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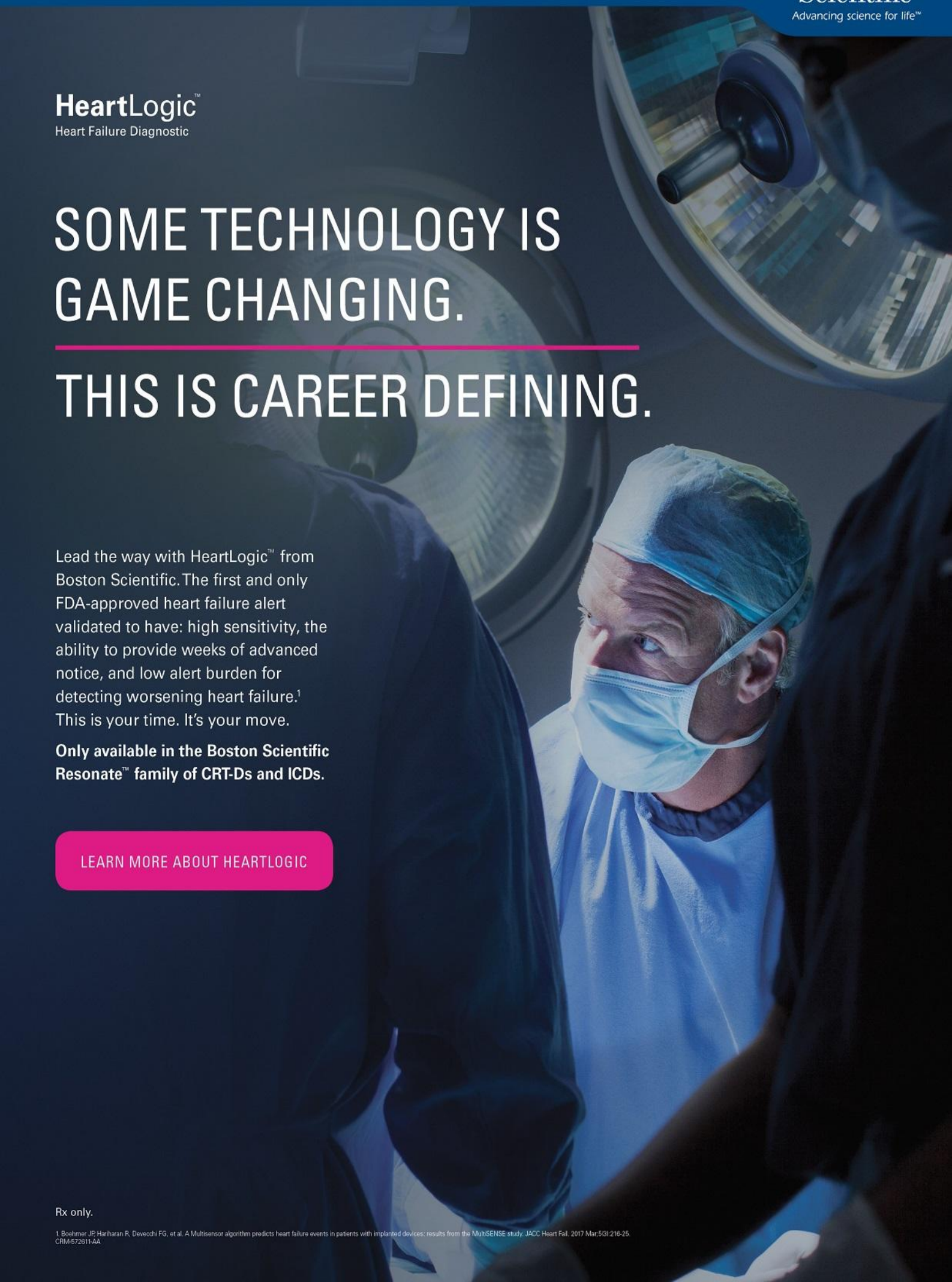

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A Left Atrial Appendage Closure Combined Procedure Review: past, present and future perspectives

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Abstract

Background and Objective: Atrial fibrillation (AF) represents the most common cardiac arrhythmia worldwide; it poses a great burden in terms of quality of life reduction and yearly stroke risk. Left atrial appendage closure (LAAC) is a stroke prevention strategy that has been proven a viable alternative to anti-thrombotic regimens in non-valvular AF patients. LAAC can be performed as a stand-alone procedure or alongside a concomitant AF trans catheter ablation, in a procedure known as “Combined Procedure”. Aim of this study is to summarize the scientific evidence backing this combined strategy.

Methods: We reviewed the whole Medline indexed combined procedure literature, to summarize all the combined procedure study data .

Results: Nine published studies regarding combined procedure were found. Data, aims, and scientific rationales were reported and commented.

Conclusion: LAA combined procedure appears to be a safe and effective procedure; a careful patient selection is necessary to maximize its benefit.

