Stratégie non pharmacologique de prévention des AVC dans la FA: Fermeture de l'auricule gauche

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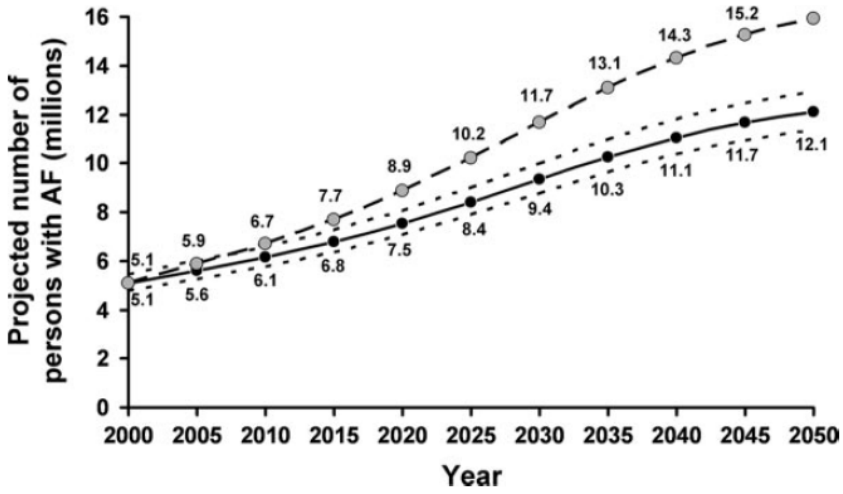
The Problem of AF gets Larger

- Number of AF patients likely increases 2.5-fold in 50 yrs[1,2]
- Reflects growing proportion of elderly individuals[3]
  - Due to an ageing population
  - Improved survival of patients with conditions which predispose AF (e.g., heart attack)

Projected number of persons with AF[2]



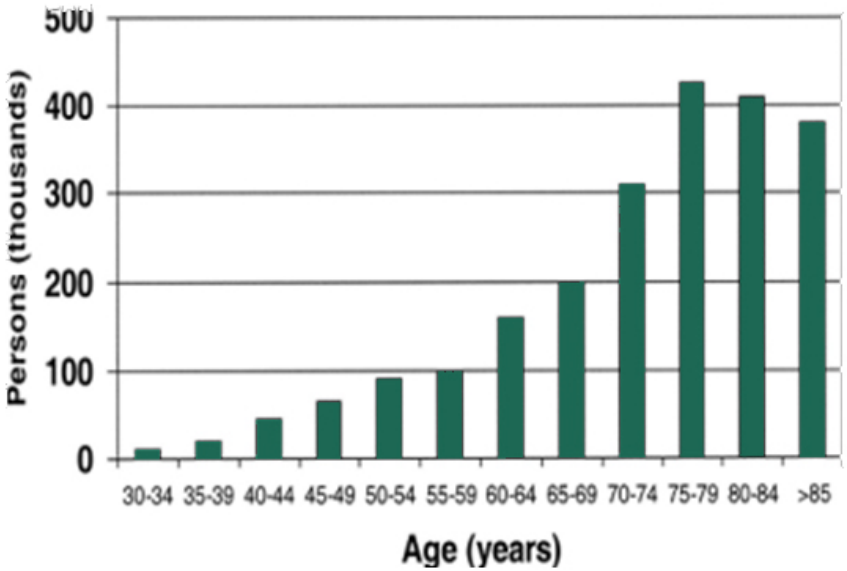
Projected number of persons with AF in the US between 2000 – 2050

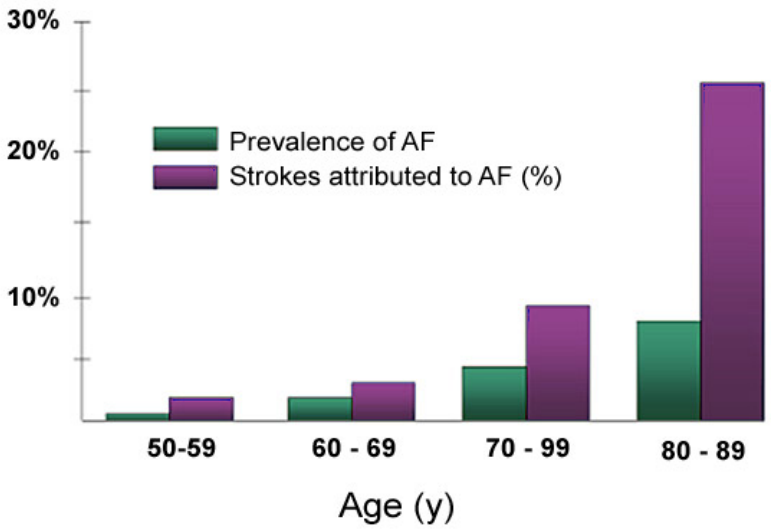
- No further increase in age-adjusted AF incidence (solid curve)
- A continued increase in incidence rate as evident 1980 - 2000 (dotted curve)

1. Go AS, et al. Prevalence of diagnosed AF in adults: national implications for rhythm mgt & stroke prev.: ATRIA Study. JAMA 2001;285:2370-5.
2. Miyasaka Y, et al. Secular trends in incidence of AF in Olmsted County, MN, 1980-2000, implications on projections for future prevalence. Circulation 2006;114:119-25.
3. Briffa T, et al. Long term survival after evidence based treatment of acute MI and revascularisation: follow-up of population based Perth MONICA cohort, 1984-2005. BMJ 2009;338:b36.

AF and Stroke

- 3 million in US and 4.5 million in the EU have AF[1]
- 2/3 of AF population are at high-risk of stroke[1]
  - 35% of patients with AF will have a stroke in their lifetime[2]
- AF is responsible for 15-20% of ischemic strokes[1]
- AF Incidence increases with age[2]
  - 0.4% in general population
  - 0.2% of 25-34 yrs of age
  - 2-5% of >60 yrs of age
  - 10% of > 80 yrs of age

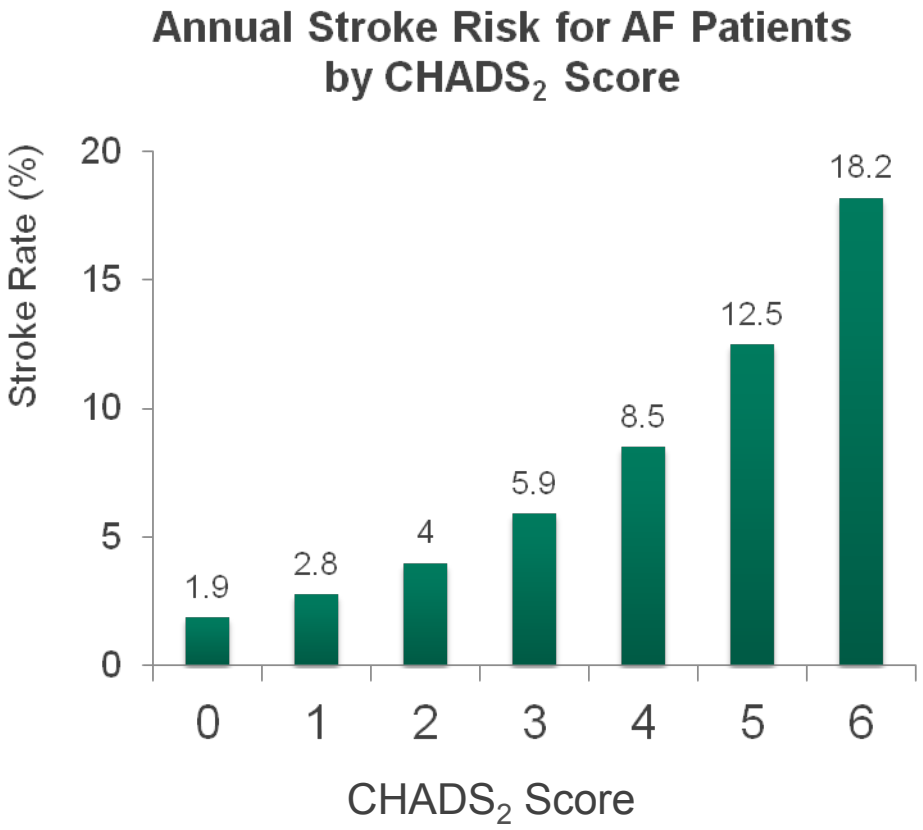




1. Fuster, et al. ACC/AHA/ESC Practice Guidelines, *Circulation*. 2006;114:700-752.
2. Wolf PA, et al. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke*. 1991;22:983-8.

Stroke Risk Stratification of AF Patients: The $CHADS_2$ Score

$CHADS_2$ Score	$CHADS_2$
Congestive heart failure	+1
Hypertension	+1
Age 75>	+1
Diabetes Mellitus	+1
Stroke or History of Cerebral Ischemia	+2



Gage, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001; 285: 2864-70.

Stroke Risk Assessment: CHA_2DS_2-VASc Score

Letter	Risk factor	Points awarded
C	– Congestive heart failure/LV dysfunction	1
H	– Hypertension	1
A	– Age >75	2
D	– Diabetes mellitus	1
S	– Stroke/TIA/thrombo-embolism	2
V	– Vascular disease	1
A	– Age 65-74	1
Sc	– Sex-category (i.e. female sex)	1
	Maximum score	**9**

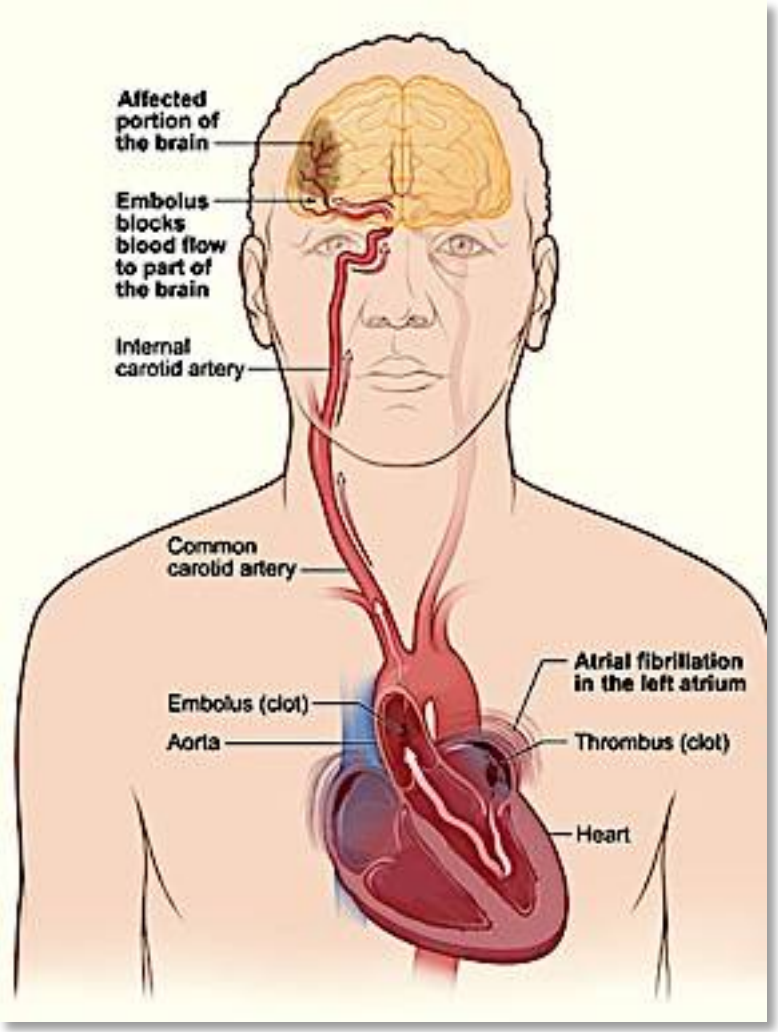
Camm, et al. ESC 2010 Guidelines for the management of Atrial Fibrillation; *European Heart Journal*. doi:10.1093/eurheartj/ehq278

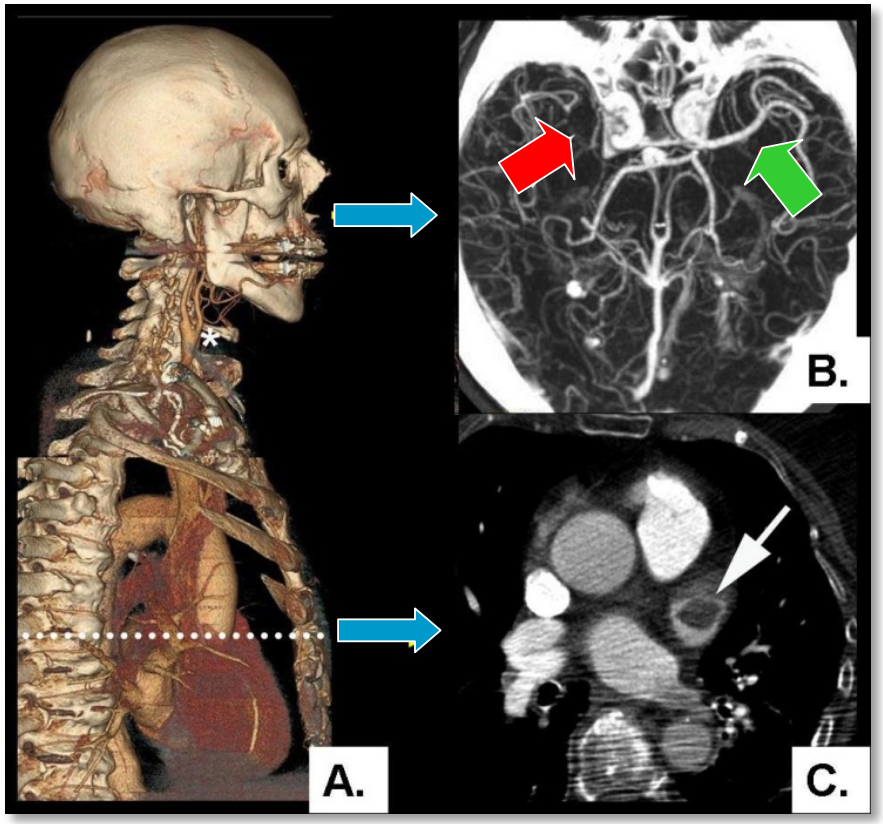
Adjusted Stroke Rate to CHA_2DS_2-VASc Score

CHA_2DS_2-VASc score	Patients (n = 7329)	Adjusted stroke rate (%/year)
0	1	0.0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

Lip, et al. Identifying patients at risk of stroke despite anticoagulation. *Stroke* 2010; in press.

