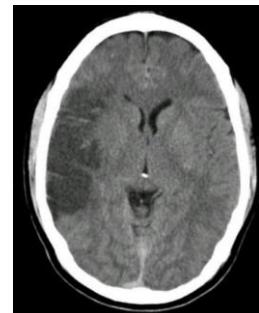


Herz und Hirn aus Sicht des Kardiologen

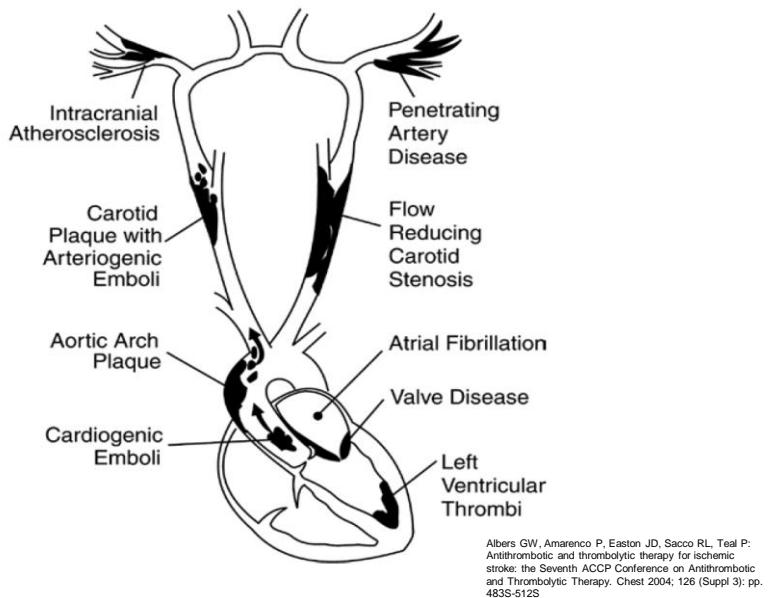
Dr. med Olaf Walter Franzen
Klinik im Park, Zürich

Fiktiver Fall

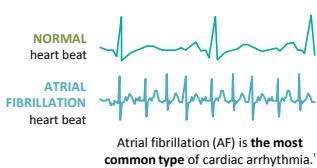
- 55 jähriger Patient mit Z.n. Schlaganfall
- Doppler Halsgefässse unauffällig
- Frage an Kardiologen : Kardiale Ursache ?



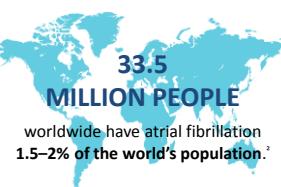
Sources for ischemic stroke



Atrial fibrillation



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 85⁴

¹ Camm A, Kirchhof P, Lip G, Schotten U, Seiwert L, Ernst S, ... Rutter F (2010). Guidelines for the management of atrial fibrillation. *European Heart Journal*; 31(20):2369–2429. ² Kirrhae B, Kamd A, Benjamin E J, Lip G Y, Francis D H, Hoffman A, ... Heeringa J (2013). Projections on the number of individuals with atrial fibrillation in the European Union from 2010 to 2050. *European Heart Journal*; 34(35):2746–2751. ³ Zee-Bergen M, Lercari F, Caracca T, & Dommerich S (2014). Epidemiology of atrial fibrillation: current knowledge and future directions in epidemiology and genetics. *Circulation*; 129(18):1982–1993. ⁵ Steffensdotter H, Aspelin T, Gustafson V, & Annar D (2013). Trends in the incidence and prevalence of atrial fibrillation: global and future projections. *European Heart Journal*; 34:1119–1127. ⁶ United Nations, Department of Economic and Social Affairs, Population Division (2015). *World Population Prospects 2015 – Data Booklet* 201504090A/F177

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 heart 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. Foster, V., Ryden, L. E., Cannon, D. S., Crijns, H. J., Curtis, A. B., Ellenbogen, K. A., ... Winn, S. (2008). ACC/AHA/ESC Practice Guidelines. Circulation, 117, 750-752.
2. Marin, C., De Groot, F., Sacco, S., Mossa, T., Olivieri, L., Totaro, R., & Carletti, A. (2005). Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke, 36, 1115-1119.
3. Brueggemann, H., Rosengart, K., Redl, S., Anderson, F. I., Salter, D., Müller-Nordhoff, F., ... Witztum, J. H. (2007). The impact of atrial fibrillation on the cost of stroke: the Berlin acute stroke study. Value Health, 10(2), 137-143.

