Fermeture de l’auricule gauche (FAG)

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AFFILIÉ À Université de Montréal

Divulgation de conflits d'intérêts potentiels

Société des sciences vasculaires du Québec (SSVQ)

14e congrès annuel de la SSVQ

21 novembre 2014

Dr Réda Ibrahim, Cardiologue/hémodynamicien, Institut de Cardiologie de Montréal

Proctor, Consultant	St-Jude
Consultant	Gore
Conférencier	Astra- Bayer - BMS – Boeringher

Objectifs

Concernant l'approche mécanique de fermeture d'auricule gauche

- 1- Connaître les bénéfices, les limites et les complications potentielles
- 2- Savoir qui référer
- 3- Définir le suivi et la médication (anticoagulants/antiplaquettaires) nécessaires post procédure.

Faits au sujet de l'anticoagulation chez les patients avec FA

- Traitement de choix chez les pts à haut risque d'événement thrombo-embolique
- Les NOACs, par opposition au coumadin, sont le nouveau standard de traitement
- Malgré tout, le traitement est limité par plusieurs facteurs

Limitations du traitement anticoagulant

- Compliance au traitement et au suivi
  - dabigatran et apixaban = BID
  - Coumadin = INRs fréquents
- Coût
  - NOACs = ≈ 5000$/an
- Risque de saignement

Procédure de fermeture d'auricule

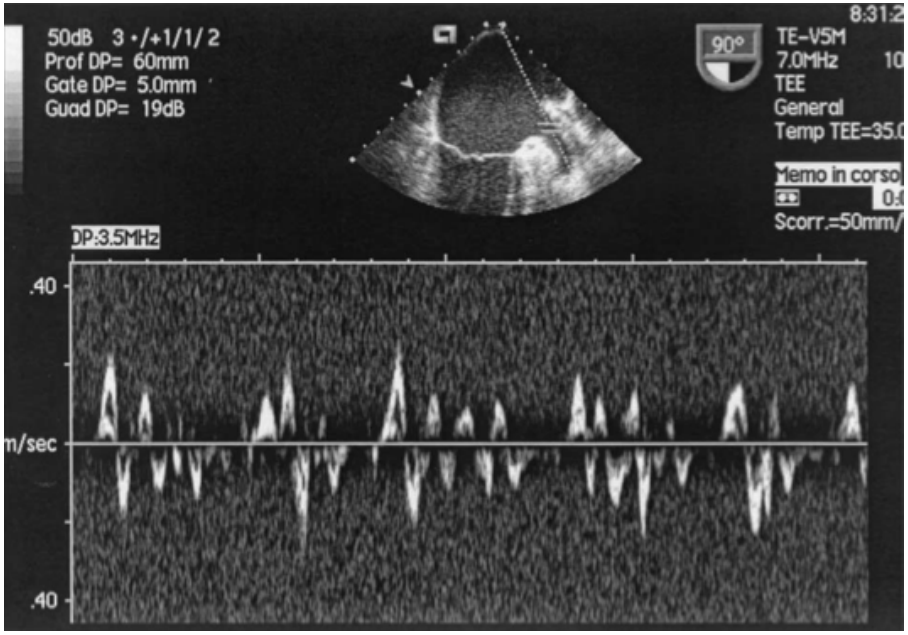
- Développée comme alternative ou en remplacement à l'anticoagulation chez les pts avec FA non valvulaire

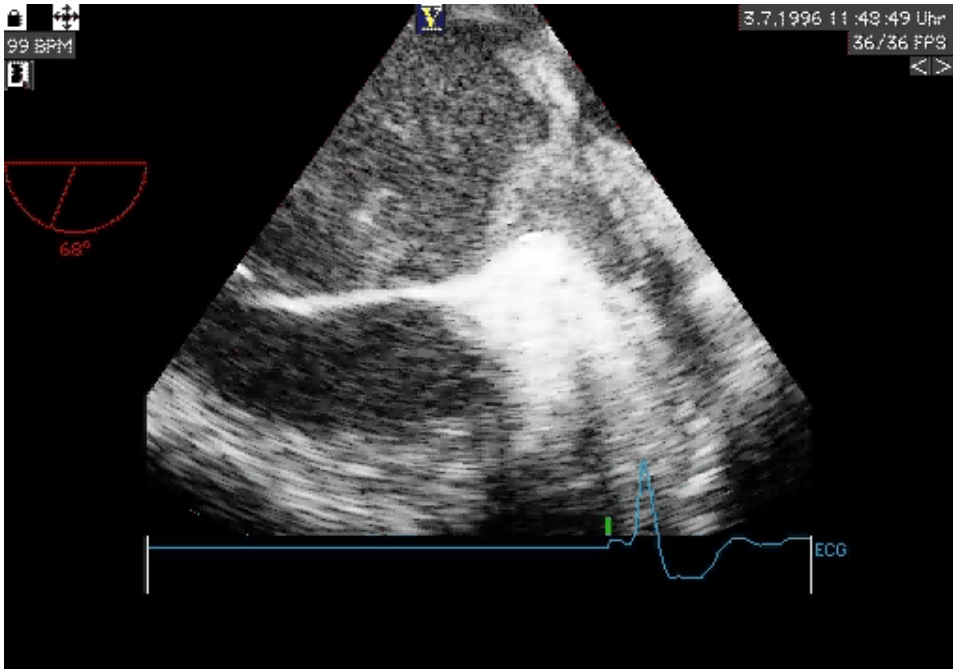
Patients à haut risque de saignement

- HASBLED $\geq$ 3
- Hémorragie majeure (surtout cérébrale) sous anticoagulant
- Angiopathie congophile, “microbleeds” cérébraux
- Épistaxis majeurs
- Cirrhose
- Hémorragie digestive récidivantes (angiodysplasie, proctite radique, etc)
- IRC
- Tumeurs urologiques
- Rendu-Osler-Weber, etc

Rationnelle FAG

- Basé sur le fait que la FA est en général associée à une réduction de la contractilité auriculaire (vélocités < 55 cm/s) = stase (échos spontannés) +/- thrombus





J Am Soc Echocardiogr. 2005 Dec;18(12):1366-72

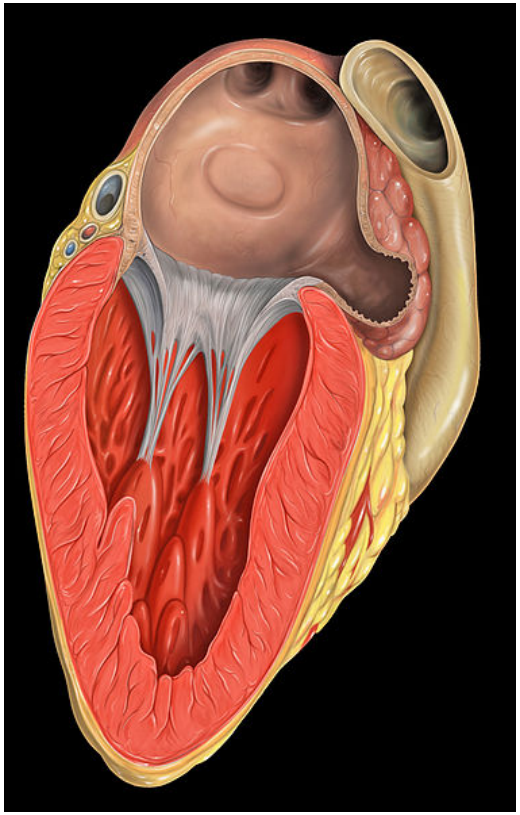
Location of Thrombus in Non-Rheumatic Atrial Fibrillation

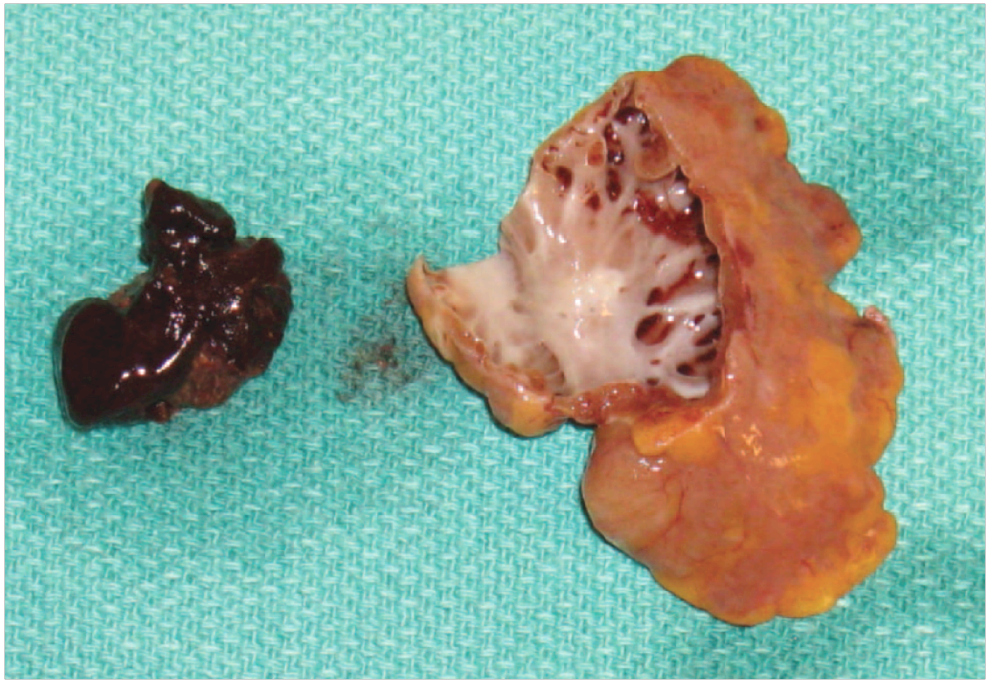
91% (201/222) of Left Atrial Thrombus Localized to the LAA