Association of LAA Clot and Stroke





A: 3-D CT
B: Angio: - normal MCA
- absence of MCA
C: CAT scan: Arrow showing LAA clot

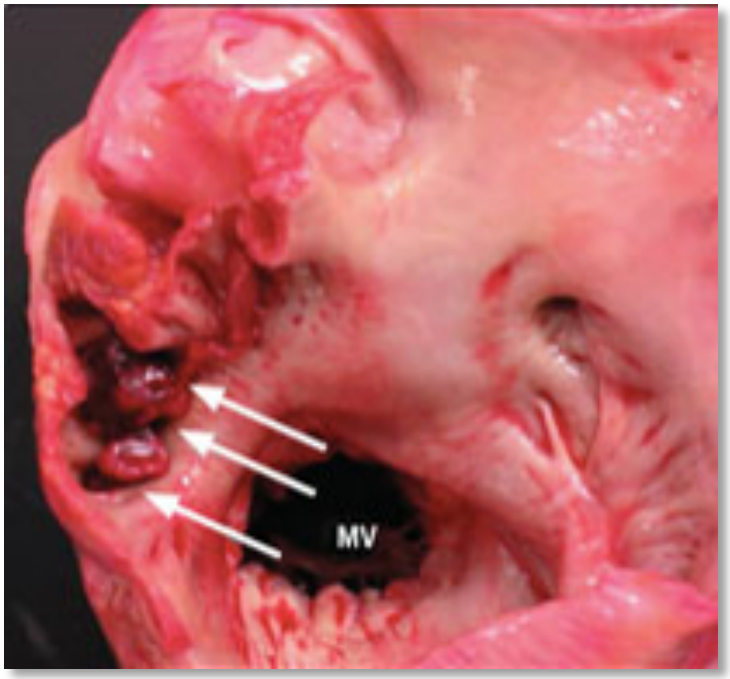
Image sources: Left image (heart and brain), http://imagegallery.taragana.com/2010/02/22/g/107404/, last accessed November 2, 2010.

Higher Incidence of LAA Thrombus in Patients with AF

- Non-rheumatic AF pts:
  - Thrombus present in 12.6% of patients.
  - 90% of the thrombi were found in the LAA

TABLE 1. Review of Published Reports Detailing the Frequency and Site of Thrombus Location in Patients With Nonrheumatic Atrial Fibrillation*

		Thrombus Location (n, %)		
Setting	No. of Patients	LA Appendage	LA Cavity	Total
TEE†	317	66 (20.8)	1 (0.3)	67 (21.1)
TEE	233	34 (14.6)	1 (0.4)	35 (15.0)
Autopsy	506	35 (6.9)	12 (2.4)	47 (9.3)
TEE	52	2 (3.8)	2 (3.8)	4 (7.7)
TEE	48	12 (25.0)	1 (2.1)	13 (27.1)
TEE and operation	171	8 (4.7)	3 (1.8)	11 (6.4)
ACUTE	549	67 (12.2)	9 (1.6)	76 (13.8)
TEE	272	19 (7.0)	0 (0)	19 (7.0)
TEE	60	6 (10.0)	0 (0)	6 (10.0)
Total	2208	249 (11.3)	29 (1.3)	278 (12.6)



Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996;61:755–9.

Warfarin: The Cornerstone Therapy

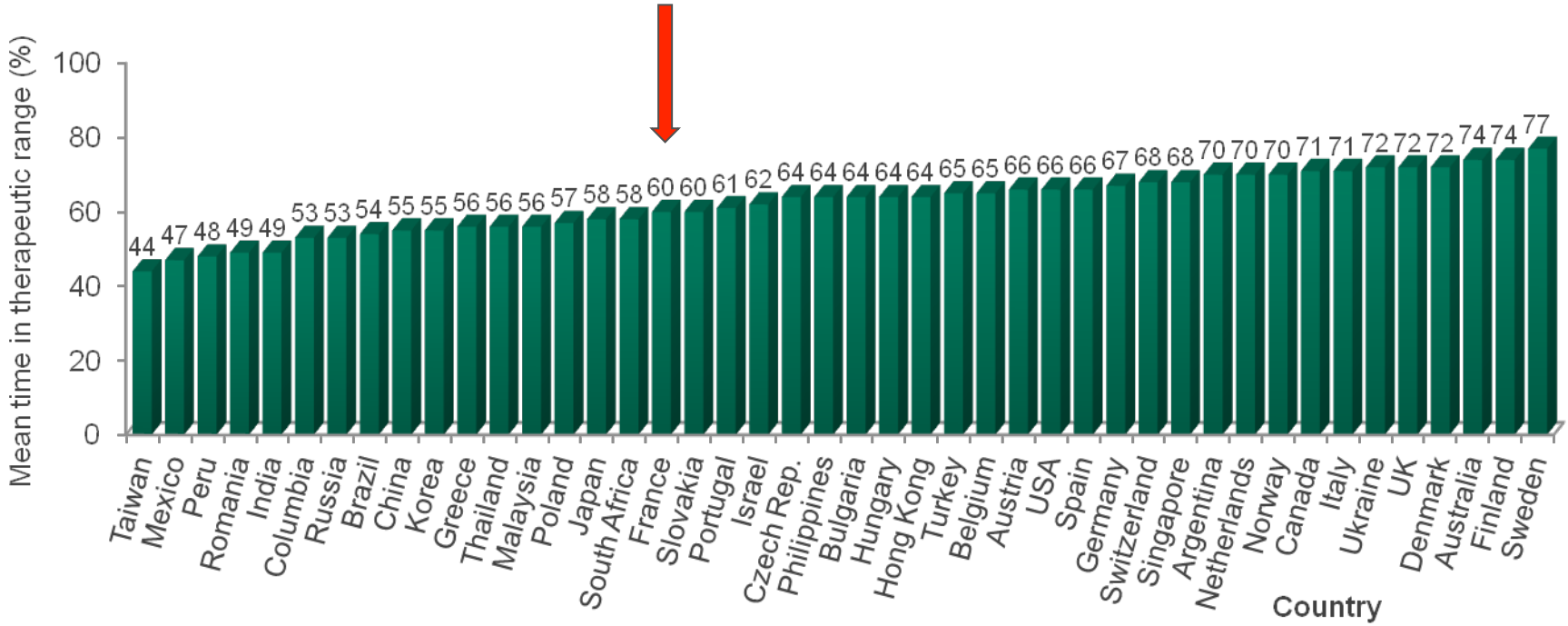
- Warfarin is the cornerstone therapy
- Adjusted-dose warfarin agents reduce stroke by approximately 60%[1] (30-40% Stroke risk reduction vs. aspirin)

- Inadequate warfarin usually seen in AF pts who are admitted with Stroke[2]
  -High-risk patients with AF, admitted with stroke, candidates for OAC:
  - Only 29% on therapeutic level for Warfarin dose
  - Of the remaining:
    - 10% were sub-therapeutic
    - 31% were on Antiplatelet
    - 29% no therapy was prescribed

- Warfarin is Contraindicated in 14-47% of pts at risk of stroke[4]
  - It is not prescribed in 21% of the indicated patients[3]
  - Less than 50% of pts eligible are being treated with warfarin due to tolerance or non-compliance issues

1. Hart, et al. Meta-analysis 28044 pts, *Ann Intern Med*. 2007;146:857-67.
2. Gladstone, et al. *Stroke*. 2009;40:235-40.
3. Waldo AL, et al. *J AM Coll Cardiol.* 2005;46:1729.
4. Holmes at ACC & i2 Summit 2009.
5. Wikipedia. Warfarin. http://en.wikipedia.org/wiki/Warfarin. Accessed November 1, 2011.

Country Distribution of Mean Time in Therapeutic Range in the RE-LY Trial



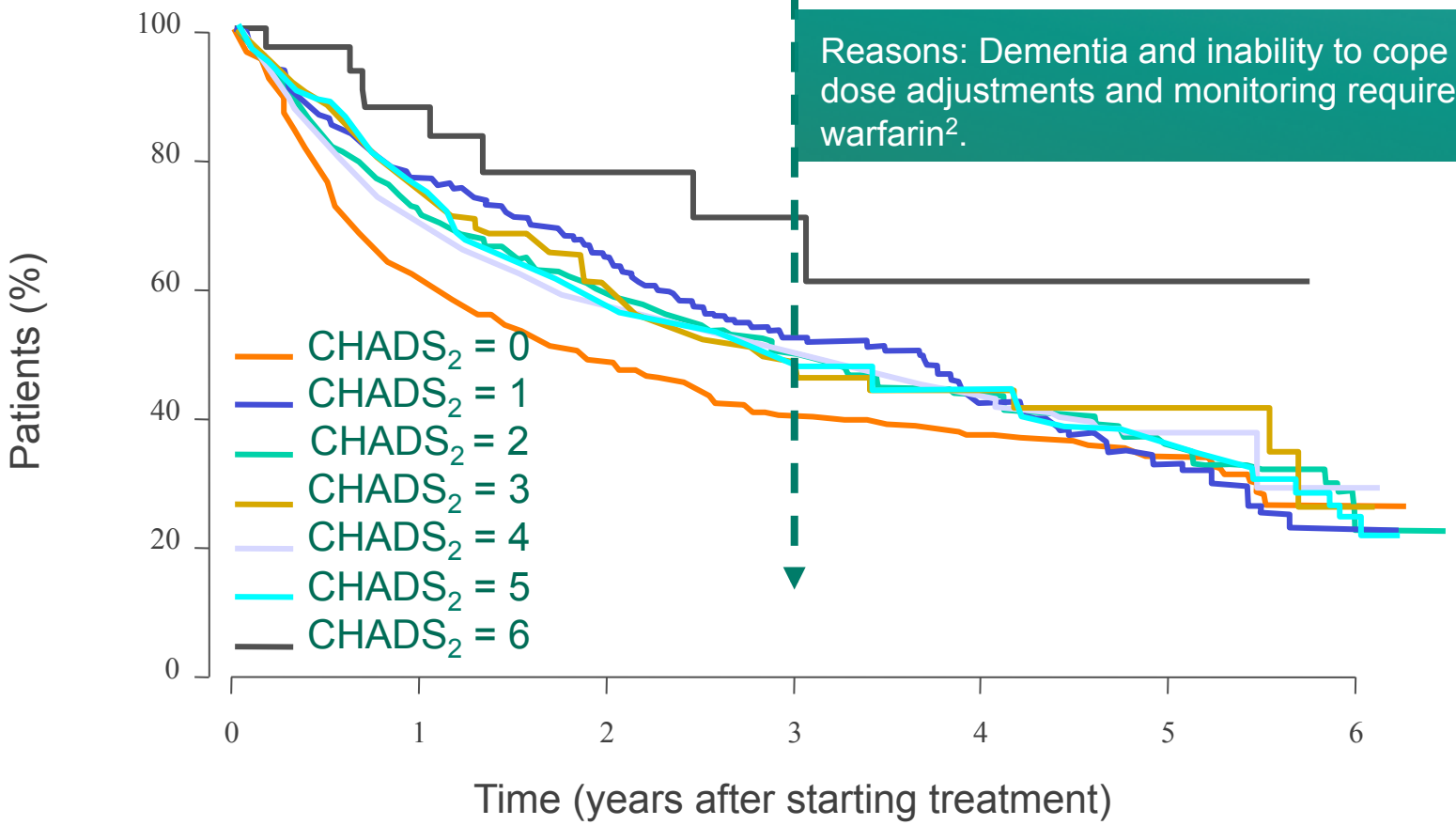
- 5791 Patients on warfarin
- A large proportion of patients were outside the therapeutic range
- Major variations between countries
  - Europe: about 3 out of 10 patients out of therapeutic range
  - Sweden: 23% out of range
  - Taiwan: 56%

Wallentin, et al. Efficacy and safety of Dabigatran compared with Warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial; *The Lancet*. 2010'376; 975-83.

Do the appropriate patients receive stroke prophylaxis?

Approximately 50% loss of compliance at 3 years[1]

Reasons: Dementia and inability to cope with the dose adjustments and monitoring required of warfarin[2].

