Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial

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Lancet 2009; 374: 534–42

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Summary

Background In patients with non-valvular atrial fibrillation, embolic stroke is thought to be associated with left atrial appendage (LAA) thrombi. We assessed the efficacy and safety of percutaneous closure of the LAA for prevention of stroke compared with warfarin treatment in patients with atrial fibrillation.

Methods Adult patients with non-valvular atrial fibrillation were eligible for inclusion in this multicentre, randomised non-inferiority trial if they had at least one of the following: previous stroke or transient ischaemic attack, congestive heart failure, diabetes, hypertension, or were 75 years or older. 707 eligible patients were randomly assigned in a 2:1 ratio by computer-generated randomisation sequence to percutaneous closure of the LAA and subsequent discontinuation of warfarin (intervention; n=463) or to warfarin treatment with a target international normalised ratio between 2·0 and 3·0 (control; n=244). Efficacy was assessed by a primary composite endpoint of stroke, cardiovascular death, and systemic embolism. We selected a one-sided probability criterion of non-inferiority for the intervention of at least 97·5%, by use of a two-fold non-inferiority margin. Serious adverse events that constituted the primary endpoint for safety included major bleeding, pericardial effusion, and device embolisation. Analysis was by intention to treat. This study is registered with Clinicaltrials.gov, number NCT00129545.

Findings At 1065 patient-years of follow-up, the primary efficacy event rate was 3·0 per 100 patient-years (95% credible interval [CrI] 1·9–4·5) in the intervention group and 4·9 per 100 patient-years (2·8–7·1) in the control group (rate ratio [RR] 0·62, 95% CrI 0·35–1·25). The probability of non-inferiority of the intervention was more than 99·9%. Primary safety events were more frequent in the intervention group than in the control group (7·4 per 100 patient-years, 95% CrI 5·5–9·7, *vs* 4·4 per 100 patient-years, 95% CrI 2·5–6·7; RR 1·69, 1·01–3·19).

Interpretation The efficacy of percutaneous closure of the LAA with this device was non-inferior to that of warfarin therapy. Although there was a higher rate of adverse safety events in the intervention group than in the control group, events in the intervention group were mainly a result of periprocedural complications. Closure of the LAA might provide an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with non-valvular atrial fibrillation.

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Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia, affecting an estimated 6 million individuals in the USA.[1] Since atrial fibrillation mainly affects elderly people, its prevalence is expected to increase in parallel with the increasing age of the population, with a predicted 15·9 million cases by 2050.[1–5] The lifetime risk for development of atrial fibrillation is one in four in men and women 40 years of age and older.[6] Stroke, the most serious complication of atrial fibrillation, occurs in 5% of non-anticoagulated patients every year. The risk of stroke increases substantially with age, from 1·5% in individuals aged 50–59 years to 23·5% for those aged 80–89 years.[6–9] Stroke is the third most frequent cause of death in the USA and the leading cause of serious disability. Therefore, stroke prophylaxis is a crucial component of management of atrial fibrillation.

Although membrane-active antiarrhythmic drugs[10–13] and catheter ablation provide symptomatic relief for patients with atrial fibrillation, neither method is sufficiently reliable in preventing thromboembolic events, and long-term oral anticoagulation therapy is recommended irrespective of the rhythm management strategy. Randomised controlled trials have shown that warfarin is effective in preventing stroke, more so than aspirin and combination aspirin-clopidogrel.[14–21] Despite its proven efficacy, warfarin is often not well tolerated by patients, has a very narrow therapeutic range, and has a high risk for bleeding complications.[22] Furthermore, the effectiveness of anticoagulation varies because of interactions with some foods and other medications; even with frequent monitoring and dose adjustments, patients' test results are outside of the therapeutic range in up to half of all blood drawings.[23] Partly for these reasons, only around 50% of patients

who are eligible for long-term warfarin are treated with it.[24]

Pharmacological alternatives to warfarin have been investigated,[25–28] and several new anticoagulants seem promising;[29] even if they prove to be safe, however, they will not address many of the problems related to bleeding or compliance or the need for lifelong treatment. On the basis of echocardiography and autopsy studies showing that the left atrial appendage (LAA) was the source of thrombi in more than 90% of patients with non-valvular atrial fibrillation,[30–32] percutaneous catheter-based devices have been developed to close and thereby effectively exclude the LAA from the systemic circulation. Pilot studies have shown acceptable risk-to-benefit ratios for these non-pharmacological alternatives to chronic warfarin therapy.[33–38]

The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) study[36] examined the efficacy and safety of percutaneous closure of the LAA in patients with non-valvular atrial fibrillation. The study was designed to assess the non-inferiority of the device against chronic warfarin therapy.

