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Horizon scanning technology Prioritising summary

WATCHMAN® left atrial appendage closure device



**Australian
Safety
and Efficacy
Register
of New
Interventional
Procedures -
Surgical**

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Enquiries about the content of the report should be directed to:

HealthPACT Secretariat
Department of Health and Ageing
MDP 106
GPO Box 9848
Canberra ACT 2606
AUSTRALIA

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This Horizon scanning prioritising summary was prepared by Mrs Deanne Forel from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).

PRIORITISING SUMMARY

REGISTER ID

S000121

NAME OF TECHNOLOGY

WATCHMAN® LEFT ATRIAL APPENDAGE CLOSURE DEVICE

PURPOSE AND TARGET GROUP

TO PREVENT CARDIOEMBOLIC STROKE IN PATIENTS WITH ATRIAL FIBRILLATION WHO ARE ELIGIBLE FOR ANTICOAGULATION THERAPY

STAGE OF DEVELOPMENT (IN AUSTRALIA)

- | | |
|--|---|
| <input type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input checked="" type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | | |
|---|-------------|---------------|
| <input checked="" type="checkbox"/> Yes | ARTG number | 167176 |
| <input type="checkbox"/> No | | |
| <input type="checkbox"/> Not applicable | | |

INTERNATIONAL UTILISATION

COUNTRY	LEVEL OF USE		
	Trials underway or completed	Limited use	Widely diffused
United States	✓		
United Kingdom		✓	
Germany			✓

IMPACT SUMMARY

The Watchman left atrial appendage closure device is used to isolate the left atrial appendage of the heart from circulation, to reduce the risk of stroke in patients with atrial fibrillation. The left atrial appendage is the origin of 90% to 100% of stroke-causing thromboemboli in patients diagnosed with paroxysmal, persistent or permanent non-valvular atrial fibrillation.

BACKGROUND

Atrial fibrillation (AF) describes an irregular and often rapid heart rhythm. AF is the most common sustained arrhythmia (abnormal electrical activity in the heart), and is associated with increased cardiovascular morbidity and mortality, the most devastating of which is preventable stroke (Medi et al 2007; Holmes and Fountain 2009). The incidence of AF increases with age, with approximately 8% of people older than 80 years suffering from the condition (Medi et al 2007). AF can be classified as:

- paroxysmal, where the condition is self-terminating (i.e. the abnormal electrical signals and rapid heart rate begin suddenly and then stop on their own) and symptoms may be mild or severe and last for seconds, minutes, hours or days (however, usually less than 24 hours)
- persistent, where the abnormal heart rhythm continues until it is stopped with treatment
- permanent, where the heart's normal rhythm cannot be restored with the usual treatments. Both paroxysmal and persistent AF may become more frequent and result in permanent AF over time (National Heart, Lung and Blood Institute 2009).

In the past, AF has been considered a relatively benign condition by the medical community; however, numerous studies have found AF to be strongly linked with stroke (Wolf and Singer 1997). Patients with AF are five times more likely to suffer from stroke than healthy individuals (Singh and Holmes 2010). One study in particular found 15% of patients suffering from stroke had AF (Wolf and Singer 1997). Stroke occurs when blood clots (thrombi) form in the atria, as a result of insufficient pumping due to AF, and travel to the brain. A thrombus that forms in one part of the body (in this case the heart) and travels in the bloodstream to another part of the body (in this case the brain) is known as an embolus (National Heart, Lung and Blood Institute 2009). When an embolus reaches the brain, blood flow is interrupted, resulting in the death of brain cells and impaired function of brain tissue in a portion of the brain due to oxygen and nutrient starvation; this is known as ischaemic stroke (National Heart, Lung and Blood Institute 2009).

Echocardiographic, surgical and postmortem studies have demonstrated that 90% to 100% of thrombi form in the left atrial appendage (LAA) in AF patients (Sievert et al 2002). The LAA is a small multilobed structure of the left atrium, located between the left upper pulmonary vein and the left ventricle (it is remnant of the embryonic left atrium) (Bayard et al 2005). The anatomy of the LAA is variable (with 80% of the population's LAA consisting of two or more lobes) (Bayard et al 2005); it is made from muscular tissue with trabeculated pectinate muscle tendons forming crypts (Singh and Holmes 2010). In healthy individuals, besides the production of atrial natriuretic peptide, the LAA plays a minor role (Bayard et al 2005). The location of the LAA is seen below in Figure 1.

