LAA occlusion

Karl Heinz Kuck
AK St. Georg, Hamburg

Disclosure Statement

Research Grants	Biosense Webster, Stereotaxis, Medtronic, St. Jude, Cardiofocus, Abbott
Consultant / Advisory Board	St. Jude, Edwards, Stereotaxis, Mitralign, Cardiofocus, BMDSys, ACT, Maya, Apama, Topera, Recor, Endosense, SynapticMed,
Ownership Interests	Cardiac implants, Jena Valve
Speaker‘s Bureau Honoraria	Biosense Webster, Medtronic, St. Jude, Abbott, Cardiofocus, Biotronik
Fellowship Support	None
Other	None
Off-label drugs/devices	None

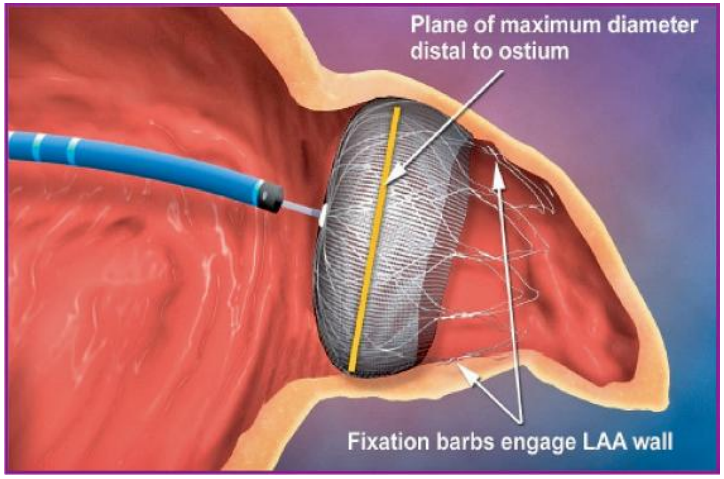
Rational for LAA closure device

- Left atrial appendage: 90% source of thrombembolic stroke
- Warfarin therapy is associated with a significant bleeding risk
- LAA occlusion and ASS monotherapy may reduce stroke and bleeding risk

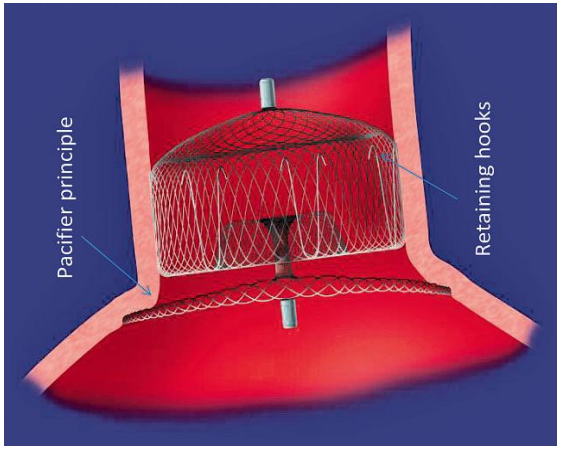
Heart Disease and Stroke Statistical Update: 2009 Update Circulation 1-27-09, AHA Statistical Update: Heart Disease and Stroke Statistics-2008, Update; NHLBI and ARIC Circulation 1-29-08, Hylek EM, et.al. NEJM.

LAA occluder types

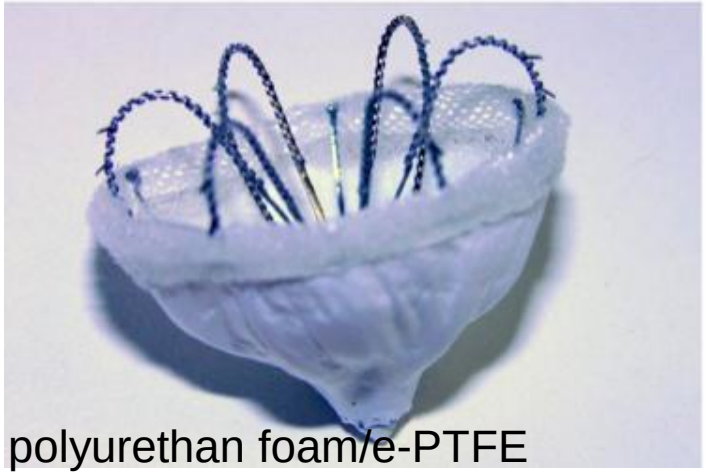
Watchman



ACP Cardiac plug

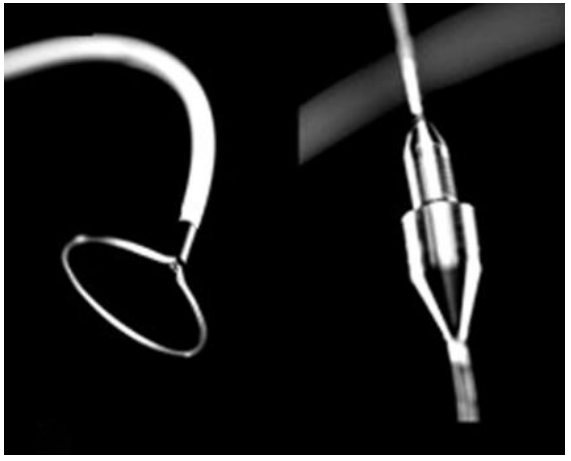


Coherex WaveCrest



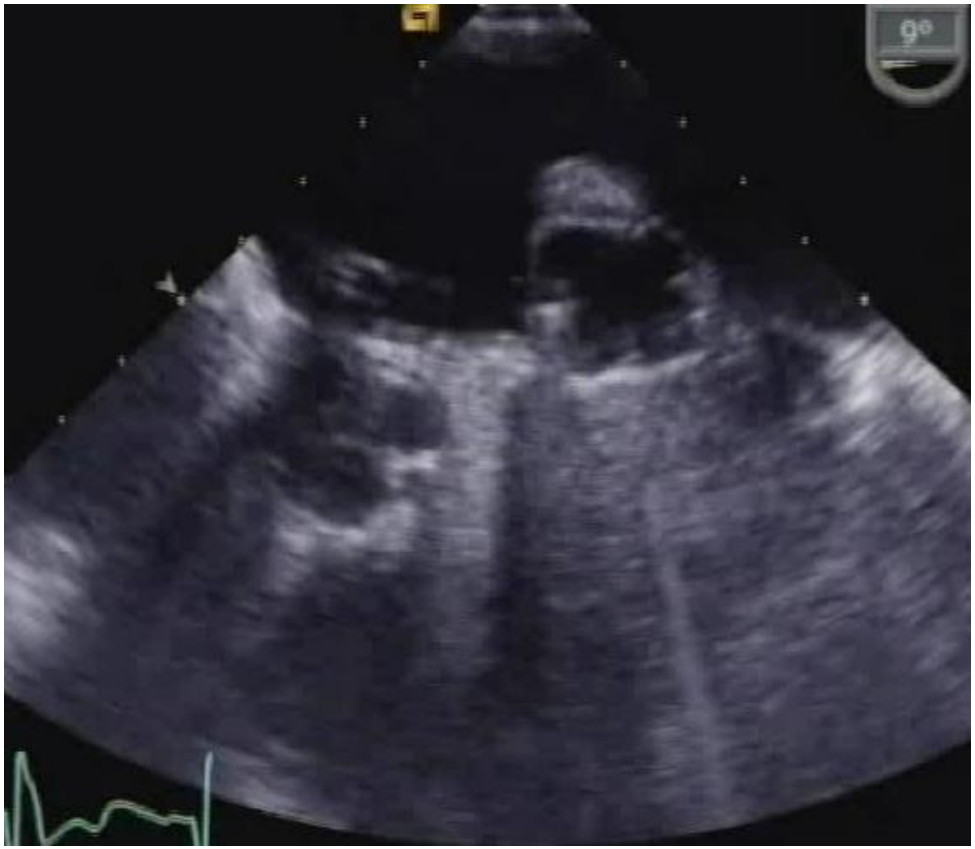
polyurethan foam/e-PTFE

LARIAT



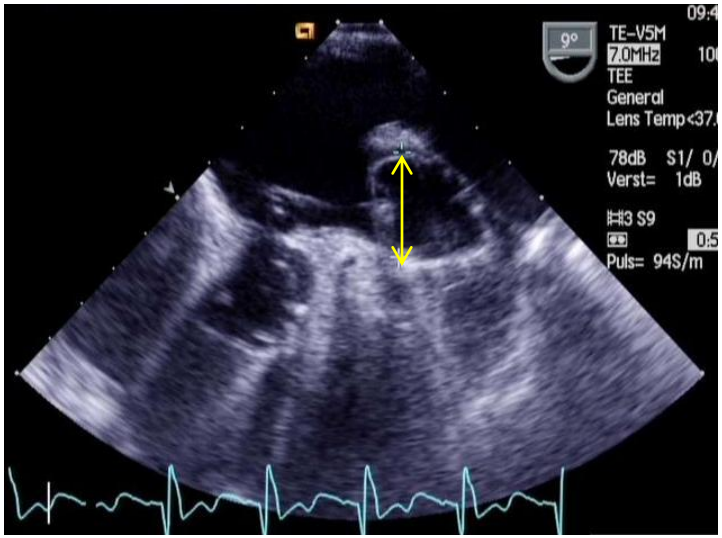
Watchman Implantation

Maximum measured LAA ostium (mm)	Implant diameter (mm)
17 -19.5	21
20 - 22.9	24
23 - 25.9	27
26 – 28.9	30
29 – 31.9	33

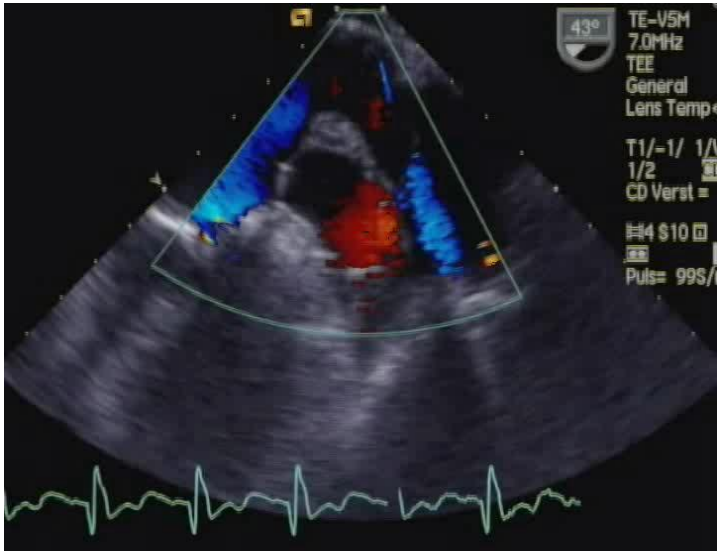


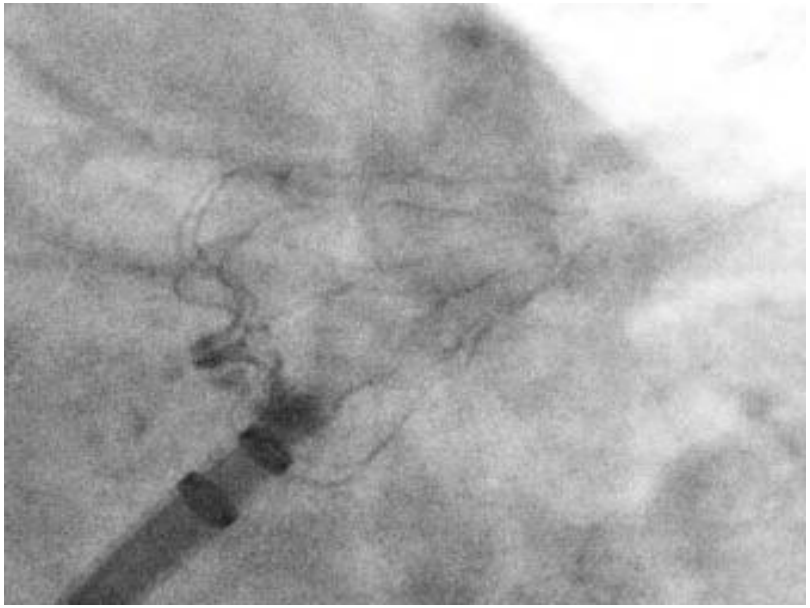
- device selection according to measurements
- Implantation of 21mm Watchman Occluder

