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Transcatheter left atrial appendage occlusion in patients with atrial fibrillation

Przezskórne zamknięcie uszka lewego przedsionka u pacjentów z migotaniem przedsionków

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Słowa kluczowe
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Summary

Atrial fibrillation is one of the most common cardiac arrhythmias. It affects 1-2% of the total population, and the frequency of its incidence increases with age. The threefold increase in the incidence of this disease is projected by 2050. In patients with atrial fibrillation there is a high risk of embolism in particular ischemic stroke. There are two main types of preventing the impact on the brain associated with occurrence of atrial fibrillation. The first is the use of chronic anticoagulant therapy, and the second is closing the left atrium appendage as a source of embolic material. The paper presents systems for transcatheter closing of the left atrial appendage in patients with atrial fibrillation. Describes the indications for this type of treatment and the results of available randomized trials.

Streszczenie

Migotanie przedsionków jest jedną najczęściej występujących arytmii serca. Obserwuje się go u ok. 1-2% ogólnej populacji, a częstość jego występowania wzrasta wraz z wiekiem. Do roku 2050 przewiduje się trzykrotny wzrost zachorowalności na to schorzenie. U pacjentów z migotaniem przedsionków występuje szczególnie duże ryzyko wystąpienia zatorowości obwodowej a w szczególności niedokrwiennego udaru mózgu. Wyróżnia się dwa główne sposoby zapobiegania udarom mózgu związanym z występowaniem migotania przedsionków. Pierwszy z nich to stosowanie przewlekłej terapii przeciwzakrzepowej, a drugi to zamknięcie uszka lewego przedsionka jako źródła materiału zatorowego. W pracy przedstawiono systemy służące do przezskórnego zamykania uszka lewego przedsionka u chorych z migotaniem przedsionków. Opisano wskazania do tego typu zabiegów oraz wyniki dostępnych randomizowanych badań.

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INTRODUCTION

Atrial fibrillation is one the most common significant heart arrhythmias. It affects 1-2% of the total population, and the frequency of its incidence increases with age (1-4). A triple increase in the incidence of this disorder is projected by 2050 (5). There occurs particularly high risk of peripheral embolism and, in particular, ischemic stroke in patients with atrial fibrillation. The risk of stroke in patients with atrial fibrillation of non valvular origin is about 5% per year (6). In the research by Framigham, it has been shown, however, that the mortality rate of patients due to a stroke resulting from the atrial fibrillation is significantly higher in comparison to the strokes not connected with arrhythmia (7). This fact indicates the necessity of effective treatment and prevention in case of the occurrence of stroke in these patients. There are two main types of preventing the impact on the brain associated with occurrence of atrial fibrillation. The first is the use of chronic anticoagulant therapy, and the second is closing the left atrium appendage as a source of embolic material. The closure may be performed with surgical, thoracoscopic or percutaneous method. Randomized clinical studies show that the use of oral anticoagulant therapy is an effective method to reduce the risk of embolism and ischemic stroke. Sometimes, however, it is not fully exploited in patients with atrial fibrillation because of the risk of bleeding, contraindications or the lack of cooperation on the part of the patient (8-13). One of the most modern and dynamically developed methods used in the prevention of stroke in patients with atrial fibrillation is transcatheter atrial appendage occlusion.

This method, however, is recommended only for patients unable to use chronic anticoagulant therapy.

THE ANATOMY OF THE LEFT ATRIAL APPENDAGE

The left atrial appendage is the remnant of the embryological left atrium. It is a tubular structure with various patches and very variable morphology. Its complicated structure is conducive to the blood retention. It is especially evident during atrial fibrillation. The appendage consists of a very soft and thin "paper wall" and its ostium of very variable size from 5-40 mm is located between the mitral ring and the left upper lung vein. Its morphology can be very diverse and may resemble a shape of: a cactus, hen comb, sleeve or a cauliflower (14, 15). Echocardiographic studies have shown that in patients with atrial fibrillation of non-valvular origin, in 90% of cases the thrombus locates in the left atrium appendage. It results from the decrease in the speed of the blood flow, its stagnation, enlargement of the cavity and the increased activity of the platelets adhesion molecules (16-18).

