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# Silent Cerebral Ischemia and Stroke: The Hidden Side of Non-Coronary Transcatheter Cardiac Procedures?

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**Abstract**

In the last two decades patients affected by cardiovascular disorders and the related disability have greatly increased in part due to the population aging. Diagnostic and therapeutic strategies for these conditions have improved, offering novel non-invasive or less-invasive interventional approaches. Indeed, selected patients affected by mitral regurgitation, aortic stenosis and atrial fibrillation with high bleeding risk, may take advantages of percutaneous transcatheter procedures such as mitral valve repair, aortic valve replacement, left atrial appendage occlusion, respectively. Randomized clinical trials and real-world data have confirmed the effectiveness of these procedures reducing the risk of death and major complications when compared to conventional surgery. Based on the available data, thromboembolic stroke is considered a rare event. However, while the peri-procedural risk of clinical brain ischemic complications is low, imaging-based evaluation have revealed the presence of a high number of clinically silent ischemic brain lesions. Magnetic resonance imaging studies have shown how this underestimated event occurs frequently in brain areas without primary motor, sensory, or linguistic function ("non-eloquent" brain areas), thus the clinical impact of these "silent" ischemic lesions remains unclear. Increasing evidences suggest, however, that silent ischemic brain injury events may have a cumulative effect, causing neuropsychological deficits or aggravating preexisting vascular dementia. Because of the exponential increase of these procedures yearly, monitoring of peri-procedural ischemic events in the brain should be considered to further optimize diagnostic and therapeutic vascular procedures in the future.

**Keywords:** Silent cerebral ischemia, stroke, cardiac catheterization

## Introduction

Thromboembolic stroke resulting from cardiac catheterization (coronary and non-coronary) is relatively low but due to the increasing number of procedures that are performed yearly worldwide and the debilitating effect associated with high morbidity and mortality rates it represents one of the most dreadful peri-procedural complication during percutaneous interventions [1,2]. The incidence of symptomatic stroke varies from 0.1 to 0.6% during diagnostic cardiac catheterization [3,4] and 0.07 to 0.4% during percutaneous coronary interventions (PCI) [5], with the higher incidence reported in studies that performed systematic brain MRI [6]. Asymptomatic brain embolism is more frequent and brain infarcts detected by diffusion-weighted MRI during invasive cardiac procedures can be present in 8% of patients [6]. Microembolism is even more common although the clinical significance is uncertain. The pathophysiology of peri-procedural stroke is in the majority of cases related to the procedure itself, mainly due to the embolization in the brain arteries of material mechanically mobilized by catheters and wires from the aortic arch (atherosclerotic and calcified material, freshly formed thrombus etc) [7,8]. While the incidence of stroke during diagnostic cardiac catheterization and PCI is relatively low, interventions for valvular and structural heart diseases are associated with a significant risk of embolic complications [9]. Peri-procedural manipulation of calcified and degenerated valves, and, more in general, any left-sided structural heart interventions account for an incidence of symptomatic stroke reported from 2% to 7%, depending on the procedure [10-13]. Silent cerebral infarcts, linked to a higher incidence of cognitive impairment and dementia [14-16], are present in the majority of these patients with up to 90% in those undergoing patients undergoing transcatheter aortic valve replacement (TAVR) [17,18], and cannot be overlooked. Considering that percutaneous approach indications for structural heart diseases are continuously expanding representing already the gold standard treatment for patients with high operative risk for traditional open surgery [19], a better understanding of the peri-procedural risk of stroke is crucial to prevent this feared complication. This article will review the risk of cerebral complications linked to the newest non-coronary transcatheter cardiac procedures, focusing on transcatheter aortic valve replacement, mitral valve repair and left atrial appendage occlusion.

## Percutaneous Transcatheter Procedures and Risk of Cerebral Ischemia and Stroke

### Transcatheter aortic valve replacement (TAVR)

In the last decades, mainly because of population aging, degenerative aortic valve stenosis has become the prevalent valvulopathy in western countries [20]. Introduced in 2002 [21], transcatheter aortic valve replacement or TAVR has become the gold standard therapeu-

tic approach in selected high-risk patients [22]. While the procedure is successful in restoring a normal trans-aortic gradient, stroke still represents one of the most important complications of TAVR, even if the improvement of materials and implant techniques (exclusive use of the transfemoral technique) have significantly reduced the incidence of stroke compared to the first experiences [23].