Watchman Implantation



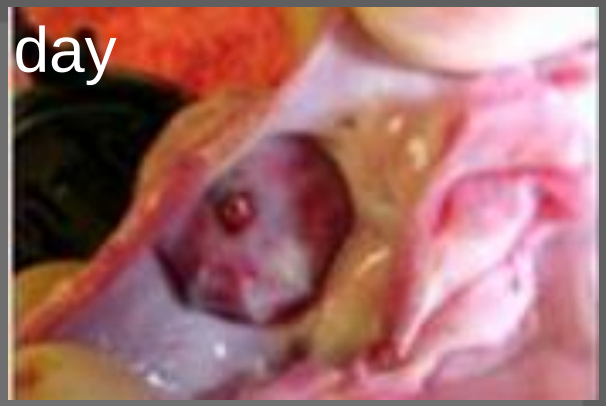
- Check position
- Check device compression
- Check residual flow
- Tug test
- Release



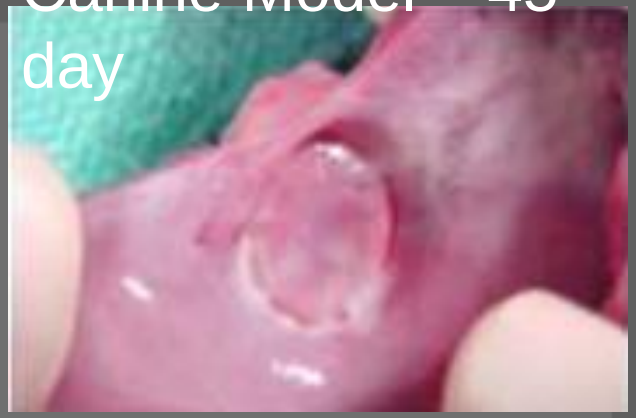


WATCHMAN® Healing Process

Canine Model – 30 day



Canine Model – 45 day



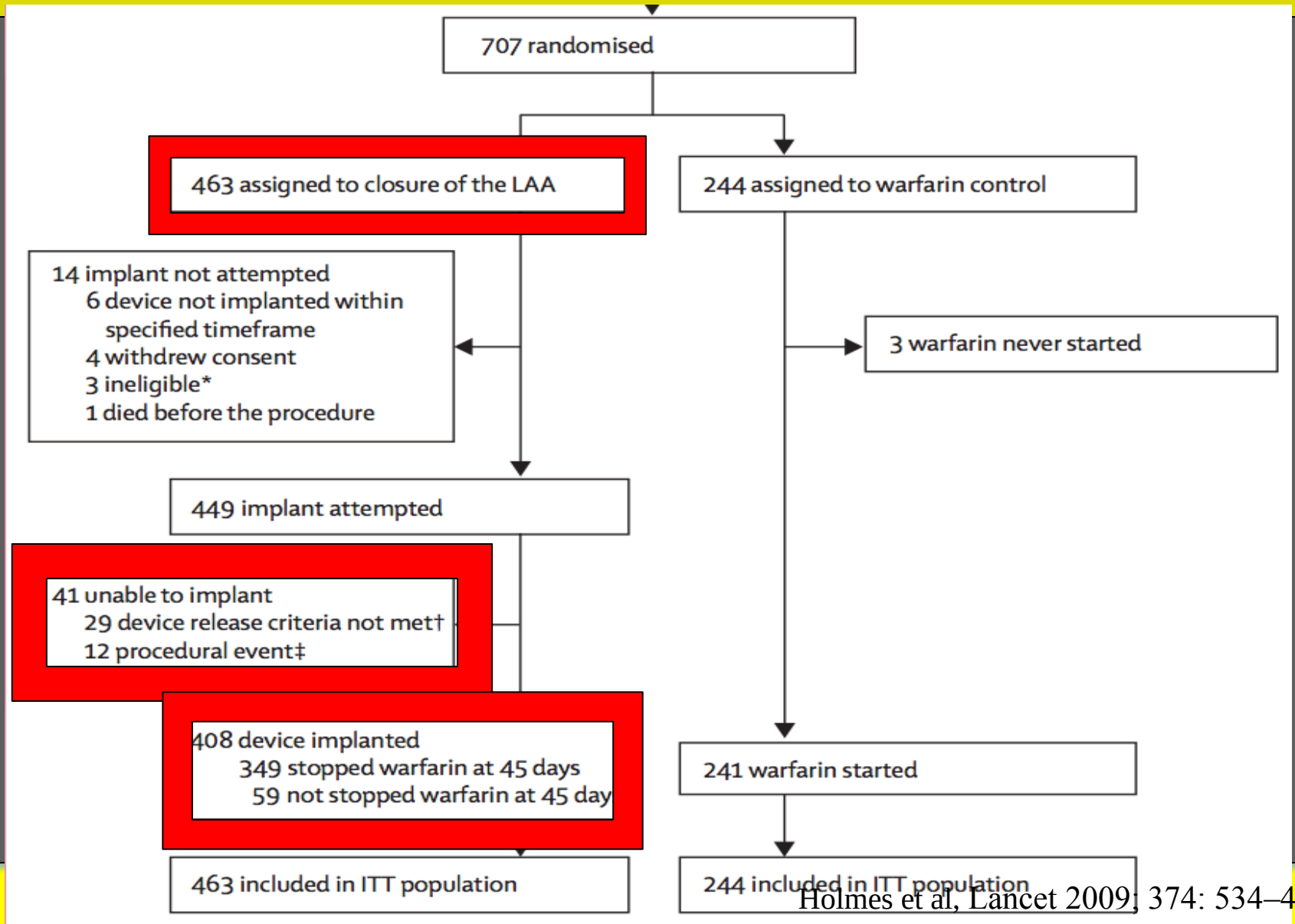
Human pathology: 9 months post-implant (non-device related)

What evidence do we have?

WATCHMAN Clinical Studies

STUDY	PATIENTS	
Pilot	66	• 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[1]	800	• 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)[2]	566	• Significantly improved safety results • Enrollment complete, continue to follow patients for 5 years
ASAP	150	• Treat patients contra-indicated for warfarin • Enrollment complete, continue to follow patients for 2 years
EVOLVE	69	• Evaluate next generation WATCHMAN • Enrollment complete, continue to follow patients for 1 year
PREVAIL	461	• Same endpoints as PROTECT AF • Revised inclusion/exclusion criteria • Initial enrollment November 2010 • Enrollment completed, continue to follow patients for 5 years
Total	2,112	

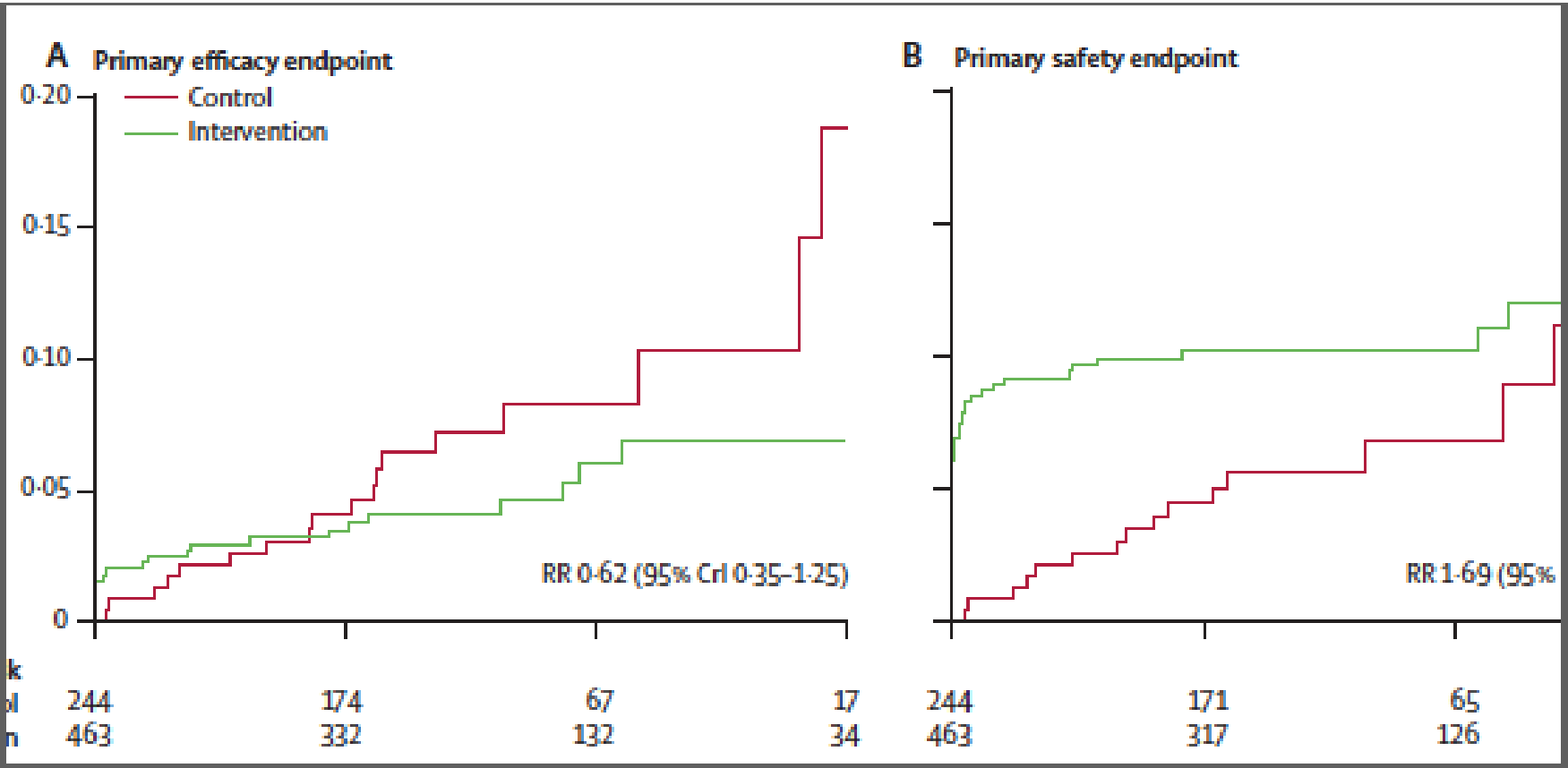
Protect AF Study



Holmes et al, Lancet 2009; 374: 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

*David R Holmes, Vivek Y Reddy, Zoltan G Turi, Shephal K Doshi, Horst Sievert, Maurice Buchbinder, Christopher M Mullin, Peter Sick, for the PROTECT AF Investigators**



Holmes et al, Lancet 2009; 374: 534–42

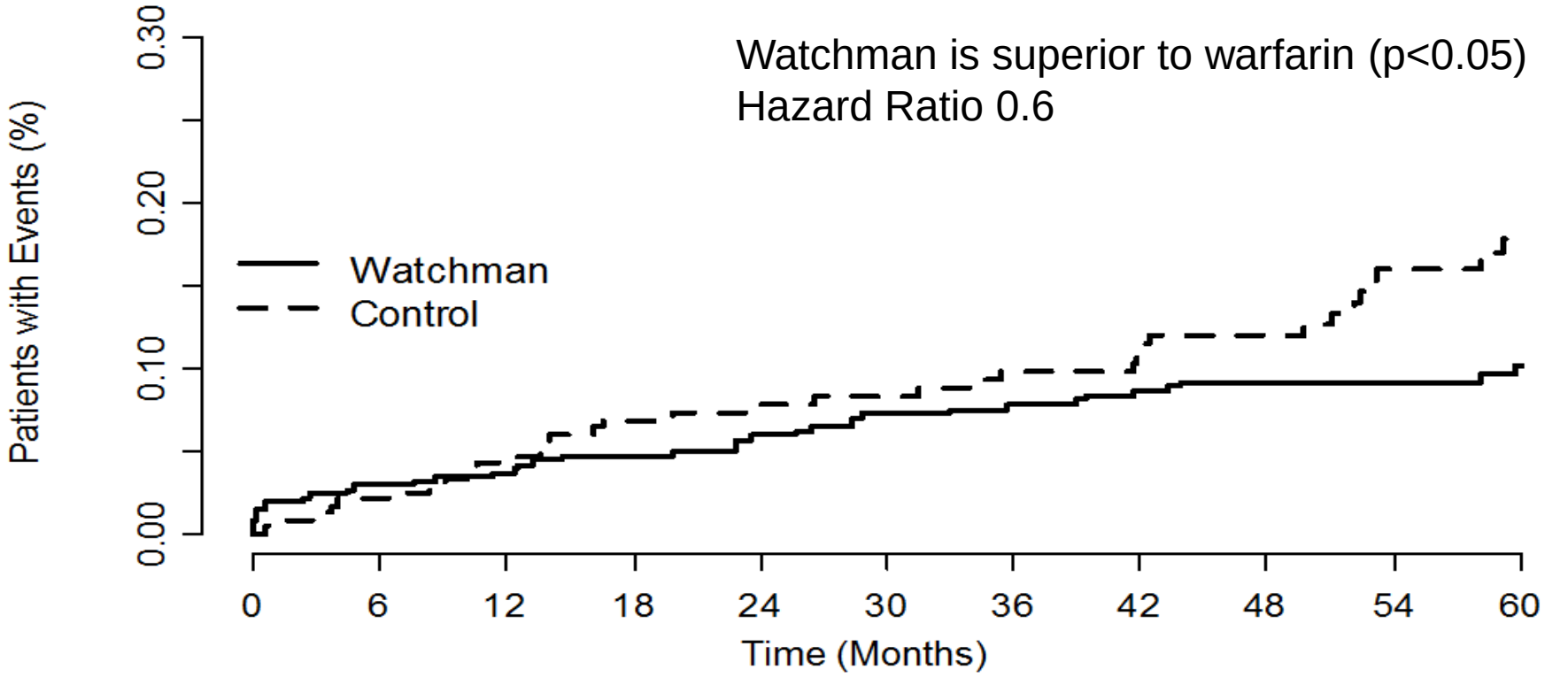
Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial

