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Review

Left Atrial Appendage Closure and Combined Procedure - Past, Present and Future Perspectives

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Introduction - Left Atrial Appendage Closure in AF Treatment

Non-valvular Atrial Fibrillation (AF) is most common cardiac arrhythmia worldwide, with one in four people expected to develop it during their lifetime; it represents a major ischemic stroke risk factor in both high and low GPI countries, accounting for 15-20% of all strokes. Stroke risk is usually managed through oral anti-coagulant (OAC) drugs [vitamin K inhibitors (VKA) or the newer non-vitamin K antagonist oral anticoagulants (NOAC)], accordingly to the CHA2DS2-VASc score [1]. Nonetheless, OAC therapy never nullifies stroke risk and some specific sub-populations may not be eligible for this treatment due to high bleeding risk. After discovering that over 90% of thrombi in AF patients form inside the left atrial appendage [2], the concept of percutaneous left atrial appendage closure (LAAC) has been developed specifically to non-pharmacologically address similar conditions.

In 2009, Holmes DR, et al. published on Lancet the PROTECT AF trial [3]; this prospective 2:1 randomized controlled trial (RCT) compared LAAC through WATCHMAN devices with Warfarin treatment; demonstration of non-inferiority was achieved, although some concerns over peri-procedural safety arose, due to a 8.7% adverse peri-procedural event rate (Mostly pericardial effusions) in the intervention arm of the trial.

A second RCT, the PREVAIL trial [4], was performed and published by Holmes DR et al. in 2014 to reassess LAAC procedural safety, that was found greatly improved (4.2%), mainly because of technical innovations and more experienced operators. The 4-year PROTECT-AF data analysis showed significantly lower adverse event rates (considering both hemorrhagic and ischemic events) in the Watchman group versus warfarin group, with the difference mainly driven by fewer hemorrhagic strokes with a non-statistically significant reduction in the stroke rate [5]. A patient level meta-analysis from 2015 on JACC reported an improvement in hemorrhagic strokes, cardiovascular/unexplained death and non-procedural bleeding in LAAC patients compared to Warfarin treatment.

The EWOLUTION registry was then designed to assess the real–world impact of LAAC, with more than 1000 patients enrolled and followed-up [6]. High rates of acute implantation success (98.5% successful occlusion with a 91.4% complete occlusion rate and 7.9% leakage < 5 mm rate) were described, with only a 2.7% serious procedure/device related events through 7 days from the LAAC [7]; investigators reported a 1.1% ischemic stroke rate (84% risk reduction from the CHADS-VASc predicted stroke rate) and bleeding (48% risk reduction from the HAS-BLED predicted stroke rate) [8]. Experience and improvement in implantation techniques had led to a consistent reduction of peri-procedural complications that were previously limiting the net clinical benefit of the LAAC procedure, allowing high performances in a long term follow up in a real life setting.

Although the WATCHMAN device was the only one used in those major prospective trials, many other devices entered the market and the clinical practice [9]; the Amplatzer Cardiac Plug (ACP) was employed as the occluder device in several registries and studies [10-14]. No direct head to head trials between WATCHMAN and ACP have been published so far, but no significant differences have been reported between those two devices in those LAAC papers including both devices either [11-13]. In current clinical practice, LAAC is nowadays accepted as a viable and effective option. In recent AF management guidelines, LAAC procedure is suggested for patients

unsuitable for OACs (e.g. high bleeding risk) or who suffered a stroke despite OACs [15]. The number of LAAC procedure performed is rising by the hour and it is expected to continue doing so in the years to come. Alongside the LAAC as a stand-alone procedure, over the years many groups have published data about the so-called "combined procedure", consisting of LAAC alongside a contextual AF catheter ablation (CA). In this article we sought to summarize the current literature regarding the combined AF ablation and LAAC procedure, its advantages and disadvantages as well as to address the future perspectives of this methodic.

