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Assessement of antithrombotic strategy after left atrial appendage closure by a watchman device - a regional experience

Anne Guenet

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Année : 2020

ASSESSEMENT OF ANTITHROMBOTIC STRATEGY AFTER LEFT ATRIAL APPENDAGE CLOSURE BY A WATCHMAN DEVICE– A REGIONAL EXPERIENCE

THÈSE PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE
DIPLÔME D'ÉTAT

Anne GUENET
[Données à caractère personnel]

THÈSE SOUTENUE PUBLIQUEMENT À LA FACULTÉ DE MÉDECINE DE GRENOBLE
Le :24/06/2020

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ABBREVIATIONS

ACP : Amplatzer Cardiac Plug

AF : Atrial Fibrillation

APT : Antiplatelet Therapy

ASA : Acid Acetyl-Salicylic (Aspirin)

AT : Anticoagulant Therapy

CHU : University hospital center

DAPT : Dual Antiplatelet Therapy

DRCI : Délégation à la Recherche Clinique et à l'Innovation

HBP : High Blood Pressure

LAA : Left Atrial Appendage

LAAC : Left Atrial Appendage Closure

NOAC : Non-warfarin Oral Anticoagulant

OAT : Oral Anticoagulant Therapy

SAPT : Single Antiplatelet Therapy

SE : Systemic Embolism

TEE : Trans Esophageal Echography

TTE : Trans-Thoracic Echography

HAS : Haute Autorité de Santé

VKA : Vitamin K Antagonist

Anne GUENET

EVALUATION DE LA GESTION DES ANTITHROMBOTIQUES POST FERMETURE DE L'AURICULE GAUCHE PAR PROTHESE WATCHMAN – EXPERIENCE RHONE ALPINE

RESUME :

Introduction : La fermeture de l'auricule gauche par prothèse Watchman est proposée pour les patients souffrant de fibrillation atriale contre indiqués aux anticoagulants. Toutefois le traitement antithrombotique post procédure est discuté. L'objectif de l'étude est de comparer l'efficacité et la sécurité des différents traitements antithrombotiques post procéduraux.

Méthodes : Cette étude observationnelle multicentrique a inclus tous les patients consécutifs implantés d'une prothèse Watchman entre janvier 2013 et décembre 2018. Le critère primaire d'efficacité était la survenue d'accident vasculaire cérébral (AVC) ischémique, d'hémorragie majeure ou décès au long terme. Le critère de sécurité composite comprenait les complications initiales et saignements majeurs durant le suivi. Les groupes de traitement étaient : aucun, mono-, bi-anti agrégation.

Résultats : 295 patients ont été inclus, la moyenne d'âge était de 77ans, les scores CHA_2DS_2-VASc et HAS BLED moyens étaient 4,92(±1.3) et 3,65(±0.85).Le suivi moyen était de 23.5(±16) mois. Il n'y avait pas de différence statistiquement significative entre la survenue du critère composite d'efficacité selon le traitement choisi (p= 0,83). Aucun surrisque en fonction du traitement choisi n'a été trouvé. On note une réduction du risque d'AVC de 54% et d'hémorragie sévère de 72% en comparaison aux scores théoriques.

Conclusion : Il n'y avait pas de différence significative d'embolie, hémorragie ou décès selon le traitement choisi. Il semble possible de simplifier le traitement post intervention chez les patients les plus fragiles.

MOTS CLÉS : fibrillation atriale, fermeture auricule gauche, watchman, antiagrégant, anticoagulant, AVC
FILIÈRE : cardiologie et maladies vasculaires

ABSTRACT

ASSESSEMENT OF ANTITHROMBOTIC STRATEGY AFTER LEFT ATRIAL APPENDAGE CLOSURE BY A WATCHMAN DEVICE– A REGIONAL EXPERIENCE

BACKGROUND: The left appendage occlusion by Watchman device is possible in patients suffering from atrial fibrillation and unsuitable for anticoagulation treatment. However, post procedural treatment is still in debate. The aim of this study is to compare the efficacy and safety of each post-operative antithrombotic strategy.

METHODS: An observational and multicentric study included all consecutive patients implanted with a Watchman device between January 2013 and December 2018 in the university hospital of Grenoble, Lyon and Saint-Etienne was performed. The primary efficacy endpoint was the occurrence of thromboembolic event, major bleeding or during follow-up. The primary safety endpoint was a composite criterion of procedural complications or major bleeding. The groups of treatment compared were no treatment, single or dual antiplatelet therapy.

RESULTS 295 patients were included, the mean age was 77 years and the mean scores $CHAD_2S_2$ VASc and HAS BLED were respectively 4.92(±1.3) and 3,65(±0.85). The mean follow-up was 23.5 months (±16). There were no statistical difference in the occurrence of the primary criterion between the three groups (p= 0,83). No additional risk depending on treatment was found. There was a risk reduction of 54% in thromboembolic events and 72% in major bleeding in comparison to the expected rate estimated by the scores.

CONCLUSION: There was no difference of embolic events, major bleeding or death depending on the chosen treatment. No specific profile was found to help choosing medication. It seems possible to simplify the post procedural treatment by a single anti aggregation for fragile patients.

Key Words: atrial fibrillation, left atrial appendage closure, Watchman, anticoagulant, antiplatelet, stroke
Specialty: cardiology and vascular diseases

BACKGROUND

A – Atrial fibrillation

A-1 Epidemiology

Atrial fibrillation (AF) is the most common arrhythmia in developed countries. In 2010: 20.9 million men and 12.6 million women worldwide suffered from it. In France, the latest data dated from 2011 and estimated its prevalence between 600 000 and 1 000 000 people and an annual incidence of 110 000 to 230 000 new cases.

2/3 of the patients suffering from AF are 75 years old or more. In the general population 10% of people aged 80 years old and over are concerned. Its growing incidence is a public issue, we estimate it will keep on rising because of the better diagnostic methods and the aging of the world population.[1-3]

A-2 Complications

The impact of AF is mostly due to its complications including strokes, heart failure and drug related iatrogenia.[4] All of them are responsible for numbers of hospitalizations, treatments expenses, mortality and quality of life deterioration. There seems to be a correlation, at least partially, between cognitive alteration and AF which reinforce the misuse of treatments and its consequences.[5]

For instance, the mean of AF related strokes' prevalence is around 5%/year, but it varies greatly dependently with coexisting factors in each patients' medical history. The CHA_2DS_2-Vasc score was created to establish a probability of a new stroke to occur within a year for a patient suffering from AF.[6]

It is calculated depending on the patient history of the following factors: congestive heart failure / hypertension / age / diabetes mellitus / stroke / vascular pathology or coronaropathy / sex. (Annex 1-2)

B- Atrial fibrillation related strokes

B-1 Physiology

The Virchow Triade attests as necessary to the clot formation the association of endothelial lesion, high coagulability state and blood stasis. In the case of AF, the strongest element seems to be the blood stasis due to the absence of effective atrial contraction. This is secondary to the incessant arrival of new order of contraction avoiding any complete ones.[7]

This is even more accurate in the left atrial appendage (LAA) an embryonal reliquat pending from the external side of the left atrium. It is therefore very appropriate to alter vidange. This appendix can have various forms, but 4 of them are more frequent: windsock / cauliflower / cactus / chicken wings.[8] *[Figure a]* In autopsy studies more than 80% of the left atrial appendages are the localization of thrombi. This is correlated with the studies of imaging after a stroke in patient suffering from AF.[9]