*David R Holmes, Vivek Y Reddy, Zoltan G Turi, Shephal K Doshi, Horst Sievert, Maurice Buchbinder, Christopher M Mullin, Peter Sick, for the PROTECT AF Investigators**

	Intervention (n=463)	Control (n=244)
Serious pericardial effusion*	22 (4·8%)	0
Major bleeding†	16 (3·5%)	10 (4·1%)
Procedure-related ischaemic stroke	5 (1·1%)	0
Device embolisation	3 (0·6%)	0
Haemorrhagic stroke‡	1 (0·2%)	6 (2·5%)
Other§	2 (0·4%)	0

Holmes et al, Lancet 2009; 374: 534–42

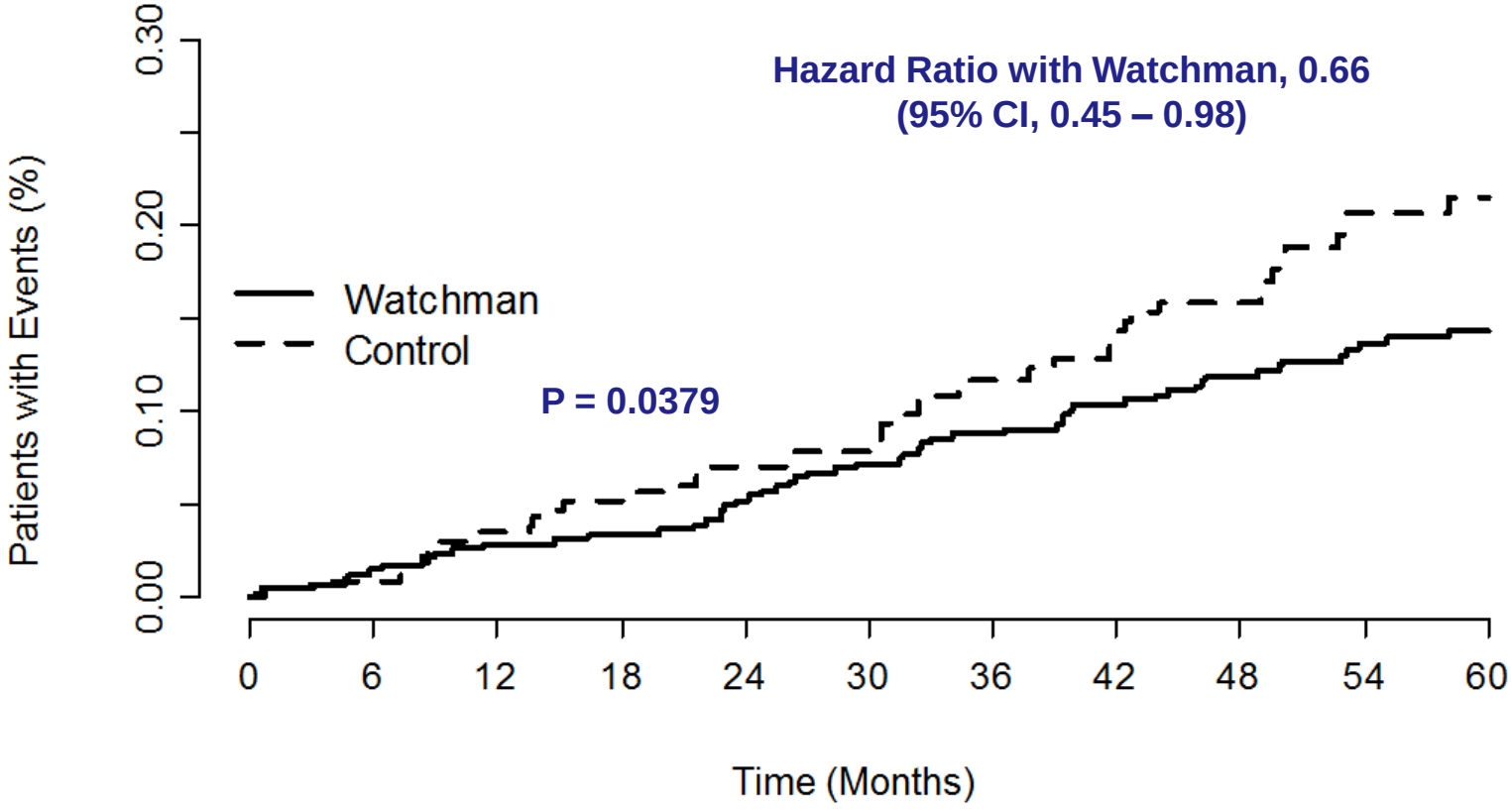
PROTECT AF 4 yrs FU: Primary Efficacy Endpoint: Stroke, Death, Systemic Embolization



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

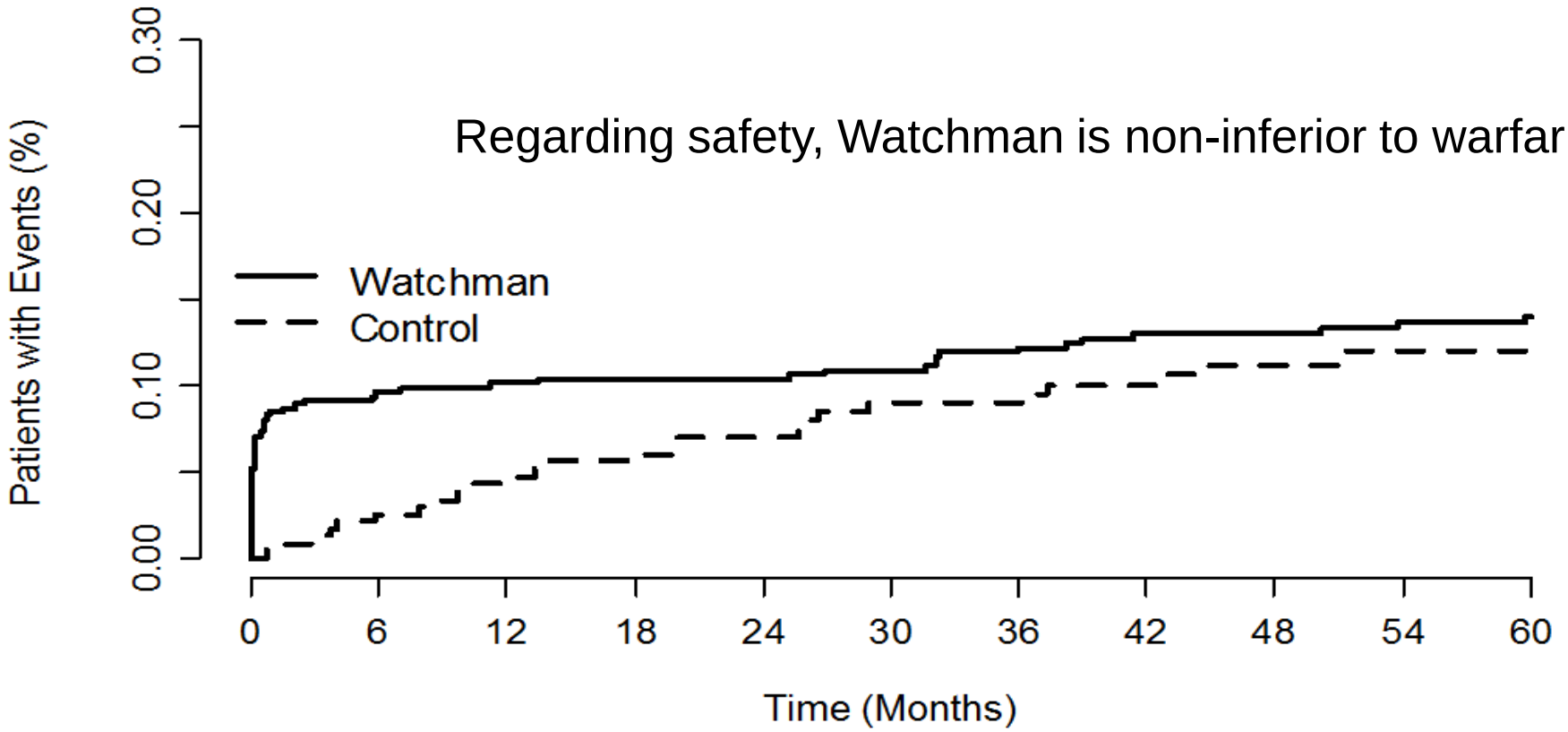
PROTECT AF 4 yrs FU: Intention-to-Treat: All-Cause Mortality



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

Primary Safety Endpoint:

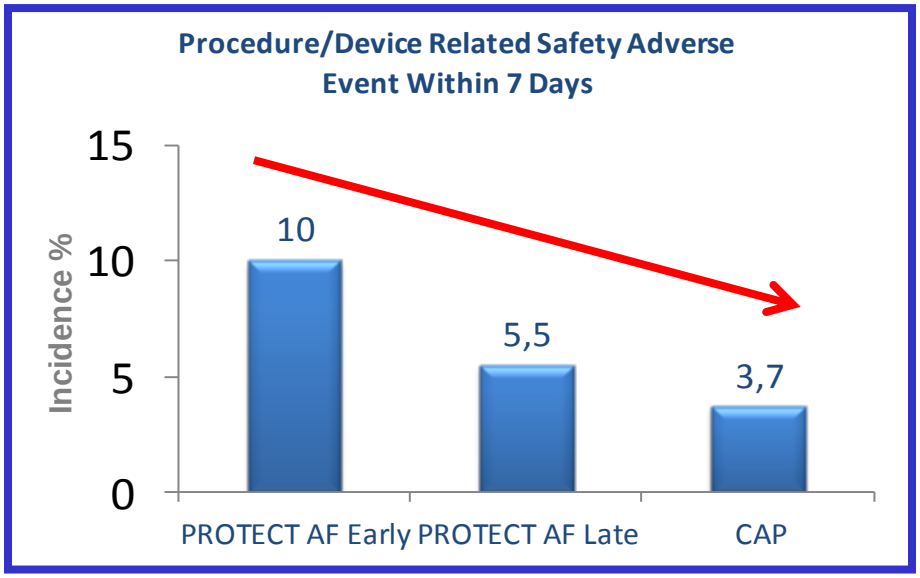
device embolization, pericardial effusion, severe bleeding