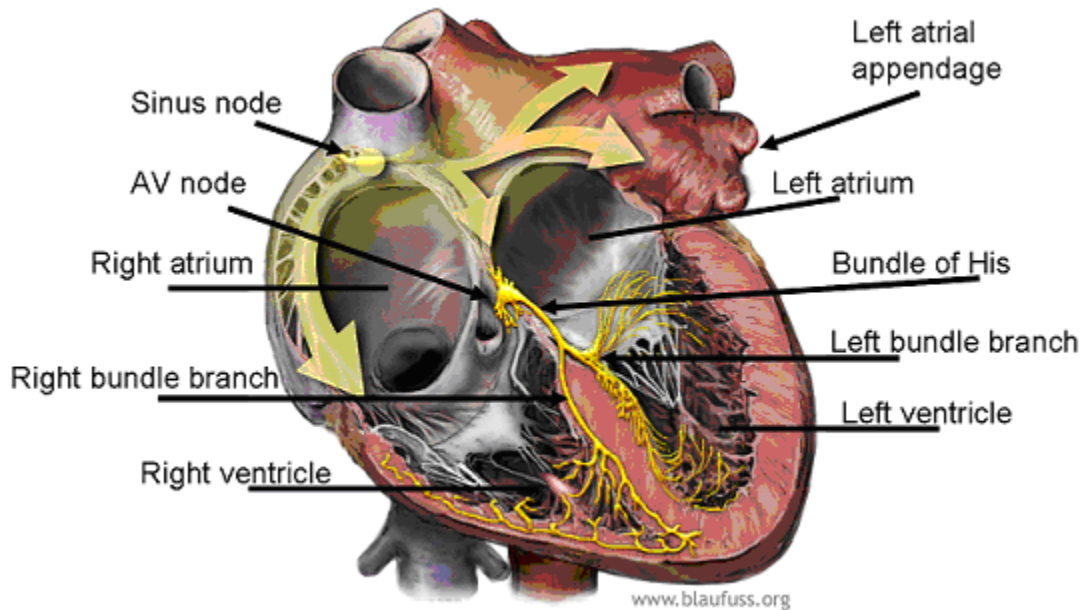


Figure 1: Structure of the heart, with normal electrical activity. The yellow arrows represent normal electrical signals originating in the sinus node and propagating through both the right and left atria. When this electrical activity is compromised, as in patients with AF, blood is not pumped correctly from the atria to the ventricle resulting in the pooling of blood in the atria, where thrombi may form (Source: www.blaufuss.org).

Common stroke prevention techniques include pharmacological approaches, involving drugs such as warfarin, antithrombins, and antiplatelet medications. The current gold standard in pharmacological stroke prevention is anticoagulation therapy using the drug warfarin (Sievert et al 2002). The success rate of warfarin for the prevention of thromboembolic events has been reported at 70% (Ostermayer et al 2003). The disadvantages of warfarin usage can be attributed to its narrow therapeutic index, that is, the dosage range for effective and safe warfarin treatment is small. An overdose of warfarin can lead to haemorrhage and an insufficient dose can lead to the formation of fatal blood clots. Warfarin also interacts with a wide range of drugs which may lead to an adverse drug interaction. These factors, along with the inconvenience of frequent dose monitoring/adjustments and the restrictions on diet and alcohol intake associated with warfarin use, may contribute to its estimated 38% discontinuation rate per year (Wrigley and Lip 2009).

Alternatives to warfarin treatment, including surgical techniques where the LAA is isolated from systemic circulation, have been developed with the aim of reducing the incidence of stroke in high-risk AF patients. The concept of excluding the LAA from circulation in patients with AF is somewhat established. Surgery for rheumatic mitral valve disease, which is often accompanied by AF, routinely incorporates LAA amputation or oversewing of its orifice to minimise the risk of future thromboembolism (Block 2007). Minimally invasive transthoracic techniques have also been applied to occlude the orifice of the LAA; however, the outcomes of these procedures have been mixed, with persistent flow through the LAA seen in some patients upon

echocardiographic follow-up (Block 2007). Most recently, percutaneous transcatheter devices to occlude the LAA have emerged. All device-related approaches have similar device deployment methodology, involving standard transseptal puncture for left atrial access and advancement of a sheath to the LAA orifice followed by insertion of a pigtail catheter (Singh and Holmes 2010). Using multiplanar transesophageal echocardiography (TEE) and fluoroscopic guidance the dimensions of the LAA are assessed and an appropriately sized device is positioned in the right atrium (Singh and Holmes 2010). Device-based techniques used for the occlusion of the LAA, in order of their introduction into clinical use, include percutaneous LAA transcatheter occlusion (PLAATO), which despite promising early results was withdrawn by its manufacturer in 2006 (Wrigley and Lip 2009), Watchman LAA occlusion, Amplatzer® septal occlusion (developed to close atrial septal defects but also used for LAA occlusion), and Amplatzer cardiac plugs, which are versatile occlusion devices also suitable for LAA occlusion (Singh and Holmes 2010).