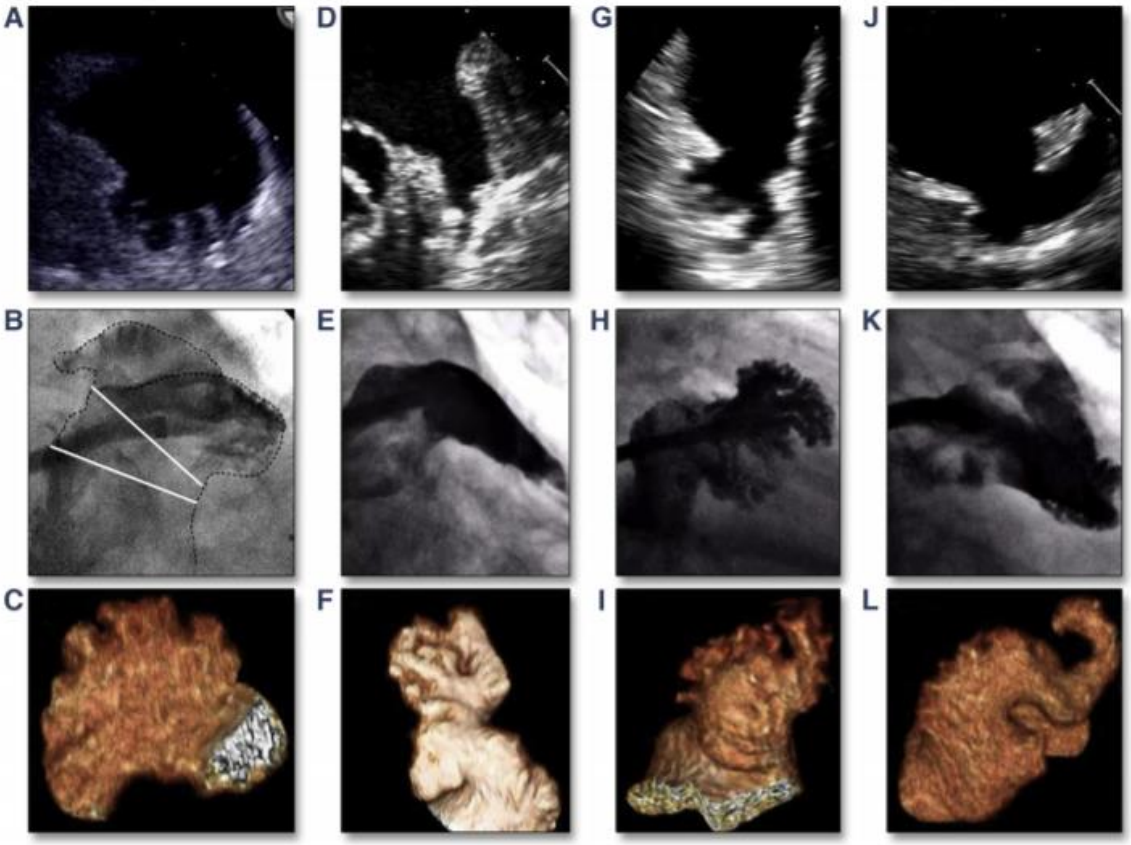

Figure a: Different LAA morphologies: in TEE/cine angiography / 3D computed tomography: From left to right: Cauliflower, Windsock, Cactus, Chicken Wing. From Beigel et al-2014.

B-2 Anticoagulation: between prevention and harm

To prevent strokes and their consequences, the European Society of Cardiology (ESC) recommends to prescribe an anticoagulant treatment for every patient in which the CHA_2DS_2-Vasc Score is:

- more than 1 for men
- more than 2 for women.

It can either be direct oral anticoagulants *(e g* apixaban, rivaroxaban, dabigatran) or the classic vitamin K antagonist (as warfarin). The current recommendations are to favour direct oral anticoagulants.[10]

These drugs are unfortunately known as the first leading drug to iatrogenia. The data from the ENEIS (enquête nationale sur les évènements indésirables graves liés aux soins) found that 31% of severe unwanted events under medication were related to them. Thus, numbers of elderly patients are ineligible for this kind of treatment. Therefore, some patients are in an impasse as they are at very high risk of stroke but absolutely unsuitable for anticoagulant. That's why the research for an alternative was launched. One of the results is the exclusion of the thrombi's site to prevent it from going in the systemic circulation.

C- History of the appendage closure

C-1 From the beginning to percutaneous intervention

The first appendage closure was made surgically. This ligature was realized during other heart surgeries. But these exclusions were at risk of ischaemia (via the circumflex artery), haemorrhage (tear of a fragile tissue) and incomplete ligature. A more recent technique was to implant a clip by epicardial access. All these procedures had divergent results depending the type of associated surgery. Some studies even showed a higher rate of early post-operative AF.[11] A randomized clinical trial is ongoing, (LAAOS III)[12] to compare the LAA occlusion to no occlusion during a routine cardiac surgery. 4812 patients were included and the results should come out in 2022. The first percutaneous trial of endovascular closing of the LAA using the PLATOO system was made in 2001. The only randomized trials on this subject were regarding the WATCHMAN system (Boston Scientifics®). PROTECT AF (Lancet 2009) and PREVAIL (JACC 2014).[13,14] The non-inferiority of left atrial appendage closure (LAAC) compared to lifelong VKA treatment in non-valvular AF was proven but only in populations accessible to anticoagulation therapy.

C-2 The Watchman device

This device is implanted via a trans-septal approach to seal the ostium of the LAA. It's formed by a nitinol frame structure recovered by a polyethyleneterphthalate. Its fixation is permitted by barbs. Different sizes are available : 21 / 24 / 27 / 30 / 33 mm. *[Figure b]*

To be noted that a new generation of the device is now used, the Watchman Flx. Its particularities are the reduced length, a reduced metal exposure, an a traumatic closed distal end. It is also available in different sizes (20/24/27/31/35), permitting to seal smaller and larger ostia. No patient of the following study was implanted by this new generation system. *[Figure c]*

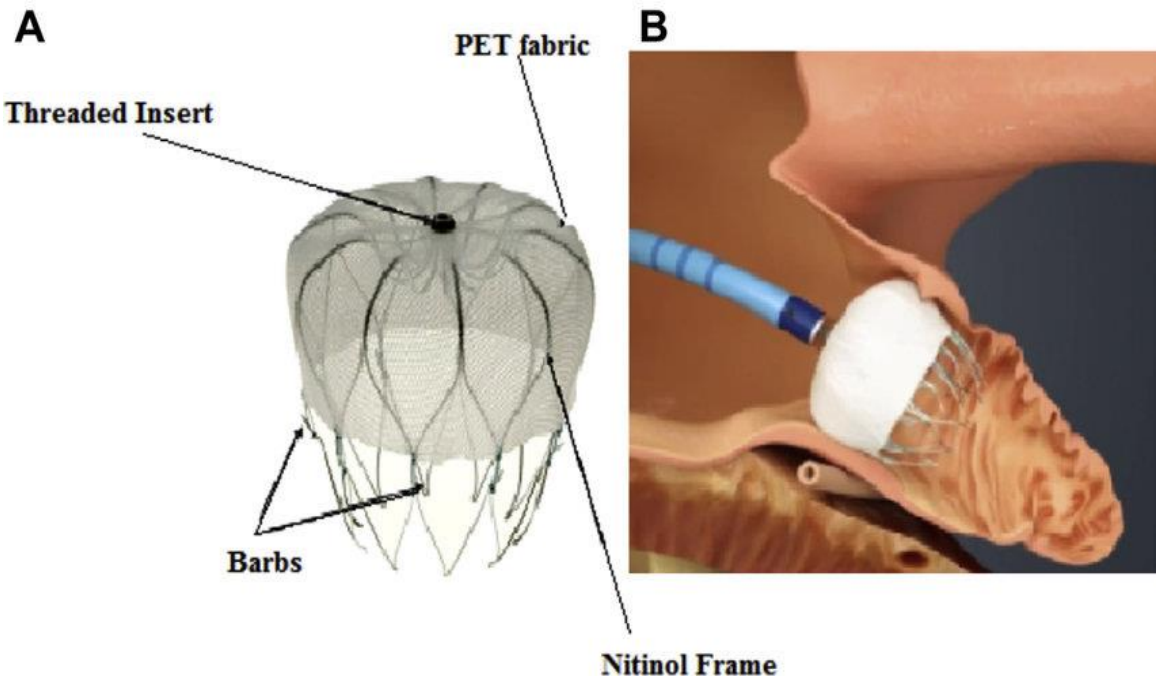

Figure b : WATCHMAN device. (A) Structure. (B) Inside left atrial appendage (Image provided courtesy of Boston Scientific).