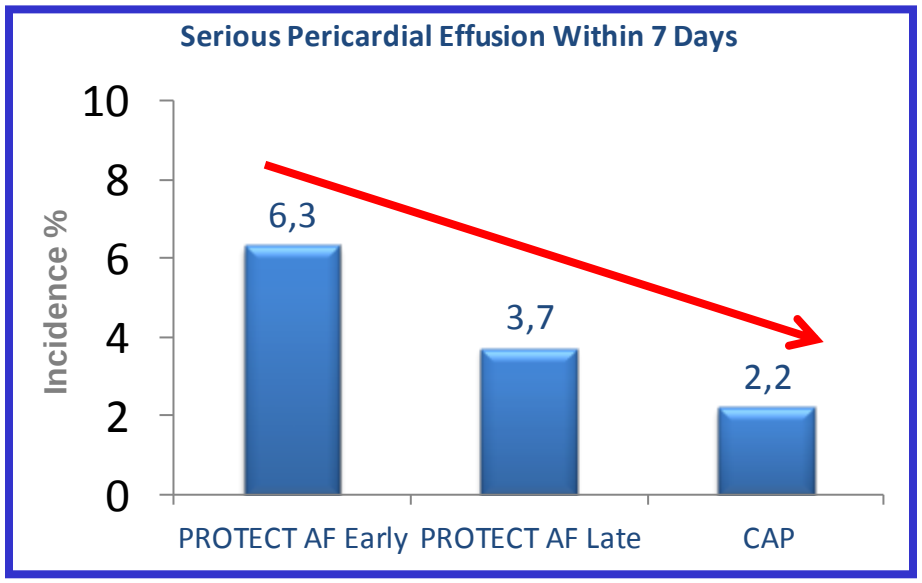


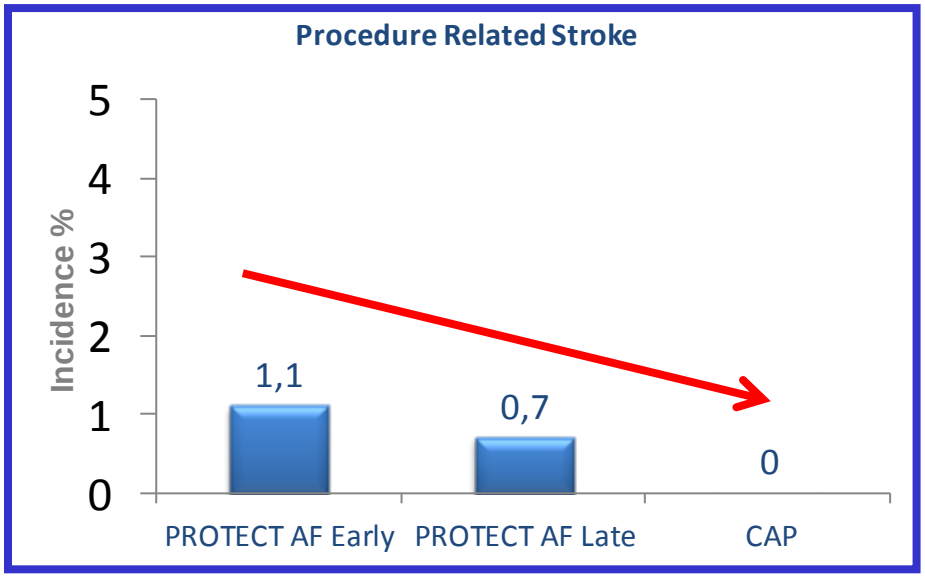
No. at Risk											
Watchman	463	376	364	357	353	341	332	320	310	277	190
Control	244	228	214	207	195	183	169	153	139	117	86

Performance – Learning Curve Effect

PROTECT-AF vs. CAP







With increased operator experience, the procedure related adverse events and serious pericardial effusions were reduced significantly. Peri-procedural strokes were eliminated

Evidence of prevention of ischemic strokes?

PROTECT- AF

	Intervention group		Control group		Rate ratio (intervention/control [95% CrI])	Posterior probabilities	
	Events/patient-years	Observed rate (events per 100 patient-years [95% CrI])	Events/patient-years	Observed rate (events per 100 patient-years [95% CrI])		Non-inferiority	Superiority
ITT population*							
Primary efficacy†	21/694·1	3·0 (1·9–4·5)	18/370·8	4·9 (2·8–7·1)	0·62 (0·35–1·25)	>99·9%	90·0%
Ischaemic stroke	15/694·6	2·2 (1·2–3·5)	6/372·3	1·6 (0·6–3·0)	1·34 (0·60–4·29)	71·8%	20·1%
Cardiovascular/unexplained death	5/708·4	0·7 (0·2–1·5)	10/374·9	2·7 (1·2–4·4)	0·26 (0·08–0·77)	>99·9%	99·3%
Haemorrhagic stroke	1/708·4	0·1 (0·0–0·5)	6/373·4	1·6 (0·6–3·1)	0·09 (0·00–0·45)	>99·9%	99·8%
Systemic embolism	2/707·8	0·3 (0·0–0·8)	0/374·9	0	–	–	–
All stroke	16/694·6	2·3 (1·3–3·6)	12/370·8	3·2 (1·6–5·2)	0·71 (0·35–1·64)	99·3%	76·9%
All-cause mortality	21/708·4	3·0 (1·9–4·5)	18/374·9	4·8 (2·8–7·1)	0·62 (0·34–1·24)	>99·9%	90·7%
Primary safety‡	49/658·8	7·4 (5·5–9·7)	16/364·2	4·4 (2·5–6·7)	1·69 (1·01–3·19)	–	–
Successfully treated population§							
Primary efficacy	11/593·6	1·9 (1·0–3·2)	17/370·2	4·6 (2·6–6·8)	0·40 (0·19–0·91)	>99·9%	98·6%
Primary safety	9/592·1	1·5 (0·7–2·8)	16/363·6	4·4 (2·5–6·7)	0·35 (0·15–0·80)	–	–

CrI=credible interval. ITT=intention-to-treat. –=not applicable. Different events have different numbers of patient-years because patients without an event or lost to follow-up were censored at the time of the last known event status. Posterior probabilities of non-inferiority are based on a two-fold non-inferiority margin. Posterior probabilities and CrIs are based on a Bayesian model stratified by CHADS2 score. *The ITT population consists of all randomised patients (intervention, n=463; control=244). †The primary composite endpoint for efficacy was the occurrence of stroke (including ischaemic or haemorrhagic stroke), cardiovascular or unexplained death, or systemic embolism. ‡The primary composite endpoint for safety consisted of events related to excessive bleeding (eg, intracranial or gastrointestinal bleeding) or procedure-related complications (eg, serious pericardial effusion, device embolisation, procedure-related stroke). §Successful treatment was defined in the intervention group as device implantation followed by discontinuation of warfarin and in the control group as the start of warfarin treatment (intervention, n=389; control=241).

Table 2: Clinical outcomes

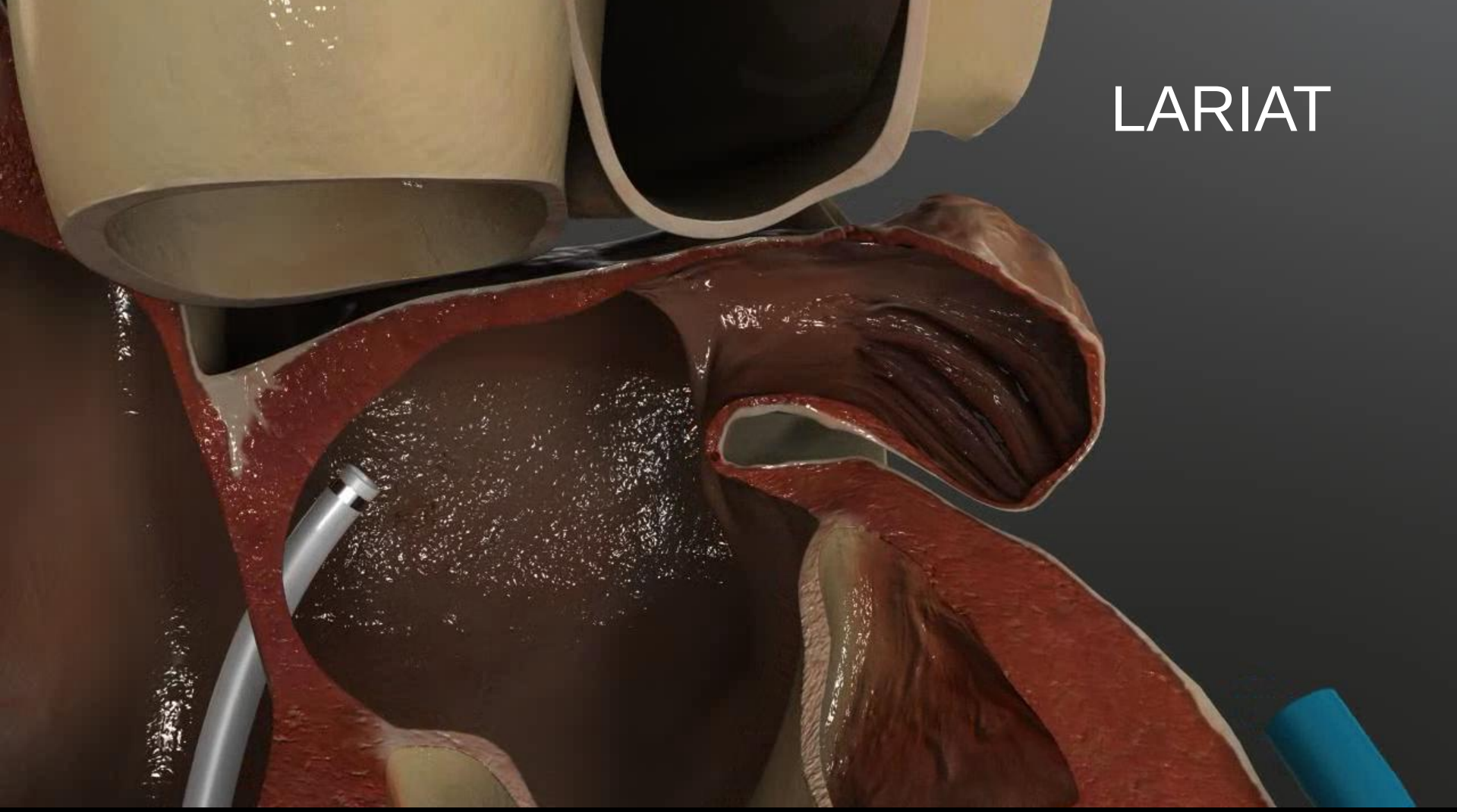
Coprimary Efficacy Endpoint Observed Events by Type: PREVAIL

	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

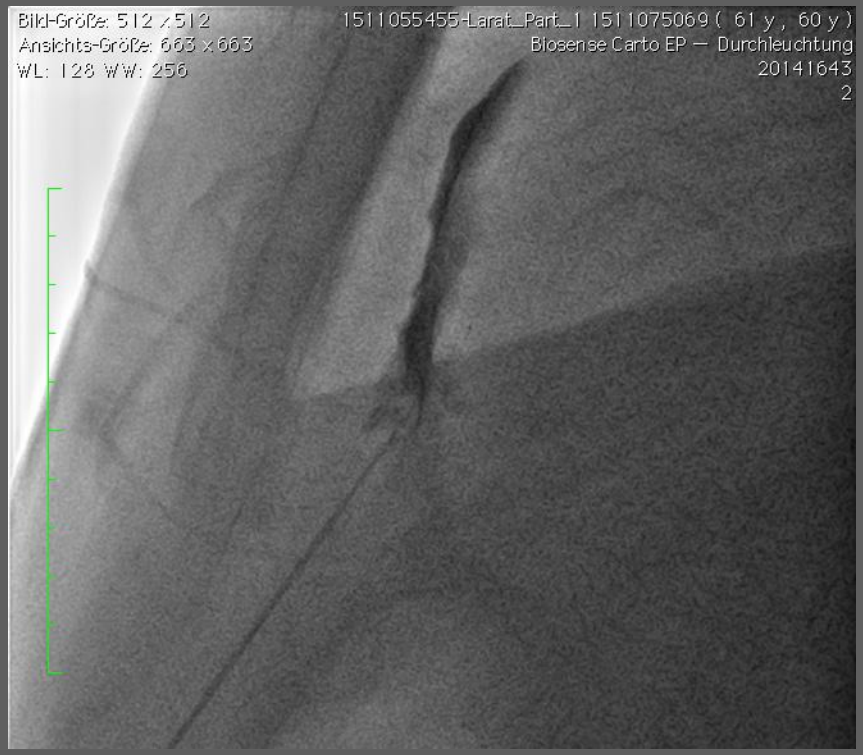
*Endpoint analysis was based on the initial event per-patient even if a patient experienced multiple events.

PREVAIL = Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy.