THE HISTORY OF LEFT ATRIAL APPENDAGE OCCLUSION

The concept of closing the left atrium appendage in patients with atrial fibrillation of non-valvular origin is based on the assumption that only 10% of the thrombi does not arise in the left atrium appendage. In conclusion, its exclusion as a potential source of embolic materials should greatly reduce the risk of ischemic stroke and pulmonary embolism. This is confirmed by the observations of patients with atrial fibrillation and congenital absence of the left atrial appendage, where the risk of embolic episodes is relatively small, though it has not been exactly estimated (19-27). Incidental occlusion treatments or resection of the left atrium appendage during the cardio surgery operations have been carried out for many years. In the literature the first of such cases was described by Madden already in 1949 (28). The effectiveness of the surgical resection of left atrium appendage methods in the prevention of stroke was described in patients undergoing coronary artery bypass surgery in a randomized study of LAAOS (LAA Occlusion Study) (29). However, this method is only additional, on the occasion of other cardio surgeries rather than as a standalone procedure. In recent times, occlusion systems have been developed using the electrocardiographic guided thoracoscopic technique (30), and special epicardial stitches led by the magnet (31). At different stages of the research there are other minimally invasive surgical and transcutaneous systems such as Aegis, AtriClip, Cardioablate.

The first transcatheter device for left atrial appendage occlusion was the PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion device). It was designed as a nitinol valve mask frame covered with a polytetrafluoroethylene membrane. The system was introduced to the left atrial appendage by venous system and interventricular septum through appropriately profiled interatrial vascular sheath of diameter of 12F. Settling in the appendage was enabled due to the hooks located on the wires of occluder and passing out through the membrane.

The first implantation of the PLAATO system in a man took place on 30 August 2001 and was conducted by Sievert and Lesh (32). The efficiency of the system has been confirmed in small clinical trials, however, due to the difficult technique of implantation and observed side effects of the system it has been withdrawn from the market in 2006. The second system which was used for the transcutaneous left atrium appendage occlusion was AMPLATZER, designed for atrial septal defect occlusion with two opposite disks. The first treatment with the use of this system was conducted on June 16, 2002 by Bernhard Meier. The treatment was carried out with a local anesthesia (33). In the following years, AMPLATZER was redesigned to match left atrium appendage. In 2008 a dedicated to the left atrial appendage occlusion Cardiac Amplatzer was introduced (ACP, St. Jude, USA) together with a specially developed bringing catheter. The system received CE mark in December 2008. The ACP system is built with nitinol meshwork covered with polyester material. It consists of three parts: central panel, carpal tunnel and disc. The disc has the task of ostium left atrium appendage occlusion. With the usage of the lobe, the position of the occluder stabilizes on the surface of small hooks. The system is available in sizes from 16 to 30 mm. In 2012, a new version of the occluder ACP called AMULET was introduced. The old platform remained the same but the lobe and isthmus was redesigned increasing the amount of catches so as to improve the fixation of the system and its effectiveness to reduce the risk of formation of thrombi. The AMULET system was, however, withdrawn from the market to successive improvements.

July 12, 2002 in Leipzig first human implantation of the system of WATCHMAN LLA Occluder (Boston Scientific, USA) was performed. The surgery was conducted by Eugen Hauptmann and Eberhard Grube. The system was designed to occlude the left atrium appendage and it consisted of nitinol self-expansible frame covered with a special material, held in the appendage due to the radial force and small anchors. The device is available in 5 sizes from 21 to 33 mm, allowing an exact match to a variable of the anatomy of the appendages. The system is fully repositionable. WATCHMAN LLA Occluder is currently the best system tested system to left atrial appendage occlusion. There are currently many other systems dedicated to left atrial appendage occlusion at different stages of design and research. The stage of development of technology to left atrial appendage occlusion is presented in table 1.

RESEARCH

The best tested occluder to the left atrium appendage occlusion is a WATCHMAN (34-38). **As the only**

Table 1. The state of development of technology for left atrial appendage occlusion.