The Valve Academic Research Consortium (VARC) indicates with the term "stroke" the onset of a new neurological deficit, focal or global, that persists for more than 24 h and is caused by embolic, ischemic or hemorrhagic phenomena. Instead, a new-onset neurological deficit is resolved as a transient ischemic attack (TIA) that resolves rapidly (generally within 1-2 h) without evidence of organ damage to neuroimaging methods [24].

Stroke can in turn be defined as disabling or non-disabling according to the mRS score (modified Raskin score - score ≥ 2 to 90 days; mRS score < 2 to 90 days) compared to baseline prior to the stroke episode [24].

The risk of cerebral ischemia in patients undergoing TAVR has been evaluated by several studies. The PARTNER-A study reported clinical events occurring at 30 days and at 1 year in 358 inoperable patients for severe aortic stenosis, randomized to undergo TAVR or medical therapy. While a net reduction in mortality (one year: TAVR 30.7% vs. medical therapy 50.7%; P < 0.001), hospitalizations and persistence of severe symptoms (NYHA III-IV) was observed, percutaneous valve replacement showed a higher incidence of ischemic stroke both in the peri-procedural phase (at 30 days: TAVI 6.7% vs. 1.7% medical therapy; P = 0.03) and in the follow up (at 1 year: 10.6% vs. 4.5% medical therapy; p = 0.04) [22].

The subsequent PARTNER-B study compared the prognosis at 30 days and 1 year in 699 high-risk surgical patients randomized to receive TAVR or surgical aortic valve replacement (SAVR) [22]. In this trial there were no significant differences between the two procedures in terms of mortality, hospitalization or major strokes while, considering all cerebral ischemic events (TIA, minor and major strokes), TAVR showed a slightly higher incidence (at 30 days: TAVR 5.5% vs. SAVR 2.4%; p = 0.04 - at 1 year: TAVR 8.3% vs. SAVR 4.3%, p = 0.04).

These data, however, have not been confirmed by the 2014 Medtronic CoreValve self-expanding prosthesis study in which no statistically significant difference was reported in the overall incidence of cerebrovascular events between the two treatments, nor to 30 days (4.9% TAVI group versus 6.2% SAVR group, p = 0.46) or one year (8.8% TAVI group versus 12.6% SAVR group, p = 0.1) [25].

In 2016 the PARTNER-2 study, involving 2,032 patients with severe aortic stenosis at intermediate operative risk, randomized to undergo TAVR or SAVR, at 2 years showed a cumulative incidence of debilitating death and stroke that could be superimposed in the two groups (TAVR 19.3% vs. SAVR 21.1%; p = 0.25) with a substantial equality of risk for each type of stroke (5.5% for TAVR vs. 6.1 for SAVR at 30 days, given that it is maintained at 1 year and at 2 years) especially in the group in which a transfemoral approach was performed exclusively.

The analysis of cerebral ischemic events did not therefore show significant differences neither in the acute phase nor in the subsequent follow-up between TAVR and SAVR, showing a common frequency of around 5% of stroke [26].

In the last randomized TAVI study (PARTNER 3), 1,000 patients from 71 centers were randomly assigned between March 2016 and October 2017, suffering from symptomatic severe aortic stenosis with low surgical risk (STS score < 4%), to undergo TAVR with the SAPIEN 3 valve or to traditional surgery with any commercially available surgical valve. All patients were followed for at least one year and a clinical follow-up with echocardiographic evaluation is planned at 10 years. TAVR achieved superiority, with a 46% reduction in the event rate for the primary endpoint of the study, a combination of all-cause mortality, stroke, and one-year rehospitalization [27]. Several secondary endpoints were also assessed, with a significant reduction in the TAVR group of stroke rates at 30 days (0.6 vs. 2.4%; p = 0.02) and a one-year stroke rate of 1.2% in patients treated with TAVR vs. 2.4% of patients treated with surgery [27].