PET: polyethyleneterphthalate.

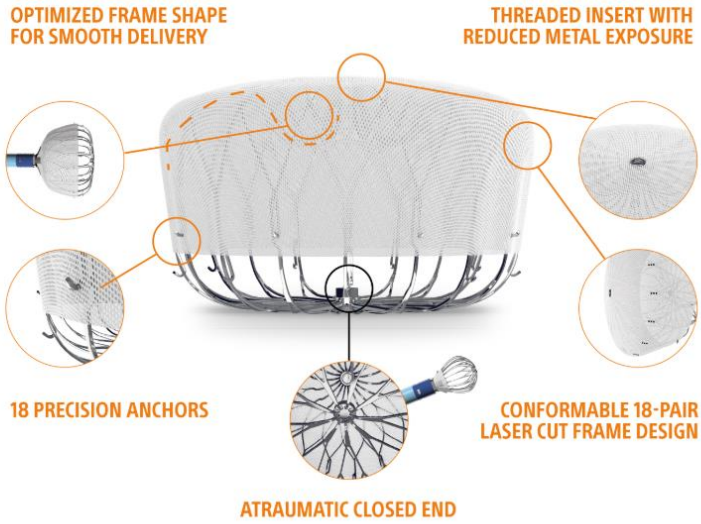

Figure c : Watchman Flx system (Image provided courtesy of Boston Scientific).

C-3 Current recommendations

Nowadays, LAAC is mentioned in the ESC recommendations of atrial fibrillation management as a class IIbC.[10] It only concerns patient with contraindication to anticoagulation therapy. In France, the official journal validates its reimbursement only in patients at high risk of stroke (CHA_2DS_2-Vasc score ≥ 4) and absolute contraindication to anticoagulation.

C-4 Gap in evidence

This intervention is based on 2 trials cited before. These trials were designed to compare the Watchman device to warfarin. In their design, patients received 45 days of warfarin and aspirin after implantation and then 6 months of dual antiplatelet therapy followed by a long-term therapy with aspirin 325mg. Such a prescription is generally impossible for our patient. The EWOLUTION registry, which collected all the implantations in Europe between 2013 and 2015 reported the possibility to use a dual antiplatelet therapy instead of OAC.[15] The latest

EHRA/EAPCI expert consensus statement ergo recommended a dual antiplatelet aggregation from 1 to 3 months followed by lifelong aspirin.[16] In practice, an interdisciplinary meeting is hold to assess the best fitted post-operative care for each individual case. Some observational studies are built to evaluate the feasibility of using only a single antiplatelet therapy with concluding results. But these studies are limited, included less than 100 patients and using multiple prosthesis including only a few Watchman system.[17–19]

Therefore, the aim of our study is to compare the long term occurrence of ischemic or hemorrhagic incident or death after a Watchman implantation depending on the postoperative care.

D- Our population

We took all the left atrial occlusion in three major centers of our region. All consecutives patients were included if they were implanted by a Watchman system. We chose to investigate only this prosthesis as it's the one that was used in the only two randomized controlled trials on the subject. There was a total of 295 patients. The three populations were comparable so we analyzed the global population as on. The baseline characteristics of patients depending on the including center are detailed in [Table 1].

Table 1: Baseline patient characteristics

Characteristics	GRENOBLE (n= 120)	LYON (n=143)	SE (n= 32)	All patients (n=295)
Mean Age, years (SD)	77 (+/-8)	77 (+/-7)	77 (+/-9)	77 (+/-8)
Male, n (%)	70 (58)	79 (57)	117 (56)	167 (57)
Hypertension n(%)	104 (87)	124 (88)	31 (97)	259 (88)
Diabetes , n (%)	36 (30)	53 (38)	12 (38)	101 (34)
Renal Impairment, n (%)	29 (25)	42 (30)	11 (34)	82 (28)
Cardiomyopathy , n(%)	54 (45)	67 (48)	21 (68)	142 (49)
LVEF, % (SD)	57.00(±7)	59.00(±10)	56.00(±12)	58.00(±9.5)
Chads Vasc score, mean (SD)	4.70(±1.2)	5.10(±1.3)	5.20(±1.1)	4.92(±1.3)
Has Bled score, mean (SD)	3.60(±0.9)	3.60(±0.8)	4.20(±0.7)	3.65(±0.85)
BMI (kg/m²), mean (SD)	26.20(±4)	25.80(±4.3)	25.10(±4.5)	25.90(±4.3)
Stroke / TIA, n (%)	55 (46)	81 (55)	18 (55)	154 (52)

TIA : transient ischaemic attack BMI body mass index; SE: Saint-Etienne; LVEF, left ventricular ejection fraction

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ARTICLE

BACKGROUND

Atrial fibrillation is one of must common arrythmia. One of its major complication is occurrence of ischemic stroke.[1] In Europe, left atrial appendage occlusion is a stroke preventing technique within patients suffering from non-valvular atrial fibrillation unsuitable to oral anticoagulation.[2] But the treatment following the procedure remains discussed. The first studies used warfarin during the 45 days following the implantation but this is rarely possible in French population assigned to the Watchman device.[3,4] The EWOLUTION registry reported that the prescription afterwards were : 60% dual antiplatelet therapy (DAPT), 7% single antiplatelet therapy (SAPT), 6% no treatment, 16% vitamin K antagonists (VKA), 11% non-vitamin K oral anticoagulant (NOAC).[5] Thus leading to current recommendations which are to prescribe either VKA / NOAC or DAPT from 1 to 3 months followed by aspirin (ASA) for at least a year.[6] In France, concerned patients are usually at high or very high risk of bleeding. We tend to try to lighten the post procedural treatment to prevent any bleeding accident.

The aim of this study was to compare the outcome (thromboembolism, hemorrhage, death) after implantation of the Watchman prosthesis depending on the chosen treatment.

METHODS

Patients

This observational, retrospective, multicenter study was undertaken at 3 sites (university hospitals) in France. Every consecutive patient aged 18 years or older implanted with a Watchman device between the 01/01/2013 and the 31/12/2018 were included. These centers acquired their data prospectively and then agreed to contribute to this retrospective analysis. Subjects eligible for LAA closure, according to appropriate local and European guidelines[2] were recruited from the general population in each institution, with a multidisciplinary decision taken in all centers. This study was validated by the Institutional Review Board of each including clinical center. The study was conducted retrospectively, patients were not involved in its conduct, there was no impact on their care. Ethical review was not therefore required. No industry support was provided for this study. Industry had no role in the design, conduct, data analysis, or manuscript writing of the study. The study has been registered on INDS (MR5816210420).