Keywords: Atrial fibrillation • Catheter ablation • Stroke prevention • Left atrial appendage • Left atrial appendage closure • Combined ablation • Review

1. Introduction - Left Atrial Appendage Closure in AF treatment

Non-valvular Atrial Fibrillation (AF) is the 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 non-vitamin K antagonist oral anticoagulants (NOAC)], accordingly to the CHA_2DS_2-VASc score[1]. Nonetheless, OAC therapy never completely nullifies stroke risk and some specific sub-populations may not be eligible for this treatment due to high bleeding risk.

Following the observation that over 90% of thrombi in AF patients form in the left atrial appendage[2] (LAA), the concept of percutaneous left atrial appendage closure (LAAC) was developed to non-pharmacologically address similar conditions.

In 2009, *Holmes D.R, et al* developed the PROTECT AF trial[3]; this randomized controlled trial (RCT) compared LAAC using 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 in the intervention arm.

A second RCT, the PREVAIL trial[4], was performed and published by *Holmes D.R., et al* in 2014 to reassess LAAC procedural safety; peri-procedural adverse events rate dropped (4.2%), due to 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 versus warfarin group, with differences mainly driven by the reduction in hemorrhagic strokes (with a non-statistically significant reduction in the stroke rate)[5]. 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; 91.4% complete occlusion rate and 7.9% leakage < 5 mm rate)

were described, with only a 2.7% serious procedure/device related events within 7 days from the LAAC[7]; investigators also reported a 1.1% ischemic stroke and bleeding rate[8]. Although the WATCHMAN device was the only one used in those major prospective trials, many other devices entered the market and 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 in clinical and procedural outcomes have been reported in those LAAC studies including both devices either[11–13].

In current clinical practice, LAAC is 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, 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.

2. 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 as energy source[16]. LAAC 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 an 80% VKA discontinuation rate. The freedom from arrhythmia rate reported at 12 months was 70%.

The authors observed that performing LAAC after CA did not appear to exceedingly prolong procedural time and the long term combined procedure AF recurrence rates were comparable to the one achieved by

CA alone at their institution; no strokes were witnessed over a 12-month follow up.

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: by closing the LAA, OAC could be in fact withhold 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 a refined way to address AF symptoms, reducing at the same time stroke risk and the need for OACs.

3. Early Experiences:

In 2015, *Alipour A. et al* furthermore expanded the combined procedure evidence, by publishing a prospective study including a larger sample of 62 patients[18]. In this study, PVI energy source was phased RF and LAAC was performed using WATCHMAN devices. The larger sample size allowed a more reliable description of the peri-procedural adverse events: in this cohort, 5 (8.1%) patients developed a minor peri-procedural bleeding, with nor pericardial effusions neither strokes. Although the adverse event rate did not result much lower to the one reported in the

first experiences, all the encountered peri-procedural events resulted mild in their gravity and posed no real danger to the patient.

This study gave valuable data about the combined procedures long term follow up, reporting a 38 [25 – 45] months as median follow up time; 95.2% of patients presented satisfactory LAA occlusion rate, with a 45% rate of < 5 mm leakages and 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 (1.7% year/stroke rate; 74% risk reduction from expected). Authors speculated that a quota of those strokes may be due to carotidal atherosclerotic plaques and not AF-related; however, 2 (3.2%) strokes interested patients with a < 5 mm leakages and, 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 ruled out.

In the same year, *Calvo N., et al*. published a prospective studying describing 35 combined procedures performed with a mixture of 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 discontinue long term OACs, regardless of arrhythmia recurrences.

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; 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 in bleeding adverse event reduction: the combined procedure was used accordingly to that indication; 3) The intra-procedural adverse event rate in this study was very high (8.5%); 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 effective in reducing stroke and bleeding risk 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, with similar results at a long term follow up[20].

4. "Here Comes The Ice": Cryo-energy Combined Procedures

In 2016, cryo-energy instead of RF as energy source was introduced in combined procedure 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

pilot study, 35 patients were enrolled and underwent cryo-balloon PVI alongside WATCHMAN or ACP LAAC; peri-procedural reported adverse event rate and procedural time resulted comparable to previous RF CA combined procedure experiences.

At a 24 ± 12 month follow up, a 80% freedom from arrhythmias was achieved; a high long term complete LAA sealing (92%) was described, with all other patients experiencing a < 5 mm leakage. These results were then confirmed at a longer follow up and in a larger patient sample by a second study from the same group[21]. Combined procedure feasibility, safety and effectiveness regardless the energy source for PVI (RF or Cryo) and device brand choice was demonstrated with this experience; no evidence of superiority of an energy source on the other are to date available, leaving to the operator the option (and the burden) of the choice.

5. The Combined Procedure Nowadays

All those small/medium- sample sized experience data were summarized by two analyses published in 2018 by an investigation group led by *L. Boersma*.

Phillips K., et al[22] assessed combined procedure 30-day outcomes by pooling data from two large prospective multicenter LAAC registries

(EWOLUTION and WASP). Their 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 rate, almost always without the need of device resizing or recapturing.