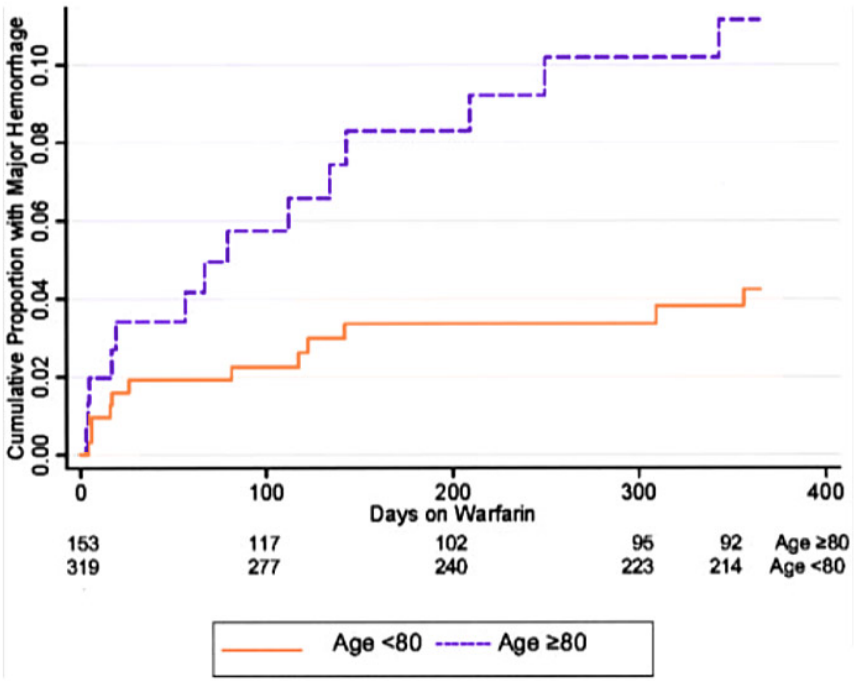


1. Gallagher AM, et al. Initiation and persistence of warfarin or aspirin in patients with chronic AF in general practice *J Thromb Haemost*. 2008;6:1500-6.
2. Khoo. Lip Initiation and persistence of warfarin or aspirin as thromboprophylaxis in chronic AF. *J Thromb Haemost*. 2008;6:1622.

Role of Major Hemorrhage on Warfarin

- Stroke prevention among elderly patients with atrial fibrillation remains challenging
- Aggregate hemorrhage rate 7.2% per person-yrs
  - 13.08% for pts ≥80 yrs
  - 4.75% pts <80 yrs
  - First 90 days associated with 3-fold increased risk.
- 26% pts ≥80 yrs taken off warfarin;
  - 81% due to safety concerns

Cumulative incidence of major bleeding (patients aged ≥80 & <80 years (n=472))



Adjusted standard dose warfarin prevented 28 strokes - at expense of 11 fatal bleeds
Aspirin prevented 16 strokes at expense of 6 fatal bleeds

Hylek, et al. Major Hemorrhage and Tolerability of warfarin in the 1st Year of Therapy Among Elderly Patients with AF; *Circulation*. 2007;115:2689-96.

Risk Assessment for Bleeding - HAS-BLED Score

Letter	Clinical characteristic	Points awarded
H	- Hypertension (systolic blood pressure > 160 mmHg)	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 (age > 65 yrs)	1
D	- Drugs or alcohol (1 point each)	1 or 2
	Maximum	**9 points**

Lip, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in AF using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest.* 2010;137:263–72.

Points System - HAS-BLED Score

HAS-BLED	0	1	2	3	4	5	Any score
n	798	1286	744	187	46	8	3071
No. of bleeds	9	13	14	7	4	1	48
Bleeds per 100 pts	1.13	1.02	1.88	3.74	8.7	12.5	1.56

- Score of ≥3 indicates 'high risk'
  - Some caution and regular review of the patient is needed following the initiation of antithrombotic therapy (VKA or Aspirin)
  - **Simple, easy bleeding risk score for everyday clinical practice; HAS-BLED score**

1. Pisters et al. A novel User-friendly score to assess one-year risk of major bleeding in AF patients; *Chest*. 2010; DOI 10.1378/Chest 10-0134.
2. Khoo, Lip. Initiation and persistence of warfarin or aspirin as thrombo prophylaxis in chronic AF - *J Thromb Haemost*. 2008;6:1622.

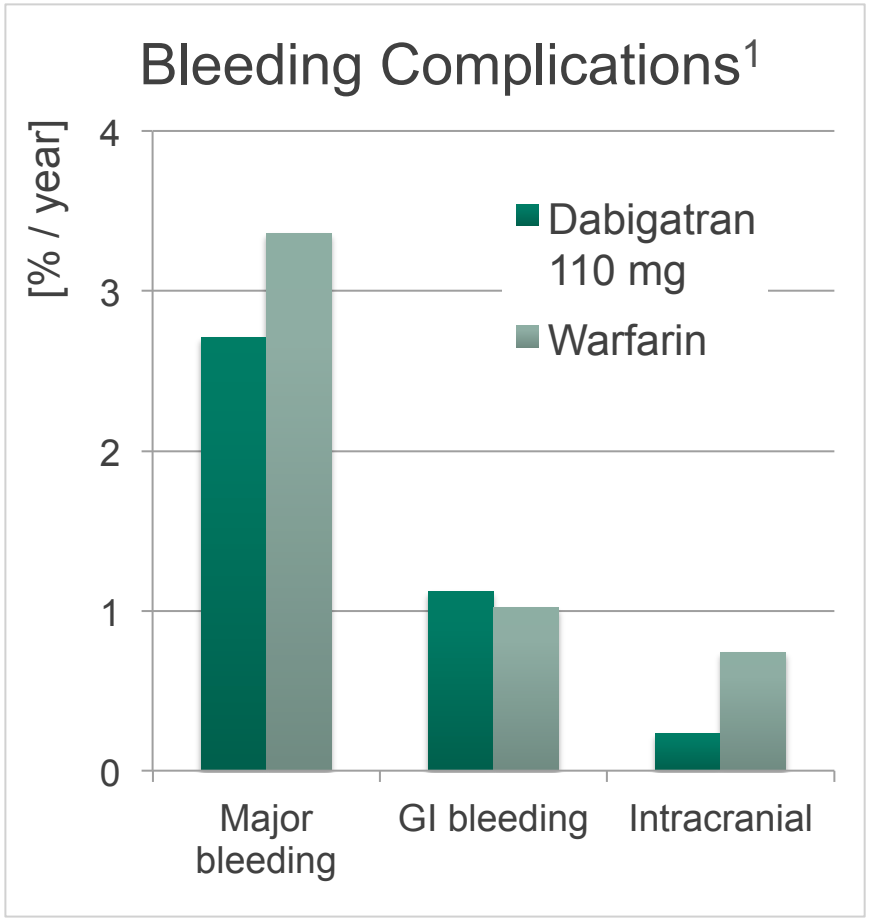
Dabigitran as Substitute for Warfarin?

- The Good News for Dabigatran (Pradaxa)
  - Reduced the annualized risk stroke/peripheral embolic events, by 34% ($p<0.001$)
  - Reduced risk of hemorrhagic stroke by 74% ($p<0.001$) compared with warfarin.
  - Patients don't require any form of monitoring
- The Not All Good News
  - Although the primary safety outcome is statistically significant better, in clinical practice Dabigatran may not prove better than warfarin. Patients still have bleeding complications.
- 357 patients need to be treated with with 2x150 mg Dabigatran (rather than warfarin) to prevent one nonhemorrhagic stroke.[2]
  - At 1 year, in the RE-LY trial, 15% of pts were off Dabigatran vs. 10% for warfarin: GI Symptoms, Bleeding and Adverse Events
  - Reimbursement: patients have to pay up to €10 per day (> € 3500 Euro per year)

Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin	
	No. of patients	%/yr	No. of patients	%/yr	No. of patients	%/yr
Major Bleeding	322	**2.71**	375	**3.11**	397	**3.36**
Life threatening	145	1.22	175	1.45	212	1.80
Non-life threatening	198	**1.66**	226	**1.88**	208	**1.76**

Connolly S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Medicine 2009; DOI 10.1056.NEJM0a0905561.

Dabigatran vs. Warfarin (RE-LY trial)



- To prevent 1 stroke, approx. 370 patients should be treated with Dabigatran vs Warfarin.[2]
- Approx. 500 patients would have to receive Dabigatran (rather than warfarin) for 1 patient to have a myocardial infarction.[2]

1. Connolly S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Medicine 2009; DOI: 10.1056.NEJM0a0905561
2. Gage BF. Can we rely on RE-LY? *N Engl J Medicine.* 2009; DOI:10.1056.NEJMe0906886.

RE-LY at 2.5 years

- More patients discontinue Dabigatran than warfarin.
- Depending on specific dose schedule, Dabigatran is either non inferior to warfarin in preventing stroke/embolization or is somewhat better.
- However, bleeding rates increase over time with either Dabigatran or warfarin.

Holmes, Oral Presentation at TCT 2010, Washington, DC September 2010

Patients for Dabigatran

- Higher dose Dabigatran more effective than Warfarin in all CHADS2 categories[1]
- RE-LY: Benefits of Dabigatran greatest in centers with lowest TTR[1]
  - The better one does on Warfarin, the less benefit from Dabigatran
- Dabigatran in the elderly[1]:
  - Lower risk of stroke and intracranial bleeding
  - Higher risk of extracranial (mostly GI) bleeding
  - For patients over age of 75 yrs, Warfarin is better
    - At 110mg Dabigatran it is similar
- Who might not be a candidate for Dabigatran:
  - Stable on Warfarin
  - Well managed time in TTR
  - High risk of GI bleeding (> 110 mg)
  - Mechanical valve
  - Elderly, frail patients[2]

1. Connolly S, et al., RE-LY Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Medicine 2009; DOI:10.1056.NEJM0a0905561
2. Legrand M, Mateo J, Aribaud A, et al. The use of dabigatran in elderly patients. Arch Intern Med 2011; 171:1285-1288

Randomized Controlled Studies on New Anti-thrombotic Medication

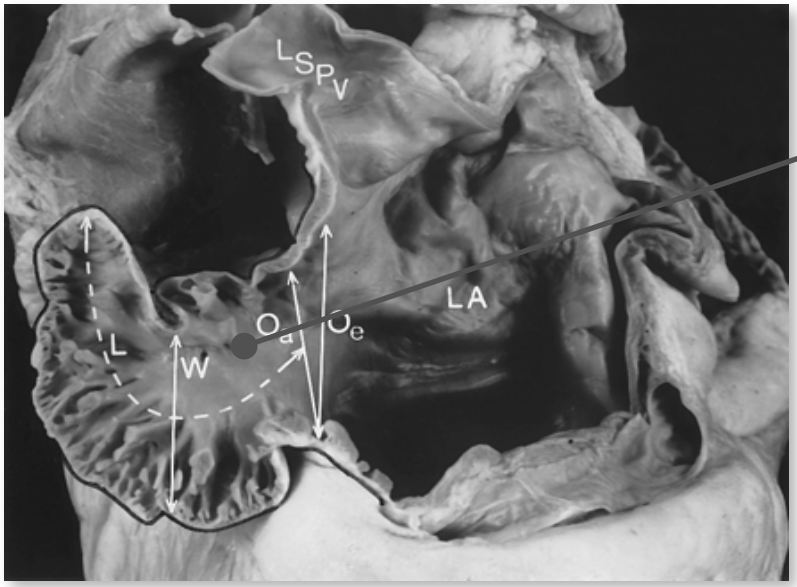
Drug / study	Baseline characteristics/ Endpoints	Randomization arms	Event rates [%/yr]		Overall outcome
			Effectiveness	Safety	
Dabigatran RE-LY (1)	*Baseline characteristics:* 18113 pts, 71 yrs, $CHADS_2$: 2.1 *Effectiveness:* Stroke and systemic embolism *Safety:* Major hemorrhage	110 mg dabigatran twice daily	1.53	2.71	Compared to warfarin: 110 mg dabigatran: non-inferior stroke prevention and significantly less bleeding. 150 mg dabigatran: superior stroke prevention and similar bleeding risk. 110 mg dose: similar risk for GI bleeding. 150 mg dose: significantly higher risk for GI bleeding.
		150 mg dabigatran twice daily	1.11	3.11	
		Adjusted dose warfarin	1.69	3.36	
Rivaroxaban ROCKET-AF (2)	*Baseline characteristics:* 14264 pts, 73 yrs, $CHADS_2$: 3.47 *Effectiveness:* All-case stroke and non-CNS systemic embolism *Safety:* Major and clinically relevant non-major bleeding	20 mg rivaroxaban daily	2.12 (ITT)	3.60	Rivaroxaban is non-inferior to warfarin in prevention of stroke and non-CNS systemic embolism. Major bleeding rates of rivaroxaban and warfarin are similar.
		Adjusted dose warfarin	2.42 (ITT)	3.45	
Apixaban AVERROES (3)	*Baseline characteristics:* 5600 pts, 73 yrs, $CHADS_2$: 2.1 *Effectiveness:* Stroke and systemic embolism *Safety:* Major bleeding	5 mg apixaban twice daily	1.6	1.4	Compared to aspirin, apixaban provides superior prevention for stroke and systemic embolism and has similar bleeding risks.
		81 – 324 mg aspirin daily	3.7	1.2	
Apixaban ARISTOTLE (4)	*Baseline characteristics:* 18201 pts, 70 yrs, $CHADS_2$: 2.1 *Effectiveness:* Systemic or hemorrhagic stroke or systemic embolism *Safety:* Major bleeding	5 mg apixaban twice daily	1.27	2.13	Prevention for stroke and systemic embolism by apixaban is non-inferior / superior to warfarin. Apixaban is associated with significantly lower major bleeding rate compared to warfarin.
		Adjusted dose warfarin	1.60	3.09	

1. Connolly et al., Dabigatran versus warfarin in patients with atrial fibrillation. 2009, N Engl J Med, Vol. 361, pp. 1139-1151.
2. ROCKET AF Study Investigators, Rivaroxaban - Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: Rationale and Design of the ROCKET AF study. 2010, Am Heart J, Vol. 159, pp. 340-347.
3. Connolly, et al., Apixaban in Patients with Atrial Fibrillation. 2011, N Eng J Med, Vols. published online at NEJM.org on February 10, 2011.
4. Granger, et al., Apixaban versus Warfarin in Patientswith AF. 2011, New Eng J Med, published online August 28, 2011, accessed Sept 2, 2011.

