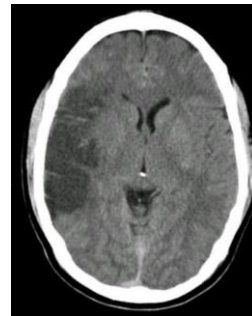


Herz und Hirn aus Sicht des Kardiologen

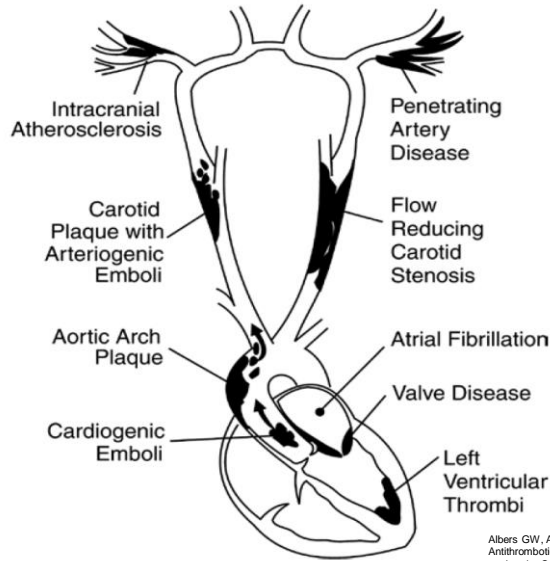
Dr. med Olaf Walter Franzen
Klinik im Park, Zürich

Fiktiver Fall

- 55 jähriger Patient mit Z.n. Schlaganfall
- Doppler Halsgefäße unauffällig
- Frage an Kardiologen : Kardiale Ursache ?

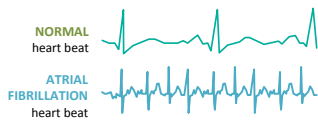


Sources for ischemic stroke



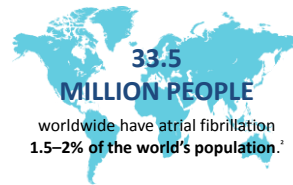
Albers GW, Amarencu P, Easton JD, Sacco RL, Teal P: Antithrombotic and thrombolytic therapy for ischemic stroke: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126 (Suppl 3): pp. 483S-512S

Atrial fibrillation



Atrial fibrillation (AF) is the most common type of cardiac arrhythmia.¹

EUROPEAN ESTIMATES			
	2014 ³	2030 ³	2050 ^{5,6}
Population	500 million	516–525 million	706 million
AF	10 million	14–17 million	25–30 million



AF prevalence increases with age, UP TO 18% OF THE POPULATION over the age of 85¹

1. Camm AJ, Kirchhof P, Lipp G, Schotten U, Savelieva I, Ervilha S, ... Boriani F, H. (2010) Guidelines for the management of atrial fibrillation: European Heart Journal. European Heart Journal, 31(21):2551-2561. 2. Wolf PA, Abbot RD, Benjamin EJ, et al. (1991) Atrial fibrillation: current knowledge and future directions. Epidemiology and prevention. Circulation, 124(11):1183-1191. 3. Subramanian M, Apaloo T, Gaitanaris C, & Arora D. (2011) Trends in the incidence and prevalence of atrial fibrillation in Ireland and future projections. European Heart Journal, 32, 1120-1127. 4. United Nations, Department of Economic and Social Affairs, Population Division (2015). World Population Prospects 2015 – Data Booklet (ST/ESA/SR/A/13/7).

Atrial fibrillation and the stroke connection



Patients with AF are **5x MORE LIKELY** To have a stroke.¹



AF is associated with a **3x HIGHER RISK** Of hearth failure.¹

AF related strokes tend to be more severe, **CAUSE GREATER DISABILITY** And have a worse outcome than non-AF-related strokes.²

AF AND MORTALITY³

50%

Likelihood of death for AF-related strokes within 1 year after a stroke.