Another randomized clinical trial on low-risk patients with severe aortic stenosis, the Evolut Low Risk trial, showed the non-inferiority of TAVR with an auto-expandable valve, the Evolut Medtronic, when compared to traditional heart valve implantation. In the primary endpoint the composite set of death for any cause or disabling stroke at 24 months was 5.3% in the TAVR group and 6.7% in the SAVR group [28,29]. However, data from meta-analysis [11,30,31] and registries [32] indicate a lower rate of stroke at both timing, 30 days and 1 year (Figure 1). What remains to be addressed is the eti-

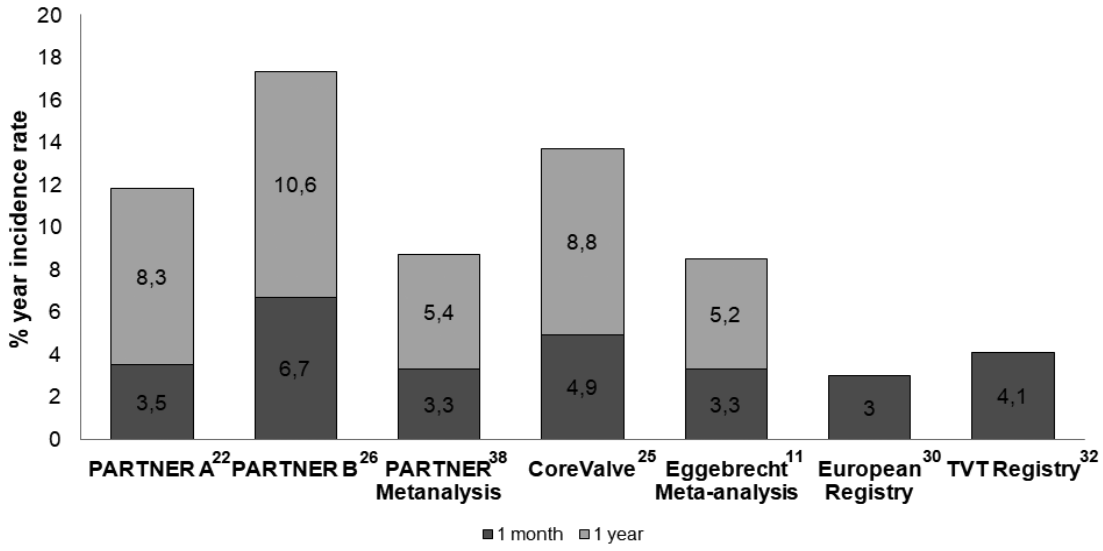


**Figure 1:** Risk of stroke after TAVR as reported in randomized clinical trials, registries and meta-analysis.

ology of stroke during and after TAVR. Interesting studies by Van Mieghem, et al. [33,34] showed, using cerebral protection systems temporarily implanted during the TAVR procedure, presence of debris or fragments of material able to determine occlusion of the cerebro-afferent vessels in 75% of the patients subjected to transcatheter implantation. The debris consisted of fibrin or amorphous calcified material and connective tissue derived from the flaps of the native aortic valve and atherothrombotic material from the aorta [35].

TAVR-related stroke risk can indeed be divided into:

- *peri-procedural risk* (a condition that is decreasing due to the improvement of intervention techniques): This risk is linked on the one hand to the procedure itself in which the passage of catheters in the aortic lumen with the possible damage to atherosclerotic plaques, the crushing of the native valve, the activation of the inflammatory cascade, determine exposure of thrombogenic material, release of large amount of tissue factor and thrombin. On the other hand, the implanted valve, in which there is presence of biocompatible but not endothelized material, mounted on a metal stent, can favour the formation of small thrombi with possible subsequent embolization [36,37];

- *post-procedural risk*: In the post-procedural period, the possibility of stroke, although smaller than in the peri-procedural period, continues to persist over the years due to phenomena mainly related to thrombosis of the valve, as well as the possibility of new onset of atrial fibrillation (AF) (this population has an incidence of about 15%) and the presence of cardiovascular (CV) risk factors [29,36-38]. The analysis of 3,687 patients enrolled in the CoreValve studies, showed a stroke rate of 8.4% at 1 year [29], In the PARTNER trial up to 3.3% of patients experienced a clinical neurological complications in the first 30 days [38].

