Editorial

The case of stroke prevention by left atrial appendage occlusion in patients with atrial fibrillation—can we close the file?

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Atrial fibrillation (AF) is the most common arrhythmia and the prevalence is increasing. Future projections predict at least a doubling of AF patients by the year 2050 (1). One of the most devastating consequences of AF is stroke. The presence of AF increases the risk for thromboembolic complications 5-fold and strokes associated with AF have increased morbidity and mortality (2). For this reason stroke risk stratification and appropriate treatment in each patient with AF is of utmost importance. The last decade, the antithrombotic treatment of AF has changed significantly. Easy to use risk scores such as $CHADS_2$ and CHA_2DS_2-VASc have facilitated the use of antithrombotic agents (3). In addition, with the introduction of direct thrombin inhibitors and factor Xa inhibitors, an alternative to warfarin is available, which is at least as effective as warfarin, but with a lower incidence of intracranial bleeding (4).

One of the primary mechanisms how thromboembolic complications as a result of AF occur is believed due to dislodgement of thrombi formed in the left atrial appendage (LAA). In 90% of AF-related left atrial thrombi, they were located in the LAA (5). This was the basis for the hypothesis that systemic and intracranial embolic events in AF patients can be prevented by closure or removal of the LAA. The last decade, several devices have been developed that can occlude the LAA.

In patients with an implantable cardiac pacemaker included in the recent ASSERT study however the direct temporal link between, atrial lead-detected AF itself and cerebrovascular events was questioned (6). In only 15% of patients with AF associated embolic events, an AF episode >6 minutes duration was observed within the month before their stroke or systemic embolism (6). In the majority, the thromboembolic events occurred before or long after the AF episode. These observations suggest that there is not necessarily a direct causal relation with the AF episode itself and clot formation, and other mechanisms may be involved. AF may simply be a marker of increased stroke risk. Local endothelial coagulation and/or anatomic factors (for example trabeculae in the LAA) may be equally or even more important.

Removal of the LAA as a concomitant procedure during cardiac surgery in patients with AF can be performed safely and effectively. However, the studies evaluating the effect of LAA removal or clipping had insufficient power to provide the evidence that LAA removal during surgery reduces the risk of stroke (7,8). Theoretically, surgical or video assisted thoracoscopic removal of the LAA has potential advantages compared to endovascular devices. With epicardial removal or clipping of the LAA, no foreign body is introduced in the systemic circulation. For this reason, thrombus formation on the device cannot occur. In addition, following endovascular implantation of a device, short-term use of warfarin and long-term aspirin is recommended during endothelialisation of the device. This is not necessary following an epicardial approach. In the large Left Atrial Appendage Occlusion Study III (LAAOS III) study, the efficacy of surgical LAA occlusion will be evaluated in patients in whom an on-pump cardiac surgical procedure is performed (9).

The currently available evidence for stroke prevention by LAA occlusion devices is mainly based on data from the PROTECT AF (10) and PREVAIL study (11). Both studies were randomized trials designed to establish non-inferiority of the endovascular implanted Watchman

device versus warfarin (2:1 design). The composite primary efficacy endpoint of the trials was all cause stroke (both haemorrhagic and ischemic), systemic embolization, and cardiovascular death. Following successful implantation, the drug regime consisted of warfarin (target international normalized ratio between 2.0 and 3.0) and aspirin (81 mg) for 45 days. Thereafter warfarin was discontinued when transesophageal echocardiography revealed no device associated thrombi or residual leak >5 mm (10). The PROTECT AF study included 707 patients with paroxysmal, persistent or permanent AF with a $CHADS_2$ risk score >1. The Watchman device was successfully implanted in 88% of patients. After a mean follow-up of 18 months, Watchman device left atrial occlusion was found to be non-inferior to warfarin for the composite primary endpoint (10). Concerns were raised about adverse events (primarily peri-procedural complications) in the Watchman device group (1.1% peri-procedural stroke and 4.8% pericardial effusion requiring percutaneous or surgical drainage). To address these issues the FDA required a follow-up study. In the PREVAIL study, 407 patients with a slightly higher $CHADS_2$ score were included (mean $CHADS_2$ score 2.6±1.0 in PREVAIL, and 2.2±1.2 in PROTECT AF). Procedure-related outcomes consisted of lower adverse events rate (2.2%) and higher successful device implantation (95%). Non-inferiority of Watchman to long-term warfarin for the composite co-primary endpoint of stroke, systemic embolism, and cardiovascular or unexplained death was not reached. Importantly, more late ischemic stroke events in the Watchman arm were observed after 14 months (11).