27%

Likelihood of death for non-AF-related strokes within 1 year after a stroke.

1. Kannel, W., Pyörälä, K., Castelli, W. P., D'Agostino, R. B., Castelli, W. P., Castelli, W. P., ... & Castelli, W. P. (2008). ACC/AHA/AESC Practice Guidelines. *Circulation*, 114, 700-752.
 2. Mair, C., De Santis, F., Caracciolo, R., Russo, T., Di Biase, A., ... & Di Biase, A. (2016). Contribution of atrial fibrillation to incidence and outcomes of ischemic stroke: results from a population-based study. *Stroke*, 47, 1215-1220.
 3. Bruggeman, R., Rossmann, K., Rott, S., Anderson, F. L., Selim, D., Miller-Nordhorn, J., ... & Willeck, S. N. (2017). The impact of atrial fibrillation on the cost of stroke: the Berlin acute stroke study. *Value Health*, 10(2), 137-143.

Strategies for stroke prevention in AF

VKA Oral anticoagulant (OAC) ¹	Non-vitamin K antagonist oral anticoagulants (NOACs) ¹	Intervention ²
Warfarin (Coumadin™)	Edoxaban Rivaroxaban Dabigatran Apixaban	Ligation Clips Left atrial appendage occlusion devices

Warfarin used to be the gold standard.
 NOACs demonstrated at least similar efficacy and less bleeding risk
 Device interventions are an alternative to patients with contraindication to OACs

1. Bull, C., Guglielmo, R., Braxatorri, C. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014 Mar 15; 383(9921):955-62. Salathielidis, S., Aggrou, M., Chariton, C., Tsiakiris, K., Zargoulidis, P., Katsigannis, N., Kougourtsi, I., Michaloudis, N., Tsouka, T., Arikas, S., Mpsika, A., Belavandi, T., Katsika, A., Zargoulidis, K. 2014 Left atrial appendage occlusion-Where do we stand? *J Pharm Med*. 2014 Mar;136(3):370-7. doi: 10.1093/jpm/2014.03.024.

Balancing the risk¹



Stroke Risk		
CHA ₂ DS ₂ -VASc		
C	Congestive heart failure	1
H	Hypertension	1
A	Age > 75	2
D	Diabetes mellitus	1
S	Stroke/TIA	2
V	Vascular disease	1
A	Age 65-74	1
Sc	Sex-category (female)	1
Maximum score		9

Higher the score the higher the stroke risk (CHA₂DS₂-VASc)

Bleeding Risk		
HAS-BLED		
H	Hypertension	1
A	Renal / liver dysfunction	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (age > 65 yrs)	1
D	Drugs or alcohol abuse	1 or 2
Maximum score		9

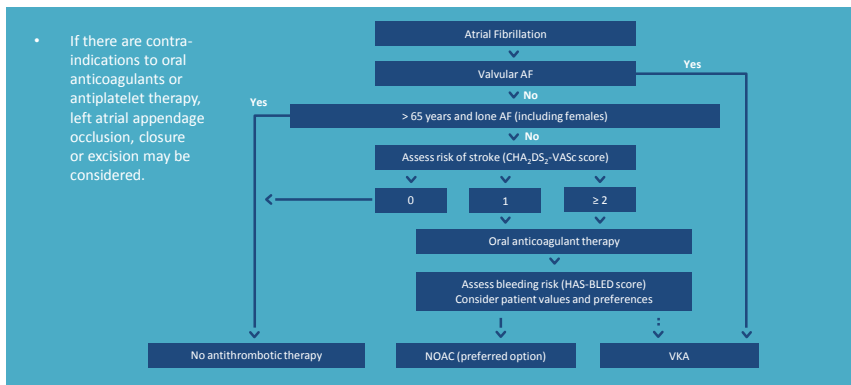
Higher the score the higher the bleeding risk (HAS-BLED)

1. Camm, A., Kirchhof, P., Lip, G., Schotten, U., Savelieva, I., Ernt, S., ... Rutten, F. H. (2016). Guidelines for the management of atrial fibrillation. *European Heart Journal*, 37(36), 2863-2928.