Principle of Left Atrial Appendage Closure

Anatomy of the Normal LAA

- Blood flow in the LAA is slowed and can become turbulent in the case of AF.



Can form a clot in the LAA which can embolize and cause a stroke

Veinot JP, et al. Anatomy of the Normal Left Atrial Appendage A Quantitative Study of Age-Related Changes in 500 Autopsy Hearts: Implications for Echocardiographic Examination. Circulation 1997;96:3112.
Image Source: http://circ.ahajournals.org/content/96/9/3112.full. Accessed November 1, 2011.

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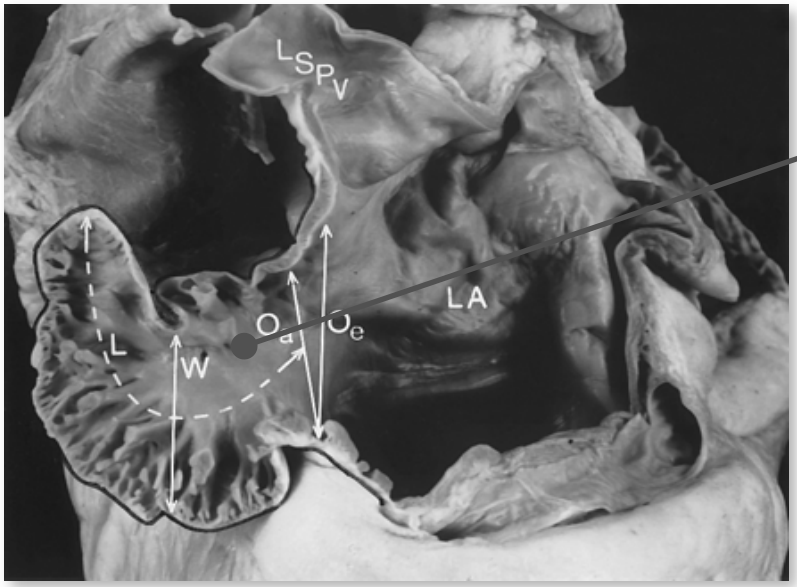

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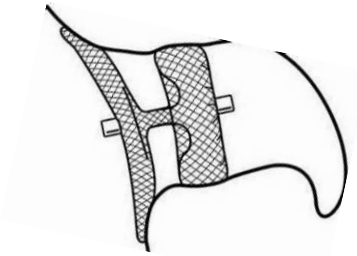

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Image Source: http://circ.ahajournals.org/content/96/9/3112.full. Accessed November 1, 2011.

Transcatheter Occlusion of the LAA

- Various types of occluding devices

PLAATO®

WATCHMAN®

AMPLATZER Cardiac Plug

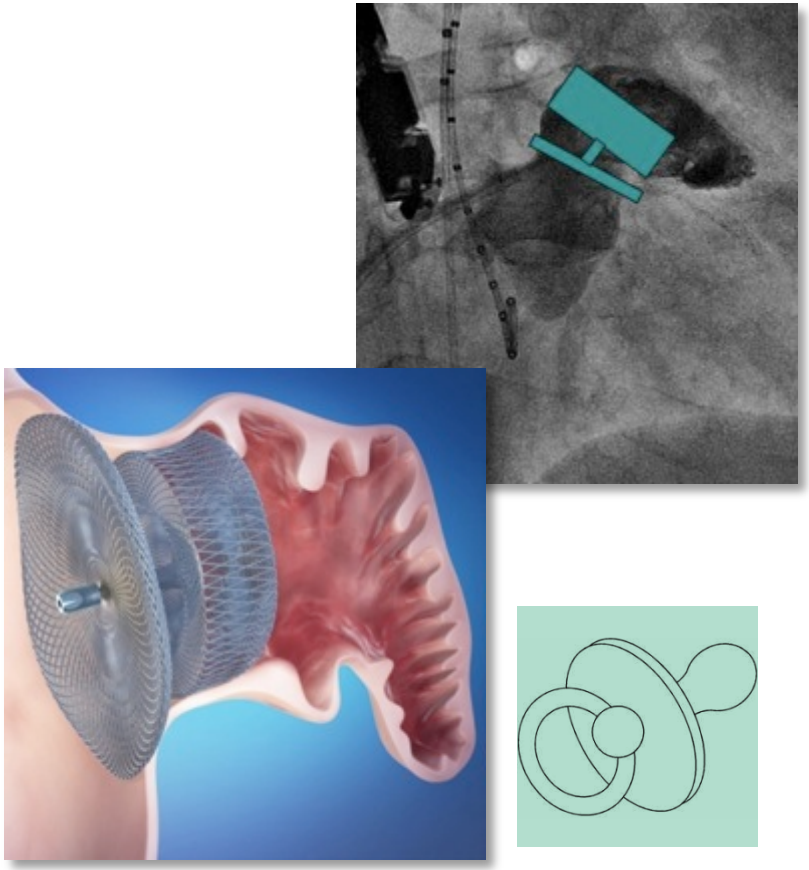
Sources:
PLAATO and WATCHMAN Images: DeMeester P et al. Percutaneous closure of the atrial appendage in atrial fibrillation: an alternative if standard treatment fails? Interv Cardiol. 2009. (1) 1:119-131.

Proof of Concept: The PLAATO Studies – Long Term + Initial Experience

Author	# patients	Follow Up	Est. ann. stroke rate (w/o device)	Act. ann. stroke rate (w/ device)
Block[1]	64	5 years	6.6%	3.3%
Park[2]	73	2 years	5.0%	0.0%
Ussia[3]	20	40 ±10 mths	6.4%	0.0%
De Meester[4]	10	3 ± 47 mths	7.1%	0.0%
Ostermeyer[5]	111	9.8 mths	6.3%	2.2%

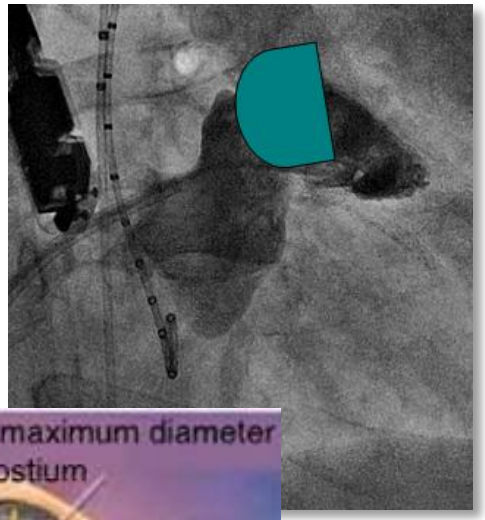
1. Block et al. Percutaneous left atrial appendage occlusion for patients in AF suboptimal for warfarin therapy: 5-year results of the PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) Study. JACC Cardiovasc Interv. 2009 Jul;2(7):594-600.
2. Park et al. Percutaneous left atrial appendage transcatheter occlusion (PLAATO) for stroke prevention in AF: 2-year outcomes. J Invasive Cardiol. 2009 Sep;21(9):446-50.
3. Ussia et al. Percutaneous left atrial appendage transcatheter occlusion in patients with chronic nonvalvular AF: early institutional experience. J Cardiovasc Med (Hagerstown). 2006 Aug;7(8):569-72.
4. De Meester et al. Prevention of stroke by percutaneous left atrial appendage closure: short term follow-up. Int J Cardiol. 2010 Jul 9;142(2):195-6.
5 Ostermeye et al. Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with non-rheumatic AF: results from the international multi-center feasibility trials. J Am Coll Cardiol. 2005 Jul 5;46(1):9-14.

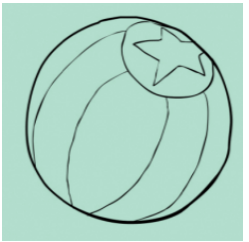
Differences in Philosophy



AMPLATZER Cardiac Plug

"pacifier principle"[1]





Watchman (Boston Scientific)

"half football principle" [2]

1. Park at CSI 2011. "Current Status of Left Atrial Appendage Closure Devices – Amplatzer ACP Occluder", Frankfurt, June 23-25, 2011.
2. Park at ENCORE 2011. "Percutaneous Left Atrial Appendage Closure with Amplatzer Cardiac Plug - European Experience", Seoul, September, 22, 2011.

Image Source: http://circ.ahajournals.org/content/96/9/3112.full. Accessed November 1, 2011.
Watchman: http://www.medscape.com/viewarticle/740799_4. Access November 1, 2011.

Etudes cliniques WATCHMAN

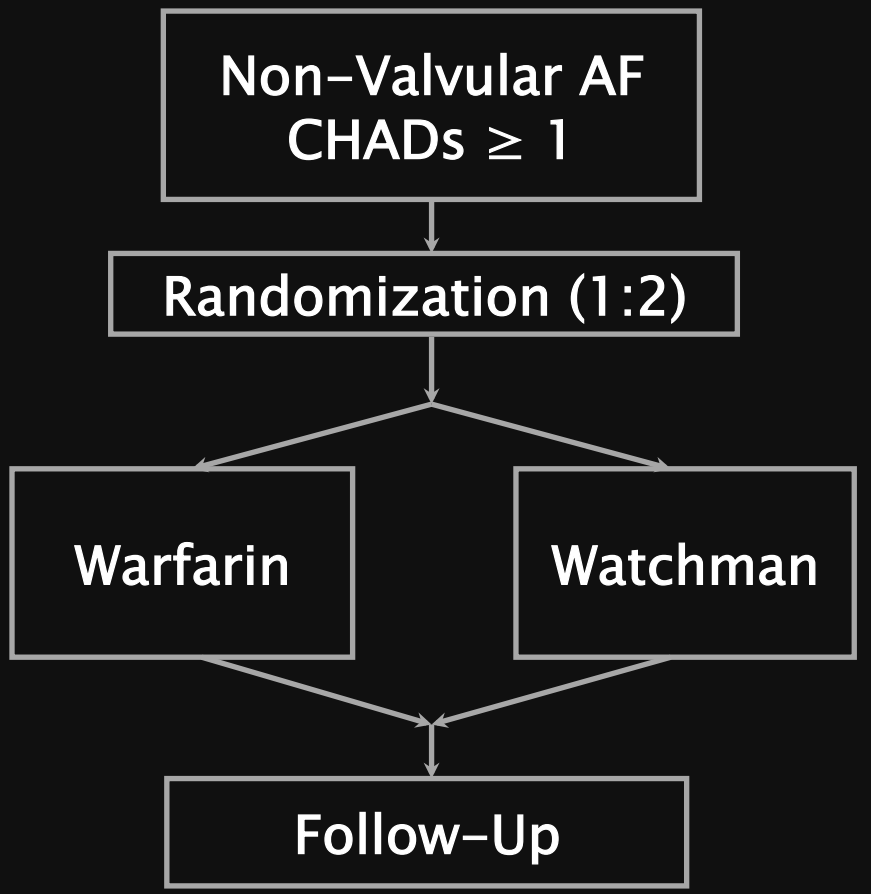
STUDY	PATIENTS	SITES	COMMENTS
Pilot	66	8 (4 US, 4 EU)	• 318 patient years of follow-up • 30 patients with 5+ years of follow-up • Enrollment complete, continue to follow patients on annual basis
PROTECT AF	800	59 (55 US, 4 EU)	• 1,500 patient years of follow-up • 27 months average follow-up per patient • Enrollment complete, continue to follow patients for 5 years
Continued Access Registry (CAP)	566	26 (24 US, 2 EU)	• Significantly improved safety results • Enrollment complete, continue to follow patients for 5 years
ASAP	126	4 (4 EU)	• Treat patients contra-indicated for warfarin • Currently enrolling up to 150 patients • Patients will be followed for 2 years
EVOLVE	69	3 (3 EU)	• Evaluate next generation WATCHMAN • Enrollment is complete, will follow patients for 1 year
PREVAIL	245	≤50	• Same endpoints as PROTECT AF • Revised inclusion/exclusion criteria • Initial enrollment November 2010 • Enrollment up to 400 randomized, anticipated enrollment completion March, 2012
Total	1,872		

