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ARTYKUŁ SPECJALNY / *STATE-OF-THE-ART REVIEW*

Transcatheter left atrial appendage occlusion in the prevention of stroke and death in patients with atrial fibrillation

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ATRIAL FIBRILLATION RELATED RISK OF STROKE AND DEATH

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with morbidity directly related to advanced age, presence of hypertension, diabetes, heart failure and coronary heart disease [1]. The threefold rise in AF morbidity predicted by 2050, together with the proven independent two to threefold higher risk of death for men and women in long term follow-up, reinforces the social importance of the disease [2]. The risk of dying is particularly high in the population of AF patients with AF related stroke. According to Framingham Study findings, patients with a history of stroke attributable to AF have 25% and 63% risks of dying within 30 days and one-year follow-up, respectively. Dramatically high mortality and morbidity emphasise the need for effective stroke prevention [3].

IMPACT OF ANTIPLATELET THERAPY ON STROKE PREVENTION

Antiplatelet therapy to prevent vascular events in AF patients has presented disappointing results. Aspirin has shown a 22% relative risk reduction of stroke compared to placebo, but a 36% higher risk than anticoagulation therapy with warfarin [4]. In the population over 75 years old, aspirin therapy has been associated with a 52% higher rate of stroke and a similar incidence of major haemorrhage (2.0% vs. 1.9% per year) compared to warfarin [5]. The combined antiplatelet treatment with aspirin and clopidogrel demonstrated better results than aspirin alone but still worse than warfarin, with a 44% higher risk of vascular complications, and a 30% higher risk of major bleeding [6].

IMPACT OF ANTICOAGULATION THERAPY ON STROKE PREVENTION

The current standard of stroke and death prevention strategy is based on life-long oral anticoagulation mainly using vitamin K antagonists (VKA), having, at a maximum, over 60% relative risk reduction compared to placebo, and more recently on novel anticoagulants [7]. Despite proven benefits, VKA remain underused in clinical practice. Among warfarin-eligible patients, only 50% are actually being treated, and furthermore only half of them are within the therapeutic range of international normalised ratio (INR) [8]. The narrow therapeutic window of VKA results in a delicate balance between lack of efficacy and a significantly elevated risk of bleeding. The variability in pharmacokinetics, leading to the necessity of frequent blood tests, and numerous food and drug interactions, have a major impact on the patient's daily life and furthermore lead to a significant proportion of patients being either sub- or supratherapeutic. In a large study of almost 42,000 patients with AF (ranging from 40 to 85+ years of age) only 70% remained on warfarin at one year and roughly 20% at six years [9]. In light of these findings, novel oral anticoagulants (NOACs) have been investigated as alternatives to VKA.

Apixaban (direct factor Xa inhibitor) proved superior to warfarin in the ARISTOTLE trial with a 21% reduction of stroke and systemic embolism and, more importantly, an 11% mortality reduction [10]. The recently published ENGAGE-AF trial compared two once-daily regimens of edoxaban (direct factor Xa inhibitor) to warfarin in patients with moderate-to-high-risk AF [11]. Both once-daily regimens of edoxaban were non-inferior to warfarin with respect to the prevention of stroke or systemic embolism, and were associated with significantly lower mortality from cardiovascular causes. Another oral factor Xa inhibitor, rivaroxaban, demonstrated non-inferiority to warfarin in the ROCKET-AF

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trial in terms of stroke and systemic embolism [12]. High dose of dabigatran (a direct oral thrombin inhibitor) in the RE-LY trial reduced the incidence of stroke and systemic embolism by 34% compared to warfarin [13]. A recently published online meta-analysis of all 71,683 participants included in the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 trials showed that NOACs compared favourably to warfarin and significantly reduced the risk of stroke (RR 0.81; 95% CI 0.73–0.91; $p < 0.0001$), mainly driven by a reduction in haemorrhagic stroke (RR 0.49; 95% CI 0.38–0.64; $p < 0.0001$) and mortality (RR 0.90; 95% CI 0.85–0.95; $p = 0.0003$). However, interestingly, low-dose regimens showed significantly more ischaemic strokes (RR 1.28; 95% CI 1.02–1.60; $p = 0.045$) [14]. The better than warfarin efficacy, and far better compliance, of NOACs speak for themselves and therefore these drugs are much to be welcomed; unfortunately they are however not free from drawbacks. The issue of having appropriate coverage for very expensive treatment is definitely one of them. The 'early adopter' aspects (four years of NAOCs vs. 50 years of warfarin) are practically crucial for the majority of patients, who are disinclined to use a new drug. The lack of specific antidote is also important especially in emergency situations. NOACs are not free from side effects leading to therapy discontinuation (21% of patients on dabigatran during 24 months of follow-up) [13]. Last, but not least, NOACs cannot be prescribed in impaired renal function. This further limits the group of patients who might start or continue life-long therapy.