Procedures

The procedure was realized under general anesthesia and consisted of a right femoral vein access followed by a transseptal approach under trans-esophageal echography (TEE) and fluoroscopy guidance. All procedures were done by an experimented operator, 50% of them by an electrophysiologist and 50% by an interventional cardiologist. The choice of post procedural treatment was at the discretion of the clinician, depending on patient characteristics. They were all validated through an interdisciplinary meeting in each center.

A single exclusion criterion was implantation of another device than a Watchman system. The failure to achieve system implantation or death during the index hospitalization were not

leading to an exclusion of the study. The data were collected through the medical reports of each cardiology unit in the three university hospitals.

The primary objective was to establish if the treatment at 46 days post discharge device had an influence on efficacy and safety by use of a composite endpoint for efficacy that consisted of the occurrence of stroke (including ischaemic or haemorrhagic stroke), cardiovascular or unexplained death, or systemic embolism. Time to first event was calculated from the date of the Watchman's implantation to the event, or to the last known status date. Event rates were calculated as the number of events per 100 patient-years of follow-up.

We used the recommendation of Tzikas *et al* to classify the events.[7] [Annex 5] We chose this composite criterion used in many recent studies comparing left atrial appendage occlusion (LAAO) to anticoagulant and because it permitted us to compare the efficacy and safety as one. The primary safety endpoint was the composite of events related to major bleeding (*eg*. intracranial or gastrointestinal bleeding) or procedure-related complications (*eg*, serious pericardial effusion, device embolization, procedure-related stroke).

The effect of treatment at day 46 on long term outcome : embolic event, hemorrhagic event, all causes mortality were analyzed . We studied also the influence of treatment at discharge on short term safety outcomes (procedure-related complications, strokes and major bleedings).

Statistical analysis

The objective of the study was to obtain data on long-term patient outcomes. Therefore, the sample size was based on the desire to obtain sufficiently precise estimates of rare adverse events and not on power requirements for a formal hypothesis test. Values are expressed as mean ± standard deviation or median [range] for continuous variables, and as numbers and percentages for categorical variables. The main criterion was compared using a Kaplan Meyer curve. We used a Cox model for the primary efficacy endpoint using as explicative variables

the CV score and the Day-46 treatment. We used a univariate analysis to include the one with a p value < 0.06 to the multivariate analysis but no variable reached the classification.

Variables with more than 20% missing data were not included in the model. For variable with less than 5% missing data, we practiced an imputation by mean for quantitative variables and by mode for qualitative ones. The missing data between 5 and 20% were imputated by an equation of MICE. Data analysis was performed using SPSS Statistics for Windows, version 25.0 (IDM Corp., Armonk, N.Y., USA).

RESULTS

Baseline characteristics and study treatments

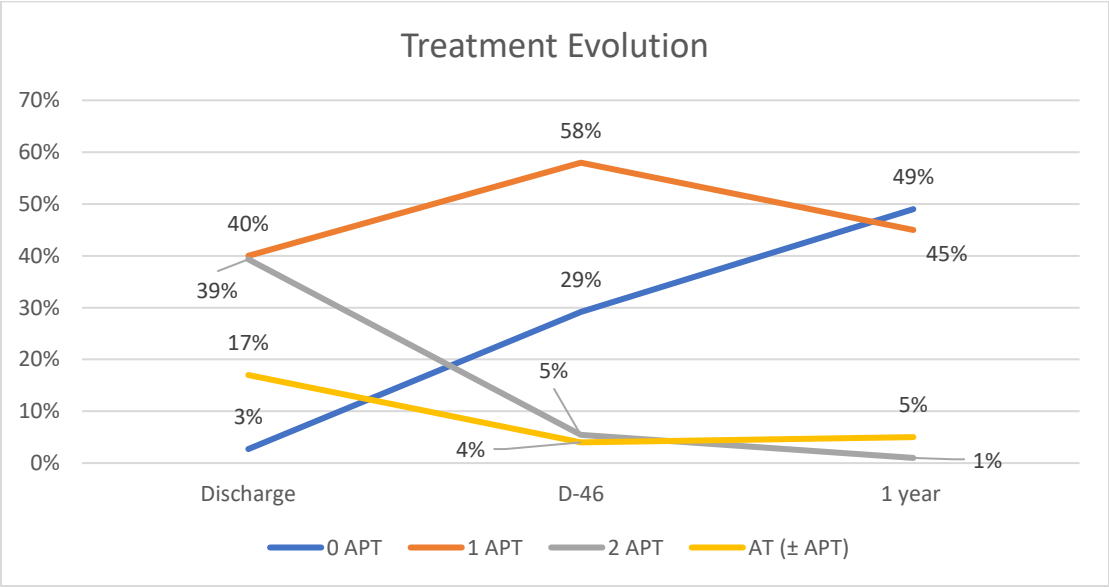
A total of 294 consecutive patients were included between 01/01/2013 and 31/12/2018. The mean age was 77.4 (+/-8) years old and 57% were men. Study treatments: Antithrombotic treatments at discharge and J 46 are detailed in Table 1, evolution of treatment within a year in Figure 1. All patients were implanted by a Watchman system, no Watchman Flx was used.

Table 1: Proportion of each treatment at discharge and day 46

Treatment	Discharge Number (%)	Day 46 Number (%)
0 APT	8 (3)	86 (29)
1 APT	118 (40)	171 (58)
2 APT	116 (39)	16 (5)
AT ± APT	49 (16)	13 (4)

APT : antiplatelet therapy; AT : anticoagulant therapy

Figure 1: Treatment evolution within a year



APT = Antiplatelet therapy; AT = Anticoagulation therapy.

Details of the baseline characteristics of the patients depending on the treatment at day 46 are represented in Table 2, clinical characteristics were comparable in the 3 groups of treatment .

Table 2: Baseline characteristics and risk factors of study participants in 0 APT, 1 APT and 2 APT groups

Characteristics	0 APT N=85	1 APT N=170	2 APT N=15	ANOVA/Khi2
Age (years)	78.6 (±5 ,54)	77.6 (±8.0)	76.9 (±7.1)	0.596
Male	48 (56%)	100 (70%)	6(40%)	0.657
CHA_2DS_2 Vasc score	4.64 (±1.26)	5.0 (±1.2)	4.9 (±1.4)	0.092
Hypertension	72(84%)	150(88%)	14(93%)	0.320
Diabetes	21 (24%)	64 (37%)	5 (33%)	0.101
Previous TIA / ischaemic stroke	44 (51%)	89 (52%)	8 (53%)	0.992
Mean BMI	25.7 (±3.76)	25.9 (±4.6)	25.9 (±2.5)	0.833
Mean LVEF %	58.1 (±7.0)	57.1 (±10.4)	58.2 (±11.7)	0.543
HASBLED	3.55 (±0.8)	3.7 (±0.8)	3.5 (±0.8)	0.428
Device size	26.6 (±3.7)	26.9 (±3.5)	25.9 (±2.5)	0.546
Renal impairment	20 (24%)	52 (31%)	3 (20%)	0.622