PROTECT AF

Study Objective:	Evaluate the efficacy and safety of the WATCHMAN LAA Closure Device as compared to long-term warfarin therapy in patients with non-valvular atrial fibrillation and $CHADS_2$ score $\geq$ 1
Study Design:	Prospective, randomized (2 Device: 1 Control), non-inferiority study of the Watchman device compared to long-term warfarin therapy
Primary Endpoint:	Non-inferiority of the WATCHMAN device to warfarin therapy for the composite of ischemic stroke, hemorrhagic stroke, systemic embolism and cardiovascular/unexplained death
Additional Endpoints:	Life-threatening events including device embolization requiring retrieval, pericardial effusion requiring intervention, cranial and GI bleeding, and bleeding requiring transfusion $\geq$ 2 units PRBCs
Patient Population:	WATCHMAN n=463 Control n=244 Roll-in n=93
Number of Sites:	59 (55 U.S., 4 EU)

PROTECT-AF:
Overview

- Randomized FDA-IDE Trial
  - Can the WATCHMAN device *replace* Warfarin?
- Efficacy Endpoint:
  - Stroke
  - CV death (& Unknown)
  - Systemic embolism
- 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



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PROTECT-AF:
Overview

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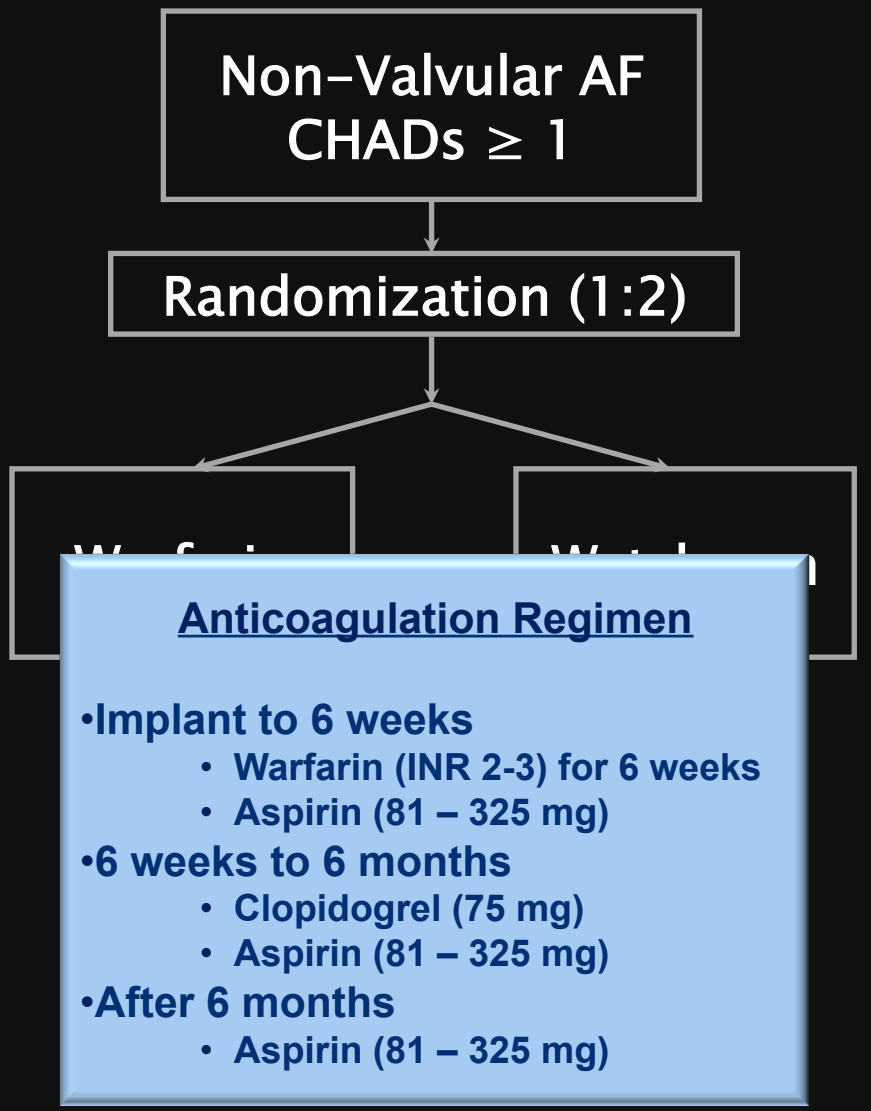

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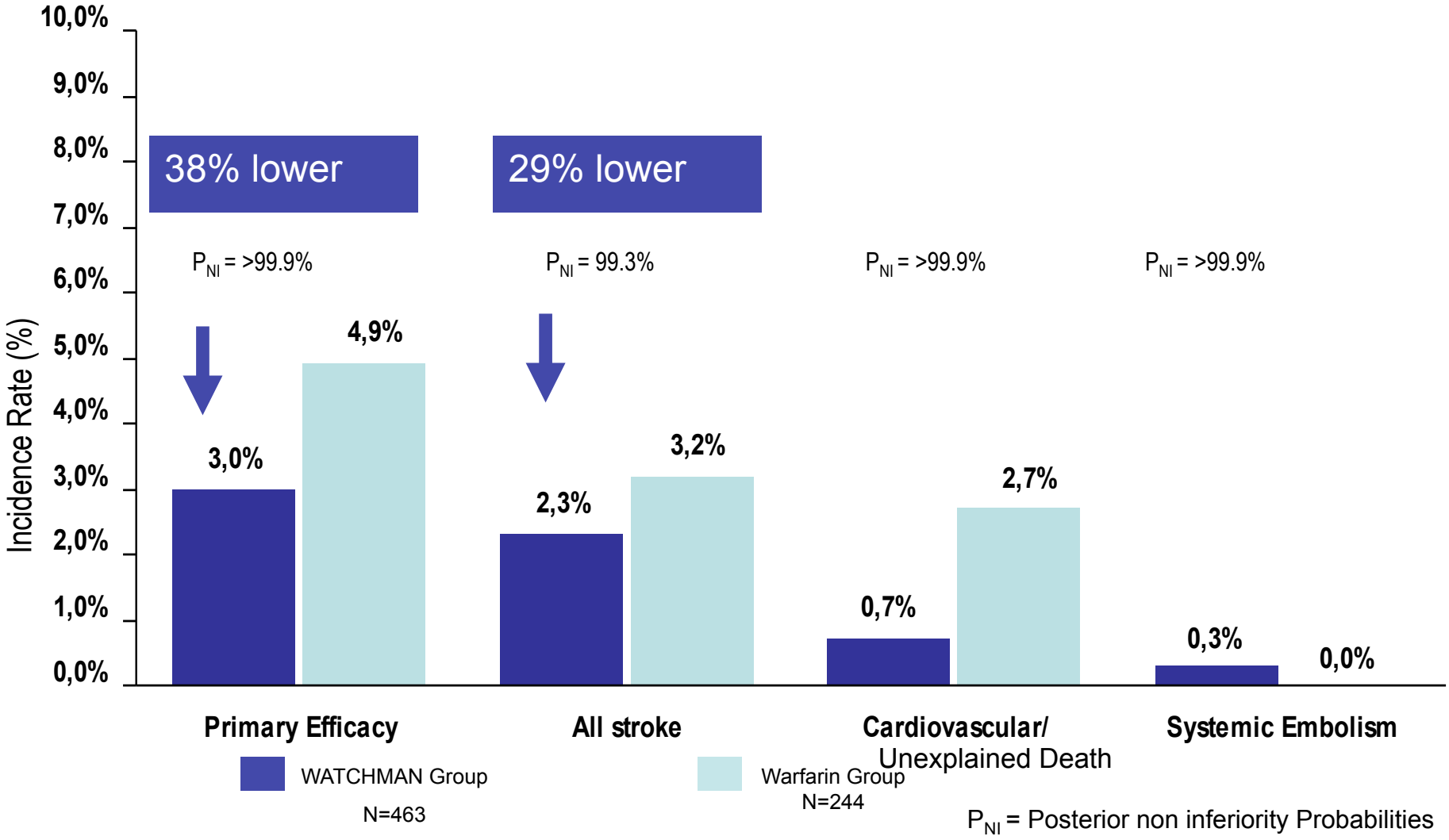
PROTECT AF

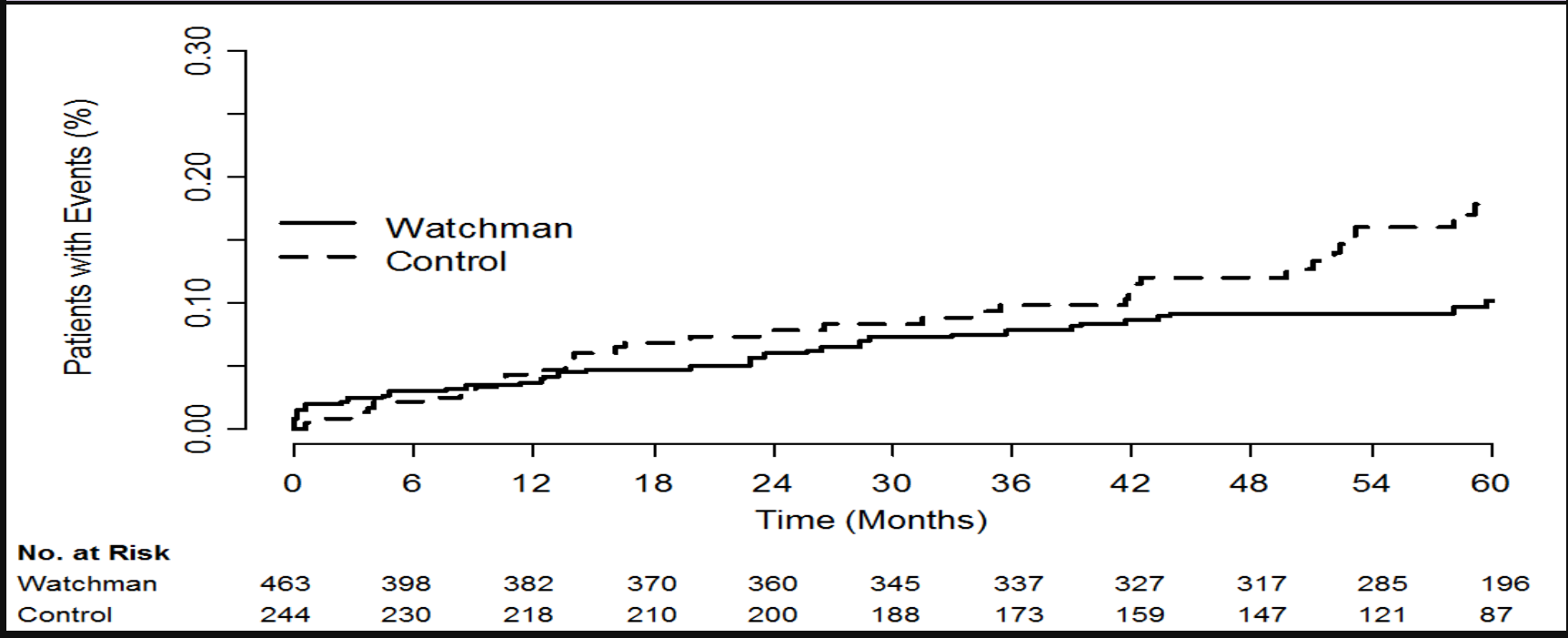
Primary Efficacy Endpoint – *1065 pt yrs*

38% Reduction



PROTECT-AF:
Primary Efficacy 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 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



No. at Risk											
Watchman	463	398	382	370	360	345	337	327	317	285	196
Control	244	230	218	210	200	188	173	159	147	121	87