7

European society of cardiology

Guidelines on stroke prevention¹



1. Camm, A. J., Lip, G. Y., De Caterina, R., Sanz-Gonzalez, L., Alcaz, G., Verheijen, S. H., ... ESC Committee for Practice Guidelines (2012). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation—developed with the special contribution of the European Heart Rhythm Association. *Europace*, 14(12), 1385-1413.

8

Patient selection & planning

Warfarin and NOAC (Non Vitamin K oral anticoagulants)

Medication	Trial data	Target	Dose*	Cost (30-day supply)*	Benefits***	Risks***	GI bleeding %/yr v warfarin (full dose) [†]	Discontinuation rate [§]
Warfarin ¹		Vitamin K antagonist	Varies (Titrated to INR)	\$10 (5mg)	<ul style="list-style-type: none"> Inexpensive Reversal agent available Can use in end-stage renal disease (CrCl<15) Well studied 	<ul style="list-style-type: none"> Bleeding Contraindicated in pregnancy Many potential food and drug interactions 		16.1-34.4%
Apixaban ^{1,2} Eliquis™	ARISTOTLE	Xa (inhibitor)	5mg twice daily	\$375	<ul style="list-style-type: none"> Stroke Major bleeding Intracranial haemorrhage All-cause mortality 	<ul style="list-style-type: none"> No reversal agent Caution with use in end stage renal disease 	76 v .86	25-28%
Dabigatran ^{1,3} Pradaxa™	RE-LY	Ila (direct thrombin inhibitor)	150mg twice daily	\$365	<ul style="list-style-type: none"> Stroke Intracranial haemorrhage Reversal agent available 	<ul style="list-style-type: none"> MI GI bleeding Not approved for use in end stage renal disease 	1.51 v 1.02	17-21% at 2 years
Edoxaban ^{1,4} Savaysa™	ENGAGE AF	Xa (inhibitor)	60mg daily	\$300	<ul style="list-style-type: none"> Major bleeding Cardiovascular mortality 	<ul style="list-style-type: none"> No reversal agent Not approved for end stage renal disease 	1.51 v 1.23	25-28%
Rivaroxaban ^{1,5} Xarelto™	ROCKET-AF	Xa (inhibitor)	20mg daily	\$375	<ul style="list-style-type: none"> Intracranial hemorrhage 	<ul style="list-style-type: none"> Bleeding (similar to warfarin) No reversal agent Not approved for use in end stage renal disease 	3.15 v 2.16	22-24%

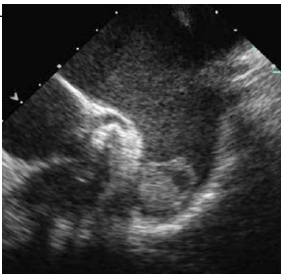
CrCl = creatinine clearance, GI = gastrointestinal, INR = international normalized ratio, MI = myocardial infarction. [†]Dose of non-vitamin K antagonist oral anticoagulant (NOAC) should be adjusted for patients with renal insufficiency. [‡]Cost is approximate and varies with pharmacy. ^{***}Benefits/risks of NOAC compared to warfarin.