5

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. Ruff, C.T., Giugliano, R.P., Braunwald, E. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials. *Lancet.* 2012 Mar 31;380(9851):954-64. 2. Sakatahara, Y., Argiroiu, M., Quattrocchi, C., Tsakiris, K., Zarogoulidis, P., Katsikogiannis, N., Koumpourou, I., Machairiotis, N., Tsoukatos, T., Archan, S., Mylonas, A., Belotti, A., Zarogoulidis, K. 2014 Left atrial appendage occlusion—Where do we stand? *J Thorac Dis.* 2014 May;6(Suppl 1):S70-7. doi: 10.5772/jtd.2013.11.24.

6

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

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 stroke risk (CHA₂DS₂-VASc)

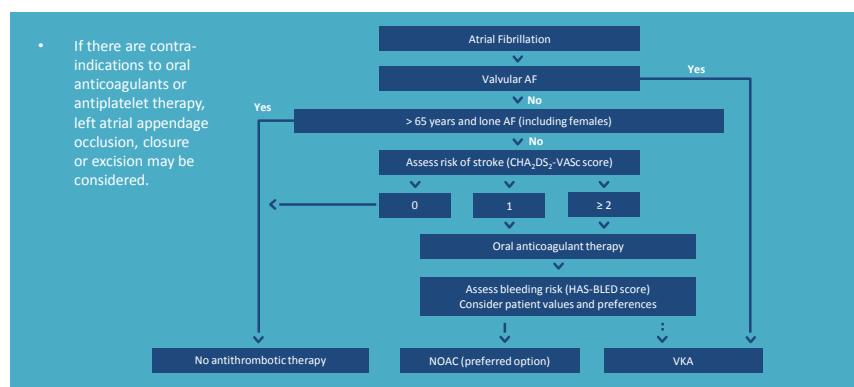
Higher the score the higher the bleeding risk (HAS-BLED)

1. Camm, A., Kirchhof, P., Lip, G., Schotten, U., Savelieva, I., Ernst, S., ... Rutten, F. H. (2010). Guidelines for the management of atrial fibrillation. *European Heart Journal*, 32(19), 2650-2652.

7

European society of cardiology

Guidelines on stroke prevention¹



1. Camm, A. J., Lip, G. Y., De Caterina, R., Savelieva, I., Asfar, D., Hohloser, S. H., ... ESC Committee for Practice Guidelines-CGQ. (2012). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation—developed with the special contribution of the European Heart Rhythm Association. *Europace*, 34(10), 1385-1413.

8

Patient selection & planning
Warfarin and NOAC (Non Vitamin K oral anticoagulants)

Medication	Trial data	Target	Dose*	Cost (\$0 – 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 Most potential food and drug interactions 		16.1–34.4%
Apixaban ^{2,3} Eliquis™	ARISTOTLE	Xa (inhibitor)	5mg twice daily	\$375	<ul style="list-style-type: none"> Stroke Major bleeding Intracranial hemorrhage 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 hemorrhage 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%

DCO = therapeutic dose ratio; 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

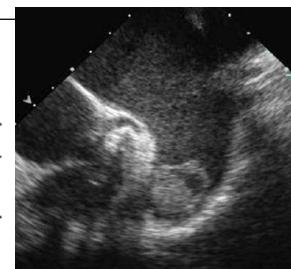
Cost is approximate and varies with pharmacy *benefits/risks of NOACs compared to warfarin

1. Frost J.L., Carpenter-Cook D., Hestberg C., Jeffries M., Lin J.W., Vaughan W., and M.D. 2011. correlated Clinical practice guideline Pharmacologic Management of Newly Detected Atrial Fibrillation. American academy of family practitioners - updated clinical practice guidelines
 2. Granger C.B., Alexander J.M., McMurray J.J., Lopez R.D., Peacock E.M., Herzig M.,...Walentin L. (2013). Apixaban versus Warfarin in Atrial Fibrillation. New England Journal of Medicine, 368(1), 981-992.
 3. Connolly S.J., Bakris G.L., Zelenko M.D., Yusuf S., Eikelboom J., Delaney J., Parekh A.,...Wallentin L. (2009). Dabigatran versus Warfarin in Patients with Atrial Fibrillation. New England Journal of Medicine, 361(27), 2393-2404.
 4. Gruber-Brennah A., Pfeffer M.A., Braunwald E., et al. (2013). Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. New England Journal of Medicine, 368(1), 2393-2404.
 5. Patel M.H., Mahaffey K.W., Garg J., Pan G., Singer D.E., Heitzke W.,...Caliari B.M. (2011). Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. New England Journal of Medicine, 365(24), 883-892.
 6. Huff C.T., Grignani R.P., Braverman E., Hoffman E.S., Desai-Singhal N., Desai E.,...Antman E.M. (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.