The Watchman device (Figure 2) specifically is a parachute-shaped device with a self-expanding nitinol frame structure and a permeable polyester membrane over the atrial side with mid-perimeter fixation bars to secure it in the LAA (Singh and Holmes 2010). The device is available in diameters ranging from 21 mm to 33 mm to accommodate the variability in LAA width (Fountain et al 2006). The difference between the Watchman and PLAATO device is that the Watchman device is temporarily permeable to blood (approximately 45 days following implantation until endothelialisation occurs) (Singh and Holmes 2010). Continued conventional thromboembolic prophylaxis (warfarin) therapy for approximately 6 weeks following Watchman implantation is necessary (Singh and Holmes 2010).

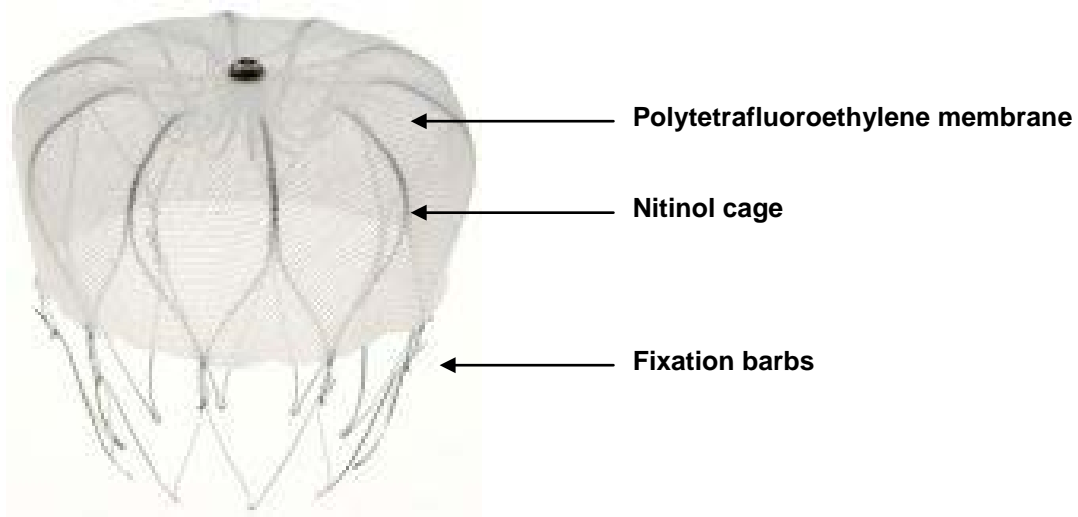


Figure 2: The Watchman LAA Closure Device (Source: Onalan and Crystal 2007)

CLINICAL NEED AND BURDEN OF DISEASE

Approximately 15 million people worldwide suffer from stroke annually (World Health Organization [WHO] 2010). AF causes 15% to 20% of ischaemic strokes and the overall risk of stroke in patients with non-valvular AF is approximately 5% per annum globally (Wrigley and Lip 2009). AF is the number one cause of long-term disability and the third leading cause of death in patients with AF (Singh and Holmes 2010).

In Australia in 2010, approximately 60,000 new and recurrent stroke events will occur, and it is estimated that 120,000 to 220,000 individuals will have a stroke at some point in their lives (National Stroke Foundation 2010). One in five people having a first-ever stroke die within one month and one in three die within a year (National Stroke Foundation 2010). Strokes cost Australia an estimated \$2.14 billion per year (National Stroke Foundation 2010).

DIFFUSION

Percutaneous LAA occlusion was first reported in the clinical arena by Sievert et al in 2002 (Singh and Holmes 2010).