1. Patel, J. L., Cameron-Chabak, D., Havelock, G., Luffness, M., Lin, K.W., Vaughan, W., Bond, M.D. (2017) updated clinical practice guideline: Pharmacologic Management of Newly Detected Atrial Fibrillation. American academy of family practitioners - updated clinical practice guidelines
 2. Connors, C. E., Alcorn, J. N., Alshamrani, A., Alcorn, J. D., Park, S. H., Ferris, M., et al. (2011) Apixaban versus Warfarin in Atrial Fibrillation. New England Journal of Medicine, 365, 981-992.
 3. Connors, C. E., Alcorn, J. N., Hylek, E., Borzak, S., Gage, B. J., Fishbein, D. C., et al. (2009) Dabigatran versus warfarin in patients with atrial fibrillation. New England Journal of Medicine, 361, 759-769.
 4. Guglin, R. S., Huff, C. T., Braunwald, E., Wang, S. A., Wilson, S. D., Halperin, J. L., et al. (2013) Edoxaban versus Warfarin in Patients with Atrial Fibrillation. The New England Journal of Medicine, 369, 2093-2104.
 5. Patel, M. R., Mahaffey, K. W., Garg, J., Paley, D., Gagne, G. J., Makhaia, M., et al. (2011) Rivaroxaban versus Warfarin in Patients with Atrial Fibrillation. New England Journal of Medicine, 365, 975-982.
 6. Huff, C. T., Guglin, R. P., Braunwald, E., Hoffman, E. B., Desai, N., Ezekowitz, M. D., et al. (2014) Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials. The Lancet, 383(9921), 955-962.

Wo sind die Thromben bei Vorhofflimmern

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

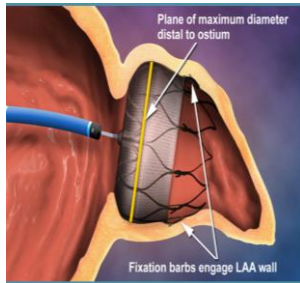
Setting	No. of Patients	Thrombus Location (n, %)		
		LA Appendage	LA Cavity	Total
TEE†	317	66 (20.8)	1 (0.3)	67 (21.1)
TEE	233	34 (14.6)	1 (0.4)	35 (15.0)
Autopsy	506	35 (6.9)	12 (2.4)	47 (9.3)
TEE	52	2 (3.8)	2 (3.8)	4 (7.7)
TEE	48	12 (25.0)	1 (2.1)	13 (27.1)
TEE and operation	171	8 (4.7)	3 (1.8)	11 (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)



Manning et al

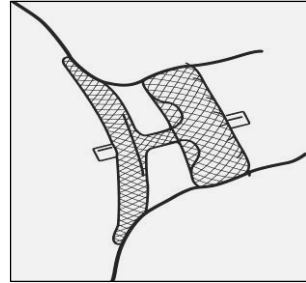
Concept of Closure

Watchman Device
- In the LAA -



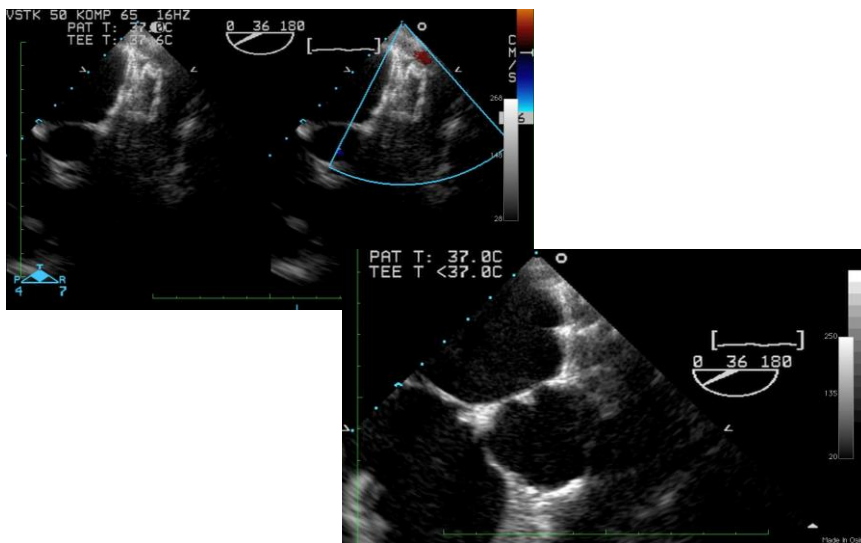
- Possible disadvantage: Slow flow a the surface of the occluder