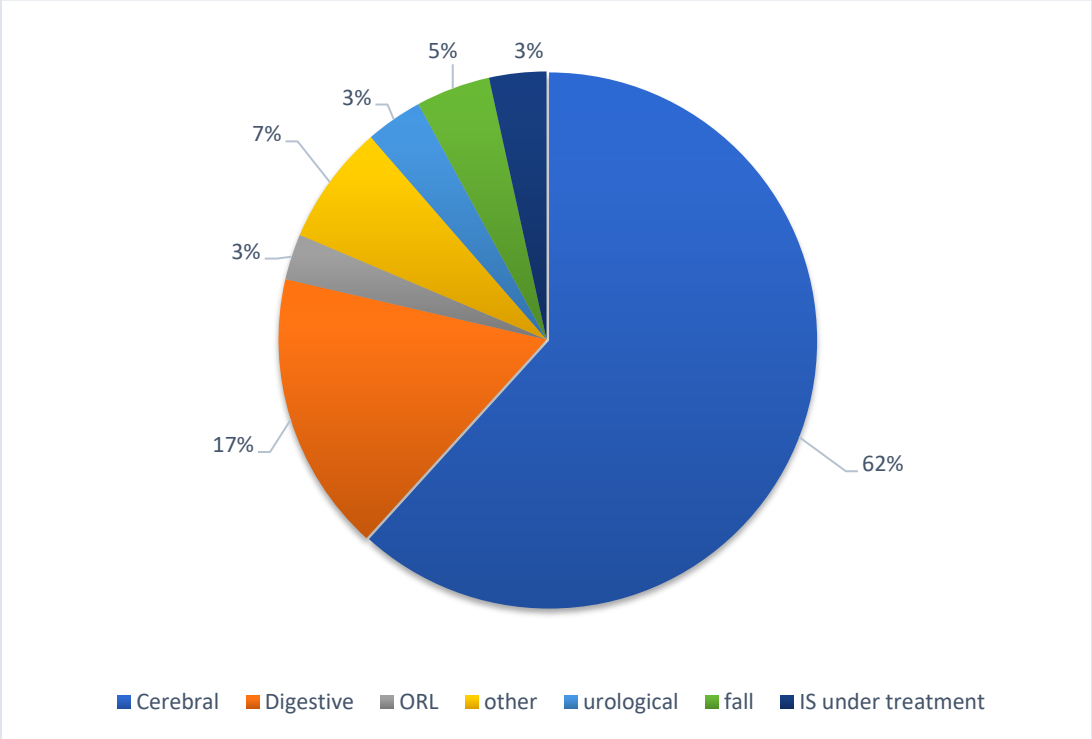
APT: antiplatelet therapy, BMI : body mass index, LVEF : left ventricular ejection fraction, TIA : transient ischaemic attack

The mean CHA_2DS_2-VASc (CV) score was 4.92± 1.26 and the mean HAS-BLED (HB) score was 3.65± 0.85. The CV score was ≥4 in 87% of all patients, and 92.5% of patients had a HB score ≥ 3 [Table 3]. 51% had a prior thrombo-embolic event and 77% had a major bleeding history. The mean follow-up was 23.5 months (±16). The reason of anticoagulation contraindications are detailed in Figure 2. The procedure was a success in 98.9%.

Table 3: CHA_2DS_2 Vasc & HAS BLED scores repartition in the global population

Value	CHA_2DS_2 Vasc n (%)	HAS BLED n (%)
0	0	0
1	0	3 (1,02)
2	3 (1,02)	18 (6,10)
3	34 (11,53)	101 (34,24)
4	80 (27,12)	133 (45,08)
5	79 (26,78)	36 (12,20)
6	69 (23,39)	3 (1,02)
7	23 (7,80)	
8	5 (1,69)	
9	1 (0,34)	
Mean	4,92±1,26	3,65±0,85
Predicted Annual Risk	10,1 %	8,7 %

Figure 2: Contraindication to anticoagulation repartition



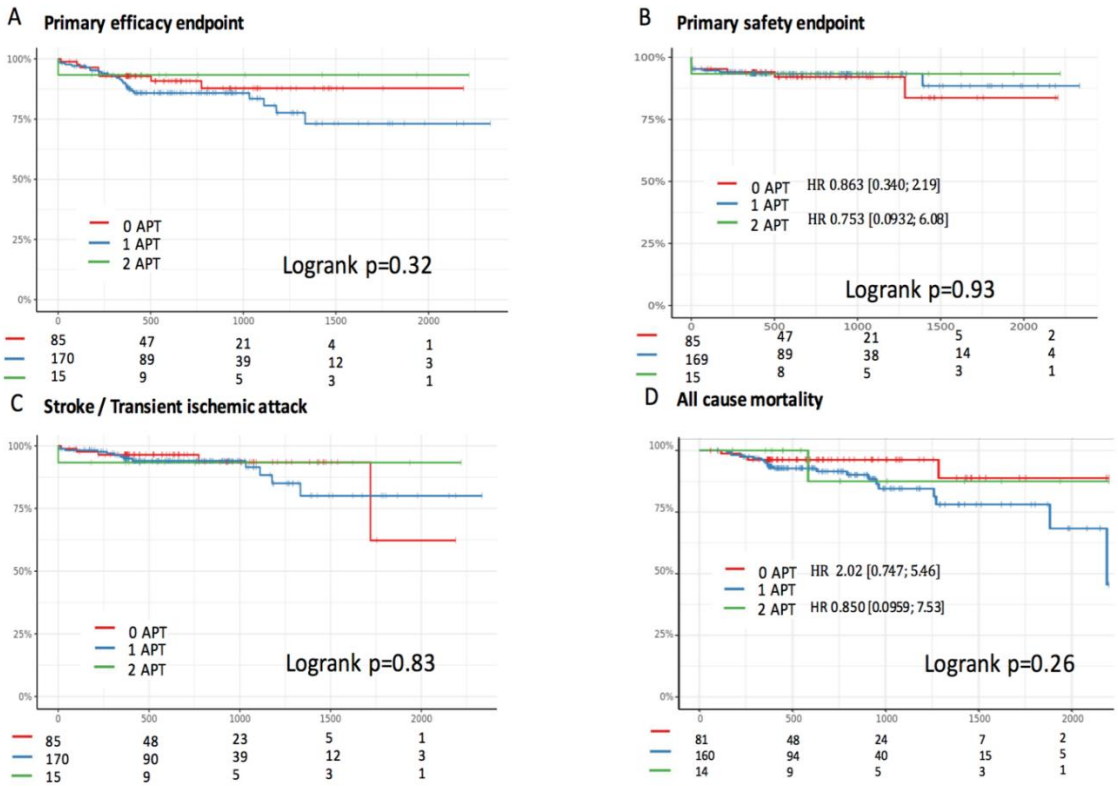
IS : ischaemic stroke

Efficacy Outcomes

The primary efficacy outcome was found in 32 patients (10.8%) in general population. There was no significant difference between the 3 groups of treatment as shown on the Kaplan Meyer curves. [Figure 3] Multivariate analysis using Cox model with adjustment on the CV score also showed no statistical difference between the 3 groups of treatment. Within a 5% risk, and adjusting on the CV score, we did not find a statistical relationship between the primary efficacy endpoint and the group of day 46 treatment.

Figure 3 Kaplan-Meier curves of incidence of study endpoints in 0 APT, 1 APT and 2 APT groups (APT treatment at day 46)

HR= Hazard ratio. Incidence probabilities are shown with time calculated as the days since date of intervention for the primary efficacy endpoint (A), the primary safety endpoint (B), all stroke, and all-cause mortality (D)



APT = antiplatelet therapy

Multivariable analysis to determine the statistical link between day 46 treatment and the primary efficacy endpoint while adjusting on each confounding factors *(e.g.* CV score) did not show any significative difference between the three groups *(p* = 0.38). On multivariable analysis, the only predicting factor of primary efficacy endpoint was diabetes. [Table 4]

Tableau 4: Multivariable analysis (Cox Regression Model) for predictors of the primary efficacy endpoint

	HR (95% CI)	***p* Value**
Sex	0.007 (-0.158-0.53)	0.53
BMI	0.007 (-0.71-0.85)	0.856
Diabetes	0.135 (0.051-0.22)	0.002
Renal Impairment	0.022 (-0.068-0.112)	0.636
LVEF	0.001 (-0.004-0.005)	0.810

BMI : body mass index; LVEF : left ventricular ejection function ; HR : hazard ratio ; CI : confidence interval

Safety Outcomes

There were a total of 16 strokes or transient ischemic attacks (4.6%), 7 hemorrhagic accidents (2.4%) and 16 deaths (5.6%) within a year. No systemic embolism occurred. One stroke lead to death, and 3 hemorrhages were fatal. 9 deaths were non related to the implantation and 3 of them were from an unknown cause. The global follow up showed a total of 20 ischemic events (6.8%), 9 hemorrhages (3.1%), 36 deaths (12.9%). The majority of death were from an unknown cause.

