Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation Versus Long-term Warfarin Therapy

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Introduction

- Atrial fibrillation is the most common type of cardiac arrhythmia. It affects 800,000 people in the UK and causes a five times increase in the risk of stroke.
- It is estimated that the cause of stroke in 90% of these patients are due to a clot forming in the left atrial appendage that travels to the blood vessels that supply the brain.
- Currently, anticoagulants like warfarin are used to treat at risk patients. However, there are many side effects associated with its long term use, which has led to issues in the management of stroke prevention; resulting in only 50% of eligible patients to take warfarin.

Rationale for work

- A similar trial (Protect Trial) has been carried out previously. Results showed that at the 45 months follow up, the device was superior to warfarin due to its long term side effects. This highlighted the fact that unwanted side effects could be avoided with mechanical intervention, but more data is required. There was also early safety risk issues in the previous trial, such as procedural stroke related air embolism, so extra safety measures were taken in this trial.
- It was important that this trial was carried out in order to improve the results previously obtained comparing warfarin therapy to LAA occlusion. In addition, the trial design had to be modified to ensure the safety of the participants, therefore the endpoints were redefined.

Objectives and Hypothesis

- **Objectives:** Assessing the safety and effectiveness of left atrial appendage occlusion, using the Watchman device. This is compared to long term warfarin therapy, in preventing the risk of stroke in patients with atrial fibrillation.

- **Hypothesis:** 90% of strokes in atrial fibrillation arise from clots forming in this pouch. By mechanically blocking it using the device, less clots are suggested to be formed. This is an alternative to taking warfarin especially in patients who cannot take it, due to its side effects or contraindications.

Main outcome measures

There were 3 agreed upon co primary efficacy endpoints for this trial:
- Primary efficacy endpoint: overall rates of stroke and death
- Late ischemic primary efficacy endpoint: stroke or systemic embolism >1 week after randomization
- Early safety primary endpoint: complications within 1 week of the procedure

Methods

- In this randomized control trial, all the participants had atrial fibrillation and were at high risk of getting stroke. The CHADS2 scoring method was used to identify these high risk patients. It is used to assess whether patients have congestive heart failure, hypertension, age>75 years, diabetes or had a previous episode of stroke. The patients are considered high risk if they score ≥2.
- The patients were randomly assigned either the device group or the warfarin therapy group. The LAA group had 269 participants and the chronic warfarin therapy had 138 participants. The participants and clinicians were aware of which treatment they were assigned, so it was not a blind trial which might cause bias.

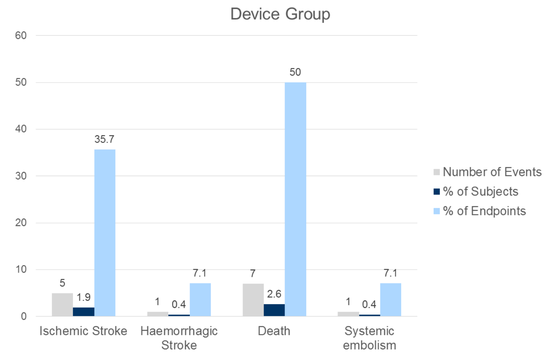
Exclusion Criteria
Long term anticoagulant therapy for reasons other than AF
Contraindications to warfarin/ aspirin
Previous stroke/ transient ischemic attack within 90 of enrolment
Symptomatic carotid disease
Patent foramen ovale
Atrial septal defect requiring treatment
Clopidogrel therapy

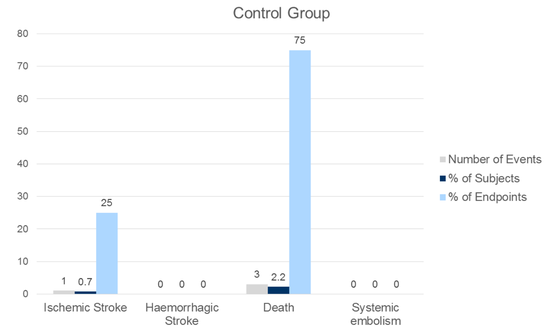
Table1: Summary of the exclusion criteria in the Prevail trial