The Watchman LAA Closure Device with Delivery System appeared on the Australian Register of Therapeutic Goods (ARTG) in October 2009 for the purpose of preventing embolisation of thrombi that may form in the appendage of patients with non-valvular AF to prevent the occurrence of ischemic stroke and systemic thromboembolism. According to the ARTG, Watchman is indicated for use in patients with non-valvular AF who require treatment for potential thrombus formation and are eligible for warfarin therapy (Therapeutic Goods Administration [TGA] 2010). The Watchman device received CE Mark approval in May of 2009 and has been commercially available in Europe and Asia Pacific since mid-2009. In April 2009, the device received a positive vote from the US Food and Drug Administration (FDA's) Circulatory Panel; however, the FDA subsequently requested a confirmatory study be conducted to further validate the available data; this study (PREVAIL) is currently enrolling patients in the US (Atritech Inc 2010).

The Amplatzer septal occluder (ARTG number 134067) and cardiac plug (ARTG number 162137) received TGA approval on 20 December 2006 and 1 June 2009, respectively. The PLAATO device does not appear on the ARTG, probably due to its withdrawal by the manufacturer in 2006.

COMPARATORS

Anticoagulation therapy with warfarin has long been the cornerstone for decreasing the risk of stroke in patients with AF (Holmes and Fountain 2009). The efficacy of warfarin for stroke prevention has been well established; however, 14% to 44% of patients with AF who are at risk of stroke are ineligible for anticoagulation therapy, mainly owing to the risks of major bleeding and falls (Wrigley and Lip 2009).

Direct comparators of Watchman are other percutaneous transcatheter devices used to occlude the LAA. As previously mentioned, these include PLAATO and Amplatzer occluders and plugs.

SAFETY AND EFFECTIVENESS ISSUES

Two studies were eligible for inclusion in this review. One was a randomised controlled trial (RCT) named the PROTECT AF (Watchman LAA system for embolic protection in patients with AF) study, which was designed to assess the non-inferiority of the Watchman device against chronic warfarin therapy (Holmes et al 2009). The other was a case series study assessing the feasibility of implanting Watchman in the LAA of patients with AF to prevent thromboembolic stroke (Sick et al 2007).

Study profile

The prospective RCT reported by Holmes et al (2009) was undertaken at 59 sites in the United States and Europe between February 2005 and June 2008. Patients with paroxysmal, persistent or permanent non-valvular AF were eligible for enrolment. A total of 463 patients were randomly assigned to the intervention (Watchman) group and 244 patients were randomly assigned to the control (warfarin) group, using a computer-generated randomisation sequence in a 2:1 ratio (stratified by clinical centre). An independent statistician with no involvement in the design or analysis of the study generated the random sequence. Blinding of patients and clinicians to treatment assignment was not possible and, therefore, did not take place. Following Watchman implantation, patients in the intervention group were treated with warfarin for 45 days to facilitate device endothelialisation. Discontinuation of warfarin therapy took place at 45 days follow-up if TEE showed complete LAA closure or if there was residual peri-device flow of < 5 mm. Patients in the control group received warfarin for the duration of the study. All patients were followed up at 45 days, and at 6, 9 and 12 months and twice a year thereafter. Mean follow-up per patient was 18 months (standard deviation [SD], 10). The composite endpoint for safety consisted of events related to excessive bleeding or procedure-related complications, and for efficacy consisted of the occurrence of all stroke (haemorrhagic or ischemic), cardiovascular or unexplained death, or systemic embolism.

Sick et al (2007) conducted an open-label, non-randomised pilot study to assess the safety and feasibility of the Watchman device. Seventy-five patients with chronic or paroxysmal AF who were eligible for warfarin therapy in 3 cardiology centres in Europe and 4 in the United States were enrolled in this study; these patients were followed up by clinical examination and TEE at 45 days and 6 months post-implantation, with annual clinical follow-up visits up to 5 years thereafter. Mean follow-up was 24 months (SD, 11 months), with 13 patients followed up for more than 4 years, 20 for more than 3 years and 29 for more than 2 years. After treatment of the initial 16 patients, patients were implanted with a revised model¹ of the device with a reinforced delivery cable and a series of barbs to facilitate device attachment and prevent embolisation. All patients were placed on aspirin (indefinitely) and warfarin (for 45 days) post-implantation to keep their therapeutic target international normalised ratio (INR) between 2.0 and 3.0. The primary endpoint of this study was successful implantation of Watchman and successful sealing of the LAA, without major adverse events including death, stroke, systemic embolism or major bleeding requiring invasive treatment or blood transfusion.

¹ Presumably the same model implanted in the RCT by Holmes et al (2009).