Methods

Patients

This prospective, randomised controlled trial was undertaken at 59 sites in the USA and Europe. Enrolment began in February, 2005, and ended in June, 2008. Patients aged 18 years or older with paroxysmal, persistent, or permanent non-valvular atrial fibrillation were eligible for enrolment if they had a CHADS2 risk score of 1 or more (ie, at least one of the following: previous stroke or transient ischaemic attack, congestive heart failure, diabetes mellitus, hypertension, or were 75 years or older).[39] Exclusion criteria included contraindications to warfarin, comorbidities other than atrial fibrillation that required chronic warfarin use, LAA thrombus, a patent foramen ovale with atrial septal aneurysm and right-to-left shunt,[40] mobile aortic atheroma, and symptomatic carotid artery disease. Eligible patients underwent baseline neurological assessment by a neurologist. For patients who had history of stroke, a CT or MRI scan was taken at baseline. Patients also had an echocardiographic examination (via a transoesophageal echocardiograph [TEE]) to assess other echocardiographic exclusion criteria.

The study was reviewed by the US Food and Drug Administration (FDA) and approved by each site's institutional review board; all patients provided written informed consent. An independent clinical events committee reviewed and adjudicated all adverse events. An independent data safety monitoring board met regularly to review study data and to recommend any changes to the protocol.

Randomisation and masking

After baseline screening, patients were randomly assigned by a computer-generated randomisation sequence to intervention or control groups in a 2:1 ratio. Randomisation was stratified by clinical centre and was done via a centralised system with block sizes of six (four intervention, two control). An independent statistician who had no involvement in the design or analysis of the study generated the randomisation sequence. The centralised computer system was password protected and accessed by the principal investigator or study coordinator after the patient gave consent and had met inclusion criteria. The patients' initials and date of birth were entered and then the patient was allocated to intervention or control. Participants and clinicians were not masked to treatment assignment.

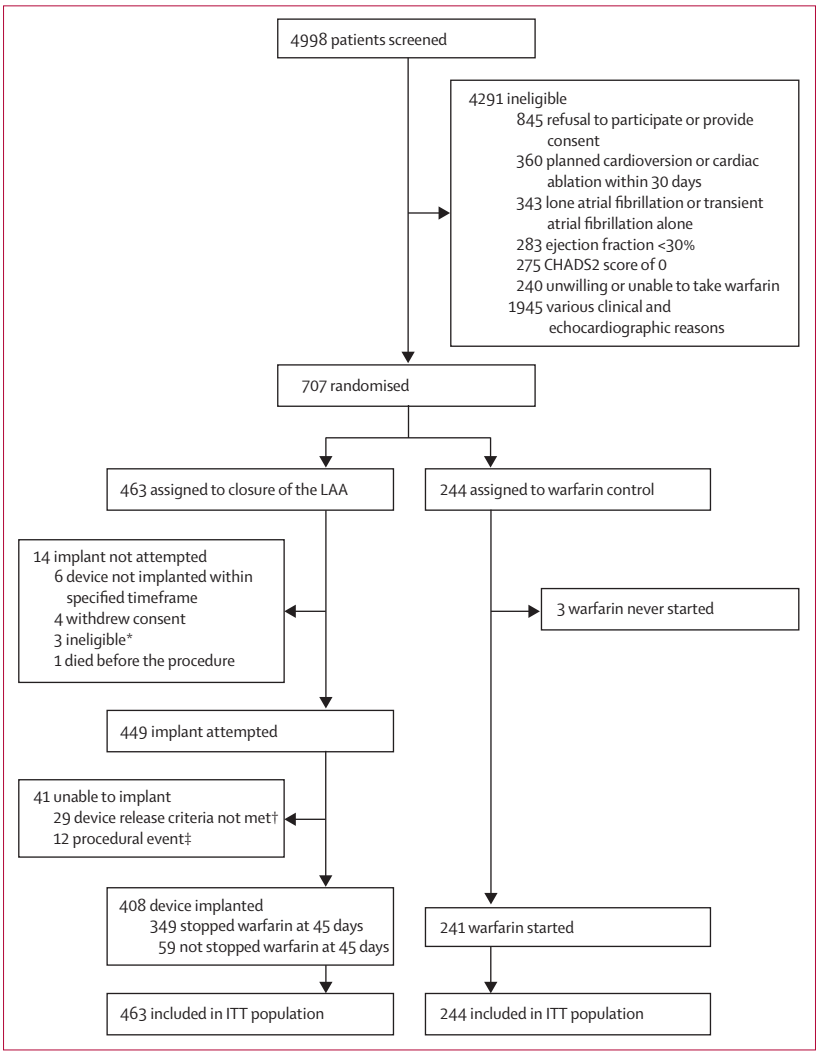

Figure 1: **Trial profile**
ITT=intention-to-treat. *Patients were classed as ineligible after new clinical findings were seen (eg, cardiac tumour, inadequate anatomy). †One or more of the release criteria of acceptable device position, in-situ size (compression), stability, and LAA seal were not met for device release. ‡Procedure-related complications that resulted in the device not being used (all of which were classified as primary safety endpoints).