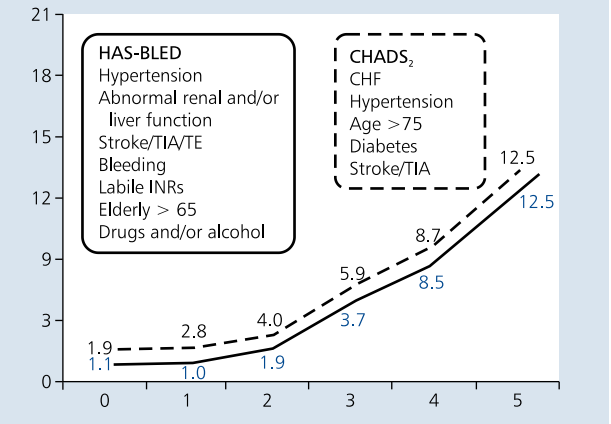

Figure 1. The annual risk of stroke and bleeding according to $CHADS_2$ and HAS-BLED scores [16]; $CHADS_2$ score (dotted black line) — the annual percentage of stroke in population of patients left without anticoagulation (black numbers on dotted line); HAS-BLED score (solid black line) — the annual percentage of patients with bleeding complications on vitamin K antagonist (blue numbers in bars on solid line); CHF — congestive heart failue; INR — international normalised ratio; TE — thromboembolism; TIA — transient ischaemic attack

SAFETY OF ANTICOAGULATION THERAPY

The goal of anticoagulation is to offer the patient therapy that better prevents ischaemic strokes at an acceptable risk of bleeding. The recommendation to treat patients with $CHADS_2$ score ≥ 1 is to offer the therapy to individuals with at least a twice higher risk of stroke than an average annual risk of major bleed carried with warfarin therapy (1.5%/year) [15]. The term 'average bleeding risk', however, is not helpful in an individualised therapy. It has been recently nicely shown that the risk of bleed due to anticoagulation should be quantified just like the stroke risk [16]. Both HAS-BLED and $CHADS_2$ scores calculation may be used to balance the risk of bleeding against the risk of stroke. Three of the clinical features that predict stroke (stroke history, hypertension, advanced age) are also predictors of bleeding. The patients at highest risk of stroke, and therefore with the greatest need for antithrombotic therapy, are precisely those who experience more bleeding (at least on VKA) (Fig. 1) [17]. Individual risk assessment may bring us to an unexpected conclusion and a difficult decision. A patient with HAS-BLED score 4 and $CHADS_2$ score 3, for instance, has a higher risk of major bleed if treated with VKA (8.5%) than the risk of stroke if left without anticoagulation (5.9%). The crucial question, as to whether NOACs may substantially alter this balance, was addressed in the AVERROES trial [18]. That study evaluated the safety and efficacy of apixaban and aspirin in patients for whom VKA were unsuitable. Apixaban reduced the risk of stroke or systemic embolism by 55% without significantly increasing the risk of major bleeding or intracranial haemorrhage. However, the very limited (3%) representation of true bleeders in the AVERROES study meant that definite safety conclusions in patients with a history of bleeding were impossible. The meta-analysis of the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 trials showed that NOACs, in fact, had a favourable risk-benefit profile, however with similar major bleeding as for warfarin, and even increased gastrointestinal bleeds [14]. In truth, there is no data allowing for safe restart of anticoagulation therapy in individuals with a bleeding history. The presence of absolute or relative contraindications limits substantially the use of any anticoagulation drug in clinical practice due to perceived risk and fear of inducing bleeding [19]. Anticoagulation related bleeds may have a devastating or even lethal effect on patient outcome and will not be fully eliminated. This excludes certain patients from any form of anticoagulation therapy. While sinus rhythm following left atrial catheter ablation is better preserved than with antiarrhythmic drugs, late recurrences, even after several attempts, are common [20]. The discontinuation of antithrombotic treatment in patients at risk of stroke is not recommended. For these reasons, device-based therapies combining high efficacy in stroke prevention and low haemorrhagic risk are currently being developed and potentially offer an alternative approach.