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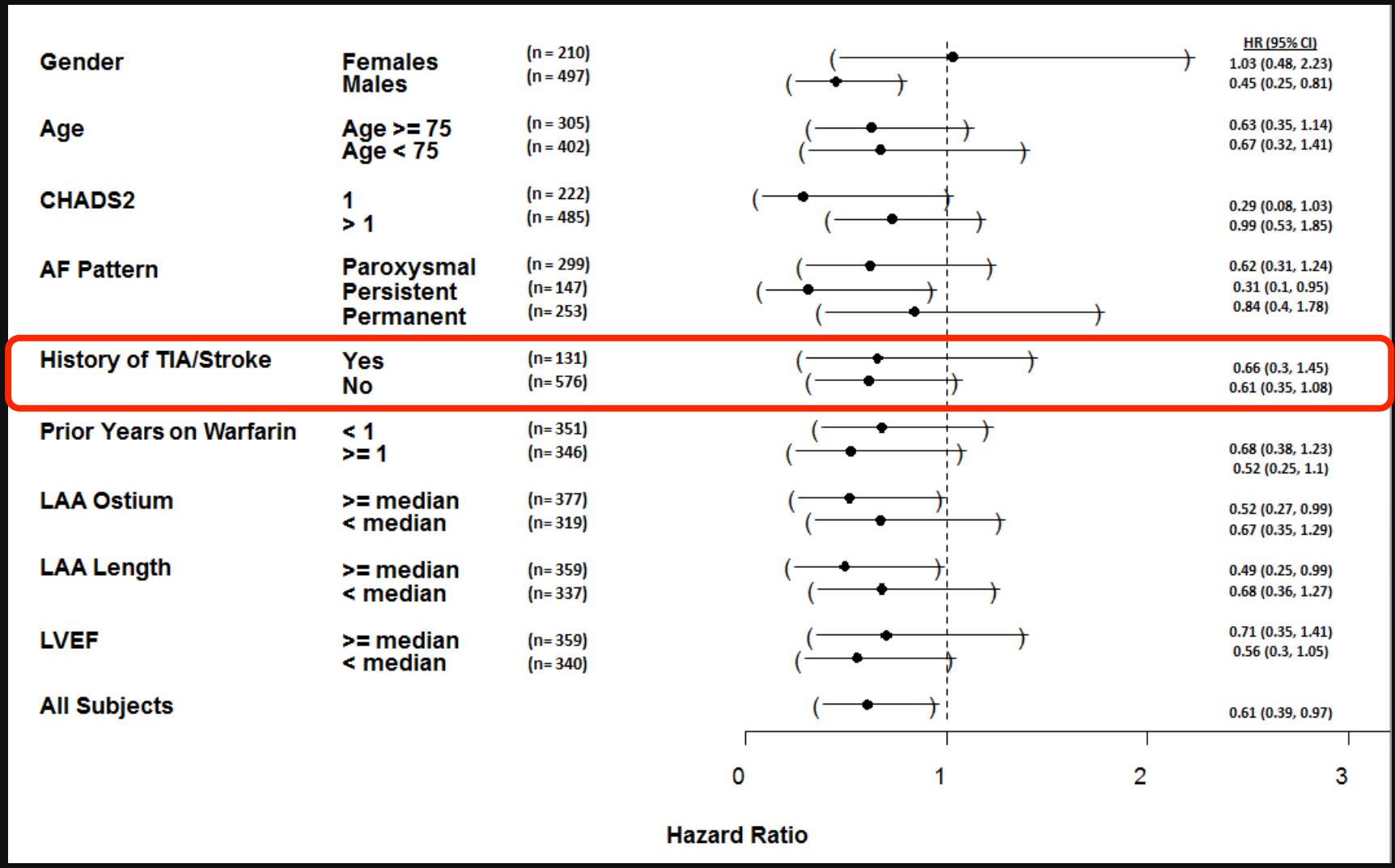
Primary Efficacy Endpoint:
Relative Risks According to Subgroups



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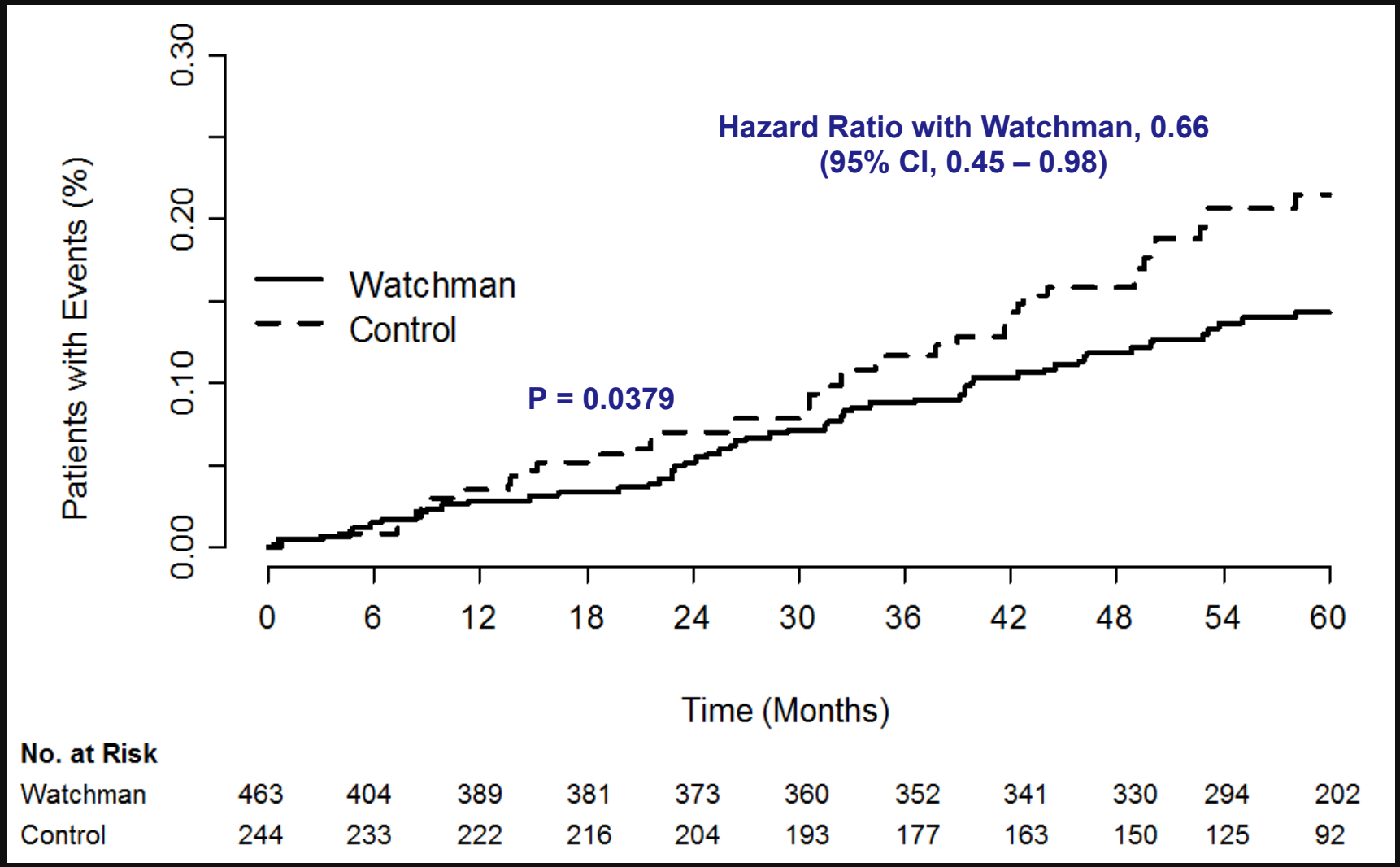
Intention-to-Treat:
All-Cause Mortality



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

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PROTECT AF:
Causes of Death

Cause	Watchman Group (n=463)	Warfarin Group (n=244)	p value
Cardiovascular	13 / 2.8%	12 / 4.9%	0.1973
Cancer	10 / 2.2%	3 / 1.2%	0.5584
Pulmonary	9 / 1.9%	9 / 3.7%	0.2082
Neurologic	5 / 1.1%	3 / 1.2%	1.0000
Multisystem organ failure	5 / 1.1%	1 / 0.4%	0.6700
Hemorrhagic Stroke	2 / 0.4%	7 / 2.9%	0.0098
Other	9 / 1.9%	6 / 2.5%	0.7844

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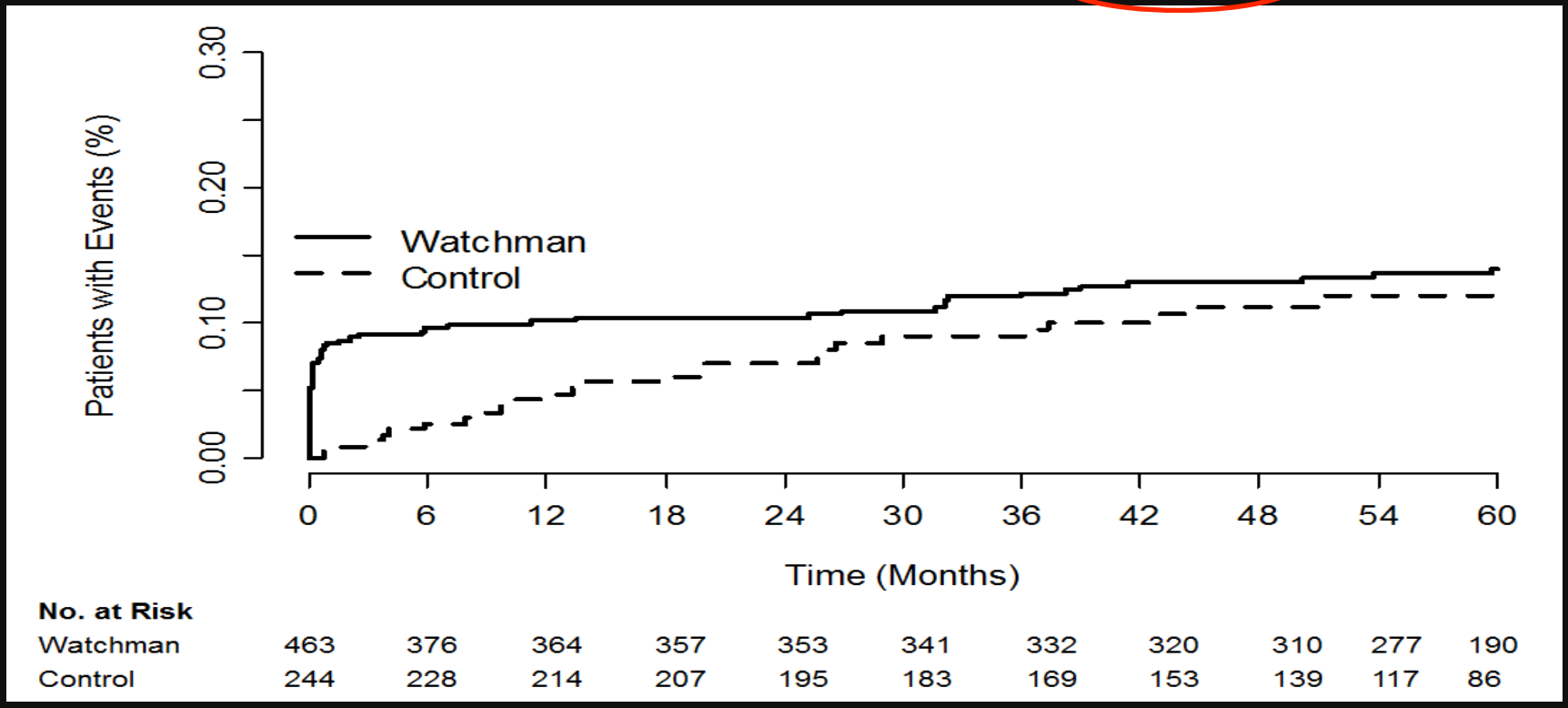
PROTECT AF:
Primary Safety Endpoint

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



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Primary Safety Endpoint:
Components of the Safety Endpoint

Event	Watchman Group (n = 463) Total Events No. (%)	Early Events No. (%)	Late Events No. (%)	Warfarin Group (n = 244) Events No. (%)
Serious pericardial effusion	22 (4.8%)	22 (4.8%)	0 (0.0%)	---
Major bleeding	22 (4.8%)	3 (0.6%)	19 (4.1%)	18 (7.4%)
Procedure-related stroke	6 (1.3%)	5 (1.1%)	1 (0.2%)	---
Device embolization	3 (0.6%)	3 (0.6%)	0 (0.0%)	---
Hemorrhagic stroke	3 (0.6%)	0 (0.0%)	3 (0.6%)	9 (3.7%)
Other	4 (0.9%)	4 (0.9%)	0 (0.0%)	---

Early = First 7 days
Late = After 7 days

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Primary Safety Endpoint:
Components of the Safety Endpoint

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Serious pericardial effusion	22 (4.8%)			
Major bleeding	22 (4.8%)			
Procedure-related stroke	6 (1.3%)			
Device embolization	3 (0.6%)			
Hemorrhagic stroke	3 (0.6%)			
Other	4 (0.9%)			

Pericardial Tamponade

- 22 requiring Tx (4.8% of patients)
  - 15 treated percutaneously
  - 7 underwent surgical intervention
- Extended hospitalization
- No Death or Long-term Disability

Effect of operator experience

- 1st Half of Cohort: 6.3%
- 2nd Half of Cohort: 3.7%

Early = First 7 days
Late = After 7 days

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Secondary Analyses:
Efficacy and Safety

- Post-Procedure Analysis (Pre-Specified Analysis)
  - Excluded patients in whom the device could not be successfully implanted, and excluded events directly related to device implantation
- Per-Protocol Analysis (Pre-Specified Analysis)
  - Outcomes after completing the requisite 45-day period of Warfarin
- Terminal Therapy (Post-Hoc Analysis, Requested by the FDA)
  - Outcomes following discontinuation of Clopidogrel,
  - Defines outcome during long-term therapy with aspirin alone

	Watchman Group (n = 463)		Warfarin Group (n = 244)			
Analysis	Events/ Patient-Years	Observed Rate (Events per 100 Patient-Years) (95% CI)	Events/ Patient-Years	Observed Rate (Events per 100 Patient-Years) (95% CI)	Hazard Ratio (Watchman/Warfarin) (95% CI)	P Value
Primary Safety Outcomes						
Intention-to-treat	60/1666.2	3.6 (2.8,4.6)	27/878.2	3.1 (2.1,4.5)	1.21 (0.78, 1.94)	0.4051
Post-procedure	33/1656.2	2.0 (1.4, 2.8)	27/878.2	3.1 (2.1,4.5)	0.68 (0.41,1.13)	0.1325
Per-protocol	20/1604.4	1.2 (0.8,1.9)	27/864.4	3.1 (2.1,4.6)	0.42 (0.23,0.74)	0.0029
Terminal therapy	13/1321.8	1.0 (0.6,1.7)	27/864.4	3.1 (2.1,4.6)	0.32 (0.17,0.63)	0.0009