Procedures

Patients allocated to the intervention group received percutaneous closure of the LAA by use of the

WATCHMAN device (Atritech, Plymouth, MN, USA). As previously described, this device[36,37] is a self-expanding nickel titanium (nitinol) frame structure with fixation barbs and a permeable polyester fabric cover. The device ranges in diameter from 21 mm to 33 mm to accommodate varying LAA anatomy and size. It is implanted via a trans-septal approach by use of a catheter-based delivery system to seal the ostium of the LAA. The implantation is guided by fluoroscopy and TEE to verify proper positioning and stability.

After the device had been implanted, patients were treated with warfarin (Coumadin, Bristol-Myers Squibb, New York, NY, USA) for 45 days to facilitate device endothelialisation. TEE imaging was done at 45 days, 6 months, and 12 months to assess residual peri-device flow and device stability and position. Patients discontinued warfarin therapy if the 45-day TEE showed either complete closure of the LAA or if there was residual peri-device flow (jet <5 mm in width). After stopping warfarin treatment, once daily clopidogrel (75 mg) and aspirin (81–325 mg) were prescribed until completion of the 6-month follow-up visit, from which point aspirin alone was continued indefinitely.

Patients in the control group received warfarin for the duration of the study (target international normalised ratio [INR] between 2·0 to 3·0). Monitoring of the INR was done by the patient's treating physician at least every 2 weeks for 6 months and at least once a month thereafter.

Follow-up visits occurred at 45 days, at 6, 9, and 12 months, and twice a year thereafter. Neurological assessments were done at baseline, 12 months, and 24 months and whenever a neurological event occurred.

The primary objective was to establish whether the device was non-inferior to warfarin treatment by use of a composite endpoint for efficacy that consisted of the occurrence of stroke (including ischaemic or haemorrhagic stroke), cardiovascular or unexplained death, or systemic embolism. The primary composite endpoint for safety consisted of events related to excessive bleeding (eg, intracranial or gastrointestinal bleeding) or procedure-related complications (eg, serious pericardial effusion, device embolisation, procedure-related stroke). Time to first event was calculated from the date of randomisation to the event, or to the last known status date. Event rates were calculated as the number of events per 100 patient-years of follow-up.

	Intervention group (n=463)	Control group (n=244)
Characteristics		
Age (years)	71·7(8·8;46·0–95·0)	72·7(9·2;41·0–95·0)
Male	326 (70·4%)	171 (70·1%)
Race/ethnicity		
Asian	4 (0·9%)	1 (0·4%)
Black/African-American	6 (1·3%)	5 (2·0%)
White	425 (91·8%)	222 (91·0%)
Hispanic/Latin American	25 (5·4%)	15 (6·1%)
Hawaiian/Pacific Islander	1 (0·2%)	1 (0·4%)
Other	2 (0·4%)	0
Risk factors		
CHADS2 score*		
1	157 (33·9%)	66 (27·0%)
2	158 (34·1%)	88 (36·1%)
3	88 (19·0%)	51 (20·9%)
4	37 (8·0%)	24 (9·8%)
5	19 (4·1%)	10 (4·1%)
6	4 (0·9%)	5 (2·0%)
Congestive heart failure	124 (26·8%)	66 (27·0%)
History of hypertension	413 (89·2%)	220 (90·2%)
Age 75 years or more	190 (41·0%)	115 (47·1%)
Diabetes	113 (24·4%)	72 (29·5%)
Previous transient ischaemic attack/ischaemic stroke	82 (17·7%)	49 (20·1%)
Previous warfarin use		
Less than 1 year	254 (54·9%)	145 (59·4%)
1 year or more	203 (43·8%)	96 (39·3%)
No estimate	6 (1·3%)	3 (1·2%)
Atrial fibrillation pattern		
Paroxysmal	200 (43·2%)	99 (40·6%)
Persistent	97 (21·0%)	50 (20·5%)
Permanent	160 (34·6%)	93 (38·1%)
Unknown	6 (1·3%)	2 (0·8%)
Atrial fibrillation onset		
Less than 1 year	69 (14·9%)	50 (20·5%)
1 year or more	360 (77·8%)	182 (74·6%)
No estimate	34 (7·3%)	12 (4·9%)
Left ventricular ejection fraction (%)	57·3% (9·7; 30·0–82·0)	56·7% (10·1; 30·0–86·0)

Data are mean (SD; range) or n (%). *At least one of the following: previous stroke or transient ischaemic attack, congestive heart failure, diabetes mellitus, hypertension, or were 75 years or older.

