Left atrial appendage occlusion using the PLAATO system in high-risk patients with atrial fibrillation – long-term follow-up

Zamknięcie uszka lewego przedsionka przy użyciu systemu PLAATO u chorych wysokiego ryzyka z migotaniem przedsionków – obserwacja długoterminowa

Krzysztof Kukuła[1], Mariusz Kłopotowski[1], Marek Konka[2], Adam Witkowski[1], Witold Rużyłło[1]

[1] 1st Department of Coronary Artery Disease and Catheterization Laboratory, Institute of Cardiology, Warsaw, Poland
[2] Department of Congenital Heart Disease, Institute of Cardiology, Warsaw, Poland

Post Kardiol Interw 2009; 5, 2 (16): 51-57

Abstract

Background: Vitamin K antagonists (VKA) remain the treatment of choice for stroke prevention in high-risk AF patients. However, there is a large proportion of patients who are not receiving VKA because of comorbidities or past adverse events. In such cases percutaneous left atrial appendage (LAA) occlusion has been proposed as an alternative to VKA. The concept was based on the fact that approximately 90% of all thrombi originate in the left atrial appendage.

Aim: The aim of the study was to assess the long-term safety and efficacy of percutaneous LAA closure using the PLAATO device.

Methods: Six high-risk AF patients, in whom an attempt was made to close the LAA using the PLAATO device, were included in the study. Follow-up data were obtained during patient visits and by telephone interview. The study was performed as part of the original European PLAATO Study.

Results: Of the 6 patients in whom device implantation was attempted, percutaneous LAA occlusion was successful in 5 cases (83.3%). The procedure failed in one patient because of unusual LAA anatomy. There were no periprocedural complications. The average $CHADS_2$ score of the five treated patients was 3.0 (range 2 to 5). Median follow-up was 54 months and ranged from 48 to 59 months. All patients discontinued VKA. No patients died. There were no cases of ischaemic stroke. There were no cases of intracranial or gastrointestinal bleeding.

Conclusions: Percutaneous LAA closure with the PLAATO device is a feasible procedure and seems to prevent ischaemic stroke in high-risk AF patients. However, large, randomized studies are needed to prove its true benefit.

Key words: atrial fibrillation, PLAATO, left atrial appendage

Streszczenie

Wstęp: Antagoniści witaminy K pozostają lekami z wyboru w prewencji udarów niedokrwiennych u chorych z migotaniem przedsionków i wysokim ryzykiem incydentów zakrzepowo-zatorowych. Duży odsetek chorych nie otrzymuje jednak zalecanego leczenia z powodu chorób towarzyszących lub wcześniejszych powikłań związanych z leczeniem przeciwkrzepliwym. W takich przypadkach alternatywą dla antagonistów witaminy K może być przezskórne zamknięcie uszka lewego przedsionka, które jest źródłem ok. 90% skrzeplin odpowiedzialnych za udar niedokrwienny w przebiegu migotania przedsionków.

Cel: Ocena bezpieczeństwa i skuteczności przezskórnego zamknięcia uszka lewego przedsionka przy użyciu systemu PLAATO w obserwacji długoterminowej.

Metody: Do badania włączono 6 chorych z migotaniem przedsionków i wysokim ryzykiem mózgowych incydentów niedokrwiennych, u których podjęto próbę przezskórnego zamknięcia uszka lewego przedsionka z użyciem systemu

Adres do korespondencji/*Corresponding author:* dr. n. med. Krzysztof Kukuła, I Klinika Choroby Wieńcowej i Pracownia Hemodynamiki, Instytut Kardiologii, ul. Alpejska 42, 04-628 Warszawa, tel. +48 22 815 30 11, faks +48 22 613 38 19, e-mail: krzysiokuk@yahoo.com
Praca wpłynęła 15.05.2009, przyjęta do druku 19.05.2009.