Combined Procedure Proof of Concept

The idea of combined procedure was first introduced in 2012, when Swaans M et al. presented a case series of 30 combined procedures, involving LAAC alongside pulmonary vein isolation (PVI), performed with phased radiofrequency with a mixture of Pulmonary Vein Ablation Catheter (PVAC), Multi-array Septal Catheter (MASC) and Multi-array Ablation Catheter (MAAC) [16]. Their procedure was performed under continuous trans-esophageal echography (TEE) and fluoroscopy guidance. A 100% LAA closure success rate was achieved acutely, with 3 (10%) minor bleeding as peri-procedural complications.

No major (> 5 mm) leakages and only a 23% of patients with minimal (< 5 mm) residual flow were found at the 60-day follow up TEE; these occlusion rates improved to a 93% complete occlusion rate at the 6-month follow up visit, resulting in almost an 80% VKA discontinuation rate. The freedom from arrhythmia rate reported at 12 months was 70%. The authors observed that performing LAAC before CA did not prolong CA procedural time and the long term combined procedure AF recurrence rate appeared comparable to the one achieved by CA alone in their institution. Moreover, being the occluding device inside the LAA and not at its ostium, LAA accessibility for an electrical trans-catheter PV isolation was not impaired. No strokes were witnessed over a 12-month follow up: the combination of AF ablation and LAAC reduced stroke risk by both removing the causing substrate and the anatomical reservoir of the thrombi.

In conclusion, authors suggested the combined approach would be especially helpful in AF patients with both high stroke and bleeding risk as well as in patients with a low expected long term efficacy of ablation alone, allowing LAA to not restart OACs upon AF recurrence. Another preliminary experience with 26 patients enrolled and similar results was described by Walker B. et al in the same year [17]. These first experience represented an elegant way to address AF symptom, reducing at the same time stroke risk and the need for OACs; the road to combined procedures was opened and ready to be paved with larger samples.

Early Experiences

In 2015, Alipour A et al. furtherly expanded the combined procedure experience, by publishing on JACC EP a prospective non-randomized study including a larger sample of 62 patients [18]. In this study, PVI energy source was phased RF and LAAC performed by WATCHMAN occluder devices. The main indication to LAAC was stroke depite OACs (29%). The larger sample size allowed a more reliable description of the peri-procedural adverse events: in this 5 (8.1%) patients developed a minor bleeding peri-procedurally, with no pericardial effusions nor strokes. Although the rate per se being not so much lower to the one reported in the first experiences, all the encountered peri-procedural events resulted mild and resulted more a discomfort than a real danger.

This study gave valuable data about the long term follow up of combined procedures, reporting over a 38 (25-45) months as median follow up; the 100% acute LAAC success (87% complete occlusion, 13% < 5 mm leakage), at the long term follow up resulted in a 95.2% satisfactory LAA occlusion rate, but with a 45% rate of < 5 mm leakages and with 1 (1.6%) device embolization. Over 58% of the population did not experience AF recurrences and the reported OAC discontinuation rate was 78%; 3 (4.8%) strokes were reported, resulting in 1.7% annualized stroke rate (74% risk reduction from expected). The authors reported the hypothesis that a quota of those strokes may had been due to carotidal atherosclerotic plaques, and therefore not AF-related, but given the fact that 2 (3.2%) strokes interested patients with a < 5 mm leakages, although a previous PROTECT AF retrospective analysis did not establish a relation between minimal flow leakages and stroke risk [19], the AF etiology could not be completely ruled out.

This study proved the combined procedure able to effectively reduce stroke risk even at a long term follow up; authors also reported that much of the improvement achieved compared to previous experiences was due to formation of a dedicated heart team, that also reduced procedural time and improved imaging quality. In the same year, Calvo N et al. published a prospective studying describing 35 combined procedures performed for the first time with a mixture of both WATCHMAN and ACP as occluder devices [13]. The main indication for LAAC was high bleeding risk (48% of patients) and the combined procedure took place to avoid long term OACs, regardless of arrhythmia recurrences. A 2 month OACs regimen was kept in place after the procedure.