Setting	N	Appendage	%	LA Body	%	Reference
TEE	317	66	21	1	0.3	Stoddard; JACC, 1995
TEE	233	34	15	1	0.4	Manning; Circ, 1994
Autopsy	506	35	7	12	2.4	Aberg; Acta Med Scan, 1969
TEE	52	2	4	2	3.8	Tsai; JFMA, 1990
TEE	48	12	25	1	2.1	Klein; Int J Card Image, 1993
TEE & Operation	171	8	5	3	1.8	Manning; Circ, 1994
SPAF III TEE	359	19	5	1	0.3	Klein; Circ, 1994
TEE	272	19	7	0	0.0	Leung; JACC, 1994
TEE	60	6	10	0	0.0	Hart; Stroke, 1994
Total Thrombus		**201**		**21**		

Blackshear JL and Odell JA, Ann Thorac Surg 1996;61:755-759

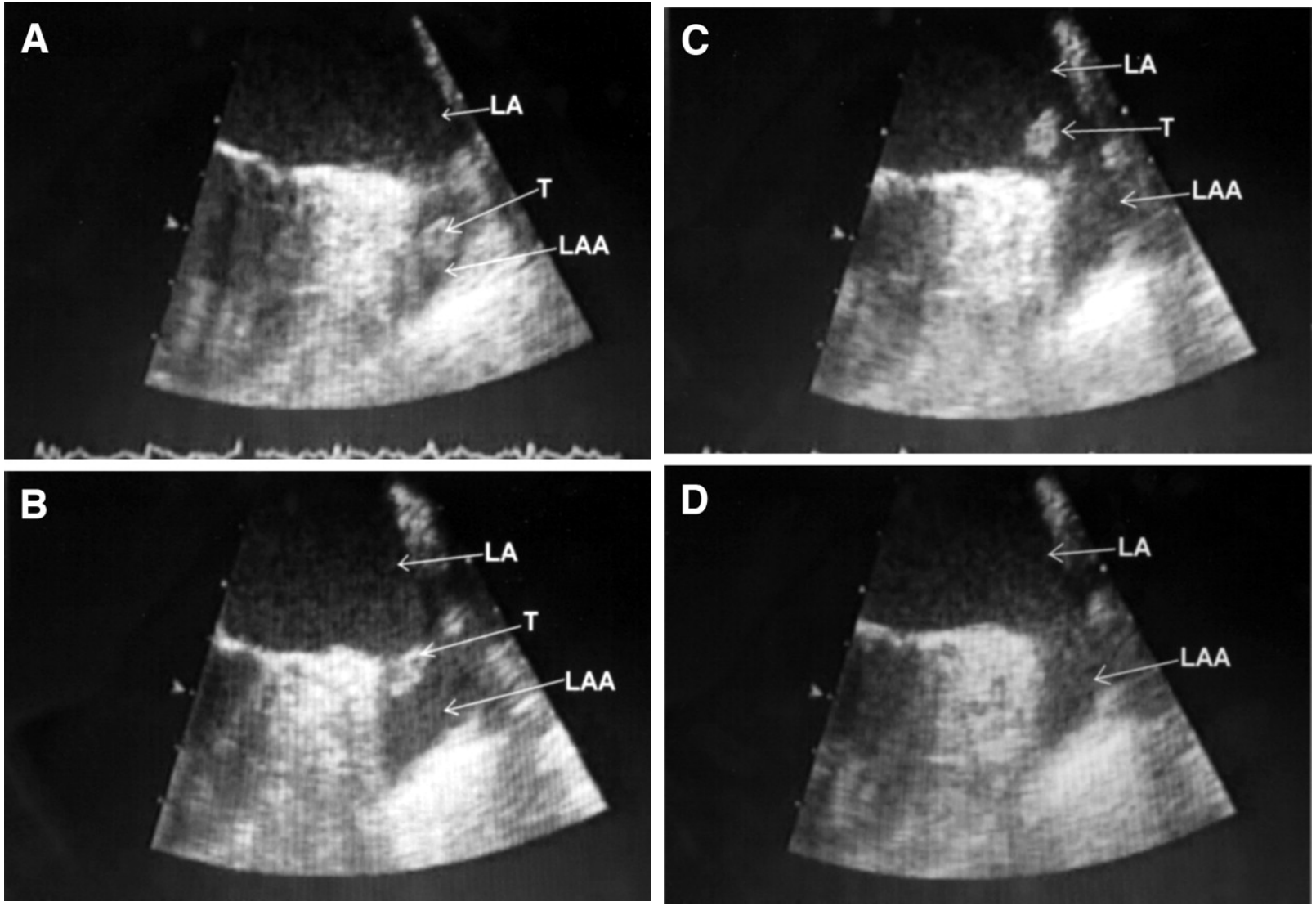
Le caillot qui se forme dans l'auricule est souvent volumineux = AVC significatif





Blackshear JL and Odell JA, Ann Thorac Surg 1996;61:755-759

Échographies trans-oesophagiennes sériées démontrant la migration d'un thrombus originant de l'appendice auriculaire gauche



Options pour exclusion d'auricule

- 1) Chirurgie

- 2) Approches percutannées
  - Méthodes endocavitaires avec installation de prothèses
  - Méthodes extra-cardiaques avec installation de suture

Indications FAG en chirurgie cardiaque

- 1) Pts avec thrombus dans l'auricule
- 2) Pts avec FA qui saignent sous anticoagulant
- 3) Lors d'une chirurgie minimalement invasive pour FA
- 4) Lors d'une chirurgie valvulaire (surtout mitrale)
- 5) Projet de recherche

Success of Surgical Left Atrial Appendage Closure

Assessment by Transesophageal Echocardiography

Anne S. Kanderian, MD,* A. Marc Gillinov, MD,† Gosta B. Pettersson, MD, PHD,†
Eugene Blackstone, MD,† Allan L. Klein, MD, FACC*

Cleveland, Ohio

JACC Vol. 52, No. 11, 2008
September 9, 2008:924–9

Table 2 Success of Different Techniques of LAA Closure

Type of Closure	n	Patent LAA	Remnant LAA	Excluded LAA With Persistent Flow	Successful LAA Closure
Excision	52	0	14 (27%)	0	38 (73%)*
Suture exclusion, n (%)	73	6 (8)	6 (8)	44 (61)	17 (23)*
Stapler exclusion, n (%)	12	2 (17)	7 (58)	3 (25)	0 (%)†
Total, n (%)	137	8 (6)	27 (20)	47 (34)	55 (40)