9

Wo sind die Thromben bei Vorhofohrflimmern

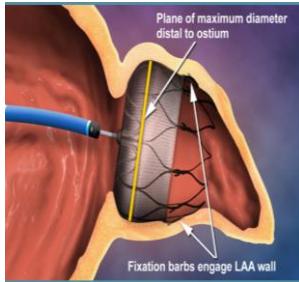
Setting	No. of Patients	Thrombus Location (n, %)		
		LA Appendage	LA Cavity	Total
TEE†	317	66 (20.8)	1 (0.3)	67 (21.1)
TEE	233	34 (14.6)	1 (0.4)	35 (15.0)
Autopsy	506	35 (6.9)	12 (2.4)	47 (9.3)
TEE	52	2 (3.8)	2 (3.8)	4 (7.7)
TEE	48	12 (25.0)	1 (2.1)	13 (27.1)
TEE and operation	171	8 (4.7)	3 (1.8)	11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



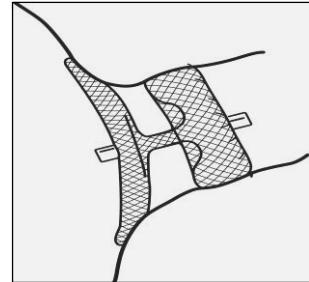
Manning et al

Concept of Closure

Watchman Device
- In the LAA -

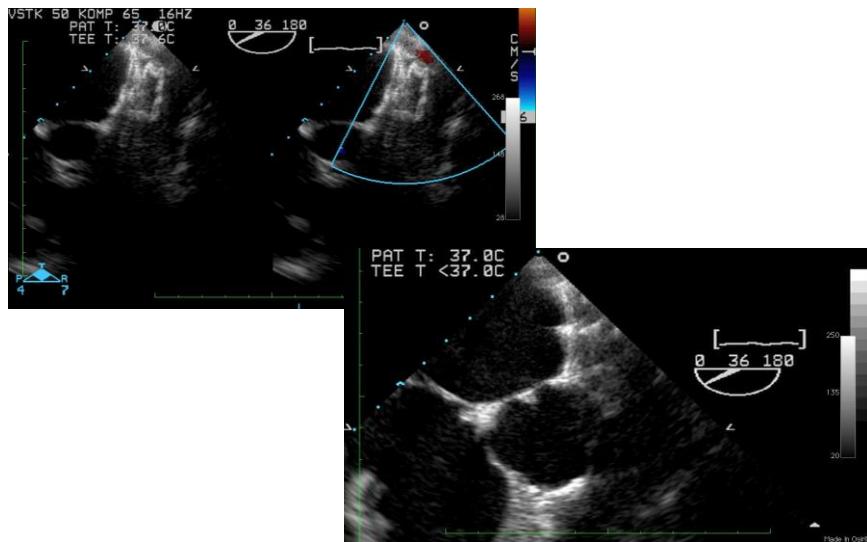


AMPLATZER Cardiac Plug
- Covers mouth of LAA -

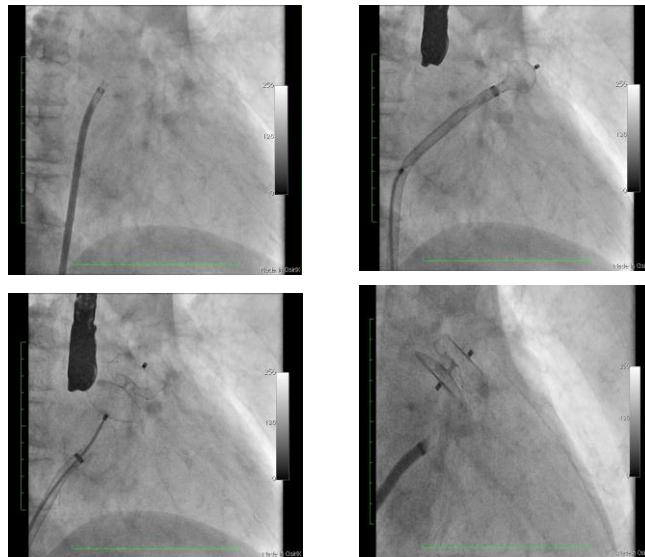


- Possible disadvantage:
Slow flow at the surface
of the occluder
- Edges of disc close to Mitral
valve, LUPV, coronaries

