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EDITORIAL

Left Atrial Appendage Closure: Feasible but Still Risky / Will it Though Obviate the Need for Anticoagulation?

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Various studies and meta-analyses have suggested that in cases of left atrial thrombi in nonrheumatic atrial fibrillation (AF) patients, approximately 90% of them are located in the left atrial appendage (LAA).[1] Patients are effectively protected from thromboembolism in this setting by anticoagulation therapy, shown to reduce the incidence by 60-70% with vitamin K antagonists and maybe more by the newer anticoagulants.[2,3] However, anticoagulation therapy is limited by an increased risk of major bleeding, in addition to other hindrances, such as difficulty in monitoring anticoagulation therapy, several drug and food interactions for classical warfarin, or cost and bleeding issues with the newer drugs, all leading to limited use of anticoagulation in clinical practice with percentages reported at 30-50%.[3-5] For these reasons, alternative device therapies with occlusion of the LAA, considered the most common source of thromboembolism in this cohort, have been recently pursued.[6-10]

In the European PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) study,[6] the first device ever used for this purpose, which, however, was subsequently withdrawn, had an initial implant success rate of 90% among 180 patients. However, there was a 1.1% mortality (2 patients) related to the procedure, while 6 cases of cardiac tamponade also occurred (3.3%). In two cases, surgical drainage of the tamponade was necessary (1.1%). In one patient the device embolized into the aorta after its release (0.6%) (at the end successfully snared and replaced). During follow-up, 3 strokes occurred (2.3% per year). The expected incidence of stroke according to the CHADS2-Score was 6.6% per year. The trial was halted prematurely during the follow-up phase, allegedly for financial considerations.

In the initial experience with a newer nitinol device, the WATCHMAN Left Atrial Appendage System (Atritech Inc., Plymouth, Minnesota),[7] among 66 patients out of 75 (88%) who underwent successful device implantation, at 45 days, 93% (54 of 58) of the devices showed successful sealing of LAA. Two patients experienced device embolization, both successfully retrieved percutaneously. No embolizations occurred in 53 patients enrolled after modification of the fixation barbs. There were 2 cardiac tamponades, 1 air embolism, and 1 delivery wire fracture. Four patients developed thrombus on the device at 6 months that resolved with additional anticoagulation. Two patients experienced transient ischemic attack, 1 without visible thrombus. There were 2 non-device-related deaths; no strokes occurred during follow-up despite that >90% of patients discontinued anticoagulation.

In the most notable randomized study using a second generation Watchman device, the Watchman Left Atrial

Appendage System for Embolic Protection in Patients With AF (PROTECT AF) randomized trial,[8] LAA closure was compared against warfarin in AF patients with $CHADS_2$ score $\geq$1. The study showed that LAA closure was noninferior to warfarin therapy for the prevention of stroke/systemic embolism/cardiovascular death (primary efficacy end-point), but there was a significantly higher risk of complications, predominantly pericardial effusion and procedural stroke related to air embolism. Specifically, adult patients with non-valvular atrial fibrillation were eligible for inclusion in this trial if they had at least one of the following: previous stroke or transient ischemic attack, congestive heart failure, diabetes, hypertension, or were 75 years or older. A total of 707 eligible patients were randomly assigned in a 2:1 ratio to percutaneous closure of the LAA and subsequent discontinuation of warfarin (intervention group; n=463) or to warfarin treatment with a target international normalised ratio between 2.0 and 3.0 (control group; n=244). At follow-up, the primary efficacy event rate was 3.0 per 100 patient-years in the intervention group and 4.9 per 100 patient-years in the control group (rate ratio [RR] 0.62). The probability of non-inferiority of the intervention was more than 99.9%. Primary safety events were more frequent in the intervention group than in the control group (7.4 per 100 patient-years, vs 4.4 per 100 patient-years; RR 1.69). The authors concluded that their strategy for closing the LAA was non-inferior to warfarin therapy in terms of the primary efficacy endpoint of all stroke, cardiovascular death, and systemic embolism. Although there was a higher initial safety event rate for device implantation, they alleged that these adverse events were without long-term sequelae for most patients and that closure of the LAA might provide an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with nonvalvular atrial fibrillation.

Further analysis of the PROTECT AF study cohort (n=452) and of a subsequent registry population (n=460) undergoing Watchman implantation,[9] indicated a significant reduction in the rate of procedure- or device-related safety events within 7 days of the procedure with increased operator experience, with 7.7% and 3.7% of patients, respectively, experiencing events (a relative reduction of 56%; *P*=0.007), and between the first and second halves of the PROTECT AF study and the registry population, with 10.0%, 5.5%, and 3.7% of patients, respectively, experiencing events (*P*=0.006).

In a recent study with use of a novel device (Amplatzer cardiac plug),[10] the success rate was 96% among the 137 patients in whom it was attempted, but the rate of serious complications culminated to 7%, including ischemic stroke (n=3), device embolization (n=2), (both percutaneously recaptured) and clinically significant pericardial effusions (n=5); there were also minor complications noted in 5%, including insignificant pericardial effusions (n=4), transient myocardial ischemia (n=2), and loss of the implant in the venous system (n=1).

