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Left atrial appendage closure for prevention of death, stroke, and bleeding in patients with nonvalvular atrial fibrillation

Steffen Gloekler [a,d,*], Jacqueline Saw [b], Konstantinos C. Koskinas [a], Caroline Kleinecke [e], Werner Jung [d], Fabian Nietlispach [c], Bernhard Meier [a]

[a] Cardiology, Cardiovascular Department, University Hospital of Bern, Bern, Switzerland
[b] Division of Cardiology, Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia, Canada
[c] University Heart Center, University Hospital of Zurich, Zurich, Switzerland
[d] Cardiology, Schwarzwald-Baar-Klinikum, Villingen-Schwenningen, Germany
[e] Department of Cardiology, Klinikum Coburg, 96450 Coburg, Germany

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ABSTRACT

Nonvalvular atrial fibrillation (AF) is the most frequent arrhythmia with a prevalence of 1%–2% in the general population. Its prevalence increases with age and its diagnosis benefits of improvement and simplification of technologies for its detection. Today, AF affects approximately 7% of individuals age > 65 years and 15%–20% of octogenarians. Due to stasis and activation of coagulation in a fibrillating atrium, patients are at increased risk of thromboembolism, in particular ischemic stroke, with an overall stroke risk of 5% per year. Since the left atrium itself is round and smooth-walled, thrombi typically do not form there, but almost exclusively in the left atrial appendage (LAA), a blind sac-like heterogeneous structure trabeculated by pectinate muscles.

In the past five decades, oral anticoagulation (OAC) with vitamin K antagonists (VKA) has been the state-of-the art treatment to prevent stroke and systemic embolism from thrombi in AF. In the last decade, nonvitamin K dependant oral anticoagulants (NOAC) have been shown to be overall superior to VKA with respect to efficacy and safety in large trials and registries. Given the safety issues of indefinite OAC with either VKA or NOAC, it is plausible to consider left atrial appendage closure (LAAC) as an alternative strategy for prevention of all three catastrophes for patients with AF on anticoagulation: death, stroke or other systemic embolization, and bleeding. In the past years, LAAC has been compared to VKA in prospective randomized trials, yielding superior results regarding efficacy and non-inferiority regarding safety in the mid-term. Today, the decision to provide the most appropriate treatment for a patient with AF (OAC, NOAC, or LAAC) is complex and needs to be individualized.

This review provides a comprehensive update on the current state of LAAC in the field of prevention of death, stroke and bleedings in patients suffering from nonvalvular AF. We describe the pathophysiology of the LAA with regard to stroke, elucidate the evidence and limitations of anticoagulation as the classical treatment paradigm, and review devices and techniques for LAAC. Most importantly, the current clinical evidence on efficacy and safety is outlined and finally, contemporary recommendations for patient selection are provided.

1. Introduction

A 69-year-old woman with persistent atrial fibrillation (AF) on vitamin K antagonist oral anticoagulation (OAC), diabetic nephropathy requiring hemodialysis, and prior major gastrointestinal bleeding underwent urgent coronary angiography because of a non-ST-segment elevation myocardial infarction. The culprit lesion, a severe stenosis in the mid segment of the left anterior descending coronary artery was treated by percutaneous coronary intervention (PCI) with a third-generation drug-eluting stent. Based on a CHA_2DS_2-VASc Score of 5 and a HAS-BLED score of 4, the patient was at high risk for both stroke and further bleeding. The acute coronary syndrome was considered an indication for ticagrelor and acetylsalicylic acid. During her emergency

Abbreviations: AF, Atrial fibrillation; ACP, Amplatzer Cardiac Plug; ASD, Atrial septal defect; BARC, Bleeding academic research consortium; CCTA, Cardiac computed tomography angiography; CE, Communauté européenne; CMS, Center of Medicare and Medicaid Services; CT, Computed tomography; DAPT, Dual antiplatelet therapy; EP, Electrophysiology; F, French; ESC, Europen Society of Cardiology; FDA, Food and Drug Administration of the United States of America; IC, Interventional cardiologist; ICE, Intracardiac echocardiography; INR, International normalized ratio; LAA, Left atrial appendage; LAAC, Left atrial appendage closure; NOAC, Non-vitamin K dependent oral anticoagulant(s); OAC, Oral anticoagulant(s); PCI, Percutanous coronary intervention; PFO, Patent foramen ovale; RRR, Relative risk reduction; TEE, Transesophageal echocardiography; TAVR, Transcatheter aortic valve replacement; TIA, Transient ischemic attack; VARC, Valve academic research consortium; VKA, Vitamin K antagonist(s).