AMPLATZER Cardiac Plug
- Covers mouth of LAA -

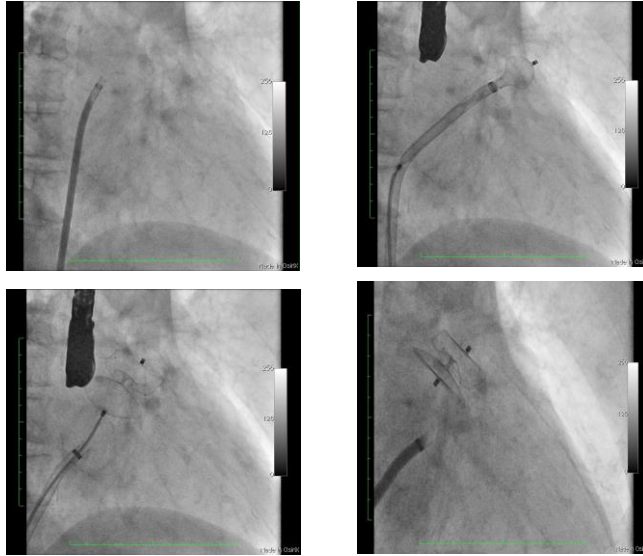


- Edges of disc close to Mitral valve, LUPV, coronaries

Concept of Closure - AGA Cardiac Plug -



Konzept Vorhofohrverschluss - AGA Cardiac Plug -



[Lancet](#), 2009 Aug 15;374(9689):534-42.

Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial.

Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P; PROTECT AF Investigators.

Protect AF

Primary Efficacy Endpoint:

composite endpoint of stroke, cardiovascular death, and systemic embolism

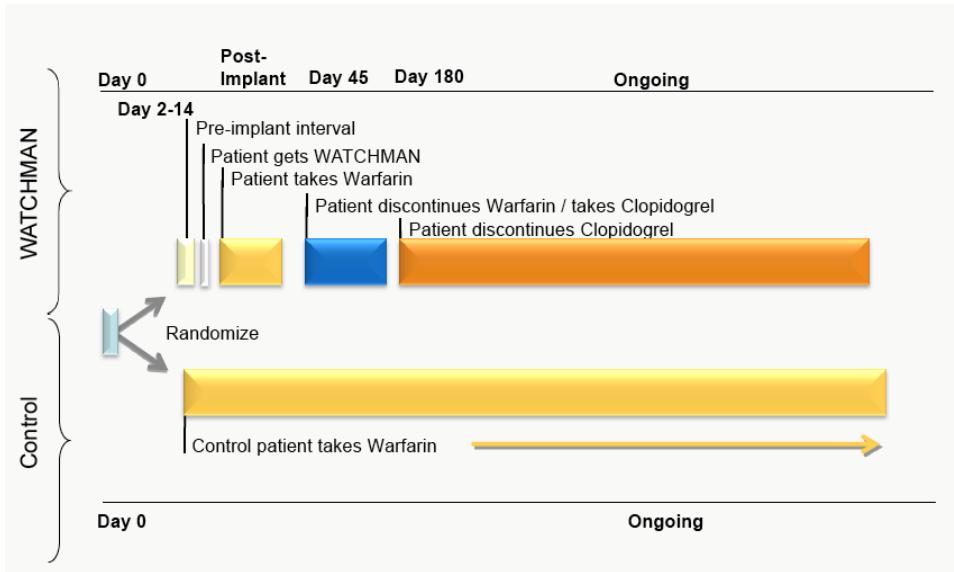
Primary Safety Endpoint:

major bleeding, pericardial effusion, and device embolisation

Lancet, 2009 Aug 15;374(9689):534-42.