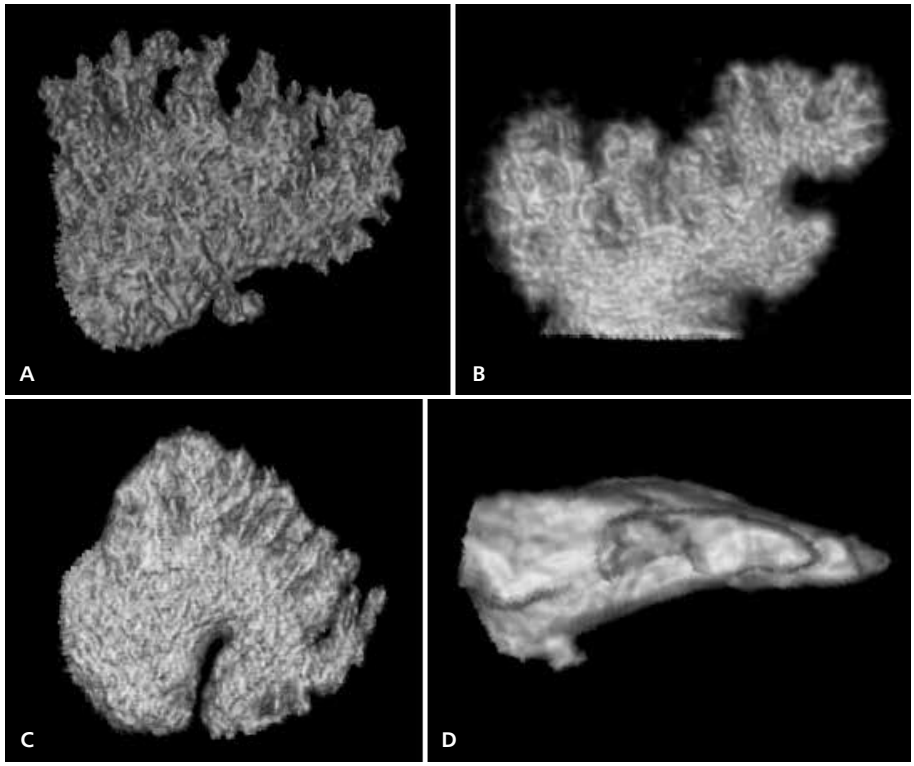

Figure 2. Morphological classification of left atrial appendage [24]; **A**. Cauliflower: a main lobe < 4 cm long without any forked lobes, **B**. Cactus: a main lobe < 4 cm long and > 2 lobes of > 1 cm, **C**. Chicken wing: a main lobe > 4 cm long with a folded angle < 100 degrees, **D**. Windsock: a main lobe > 4 cm long with a folded angle > 100 degrees

ANATOMY AND PHYSIOLOGY OF LEFT ATRIAL APPENDAGE

The left atrial appendage (LAA) is the remnant of the original embryonic left atrium. It has highly variable volume and length and a fragile 'paper-thin' wall [21]. 80% of LAAs have a multilobed anatomy [22]. An oval-shaped ostium, located between the mitral ring and the left upper pulmonary vein, is also highly variable in terms of size (5–40 mm). The LAA morphology categories were developed as part of the evaluation for LAA closure procedures. As with coronary morphology patient risk stratification, an attempt has been made to stratify the risk of stroke according to computed tomography-based LAA anatomy reconstruction [23]. A 'cauliflower' shape, one of four LAA morphologies, (the others are 'cactus', 'windsock', and 'chicken wing' (Fig. 2), independently added to stroke risk stratification in patients with a low risk as measured by $CHADS_2$ score. That was true even after adjustment for the more discriminating CHA_2DS_2-VASc score [24]. Interestingly, the congenital absence of LAA in humans has been documented [25].

The risk of embolic events in patients with AF with a congenital absence of LAA is intuitively low, although the actual risk remains unclear.