It has been reported in an observational study that the risk of cerebro-vascular events is highest in the hours immediately following the procedure [39]. In particular, the results of this study showed that acute events (within the first 24 hours of the procedure) were mainly related to mechanical procedural factors [39]. Conversely, subacute cerebrovascular events (1 to 30 days after TAVI) were mainly associated with the occurrence of new AF [39]. The incidence of late events (between 30 days and one year) correlated instead with the presence of pre-existing AF, atherosclerotic load (peripheral and cerebrovascular arteriopathy) and the number of CV risk factors [39].

However, thank to novel imaging techniques evaluation, phenomena of hyperacute, subacute and chronic thrombosis in patients with normal trans-prosthetic gradients (< 20 mmHg of average gradient) have been reported [40].

This condition supports the presence of silent stroke (stroke detectable only through neuroimaging methods) in subjects subjected to TAVR evaluated by MRI. As already reported in various observations, about 2/3 of TAVR patients show lesions compatible with ictal events which, although not clinically important, could lead to an increase in cognitive dysfunction [17,41,42].

Ultimately, although the incidence of clinically manifested stroke is decreasing compared to the first observations, neuroimaging methods demonstrate that silent brain embolization is a very frequent event. Long-term outcome remains unknown and, possibly, the use of cerebral protection devices during TAVR should be encouraged.

## Mitral valve repair and replacement

Mitral regurgitation is the second most frequent indication for valve surgery [19] and it affects more than 10% of people above 75 years [43]. Despite the lack of randomized clinical trials between the results of mitral valve replacement and repair, it is widely accepted that, when feasible, surgical valve repair is the preferred treatment [19]. In the last decade, percutaneous edge-to-edge mitral valve repair with MitraClip device (Abbott, California) has spread as the preferred transcatheter treatment for severe and moderate-to-severe mitral regurgitation in patients who cannot be candidate to cardiac surgery [44]. Despite the controversial results available to date on the efficacy of this procedure (transcatheter edge-to-edge repair seems to reduce mortality only in certain subgroups of patients) and the need of an appropriate selection of the patients, there is a wide consensus on the safety and feasibility of this procedure. In the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) II, transcatheter mitral repair with the MitraClip device was safer than surgery but was not as effective in reducing the severity of mitral regurgitation [44]. In the safety analysis of the MITRA-FR study the peri-procedural complications accounted for 14.6% of the patients, which included two cases (1.4%) of embolism, resulting in overt stroke. Moreover, in the prespecified serious adverse events at one year, the rate of ischemic or hemorrhagic stroke was 4.6% [45].

After MitraClip implantation, reported clinically overt stroke occurs in very small percentage of patients, ranging from 0.2 to 0.8% [46,47], but the rates appear higher in hospitalized patients, ranging from 0.9% to 2.6% [13,48,49].

The risk of clinically silent microembolism remains mainly unknown, but it could lead to neurocognitive impairment and dementia [50]. In a recent study, Blazek, et al. [51] enrolled 27 high risk patients to assess the incidence and impact of both clinically apparent and silent cerebral ischemia using serial diffusion-weighted magnetic resonance imaging before and after MitraClip procedure. As for Heart team discussion, the study population was considered ineligible for heart surgery and almost 67% of the patients had atrial fibrillation, whereas 18% of the patients had a story of previous stroke, reflecting a high grade of comorbidities. Comparison of pre and post-interventional brain MRI showed new embolic lesions spread in both hemispheres with a diffuse pattern in 85% of the patients without any clinically overt stroke. Multivariate analysis revealed that only device time was an independent predictor of new ischemic MRI lesions, probably as this parameter can be considered a marker of the procedure complexity and the degree of valvular or subvalvular damage. High BMI, and the number of clips needed for valve repair were not significatively associated to new lesions, despite a trend towards a higher burden of embolism [51].

There was no significant decrease in the post procedural cognitive function assessed by the Montreal Cognitive Assessment (MoCA) score compared with baseline, although the presence of more than 3 lesions and valve calcifications were predictors of lower scores in univariate analysis. Despite this findings, only pre-procedural MoCA score was significantly associated to a post procedural worsening of cognitive function [51].