There was respectively no statistical difference of major bleeding *(p*=0.832) or embolic event rate (stroke or TIA) (*p*=0.833) depending on the antithrombotic treatment at Day 46. Also no statistical relationship between all-cause mortality and each group of treatment. *(p* = 0.26).

Survival

There was no significant difference of the primary safety outcome between the 3 groups. [Figure 3]. The log rank test did not reach statistical significance, p=0.93.

Peri procedural complications

The rate of peri-procedural major event was 3.3% [Table 5]. Minor complications were composed of 6.4% pericardial effusion treated with a conservative approach, 3.1% hematoma on the puncture site without secondary infection or need of transfusion nor any invasive treatment, 1% of minor arterio-venous fistula. There was no difference in occurrence of stroke or all-cause mortality depending on the chosen treatment, respectively p= 0.83 and p=0.26.

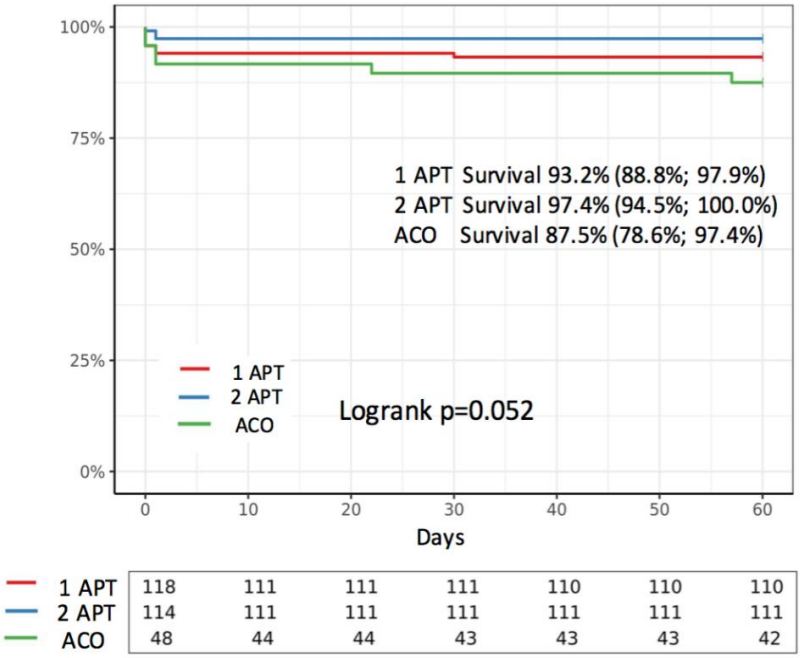
Table 5 Major periprocedural complications

Type	Numbers	%
Tamponnade	3	1,0%
Device embolisation	1	0,3%
Transient Ischemic Attack	1	0,3%
Stroke	3	1,0%
Major hematoma	3	1,0%
Major fistula	3	1,0%
Respiratory distress	1	0,3%

Major complications while on discharge treatment

With adjustment on age and HB score, there was no statistical difference between the discharge treatment and immediate safety. (major procedural complication and early major bleeding within 2 months). [Figure 4]

Figure 4: Complication-free survival depending on discharge treatment (procedure related complication / stroke or severe bleeding within 2months)

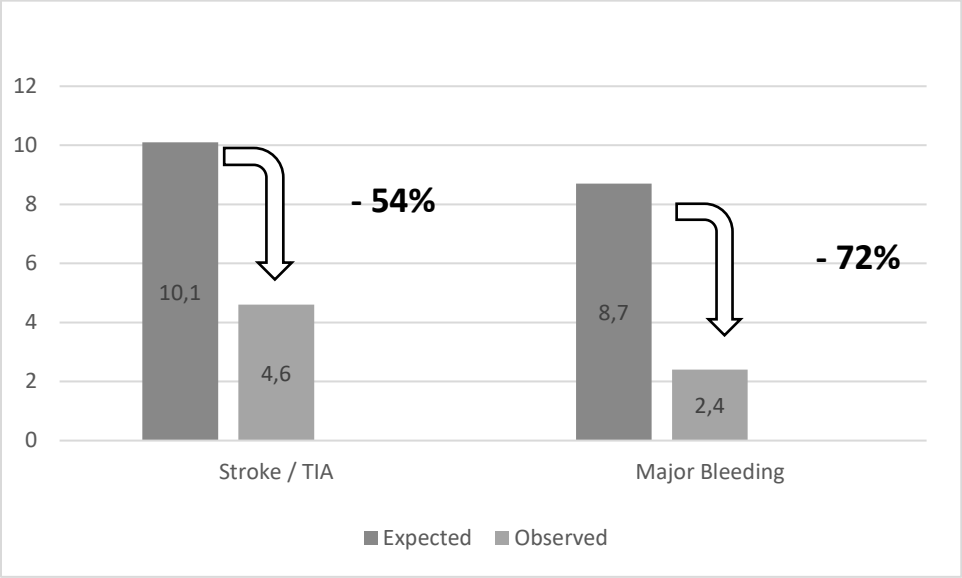


APT : antiplatelet therapy ACO : anticoagulant

Risk reduction

The rate of embolic event was 4.6% representing a risk reduction of 54% if we took the estimated risk of the mean CV score of the population. Major bleeding rate was 2.4% instead of the 8.7% estimated rate depending on the mean HB of the population, so a risk reduction of 72%. [Figure 5]

Figure 5: Risk Reduction



TIA: transient ischemic attack

DISCUSSION

This study enables us to explore real-life practice through three different French centers. The population is relatively old. Mean age was 77 years whereas it was 71 and 74 in the two princeps articles of Holmes *et al* and 73 years in EWOLUTION registry.[3-5] Our population is at high risk of thromboembolism accident as the mean CV was 4.92 therefore corresponding to a risk assessment of 10.1% of thromboembolic event within a year. A very high risk of bleeding showed by the mean HB at 3.65 corresponding to an 8.7% risk of major bleeding within a year. In comparison, the mean scores were respectively 4.5 and 2.3 in EWOLUTION registry which summarize all the Watchman implantations between October 2013 and May 2015 throughout Europe.[8]

We chose to investigate only Watchman device, the only system validated through randomized clinical trials. Therefore our results cannot be extended to other devices.

There was no statistical difference of the composite efficacy criterion between the three groups of treatment, suggesting that it was possible to minimize intensity and duration of antithrombotic therapy after implantation. It is correlated by results of the 2 years follow-up of EWOLUTION which showed no statistical difference in term of thromboembolic events and death between the different treatments.[5] Rate of embolic event (stroke/ TIA/SE) was 4.6% at one year. It is much higher than the one in EWOLUTION subgroup under DAPT which was 1.8%, and the 1.3% in the LAARGE registry.[9,10] But these registries included younger patients and with lower CV and HB scores. Rate of ancient ischemic cerebral attack in our population was 52% which is comparable with similar studies. For instance, 4% of embolic event in Fauchier and Defaye study and 4.7% in Korsholm one.[11,12]

These results are also in line with recent studies of light treatment afterwards which showed feasibility of LAAC followed by a lighten antithrombotic treatment.[13,14] Nevertheless there was a high proportion of device related thrombus (DRT) (5.4%). In comparison there was 4% of DRT on DAPT in EWOLUTION, 5.5% on SAPT post Watchman in Fauchier *et al* study, and 3.4% in the review on DRT post LAAC of Lempereur in the Watchman subgroup (3.9% if all device included).[11,15] It is important to note that our DRT rate may be underestimated because of the lack of many data of TEE/CTTA control (27%).