- In this trial, patients with certain conditions were not selected to exclude interference with the results, summarized in Table 1.
- The mean demographics in both groups such as age, height, sex and ethnicity were very similar, which helps reduce any bias that might be caused by these factors . The average CHAD2 score in both groups is 2.6±1, which also help improve the reliability of results.
- Participants in the LAA occlusion group had the device inserted and guided by transesophageal echocardiography (TEE). They also had to take warfarin and aspirin for 45 days after the implantation to prevent the risk of a thrombus forming before the device fully implants to the walls of the atrium. To assess the stability of the device, a TEE was performed at 45 days, 6 and 12 months.
- The control patients received warfarin treatment and were monitored to check that their international normalized ratio is between 2.0 and 3.0. This measurement was taken every 2 weeks for 6 months and then every month after that.
- Follow ups were made at 45 days, 6 months and 9 months then twice a year after that. A neurological assessment was also made at 12 months and 24 months and whenever a neurological event was suspected.
- There were 4 patients from the LAA occlusion group in which the device implantation was not attempted because either the device was not a suitable size for the patients' LAA, a thrombus was found or the patient didn't stop taking anticoagulation before the procedure.

Results

- Primary Efficacy: The rate of the first co primary endpoint of this trial (stroke, death) at 18 months was 0.064 in the device group and 0.063 in the warfarin group. The rate ratio calculated was 1.07 with a 95% confidence interval. The results show that there is a 95% certainty that the true value of the rate ratio lies between 0.57 to 1.89. This however did not meet the predefined non-inferiority criterion, as the upper boundary (1.89) crosses the pre-defined non-inferiority margin of 1.75.





Graph2: Co-primary efficacy endpoint observed events by type

- Late ischemic efficacy: The rate of stroke or systemic embolism (SE) 7 days after randomization was 0.0253 in the device group and 0.0200 in the control group. The risk difference calculated by subtracting the rates in the control group from the device group is 0.0053. The results show that there is a 95% certainty that the true value of the risk difference lies between -0.0190 to 0.0273. This is less than the predefined non-inferiority criterion of 0.0275; so non-inferiority was established.
- Early Safety: 2.2% of the patients in the device group had one of the following complications: embolization, ateriovenous fistula, heart perforation, pericardial effusion and bleeding. This was lower than the results obtained in the previous PROTECT AF trial and the prespecified safety performance goal of 2.652%. The early safety endpoint success was achieved.

Discussion

- This trial has proven that occluding the LAA is a reasonable method of reducing the risk of stroke. It also proves the hypothesis that the left atrial appendage is the primary source of the thromboembolism that causes stroke.
- It also provides additional data to evaluate the effectiveness of LAA occlusion compared to chronic warfarin therapy. The drawbacks with warfarin consumption include increased risk of systemic bleeding and need for constant monitoring. The Watchman device is a local intervention where as warfarin has systemic side-effects. This shows the importance of finding an alternative stroke prevention strategy and the Watchman device proves to be a viable one.
- There was no significant difference between the complication rates of experienced operators (96.3% implantation success) and new operators (93.2%). This is important as it shows that knowledge from previous trial can easily be transferred to new operators.

Conclusion

- This trial has provided vital additional evidence that closure of the left atrial appendage is a reasonable alternative to chronic warfarin therapy in stroke prevention in patients with atrial fibrillation.

Future Work

- Participants randomly chosen to get the Watchman implant have to take warfarin for a few days as a safety precaution until the device fully implants. Therefore, this trial does not consider patients that have an absolute contraindications to warfarin.
- Event rates were lower than expected in the warfarin group, so non-inferiority was not established. Repeating the trial with a larger number of participants would be useful in achieving a non-inferiority for the overall all rate of stroke and death in the device group.
- This trial has not compared the safety of the watchman device to other oral anticoagulants, such as rivaroxaban. It has also not looked into the clinical significance of occluding the left atrial appendage. It might interfere with hormonal regulation of blood pressure as LAA is the main site that produces atrial natiuretic peptide.
- Participants in this trial also had to be candidates for chronic anticoagulants, to make it easier to randomize against the control group. This might have affected the reliability of the results. Perhaps a longer study with more participants would be useful to address and evaluate these issues.

References

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