Table 1: **Baseline characteristics and risk factors of study participants**

Statistical analysis

The preplanned primary analysis of efficacy and safety used a Bayesian Poisson model, stratified for CHADS2 score, with a non-informative gamma conjugate prior distribution.[41] Posterior sampling was used to calculate probabilities and Bayesian credible intervals (CrIs). This model used data from this study only and assumed a constant hazard rate with the number of events following a Poisson distribution. The Kaplan-Meier method was used for graphical assessment of time-related events. Post-hoc sensitivity analyses for the primary endpoint were done by use of Cox proportional hazards models and confidence intervals (CIs) for differences in Poisson rates. Analysis of the primary efficacy and safety endpoints was by intention to treat. All patients without an event or lost to follow-up were censored at the time of the last known event status. Consistency of the primary efficacy results across prespecified patient subgroups

	Intervention group		Control group		Rate ratio (intervention/control [95% CrI])	Posterior probabilities	
	Events/patient-years	Observed rate (events per 100 patient-years [95% CrI])	Events/patient-years	Observed rate (events per 100 patient-years [95% CrI])		Non-inferiority	Superiority
ITT population*							
Primary efficacy†	21/694·1	3·0 (1·9–4·5)	18/370·8	4·9 (2·8–7·1)	0·62 (0·35–1·25)	>99·9%	90·0%
Ischaemic stroke	15/694·6	2·2 (1·2–3·5)	6/372·3	1·6 (0·6–3·0)	1·34 (0·60–4·29)	71·8%	20·1%
Cardiovascular/unexplained death	5/708·4	0·7 (0·2–1·5)	10/374·9	2·7 (1·2–4·4)	0·26 (0·08–0·77)	>99·9%	99·3%
Haemorrhagic stroke	1/708·4	0·1 (0·0–0·5)	6/373·4	1·6 (0·6–3·1)	0·09 (0·00–0·45)	>99·9%	99·8%
Systemic embolism	2/707·8	0·3 (0·0–0·8)	0/374·9	0	..	..	..
All stroke	16/694·6	2·3 (1·3–3·6)	12/370·8	3·2 (1·6–5·2)	0·71 (0·35–1·64)	99·3%	76·9%
All-cause mortality	21/708·4	3·0 (1·9–4·5)	18/374·9	4·8 (2·8–7·1)	0·62 (0·34–1·24)	>99·9%	90·7%
Primary safety‡	49/658·8	7·4 (5·5–9·7)	16/364·2	4·4 (2·5–6·7)	1·69 (1·01–3·19)	..	..
Successfully treated population§							
Primary efficacy	11/593·6	1·9 (1·0–3·2)	17/370·2	4·6 (2·6–6·8)	0·40 (0·19–0·91)	>99·9%	98·6%
Primary safety	9/592·1	1·5 (0·7–2·8)	16/363·6	4·4 (2·5–6·7)	0·35 (0·15–0·80)	..	..

CrI=credible interval. ITT=intention-to-treat. ..=not applicable. Different events have different numbers of patient-years because patients without an event or lost to follow-up were censored at the time of the last known event status. Posterior probabilities of non-inferiority are based on a two-fold non-inferiority margin. Posterior probabilities and CrIs are based on a Bayesian model stratified by CHADS2 score. *The ITT population consists of all randomised patients (intervention, n=463; control=244). †The primary composite endpoint for efficacy was the occurrence of stroke (including ischaemic or haemorrhagic stroke), cardiovascular or unexplained death, or systemic embolism. ‡The primary composite endpoint for safety consisted of events related to excessive bleeding (eg, intracranial or gastrointestinal bleeding) or procedure-related complications (eg, serious pericardial effusion, device embolisation, procedure-related stroke). §Successful treatment was defined in the intervention group as device implantation followed by discontinuation of warfarin and in the control group as the start of warfarin treatment (intervention, n=389; control=241).

Table 2: **Clinical outcomes**

was assessed by use of Cox proportional hazard models that incorporated an interaction term between randomised groups and patient subgroups.

We also undertook a prespecified prospective analysis of primary event rates in successfully treated patients. For this analysis, successful treatment was defined in the intervention group as device implantation followed by discontinuation of warfarin and in the control group as the start of warfarin treatment. Since this was a sensitivity analysis to support the primary analysis, no alpha-level adjustment was made. p values were two-sided and were not adjusted for multiple comparisons. SAS version 9.2 was used for statistical analyses.

The sample size was based on an expected primary endpoint event rate of 6·15 per 100 patient-years in the control group, calculated by use of data from the Stroke Prevention in Atrial Fibrillation studies database.[42,43] Simulations were done to ensure 80% power and a 5% false-positive (type I error) rate under a group sequential analysis plan that included a first interim analysis after 600 patient-years of follow-up with subsequent analyses after each additional 150 patient-years, up to a maximum of 1500. Stopping rules were based on posterior probabilities; the trial was to be stopped for futility if the probability that the primary efficacy event rate for the intervention group was higher than the rate for the control group exceeded 95%. We selected a one-sided probability criterion of non-inferiority for the device of at least 97·5%, by use of a two-fold non-inferiority margin.