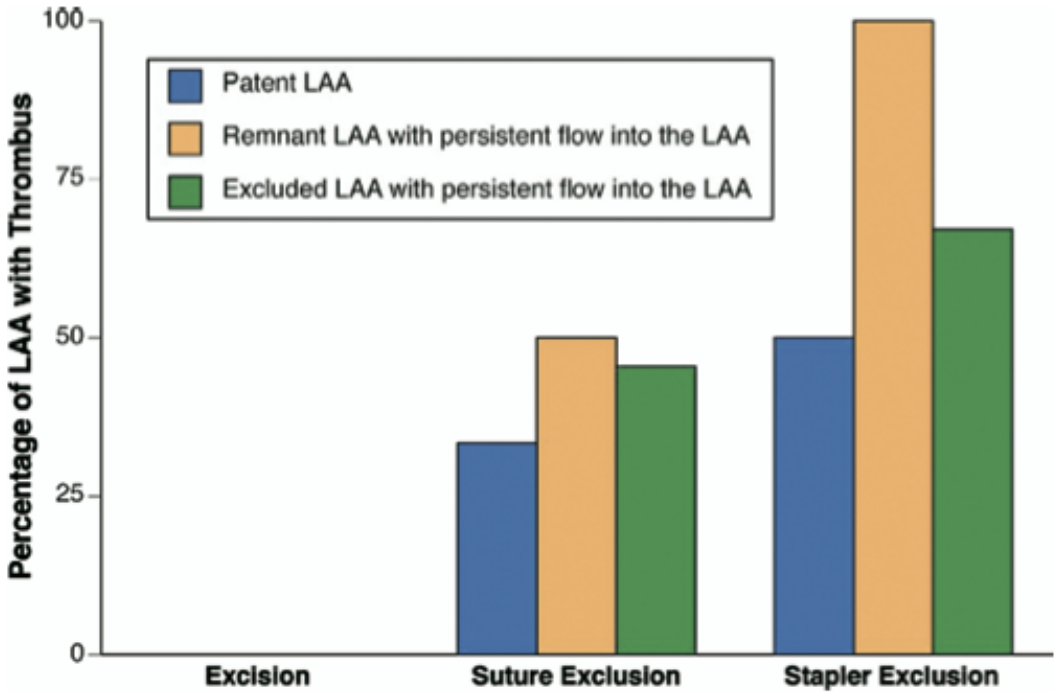
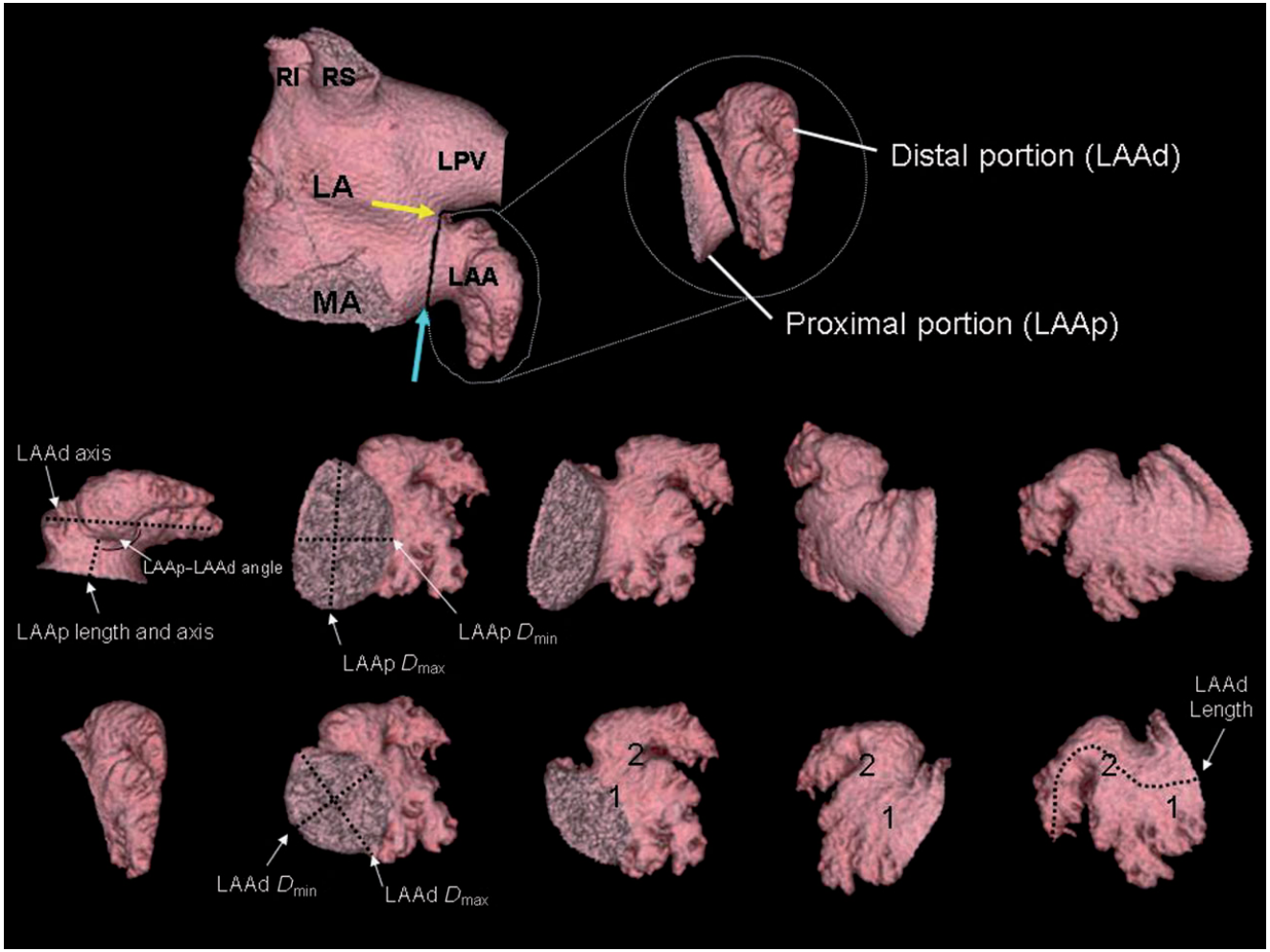


Figure 4 Occurrence of LAA Thrombus in Unsuccessful Surgical Closure

JACC Vol. 52, No. 11, 2008
September 9, 2008:924–9

Anatomie de l'auricule



Lacomis JM et al. Europace 2007;9:1134-1140.

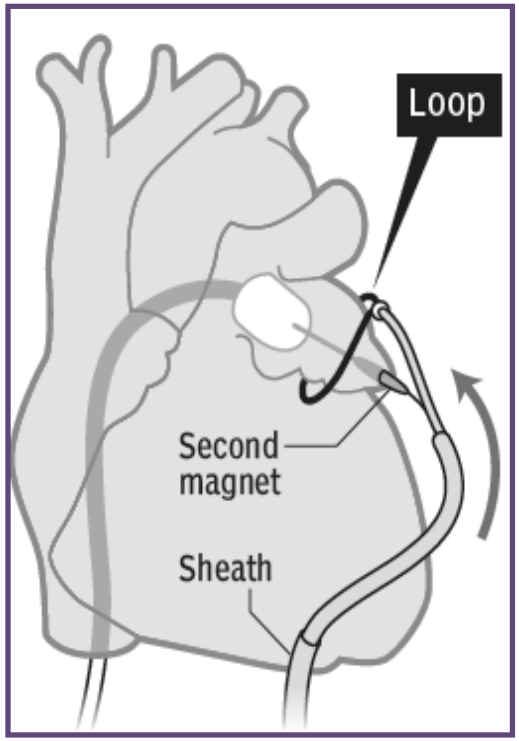
Approches par cathéter

- 1) Extra-cardiaque

- 2) Intra-cardiaque

Approche par cathéter extra-cardiaque

Lariat (SentreHeart)*

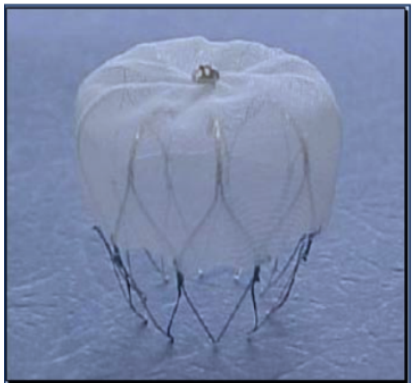


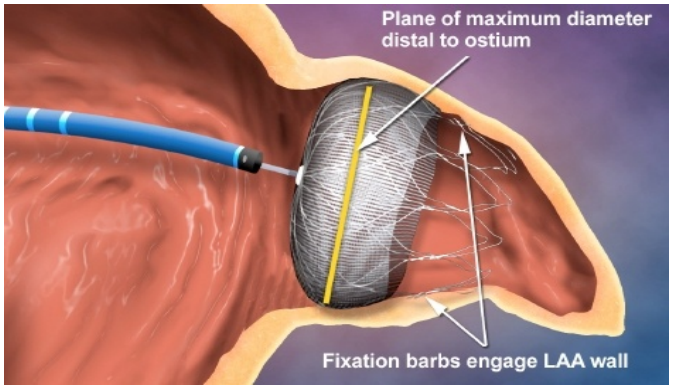
- **Limitée par:**
  - Complexité
  - Risques reliés à l'approche péricardique et transseptale
  - Haut taux de péricardite post-procédure
  - Shunt résiduel central chez ≈5% des pts

* FDA approved mais pas disponible au Canada

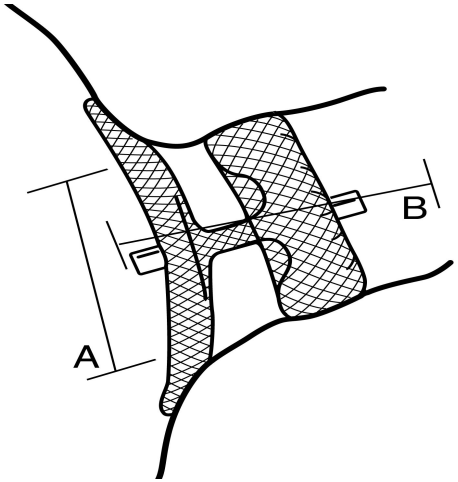
Approche par cathéter avec prothèse intra-cardiaque

WATCHMAN
(Boston Scientific)

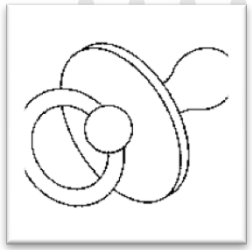


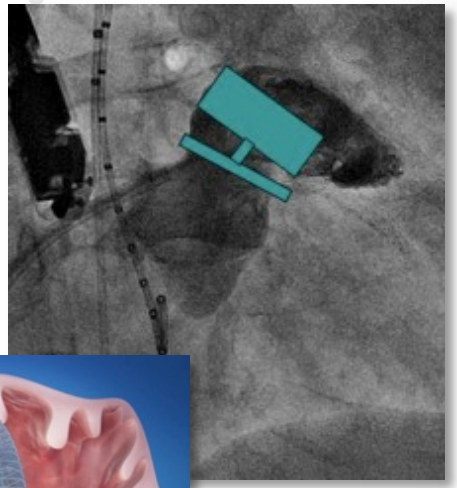


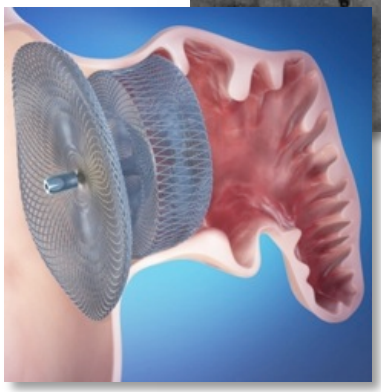
Amplatz Cardiac Plug
(St-Jude Medical)