The company	The device	Description	Implantation method	The advancement of the process of implementation of the clinical practice
Aegis Medical	Aegis Appendage Grasper	Transcutaneous system, epicardialligation of LAA; deep ligation of LAA, based on a record of ECG, including navigation, identification and localization of the tissue	Transcutaneous	Implantations outside the US.
Atricure	AtriClip FLEX	Elimination of LAA with very flexible aluminium ligature system		Met 510 (k) of the FDA
Atricure	AtriClip Long	LAA elimination system with a long wire (25 cm)	Used during open heart surgery (bypass grafting)	Met 510 (k) of the FDA
Atricure	AtriClip Pro	The next generation of the version of AtriCure 1-generation (for use on an open heart) clip for the isolation of LAA. This version is articulated, "robot friendly" and dedicated to small invasive access (right side thoracotomy)	A small invasive cardiac bypass surgery access	Met 510 (k) of the FDA
Atricure	AtriClip Standard	A platform based on a dacron clip to epicardial closing and elimination of LAA; has been developed for both open and small invasive access cardiac surgery; similar to 1-generation developed for the use during open heart treatments	The use of an open heart bypass grafting during surgery	Met 510 (k) of the FDA. Given the CE mark
Atricure	MIS AtriClip	LAA clamping technology using transcutaneous, suprasternal access	Minimally invasive cardiac surgery access	In the study
Boston Scientific	WATCHMAN	Self-expandable device constructed with permeable polyester fabric covered with scaffolding nitinol, equipped with hooks for fixation, implanted from the left part of left atrial appendage by transseptal puncture of interatrial septum	Transcutaneous	Requested PMA/ Given the CE mark. Approved for use by the FDA (13.03.2015)
Boston Scientific	WATCHMAN FLX	The new generation of device WATCHMAN to percutaneous isolation of LAA	Transcutaneous	Completed research FIM
Cardia	Ultrasept	The soft cap for closing LAA, which adapts to the shape of the LAA; can be entered and withdrawn from the LAA by the original guided system	Transcutaneous	FIM study in progress
Coherex	Wavecrest	Occluder LAA, which enables occlusion regardless of the anchoring. There is a possibility of multiple repositioning and withdrawal of the device, it is characterized by a leading edge fabricates more easily	Transcutaneous	Given the CE mark. In preclinical studies in the United States
Custom Medical Devices	Sideris Path	Bio-absorbent of LAA occluder, available in 2 models. Traditional transcutaneous patch delivery system without guide, with a balloon to implantation, has got matching properties and adhesion to surrounding tissues, with immediate release combined with a balloon catheter	Transcutaneous	During the procedure of transmitting the CE mark
Berlin	Tiger Paw II	Disposable device with snap closure/implantation for LAA	Minimally invasive cardiac surgery	Met 510 (k) of the FDA. Approved by the CE mark
Gore	Gore LAA Closure Device	LAA closure system in the early stages of the project. In the United States during the patent procedure, the patent number: 20130018414. The company describes the device as a system consisting of a balloon covered with an adhesive substance stimulating the growth of tissue	Transcutaneous	Work on the development of the idea
IDX Medical	IDX Medical LAA Occlusion Device	Device for closing LAA consisting of terminals, which form a closed ring form matching to a occlusive structure	The use of an open heart bypass grafting during surgery	Work on the development of the idea

Table 1. Cnt.

Javelin	Javelin Embolic Capture Device	Miniature anti-embolic protection device placed under the control of echocardiography, "injected" by the appropriate needle directly into the carotid artery. The device is designed for patients with paroxysmal atrial fibrillation persisted or in cases when anticoagulant treatment is contraindicated	Transcutaneous	During pre-clinical tests
Lifetech	Lambre	Occluder of LAA consisting of parts covering the inner surface of the LAA and specially designed umbrellas that can be repositioned before the final implantation	Transcutaneous	During the broadcasting of the CE mark
Occlutech	Occlutech LAA Occluder	Valve mask nitinol LAA occluder, fixation due to loops instead of hooks, resembling a system Flex II connected with high flexibility	Transcutaneous	FIM study in progress
PFM	PFM LAA Occluder	Nitinol, non-anchor, non-perforating LAA closure system	Transcutaneous	Planned research FIM
SentreHE-ART	Lariat	One part, disposable delivery system establishing and delivering stitch consisting of previously knoted loop of thread size-0	Minimally invasive cardiac surgery	Met 510 (k) of the FDA
St. Jude	ACP	Device for closing LAA consisting of a flexible, plaited, distal nitinol body and proximal disk filled with polyester fabric and connected with a long articulated midriff	Transcutaneous	In the United States scheduled a crucial test. Approved by the CE mark
St. Jude	AMPLATZER AMULET	The next generation of occluder to close LAA from the Jude St company using the design and the success of AMPLATZER clinical Cardiac Plug, available in eight sizes. Occluder is the factory-preset loaded to the delivering system	Transcutaneous	In the United States scheduled a crucial test. Approved by the CE mark