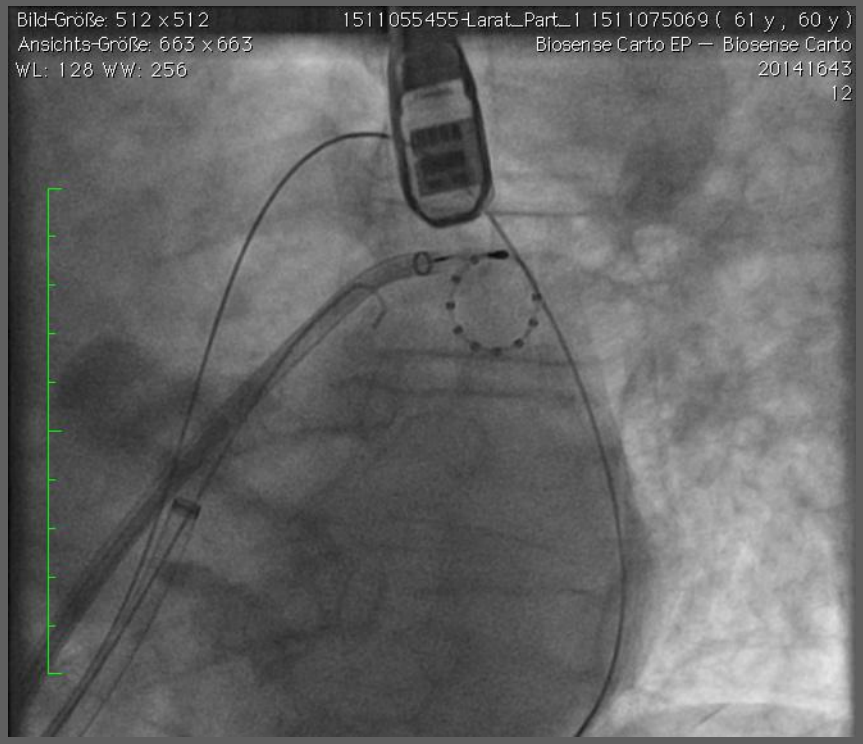
Holms et al. (2014). JACC et al , *64*(1), 1–12. doi:10.1016/j.jacc.2014.04.029


LARIAT

Dry Epicardial Puncture with Micropuncture Needle



LAA Angiography



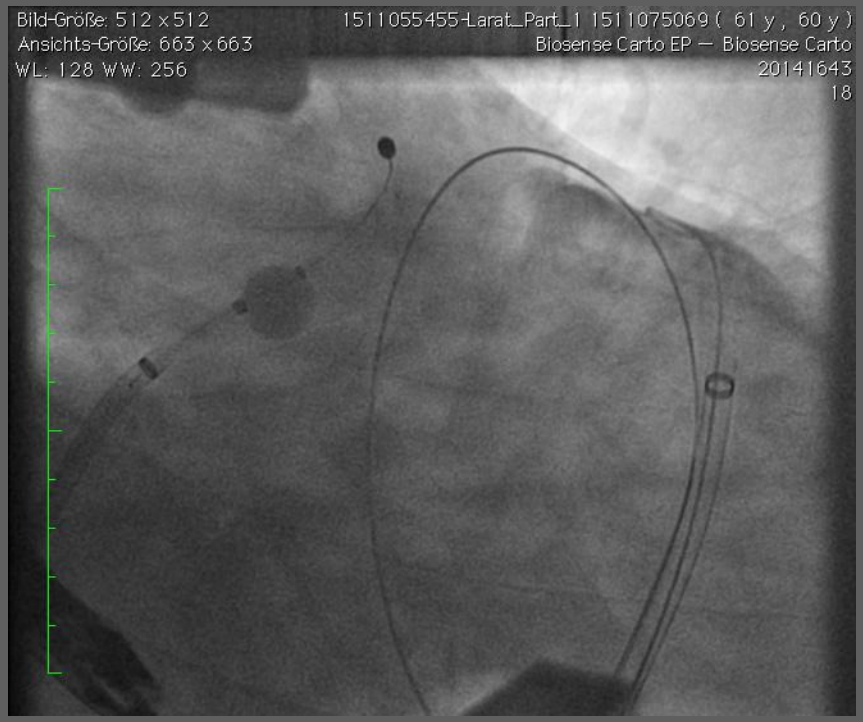


Bild-Größe: 512 x 512
Ansichts-Größe: 663 x 663
WL: 128 WW: 256
1511055455-Larat_Part_1 1511075069 (61 y , 60 y)
Biosense Carto EP — Biosense Carto
20141643
18

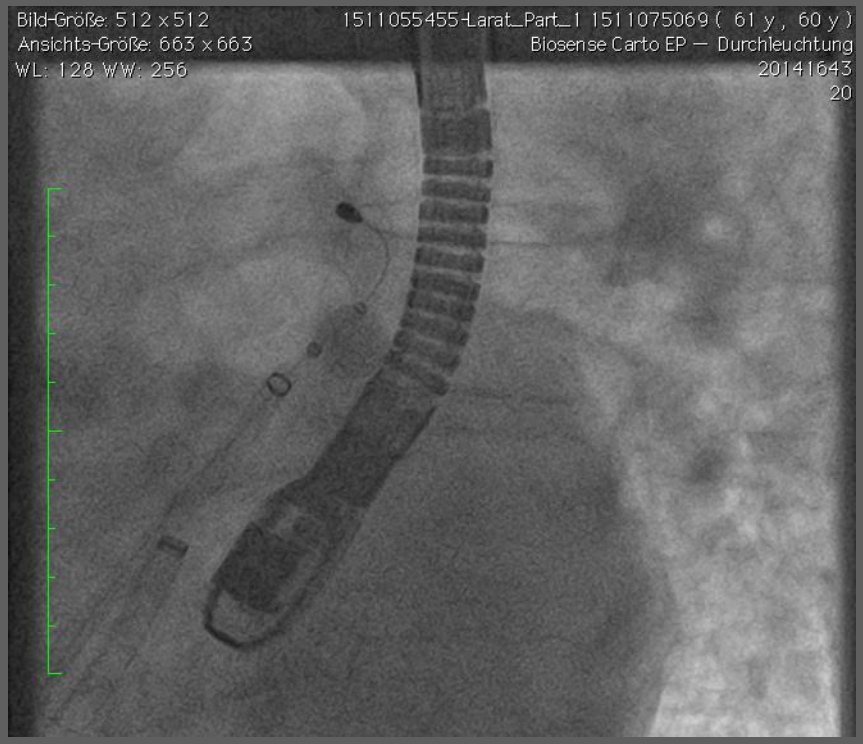


Bild-Größe: 512 x 512
Ansichts-Größe: 663 x 663
WL: 128 WW: 256
1511055455-Larat_Part_1 1511075069 (61 y , 60 y)
Biosense Carto EP — Durchleuchtung
20141643
20

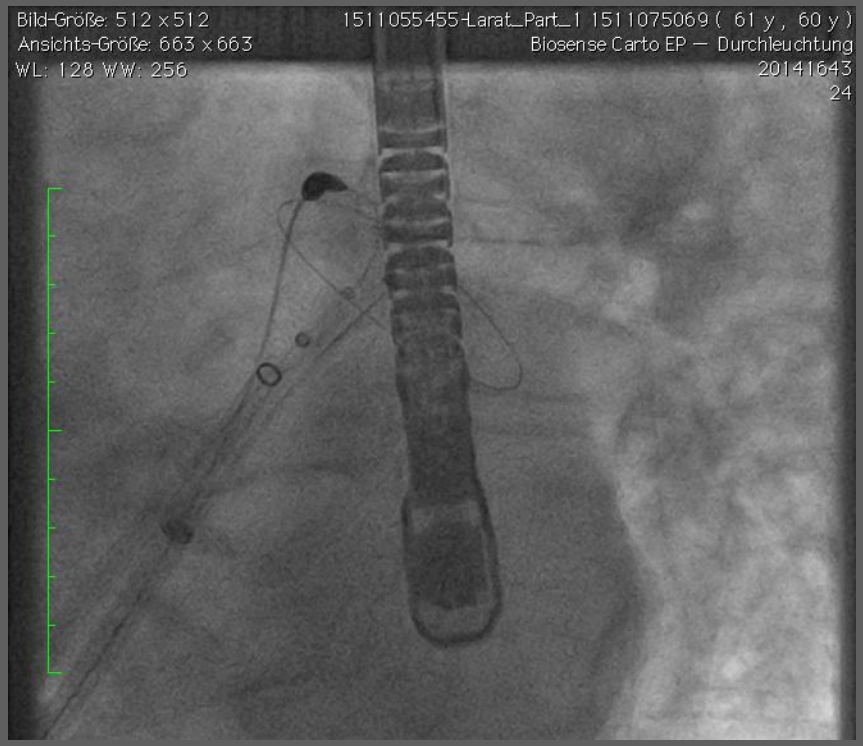


Bild-Größe: 512 x 512
Ansichts-Größe: 663 x 663
WL: 128 WW: 256
1511055455-Larat_Part_1 1511075069 (61 y , 60 y)
Biosense Carto EP — Durchleuchtung
20141643
24

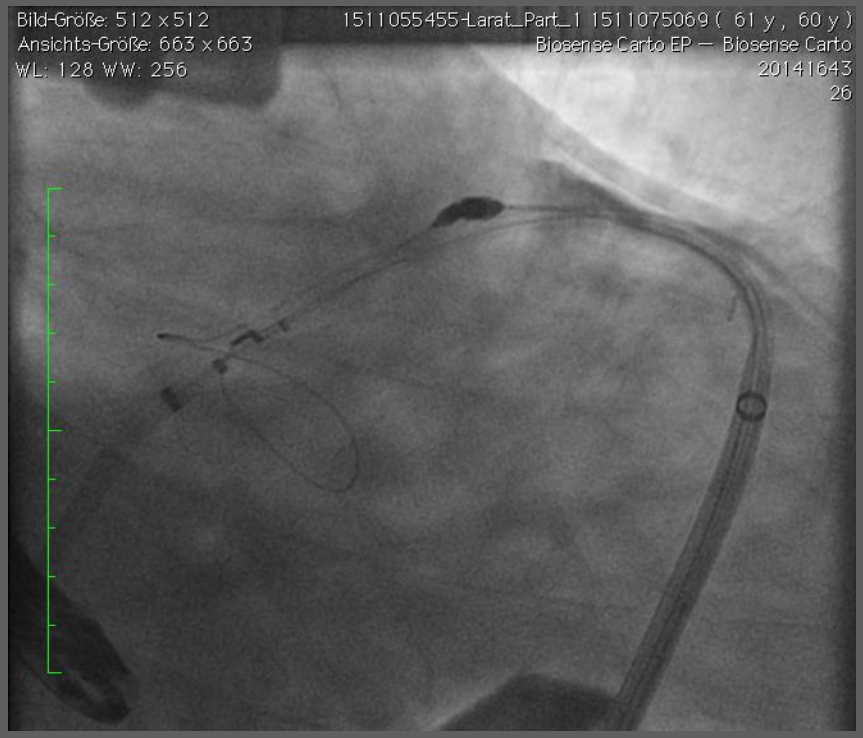


Bild-Größe: 512 x 512
Ansichts-Größe: 663 x 663
WL: 128 WW: 256
1511055455-Larat_Part_1 1511075069 (61 y , 60 y)
Biosense Carto EP — Biosense Carto
20141643
26

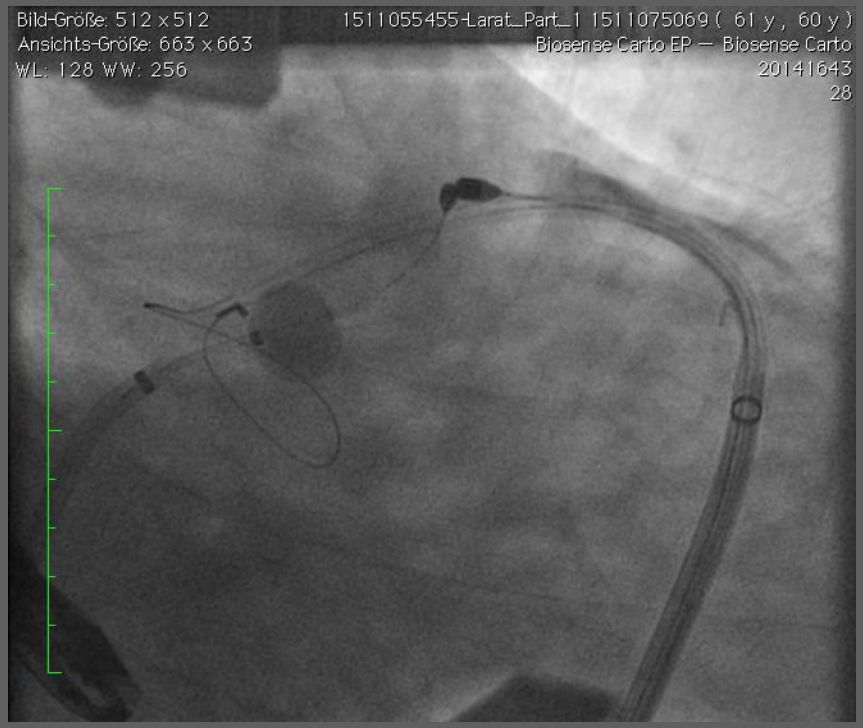


Bild-Größe: 512 x 512
Ansichts-Größe: 663 x 663
WL: 128 WW: 256
1511055455-Larat_Part_1 1511075069 (61 y , 60 y)
Biosense Carto EP — Biosense Carto
20141643
28