Non-inferiority was formally achieved at the first prespecified interim analysis. However, in accordance with the prespecified analysis plan, follow-up continued and analyses were done at subsequent 150 patient-year intervals. This report summarises the results at the most recent evaluation (the fourth planned interim analysis) following the review of the trial results by the Circulatory Advisory Panel of the FDA. The analysis is based on an aggregate of 1065 patient-years of follow-up for the primary endpoint. Each of the interim analyses was consistent with the initial primary finding of non-inferiority. This study is registered with Clinicaltrials.gov, number NCT00129545.

Role of the funding source

This study was designed by the principal investigator (DRH) in collaboration with the sponsor after consultation with the FDA. The sponsor of the study had no role in data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Patients were followed for an aggregate of 1065 patient-years. Mean follow-up per patient was 18 months (SD 10). Table 1 shows the baseline characteristics and risk factors of the study participants.

The device was successfully implanted in 88% (408/463) of patients assigned to this intervention and in

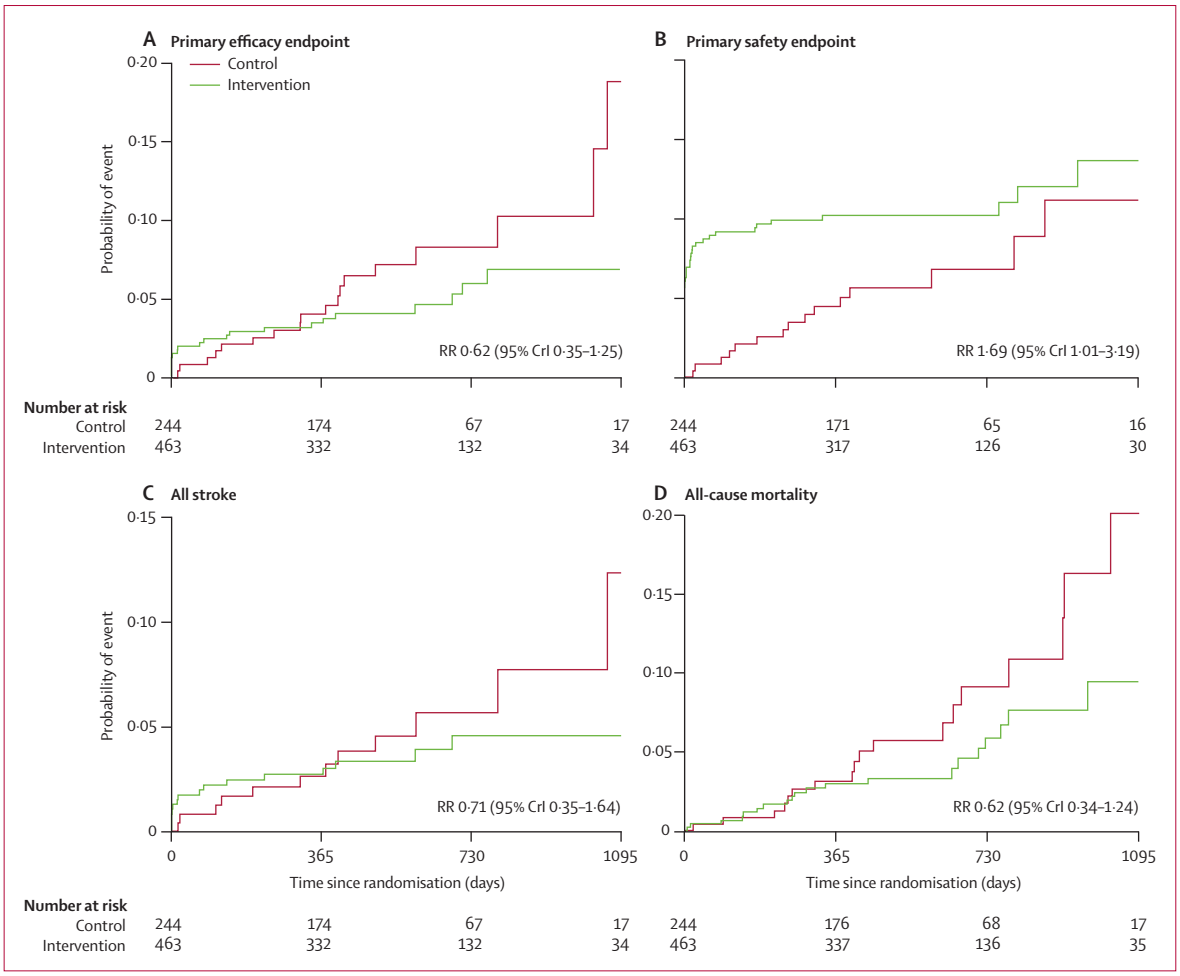

***Figure 2*: Kaplan-Meier curves of incidence of study endpoints in intervention and control groups**
RR=rate ratio. Incidence probabilities for the intention-to-treat analysis are shown with time calculated as the days since randomisation for the primary efficacy endpoint (A), the primary safety endpoint (B), all stroke (C), and all-cause mortality (D).