The LAA is actively contracting and has a characteristic Doppler flow pattern in sinus rhythm. In patients with AF, blood flow velocity in the LAA frequently decreases, resulting in stasis, volume overload followed by cavity enlargement and increased activity of the platelet adhesion molecules [26]. Structural and biochemical factors in AF favour thrombus formation in LAA. Transoesophageal echocardiographic, surgical and post mortem studies have shown that LAA is the site for thrombus formation in 90% of patients with thrombosis owing to nonvalvular AF [27, 28]. This finding formed the rationale for LAA closure procedures as a stroke prevention therapy among AF patients.

HISTORY OF LEFT ATRIAL APPENDAGE CLOSURE

Surgical exclusion of LAA has more than 60 years of history, with the first resection in a human being described in 1949 [29]. Its efficacy in stroke prevention has been described in several retrospective analyses and in LAAOS (LAA Occlusion Study), the first randomised trial in patients undergoing coronary artery bypass grafting [30]. According to current recommendations, it is only performed as a 'bystander' operation, not as a stand-alone procedure [31]. The transcatheter device-based approach is the next step in the development of a less invasive therapeutic strategy for LAA closure.

The first technology developed was the Percutaneous Left Atrial Appendage Transcatheter Occlusion device ('PLAATO', EV3 Inc., USA). The 'PLAATO' system was designed as a self-expanding nitinol cage covered with an expanded polytetrafluo-

roethylene membrane to be delivered via a venous access and transseptal crossing into the left atrium through a 12 F curved sheath. Anchoring of the device was achieved by hooklets along the struts and passing through the membrane. Animal studies demonstrated the safety and feasibility of implantation, and revealed complete LAA occlusion and healing three months after device implantation with no evidence for thrombi on the implant surface. Sievert and Lesh performed the first human percutaneous LAA occlusion in 2001 [32]. Thereafter, small clinical reports and one prospective observational study have demonstrated efficacy in stroke prevention using 'PLAATO'. However, in 2006 the company took the device off the market because a significant rate of serious adverse events predicted that overly high financial resources would be needed to reach device clinical approval. In 2002, Meier implanted to LAA an 'AMPLATZER' double-disc septal occluder (designed for closure of atrial septal defects). The procedure was performed in an awake patient with local anaesthesia and without transoesophageal echocardiography (TEE) guidance [33]. The practice of implanting septal occluders in LAA was discouraged by the results of a small feasibility study, but pioneering experience provided enormous support for the further development of the devices, TEE omittable technique of implantation and post implantation pharmacotherapy. The 'WATCHMAN' LAA occluder (Atritech Inc. initially and Boston Scientific currently, USA), first implanted in 2002 in Leipzig, is a self-expanding nitinol frame, covered partially by a permeable fabric cap and kept stable in the tissue by its radial force and tiny anchors. The device in available in five sizes ranging from 21 mm to 33 mm, allowing correct accommodation to individual LAA anatomy variations. The device is fully repositionable. Proper sizing prior to implantation as well as a deep enough access sheath intubation is crucial for final success. 'WATCHMAN' is the best-studied device, and has paved the way for the clinical adoption of this therapy. A revised version of the occluder, redesigned according to the closed distal end, is expected this year. Continuous refinement of the Amplatzer technique has led to the development of the dedicated Amplatzer LAA occlusion device system, the Amplatzer Cardiac Plug ('ACP'; St. Jude, USA), which received Conformite Europeenne mark approval in December 2008. The 'ACP' is made of a nitinol mesh and a polyester patch. It consists of three parts: a lobe, a central waist, and a disc. The disc pacifies ostium of the LAA. Device diameter ranges from 16 mm to 30 mm referring to the lobe, being available in eight sizes stepwise by 2 mm. The lobe has stabilising tiny hooks to improve device fixation. The new version of ACP, called 'AMULET', had been introduced in 2012. It kept the existing ACP 1 platform but had been redesigned in terms of the size of lobe and waist and increased number of hooks to improve its performance. The disc-end screw was inverted with the intention of reducing the risk of thrombus formation. The AMULET, however, has been withdrawn from the market for further improvements. The 'WATCHMAN' and 'ACP 1' are the two currently most widely used occluders. Both have unique features and drawbacks, which determine directions for improvements aimed at simplifying the procedure, decreasing the necessity for repositioning, increasing the safety and progressing the feasibility as well as the performance in difficult anatomy. The design of 'LAmbre' (Lifetech), 'WaveCrest' (Coherex), 'Figulla' (Occlutech) LAA occluders and other devices currently entering the clinical arena aim to fulfill the abovementioned criteria. A more complex, although well clinically evaluated, procedure is a 'Lariat suture' (Sentre Heart), applied epicardially via a percutaneous dry pericardiocenthesis and directed toward a magnet wire placed in the LAA via a transseptal approach [34]. This procedure has a unique clinical advantage in patients with paroxysmal AF, combining anatomical and electrophysiological LAA ligation, excluding (as the only LAA occlusion device) potential source for AF initiation [35].