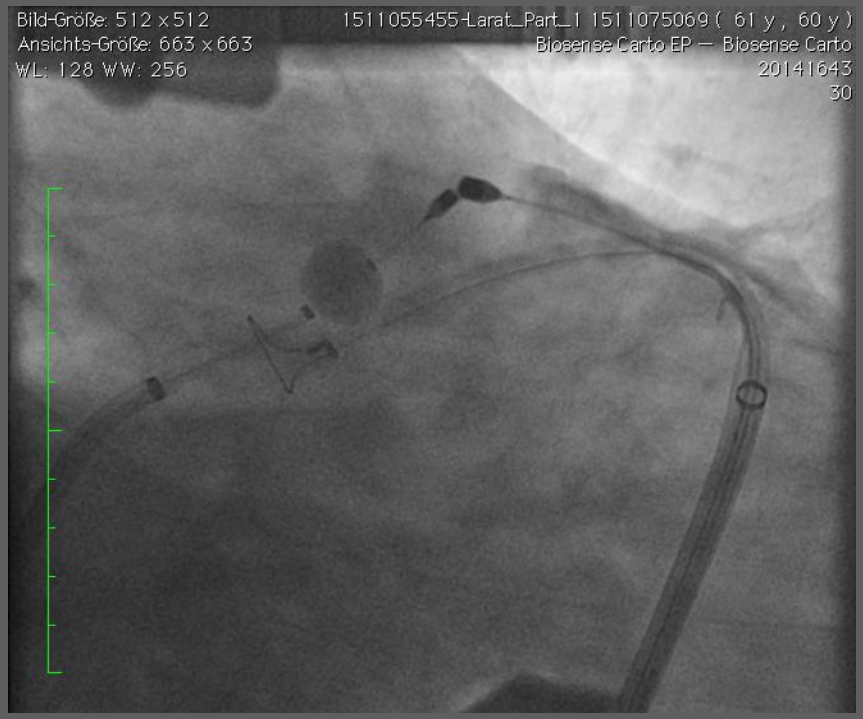


Bild-Größe: 512 x 512
Ansichts-Größe: 663 x 663
WL: 128 WW: 256
1511055455-Larat_Part_1 1511075069 (61 y , 60 y)
Biosense Carto EP — Biosense Carto
20141643
30

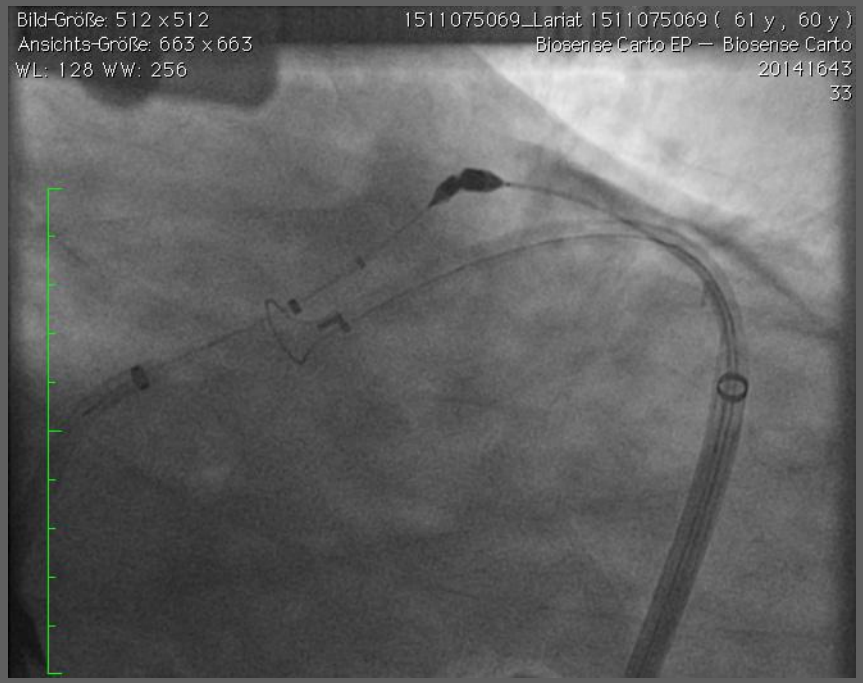


Bild-Größe: 512 x 512
Ansichts-Größe: 663 x 663
WL: 128 WW: 256
1511075069_Lariat 1511075069 (61 y , 60 y)
Biosense Carto EP — Biosense Carto
20141643
33

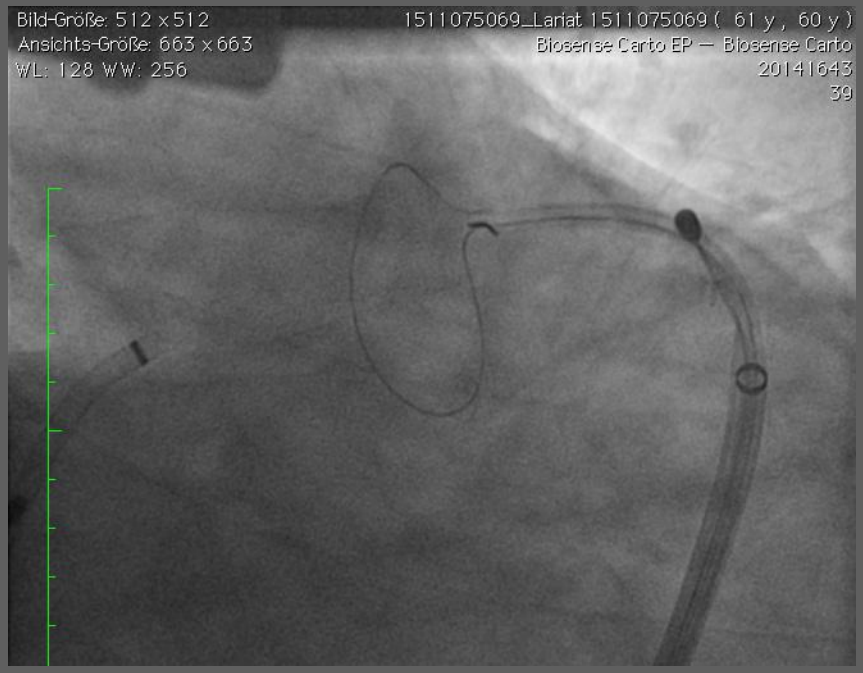


Bild-Größe: 512 x 512
Ansichts-Größe: 663 x 663
WL: 128 WW: 256
1511075069_Lariat 1511075069 (61 y , 60 y)
Biosense Carto EP — Biosense Carto
20141643
39

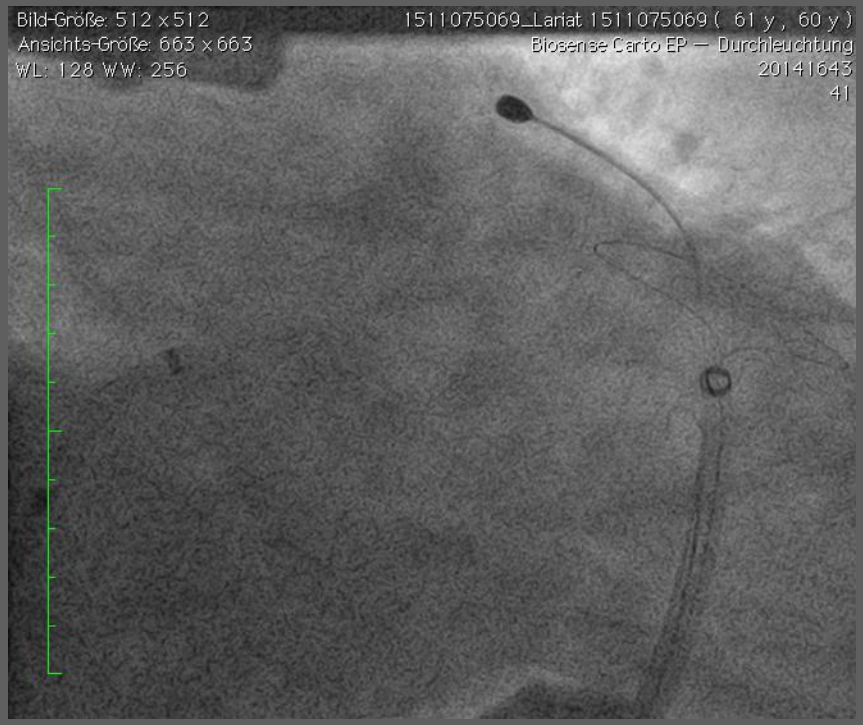
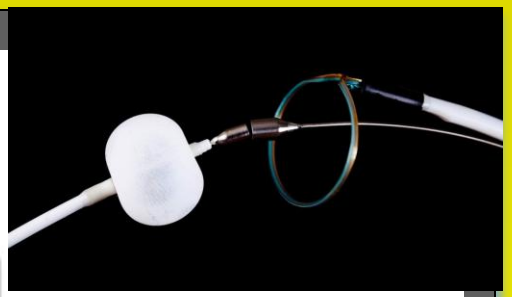


Bild-Größe: 512 x 512
Ansichts-Größe: 663 x 663
WL: 128 WW: 256
1511075069_Lariat 1511075069 (61 y , 60 y)
Biosense Carto EP — Durchleuchtung
20141643
41

Patients Screened for LAA Exclusion (LARIAT)



PATIENTS SCREENED
N=119

PATIENTS EXCLUDED
N=16 (13.4%)

LAA Width ≥40mm
N=8 (6.7%)

Unsuitable AA Orientation
N=8 (6.7%)

ELIGIBLE PATIENTS
N=103 (86.5%)

Presence of Adhesion
N=3 (2.9%)

Mobile Thrombus*
N=11 (10.7%)

EXCLUDED AT TIME OF PROCEDURE
N=14 (13.6%)

PATIENTS TO BE TREATED
N=89 (86.4%)

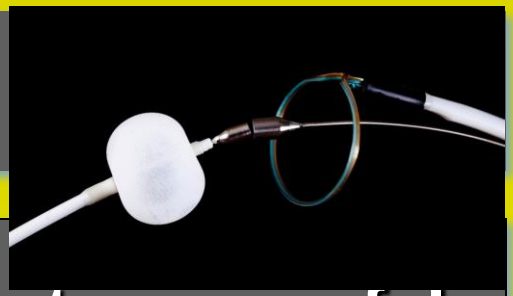
PT 9: Pericardial effusion due to inadvertent RV dilation
PT 24: Pericardial effusion at intiation due to epigastric vessel laceration
PT 25: Anatomic contraindication prior to transseptal (dilated RA)
PT 93: Unable to capture LAA due to localized adhesions on LAA sulcus

FAILURE TO TREAT
N=4 (4.5%)

SUCCESSFUL LAA CLOSURE
N=85 (95.5%)

Bartus et al, JACC 2013, *62*(2)

Results



- Eighty-five (96%) of 89 pts underwent successful LAA ligation. 81/85 patients had complete closure immediately. 4/85 patients had a ≤3mm residual LAA leak jet by TEE.
- Complications: 3 access- related complications (during pericardial access, n = 2; and transseptal catheterization, n = 1).
- Adverse events included severe pericarditis post-operatively (n = 2), late pericardial effusion (n = 1), unexplained sudden death (n = 2), and late strokes thought to be non-embolic (n = 2).

Bartus et al, JACC 2013, *62*(2)

Results: Follow up

- At 1 month (81 of 85) and 3 months (77 of 81) post-ligation, 95% of the patients had complete LAA closure by TEE. Of the patients undergoing 1-year TEE (n = 65), there was 98% complete LAA closure, including the patients with previous leaks.