PLAATO w ramach Europejskiego Badania PLAATO. Informacje o chorych podczas obserwacji zbierano w czasie regularnych wizyt ambulatoryjnych i poprzez kontakt telefoniczny.

Wyniki: Przezskórne zamknięcie uszka lewego przedsionka było skuteczne u 5 chorych (83,3%). W jednym przypadku nie implantowano okludera z powodu nietypowej anatomii uszka. Nie obserwowano powikłań okołozabiegowych. W skali $CHADS_2$ ryzyko chorych oceniono średnio na 3 punkty (2–5). Mediana czasu obserwacji wyniosła 54 miesiące (48–59 miesięcy). Wszyscy chorzy zaprzestali przyjmowania antagonisty witaminy K. Żaden chory nie umarł, u żadnego nie wystąpił udar niedokrwienny mózgu. Nie obserwowano krwawień wewnątrzczaszkowych ani krwawień z przewodu pokarmowego.

Wnioski: Przezskórne zamknięcie uszka lewego przedsionka przy pomocy systemu PLAATO jest technicznie możliwe do wykonania i wydaje się skuteczne w profilaktyce udarów niedokrwiennych u chorych wysokiego ryzyka z migotaniem przedsionków. Niezbędne są jednak duże badania z randomizacją, które jednoznacznie ustalą korzyści związane z tym sposobem leczenia.

Słowa kluczowe: migotanie przedsionków, PLAATO, uszko lewego przedsionka

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and affects 3% to 5% of the population older than 65 years [1]. Its incidence increases with age. Patients with AF have a five-fold increased risk of stroke, which remains the first leading cause of long-term disability and one of the major causes of death in this group [2]. The annual risk of stroke in patients with non-valvular AF is approximately 5% [3]. It is estimated that 15% of all strokes may be a consequence of atrial fibrillation [4]. Importantly, it is believed that in AF patients more than 90% of thrombi originate in the left atrial appendage (LAA) [3, 5]. Thromboembolic strokes in AF tend to be more serious than other ischaemic cerebral infarcts, possibly due to the larger dimensions of left atrial appendage thrombi [6, 7]. Currently the first line therapy to prevent cardioembolic complications in AF patients is chronic oral anticoagulation (COA) [2]. A number of prospective randomized trials (e.g. AFFIRM, RACE) have clearly confirmed the efficacy of vitamin K antagonists (VKA) in reducing the risk of death and stroke in patients with AF [8, 9]. VKA are superior to both aspirin and combined antiplatelet therapy [10, 11]. Indications for anticoagulation depend on calculated stroke risk. There are several methods adopted from previous clinical trials used to assess this risk, such as the Atrial Fibrillation Investigators, Stroke Prevention in Atrial Fibrillation, $CHADS_2$ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or transient ischaemic attack) index, Framingham score and others [12]. Out of these, the $CHADS_2$ index is most often used to delineate high-risk patients. Based on the $CHADS_2$

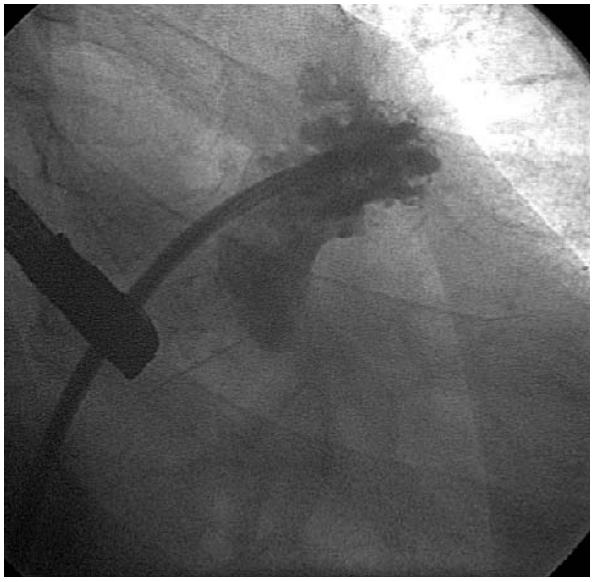

Fig. 1. Fluoroscopic image showing contrast medium injected into the left atrial appendage in order to assess its size before selecting the PLAATO occluder
Ryc. 1. *Obraz fluoroskopowy. Kontrast podany do uszka lewego przedsionka w celu oceny jego wymiarów i wyboru rozmiaru okludera PLAATO*

