAN™ implantation procedures with procedures such as transcatheter aortic valve implantation (TAVI)?”

### References

Exploring the benefits of LAA closure as a minimally invasive procedure

Left atrial appendage closure (LAA) with the WATCHMAN™ device is a one-time minimally invasive implant procedure, usually performed by a heart team including electrophysiologists, interventional cardiologists and transoesophageal echocardiographers in a cardiac cath lab or electrophysiology suit. The procedure, which requires transfemoral access, can take less than an hour and one-day hospital stay. Electrophysiologist Timothy Betts (John Radcliffe Hospital Oxford University Hospitals NHS Trust, Oxford, UK) discusses the procedure in detail.

Why do both electrophysiologists and interventional cardiologists have the skills and experience to implant the WATCHMAN™ device?

Working together and sharing expertise is the best way to start a left atrial appendage closure programme. In time, as new skills are learned, this may not always be necessary. The third team member—the transoesophageal echocardiographer—should not be forgotten. High quality periprocedure imaging is just as important as manual skills.

In your experience, how long does the WATCHMAN™ procedure take?

Once the learning curve is overcome, a typical procedure takes less than 60 minutes (sometimes less than 30 minutes) from the point at which venous access is gained. There is of course the additional time required to induce and recover from general anaesthesia or deep sedation.

After undergoing a procedure to receive the WATCHMAN™ device, how long is a patient in hospital?

We still keep people in for one night afterwards, but this is often because they are elderly and have travelled a long way. I am sure many could be done as a day-case procedure.

During the recovery period in hospital, what are the key priorities when monitoring the patient?

The usual monitoring of the femoral vein puncture site—as with any interventional procedures—is the priority. We also monitor vital signs to look for rare complications such as a late presentation of pericardial effusion, but in my experience this is less than 1% of patients. The recovery period is usually quick and uncomplicated.

After hospital, how frequently should the patient be followed-up?

Conventionally, patients are seen at six to eight weeks. A transoesophageal echocardiogram is done to check whether the device remains in place, has sealed the appendage and there is no thrombus on the surface. Significant leaks are fortunately very rare, less than one in 50 patients. Thrombus may be seen in one out of 25–30 patients. It almost never results in an adverse event, but most would treat with a short course of anticoagulation (or extending the use of periprocedure anticoagulation). The sixth-week transoesophageal echo is largely historical, coming from clinical trial protocols, but I still think it is a good way to monitor and audit the effectiveness of this novel technology. The sixth-week visit also allows the reduction or cessation of periprocedure antiplatelet or anticoagulant therapy.

What are the key priorities when monitoring the patient postdischarge?

As mentioned above—it is important to check whether the device remains in place (late embolisation of a WATCHMAN™ occurs in well under 0.5% of patients), if there is a good seal, with no large peri-device leaks and no device-related thrombus, so antiplatelets or anticoagulants can be reduced and/or stopped.

Which specialists should be involved in the follow-up?

The implanter and the imaging specialist.

Selecting the right patient for percutaneous LAA closure with WATCHMAN™

Gilles Montalescot (Institut de Cardiologie, Centre Hospitalier Universitaire Pitié-Salpêtrière (AP-HP), Paris, France) discusses which patients would benefit the most from undergoing LAA occlusion with WATCHMAN™.

How many patients with atrial fibrillation cannot take oral anticoagulation?

It is difficult to say exactly because the figure is changing. Some patients have contraindications or are not suitable for warfarin, but can be treated with the non-vitamin K antagonist oral anticoagulants (NOACs). Other patients receive aspirin instead of warfarin; according to the AVERROES trial, such patients would be eligible for apixaban (Eliquis, Bristol-Myers Squibb) at least. In real life, according to registry data, half of...
Richard Yates, a 70-year-old retired businessman from Great Missenden (UK), has had atrial fibrillation for almost 20 years and was well-controlled on warfarin for 14 years. However, he had to stop taking warfarin after he suffered a haematoma in his left leg in 2011; meaning he was no longer protected against the risk of stroke. He explains how undergoing left atrial appendage closure with the WATCHMAN™ device has made him feel more confident.

“I am not worried about having a stroke now that I have had a WATCHMAN™ fitted”