91% (408/449) of those in whom implantation was attempted (figure 1). At the 45-day follow-up, 349 (86%) of 408 patients with an implanted device met TEE criteria and were able to stop taking warfarin. 355 (92%) of 385 patients had met the criteria by 6 months, mainly because of a reduction in peri-device leak. For the control group, plasma warfarin concentration was in the therapeutic INR range (between 2·0 and 3·0) 66% of the time.[44]

Table 2 shows the clinical outcomes of the intervention and control groups. The primary efficacy event rate was 3·0 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 (rate ratio [RR] 0·62, 95% CrI 0·35–1·25). The probability of non-inferiority of the intervention was greater than 99·9% based on a two-fold non-inferiority margin. Results obtained by use of a Cox proportional hazards model stratified by CHADS2 score were consistent with the primary analysis (hazard ratio 0·70, 95% CI 0·37–1·32). At 2 years, 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 (figure 2).

The efficacy results were consistent across all subgroups apart from sex: the HR in men was lower than that for women (p=0·03; all other interaction tests p>0·40; figure 3). Exclusion of patients at lowest risk for thromboembolic events (ie, patients with a CHADS2 score of 1) did not affect the results of the primary efficacy analysis: the rate ratio in patients with CHADS2 score of more than 1 was 0·68 (95% CrI 0·35–1·42).

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 control patients who received warfarin (RR 0·40, 95% CrI 0·19–0·91; table 2).

The rate of ischaemic stroke was higher in the intervention group than in the control group. In the intervention group, one patient had a stroke after

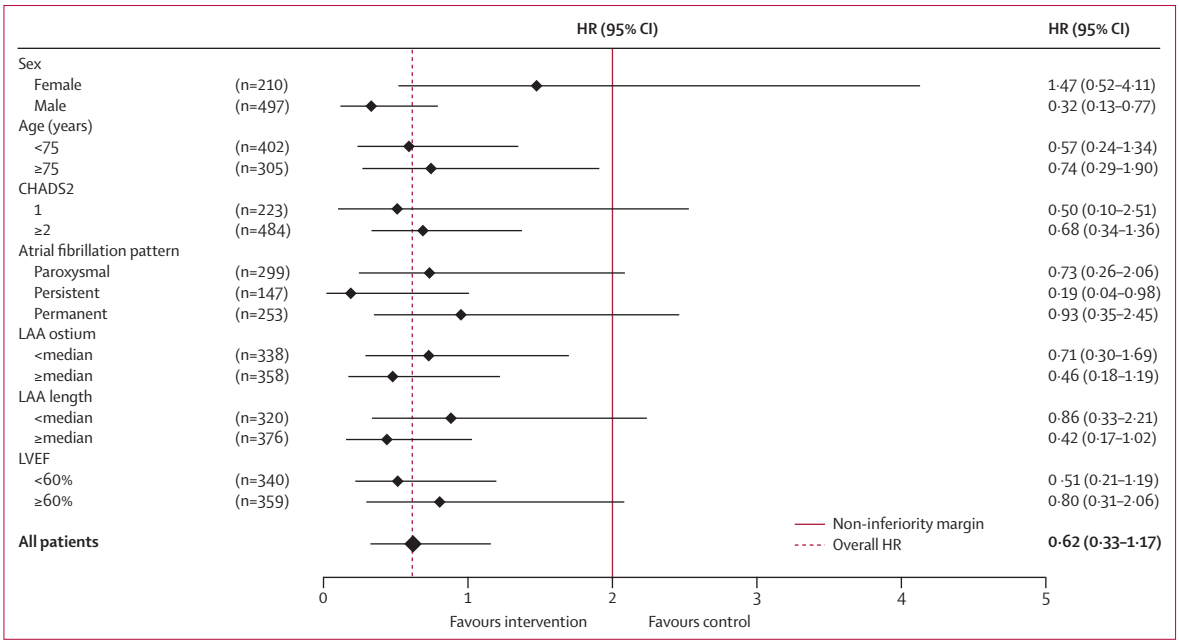

***Figure 3*: Primary efficacy results by patient subgroup**

HR=hazard ratio. LAA=left atrial appendage. LVEF=left ventricular ejection fraction. HRs (95% CIs) are shown for the primary efficacy endpoint for all patients and for prespecified patient subgroups. Results are from Cox proportional hazards models, with each subgroup examined in a separate model. The number of randomised patients with data available for the subgroup variable are shown.