The study by Blazek, et al. also revealed some differences in the distribution pattern of the lesions between edge-to-edge transcatheter mitral valve repair and TAVR [23,52]. Both procedures are associated to the development of new ischemic lesion at brain MRI (85% for MitraClip and 80-85% for TAVR patients, respectively), but total lesion's volume is reported to be higher in TAVR patients [13,51,52]. The distribution pattern is bilateral in both groups, suggesting an embolic origin of these lesions [53]. In the MitraClip MRI study population most of the lesions could be found in the vascular territory of the middle and posterior cerebral artery, whereas in patients who underwent TAVR procedure the majority of embolic foci was found in the anterior and vertebrobasilar artery distribution territory but these trends are not significative [51,52].

In TAVR patients, hyperlipidemia, renal dysfunction, lower aortic atheroma thickness, porcelain aorta, increased left atrial appendage velocity, and reduced aortic valve area at baseline were potentially associated with the amount of new foci at brain MRI [52]. Another study involving 81 patients who underwent TAVR with a dual filter–based embolic protection device (Montage Dual Filter System, Santa Rosa, California) [33], identified balloon expandable transcatheter heart valves (THV) and post-procedural dilatation as independent predictors of new embolic lesions, suggesting that the mobilization of calcified tissue from the valve apparatus could be the main mechanism. On the other side, the origin of embolic particles is less clear in patients undergoing MitraClip.

The use of cerebral embolic protection devices (CEP) during MitraClip procedure has provided some insights on the mechanisms and pathophysiology of procedure-related stroke.

A recent study by Frerker, et al. [54] included 14 high risk patients undergoing MitraClip with the dual filter Sentinel system (Claret Medical, Santa Rosa) *in situ*. Interestingly, debris was found in 100% of the 14 patients who underwent MitraClip. The microscopical analysis of the 28 (proximal and distal) filters showed that, in patients treated with 2 clips instead of 1 clip, embolic particles had higher diameter (maximum particle diameter 402 µm [interquartile range: 275 to 589 µm] vs. 134 µm [interquartile range: 56 to 336 µm]; $p < 0.0001$), the cumulative particle area was bigger in patients who were treated with 2 clips [range: 3.45 (2.80-6.80) $mm^2$ vs. 0.81 (0.36-2.06) $mm^2$]. The most common debris composition were acute thrombus and small fragments of basophilic foreign material consistent with hydrogel, which were found in 85.7% of the patients each [13,54]. Valve tissue and/or superficial atrial wall tissue were found in 64.3% of the patients, followed by organizing thrombus (28% of the patients) and microparticles of myocardium (14.6% of the patients). Interestingly, calcium was not found on the dual filter CEP devices, according to the previous observation that mitral calcification seemed to have no correlation with the development of new ischemic lesions [51].

Apart from demonstrating the safety and feasibility of cerebral embolic protection devices during transcatheter mitral valve repair, the study opened to new unanswered questions. It is not clear [34] if the risk of overt and subclinical stroke could be reduced by the use of CEP devices and further studies are needed [55]. The origin of the debris particles is another matter of debate. Acute thrombus formation could derive from guidewire system or transseptal sheat as well as from thrombogenic surfaces of the clip delivery system: interestingly a rate of 9% of thrombus detection despite optimal anticoagulation was found on the transseptal sheat in a recent study [56]. The small fragments of non polarizable, hydrophilic material found in the 85% of the patients were consistent with hydrogel. This polymeric coat can usually be found on sheath and catheters where it contributes to reduce mechanical friction between catheters and vessel wall. Hydrogel embolism has been previously described in many intravascular procedures, where it seems to cause multisystemic embolism [57-59]. While organizing thrombus embolization during MitraClip procedure seems to be related to the high prevalence of atrial fibrillation in the study population, the presence of fibroelastic tissue consistent with atrial or valve tissue could be attributed both to the transseptal puncture and to a procedural injury: not surprisingly, it is associated to the delivery of multiple clips and to a longer device time, reflecting numerous grasping attempts [54].