Bartus et al, JACC 2013, *62*(2)

HAMBURG experience: Baseline characteristics	
Total number of patients: n	8
Age [yrs.]	67±6
Male [%]	50 (4)
LA diam TEE [mm]	50±7
LAA flow [m/s]	0,2±0.1
Oral anticoagulation before procedure [%] Warfarin [%] NOAK [%]	100 (8) 50 (4) 50 (4)
CHA2DS2-VASc score	3±1
HASBLED score	1,9±0.8
INR before procedure [%]	1,7±0.6
History of LAA thrombus [%]	12,5 (1)
Arrhythmia before LAA isolation: n (%) Paroxysmal AF Persistent AF/AT	 1 (13%) 7 (8.8%)
Number of ablation prior LAA closure	3±2

HAMBURG experience

Procedural data	
Successful LAA ligation without any residual leak [%]	100 (8)
Leakage after LAA ligation [%]	0
Procedure duration [min]	98±23
Flouroscopy time [min]	17±5
Flouroscopy dosage [cGy*cm2]	11456±14405
Adverse events: n [%] pericardial effusion due to injury of a subcutaneous vessel Pericarditis	 12,5 (1) 38 (3)
Rhythm at discharge SR: n [%] AF: n [%]	 87,5 (7) 12,5 (1)

LAA Isolation Improves Ablation Outcomes

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

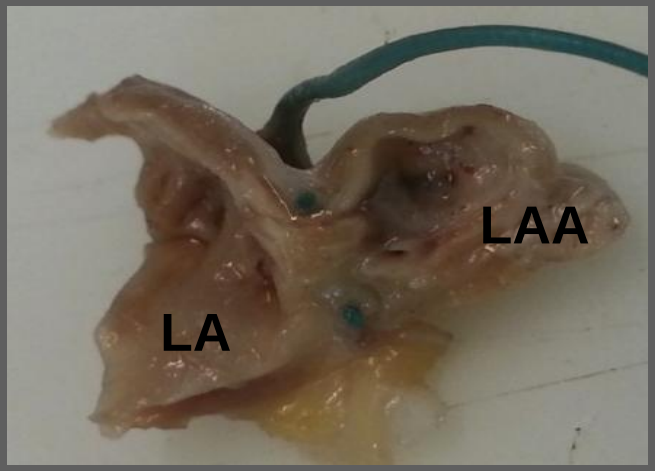
Learn and Live℠

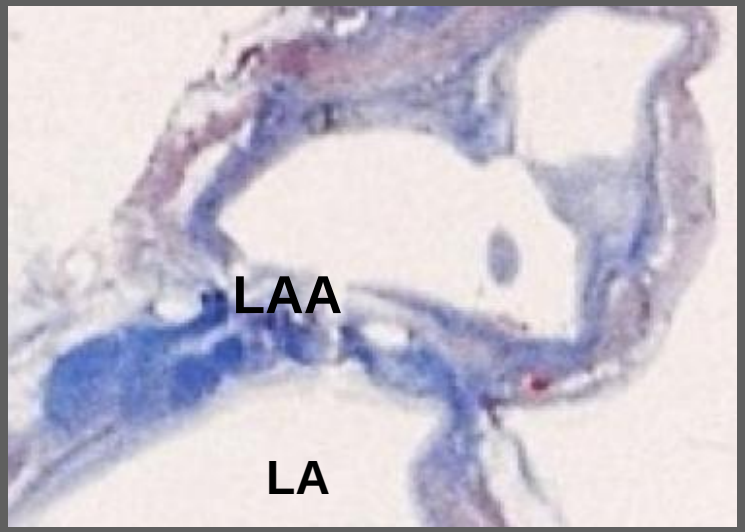
Left Atrial Appendage : An Underrecognized Trigger Site of Atrial Fibrillation

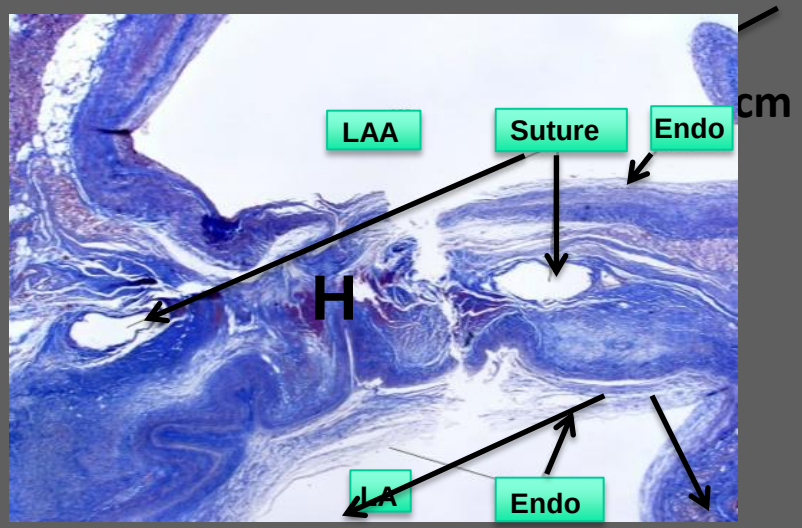
Luigi Di Biase, J. David Burkhardt, Prasant Mohanty, Javier Sanchez, Sanghamitra Mohanty, Rodney Horton, G. Joseph Gallinghouse, Shane M. Bailey, Jason D. Zagrodzky, Pasquale Santangeli, Steven Hao, Richard Hongo, Salwa Beheiry, Sakis Themistoclakis, Aldo Bonso, Antonio Rossillo, Andrea Corrado, Antonio Raviele, Amin Al-Ahmad, Paul Wang, Jennifer E. Cummings, Robert A. Schweikert, Gemma Pelargonio, Antonio Dello Russo, Michela Casella, Pietro Santarelli, William R. Lewis and Andrea Natale

Circulation. 2010;122:109-118

LAA ligation results in a permanent transmural lesion

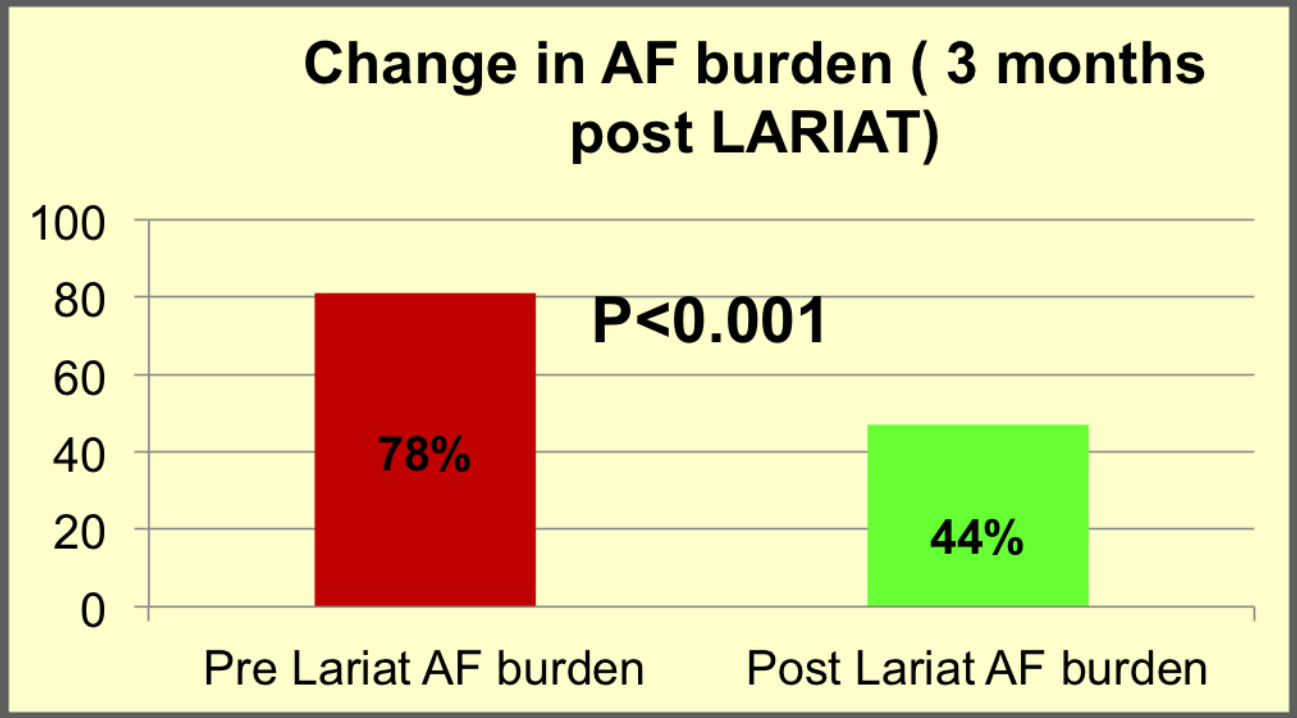






Bartus et al., Circ Arrhythmia 7:764-767, 2014

Effect of Epicardial Percutaneous LAA Ligation on Arrhythmia Burden in Patients with AF



Afzal et al., Heart Rhythm 2014

Indication for LAA occluder device

- AF and stroke/TIA/TE/LAA thrombus despite OAC/NOAC
- Pts on hemodialysis and bleeding on warfarin (contraindication for NOACs)
- Patients unwilling or intolerance to NOAC
- Contraindication to NOAC: LARIAT only
- Patients compliance: LARIAT only

Conclusions I: LAA occulsion

- Both endo and epicardial LAA occluder devices are an excellent treatment for selected pts with AF
- In experienced hands, periprocedural complication rate is acceptable
- Lifelong ASS therapy is mandatory following endocardial device implantation according to present data, but not for epicardial device implantation
- Clinical data following LAA occluder implantation is sparse
- Therefore OAC therapy with warfarin/NOACs remains the gold standard in the majority of pts

Conclusions

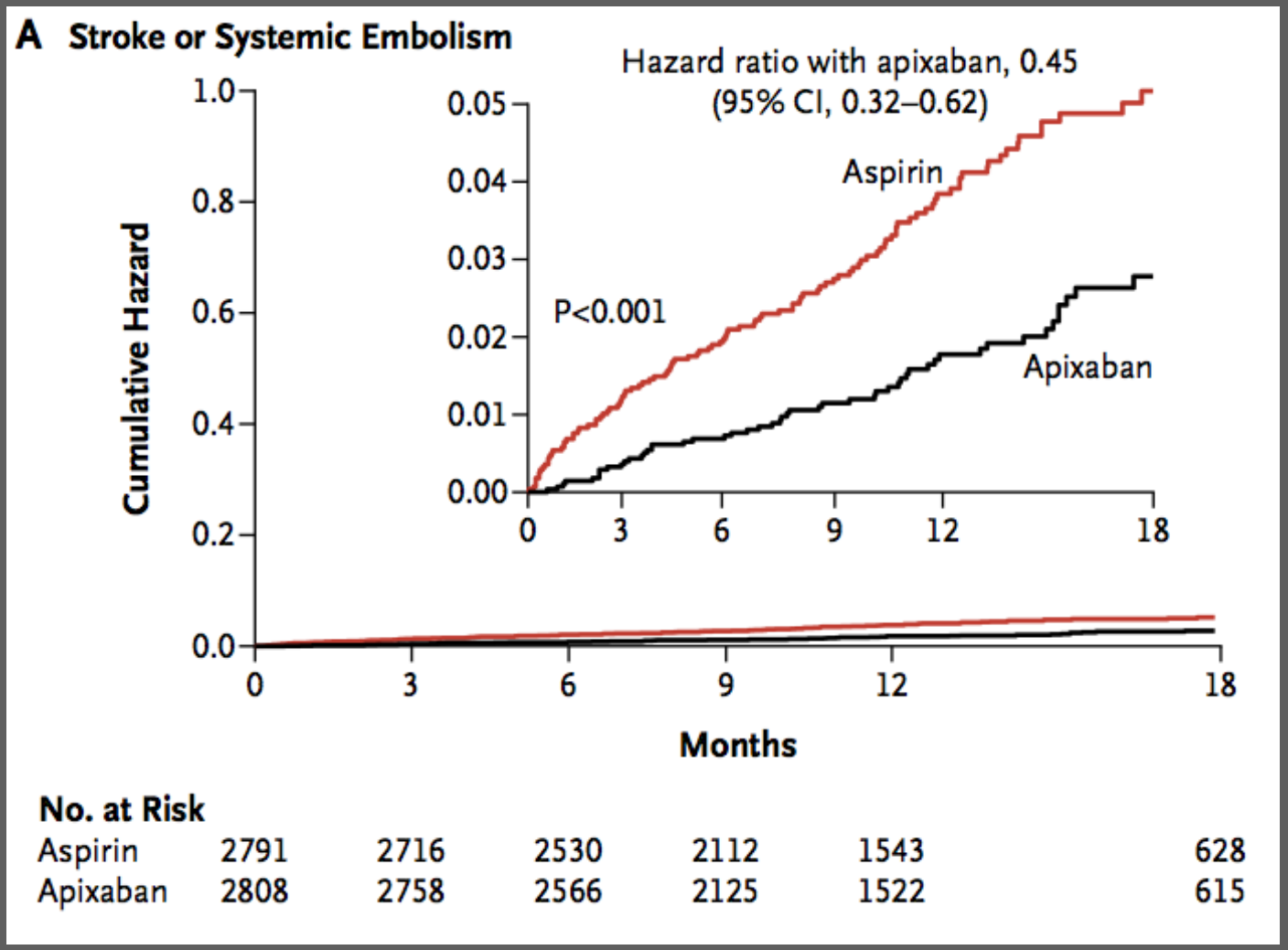
- Epicardial LAA closure device is an excellent treatment option for patients with AF and high risk for embolic stroke and have contraindications/intolerance to anticoagulation therapy.
- Initial results are encouraging. Beneficial effect of this device needs to be proven by randomized trials.