This study reported several interesting points: 1) at 13 months, 78% of patients were free from AF, despite elevated rates of persistent and long standing persistent AF patterns; at the time new generation irrigated tip catheters with contact-force technology were achieving high long term results in AF RFCA and, since this study,

Table1. Summary of all combined procedure studies .

	Swaans	Walker	Alipour	Calvo	Phillips	Fassini	Wintgens L.
Patients, n	30	26	62	35	98	35	349
Age	62.8 ± 8.5	63 ±7	64 ± 8	70 ± 7	65 ±7	72 ± 4	63.1 ± 8.2
Male	70%	77%	64,5%	71%	68%	79%	57.9%
Main LAAC reason	Stroke despite OAC (30%)	High stroke risk (100%)	Stroke despite OAC (29%)	Major bleeding (48%)	High stroke risk (100%)	Stroke despite OAC (74%)	Stroke despite OAC (38%)
Device	W	W	W	W or ACP	W	W or ACP	W
AF type:							
pxAF, n (%)	43%	54%	63%	29%	57%	80%	56%
pAF, n (%)	57%	46%	37%	71%	43%	20%	44%
CHA_2DS_2-VASc	3 [3 – 5]	2,6 ±0.8	3 [2.75 – 4]	3.1 [2 – 6]	2.6 ± 1	3 [2 – 5]	3 [2 – 4]
HAS-BLED	2 [1 – 3]	n.d.	2 [2 – 3]	3 [2 – 6]	2 [1 – 3]	3 [2 – 5]	3 [2 – 3]
Procedural Success	100%	100%	100%	97%	100%	100%	100%
PVI energy source	Phased RF	Irrigated RF	Phased RF	Irrigated RF	Irrigate RF	Cryoballoon	Irrigated RF 79% Phased RF 21%
LAAC acute closure							
- Complete	90%	96%	87%	n.d	94%	86%	92.6%
- Satisfactory	10%	4%	13%		6%	14%	7.4%
Peri-procedural adverse events	10%	0%	8.1%	8.5%	8%	11%	7.2%
FU time, months	12	12	38 (25 – 45)	13 (3 – 75)	27±14	24 ± 12	34.5 (24 – 44)
Stroke Annualized rate	0%	0%	1,7%	2.6%	0.5%	0%	0.7%
Bleeding	10%	n.d.	1,7%	2.9%	n.d.	n.d.	1.1%
LAAC at First TEE							
- Sealed	77%	77%	50%	97%	86%	86%	70.2%
- < 5 mm leak	23%	23%	45,2%	3%	14%	14%	28.6%
- > 5 mm leak	0%	0%	4,8%				1.2%
Device embolization	3%	0%	1,6%	0	3	0	0.5%
Device Thrombi	0%	0%	0%	0%	0%	0	1.1%
AF recurrence rate	30%	23%	42%	22%	46%	29%	51%
Freedom from OAC	77%	96%	78%	97%	n.d.	86%	84.9%

ND.: not discussed; LAAC: left atrial appendage closure; OAC: oral anti-coagulants; W: Watchman; ACP: amulet cardiac plug; pxAF: paroxysmal atrial fibrillation; pAF: persistent atrial fibrillation; PVI: pulmonary vein isolation; FU: follow up; TEE: trans esophageal echography.