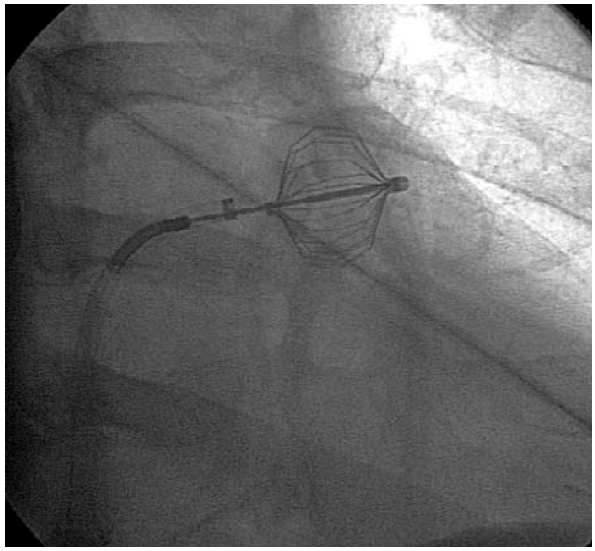

Fig. 2. Fluoroscopy showing PLAATO device expanded in the orifice of the left atrial appendage, still fully retrievable – mounted on the delivery catheter
Ryc. 2. *Obraz fluoroskopowy. Rozprężony okluder PLAATO w ujściu uszka lewego przedsionka. Na tym etapie zabiegu urządzenie jest nadal umocowane na cewniku i może być ponownie wycofane do systemu wprowadzającego*

score, high-risk patients (previous stroke or transient ischaemic attack or the presence of more than one risk factor: congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus) should be treated with VKA, whereas aspirin can be offered for low-risk cases (0 or 1 risk factor) [13]. However, around 54% of all high-risk patients do not receive COA for a variety of reasons, including: poor and difficult INR control, concern about bleeding, allergy, poor tolerance or just patient's preference [14-16]. In addition, only 60% of VKA treated patients are within the therapeutic INR range [17]. New oral anticoagulants, such as direct thrombin inhibitors and factor Xa inhibitors, do not require regular INR controls and are being studied in randomized clinical trials in AF patients, but they are not available on the market for this indication [18]. In some cases combined antiplatelet therapy may be used as an alternative treatment for high-risk patients unsuitable for VKA, but one must take into account their lower efficacy than COA and similar risk of severe bleeding [10, 11]. Assuming that the left atrial appendage is the major source of emboli, a way to prevent ischaemic stroke among AF patients is to exclude the LAA from circulation [3]. This may be done surgically by LAA ligation if the patient is undergoing cardiac surgery for other reasons [5, 19]. However, surgical LAA exclusion is grossly impractical and sometimes incomplete, increasing in this last instance the risk of thromboembolic complications [20]. In the last decade a method of percutaneous transcatheter occlusion of the LAA was introduced into clinical practice in an attempt to replace COA, at least in selected patients, and avoid bleeding complications [3]. Initial studies have demonstrated the feasibility and short-term benefit of this strategy [21, 22]. However, long-term data are still very limited [23-26]. Several devices have been used for this purpose, such as the PLAATO system (percutaneous left atrial appendage transcatheter occlusion, ev3, Plymouth, Minnesota, USA), WATCHMAN filter system (Atritech, Plymouth, Minnesota, USA) and several types of Amplatzer septal occluders (AGA Medical Corporation, Golden Valley, Minnesota, USA) [3]. The present study was performed as part of the original European PLAATO Study to give some insight into the long-term safety and efficacy of LAA occlusion with the PLAATO device in several AF patients unsuitable for COA, recruited in our centre.