Apart from MitraClip, recent interest has raised about transcatheter mitral valve replacement procedures (TMVR), and new devices have been designed for both native and prosthetic valves [60-62].

Although the feasibility of these interventional procedures has been demonstrated, most of the clinical studies are in very early stage, and no valid conclusion can be drawn both on the clinical efficacy and the stroke risk of these procedures. In a recent study enrolling 64 high-risk patients undergoing TMVR with compassionate use of balloon expandable valves, the 30-day burden of clinically relevant stroke was 6.9% [62], but this high percentage has to be interpreted in the light of a high rate of comorbidities in the study population. Mitral valve calcifications have been addressed as the potential source of embolic particles [63]. The relative risk of stroke is almost double in patients with mitral annular calcifications [relative risk 2.10 (95 percent confidence interval, 1.24 to 3.57; P = 0.006)] after adjustment for many common risk factors, and the statistical association between stroke and MAC is a continuous variable: on multivariate analysis, each millimeter of calcification increased the relative risk of stroke by 1.24 (95 percent confidence interval, 1.12 to 1.37; P < 0.00) [64]. Nonetheless, the available evidence is not sufficient to draw valid conclusions about the prognostic weight of mitral valve calcifications in patients undergoing transcatheter mitral valve replacement.

It seems clear, in conclusion, that the association between stroke and mitral valve procedures is multifactorial. Many conditions, such as procedural complexity, myocardial or atrial tissue damage during grasping, air embolism, acute thrombus formation, paradoxical embolism through septal defect, mitral valve calcifications and mobilization of pre-existing thrombus (mainly in patients affected by atrial fibrillation) are potentially involved in peri- and post-procedural stroke [13]. These challenging clinical scenarios will be addressed in future prespecified randomized clinical trials in order to explore the epidemiological and pathophysiological association between stroke and mitral valve transcatheter interventions.

## Left atrial appendage occlusion

Atrial fibrillation is the most common cardiac arrhythmia in general population, with an estimated prevalence of 1% but expected to be higher in the next decades, both in Europe and US, because of population aging [65,66]. AF increases the risk for ischemic stroke, silent cerebral ischemia and related cognitive dysfunction [67]. Prothrombotic processes due to blood stasis, mostly in the left atrial appendage (LAA), are responsible for atrial thrombus formation. This is particularly true in the setting of nonvalvular AF, as demonstrated by Blackshear and Odell [68], while this percentage seems to be lower in other etiologies, such as rheumatic AF. Subsequently, other parameters have been used for the stratification of embolic risk in AF, primarily the anatomy of the LAA, which has been divided in four subtypes, with the" chicken wing" configuration being associated with the lowest risk [69].

Anticoagulation with Vitamin K Antagonists (VKAs) or Direct Oral Anticoagulants (DOACs), following annual stroke risk evaluation with the CHA2Ds-VASC2 score, represents the standard care in patients with AF, in order to prevent stroke and peripheral embolization [66]. Although these drugs are widely used and DOACs have shown non-inferiority and sometimes even superiority for stroke prevention while having significantly less bleeding complications compared to Warfarin [70-73], some issues still remain matter of debate, including contraindications, side effects and adherence.

The small but significant percentage of patients cannot take warfarin or DOACs because of high bleeding risk or experienced bleeding events have benefit, in the last few years, from transcutaneous Left Atrial Appendage Occlusion (LAAO) to reduce the risk of thrombotic embolism [74]. Various devices have been developed over the last years, not all have been approved in Europe and with some of them still under clinical investigation [75]. Currently, the vast majority of implanted devices for catheter-based LAAO are the Watchman and the Amulet [76,77]. The procedure always requires

transesophageal echocardiography, anesthesia, femoral vein access and transeptal puncture with a 14 French catheter system [78].

- *WATCHMAN LAA occluder*: It is important to emphasize that this is the only device that has been tested in randomized clinical trials [76]. Experience with other devices is more limited and, consequently, less data is available.