Safety

The RCT by Holmes et al (2009) reported a higher rate of primary safety events in the intervention group compared with the control group (rate ratio [RR], 1.69; 95% credible interval [CrI], 1.01–3.19). Most of the complications (27/49 [55%]) occurring in the intervention group occurred on the day of the procedure and most of the complications (8/16 [50%]) occurring in the control group were recorded between 45 days and 1 year follow-up. At 2 years follow-up the cumulative primary safety event rate was 10.2% (95% confidence interval [CI], 7.4–13.0) for the intervention group and 6.8% (95% CI, 3.0–10.6) for the control group. When successfully treated patients were analysed, the primary safety event rate was lower in the intervention group (RR, 0.35; 95% CrI, 0.15–0.80). The most frequent primary safety event encountered in the intervention group was serious pericardial effusion (defined as that requiring percutaneous or surgical drainage), which occurred in 4.8% (22/463) of patients. The need for reintervention in these patients led to an increase in hospitalisation time and it was noted that effusion rate decreased with investigator experience among the 542 patients in whom implantation was attempted. Major bleeding occurred in 3.5% (16/463) of patients in the intervention group and 4.1% (10/244) of patients in the control group. Device embolisation occurred in three patients (all requiring reoperation; one required surgery at the time of the procedure, one was percutaneously snared and a third required a cutdown of the iliac vessel to remove the device) but was not associated with increases in stroke or mortality.

Sick et al (2007) noted a number of complications associated with the first-generation Watchman device in the 16 patients in whom the device was implanted. Of these patients, three had device failure, two of which were device embolisations and one was a delivery system failure (fractured delivery wire). After modification of the delivery system of the Watchman device no further embolisation or delivery failures were encountered (in the remaining 53 patients). Pericardial effusions related to the trans-septal puncture procedure occurred in 2.7% (2/75) of cases overall and there were three cases of major bleeding encountered, two of which were pericardial effusions (as previously reported) and one was an internal bleed due to retrieval after device embolisation. Two additional bleeds with haematomas in the groin, described by the authors as ‘minor’, also occurred; however, both of these required transfusion which may indicate they were major bleeding events.

Effectiveness

In the RCT by Holmes et al (2009) the Watchman device was successfully implanted in 88% (408/463) of patients in the intervention group and in 91% (408/449) of patient in whom implantation was attempted. At 45-day follow-up, 86% (349/408) of patients implanted with Watchman met TEE criteria for warfarin cessation. Ninety-two percent (355/385) of patients met this criterion by 6-month follow-up. In the control group plasma warfarin concentration was in the therapeutic target INR (2.0-3.0) 66% of the time. The primary efficacy event rate was 3% per 100 patient-years (95% CrI, 1.9-4.5) in the intervention group and 4.9% per 100 patient-years (95% CrI, 2.8-7.1) in the control group (RR, 0.62; 95% CrI, 0.35-1.25). The probability of non-inferiority of the intervention was greater than 99.9%. At 2-year follow-up the cumulative event rate for the intervention group was 5.9% (95% CI, 3.1-8.8) compared with 8.3% (95% CI, 4.0-

12.5) for the control group. Exclusion of patients with the lowest risk of thromboembolic events did not affect the results of the primary efficacy analysis. The primary efficacy event rate was 1.9% per 100 patient-years (95% CrI, 1.0-3.2) in successfully treated patients who discontinued warfarin in the intervention group compared with 4.6% per 100 patient-years (95% CrI, 2.6-6.8) in patients in the control group who received warfarin (RR, 0.40; 95% CrI, 0.19-0.91).

Also seen in this RCT was a higher rate of ischaemic stroke in patients in the intervention group compared with the control group. In the intervention group, one patient had a stroke after randomisation but before implantation, and five patients had peri-procedural stroke events (mainly due to air emboli). In the five patients with procedure-related stroke, three had no long-term deficits and two were admitted to nursing homes and subsequently died. Ischaemic stroke after the peri-procedural timeframe occurred in nine patients in the intervention group and six in the control group. Of the patients whose INR measurements were available at the time of their stroke, INR level was found to be subtherapeutic in all cases (in both groups). Two ischaemic strokes were fatal, one in each group, whereas the rate of all ischaemic and haemorrhagic strokes² was lower in the intervention group than the control group. Overall, 83% (5/6) of haemorrhagic strokes in the control group were fatal (all in patients with therapeutic INR levels). Haemorrhagic stroke was fatal in one patient in the intervention group (during the 45-day post-implantation warfarin therapy period).