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- 76% of randomized patients discontinued Warfarin at 45 days
- 87% of implanted patients discontinued Warfarin at 45 days

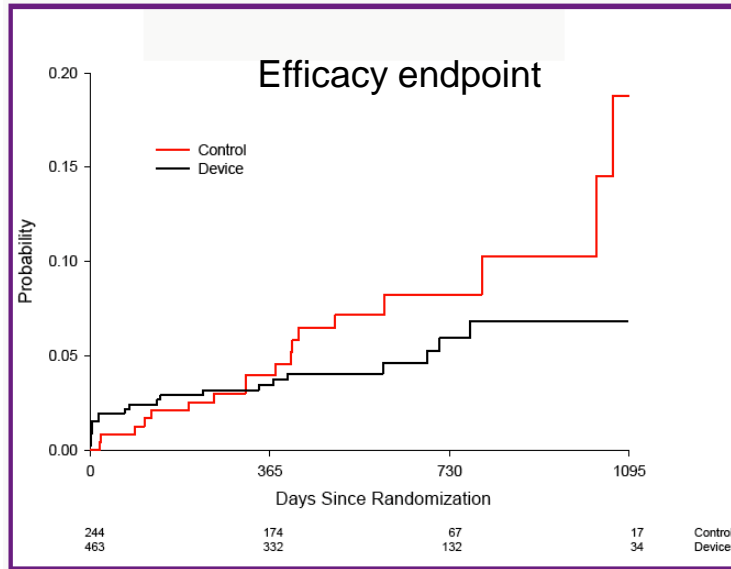
Visit	Warfarin Discontinuation N / Total Implanted (%)	
45 day	348/401	86.7%
6 month	355/385	92.2%
12 month	345/370	93.2%
24 month	293/311	94.2%

Reason for Continuation / Reinitiation	At 45 days N / Total (%)		At 6 months N / Total (%)	
Observation of Flow in the LAA	30	7.5%	14	3.6%
Physician Discretion	23	5.7%	16	4.2%

[Lancet](#), 2009 Aug 15;374(9689):534-42.

Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial.

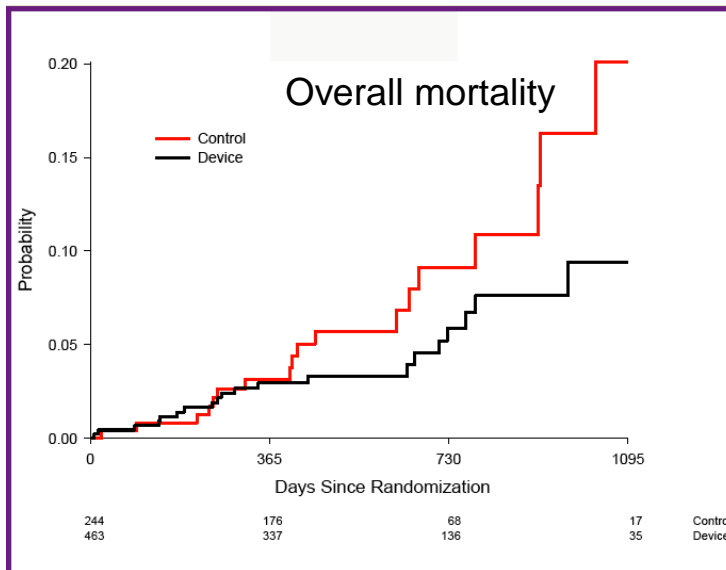
Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sicks P; PROTECT AF Investigators.



[Lancet](#), 2009 Aug 15;374(9689):534-42.

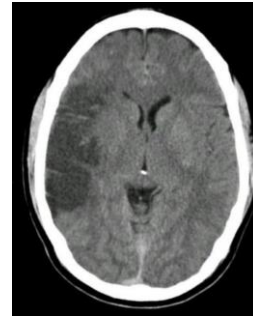
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Fiktiver Fall

- 55 jähriger Patient mit Z.n. Schlaganfall
- Doppler Halsgefäße unauffällig
- Frage an Kardiologen : Kardiale Ursache ?