EVIDENCE BASED FEASIBILITY AND EFFICACY OF LEFT ATRIAL APPENDAGE CLOSURE

The currently available LAA occluders, especially in experienced hands, fulfill high feasibility criteria. The studies report almost a 90% success rate of new implanters, rising to 95–96% if performed by experienced operators [36]. There are also reports published in the literature with 98% and even 100% of successful implantations in study groups of 50 and 100 patients, respectively [37, 38]. With growing experience, the procedure related time has substantially decreased, from 70 to 50 min, and the presence of peri-device residual leaks has fallen from 17% to 5% [36]. There is ongoing discussion as to whether the leaks left around the device during the procedure or leaks appearing late due to the dynamic alterations of the left atrial haemodynamics matter in terms of future stroke risk. Although common sense suggests complete closure, there is published data negating the clinical significance of residual leaks [39].

The efficacy measurements criteria are not unified and differ substantially between studies. The 50% to 77% decrease in the incidence of stroke reported during follow-up in light of the expected risk, derived from the average $CHADS_2$ score of the study population, has to be interpreted with caution [40]. The anticipated risk may in fact be truly misleading. In the PREVAIL study, for instance, the observed rate of stroke in the control group was 0.7% in spite of high 2.6 average $CHADS_2$ score [41]. The PROTECT AF, multicentre prospective randomised trial, designed as a non-inferiority study, delivered the highest level of evidence [42]. 707 patients with nonvalvular AF and one or more risk features for systemic embolism (previous stroke, transient ischaemic attack, congestive heart failure, diabetes, hypertension or age ≥ 75 years) were randomised 2:1 into the percutaneous LAA closure with WATCHMAN or chronic warfarin therapy targeting INR of 2–3. A composite of stroke, cardiovascular death and systemic

embolism constituted the primary efficacy end point. During an aggregate of 1,065 patient-years (mean of 18 months follow-up for a patient) the primary efficacy event rate was 3 per 100 patients-years in the device group compared to 4.9 in the control group (rate ratio 0.62 with probability of non-inferiority > 99.9%). The criteria for non-inferiority were also met during prolonged to 1,588 patient-years follow-up (mean of 2.3 years for a patient). The primary efficacy event rate was 3 and 4.3 per 100 patients-years in WATCHMAN and control group, respectively (rate ratio 0.71 with probability of non-inferiority > 99.9%) [43]. Extremely interesting results of long-term (2,621 patient-years) follow-up (mean of four years for a patient) have been recently presented [44]. The primary efficacy event rate per 100 patient-years was lower with the WATCHMAN device compared to controls (2.3 vs. 3.8), demonstrating for the first time the superiority of a device with a 40% relative risk reduction (rate ratio 0.60 with probability of superiority = 96%). The reduction of the primary efficacy end point by WATCHMAN implantation was confirmed in intention-to treat, post-procedure, per-protocol and terminal therapy analyses. In addition, in an intention-to-treat analysis, patients after LAA occlusion were at reduced risk compared to warfarin-treated patients for both all-cause mortality (3.2% vs. 4.8%; HR 0.66; 95% CI 0.45–0.98; p = 0.0379) and cardiovascular mortality (1.0% vs. 2.4%; HR 0.40; 95% CI 0.23–0.82; p = 0.0045). This reduced incidence of primary efficacy end point was driven mainly by mortality and haemorrhagic stroke reduction in the device group.