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

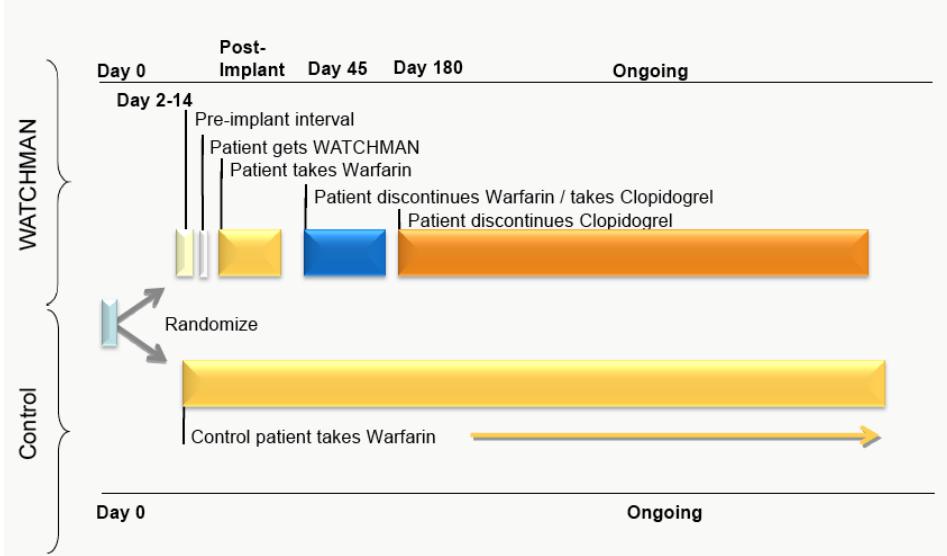
Primary Safety Endpoint:

major bleeding, pericardial effusion, and device embolisation

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

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.



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.

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

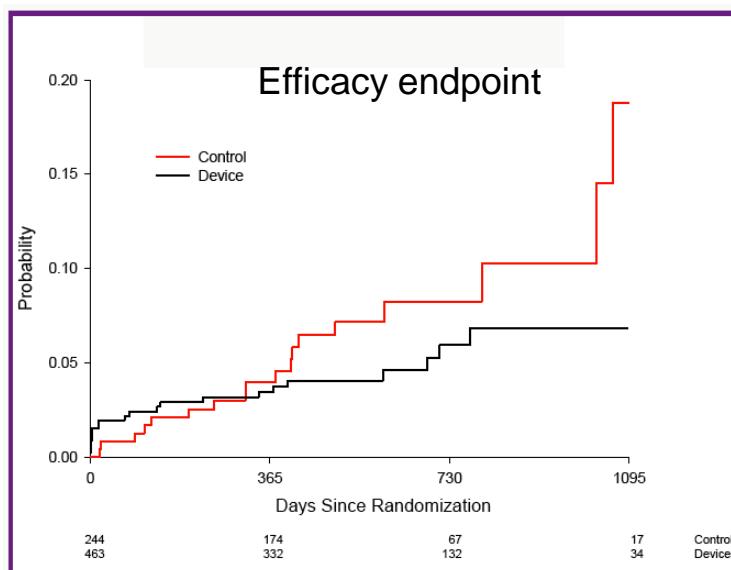
Visit	Warfarin Discontinuation N / Total Implanted (%)	
45 day	348	401 86.7%
6 month	355	385 92.2%
12 month	345	370 93.2%
24 month	293	311 94.2%

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.