PROTECT AF:
Summary

- The LAA is critical to the pathogenesis of stroke
- "Local" therapy with WATCHMAN was superior to Warfarin
  - 40% reduction of stroke / systemic embolism / CV death
  - 60% reduction in Cardiovascular Mortality
  - 34% reduction in All-Cause Mortality
- Efficacy preserved in patients at highest risk (secondary prevention patients = prior stroke/TIA)
- Similar rate of safety events but Bimodal distribution:
  - Event rate diminished with operator experience
    - 2.2% (CAP Registry)
    - 1.9% (PREVAIL: 40% New Operators)

Adapted from HRS LBCT 2013 by Dr. Vivek Reddy
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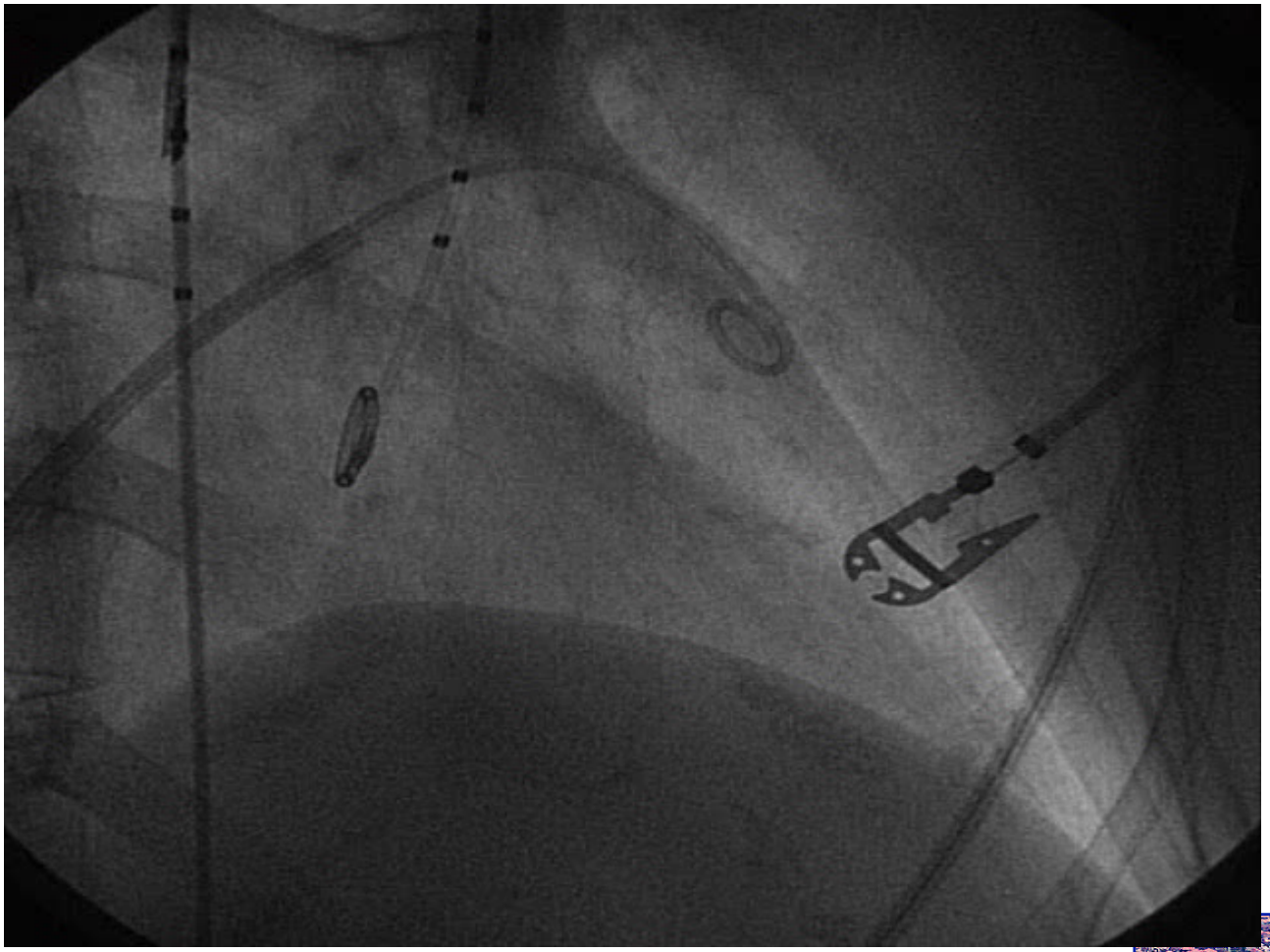
Guidelines - NICE

Guidance

- Current evidence suggests that percutaneous occlusion of the left atrial appendage (LAA) is efficacious in reducing the risk of thromboembolic complications associated with non-valvular atrial fibrillation.
  - With regard to safety, there is a risk of life-threatening complications from the procedure, but the incidence of these is low.
  - Therefore, this procedure may be used provided that normal arrangements are in place for clinical governance, consent and audit.
- Patient selection should be carried out by a multidisciplinary team including a cardiologist and other appropriate clinicians experienced in the management of patients with AF at risk of stroke.
  - Patients should be considered for alternative treatments to reduce the risk of thromboembolism associated with AF, and should be informed about these alternatives.
- Percutaneous occlusion of the LAA is a technically challenging procedure which should only be carried out by clinicians with specific training and appropriate experience in the procedure.
- Procedure should be carried out only in units with on-site cardiac surgery.

National Institute for Health and Clinical Excellence, UK. Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism. Issue date: June 2010, Interventional procedure guidance 349



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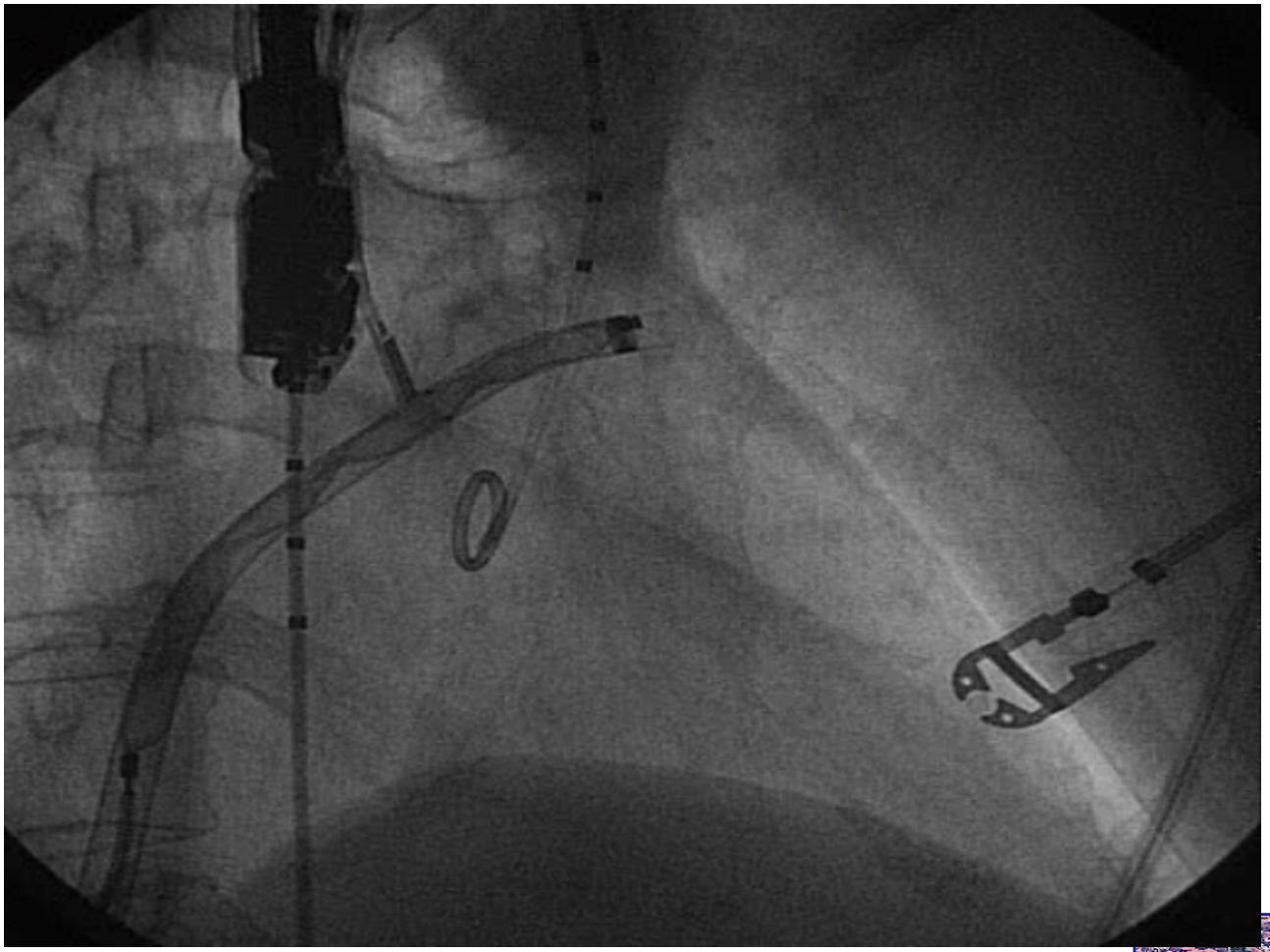

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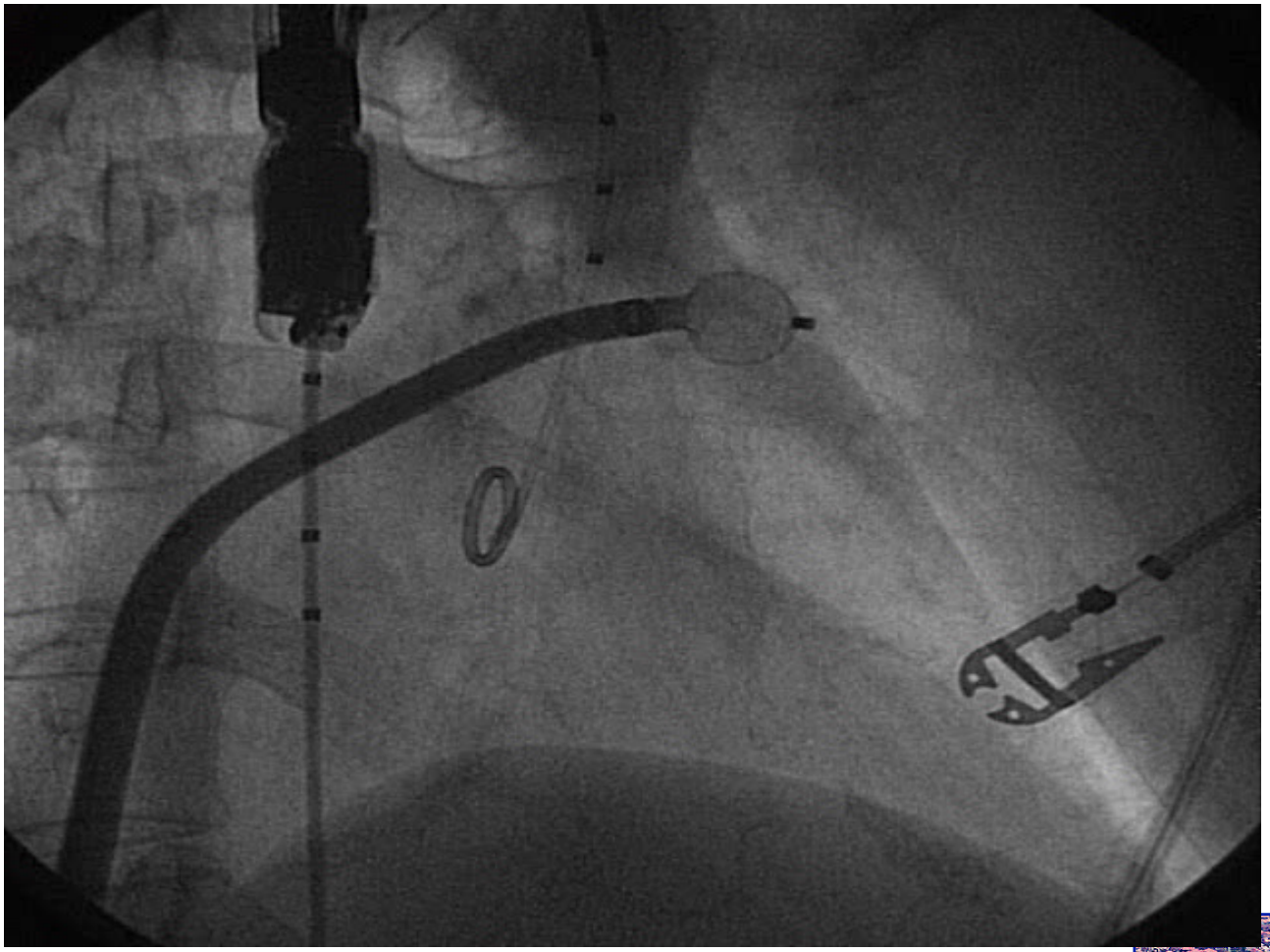