Methods

From May 2004 until April 2005 six patients were included in whom an attempt was made to close the left atrial appendage using the Ev3 PLAATO device (X-Sept transseptal sheath and X-Caliber System). This is a self-expandable nitinol implant covered with polytetrafluoroethylene membrane (ePTFE) on the orifice side. Patients read and signed the informed consent to participate in the trial. The study has been approved by

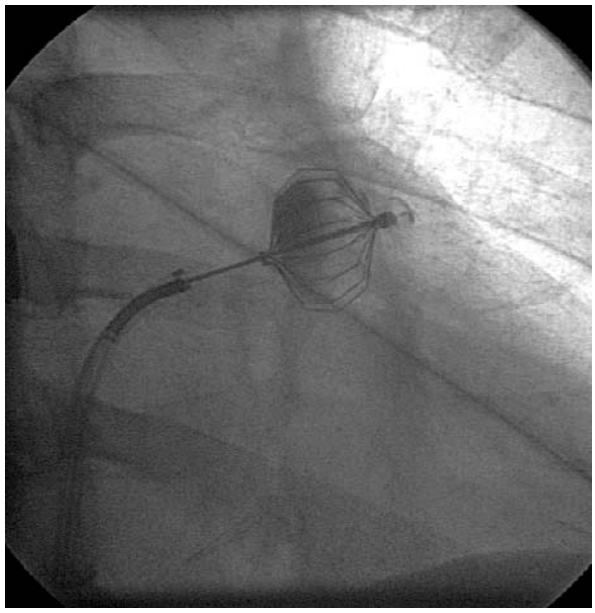

Fig. 3. Fluoroscopy showing contrast injected from the distal end of the delivery catheter trapped inside the occlusion device, confirming correct exclusion of the left atrial appendage (LAA). During the control of device position and LAA exclusion adequacy, contrast medium was also injected proximally to the device – not shown here

Ryc. 3. *Obraz fluoroskopowy ukazujący podanie kontrastu z dystalnego końca cewnika. Kontrast uwięziony w uszku lewego przedsionka dowodzi szczelności jego zamknięcia. W tym samym celu na tym etapie zabiegu kontrast podawano również proksymalnie do okludera (tego elementu zabiegu nie przedstawiono na rycinie)*

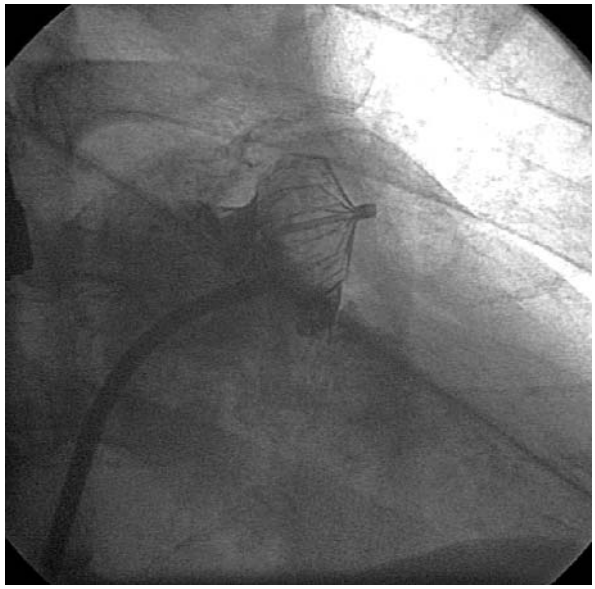

Fig. 4. Fluoroscopic image showing implant released from the delivery catheter and contrast injected proximally, confirming left atrial appendage closure