Philosophies différentes, même objectif

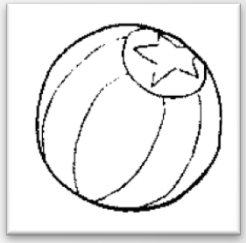


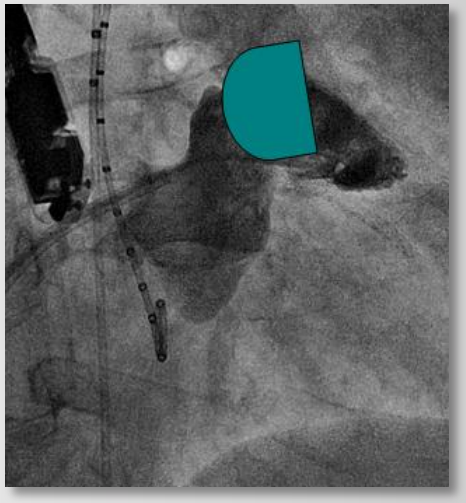


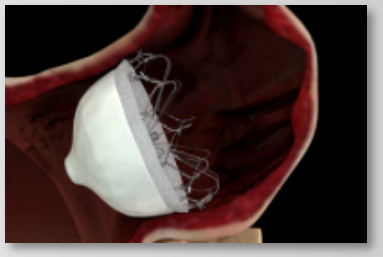


AMPLATZER Cardiac Plug

"pacifier principle"[1]







Watchman
(Boston Scientific)

Wavecrest
(Coherex)

"half football principle" [2]

Park at CSI 2011. "Current Status of Left Atrial Appendage Closure Devices – Amplatzer ACP Occluder", Frankfurt, June 23-25, 2011.

Long Term Results of PROTECT AF: The Mortality Effects of Left Atrial Appendage Closure *versus* Warfarin for Stroke Prophylaxis in AF

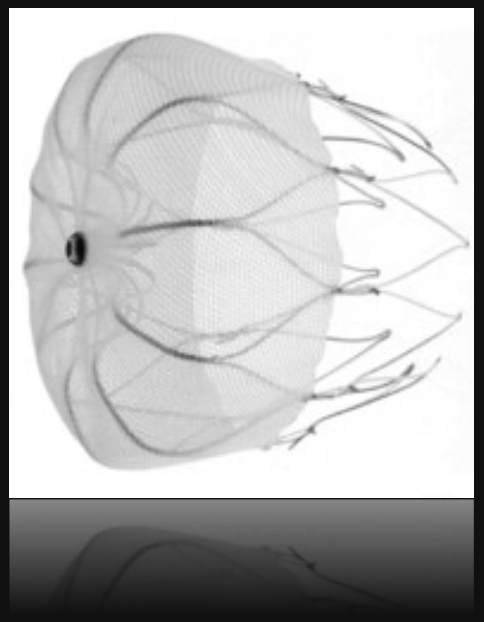
Vivek Y. Reddy[1,2,3], Shephal K Doshi[2], Horst Sievert[4], Maurice Buchbinder[5], Petr Neuzil[3], Kenneth Huber[6], Saibal Kar[7], Jonathan L. Halperin[1], Brian Whisenant[8], Vijay Swarup[9] and David Holmes[10]

[1]Mount Sinai School of Medicine, NY; [2]Pacific Heart Institute, CA; [3]Homolka Hospital, Prague; [4]Sankt Katharinen, Frankfurt; [5]Foundation for Cardiovascular Medicine, CA; [6]St Luke's Hospital, MO; [7]Intermountain Medical Center, UT; [8]Cedars Sinai Medical Center, CA; [9]Arizona Heart Rhythm Center, AZ; [10]Mayo Clinic, MN

Adapted from HRS LBCT 2013 by Dr. Vivek Reddy
SH-158101-AA- MAY 2013

PROTECT-AF: Design

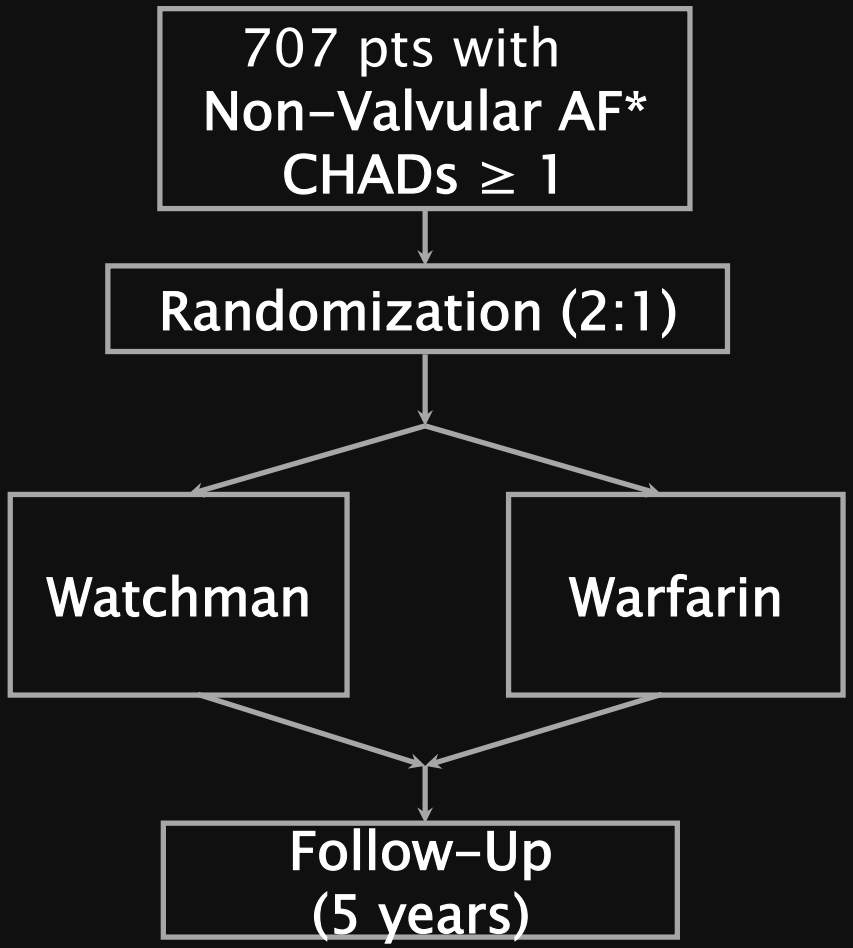
- Randomized FDA-IDE Trial
  - Can the WATCHMAN device replace Warfarin?
- Primary Efficacy Endpoint:
  - Stroke
  - CV death (& Unknown)
  - Systemic embolism
- Primary Safety Endpoint
- Non-inferiority & Superiority
  - Bayesian Sequential Design
  - Analysis at 600 pt-yrs & every 150 pt-yrs thereafter → 1500 pt-yr
  - Follow-up till 5 years