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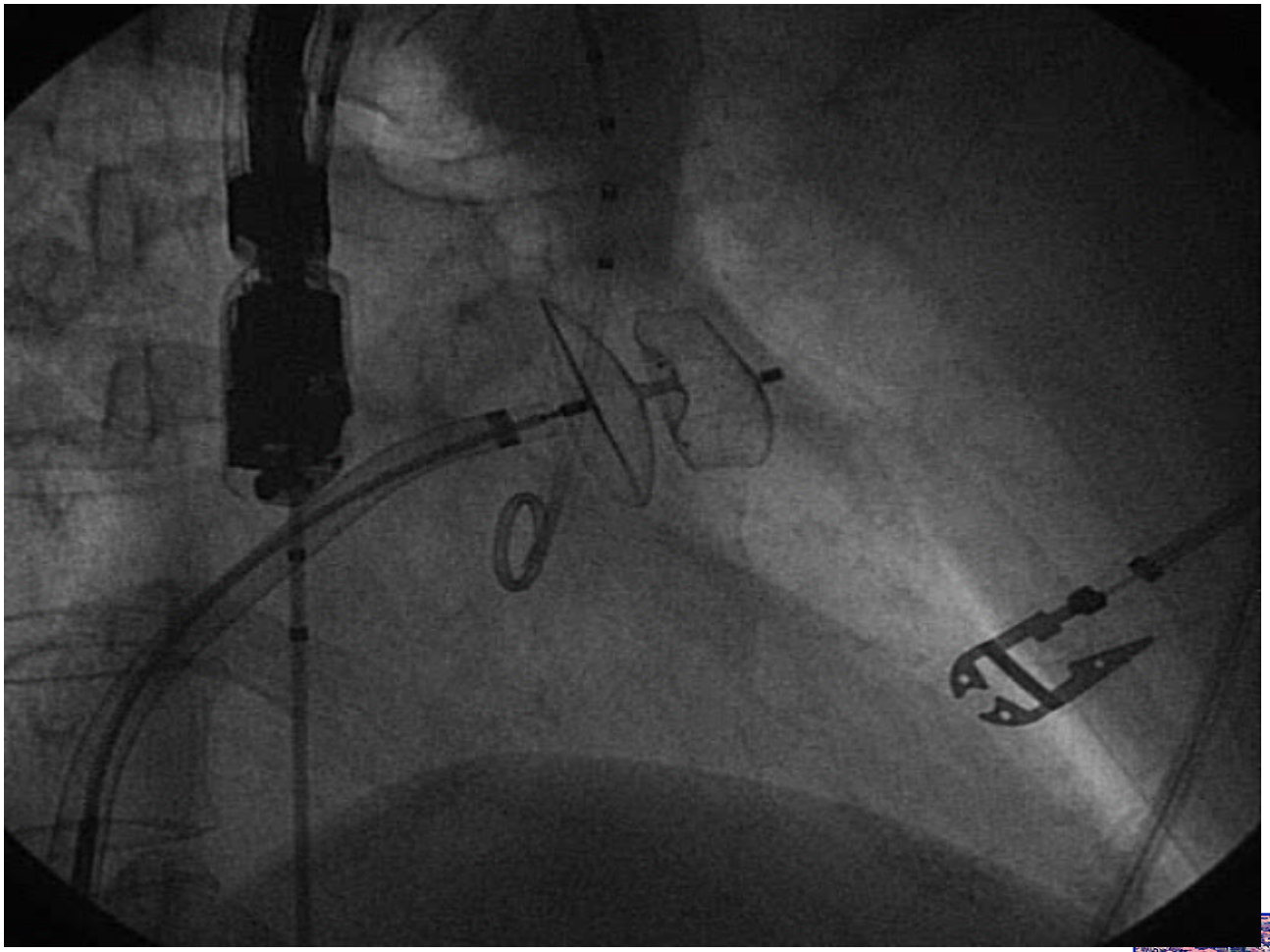

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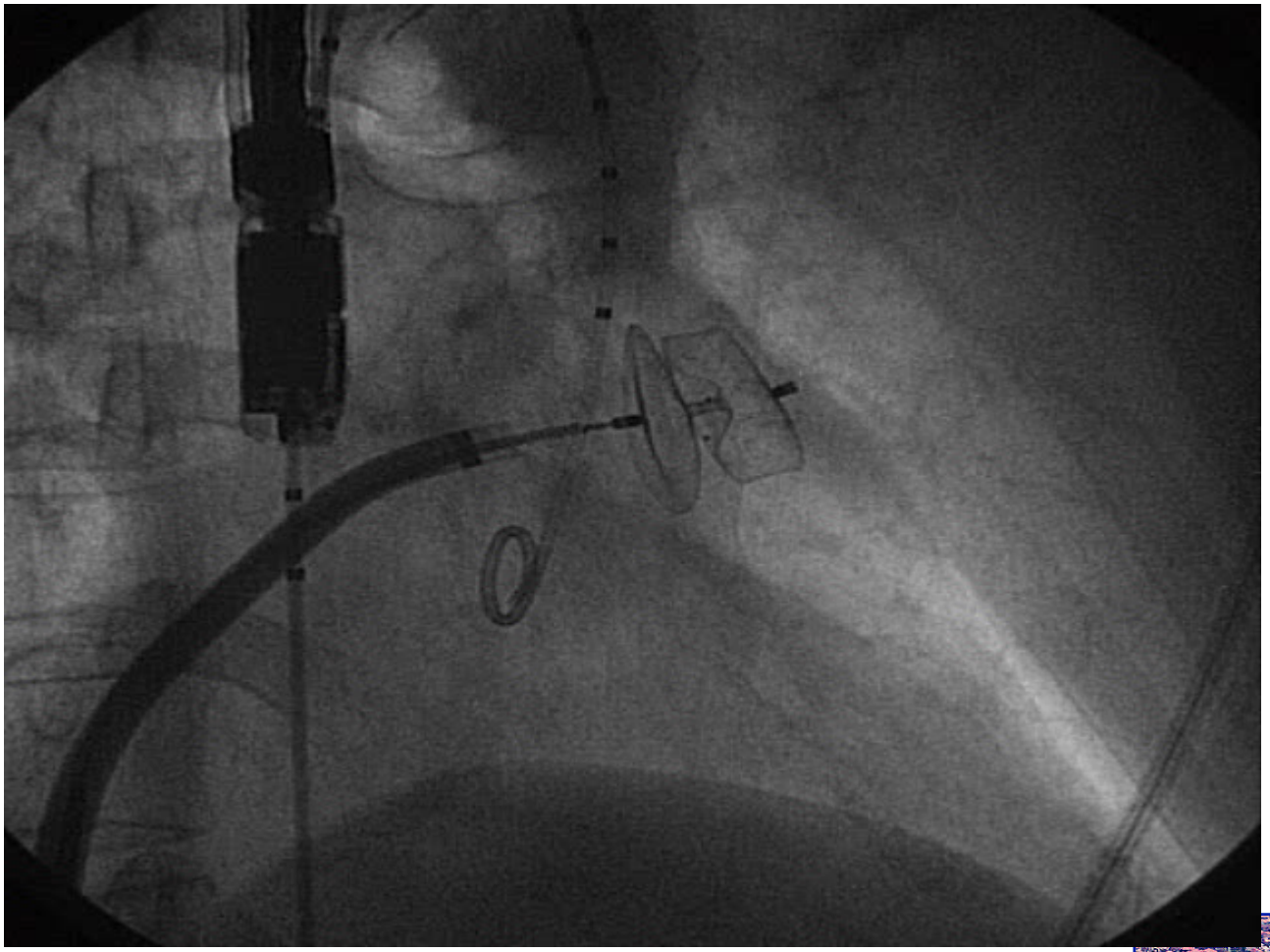

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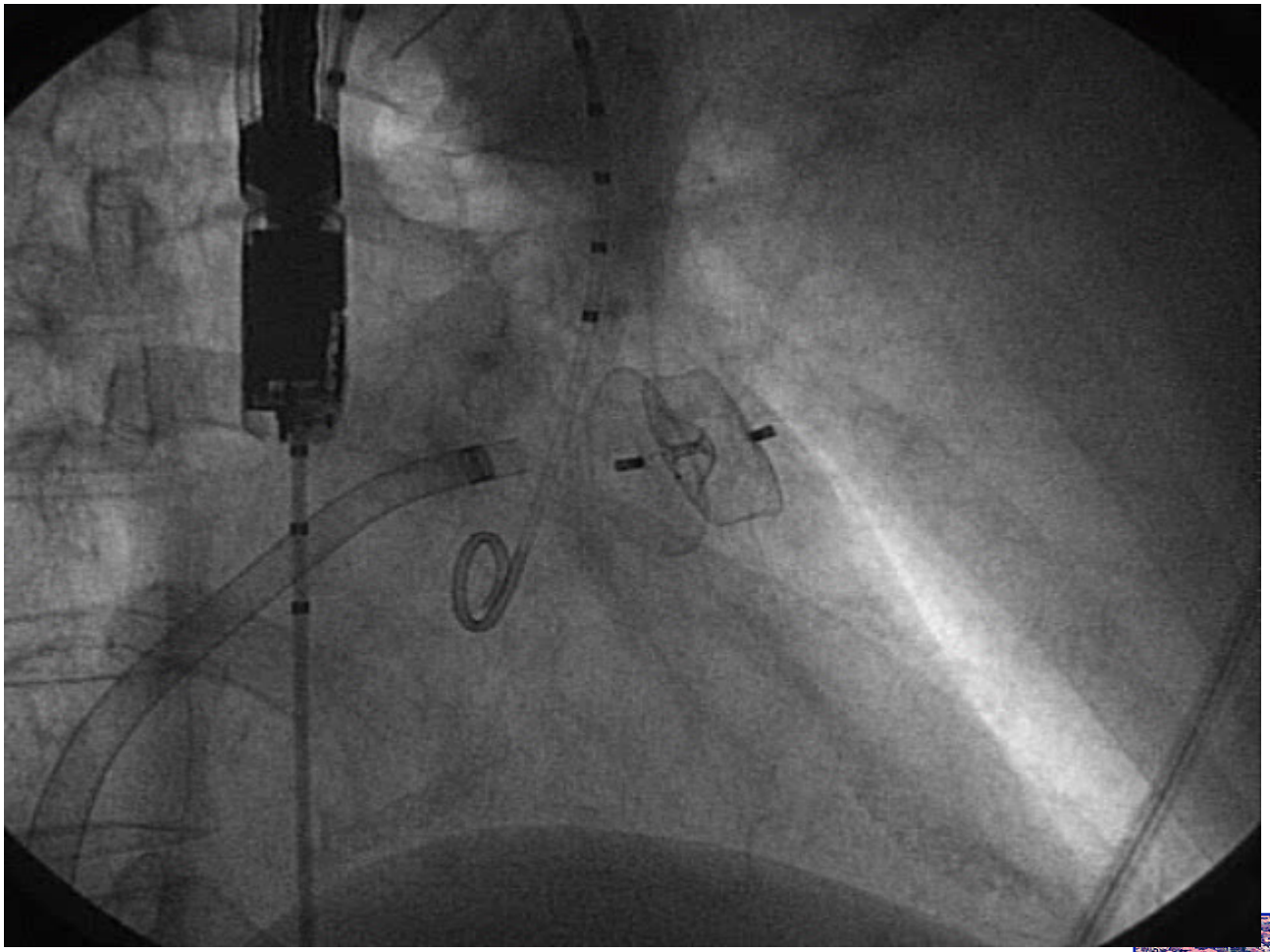

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Série du CHU Henri Mondor

Caractéristiques de la population

- Age: 75±7 (63-87)
- Sexe: 10 hommes
- Type de FA: 10 paroxystiques
- HTA: 12
- Diabète: 9
- Insuffisance cardiaque: 9
- ATCD AVC: 10 ischémiques/ 5 hémorragiques
- CHADS-Vasc: 5 (3-8) (risque annuel 6.7%)
- HAS-BLED: 4.1 (3-5)
- Valvulopathie > grade 2 (1 IM, 1 IAo, 5 IT)

Indications

- Contre indication aux AVK : n=18

-AVC hémorragique=4
-HSD/H méningée=2
-Méningiomes hémorragiques=1
-H digestive récidivante=6
-Hématome musculaire=3
-Cirrhose=1
-Rendu Osler=1

- Récidive thrombo-embolique sous AVK: n=2 (1échec de fermeture)

Paramètres KT

- Taille prothèse: 25.4mm (18-34)
- Durée de procédure: 63±26min (35-130)
- Temps de scopie: 16±10min (6.9-50.1)
- Dose: 74±52gy.cm² (22-211)
- Echec: 1 (non fixation après essai de 3 prothèses) et utilisation de 2 prothèses chez 2 patients pour mauvais sizing

Complications, suivi clinique

- Tamponnade: 0
- Migration: 0
- Thrombose tardive: 1 (non compliquée)
- AVC ischémique: 1 (sur thrombose carotidienne)
- Hémorragie intra cranienne: 0
- Hémorragie autre: 0
- Décès: 1 (complication de cirrhose)

Traitement de sortie

- Aspirine seule: 7 patients
- Aspirine + plavix: 9 patients
- AVK: 2 patient (récidive d'AVC, échec fermeture)
- Aucun: 2 patients

Conclusion

- Nouvelle option thérapeutique pour les patients en FA
- Identification des meilleurs candidats
- Création de l'acte, du GHS et remboursement du DM en cours (GACI, CNPC)
- FLAAC Registry (French Left Atrial Appendage Closure)