EP Team St. Georg Hospital

Agenda

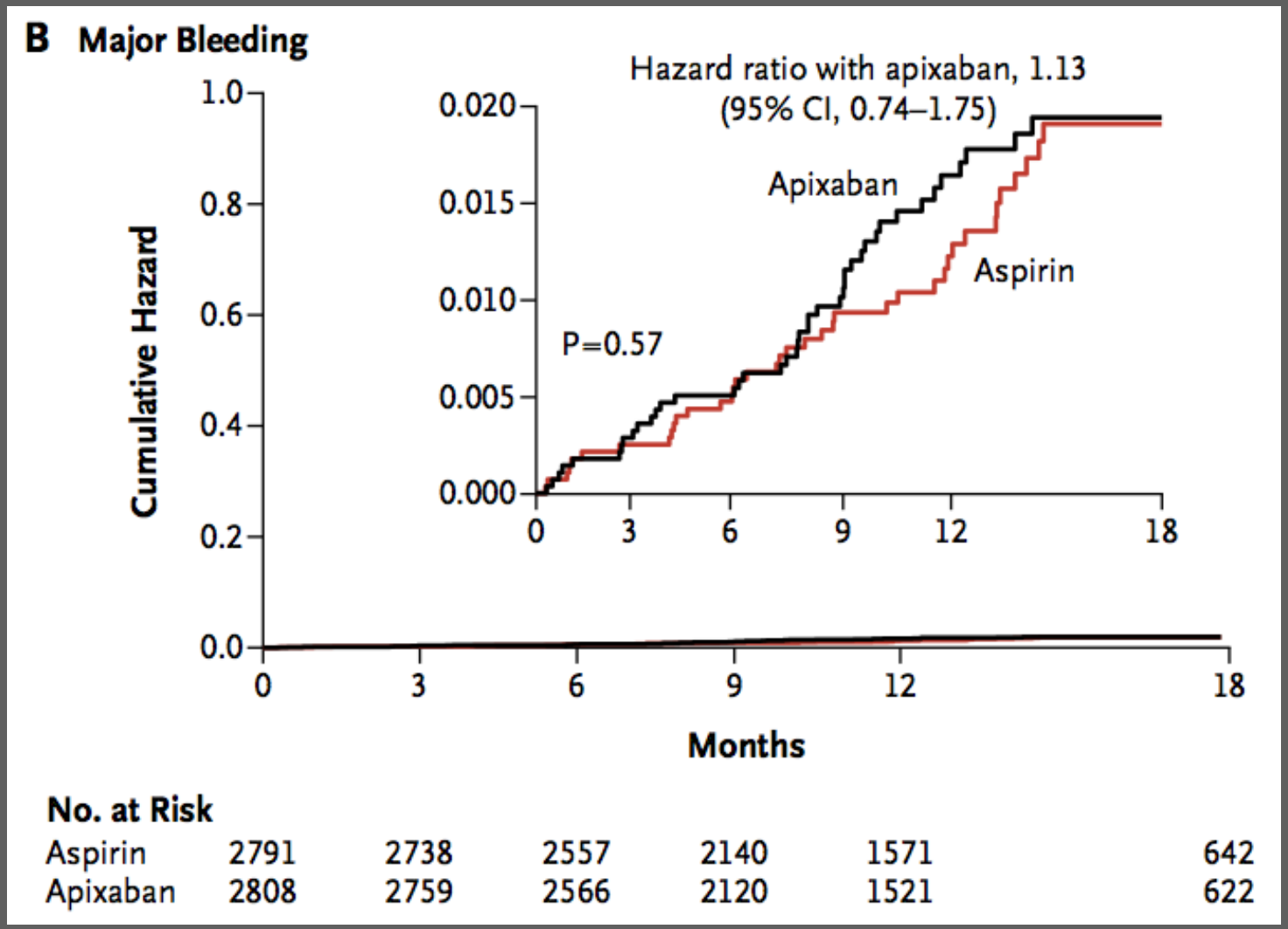
- Background
- Lariat System
- Case
- Clinical experience

AVERROES Trial
ASS vs. Apixaban: Schlaganfall/Embolie



Connoly et al, N Engl J Med 2011;364:806-17.

AVERROES Trial
ASS vs. Apixaban: Blutungen



Connoly et al, N Engl J Med 2011;364:806-17.

LAA Ligation in AF Patients at High Risk for Embolic Events with Long-term Ineligibility to Oral Anticoagulants: Long-term clinical outcomes

Randy Lee, MD, PhD
Professor of Medicine

Multi-center Observational Study

- Sankt Katharinen Hospital, CVC, Frankfurt Germany (H. Sievert)
- St Luke's Hospital, Houston, TX (A. Rasekh and A. Massumi)
- John Paul II Hospital, Krakow, Poland (K. Bartus)
- St Mary's Hospital, San Francisco (R. Morelli, N. Badhwar and R. J. Lee)
- University of California, San Francisco (N. Badhwar and R. J. Lee)

Study Objectives

- Determine efficacy of LAA Closure with the LARIAT device
- Assess procedural and 30 day peri-procedural safety
- Long-term clinical follow up

Patient Cohort

- 143 consecutive AF patients with long-term ineligibility to OAC therapy
- Patients underwent attempted LAA ligation with the LARIAT device
- Patients did not receive OAC therapy after LAA ligation
- Patients received ASA, ASA with clopidogrel or no anti-platelet therapy after LAA ligation
- Dec 2009 through Nov 2012

Long-term Clinical Endpoints

- Patients followed for their first event of:
  - Stroke (ischemic, hemorrhagic or undefined) or systemic embolism
  - Stroke, systemic embolism or death of any cause

Inclusion Criteria

- Age 18 years or older
- Non-valvular atrial fibrillation
- At least one risk factor of embolic stroke (CHADS $\geq$1)
- Ineligible for long-term OAC therapy
- A life expectancy of at least 1 year

Exclusion Criteria

- History of pericarditis
- History of cardiac surgery
- Thoracic radiation
- Pectus excavatum
- Recent MI within 3 months
- Prior embolic event within the last 30 days
- NYHA class IV heart failure symptoms

Exclusion Criteria Based on LAA Anatomy

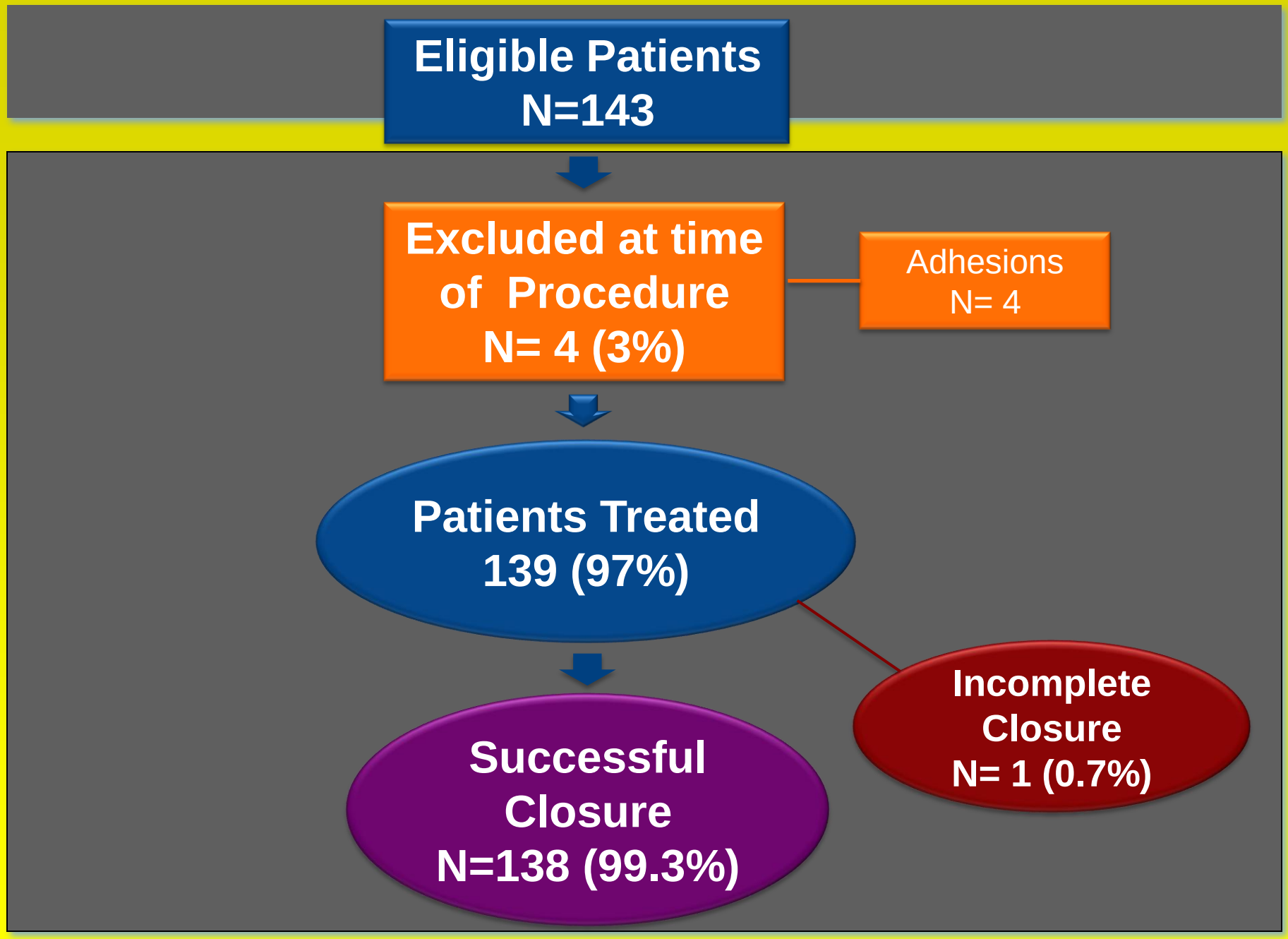
- A LAA width > 40mm
- A superiorly oriented LAA with the LAA apex directed behind the pulmonary trunk
- Bi-lobed LAA or multi-lobed LAA in which lobes were oriented in different planes exceeding 40mm

Clinical Characteristics and Stroke Risk

Clinical	
Age	67±11
Male	85 (61%)
Stroke risk Factor	
Heart Failure	32 (24%)
Hypertension	127 (95%)
Age>=75 yrs	41 (30%)
Diabetes mellitus	31 (23%)
Prior stroke or TIA	43 (32%)
Vascular disease	29 (22%)
Age 65 to 74 yrs	43 (32%)
Female	54 (39%)
$CHADS_2$ score	
1	38 (27%)
2	47 (34%)
3	31 (22%)
4	13 (9%)
5	8 (6%)
6	2 (1%)
Mean $CHADS_2$ score=	2.4±1.2

CHADS2-VASC score	
1	22 (16%)
2	20 (14%)
3	22 (16%)
4	34 (25%)
5	22 (17%)
6	10 (7%)
7	4 (3%)
8	2 (1%)
9	1 (1%)
Mean score=	3.6± 1.8

Has-Bled Score	
0	1 (1%)
1	19 (14%)
2	40 (29%)
3	42 (30%)
4	26 (19%)
5	11 (8%)
Mean Has-Bled score	2.8±1.2
Patients year of F/p	2.8 ±1.1
Total Patients year of F/p	396


Eligible Patients
N=143
Excluded at time of Procedure
N= 4 (3%)
Adhesions
N= 4
Patients Treated
139 (97%)
Incomplete Closure
N= 1 (0.7%)
Successful Closure
N=138 (99.3%)

Device Success

- Successful acute closure (angiographic and color flow TEE full closure at end of procedure) 138/139 = 99%
  - One patient had an uncaptured lobe
- Residual Leak at 6 week TEE
  - 12 patients did not have follow up TEE
  - Less than 1mm leak: 114/127 (90%)
  - Leak 2-4 mm: 13/127 (10%)
  - Leak greater than 5 mm: 0/127 (0%)

LARIAT: Efficacy Rates

	LARIAT 2014
Follow up	2.8+/-1.1 years
Patient-years	396
Death rate	1.8% (n=7)
Stroke rate	1.0% (n=4)
Death/Stroke/Systemic Embolism	2.8%

Adverse Events

Procedure related

- Chest pain
- Pericardial effusion 1 (0.7%)
- Pulmonary embolus 1 (0.7%)
  - Periprocedural death 1 (0.7%)
- Cardiac Perforation 2 (1.4%)
  - Surgery 2 (1.4%)

Inflammation related

- Pericarditis (>2 days) 8 (5.8%)
- Late Hemopericardium 1 (0.7%)
- Late Pericardial effusion 1 (0.7%)
- LA thrombus 2 (1.4%)

LAA Ligation

- Feasible and effective LAA closure
- Acceptably low access complications and peri-procedural adverse events
- Results support previous studies that exclusion of the LAA prevents cardioembolic strokes