Three major points were highlighted: 1) In the hands of experienced operators, the encountered pericardial effusion rate was 1.4%, with no peri-procedural stroke or deaths. These outcomes resulted 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 on peri-procedural adverse event rate in 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 from the start of the combined procedure experience, with VKAs being the employed drug of choice. In this analysis, NOACs as discharge therapy were analyzed on a large sample and found safe and compatible with the WATCHMAN prosthetic material: the reported 30-day bleeding

adverse event rate (2.9%) resulted equally divided between VKA and NOACs users and consistent with contemporary results experienced in CA PVI alone[24].

3) New peri-device leaks were noted at the first TEE follow up (from 2.9% intra or post-procedure to 39%); these leaks resolved or reduced in size over the following follow-up months. Authors reported this phenomenon as experienced in many previous LAAC trials[3,4] and it was attributed to a mix of factors: a circular device and non-circular LAA mismatch, edema masking LAA size and causing mismatch at implant time, 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 low peri-procedural adverse event rate previously reported was confirmed: the peri-procedural adverse (considering pericardial effusion, air emboli and stroke) event rate was 2.2%, much lower than those in PROTECT-AF, PREVAIL, and EWOLUTION trials. Furthermore, most of the complications observed resulted femoral-access-derived and not device-related; these results supported the previous studies, showing substantial improvement in 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%, respectively, 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 CHAD-VASC and HAS-BLED prediction in the population. A 84.9% long time OACs discontinuation rate was achieved in this experience.

6. LAA Contemporary Occlusion and Isolation

Over the years, several studies have described LAA electrical activity as one of the potential triggers sustaining arrhythmic events and recurrences in persistent and long standing persistent AF[26,27]; LAA isolation during AF CA has therefore emerged as a procedural answer to this clinical observation[26-29]. One of the possible drawbacks of LAA isolation is represented by the possible increased stroke risk due to LAA post isolation loss of contractility and mechanical dysfunction[26,30], and long term OAC is generally recommended (even if a recent retrospective large sample study seems to question this risk, reporting a very low long term event rate even in the absence of OACs[31]). LAA concomitant isolation and occlusion therefore seemed a reasonable approach to reduce this risk:

this approach was first explored and demonstrated in humans by *Panikker S et al* in a propensity-matched interventional study, where they suggested that this technique may increase the success of persistent AF ablation while obviating the need for chronic OAC[32]. This combined approach appears safe and effective, but still requires larger sample size for further validation analysis. To date, no consensus has been yet reached in the scientific community on whether or not to routinely implement LAA occlusion (staged or concomitant) after LAA isolation: expert opinions have both called for a routinely LAAC after isolation[33], as well as for a case-by-case approach, mainly due to the non-standardized LAA contractility response to electrical isolation and the economical drawbacks[34].

7. Future Directions:

Combined procedure generally evolves following innovations in the two procedural stages that it is composed of. 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 TEE, intra cardiac echography (ICE) has been used and described as an effective guidance modality of LAAC; although no RTCs TTE vs ICE have been published yet, feasibility and effectiveness has

already been reported[35-37] and this modality will definitely find its way also into the LAAC stage of the combined procedure.

2) Current clinical practice suggests the use of a 60-day post procedural regimen of OAC (VKA or NOACs), followed by a 6-month dual anti platelet regimen and then lifelong aspirin; the need of OACs at discharge has been justified with the increased thrombotic risk posed by the AF ablation stage of the procedure. With this regimen, stroke rates in the initial follow up phase after combined procedure resulted comparable with those reported in cohorts undergoing LAAC procedures alone; however, given the high bleeding risk of most candidates to the combined procedure, bleeding events during those first 60 days represent one of the major issues with the combined procedure[22,25]. Faster de-escalating protocols than those proposed by official occluder devices guidelines have already been introduced in LAAC procedure alone for high bleeding risk patients[38,39]; similar lighter post-procedural protocols may be evaluated in the combined procedure setting in the near future.

3) A recent paper from *Conti M., et al*[40] 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) Ablation related-edema in the LA ridge area, during an extended PVI or direct LAA isolation approach, could represent an intra-procedural confounding parameter when assessing occluder device size during combined procedure. To date, no direct comparison in sizing accuracy and peri-device leakage rate between staged and combined procedures have been published; further dedicated studies are needed to address the magnitude of this problem.

5) One of the major limitations to the widespread use of the combined procedure so far has been its economical drawback: most national health care systems, as well as insurance companies, do not reimburse both procedures if performed at the same time, making the combined procedure an economical pitfall for many institutions. The idea of performing LAA occlusion and AF ablation over a 30 days window ("Short Interval Stated Procedure") has been introduced to overcome this burden: although similar experiences make perfect sense from an economical point of view, they lose the combined procedure main advantage of bringing the patient only once into the operating theatre. The combined procedure presents an overall cost that is inferior to the two independently staged procedure (e.g. single in-hospital stay; single use of the OR; less overall procedural time) and it is not unreasonable to foresee its economic status recognized in the near future

8. 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, trans septal 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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Table 1 – 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%

n.d.: 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