While peri-procedural issues have been reported including pericardial effusion, cardiac tamponade, device embolization and major bleeding, major stroke appears to be a rare complication during the procedure, irrespective of the implanted device [79-81]. There are many possible mechanisms that explain cerebral embolism during transcatheter closure of the LAA such as embolism of trapped air during contrast dye injection or saline flush, embolism of parts of the interatrial septum during transseptal puncture, embolism of thrombi from guidewires and mobilization of thrombotic material from the LAA during catheter manipulation [78]. All these mechanisms can generate major clinical strokes (which are the only ones reported in clinical randomized trials and registries), but more often microembolism as reported by Majunke, et al. [82]. Using transcranial doppler study (TCD) and MRI examination they found microembolic signals on periprocedural TCD monitoring and new ischaemic cerebral lesions in 32% of patients soon after the catheterization, not related with the microembolic signals on TCD. Only in 10% of patients, lesions were still detectable in a second MRI 45 days later. These results suggest that transcatheter LAA closure is associated with asymptomatic cerebral embolism, even if no longer detectable weeks after the procedure. In this study the majority of patients were implanted with the WATCHMAN LAAO [82].

Two randomized clinical trials have tested safety and efficacy of the Watchman occluder: PROTECT AF and PREVAIL, both designed to show non-inferiority against dose-adjusted Warfarin [76,81]. In the PROTECT AF trial, peri-procedural clinical stroke incidence in 463 patients implanted was about 1%. This percentage has further decreased in the PREVAIL trial, where a 0.4% was reported. The decreasing trend has been confirmed also by the subsequent prospective registries [CAP [80], CAP2 [79], EWOLUTION [83]], which have shown no procedure-related strokes. All these data were obtained in patients treated with Warfarin for 45 days post-implantation followed by aspirin and clopidogrel for 6 months and then aspirin