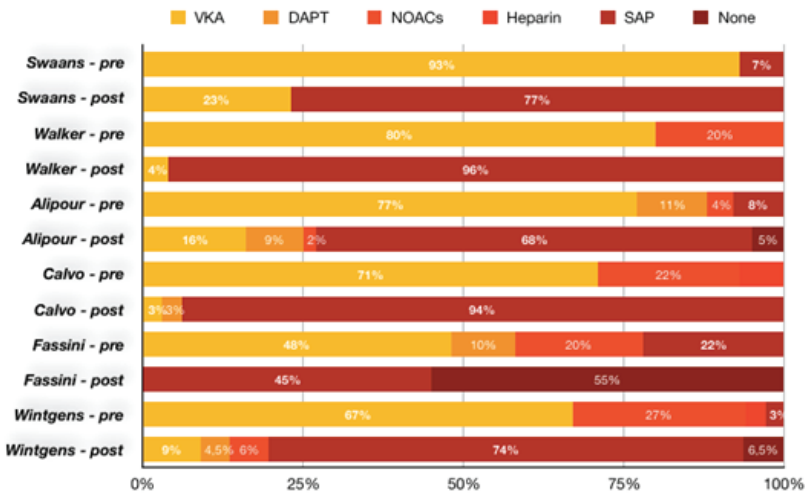

Figure 1. Anti-thrombotic regimen frequencies pre and post combined procedure in different studies.
VKA: vitamin K antagonists; DAPT: dual anti platelet; NOACs: non vitamin K antagonist oral anti coagulants; SAP: single anti platelet

has become the most commonly employed catheters in RFCA even during combined procedures; 2) for the first time, the main indication for combined procedure was a high bleeding risk; the PROTECT-AF trial established LAAC significant superiority over Warfarin mainly in reducing bleeding adverse events on the long term follow up and the combined procedure was used likewise; 3) The intra-procedural adverse event rate in this study was very high (8.5%), with many pericardial effusions; authors attributed it to the longer learning curve required by using a mixture of devices instead than a single one.

At the end of 2015, combined procedure had emerged as a reliable and long-term effective in reducing both stroke and bleeding procedure; many dedicated team were developed, to overcome the learning curve effect and lower the peri-procedural risks. A paper from Phillips K et al. summarized this experience, presenting 98 combined procedures performed with RF, reaching the same conclusions, with a large patient population and a long term follow up [20].

Here Comes the Ice - Cryoablation in Combined Procedures

In 2016, a change in the combined procedure paradigm was introduced by Fassini G et al. They reported the safety and feasibility of the technique using cryo-energy delivered through 1st and 2nd generation cryo-balloons in a high-stroke risk population. In their study, 35 patients were enrolled and underwent cryo-balloon PVI alongside WATCHMAN or ACP LAAC; peri-procedural reported adverse event rate (8% slight pericardial effusion and 3% vascular accesses complications) and reported procedural time resulted comparable to previous RF CA combined procedure experiences.

At long term follow up (24 12 months), almost a 80% freedom from arrhythmic recurrences was achieved; a high long term complete LAA sealing (92%) was achieved, with all the other patients experiencing only a < 5 mm leakage. Cryoablation has been previously demonstrated to promote less peri-procedural thrombosis [21] and pooled data from AF CA showed great long term durability and effectiveness in PVI lesions when cryo-energy was employed. Combined procedure feasibility, safety and effectiveness regardless the energy source for PVI (RF or Cryo) and device brand choice was demonstrated with this study.

The Combined Procedure Nowadays

All those small/medium- sampled experiences data were summed up when two analyses were published in 2018, by an investigation group led by L Boersma Phillips K et al. [22] assessed combined procedure 30-days outcomes by pooling data from two large prospective multicenter LAAC registries (EWOLUTION and WASP, both employing WATCHMAN devices). This analysis included 139 combined procedures, performed with irrigated RF by experienced operators and certified device implanters. Acute success rate was confirmed to be 100%, with a 97% complete appendage occlusion, in most cases without the need of device resizing or recapturing.

Three major points were therefore highlighted: 1) In the hands of experienced operators, the encountered pericardial effusion rate was 1.4%, with only half of the events requiring intervention, and no peri-procedural stroke or deaths. These results were consistent with a previous EWOLUTION registry analysis [7], demonstrating that with new LAA device implanting techniques a low peri-procedural adverse event rate can be achieved even in high risk patient groups during combined procedure. The pooled data peri-procedural adverse event rate on combined procedures resulted even lower than complication rates reported in worldwide AF ablation surveys [23], stating that for high volume operators, adding LAAC to an AF ablation procedure does not increase the chance of complications. 2) A 2-month post procedural OAC regimen has been considered routine protocol almost since the start of the combined procedure experience, with VKAs being the employed drug of choice. In this analysis, NOACs as a discharge therapy were analyzed on a large sample and were found safe and compatible with the WATCHMAN prosthetic material: the 30-day bleeding adverse event rate (2.9%) reported in their population resulted equally divided between VKA and NOACs users and even consistent with contemporary results experienced in cather ablation PVI alone [24]. 3) New peri-device leaks were noted at the first TEE follow up (from 2.9% to 39% of patients) that resolved or reduced in size over the following months. Authors reported the increase in peri-device leakages at 8-week follow up with a later reduction over the first 12 months as a phenomenon experienced in many LAAC trials [3,4]; the proposed explanation was a mixture among a circular device and a non-circular LAA mismatch, edema masking mismatch at implant, and a potential atrial remodeling.