Ryc. 4. *Obraz fluoroskopowy. Okluder uwolniony z cewnika. Proksymalnie podany kontrast potwierdza zamknięcie uszka lewego przedsionka*

the appropriate Ethics Committee. All patients received a loading dose of 300 mg of aspirin and 300 mg of clopidogrel at least 4 h before the procedure. Clopidogrel was continued for 6 months after the procedure at the maintenance dose (75 mg daily), while aspirin was given indefinitely at a dose of 75--100 mg daily. The procedures were performed under general anaesthesia and were guided by fluoroscopy and transoesophageal echocardiography (TEE). After transseptal puncture unfractionated heparin was given in a dose sufficient to increase the activated clotting time to over 250 s (usually the starting bolus dose was about 100 units per kg). Contrast medium was then injected into the LAA to assess its size and location with respect to the delivery system (fig. 1). LAA orifice diameter was also assessed by TEE and the reference size was calculated as a mean of both measurements. The chosen PLAATO device size was around 20% larger than the calculated reference LAA diameter. After positioning in the LAA the implant was expanded by retracting the delivery sheath. Its position and sealing were then checked by contrast injection and TEE (fig. 2 and 3). Afterwards, the delivery catheter was gently moved back and forth to ensure adequate anchorage and positioning. This was monitored with fluoroscopy and TEE. If repositioning was required, the occluder was retracted into the delivery sheath and reimplanted or a larger device was used. Positioning satisfactory, the implant was released and one more contrast injection into the left atrium to demonstrate sealing and device position was performed (fig. 4). Patients were discharged within 48 h of the procedure. The first follow-up visit was performed after one month. A follow-up visit with TEE assessment was performed after 2 months post-procedure and after that visits with clinical assessment were scheduled at 6 months, 1 year, 2 years and 4 years. Additionally, in April 2009 each patient completed a telephone interview.

Results

Baseline clinical and echocardiographic characteristics of all included patients are presented in tables 1 and 2.

Of the 6 patients in whom device implantation was attempted, percutaneous LAA occlusion was successful in 5 cases (83.3%). In one female patient with unusual LAA anatomy the procedure was unsuccessful due to inability to position the implant securely within the LAA after crossing the septum. The delivery sheath was too stiff and the operator was not able to bend it appropriately. There were no periprocedural deaths or severe complications related to the procedure. In one patient the device implantation evoked an atrial flutter episode that was subsequently treated with DC cardioversion. The average LAA diameter was 22.8 mm in echocardiography and 22.6 mm in fluoroscopy.

Table 1. Clinical and demographic characteristics of treated patients
Tabela 1. *Charakterystyka kliniczna i demograficzna chorych*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex	male	male	male	male	female	male
Age [years]	67	36	75	46	78	72
CAD	yes	no	yes	no	yes	yes
Atrial fibrillation	paroxysmal	chronic	paroxysmal	chronic	chronic	chronic
DCM	no	yes	no	yes	no	no
Diabetes	yes	no	no	no	no	yes
NYHA class	III	II	I	II	III	II
LVEF [%]	50	30	60	30	55	35
Hypertension	yes	no	yes	yes	yes	yes
Stroke or TIA	no	yes	no	no	no	yes
$CHADS_2$ score	3	3	2	2	3	5
Annual risk for ischaemic stroke (without VKA) based on $CHADS_2$ score [%]	5.9	5.9	4	4	5.9	12.5
Antiarrhythmic and 'rhythm control' agents	bisoprolol amiodarone	carvedilol	metoprolol propafenone	atenolol digoxin	bisoprolol digoxin	bisoprolol
Reason for inclusion	difficulties to maintain INR within the therapeutic range	non-compliant on VKA; TIA while on VKA	not willing to take VKA	difficulties to maintain INR within the therapeutic range	recurrent severe nosebleed during VKA treatment	stroke despite VKA treatment