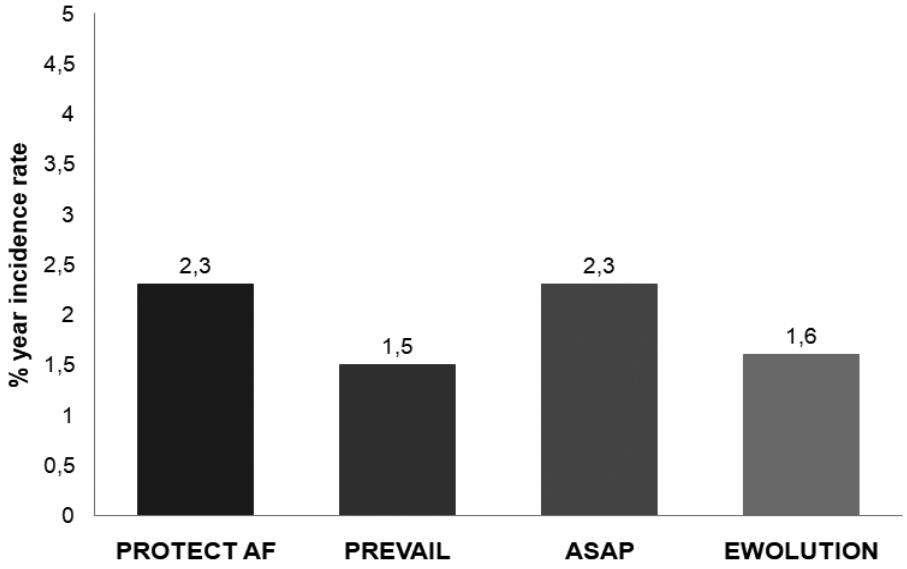


**Figure 2:** Risk of stroke after WATCHMAN implantation as reported in randomized clinical trials and registries.

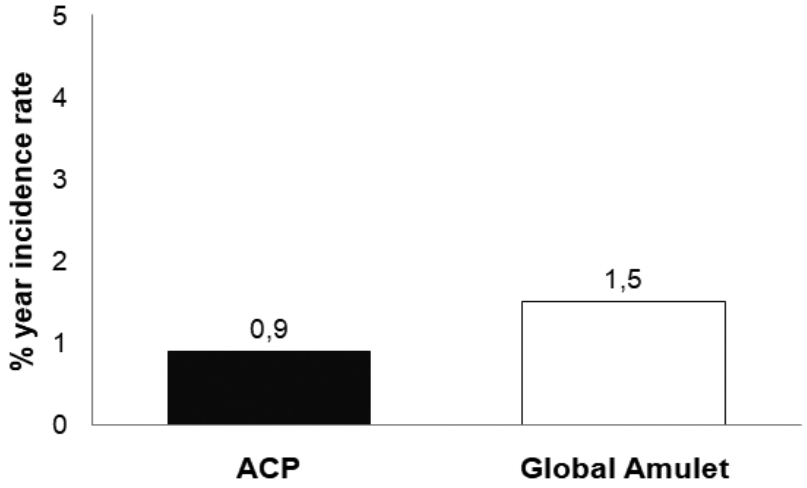


**Figure 3:** Risk of stroke after Amplatzer Cardiac Plug and Amulet implantation in registries.

alone. The only exception was the EWOLUTION registry, where 27% of patients were treated with oral anticoagulants, 59% with dual antiplatelets, 7% single antiplatelet, 6% without any therapy. Cumulative post-approval success procedural rate was 95.6%, with peri-procedural stroke occurring in 0.08% of cases overall [83]. The risk of stroke after WATCHMAN implantation as reported in RCTs and registries is summarized in Figure 2.

- *AMPLATZER CARDIAC PLUG (ACP)and AMULET*: Only case series and post marketing observational registries are available for ACP and Amulet device (Figure 3). In all cases patients were treated with variable combinations of aspirin and clopidogrel at the time of procedure. Data from large multicenter ACP studies consisting of 1,822 patients with an average follow up of 16 months showed a procedure related stroke incidence between 0.8 and 1.2% [17-19)]. The most recent data for the Amulet device comes from a large prospective registry published by Landmesser, et al. [77]. They reported (n = 1,088) a cumulative 0.3% of peri-procedural stroke incidence. No data are available about microembolism and silent cerebral lesions.

- *LARIAT*: this device (SentreHeart , Redwood, CA, USA) is characterized by percutaneous left atrial appendage suture ligation from dual-wire access femoral and epicardial approach. As LAA seems to be a non-pulmonary vein focus of origin of AF, the epicardial based exclusion procedure might also have the benefit of reducing AF burden. Two prospective [84,85] and one retrospective [86] registers are current available on the device. The success rate was between 94 and 98%. No peri-procedural stroke was found in any of the registers. Nearly two-thirds (59%) of patients were treated only with single antiplatelet agent at the time of procedure while 22% were on dual antiplatelet drugs and 19% on oral anticoagulation. No data is available about silent strokes and small brain lesions.

Few important studies are ongoing and can potentially change the utilization of LAAO and improve the knowledge of peri-procedural risk on the brain: The Amplatzer Amulet LAA Occluder trial (Amulet IDE , NCT02879448), a prospective randomized multicenter worldwide trial in a 1:1 fashion to either the Amulet device or the Watchman device and the Interventional Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in High-risk Patients with Atrial Fibrillation (PRAGUE-17 Study, NCT02426944). Both of them will evaluate, as a part of primary safety endpoint, the rate of peri-procedural brain lesions, enrolling more than 1,200 patients overall.

In conclusion, LAAO represents a safe alternative for those patients who are not eligible for oral anticoagulation. Peri-procedural major stroke is a very rare complication. However, more data is needed about long-term outcome of patients with MRI-detectable brain lesions, as microembolism and silent ischemic strokes seem to be frequently associated with the procedure.

## Conclusions

In the last decade the use in clinical practice of non-invasive or less-invasive transcatheter cardiac procedures has expanded, with an increasing number of patients taking advantages from these new therapeutic strategies. Newer technologies are allowing indications for the use of these devices to change, extending the use to younger and lower surgical risk patients, thus increasing the number of treated patients in the years to come. A number of evidences suggest that cerebral embolism is underestimated and the rate of silent ischemic stroke or silent cerebral ischemia is much higher than the one reported in the available studies. Despite of the lack of clinical manifestations, the cumulative effect of this cerebral ischemia may be linked to dementia and cognitive dysfunction. Based on these considerations, much attention should be drawn to cerebral embolism and preventive strategies to further reduce peri- and post-procedural risk of silent cerebral ischemia.

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