A few months later, a prospective multicenter trial by Wintgens L, et al. [25] described the largest combined procedure population sample (349 patients) with the longest median follow up (34.5 months) to date ever presented. The procedure was once again proven feasible and safe, with procedural times of around 2.5 hours and fluoroscopy time of 30 mins. The low peri-procedural adverse events rate previously reported was confirmed: the peri-procedural serious adverse (considering pericardial effusion, air emboli and stroke) event rate was 2.2%, resulting much lower than the SAE rates in PROTECT-AF, PREVAIL, and EWOLUTION trials, with no mortality. Furthermore, most of the complications observed resulted femoral access derived and not device related; these results supported the previous studies,

reporting substantial improvement of safety with increasing experience of the combined procedure team.

Rates of complete and satisfactory LAA sealing were comparable to those described by Phillips K et al. [22] both in acute and at follow up, de facto confirming their previous assessment. An annualized stroke and major bleeding rate of only 0.7% and 1.1% were observed in this population, regardless of a 51% rate of arrhythmic recurrences; the effectiveness of combined procedure was assessed in a 75% stroke and 71% bleeding risk reduction respectively, from what had been predicted by the CHAD-VASC and HAS-BLED scores of the population. A 84.9% long time OACs discontinuation rate was achieved in this experience.

Future Directions

Combined procedure generally evolves following evolutions of the two stages that compose it. These authors would like to highlight some points that to our opinion will represent major hot topics in the combined procedure in the future: 1) Alongside trans-esophageal monitoring, intra cardiac echography (ICE) has been used and described as an effective guidance modality of LAAC guidance; although no ICE-guided LAAC large data sample has been published yet, feasibility and effectivenss has already been reported [26]. Larger studies are soon to follow and this modality will definitely find its way also into the LAAC part of the combined procedure. 2) Faster de-escalating protocols than those proposed by official occlude devices guidelines have already been described in LAAC procedure alone performed in high bleeding risk patients [27,28]; although the concomitant ablation requires some form of OACs, the still not so low bleeding rates will probably lead to the evaluation of lighter anti-thrombotic regimens. 3) A recent paper from Conti M et al. [29] proposed the use of 3D printing technology to achieve patient customized occluder devices; although being still an embryonal technology, in the near future customized occlude devices may become an everyday reality in LAAC and combined procedures. 4) Finally, the combined procedure standard ablative protocol usually comprehends a PVI limited approach; given many evidences of an important pathogenetic role of LAA electrical activity in persistent AF recurrences, it is not unlike that the LAA contemporary isolation and closure will be introduced into standard combined procedure protocols.

Conclusions

Today the combined procedure represents a clinical reality in many experienced centers and it is usually offered to patients with paroxysmal/persistent AF and/or high bleeding risks. Procedural success rates are close to 100% and its benefits appear to greatly exceed the low peri-procedural complication rate in the hands of experienced operators, with an average of a 70% bleeding and stroke risk reduction, regardless of the energy source or the occluder device bran employed. The combined approach is associated with a reduced risk of new vascular access, transseptal puncture and allows to reach a long term OACs withdraw of 85+%. However, for the time being, this approach needs to be confined to high volume centers and devoted to a very selected patient population, until future larger clinical trials will be designed as to corroborate the current clinical data.

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