Adapted from HRS LBCT 2013 by Dr. Vivek Reddy
SH-158101-AA- MAY 2013

PROTECT-AF: Overview

Enrollment from February 2005 to June 2008



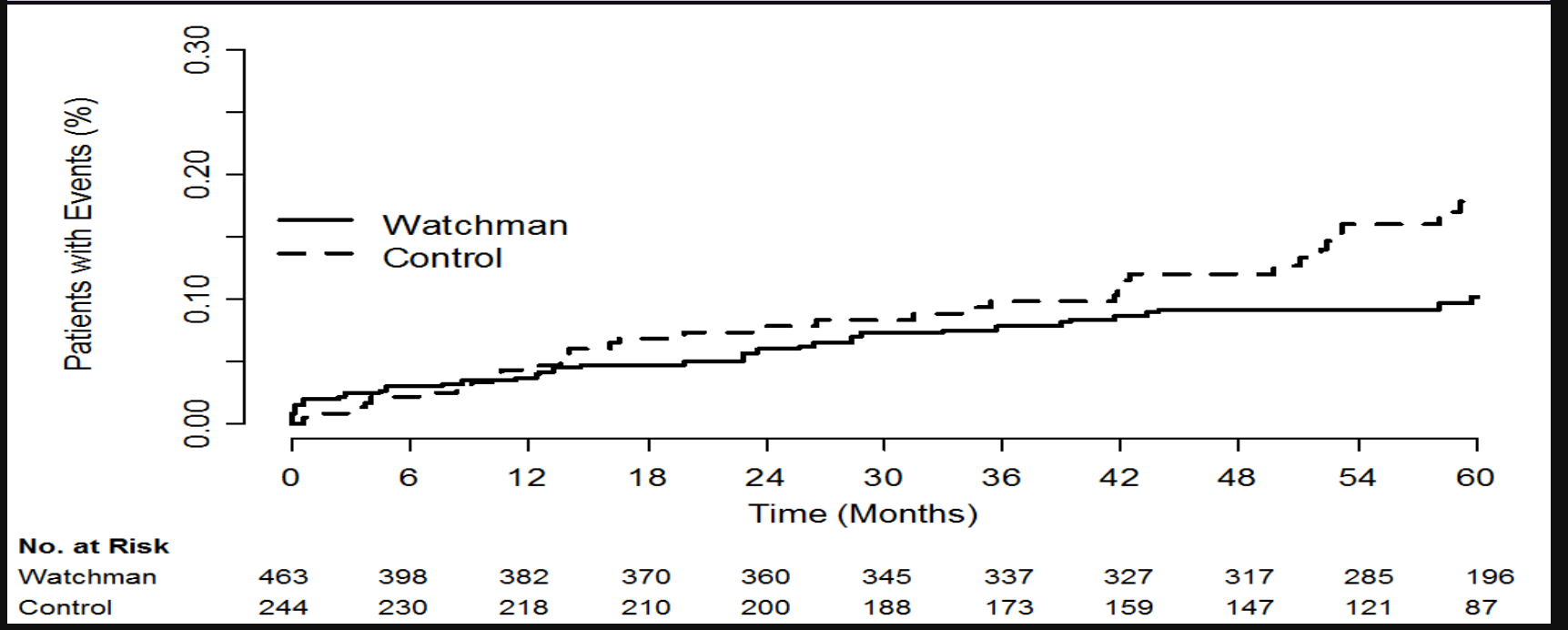
Anticoagulation Regimen

- **Implant to 6 weeks**
  - **Warfarin (INR 2-3) for 6 weeks**
  - **Aspirin (81 – 325 mg)**
- **6 weeks to 6 months**
  - **Clopidogrel (75 mg)**
  - **Aspirin (81 – 325 mg)**
- **After 6 months**
  - **Aspirin (81 – 325 mg)**

*Paroxysmal / Persistent / Permanent AF

PROTECT-AF: Primary Efficacy Endpoint (stroke / systemic embolism / CV death)

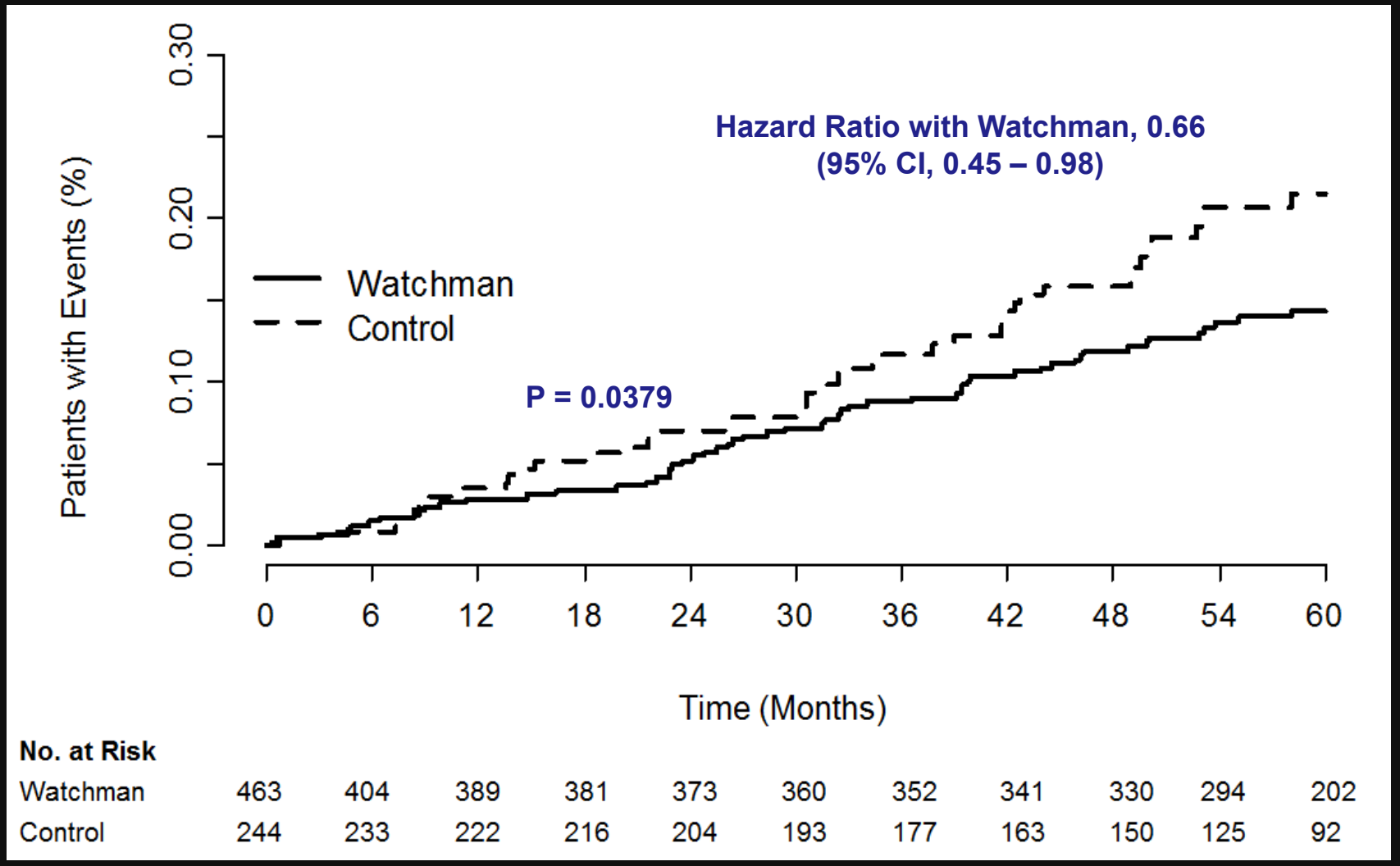
Event	Watchman Group (n = 463) Events/ Patient-Years	Watchman Group (n = 463) Observed Rate (Events per 100 Patient-Years) (95% CrI)	Warfarin Group (n = 244) Events/ Patient-Years	Warfarin Group (n = 244) Observed Rate (Events per 100 Patient-Years) (95% CrI)	Rate Ratio (Watchman/Warfarin) (95% CrI)	Posterior Probabilities Non-inferiority	Posterior Probabilities Superiority
Primary Efficacy Endpoint	39/1720.2	2.3 (1.7, 3.2)	34/900.8	3.8 (2.5, 4.9)	0.60 (0.41, 1.05)	>0.999	0.960



*For Bayesian analysis, posterior probabilities are used to determine superiority; ≥95% represents superiority

Adapted from HRS LBCT 2013 by Dr. Vivek Reddy
SH-158101-AA- MAY 2013

Intention-to-Treat: All-Cause Mortality

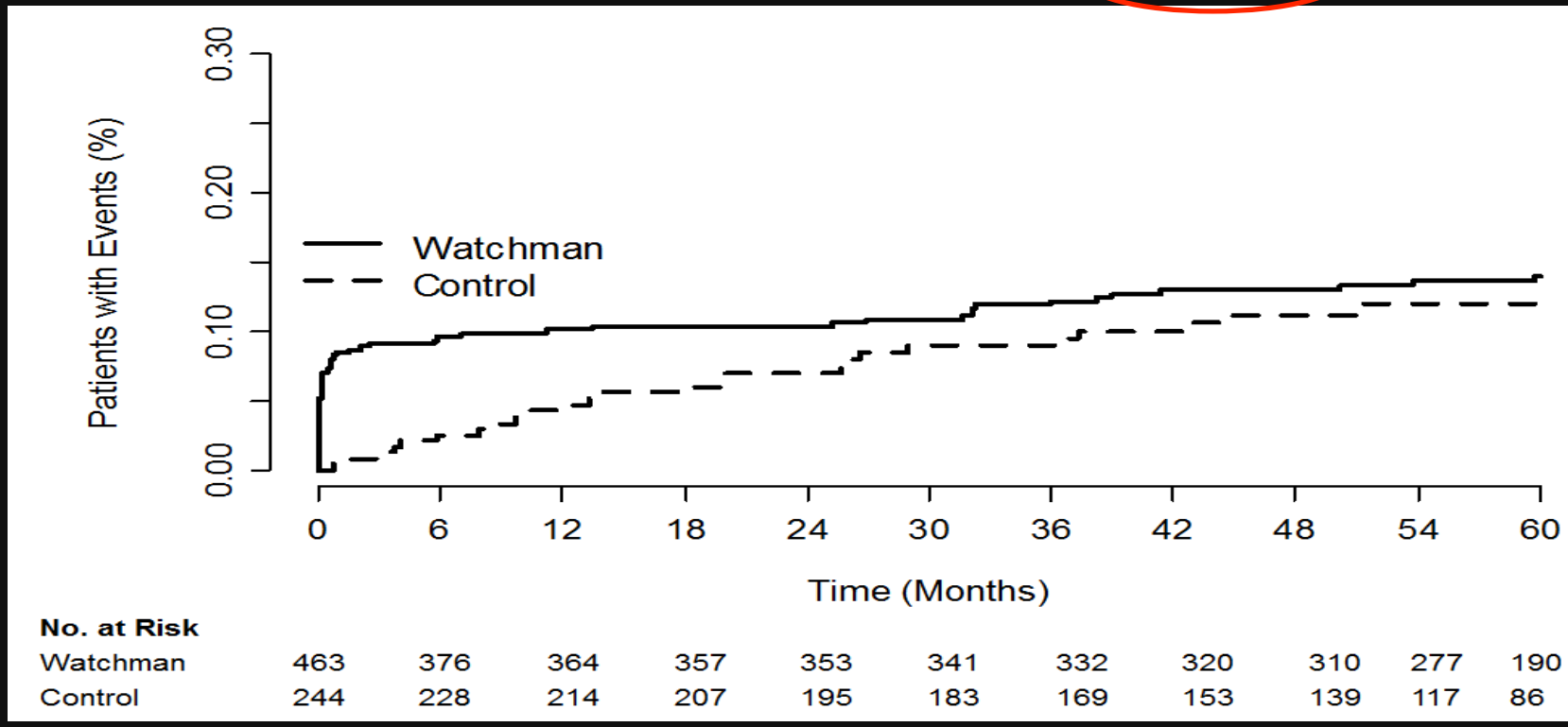


No. at Risk											
Watchman	463	404	389	381	373	360	352	341	330	294	202
Control	244	233	222	216	204	193	177	163	150	125	92