In **conclusion**, percutaneous LAA closure with current devices is feasible and may be non-inferior to anticoagulation therapy in patients with AF, however, current device technology and operator experience leave much room for improvement and should be viewed with great caution due to significant complication rates that this procedure confers even at most experienced centers. Another source of concern is the device potential thrombogenicity, especially when not well seated in the appendage, as well as the non-LAA sources of thrombi, such as the recently described left atrial pouch, not addressed by this strategy.[11]

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New Agents in the Treatment of Pulmonary Hypertension

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Pulmonary Hypertension (PH) is defined as an increase in mean pulmonary arterial pressure (PAP) ≥25 mmHg at rest as assessed by right heart catheterization (RHC). As stated in the European Society of Cardiology (ESC) 2009 guidelines, it can be classified into 5 main categories, presented in Table 1. Pulmonary arterial hypertension is a rare disease with a prevalence of 15 cases /million adult population and an incidence of 2.4 cases/million adult population/year.[1,2] The pathophysiology of PH is complex and it has not been elucidated in detail since it involves various biochemical pathways and cell types. Vasoconstriction, remodeling with extensive proliferation of the vessel wall cells causing progressive obstruction, inflammation and thrombosis have been implicated. Structural or functional abnormalities of potassium channels in the smooth muscle cells and endothelial dysfunction characterized by impaired nitric oxide (NO) and prostacyclin production or increased expression of thromboxane A2 and endothelin-1are thought to underlie the cellular changes.[3]

Although groups two and three account for the majority of the cases, the trials testing and validating therapeutic options involve mostly patients with group one PH (Pulmonary Arterial Hypertension-PAH). Apart from conventional therapy including diuretics, oral anticoagulants, calcium channel blockers in case of established vasoreactivity, digoxin, oxygen administration and exercise –rehabilitation programs, specific drugs have emerged and gradually find their place in the management of PAH during the last decade. *Prostanoids* such as intravenous (IV) epoprostenol, iloprost inhaled and IV and treprostinil subcutaneously (SC) or IV have been established agents in the management of PAH, improving performance ability and survival (epoprostenol). *Beraprost* has shown promising albeit short –term results in the ALPHABET trial.[4-10] *Phosphodiesterase (PDE) type-5 inhibitors (sildenafil, tadalafil)* and *endothelin receptor antagonists (bosentan, ambrisentan*) improve exercise capacity and hemodynamic parameters and are widely used in the treatment of PAH.[11-16] Sitaxentan demonstrated favourable results initially [17, 18] but was subsequently withdrawn in early 2011 due to a few cases of fatal hepatic toxicity considered to be idiosyncratic, unpredictable and thus unpreventable.

Table 1. Classification of Pulmonary Hypertension

Pulmonary Arterial Hypertension (PAH)	**PH due to Lung Diseases &/or Hypoxia**
Idiopathic (IPAH)	Chronic obstructive pulmonary disease (COPD)
Heritable/familial (FPAH)	Interstitial lung disease
BMPR2 ALK1, Endoglin Unknown	Other pulmonary diseases with mixed restrictive & obstructive pattern
Drug and toxin-induced	Sleep disordered breathing
Associated with APAH	Alveolar hyperventilation dis.
Connective tissue disorders	Chronic exposure of high altitude
HIV infection	Developmental abnormalities
Portal hypertension	
Congenital heart diseases	**Chronic Thromboembolic PH (CTEPH)**
Schistosomiasis	
Chronic hemolytic anemia	**PH with Indistinct, Multi-factorial Mechanisms**
Persistent PH of the newborn (PPHN)	Hematological dis. (e.g. myelo-proliferative dis., splenectomy, hemoglobinopathies)
Pulmonary Veno-Occlusive Disease (PVOD) & Pulmonary Capillary	Systemic dis. (e.g. sarcoidosis, pulmonary Langerhans cell histocytosis, lymphangiomatosis)
	Metabolic dis. (e.g. glycogen storage disease, Gaucher's disease, thyroid disorders)
PH with Left Heart Disease	
Systolic dysfunction	
Diastolic dysfunction	Others (e.g. tumoural obstruction, fibrosing mediastinitis, chronic renal failure & dialysis)
Valvular disease	

ALK-1 = activin receptor-like kinase 1 gene; APAH = associated pulmonary arterial hypertension; BMPR2 = bone morphogenetic protein receptor, type 2; dis. = disorders; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension

In spite of the remarkable progress in the management of PAH, the response cannot yet be characterized satisfactory. Moreover, the cost of specific treatment is still considerably high. Thus, the need for novel medical approaches is still present. New agents of the already used categories are tested. *Macitentan*, a novel endothelin (ET)-A/ET-B receptor antagonist, is being evaluated in