Association between DRT and stroke remains uncertain. In our cohort there were no relation between them, as in Søndergaard study, review of Lempereur and EWOLUTION registry.[16] On the other hand, Fauchier *et al* and Dukkipati team found that the presence of DRT was significatively associated with stroke, even if the actual rate of stroke was low.[11,17]

We found no statistical differences in baseline characteristics of patients depending on their group of treatment. Thus, we could not elaborate a profile type for SAPT. This suggests that each center has its own habits on choosing the treatment depending on the benefice/risk balance between thromboembolic and bleeding risk of each patient.

Although the statistical meaning of a comparison between actual and predicted rate depending on a risk score has its limitation. It is the one used in every study on the subject lacking control groups. In the same way, these two scores are the most accurate in AF.[18,19]

Mortality rate in our study is quite high (5.6% per year and 12.9% at two years), which may be explained by clinical severity of our population. However, it is comparable and even lower than the rate in big registries as observed in EWOLUTION (9.8%) and LAARGE (12.4%) registries.[5,9]

In our study a majority of patients were on SAPT (58%) or even no treatment (29%) as soon as day 46. To our knowledge there is very few studies with such quick simplification of antithrombotic therapy. Current recommendation for Watchman device is 3months of DAPT or

AT followed by at least one year of SAPT. It may be explained by the gravity of our population, an old one and at very high risk of bleeding. On top of it, all of them (except 7) had an absolute contraindication to anticoagulation (whether long or short term). 77% of them had a major bleeding prior LAAC, and 52% were known to have had a stroke. The only studies that matched our treatments were the ones for LAAC after an intracerebral bleeding. But even in that case many of them used a short term anticoagulation or at least one year of ASA. Pouru *et al* used SAPT for less than 6 months in a majority of patients and had an acceptable rate of stroke, and surprisingly the stroke occurred preferentially during the treatment rather than after their discontinuation.[20] This may be explained by the fact that endothelialization seems to be accurate after the first months. Merella study also showed the feasibility of simplified treatment with an acceptable rate of stroke (1.4%) but it was a very small population of 68 patients and only one year of follow up.[13] The cohort of Weise, used only 6 weeks of DAPT but followed by lifelong SAPT, their rate of stroke was 1.7% per year so a risk reduction of 78%.[21] On the other hand if we look at the different registries of LAAC, the German one LAARGE showed that 74% of patients were still on acid acetyl salicylic (ASA) at one year follow up.[9] In the European EWOLUTION registry, 71% were still on SAPT and only 14% had no treatment at two years. In the Amplatzer registry, there were only 21.2% of patients under no treatment and 62.8% on SAPT at two years.[22]

Study limitations

This study has some limitations. Due to its retrospective design, there may be bias linked to missing data. No causality can be proven because of the observational character of this study, but it gives us an idea of current practice in French centers. The number of event was relatively low due to its limited size of population. Nevertheless, this sample is quite large when comparing to study of such severe patients.

CONCLUSION

We found no statistical difference of the composite outcome of thromboembolic event, major bleeding or death depending on the choice of treatment following the implantation of Watchman device. It appears that the choice of treatment is always personalized, therefore there is not one specific patient's profile for a chosen treatment. It seems possible to use a single antiplatelet therapy of a short-term duration if the bleeding risk is very high. This needs to be proven by a randomized control trial.

THÈSE SOUTENUE PAR : Anne GUENET

TITRE :

EVALUATION DE LA GESTION DES ANTITHROMBOTIQUES POST FERMETURE DE L'AURICULE GAUCHE PAR PROTHESE WATCHMAN – EXPERIENCE RHONE ALPINE

CONCLUSION :

Cette étude observationnelle multicentrique a inclus tous les patients consécutifs implantés d'un Watchman entre janvier 2013 et décembre 2018 aux CHU de Grenoble, Lyon et Saint Etienne. Le critère primaire d'efficacité était la survenue d'accident vasculaire cérébral (AVC) ischémique, d'hémorragie majeure ou décès dans l'année suivant le geste. Le critère de sécurité composite comprenait les complications initiales et saignements majeurs durant le suivi. Les groupes de traitement étaient : aucun, mono-, bi-anti agrégation.

295 patients ont été inclus, la moyenne d'âge était de 77ans, les scores CHA2DS2-VASc et HAS BLED moyens étaient 4,92 et 3,65. Il n'y avait pas de différence statistiquement significative entre la survenue du critère composite d'efficacité selon le traitement choisi (p= 0,83). Aucun surrisque en fonction du traitement choisi n'a été trouvé. On note une réduction du risque d'AVC de 54% et d'hémorragie sévère de 72% en comparaison aux scores théoriques. Il n'y avait pas de différence significative d'embolie, hémorragie ou décès selon le traitement choisi. Aucun profil type n'a été retrouvé pour le choix du traitement. Il semble donc possible de simplifier le traitement post intervention par une simple anti agrégation chez les patients les plus fragiles.

VU ET PERMIS D'IMPRIMER

Grenoble, le : 21/06/2

LE DOYEN | **LE PRÉSIDENT DE LA THÈSE**

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Pour le Président et par délégation
Le Doyen de la Médecine
Pr. Patrice MOMMEJA

Pr. Patrice MOMMEJA | **Pr. Gérald VANZETTO**

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ANNEXE

Annexe 1 score CHA_2DS_2 VASC

$CHADS_2$ -> CHA_2DS_2VASc

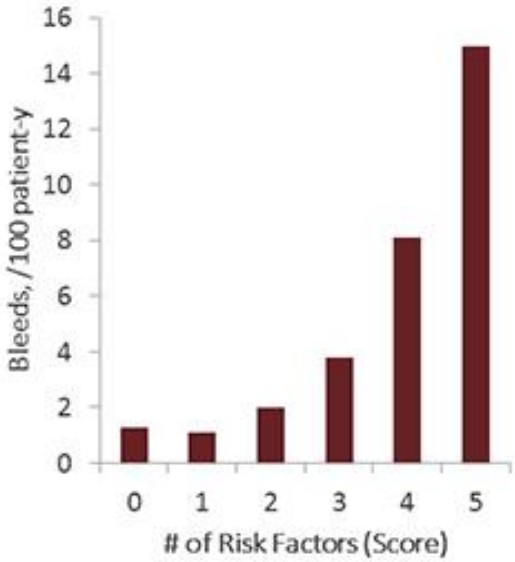
CHADS2 Risk	Score
CHF	1
Hypertension	1
Age > 75	1
Diabetes	1
Stroke or TIA	2

CHA2DS2-VASc Risk	Score
CHF or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke/TIA/ Thromboembolism	2
Vascular Disease	1
Age 65 - 74	1
Female	1

From ESC AF Guidelines http://escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-afib-FT.pdf

Annexe 2 score HAS BLED

Bleeding Risk: HAS-BLED



Letter	Clinical characteristic	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

The HAS-BLED score can be used to evaluate major bleeding risk in patients with AF taking warfarin or NOAC therapy.