Designation/Marking CE (Conformité Européenne) – placed on the article is a statement of the manufacturer that the marked product fulfils the requirements of directives the so-called "A New Approach" Of The European Union (Eu)
510 (k) – reporting to the FDA before being placed on the market showing that the device is at least as safe and effective and is essentially equivalent to other devices of a particular type (1)
PMA (premarket approval) – any request for approval of premarket class III medical device, including all of the information submitted with the inclusion or by reference. PMA includes a new drug application for the device under section 520 FD & C Act
FIM (first-in-man) – the study of the application of the medical device/drug for the first time in humans (40, 41)

one it was evaluated in randomized prospective studies. The first of these, the study PROTECT AF aimed to show at least the same effectiveness of occluler WATCHMAN as chronic anticoagulant therapy with warfarin (a non-inferiority study). The study included 707 patients with atrial fibrillation and non-valvular with at least one risk factor for peripheral embolism such as the earlier stroke, transient episode of ischemia CUN, heart failure, diabetes, hypertension, age $\geq$ 75. Patients randomly picked 2:1 to transcutaneous left atrium appendage occlusion using WATCHMAN (463) and chronic warfarin therapy with the target indicator of INR between 2 and 3 (244). Patients undergoing intervention received warfarin for 45 days. If transesophageal echocardiography performed after thisperiod showed no leaks around the closing device, the medicine was gradually replaced by clopidogrel and aspirin. Clopidogrel treatment lasted for 6 months. In the group using warfarin – INR measurement was performed not less frequently than every two weeks during the first 6 months and every month thereafter. Observation period amounted to a total of 1588.4 per day (1025.7 in the treatment group and 562.7 in the warfarin group). The left atrium appendage was occluded successfully in 90.9% of patients. Complex endpoint performance evaluation (ischemic stroke, sudden death or heart, hemorrhagic stroke, pulmonary embolism) occurred in 3.0% of patients with treatment group/year and 4.3% in group of warfarin/year (RR 0.71; 95% CI 0.44-1.30, the probability of at least equivalence > 0.999). In assessing the safety of the therapy, the original endpoint was 5.5% in the/year group, in which left atrium appendage wasoccluded in comparison to 3.6% of the/year in the group treated with warfarin (RR 1.53; 95% CI 0.95-2.7). After excluding the incidents that occurred on the day of the intervention, fewer patients from occuler group have experienced primary performance assessment endpoints than the group treated pharmacologically (2.5%/year vs 4.3%/year; probability of superiority = 0.953). Similar results were obtained in the evaluation of patients treated with procedures who stopped the warfarin treatment (2.3%/year vs 4.1%/year; probability of superiority = 0.955). After the extension of the analysis to the patients who have completed the therapy both with warfarin and clopidogrel and those treated only with aspirin, resulted in the incidence of end point security 2.3%/year in the group treated with pro-

cedures and 4.1%/year in the group treated pharmacologically (probability advantage = 0.945). The analysis of these subgroups in terms of the prevalence of safety endpoints (mostly bleeding) showed that they were not more common in the treated group with the procedures than in the group treated pharmacologically (RR 0.77; 95% CI 0.45-1.45) and they were even less common during the aspirin treatment after the surgery (RR 0.35; 95% CI 0.16-0.79) (34, 35). Extremely interesting are the data of a long-term observation of 2621 man-year (that gives the average of ca. 4 years per patient). Originally established endpoint on the 100-year-old was lower in the WATCHMAN group and amounted from 2.3 in comparison to 3.8 in the warfarin group, demonstrating for the first time, the superiority of occluder on anticoagulant therapy (RR 0.60 with the probability of the superiority of 96%) (36). The final analysis of the research PROTECT AF during 1588 persons-years showed that the left atrial appendage occluder WATCHMAN is at least as effective as oral anticoagulant therapy with warfarin in preventing strokes, congestion and deaths. Data from a long-term observation 2621 man-year show the superiority of the occluder procedure LAA on pharmacotherapy.