Holmes *et al.* recently performed a meta-analysis with the combined data of the PREVAIL and PROTECT AF trials (12). In addition, outcome data from two registries (CAP and CAP 2) were included in the analysis. A total of 2,406 patients were studied (1,877 were treated with the Watchman device and 382 received warfarin) with 5,931 patient-years follow-up available.

The hazard ratio for the composite efficacy endpoint was 0.79 (95% confidence interval: 0.53-1.2; P=0.22) meeting non-inferiority of LAA occlusion *vs.* warfarin. All-cause stroke or systemic embolism rates per 100 patient-years were 1.75 for device *vs.* 1.87 for warfarin (P=0.94). There were more ischemic strokes in the device group (1.6 *vs.* 0.9 events/100 patient-years, P=0.05) but this was only the case if procedure-related strokes were included. The Watchman group had less haemorrhagic strokes (0.15 *vs.* 0.96 per 100 patient-years, P=0.004). Finally there was a significant reduction in cardiovascular and unexplained death with the Watchman device (hazard ratio: 0.48; P=0.006). This mortality benefit was believed to be the result of a reduction in haemorrhagic strokes.

The findings of the meta-analysis suggest that LAA occlusion with the Watchman device can provide stroke protection with comparable efficacy as warfarin and at the same time there is less change of haemorrhagic strokes. On the other hand remaining procedural safety concerns warrant cautious use.

In March 2015, the FDA approved the use of the Watchman in the United States for stroke prevention in patients who: "*1. are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores and are recommended for anticoagulation therapy; 2. are deemed by their physicians to be suitable for warfarin; and 3. have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin*". The clinical reality is that LAA occlusion procedures are mainly performed in patients who are considered ineligible for anticoagulation because of (recurrent) episodes of serious bleeding. It should be mentioned however that these patients were not included in PROTECT AF and PREVAIL. In fact, all four Watchman studies excluded patients with a contraindication for warfarin. Thus, the long-term safety has not been studied properly in a sufficiently powered study. A special concern is the short-term use of both warfarin and antiplatelet agents following implantation in these high-risk patients. Although the risk of bleeding was lower in the device arm compared to warfarin in the PROTECT AF and PREVAIL trial, it remains to investigate whether this is also the case in a group of patients with a high bleeding risk. In these patients, especially those who had a previous intracranial bleeding, an alternative approach may also be a non-vitamin K antagonist anticoagulant drug.

Notwithstanding these limitations, for those patients who have an absolute contraindication for oral (novel) anticoagulation drugs but who also have a strong indication for anticoagulation, LAA occlusion is the best available alternative treatment. With further improvements in device design of the Watchman and other LAA closure devices, and increased implantation experience, safety is likely to improve in the years to come. An improved risk benefit ratio will favour use of LAA occlusion devices and establish its role in clinical practice.

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Footnote

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References

1. Ball J, Carrington MJ, McMurray JJ, et al. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. Int J Cardiol 2013;167:1807-24.
2. Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham Study. Stroke 1996;27:1760-4.
3. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137:263-72.
4. Dogliotti A, Paolasso E, Giugliano RP. Current and new oral antithrombotics in non-valvular atrial fibrillation: a network meta-analysis of 79 808 patients. Heart 2014;100:396-405.
5. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996;61:755-9.
6. Brambatti M, Connolly SJ, Gold MR, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. Circulation 2014;129:2094-9.
7. Cox JL, Ad N, Palazzo T. Impact of the maze procedure on the stroke rate in patients with atrial fibrillation. J Thorac Cardiovasc Surg 1999;118:833-40.
8. Almahameed ST, Khan M, Zuzek RW, et al. Left atrial appendage exclusion and the risk of thromboembolic events following mitral valve surgery. J Cardiovasc Electrophysiol 2007;18:364-6.
9. Whitlock R, Healey J, Vincent J, et al. Rationale and design of the Left Atrial Appendage Occlusion Study (LAAOS) III. Ann Cardiothorac Surg 2014;3:45-54.
10. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet 2009;374:534-42.
11. Holmes DR Jr, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol 2014;64:1-12.
12. Holmes DR Jr, Doshi SK, Kar S, et al. Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation: A Patient-Level Meta-Analysis. J Am Coll Cardiol 2015;65:2614-23.

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