Table 2. Left atrial appendage and PLAATO occluder sizes used in treated patients
Tabela 2. *Wymiary uszka lewego przedsionka i wybrane rozmiary okluderów PLAATO u chorych biorących udział w badaniu*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
LA dimension [mm]	57 × 54	38 × 42	44 × 56	26 × 52	41 × 46	50 × 67
LAA diameter echo-cardiography [mm]	22.4	20.0	16.4	31.1	20.0	27
LAA diameter fluoroscopy [mm]	23.2	20.7	20.9	22.5	21.2	27.7
Expanded implant diameter on fluoroscopy [mm]	23.6	25.0	22.4	27.3	device not implanted	27.7

The median implant size was 25 mm. Angiography and transoesophageal echocardiographic examination immediately after the procedure confirmed LAA occlusion in all 5 patients, with a mild residual leak in two patients. There were no pericardial effusions noted after the procedures.

Median follow-up was 54 months and ranged 48-59 months. All patients discontinued COA. No patients died. There were no cases of ischaemic or haemorrhagic stroke. Systemic embolization or long-term complications associated with the device were not observed. TEE performed after 2 months confirmed correct and stable positioning of the PLAATO device in all patients, with mild leak persisting in one case. During follow-up there were no cases of intracranial or gastrointestinal bleeding. Of the seven hospitalizations that took place during follow-up one was for unstable coronary artery disease, two were for heart failure exacerbations and four were due to atrial fibrillation episodes.

The average $CHADS_2$ score of the five treated patients was 3.0 (range 2 to 5). One patient had a history of stroke and one of transient ischaemic attack (TIA). On this basis the calculated annual risk for stroke in the treated group would be around 6.5% with no anticoagulation, around 5% assuming they were taking aspirin (22% risk reduction) and 2.1% on COA (67% risk reduction). In our group the event-free survival during median 54-month follow-up was 100%, but one must consider the very small sample size, making most statistical comparisons inappropriate.

Discussion

This is yet another study stemming from the original PLAATO evaluation trial, demonstrating in a small group of patients, during long-term follow-up, the safety and apparent efficacy of LAA occlusion using the PLAATO transcatheter occlusion device [22-26]. There have been other small reports published, all demonstrating the efficacy of the PLAATO occluder, all of which were non-randomized [24, 25]. Shorter term data based on a large patient group are available from the North American and European PLAATO feasibility studies that included 210 patients overall with a mean follow-up of 14.7 months [3, 23]. In those studies procedural success was achieved in 97.6%, while 5 patients experienced stroke, amounting to a 61% reduction from the expected stroke risk in this group. These results are attractive, but it must be taken into account that this is only an indirect comparison in a group of patients with contraindications to COA. A planned randomized PLAATO/COA study was abandoned, reportedly for financial reasons [3].

One of the most important issues associated with atrial fibrillation is the need for anticoagulation to reduce the risk of stroke weighed against the risk of bleeding when anticoagulation is given [2]. VKA remain the treatment of choice, but despite their efficacy, are a solution far from perfect in the prevention of stroke in AF patients. COA is difficult to maintain, has potential significant serious adverse effects, of which the risk of bleeding is the most important, and is inconvenient due to the need of repeated international normalized ratio (INR) assessments. Because of this, nearly half of eligible patients are not treated with VKA [13-15]. Out of the remaining 50% many have unstable or often sub-therapeutic INR values [16]. A solution to this vital clinical problem may lie in oral factor Xa antagonists or direct thrombin inhibitors, currently undergoing evaluation in advanced phase clinical trials. However, it is likely that these new drugs will not eliminate the danger of bleeding, especially in the high bleeding risk patient group. Bleeding is often a serious adverse event, increasing patient morbidity and mortality. It has repeatedly been shown that the patients with high risk of bleeding are also those with a high risk of thromboembolic complications.