Some kind of a continuation of the study PROTECT AF was a record of CAP Registry (Continued Access Protocol). The participating centers took part in the study, and patients were excluded on the basis of the same criteria. It confirmed the decline in the percentage of complications related to the procedure, together with the increase in experience of the centre and operators (38).

A second randomized study assessing the efficacy and safety of transcutaneous treatment of left atrial appendage occlusion using the WATCHMAN was PREVAIL trial (prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy). It was to confirm and consolidate the results of the PROTECT AF research. The study included 407 people. Patients were randomized 2:1 to transcutaneous left atrium appendage occlusion using WATCHMAN (269) and chronic warfarin therapy (138). The two endpoints were analyzed to assess the effectiveness of the main (instance of the stroke, peripheral embolism, death from cardiac and unexplained causes within 18 months) and late (instance of the stroke, peripheral embolism during the period between 7 days and 18 months after the surgery) and one safety evaluator (death, ischemic stroke, peripheral pulmonary complications of surgery requiring the cardiac surgery or endovascular intervention within 7 days after surgery). The main established endpoint evaluating the efficiency was 0.064 in the group treated with procedures and 0.063 in warfarin group (RR 1.07; 95% CI 0.57-1.98) and thus has not reached criterion of at least equivalence (non-inferiority). Late complex endpoint of efficacy was 0.0253 in the occluder group in comparison to 0.0200 in the group treated pharmacologically (risk difference 0.0053; 95% CI 0.0190-0.0273) and has reached criterion of at least equivalence. The safety analysis of the treatment showed a significant increase in the effectiveness of the implantation of PREVAIL test 95.1 in comparison to 90.9% in the PROTECT AF. Early security evaluator of the endpoint amounted 2.2% in the occluder group and was substantially lower in relation to the tests of PROTECT AF. Additional safety analysis showed a 52% reduction in serious complications depending on the procedure in relation to the tests of PROTECT AF (respectively 4.5 vs 8.7%), a reduction of 64% percentage of bleeding into the pericardial sac (up 1.9 vs 4%) and dependent on the strokes treatment, 64% (up 0.4 vs 1.1%) (37). Although the main endpoint of efficacy was not obtained, the study showed that the treatment is safe and the percentage of complications is low and decreases when compared to the previous research of PROTECT AF. It also confirmed at least the same efficiency of the transcutaneous closure of the left atrium appendage in comparison to warfarin therapy in the prevention of stroke and peripheral embolism during more than 7 days after the surgery. This seems to confirm the hypothesis that the appendage is the source of embolic material in atrial fibrillation.

CONCLUSIONS

The European Society of Cardiology now recommends transcutaneous treatment for the left atrium appendage occlusion in patients with a high risk of ischemic stroke and administered to chronic oral anticoagulant therapy (class IIb recommendation/B) (39). Absolute contraindication to surgery is unfavorable anatomy or the thrombus present at the left atrial appendage. These recommendations are based on early research results of PROTECT AF and it seems that now they require verification. The data obtained from long observation trial of PROTECT AF registry and CAP suggest the advantage of transcutaneous left atrium appendage occlusion over the chronic oral anticoagulant therapy and decrease the amount of surgery-related complications with the increase in the amount of procedures preformed, the experience of the centre and operators. This treatment may to become an alternative to pharmacological therapy. There is a constant increase in the patients who may become candidates for this type of treatment. These include people with a risk of bleeding, those who do not feel convenient with the prospect of admitting a lifetime of oral anticoagulant medicines, patients with a renewed strokes in spite of the use of oral anticoagulants, patients badly tolerating those medicines, as well as individuals with ischemic heart disease requiring triple anticoagulant therapy, for example after stent implantation DES. The modernization of already existing, as well as the development of new systems of mechanical trombectomy of left atrial appendage can also cause reduced contraindications to these types of treatments. It is also necessary to perform research comparing the effectiveness of different systems to occlude the appendage and the types of therapies used after surgery.

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