During the initial 18 month observation, haemorrhagic stroke were less frequent in the WATCHMAN group (0.1 vs. 1.6 events per 100 patient-years) and ischaemic strokes occurred more frequently (2.2 vs. 1.6 events per 100 patient-years), due to five periprocedural events, mainly attributable to air embolism. After the periprocedural timeframe, ischaemic strokes occurred less frequently in the WATCHMAN group (1.3 events per 100 patient-years) compared to the control group (1.6 events per 100 patient-years). After four years, the difference in the number of ischaemic strokes had equalised between the groups (1.4 vs. 1.1 events per 100 patient-year; RR 1.26; 95% CI 0.72–3.28) and the number of haemorrhagic strokes remained higher in the controls (0.2 vs 11 events per 100 patient-year; RR 0.15; 95% CI 0.03–0.49). The patients on warfarin were more likely to die from haemorrhagic stroke (0.4% vs. 2.9%; p = 0.0098).

The data derived from the PROTECT AF trial sustains the current view, i.e. that LAA is a critical component of stroke in patients with AF and that eliminating the appendage may have a profound impact on the long-term outcome.

EVIDENCE BASED SAFETY OF LEFT ATRIAL APPENDAGE CLOSURE

The safety of any procedure is crucial for routine clinical implementation. LAA closure is a complicated procedure requiring the insertion of large catheters (12–16 F) through the groin, transseptal puncture and manoeuvring catheters within the left atrium and LAA cavities. Each of these stages may result in complications, beginning with haemorrhage, vascular rupture, stroke, myocardial infarction, and finally pericardial effusion. After successful implantation, the device may possibly be the source of embolisation or thrombosis. These complications are likely to happen in any interventional or surgical heart procedures, and unfortunately some may result in persistent disability or may even be life-threatening. The low frequency of potential complications is therefore mandatory for the clinical appreciation of LAA closure. The early registries show a 7–10% incidence of serious procedure-related complications, and therefore were not encouraging, but lack of control groups on anticoagulation precluded definite conclusions. The concept of 'early risk and late gain' could only be tested and proved in a rigorously designed prospective, controlled, randomised study. The primary safety end point in the PROTECT AF trial included major bleeding, pericardial effusion and device embolisation. During an aggregate of 1,065 patient-years (mean 18 month follow-up for a patient), the primary safety events were more frequent in the WATCHMAN group (7.4 vs. 4.4 per 100 patient-years; RR 1.69; 95% CI 1.01–3.19). By contrast, 55% of primary safety events occurred in the intervention group on the day of the procedure; events in the control group mainly occurred later, with 50% between 45 days and one year. The downward tendency in the WATCHMAN group and the opposite trend in the control group have remained unchanged, and after four years (the aggregate of 2,621 patient-years) the difference in the number of events was no longer seen between the groups (3.6 vs. 3.1 events per 100 patient-year; RR 1.21; 95% CI 0.78–1.94) for WATCHMAN vs. warfarin (intention to treat analysis).

Based on the current data, we have to wait for four years to reach the superiority of LAA closure over warfarin in terms of efficacy and to equalise the risk. The reduction of the adverse events is the key issue to shorten this time period. In the PROTECT AF study, the incidence of severe pericardial effusion was related to the centre and operator experience, being 50% higher at newly initiated sites. The data derived from the early and late phase of the PROTECT AF study and from the Continued Access Protocol (CAP) registry performed in the centres participating in PROTECT AF after the study was completed, proved the cause-effect relationship between the level of expertise and the risk of complication [45]. The comparison of procedure/device related events in early and late phase of PROTECT AF and in CAP reveals a decrease of complications: 10% vs. 5.5% vs. 3.7%, respectively. The high risk of pericardial effusions in an early phase (6.3%) dropped to 3.7% in the late phase of the study and further to 2.2% in the registry. Peri-procedural strokes were eliminated (1.1% vs. 0.7% vs. 0%). The recently presented preliminary results

of the second randomised trial with WATCHMAN–PREVAIL study, similarly to CAP registry, reported a low incidence of adverse events. The rate of pericardial effusion requiring pericardiocenthesis was 1.5%; tamponade requiring surgical repair — 0.4%; device/procedure related stroke 0.4%; and device embolisation 0.8% [41].