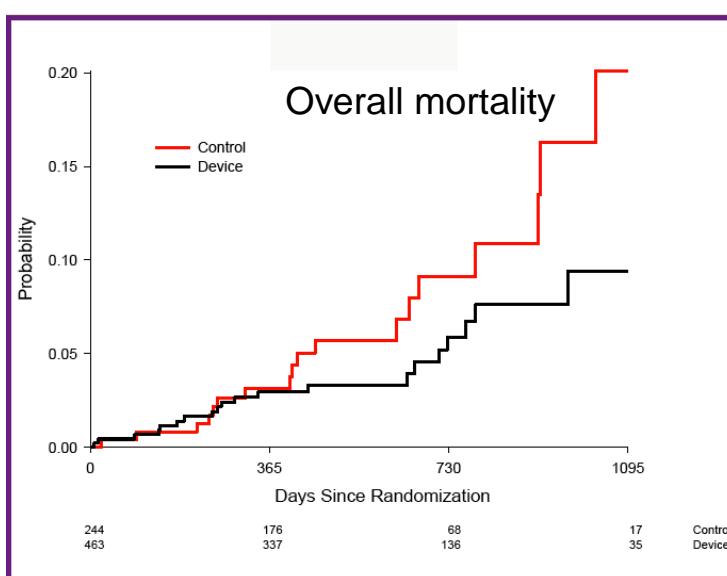
Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P; PROTECT AF Investigators.



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

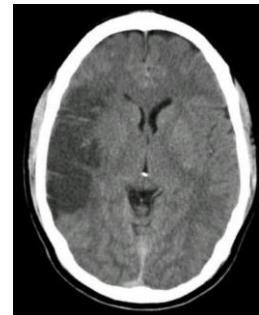
Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial.

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



Fiktiver Fall

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



=> 7 day Holter ECG without Afib

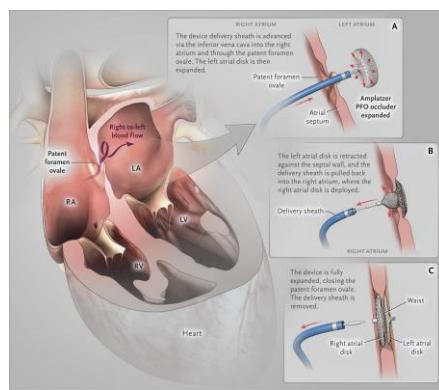
Kontrastecho



TEE



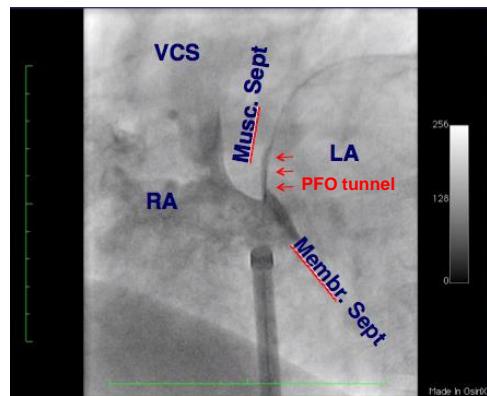
PFO Closure



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

Case example A

Angiography LAO 50/0



The NEW ENGLAND JOURNAL of MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

The NEW ENGLAND JOURNAL of MEDICINE

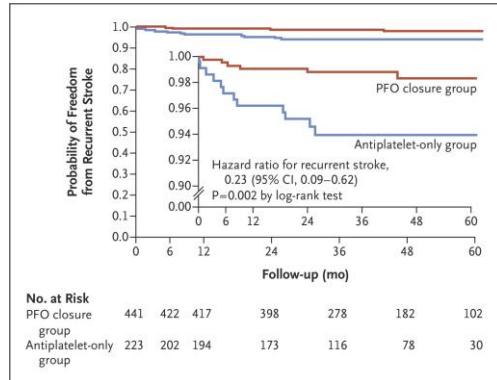
ESTABLISHED IN 1812

SEPTEMBER 14, 2017

VOL. 377 NO. 11

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

J.-L. Mas, G. Derumeaux, B. Guillou, E. Massardier, H. Hosseini, L. Mechtouff, C. Arquizan, Y. Béjot, F. Vuillier, O. Detante, C. Guidoux, S. Canaple, C. Vadiva, N. Degautre-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. Lusson, B. Bertrand, J.-M. Schleich, F. Godart, J.-B. Thambo, L. Leborgne, P. Michel, L. Pierard, G. Turc, M. Barthéléty, A. Charles-Nelson, C. Weimar, T. Moulin, J.-M. Juliard, and G. Chatellier, for the CLOSE Investigators*



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

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 elvated bleeding risk