randomisation but before scheduled device implantation, and five patients had periprocedural events, mainly air embolism. The five patients with procedure-related strokes stayed in the hospital for a mean of 9 days (range 5–19); three had no long-term residual deficit, whereas two were discharged to nursing homes and subsequently died. After the periprocedural timeframe, ischaemic stroke occurred in nine patients in the intervention group (1·3 events per 100 patient-years) compared with six patients in the control group (1·6 events per 100 patient-years). In both groups, all ischaemic strokes that had INR measurements available at the time of the event occurred at a subtherapeutic INR level. Two of the ischaemic strokes were fatal, one in each group.

Haemorrhagic strokes were less frequent in the intervention group than in the control group. Five of the six haemorrhagic strokes in the control group were fatal and all occurred in patients with therapeutic INR levels. The haemorrhagic stroke in the intervention group occurred in a patient on warfarin during the 45-day period after implanting the device and was fatal. The rate of all ischaemic and haemorrhagic strokes was lower in the intervention group than in the control group (table 2).

21 patients assigned to the intervention and 18 controls died during the study. The deaths in the intervention group were caused by stroke (n=2), unknown or other cardiovascular causes (n=4), and non-cardiovascular causes (eg, cancer, urosepsis; n=15). No deaths were deemed related to the LAA closure device. The deaths in the control group resulted from stroke (n=6), unknown or other cardiovascular causes (n=6), and non-cardiovascular causes (eg, pneumonia; 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 (figure 2).

Primary safety events occurred at a higher rate in the intervention group than in the control group (RR 1·69, 95% CrI 1·01–3·19; table 2). By contrast with the intervention group, in which 27 (55%) of 49 primary safety events occurred on the day of the procedure, the events in the control group usually occurred later, with eight (50%) of 16 recorded between 45 days and 1 year. At 2 years after randomisation, the cumulative primary safety event rate was 10·2% (95% CI 7·4–13·0) for the intervention group and 6·8% (95% CI 3·0–10·6) for the control group. In the analysis of successfully treated patients, the primary safety event rate was lower in the intervention group than in the control group (RR 0·35, 95% CrI 0·15–0·80).

The most frequent primary safety event in the intervention group was serious pericardial effusion (defined as the need for percutaneous or surgical drainage), which occurred in 22 (4·8%) of patients. 15 of these patients were treated with pericardiocentesis, and seven underwent surgical intervention. No patients with pericardial effusion died, although length of hospital stay in these patients was longer than it was in patients without a pericardial effusion (median 4 days longer). Effusion rates declined with investigator experience;

among 542 patients for whom an implant was attempted, including 93 non-randomised roll-in patients, serious effusions occurred in 7·1% (11/154) of the first three patients at each site and in 4·4% (17/388) of subsequent patients (p=0·19). Device embolisation occurred in three patients; one was noted during the procedure and two were discovered by TEE on day 45. One device embolisation was removed percutaneously by use of a vascular snare; the other two patients underwent surgery, one of whom had concomitant aortic valve replacement. Device embolisation was not associated with increases in stroke or mortality. Table 3 shows the primary safety events by treatment group. Other adverse events in the intervention group that were not included in the primary safety endpoint included eight procedure-related or device-related pericardial effusions that were deemed non-serious because no drainage was required. There were no pericardial effusions in the control group.

	Intervention (n=463)	Control (n=244)
Serious pericardial effusion*	22 (4·8%)	0
Major bleeding†	16 (3·5%)	10 (4·1%)
Procedure-related ischaemic stroke	5 (1·1%)	0
Device embolisation	3 (0·6%)	0
Haemorrhagic stroke‡	1 (0·2%)	6 (2·5%)
Other§	2 (0·4%)	0

*Defined as the need for percutaneous or surgical drainage. †Major bleeding is defined as a bleeding event that required at least 2 units of packed red blood cells or surgery to correct. ‡Of the seven haemorrhagic strokes, six resulted in death (intervention group, n=1; control group, n=5). §An oesophageal tear and a procedure-related arrhythmia.

Table 3: **Adverse events**

Discussion

In view of the prevalence of atrial fibrillation and the difficulties associated with chronic treatment with warfarin—such as complications related to bleeding and the need for continuous monitoring of INR—new approaches for stroke prevention in cases of atrial fibrillation have been pursued. The strategy of LAA obliteration evolved from the finding that in patients with non-valvular atrial fibrillation, the LAA is the most common site of thrombi.[30–32,45] This randomised controlled trial showed that the efficacy of a strategy for percutaneous closure of the LAA was non-inferior to that of chronic warfarin therapy, providing evidence for the role of the LAA in stroke pathogenesis and for a new treatment strategy. This notion is also supported by the secondary analysis, which showed that the efficacy and safety event rates were lower in patients who had closure of the LAA and who had stopped warfarin therapy than in control patients who received warfarin.