=> 7 day Holter ECG without Afib

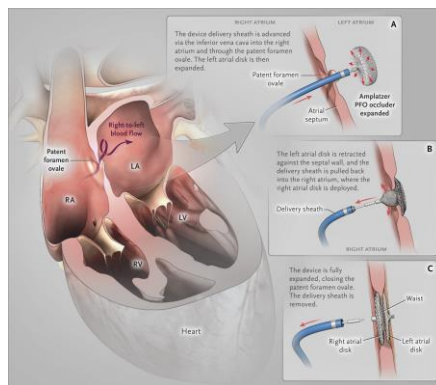
Kontrastecho



TEE



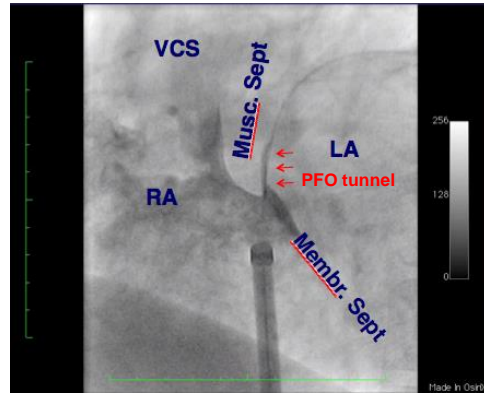
PFO Closure



Farb A et al. N Engl J Med 2017;377:1006-1009.

Case example A

Angiography LAO 50/0



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ORIGINAL ARTICLE

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812

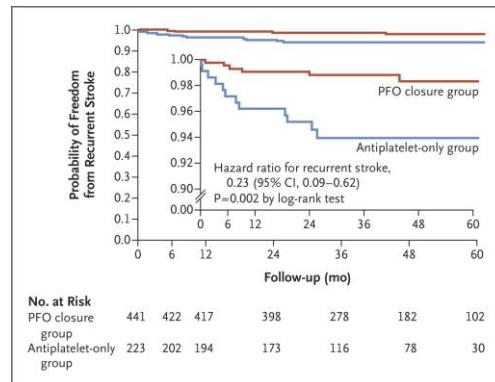
SEPTEMBER 14, 2017

VOL. 377 NO. 11

Patent Foramen Ovale Closure or Anticoagulation
vs. Antiplatelets after Stroke

J.-L. Mas, G. Derumeaux, B. Guillon, E. Massardier, H. Hosseini, L. Mechtouf, C. Arquizan, Y. Béjot, F. Vuillier, O. Detante, C. Guidoux, S. Canaple, C. Vaduva, N. Dequatre-Ponchelle, I. Sibon, P. Garnier, A. Ferrier, S. Timsit, E. Robinet-Borgomano, D. Sablot, J.-C. Lacour, M. Zuber, P. Favrole, J.-F. Pinel, M. Apoil, P. Reiner, C. Lefebvre, P. Guérin, C. Piot, R. Rossi, J.-L. Dubois-Randé, J.-C. Eicher, N. Meneveau, J.-R. Lussion, B. Bertrand, J.-M. Schleich, F. Godart, J.-B. Thambo, L. Leborgne, P. Michel, L. Pierard, G. Turc, M. Barthelet, A. Charles-Nelson, C. Weimar, T. Moulin, J.-M. Juliard, and G. Chatellier, for the CLOSE Investigators*

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Søndergaard L et al. N Engl J Med 2017;377:1033-1042.

DOI: 10.1056/NEJMoa1701582

Summary

- In patients with cryptogenic stroke and PFO the closure of the PFO is an valid option
- LAA closure is an option in patients with atrial fibrillation and an elevated bleeding risk