If we accept the somewhat uncertain data that in non-valvular AF more than 90% of strokes are caused by thrombi originating from the LAA [5], the potential benefit of LAA occlusion stands out as a nearly ideal treatment for high stroke and bleeding risk patients. Two possibilities of occluding the LAA exist – the surgical and the percutaneous method [3]. The surgical method has been used for many years with mixed results, as a high percentage of residual leaks was reported (13–57%), which could actually increase stroke risk [27]. Currently

this method is being evaluated in the LAAOS randomized trial, which is planned to include 2500 patients [28]. Until the results are published there is really no evidence base supporting this approach.

An alternative is to exclude the LAA from the circulation using a percutaneously implanted occluding device. Three types of these devices have been used so far. They are the PLAATO system, the Watchman device and several types of Amplatzer septal occluders. All have been shown to be feasible and seemingly efficacious, with the PLAATO occluder probably the most difficult to use of the three because of the rather stiff delivery system [29]. However, only one of these has undergone evaluation in a randomized study [30].

The results of the PROTECT AF study have been made public recently [31]. This randomized study compares the Watchman device to COA in 800 non-valvular AF patients. COA was discontinued in 87% of the LAA occlusion group. The risk of stroke was similar in both groups (risk ratio 0.96; 95% CI 0.43-2.57), but one must take into account that this was a low or moderate stroke risk population (approximately 65% of patients were $CHADS_2$ 1 or 2). Unfortunately, there was a 7.2% incidence of periprocedural complications in the Watchman device group (usually pericardial effusions), of which 5% were serious. PROTECT AF is the first study clearly demonstrating the potential of LAA occlusion in stroke prevention, in non-valvular AF patients. Because of some safety issues (risk of serious pericardial effusion and small added risk of periprocedural stroke) it has not been accepted so far by the FDA (American Food and Drug Administration), although the advisory panel voted 7 to 5 in favour of approving the device [32]. As other percutaneous devices lack randomized studies, none of them have received FDA clearance for this indication.

As it is, for the time being there is no valid alternative to COA and until further data are available from randomized trials or the Watchman device is approved, neither percutaneous devices nor surgical closure may be recommended for stroke prevention in high-risk AF patients.

Conclusions

Stroke complicating chronic or paroxysmal AF constitutes a clinical challenge for which currently only COA is a valid treatment. Other methods are under evaluation, which may soon completely change the way we treat AF patients. An attractive therapeutic option is LAA occlusion. However, none of the currently available devices have been approved by the FDA for this indication. Until more data become available and some improvements to the technology are introduced, LAA occlusion should not be viewed as an alternative to COA.

However, our and previous data support the idea of percutaneous LAA closure for selected AF patients with contraindications to VKA, especially those with high risk of serious bleeding.