Adapted from HRS LBCT 2013 by Dr. Vivek Reddy
SH-158101-AA- MAY 2013

PROTECT AF: Primary Safety Endpoint

Event	Watchman Group (n = 463) Events/ Patient-Years	Watchman Group (n = 463) Observed Rate (Events per 100 Patient-Years) (95% CrI)	Warfarin Group (n = 244) Events/ Patient-Years	Warfarin Group (n = 244) Observed Rate (Events per 100 Patient-Years) (95% CrI)	Rate Ratio (Watchman/Warfarin) (95% CrI)	Posterior Probabilities Non-inferiority	Posterior Probabilities Superiority
Primary Safety Endpoint	60/1666.2	3.6 (2.8, 4.6)	27/878.2	3.1 (2.0, 4.3)	1.17 (0.78, 1.95)	0.980	0.196



No. at Risk											
Watchman	463	376	364	357	353	341	332	320	310	277	190
Control	244	228	214	207	195	183	169	153	139	117	86

Adapted from HRS LBCT 2013 by Dr. Vivek Reddy
SH-158101-AA- MAY 2013

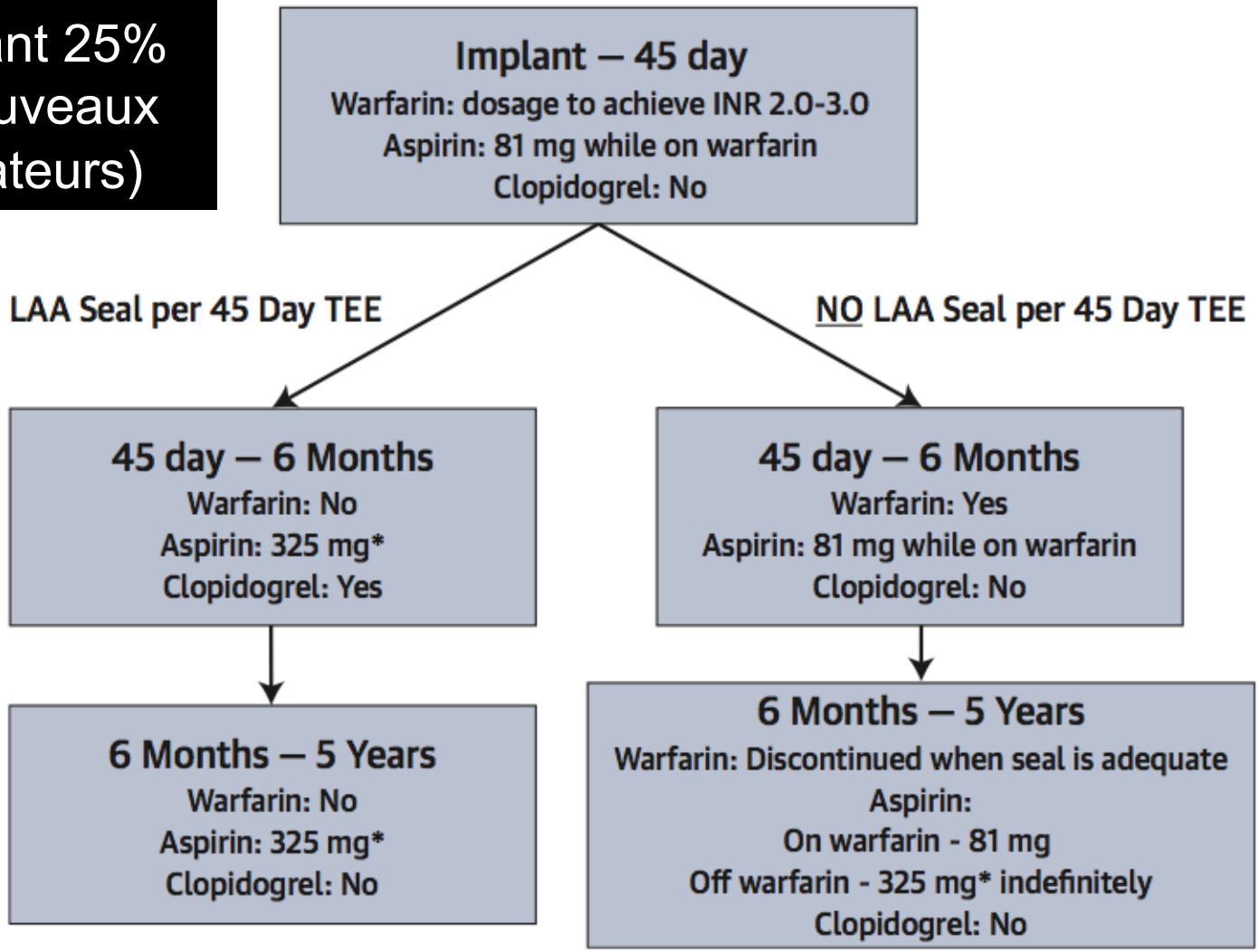
Randomized Trial of LAA Closure vs Warfarin for Stroke/ Thromboembolic Prevention in Patients with Non-valvular Atrial Fibrillation (PREVAIL)

David R. Holmes, Jr., M.D.
Mayo Clinic, Rochester

ACC 2013 – JACC Juillet 2014

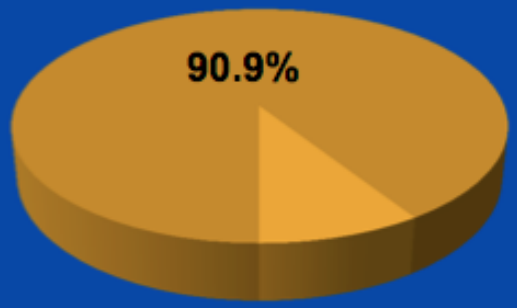
Design PREVAIL = idem PROTECT-AF

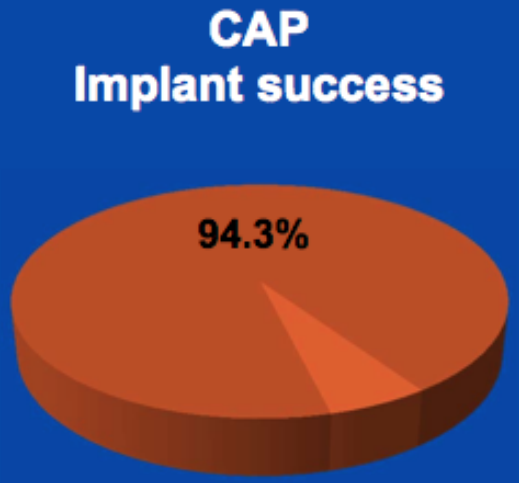
407 pts from 41 US centers (incluant 25% de nouveaux opérateurs)

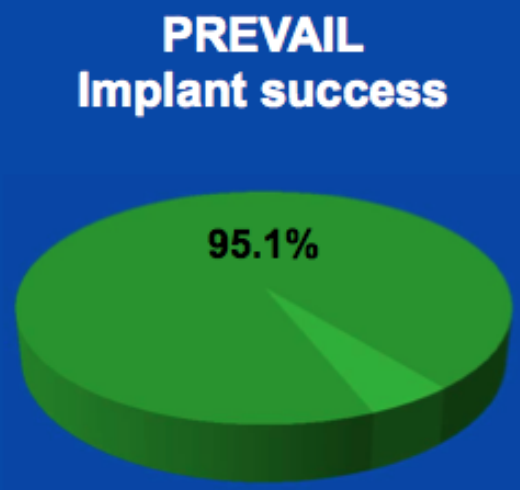


JACC 2014 64(1); 1-12

Procedure Implant Success







+ Less complications

p = 0.04

* Despite at least 25% of new operators

Implant success defined as deployment and release of the device into the left atrial appendage

MAYO CLINIC

PROTECT AF and CAP data
from Reddy, VY et al. *Circulation*. 2011;123:417-424.

PREVAIL – 1er co-point d'aboutissement primaire en terme d'efficacité (AVC, embolie systémique et mortalité CV à 18 mois)

TABLE 2 Coprimary Efficacy Endpoint Results (Stroke, Systemic Embolism, or Cardiovascular/Unexplained Death)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Noninferiority Criterion
0.064	0.063	1.07 (0.57, 1.89)	95% CrI upper bound <1.75

CrI = credible interval.