In the control group, the therapeutic INR range was achieved 66% of the time, despite close INR follow-up. Recent trials of anticoagulation therapy in atrial fibrillation have shown similar rates (64–68%[26–28]). The most common primary safety events in patients assigned to control were major bleeding and haemorrhagic stroke; these events occurred throughout follow-up. By contrast, in patients assigned to the intervention, there was a 90% reduction in the rate of haemorrhagic stroke, and the adverse events tended to occur early (periprocedurally), with incidence rate declining over the course of the trial. The high initial risk associated with implantation of the LAA closure device is offset by the progressive cumulative risk of chronic warfarin therapy. At 6 months, 355 (92%) of 385 patients in the intervention group with implanted devices discontinued warfarin therapy without an increased risk of subsequent stroke.

In the recent ACTIVE W trial of patients with atrial fibrillation,[25] the annual risk of stroke, non-CNS systemic embolus, myocardial infarction, or vascular death was 3·9%. In the combined SPORTIF III, IV, and V trials in elderly patients,[27] stroke and systemic emboli occurred at a rate of 2·2% per year in patients treated with warfarin. Additionally, haemorrhagic strokes were more frequent in older patients. The frequency of these events is similar to that for the control group in this study, when adjusted for time of follow-up and heterogeneity of populations studied.

The pronounced time dependency of the primary safety events in the intervention group was caused by two types of procedure-related complication: pericardial effusions needing intervention and air embolism. Although the rate of pericardial effusions in the intervention group (4·8%) was substantially higher than the rate in the control group (no events), none of the cases resulted in permanent impairment or mortality. Air embolism has been reported with other left-heart catheter interventions, such as atrial septal defect closure and catheter ablation of left-sided arrhythmias.[46] In view of the learning curve effect—as seen in this trial and with a variety of other procedures that involve structural heart disease and electrophysiological interventions requiring anticoagulation[47]—it is expected that these event rates will further decrease with increased operator training and experience. Physicians who inserted the LAA closure device had undergone comprehensive training in LAA device implantation and had the benefit of intraprocedural TEE guidance.[48]

Since implantation of the device for closure of the LAA required concomitant warfarin treatment until sealing was confirmed by TEE, this study did not address the potential role for closure of the LAA in patients with contraindications to warfarin therapy. Thus, the safety and efficacy of LAA closure without short-term warfarin treatment is unknown.

Most safety events occurred early in the intervention group but continually in the control group. We do not know if there might have been more or fewer events with longer follow-up and we now need to establish the longer term outcomes of patients who have undergone closure

of the LAA. Additionally, there is a need to assess other patient populations, especially patients with contraindications for warfarin.

Patients in the intervention group who remained on warfarin could have biased the recorded efficacy event rate. However, because the primary efficacy event rate in the intervention group was lower than it was in the control group, the true efficacy of the device might be underestimated. Furthermore, warfarin was discontinued by 45 days in most patients in the intervention group, so that most of the observed follow-up in the trial (83%) occurred after anticoagulation had been stopped. Finally, the separate analysis of patients who had successful implantation of the device included only patients who had stopped taking warfarin, thereby providing data that exclude the protective or harmful effects of warfarin, lending support to the hypothesis that successful closure of the LAA is not inferior to warfarin for prevention of stroke.

Inadequate maintenance of the INR in the control group could have increased the event rates for efficacy and safety in these patients. The difficulties in maintaining the INR in clinical practice are well established; furthermore, the monitoring protocol in this study was more stringent than current recommendations[49] and the time in the therapeutic range was similar to that reported in other recent trials of anticoagulation in atrial fibrillation.[26–28] Even with pharmacogenetic approaches, INR control is variable, and there is a danger that tighter control, if achieved in a clinical trial, would not reflect that of clinical practice.[50]

Thus, our strategy for closing the LAA was non-inferior to warfarin therapy in terms of the primary efficacy endpoint of all stroke, cardiovascular death, and systemic embolism. Although there is a higher initial safety event rate for device implantation, adverse events were without long-term sequelae for most patients. Closure of the LAA might provide an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with non-valvular atrial fibrillation.

Contributors

All authors contributed to data analysis and writing and reviewing of the report. All authors saw and approved the final version of the report.

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Conflicts of interest

DRH and the Mayo Clinic have a potential interest in Atritech. VYR has received clinical grant support as an investigator in the PROTECT AF study. CMM is an an employee of the Integra Group, which has a consulting contract with Atritech. All other authors declare that they have no conflicts of interest.

Acknowledgments

This study was sponsored by Atritech.

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