CONTROVERSIES OF LEFT ATRIAL APPENDAGE OCCLUSION

The European Society of Cardiology (ESC) recommends LAA occlusion in patients with a high stroke risk and contraindications for long-term oral anticoagulation (class IIb/B) [46]. This recommendation, however, should be debated. In fact, no direct comparison between LAA occlusion and control group without anticoagulation has been done in a randomised model, so far. On the contrary, the ESC recommendation is based on the early results of the PROTECT AF study, which recruited warfarin eligible patients. The low level of current recommendations is based on the safety issues of the devices and (even more important) procedures performed by inexperienced operators, and revealed in the early reports. The long-term follow-up data of the PROTECT AF study and ongoing AMPLATZER Cardiac Plug Clinical Trial may influence future guidelines [47]. The long-term PROTECT AF data provides additional support for LAA closure as a potentially viable long-term alternative to chronic warfarin therapy for patients to reduce the risk of stroke. The WATCHMAN device underwent recent review by the Food and Drug Administration's (FDA) Circulatory System Devices Panel. The totality of the data available from the initial PROTECT AF study, supplemented by the results of the CAP registry and PREVAIL trial, were analysed. The committee voted near-unanimously (13/1) that the benefits of treatment with the device outweigh its risks in patients with non-valvular AF who are eligible for warfarin therapy. The FDA Panel also voted 13/1 that the data provides reasonable assurance of the safety and efficacy of the device. The WATCHMAN is not yet FDA approved, but the voting has paved the way for final approval.

LAA occlusion may have a remarkable upside potential for patients at bleeding risk who feel uncomfortable with the perspective of life-long systemic anticoagulation therapy. The ideal candidate would be a patient with a high $CHADS_2$ score and a history of major bleeding (especially gastrointestinal) or a patient with haemorrhagic stroke. Patients with stroke recurrence under anticoagulation therapy or with persistent non-compliance or non-tolerability or those simply refusing their intake should also be considered. Ischaemic patients with AF treated with drug-eluting stents and requiring triple antithrombotic therapy constitutes another group of potential candidates for LAA closure as an alternative therapeutic option. The presence of thrombus in LAA and unfavourable anatomy are considered absolute contraindications for closure. This may possibly be changed in the near future, according to the implementation of new generations of devices and new interventional techniques such as mechanical LAA thrombectomy [48].

Many questions still remain, such as the difference in event rate in subgroup analysis based on gender, $CHADS_2$ score and AF pattern, LAA morphology, for instance. The accumulation of data will probably help us to figure out which patient will do best with which therapy. Other important and unresolved issues are the lack of direct data comparing LAA occlusion with NOACs and the lack of data comparing devices, implanting strategies and therapies following implantation. Two LAA occlusion systems, WATCHMAN and ACP, have distinct post-implantation regimens. Patients implanted with ACP are maintained on dual antiplatelet therapy (aspirin and clopidogrel) for 1–3 months followed by at least five months of aspirin. Patients with WATCHMAN are on warfarin for 45 days to facilitate device endothelialisation. The complete closure on 45-day TEE or the presence of an acceptable residual peri-device leak (less than 5 mm in width) allows for warfarin therapy discontinuation. After warfarin treatment is stopped, dual antiplatelet therapy for five months is prescribed and then aspirin alone life-long. There are also two distinct approaches to LAA occluder implantation. The first requires TEE or intracardiac echocardiographic accurate imaging prior to device implantation and careful echo guidance during the procedure. This approach is accepted in the majority of centres for safety reasons and is mandatory for WATCHMAN due to the necessity of deep access sheath canulation. The second, extensively and successfully practiced in Bern (with ACP device), relies on fluoroscopic visualisation for safe transseptal puncture, reliable exclusion of thrombus in the LAA, device size selection, and finally, device implantation [49]. The feasibility of ad hoc LAA closure, solely using fluoroscopic guidance without pre or peri-procedural echo guidance, has been reported [50]. And finally, the issues of LAA closure in patients referred for pulmonary veins isolation and the atrial natriuretic peptide secretion following LAA occlusion remain open. These are subjects of ongoing studies and we will see the results shortly.

Conflict of interest: *W.C. Wąsek: lectures on LAAO implantation sponsored by Boston Scientific; R. Rosso has been proctoring implantations of the Watchman LAAO system (Boston Scientific).*

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