

# A meta-analysis of left atrial appendage closure for stroke prevention in atrial fibrillation—adding to the debate but elements remain unresolved

Syed Mohammad Afzal Sohaib<sup>1</sup>, Kevin F. Fox<sup>2</sup>

<sup>1</sup>Department of Cardiology, Imperial College Healthcare NHS Trust & National Heart & Lung Institute, Imperial College London, Hammersmith Hospital, London, W12 0HS, UK; <sup>2</sup>Department of Cardiology, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, W12 0HS, UK  
Correspondence to: Dr. S M Afzal Sohaib, MBBS, MRCP, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London W12 0HS, UK.  
Email: s.sohaib@imperial.ac.uk.

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## Background

Managing the trade off between stroke risk and bleeding risk is a key challenge in patients with atrial fibrillation (AF). In 90% of patients with non-valvular AF and intracardiac thrombus, the left atrial appendage (LAA) is thought to be the location (1). The advent of devices to occlude the LAA therefore raised the possibility that stroke risk could be eliminated in this group of patients without the need for long term anticoagulation. However, since the first reports of percutaneous LAA closure with the PLAATO device were published in 2002, progress has been somewhat limited (2). Despite the initial optimism, concerns surrounding safety and efficacy have restricted the number of devices receiving FDA approval (3) and limited commissioning of this treatment in the United Kingdom (4). Guidelines for the management AF to date have varied their advice on this technology with European Guidelines giving LAA closure devices a “IIb” recommendation (usefulness/efficacy is less well established by evidence/opinion) and this only in patients who have a contraindication to warfarin (5). North American Guidelines do not currently recommend LAA closure at all (6). In some ways the caution in recommending this technology is understandable given the paucity of data to support their use.

Holmes *et al.* publish a meta-analysis in the *Journal of the American College of Cardiology* (7) which helps to address the deficit to some degree. This individual patient meta-analysis brings together data from two randomised controlled trials and two observational studies of the Watchman LAA occlusion device. Analysing data from 2,406 patients

(5,931 years of patient follow), the authors conclude that rates of haemorrhagic stroke, non-procedural bleeding, and cardiovascular/unexplained death are reduced in patients with non-valvular AF who receive LAA closure compared to patients on long term oral anticoagulation. However once peri-procedural complications are included, all cause stroke and systemic embolism were similar between the two groups, and there was no significant difference in all cause mortality nor in major bleeding complications.

They include the only two randomised trials of LAA closure: the PROTECT-AF study (8) and the more recent the PREVAIL study (9). In addition data are incorporated from registries from both these trials (CAP1 and CAP2 respectively). In terms of size, this therefore dwarfs any previous publication on LAA closure, which often have included no more than 100 participants (10).

Some important observations should be noted when interpreting the results of this analysis. Of the quoted 2,406 patients, the total number of controls treated with long term warfarin was comparatively small at 382. A total of 1,145 of the participants come from study registries and so have not been randomised. In their analysis, the authors focus mainly on a separate meta-analysis just of the two randomised controlled trials. When these randomised trials are analysed alone, Watchman device implantation was non-inferior to warfarin therapy for a primary composite endpoint of systemic embolism, cardiovascular/unexplained death, and stroke (2.72 v 3.5 events per 100 patient years,  $P=0.22$ ). There was no difference in all cause stroke ( $P=0.94$ ) nor all cause bleeding ( $P=0.95$ ). However, if procedure

related bleeding was excluded, Watchman devices proved superior to warfarin ( $P=0.02$ ) for bleeding risk.

The authors present further meta-analysis data including the patients from the linked registries from the two trials, and here some caution is also required in interpreting the data. The authors do make the point that there is little difference to the data looking at the randomised controlled trials and registries and in particular event rates in the treatment arms of the randomised trials were similar to the event rates in the registry patients.

### Mortality reduction

Much is made by the authors of a tendency towards a reduction in all cause mortality in the Watchman group which did not meet statistical significance. The implication is that while non-significant, it might represent an important signal. The meta-analysis is dominated by data from the PROTECT-AF study as it is both larger and has a much longer period of follow-up than PREVAIL (2,717 patient years follow-up versus 860). PROTECT-AF had a lower risk group of patients with a lower mean CHADS<sub>2</sub> score than PREVAIL (mean CHADS<sub>2</sub> score 2.2 versus 2.6 respectively). One reason why PREVAIL was designed was in response to criticisms that PROTECT-AF included a relatively low risk group of patients, many of whom had a CHADS<sub>2</sub> score of 1. If the data contributing to this meta-analysis included a greater number of patients with a higher CHADS<sub>2</sub> score, the group might have which benefited more greatly from LAA closure, and we might have seen a significant mortality benefit.

### Stroke risk

A slightly increased risk of haemorrhagic stroke in the warfarin arm was offset by an increased risk of ischaemic stroke in the Watchman group. The increased risk of ischaemic stroke persisted after strokes in the first 7 days were excluded. This suggests that warfarin continues to confer a benefit over Watchman in the longer term for ischaemic stroke, presumably because most, but not all strokes are due to emboli from the LAA and warfarin continues to offer protection in this situation. In this analysis approximately a quarter of participants had heart failure and 90% were hypertensive.