* Corresponding author at: Department of Cardiology, Schwarzwald-Baar Klinikum, 78052 Villingen-Schwenningen, Germany.
E-mail address: steffen.gloekler@med.unibe.ch (S. Gloekler).

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PCI she was offered ad hoc left atrial appendage closure (LAAC) to provide stroke prophylaxis without the excessive bleeding risk with triple anticoagulation either with OAC anticoagulation or non-vitamin K dependant oral anticoagulation (NOAC). The access to the left atrium was facilitated by an incidentally searched and found persistent foramen ovale (PFO). Biplane angiography of the left atrial appendage (LAA) from a distance was first done to exclude a thrombus and to determine the device size. The LAA was closed with a 22 mm Amplatzer Amulet device through a 14 French sheath. The PFO was then closed with an Amplatzer 25 mm PFO occluder through the same sheath. After the uncomplicated combined intervention, OAC was stopped and the patient returned to the referring hospital the same day. The transesophageal echocardiography (TEE) four months later showed complete exclusion of the LAA and closure of the PFO by the devices without adverse findings. In the latest follow-up two years after the procedure, the patient was on acetylsalicylic acid 100 mg/d only without any bleeding or ischemic events. This example illustrates both sustained protection from stroke and systemic embolism, and minimized risk of recurrent bleeding by obviating longterm (N)OAC in a complex clinical scenario.

1.1. Atrial fibrillation and ischemic stroke

AF is a common arrhythmia with a prevalence of 1%–2% in the general population, increasing with age and affecting approximately 7% of individuals age > 65 years and 15%–20% of octogenarians [1–3]. Patients with AF are at increased risk of thromboembolism, in particular ischemic stroke. It is estimated that every fifth stroke is related to AF [3]. AF related strokes tend to be especially severe and disabling and half of patients die within one year of the event. In contrast to the slow vessel occlusion by atherosclerosis having time for collateralization, embolic vessel occlusions typically hit normal vessels without collaterals. Patients with AF are at two-fold risk of death and three-fold risk for heart failure. AF is also responsible for 3%–6% of acute medical admissions for management of arrhythmia [4]. Furthermore, AF is underdetected, and therefore not all affected patients receive appropriate treatment [5,6].

For estimation of individual stroke risk, the comorbidities of any patient suffering from AF must be taken into consideration. Current guidelines recommend the use of the CHA_2DS_2-VASc score, which provides an estimate of the annual stroke risk with an indication to start OAC for prevention of thromboembolism in case of CHA_2DS_2-VASc scores ≥2 [7].

1.2. Origin, function, and shape of the left atrial appendage

During cardiac development in the embryonic state, the lung veins and their major branches merge and form the left atrium (LA) [8]. The LAA is a residual pouch derived from such a primordial lung vein. It is located anteriorly in the atrioventricular groove in close proximity to the left circumflex coronary artery, the annulus of the mitral valve, the left upper pulmonary vein, and the left phrenic nerve [9]. Since its volume is rather small (5–15 ml), LAA contractility during normal sinus rhythm plays only a minor role in the regulation of left atrial pressure, volume, and left ventricular filling [10]. The LAA is markedly smaller than the right atrial appendage and its inner surface is trabeculated by pectinate muscles [11,12]. Being very heterogeneous in shape and size, the LAA usually resembles a rather narrow tube with an elliptic ostium and numerous bends or lobes. Four principal morphologies have been described and can be classified: cactus, chicken wing, windsock, and cauliflower appearances: The cauliflower type is characterized by a limited overall length with complex trabecula ion and often multiple small lobes. The windsock type has one dominant and relatively long primary tubular lobe, often with secondary or tertiary smaller side-lobes. The cactus type has also one central lobe and is usually longer than the cauliflower, but has also secondary lobes, whereas the chicken wing is similar to the windsock with a relatively long primary tube, which bends in the proximal part of the dominant lobe, folding backwards [12,13]. LAA morphology seems to be directly linked to the risk of stroke [13,14]. Patients with other than chicken wing LAA morphology appear at higher risk for thromboembolic events after controlling for comorbidities and $CHADS_2$ score [15].