Non infériorité manquée

TABLE 3 Coprimary Efficacy Endpoint Observed Events by Type: PREVAIL Subjects Only (Intention-to-Treat)*

	Device Group			Control Group		
	No. of Events	% of Subjects	% of Endpoints	No. of Events	% of Subjects	% of Endpoints
Ischemic stroke	5	1.9	35.7	1	0.7	25.0
Hemorrhagic stroke	1	0.4	7.1	0	0.0	0.0
Death (cardiovascular/unexplained)	7	2.6	50.0	3	2.2	75.0
Systemic embolism	1	0.4	7.1	0	0.0	0.0

*Endpoint analysis was based on the initial event per-patient even if a patient experienced multiple events.
PREVAIL = Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy.

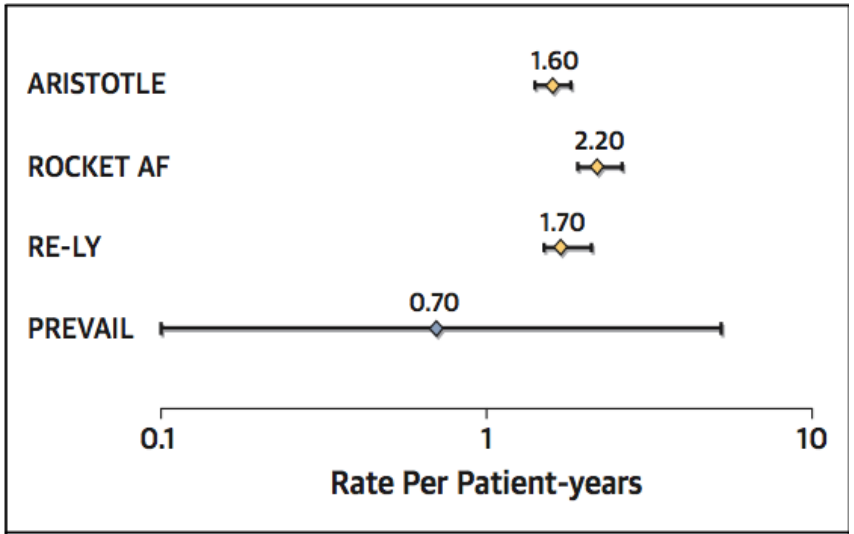


FIGURE 4 Ischemic Stroke Rates in Warfarin Control Groups

Control (warfarin) ischemic stroke rates per 100 patient-years in new oral anticoagulant NOAC trials and the PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial. The relatively small sample size and an unexpected overperforming control group could have contributed to the results seen in the first primary endpoint.

Nombre d'AVC clairement moindres que prévue dans groupe coumadin

PREVAIL – 2e co-point d'aboutissement primaire en terme d'efficacité (AVC ou embolie systémique >7 jours post-randomization)

TABLE 4 Late-Ischemic Coprimary Endpoint: PREVAIL Subjects Only (Intention-to-Treat)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Noninferiority Criterion	18-Month Rate Difference (95% CrI)	Rate Difference Noninferiority Criterion
0.0253	0.0200	1.6 (0.5 to 4.2)	95% CrI upper bound <2.0	0.0053 (-0.0190 to 0.0273)	95% CrI upper bound <0.0275

Non infériorité atteinte

PREVAIL – Sécurité = meilleure que PROTECT

TABLE 5 Safety Coprimary Endpoint Results and Events by Type (Intention-to-Treat): Device Group Only

	% (n/N)	95% CrI
Safety primary endpoint results	2.2% (6/269)	2.652%
	No. of Events	**% of Subjects**
Safety events by type		
Device embolization	2	0.7
Arteriovenous fistula	1	0.4
Cardiac perforation	1	0.4
Pericardial effusion with cardiac tamponade	1	0.4
Major bleed requiring transfusion	1	0.4

Basé sur Protect AF et PREVAIL

?

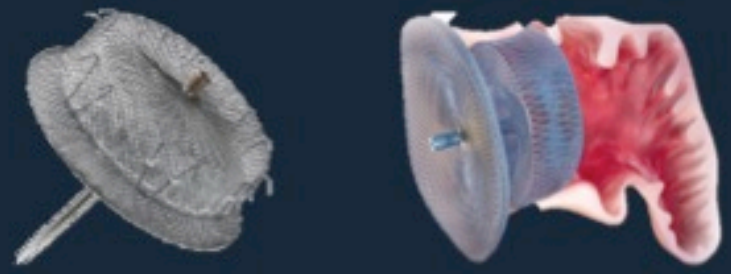
Si approuvé, doit être offert à la majorité des pts sous coumadin

Multicenter Experience with the Amplatzer Cardiac Plug (ACP)

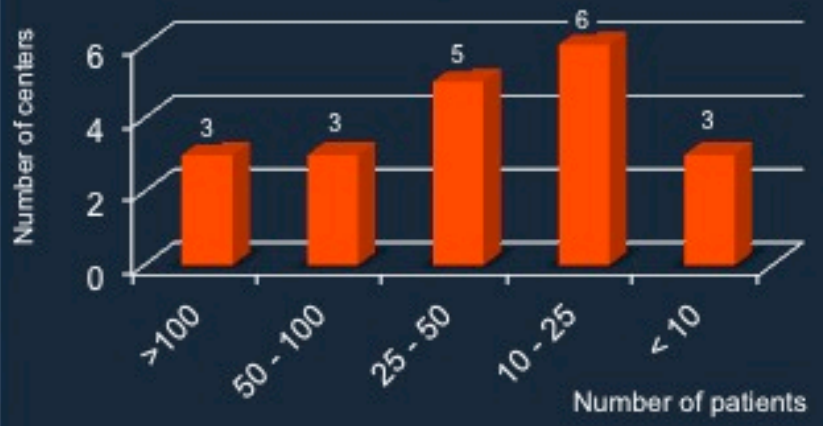
Study group

- **20 participating centers:** Germany, Switzerland, Italy, Belgium, Canada, Denmark, UK, Portugal
- **Enrollment:** December 2008 – August 2013
- **Final report on 969 patients**
- **1216 patient follow-up years**

Device



Enrollment per center



Enrollment per year

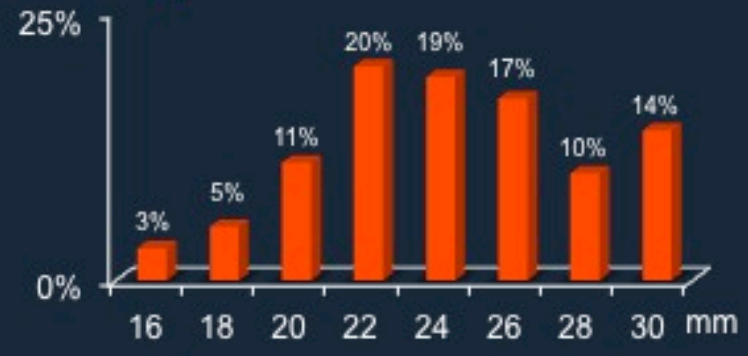
Eurointervention, accepted for publication

Implant Results

Success rates

- 97.2% (942/969) attempted were successfully implanted
- In 93.2%, first device selected was implanted

Implanted ACP size



Median (IQ range): 24 (22-26) mm

Access	
TSP	86.0%
PFO	9.8%
Unknown	4.2%

Combined Procedure	
Coronography	9.8%
PFO closure	6.3%
PCI	5.8%
TAVI	1.7%
AF ablation	1.3%
ASD closure	0.9%
Mitra-Clip	0.6%
Total	**26.4%**

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Peri-procedural complications (MAEs)

- **MAEs: Acute (7-day) occurrence of death, ischemic stroke, systemic embolism and procedure or device related complications requiring major cardiovascular or endovascular intervention***

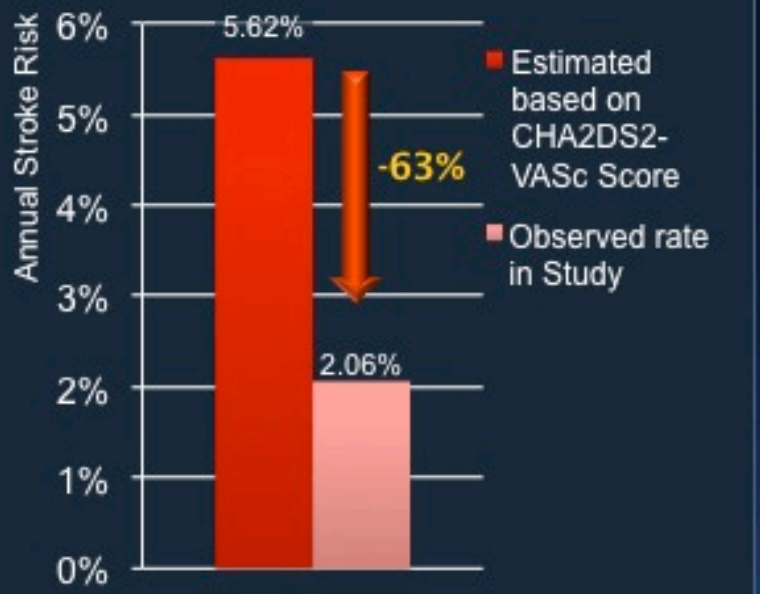
MEA	N	%
Death	6	0.62%
Pericardial tamponade	12	1.24%
Major bleeding	12	1.24%
Stroke	7	0.72%
Device embolization	2	0.21%
MI	1	0.10%
Total	**40**	**4.13%**

Complication	N	Remarks
Major (IC) bleeding	1	Procedure
Pericardial tamponade	2	Procedure, Day 4
Arrhythmia	1	Day 2
Device embolization	1	Procedure
Pneumonia	1	Day 4