A total of 21 and 18 patients died in the intervention and control groups, respectively. Death resulted from stroke (n=2 intervention patients versus n=6 control patients), unknown or other cardiovascular causes (n=4 versus n=6) and non-cardiovascular causes (n=15 versus n=6). The cumulative mortality rates for the intervention and control groups were 3.0% (95% CI, 1.3–4.6%) versus 3.1% (95% CI, 0.8–5.4%) at 1 year, and 5.9% (95% CI, 2.8%–8.9%) versus 9.1% (95% CI 4.2–14.1) at 2 years, respectively. No deaths were considered to be associated with the LAA closure device.

In the case series study by Sick et al (2007) successful device deployment occurred in 88% (66/75) of patients and at 45-day follow-up, 93% (54/58) of patients exhibited successful healing of the LAA. No major strokes occurred during the mean 24-month follow-up period, despite more than 90% of patients discontinuing anticoagulation therapy. Two patients experienced a transient ischaemic attack³ (TIA) at 4- and 6-month follow-up, respectively. One of these patients had a history of TIA and did not have thrombus visible on their device at the time of their subsequent attack, and the other patient had a smooth layer of thrombus detected on the surface of their device. Overall, there were two deaths during the follow-up period, one at 9 months due to an ascending aortic dissection (autopsy documented stable, well-endothelialised device with complete LAA occlusion) and the other from non-device related causes.

² Haemorrhagic stroke results from a weakened vessel that ruptures and bleeds into the surrounding brain. The blood accumulates and compresses the surrounding brain tissue.

³ Transient ischaemic attacks ('warning strokes') are caused by clots where the blockage is transient so that there is no permanent injury incurred by the brain.

COST IMPACT

There were no cost-effectiveness studies identified from the retrieved material for the Watchman device. If vascular events, anticoagulation monitoring and hospitalisation time is reduced, it is likely the device will confer cost savings for the treatment of patients with AF.

It has been indicated that the cost of the Watchman device (and delivery system) may range from AU\$8,000 to AU\$20,000. This excludes the procedural costs associated with staff and theatre time (usually 1-2 hours in theatre plus anaesthetist and ultrasound assessment) and hospitalisation costs (usually an overnight stay).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

There were no issues identified from the retrieved material.

OTHER ISSUES

The RCT by Holmes et al (2009) received funding from Atritech (the manufacturer of the Watchman device); however, the sponsor of the study (Atritech) had no role in data analysis, data interpretation or writing of the report.

SUMMARY OF FINDINGS

The rate of primary safety events reported was higher in patients implanted with the Watchman device compared with those receiving warfarin therapy; however, when successfully treated patients were analysed, the primary safety event rate was lower following Watchman implantation. It was noted that the most common adverse event following implantation was pericardial effusion, the occurrence rate of which decreased with surgeon experience. Major bleeding events occurred in more patients receiving warfarin therapy than those implanted with Watchman. Both of the studies included in this summary reported successful Watchman implantation in 88% of patients. Ischaemic stroke occurred in more patients implanted with Watchman than those receiving warfarin, whereas the rate of all stroke events was lower in patients in the Watchman group. The included case series study reported no major stroke events during follow-up. Overall, the probability of non-inferiority of the treatment of AF with the Watchman device was >99.9%.

HEALTHPACT ASSESSMENT

The Watchman device does not appear to be inferior to traditional warfarin therapy in preventing cardioembolic stroke in patients with AF; however, the superiority of either preventative approach cannot be determined at this stage given the lack of high-quality evidence available. Despite this, it is likely the device would only be a viable treatment in patients who were opposed to long-term warfarin therapy. Based on this it is recommended that no further assessment of Watchman is necessary at this time:

- | | |
|--|--|
| <input type="checkbox"/> Horizon Scanning Report | <input type="checkbox"/> Full Health Technology Assessment |
| <input type="checkbox"/> Monitor | <input checked="" type="checkbox"/> Archive |

HEALTHPACT ACTION

NUMBER OF STUDIES INCLUDED

Total number of studies	2
Level II evidence	1
Level IV evidence	1

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SEARCH CRITERIA TO BE USED

((Watchman) OR (Watchman left atrial appendage)) OR ((Left atrial appendage occlusion) OR (Left atrial appendage occluder)) AND (Cardioembolic stroke prevention))

HEALTH PACT DECISION

- | | |
|--|--|
| <input type="checkbox"/> Horizon Scanning Report | <input type="checkbox"/> Full Health Technology Assessment |
| <input type="checkbox"/> Monitor | <input type="checkbox"/> Archive |
| <input type="checkbox"/> Refer | <input type="checkbox"/> Decision pending |

PRIORITY RATING

- High** **Medium** **Low**