1.3. Thrombus formation in atrial fibrillation

AF results in loss of physiologic atrial systole and irregular ventricular activation, which in turn affects left ventricular filling, contractility, and cardiac output. Thus, left atrial pressures and volumes are typically increased due to stasis. Depending on the frequency and duration of AF as well as left ventricular systolic and diastolic function and afterload, both LA and the LAA undergo a progressive process of dilatation and fibrotic remodeling with reduced blood flow velocities including turbulent flow and stasis [12,16–18].

In contrast to the smooth-walled and roundish LA, the LAA is a small blind-sac with heterogeneous structure and mostly distinct trabeculation and lobulation. Therefore, this is plausibly the most likely site of thrombus formation in AF. Not surprisingly, the LAA has been known as a nidus of thrombus formation and embolization for >60 years and consequently, its first resection was performed already when cardiac surgery set off in the late 1940ies [19]. A recent meta-analysis of >20,000 AF patients with nonvalvular AF reported a mean prevalence for left atrial thrombi of 10%, which was linked to a 3.5-fold increase in stroke risk [20]. Further evidence from echocardiographic, surgical, and postmortem studies confirmed that the vast majority of intracardiac thrombi in patients with nonvalvular AF are located in the LAA because of the above-mentioned reasons. In a large study using TEE, 91% of thrombi in nonvalvular AF were located in the LAA [21]. Of note, thrombi already form within a relatively short period of time in the LAA in up to 14% of patients with acute or new onset (<3 days) AF [22]. Accordingly, in case of concomitant LAA amputation during cardiac surgery, the incidence of early postoperative stroke can be effectively reduced [23].

In contrast to nonvalvular AF, in valvular AF, which denotes patients with rheumatic mitral stenosis or mechanical (metallic) valve prostheses, left atrial flow is far more reduced and the prevalence of LA thrombi is up to 45% [24]. At variance to nonvalvular AF and owing to the even more thrombogenetic milieu in the presence of mitral stenosis or a mechanical prosthesis, thrombi originate also from the LA: In a clinicopathologic study, about half of the left-sided thrombi were observed in the LAA, whereas the remainder was located at the free walls of the left atrium [25].

1.4. The concept of anticoagulation and its benefit for stroke prevention

OAC with VKA or more recently NOAC are the mainstay in the prevention of thromboembolism among patients with AF. OAC with VKA as compared with placebo is associated with an absolute stroke risk reduction of 2.7% per year, which corresponds to a relative risk reduction of 64% and a number needed to treat of 37 per year [26]. Although antiplatelet therapy with acetylsalicylic acid alone or dual antiplatelet therapy consisting of acetylsalicylic acid and clopidogrel lowers the relative risk of stroke as compared to placebo by approximately 20%, OAC with VKA is substantially more effective than antiplatelet therapy by approximately 40%. More recently, NOACs have been introduced into clinical practice. Currently, four substances (one direct thrombin inhibitor and three factor Xa inhibitors) are approved for stroke prophylaxis in patients with AF. They feature several advantages over VKA including rapid onset (2–4 h), rapid offset (24 h), and predictable pharmacokinetic effects combined with a favorable safety and efficacy profile. A prespecified, pooled analysis of the four randomized clinical trials (RELY), [27] (ROCKET AF), [28] (ARISTOTLE), [29] (ENGAGE AF-TIMI) [30] included 71,683 patients with AF and compared clinical outcomes of different NOAC with VKA [31]. There was 19% lower risk of stroke and systemic embolism (RR = 0.81, 95% CI 0.73–0.91), 50% lower risk of hemorrhagic stroke (RR = 0.49, 95% CI 0.49–061, $p < 0.0001$), and