References

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. JAMA 2001; 285: 2370-2375.
2. Crystal E, Connolly SJ. Role of oral anticoagulation in management of atrial fibrillation. Heart 2004; 90: 813-817.
3. Onalan O, Crystal E. Left atrial appendage exclusion for stroke prevention in patients with nonrheumatic atrial fibrillation. Stroke 2007; 38: 624-630.
4. Kannel WB, Wolf PA, Benjamin EJ, et al. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998; 82: 2N-9N.
5. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996; 61: 755-759.
6. Anderson DC, Kappelle LJ, Eliasziw M, et al. Occurrence of hemispheric and retinal ischemia in atrial fibrillation compared with carotid stenosis. Stroke 2002; 33: 1963-1967.
7. Harrison MJ, Marshall J. Atrial fibrillation. TIAs and completed strokes. Stroke 1984; 15: 441-442.
8. Lip GY, Boos CJ. Antithrombotic treatment in atrial fibrillation. Heart 2006; 92: 155-161.
9. Sherman DG, Kim SG, Boop BS, et al. National Heart, Lung, and Blood Institute AFFIRM Investigators. Occurrence and characteristics of stroke events in the Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management (AFFIRM) study. Arch Intern Med 2005; 165: 1185-1191.
10. Laupacis A, Boysen G, Connolly S, et al. The efficacy of aspirin in patients with atrial fibrillation: analysis of pooled data from 3 randomized trials. Arch Intern Med 1997; 157: 1237-1240.
11. ACTIVE Writing Group of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006; 367: 1903-1912.
12. Fang MC, Go AS, Chang Y, et al. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. J Am Coll Cardiol 2008; 51: 816-817.
13. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke. JAMA 2001; 285: 2864-2870.
14. Waldo AL, Becker RC, Tapson VF, et al. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. J Am Coll Cardiol 2005; 46: 1729-1736.
15. Hylek EM, D'Antonio J, Evans-Molina C, et al. Translating the results of randomized trials into clinical practice: the challenge of warfarin candidacy among hospitalized elderly patients with atrial fibrillation. Stroke 2006; 37: 1075-1080.
16. Somerfield J, Barber PA, Anderson NE, et al. Not all patients with atrial fibrillation-associated ischemic stroke can be started on anticoagulant therapy. Stroke 2006; 37: 1217-1220.
17. Van Walraven C, Jennings A, Oake N, et al. Effect of study setting on anticoagulation control: a systematic review and metaregression. Chest 2006; 129: 1155-1166.
18. Kłopotowski M, Małek LA, Rużyłło W. Direct factor Xa inhibitors in acute coronary syndromes. Post Kardiol Interw 2009; 1: 35-40.
19. Johnson WD, Ganjoo AK, Stone CD, et al. The left atrial appendage: our most lethal human attachment! Surgical implications. Eur J Cardiothorac Surg 2000; 17: 718-722.
20. Katz ES, Tsiamtsiouris T, Appelbaum RM, et al. Surgical left atrial appendage ligation is frequently incomplete: a transesophageal echocardiographic study. J Am Coll Cardiol 2000; 36: 468-471.
21. Sievert H, Lesh MD, Trepels T, et al. Percutaneous left atrial appendage transcatheter occlusion to prevent stroke in high-risk patients with atrial fibrillation: early clinical experience. Circulation 2002; 105: 1887-1889.

22. Ostermayer SH, Reisman M, Kramer PH, et al. Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: results from the international multicenter feasibility trials. J Am Coll Cardiol 2005; 46: 9-14.
23. Bayard Y, Omran H, Kramer P, et al. Worldwide experience of percutaneous left atrial appendage transcatheter occlusion (PLAATO). J Neurol Sci 2005; 238: S70-S70.
24. Schmidt H, Hammerstingl C, von der Recke G, et al. Long-term follow-up in patients with percutaneous left atrial appendage transcatheter occlusion system (PLAATO): risk of thrombus formation and development of pulmonary venous obstruction after percutaneous left atrial appendage occlusion. J Am Coll Cardiol 2006; 47: 36A.
25. De Meester P, Thijs V, Van Deyk K, et al. Prevention of stroke by percutaneous left atrial appendage closure. Short term follow-up. Int J Cardiol 2008; article in press.
26. Hanna IR, Kolm P, Martin R, et al. Left atrial structure and function after percutaneous left atrial appendage transcatheter occlusion (PLAATO): six-month echocardiographic follow-up. J Am Coll Cardiol 2004; 43: 1868-1872.
27. Healey JS, Crystal E, Lamy A, et al. Left Atrial Appendage Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke. Am Heart J 2005; 150: 288-293.
28. Mobius-Winkler S, Schuler GC, Sick PB. Interventional treatments for stroke prevention in atrial fibrillation with emphasis upon the WATCHMAN device. Curr Opin Neurol 2008; 21: 64-69.
29. Bayard YL, Ostermayer SH, Sievert H. Alternatives to warfarin in atrial fibrillation: drugs and devices. Heart 2008; 94: 1113-1116.
30. Fountain RB, Holmes DR, Chandrasekaran K, et al. The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients with Atrial Fibrillation) trial. Am Heart J 2006; 151: 956-961.
31. http://www.theheart.org/article/951777.do, from i2 Summit of the American College of Cardiology 2009 Scientific Sessions
32. http://www.theheart.org/article/962955.do