* *Holmes et al. ACC 2013 (PREVAIL Study)*

Results

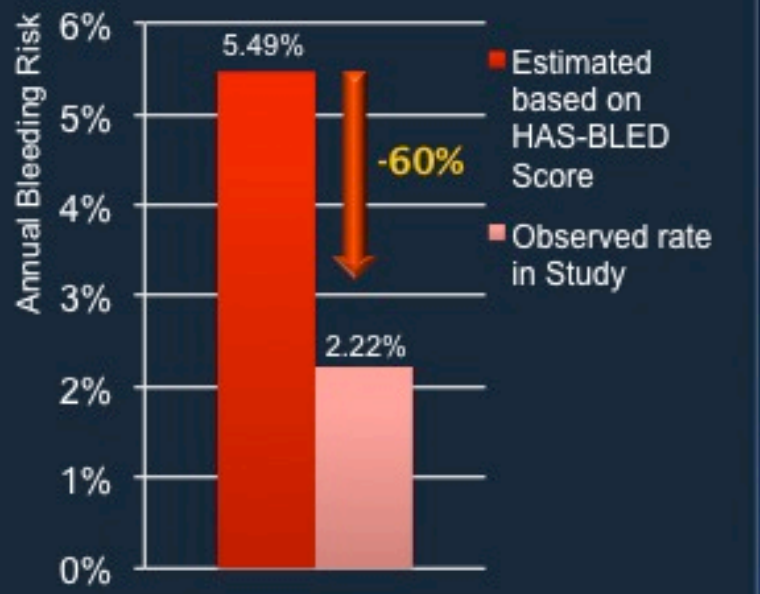
Effectiveness in Stroke Reduction vs estimated



Total Patients	Total Patient Years	CHA_2DS_2-VASc score
928	1216.2	4.41

Estimated Stroke Rate per $CHA2DS_2$-VASc	Actual Annual Stroke Rate (N strokes + TIA)
5.62%	2.06% (25)

Effectiveness in Bleeding Reduction vs estimated



Total Patients	Total Patient Years	HAS-BLED score
928	1216.2	3.18

Estimated Bleeding Rate per HAS-BLED	Actual Annual Bleeding Rate (N major bleeds)
5.49%	2.22% (27)

tct 25

Eurointervention, accepted for publication

CARDIOVASCULAR RESEARCH FOUNDATION

Limitations et préoccupations

ESC Guidelines for AF:

Interventional percutaneous occlusion/exclusion/closure of the LAA has a role in patients with thromboembolic risk who cannot be managed in the long-term using any form of OAC.

Recommendations for LAA closure/occlusion/excision

Recommendations	Class[a]	Level[b]	Ref[c]
Interventional, percutaneous LAA closure may be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulation.	IIb	B	115, 118
Surgical excision of the LAA may be considered in patients undergoing open heart surgery.	IIb	C	

LAA = left atrial appendage.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

* Camm, et al., *Eur Heart J (2012) doi:10.1093/eurheartj/ehs253*

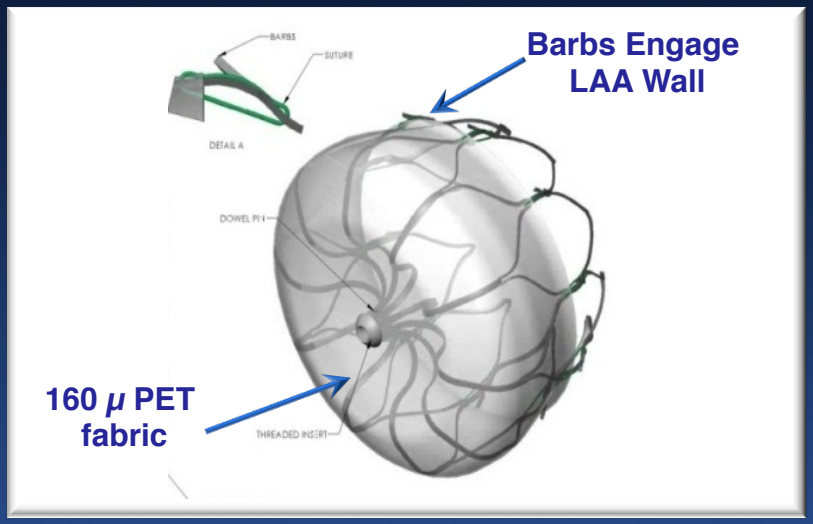
Limitations et préoccupations

- Warfarin n'est plus le "standard of care"
  - NOACs sont meilleurs

- Quel est notre niveau de confiance statistique des études randomisées?
  - Études relativement petites (1100 pts)
  - Design Bayesian
  - Intervalles de confiance pour la non infériorité sont larges avec 1 co-point d'aboutissement primaire non significatif dans PREVAIL

Préocupations potentielles

- **Quel est la sécurité à long terme des prothèses surtout chez les patients avec contraction auriculaire résiduelle?**

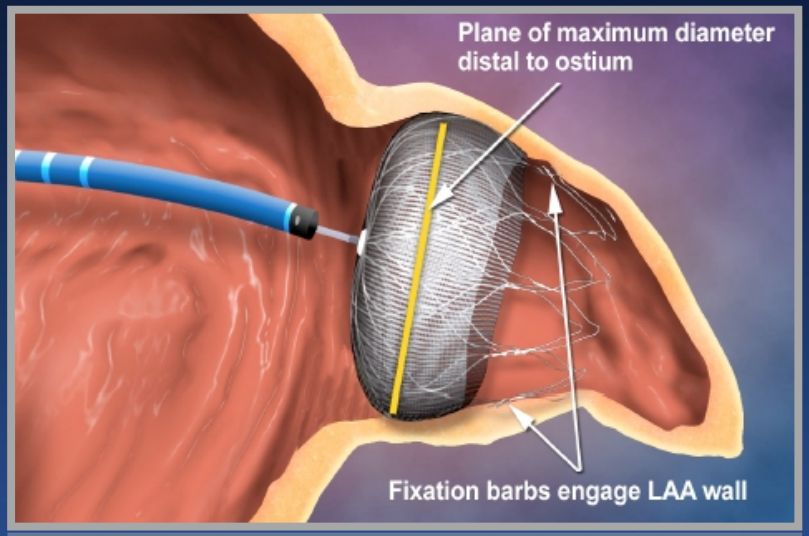


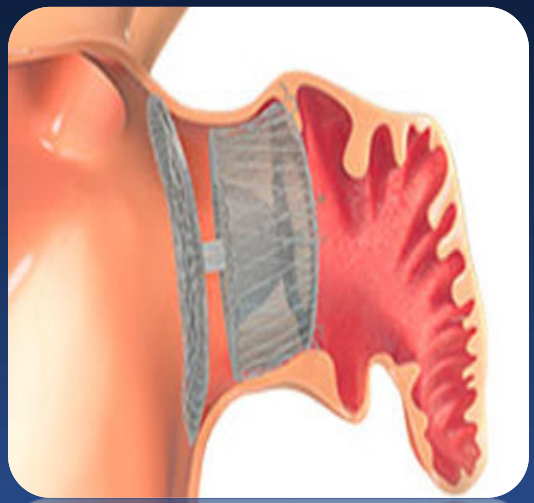
Watchman

Cardiac Plug

Questions à résoudre

- **Est-ce qu'on peut extrapoler les résultats de Protect AF et PREVAIL (avec le Watchman) aux autres prothèses d'occlusion?**





Questions à résoudre

- **Est-ce cost-effective?**

Health Services and Outcomes Research

Economic Evaluation of Percutaneous Left Atrial Appendage Occlusion, Dabigatran, and Warfarin for Stroke Prevention in Patients With Nonvalvular Atrial Fibrillation.

Singh, Sheldon; Micieli, Andrew; Wijeysundera, Harindra; MD, PhD

  - **Average discounted lifetime cost**
    - **$21 429 warfarin**
    - **$25 760 dabigatran**
    - **$27 003 for LAA occlusion**

Circulation 2013;127:2414-2423
P. Heidenreich. Circulation 2013;127:2375-2375

Indications de fermeture d'auricule

- FA non valvulaire
  - CHADS OU CHADS VASC ≥ 1

    ET
  - Haut risque de saignement ou saignement sous anticoagulants

Post-procédure

- ETO de contrôle à 6 semaines pour éliminer thrombus et/ou shunt résiduel

- Prophylaxie endocardite 1 an

Post-procédure

- Si patient anticoagulé
  - Poursuivre anticoagulation pour 45 jours en attendant l'ETO de contrôle
  - Si pas de thrombus ou de shunt significatif résiduel = aspirine + clopidogrel X 1-6 mois puis monothérapie à vie

Post-procédure

- Si patient non anticoagulé
  - Aspirine + clopidogrel 1-6 mois puis monothérapie à vie

Conclusions

- **L'exclusion d'auricule gauche (une thérapie locale) est une alternative raisonnable à l'anticoagulation orale (un traitement systémique) pour prévenir l'AVC chez les pts avec FA en alternative au coumadin ou chez les pts qui saignent sous médication**

- **Les prothèses d'occlusion de l'auricule devront être testées contre le standard de traitement, incluant les NOACs**

Conclusions

- **Plusieurs questions et préoccupations restent à résoudre au sujet de la fermeture de l'auricule gauche avant un remplacement diffus de l'anticoagulation orale chez les pts avec FA**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