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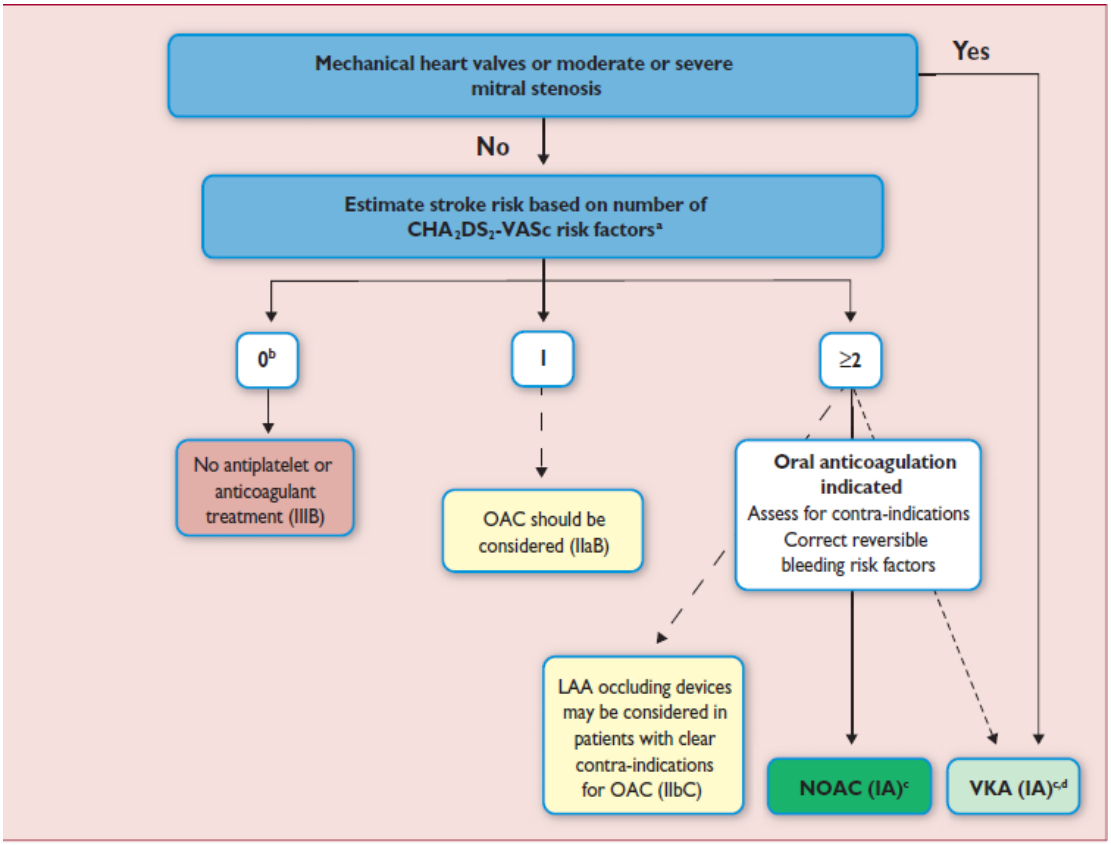
Annexe 3 The ESC recommendations of stroke prevention for AF patients



= atrial fibrillation; LAA = left atrial appendage; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; VKA = vitamin K antagonist.
ongestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes, prior Stroke/TIA/embolus (2 points), Vascular disease, age 65–74 years, female Sex.
cludes women without other stroke risk factors.
B for women with only one additional stroke risk factor.
for patients with mechanical heart valves or mitral stenosis.

Annexe 4 classification des évènements (Tzikas)

Diagnostic criteria for stroke or transient ischemic attack

Identification of neurological deficit	An acute episode of a focal or global neurological deficit with at least one of the following: – Change in the level of consciousness – Hemiplegia – Hemiparesis – One-sided numbness or sensory loss – Dysphasia or aphasia – Hemianopia – Amaurosis fugax – Any other neurological signs or symptoms consistent with stroke
Absence of non-vascular aetiology	No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumour, trauma, infection, hypoglycaemia, peripheral lesion, pharmacologic influences), to be determined by or in conjunction with the designated neurologist.
Stroke vs. TIA	Stroke is defined by an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction. The event classifies as a stroke rather than a TIA based on any of the following: – Duration of neurological dysfunction >24 hrs. – Duration of neurological dysfunction <24 hrs in case of imaging-documented new haemorrhage or infarction. – A neurological dysfunction resulting in death. A TIA is defined by any neurological dysfunction not satisfying the above criteria for stroke, specifically if lasting <24 hrs without imaging-documented acute brain infarction.
Confirmation	For a confirmed diagnosis, these elements (i.e., identification of a neurological dysfunction, absence of a non-vascular mechanism, and differentiation between stroke and TIA) should be supported by both: – Assessment by neurologist or neurosurgical specialist. – Neuroimaging procedure (CT scan or brain MRI) findings.

CT: computed tomography; MRI: magnetic resonance imaging; TIA: transient ischaemic attack

Bleeding definition

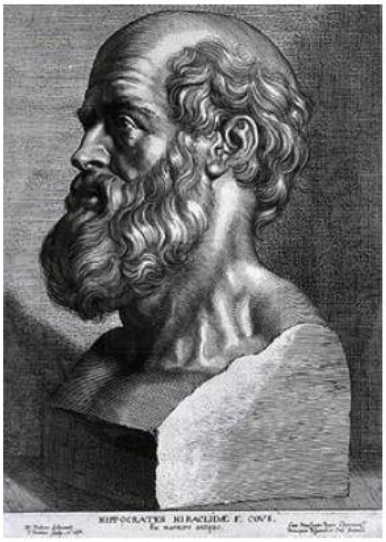
Life-threatening or disabling	Fatal bleeding (BARC type 5) OR – Symptomatic bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or intramuscular with compartment syndrome (BARC type 3b and 3c) OR – Symptomatic pericardial bleeding (with or without tamponade) occurring after hospital discharge for the index procedure OR – Bleeding causing hypovolaemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR – Overt source of bleeding with drop in haemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units (BARC type 3b)
Major bleeding (BARC type 3a)	– Overt bleeding either associated with a drop in the haemoglobin level of at least 3.0 g/dL or requiring transfusion of two or three units of whole blood/RBC, or causing hospitalisation or permanent injury, or requiring surgery OR – Pericardial bleeding (with or without tamponade) occurring during the index procedure or during hospitalisation for the index procedure – Bleeding causing discontinuation of antithrombotic therapy for stroke prevention, including antiplatelets, VKA and NOAC AND – Does not meet criteria of life-threatening or disabling bleeding
Minor bleeding (BARC type 2)	Any bleeding worthy of clinical mention (e.g., access-site haematoma) that does not qualify as life-threatening, disabling or major

BARC: Bleeding Academic Research Consortium; NOAC: non-VKA oral anticoagulant; VKA: vitamin K antagonist

Definition and severity of pericardial effusion

Clinically non-relevant	– Requiring no intervention – Treated pharmacologically
Clinically relevant	– Treated with therapeutic pericardiocentesis – Treated with surgical intervention – Requiring blood transfusion – Resulting in shock and/or death
LAAO therapy associated with epicardial approach	– Clinically non-relevant (minor): requiring no intervention, treated pharmacologically or <500 ml of bloody fluid was aspirated and not requiring blood transfusion or surgical intervention – Clinically relevant (major): aspiration of >500 ml of bloody fluid or an effusion that required blood transfusion or surgical intervention Presence or placement of pericardial catheter/drain at the end of the procedure should not be considered as clinically relevant effusion
Time of occurrence	Intraprocedural: occurred during the index procedure Acute: up to 48 hours from the index procedure Late: more than 48 hours from the index procedure

SERMENT d'HIPPOCRATE



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.