### Procedural risk

This analysis further highlights the impact of peri-

procedural events on the safety of Watchman implantation, but also an ongoing risk associated with late complications with Watchman implantation. The risk of pericardial effusion requiring drainage in the PROTECT AF study was substantial at 4.8%. There is clearly a learning curve associated with this procedure as this complication rate fell in the PREVAIL study to 2.2%, despite a sicker group of patients (30% had a HASBLED score  $>3$  in PREVAIL versus 20% in PROTECT-AF), and the implant success rate similarly improved to 95% in PREVAIL compared to 88% in PROTECT-AF.

### Clopidogrel as a confounder

Anti-platelet use continues to cloud our understanding of this treatment. In the Watchman group all patients received aspirin long term, and if warfarin was discontinued both aspirin and clopidogrel were given for a 6-month period. There remains the possibility that some of the benefits or non-inferiority at least, is related to clopidogrel use rather than the device. The benefits of aspirin and clopidogrel over aspirin alone have previously been demonstrated in patients with AF in the ACTIVE-A trial (11). Are these Watchman trials an unwitting comparison of a combination of aspirin and clopidogrel versus warfarin? The patients recruited to ACTIVE-A are indeed those in whom the benefits of LAA closure would be more obvious—those with a contraindication to warfarin. The benefits of aspirin and clopidogrel in this group have already been demonstrated, and this drug combination is required for LAA closure. A clinical trial of aspirin plus clopidogrel with or without LAA closure would address this uncertainty.

### What this analysis adds

While this is an impressive collation of data, and a necessary publication in this field, whether it has moved our understanding of the role of the Watchman device in clinical practice is more difficult to quantify. Many of the conclusions are quite similar to the original findings of the PROTECT-AF trial. The primary composite endpoint is similar despite the additional data. However, the additional patients and extended follow-up have certainly allowed us to analyse some of the secondary endpoints more meaningfully such the development of ischaemic versus haemorrhagic stroke. It also allows us to appreciate how the safety of this procedure has improved with the passage of time.

## Unanswered questions

On balance this study confirms that LAA closure with a Watchman device is potentially a viable long term option for stroke prevention in AF. Currently some of the benefits of Watchman implantation are masked by procedure related complications but that may yet improve as the implanters progress along the learning curve. Many unanswered questions remain in this field however.

First and foremost, this analysis does not answer whether LAA closure provides what is ultimately required—stroke prevention without oral anticoagulation. In all four studies, the participants were required to take warfarin for at least 45 days. LAA closure was envisioned as a therapy where anticoagulation is not required. What are the risks associated with this procedure if warfarin is not used at all? Forty-five days however may be considered to be a short enough period for both clinicians and patients to accept the limitations of oral anticoagulant therapy.

Second, these studies will need to be interpreted differently in the era of novel oral anticoagulants (NOACs). We know that, certainly for intracranial bleeds, these have a lower bleeding risk than warfarin, and have favourable outcomes in terms of stroke and mortality (12). In contemporary practice, it may be fairer to compare LAA closure to NOAC use. There is a potential advantage that LAA closure may continue to offer over NOAC use. Unlike drug treatment, once LAA closure is achieved, the issue of compliance and discontinuation of therapy is no longer a consideration. We know that with NOACs, there is a discontinuation rate varying between 21–24% after 1 year (10), and a similar order of magnitude to warfarin from the control arm of the PROTECT-AF trial at 16–34% (8).

Third, there remains the question of the alternative approaches to LAA closure. While the data on the Watchman device is most extensive, alternatives exist. These include a range of different Amplatzer closure devices where only retrospective non-randomised studies have been published (13), and the Coherex WaveCrest device for which there currently are no peer reviewed data published (3). Alternative approaches also include the LARIAT suture where a combined epicardial and pericardial approach is used to lasso and occlude the LAA externally with a stitch. Again, evidence of efficacy is limited to non-randomised case series, but data on safety can be ascertained and major complications rates approaching 10% are seen with this (14). Finally a range of surgical techniques are also described (15). It remains to be seen whether over the longer term any

of these alternatives prove to be better than a Watchman, or indeed oral anticoagulation, but until a randomised controlled trial is done we will never know.

## Moving forward

The available data on LAA closure is evolving and emerging, and new technologies will potentially act as game changers in this field. We have seen from this analysis that many of the limitations of LAA closure relate to peri-implant complications, and as with any new procedure with the inevitable learning curve these are declining. The North American Societies, SCAI, HRS, and the ACC have recently issued joint guidance on best practices and procedures to help guide dissemination of this technology (3). So we may in the future be in a situation where we are able to demonstrate superiority over traditional warfarin anticoagulation. However the demand for an alternative to warfarin may decline with wider use of NOACs, illustrating the constant evolution of options for best care. Overall it remains hard to predict quite where we will be with this technology in the next 5 to 10 years.

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## Footnote

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*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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