Data Behind LAA Closure – This is Ready for Prime Time!

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Mount Sinai Heart

Disclosures

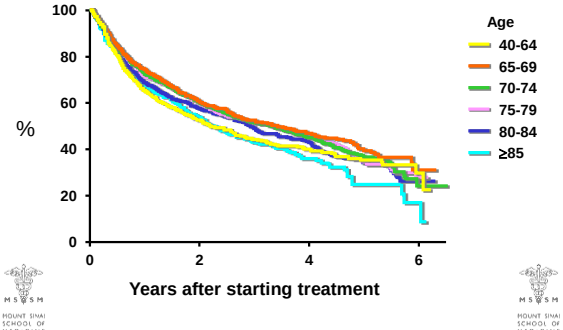
- Grant support and/or Consultant:
  - Boston Scientific Inc, Coherex Inc, St Jude Medical Inc

  (I have no equity interest in LAAC)

- I will be discussing non-approved catheter devices.

Preventing Stroke in Atrial Fibrillation

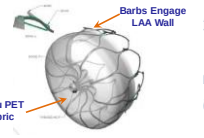
Warfarin Intolerance / Non-Compliance



A.M.Gallagher *J Thromb Haem* 6:1500 (2008)

Left Atrial Appendage Closure
Important Results from the Watchman Experience

1. Can a thrombus originate from outside the LAA?
2. Were the patients enrolled in the trials of sufficient risk?
3. How sa… …cation procedu…
4. PROTE… …domized against … …we have NOACs
5. How cost-effective is LAAC?



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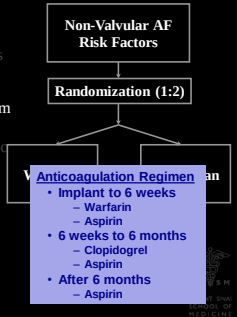
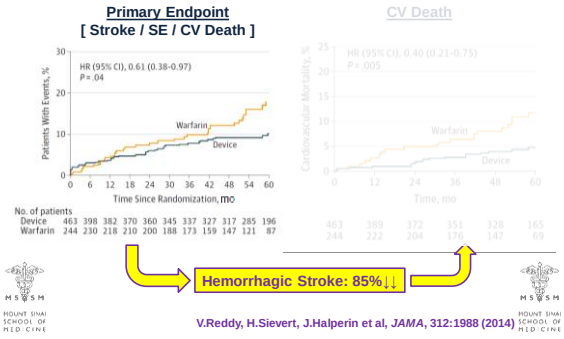
PROTECT-AF & PREVAIL
Design & Overview

- Randomized FDA-IDE Trials
  - Can the WATCHMAN device ***replace*** Warfarin?
  - PREVAIL: At Least 25% new operators
- Efficacy Endpoints:
  - 1st Endpoint: Stroke / Systemic embolism / CV death (& Unknown)
  - 2nd Endpoint: Ischemic Stroke / Systemic embolism (Post 7 days)
- Bayesian Statistical Plan
  - Non-inferiority & Superiority
  - Informative Prior?
    - PROTECT-AF: (None)
    - PREVAIL: Discounted data from PROTECT-AF



PROTECT AF

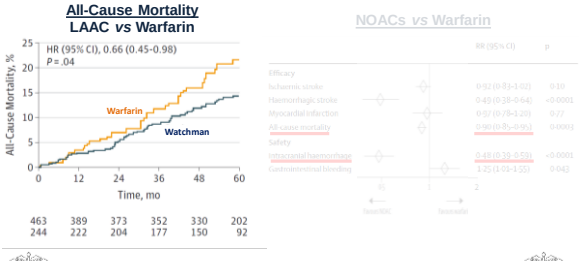
Superiority of Watchman over Warfarin



V.Reddy, H.Sievert, J.Halperin et al, *JAMA*, 312:1988 (2014)

All-Cause Mortality *vs* Warfarin

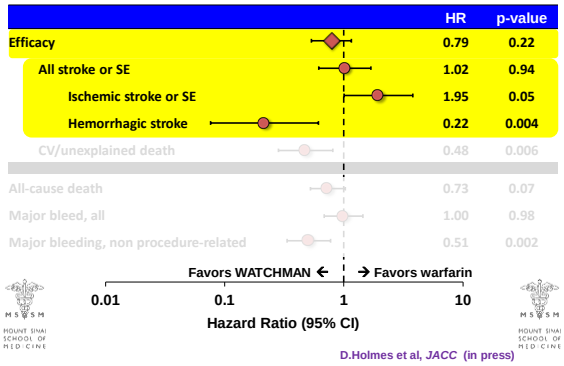
Is a 34% Mortality Benefit by LAAC Plausible?



V.Reddy, H.Sievert, J.Halperin et al, *JAMA*, 312:1988 (2014)
Ruff et al. *Lancet*, 383:955 (2014)

PROTECT-AF & PREVAIL

Combined Analysis



D.Holmes et al, *JACC* (in press)

PROTECT-AF & PREVAIL
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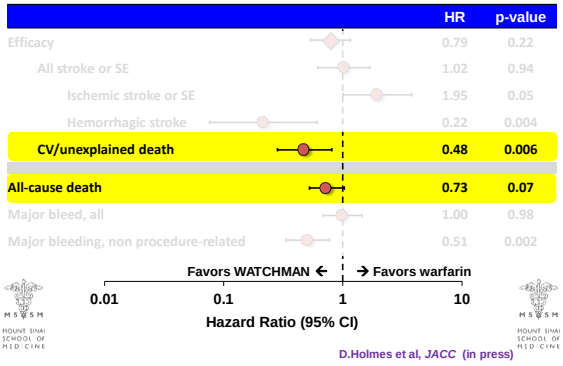

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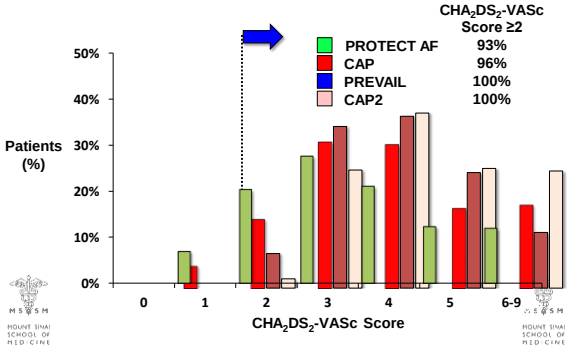
Watchman Clinical Trials
Patients were at High Risk



Modified HAS-BLED Score

> 90% Patients at Moderate/High Bleeding Risk

Study	Patients (%) with HAS-BLED* Score		
	Low Risk (0)	Moderate Risk (1-2)	High Risk (3+)
SPORTIF (Ximelegatran)	24.0	61.0	15.1
PROTECT AF (N=707)	6.4	73.7	19.9
PREVAIL (N=407)	1.7	68.6	29.7
CAP (N=566)	2.8	61.0	36.2
CAP2 (N=579)	2.8	69.9	28.3

* Estimated – HAS-BLED Score retrospectively calculated. Labile INR and Abnormal LFT were not prospectively collected. Therefore, maximum score that WATCHMAN clinical trial patients could attain was 7.

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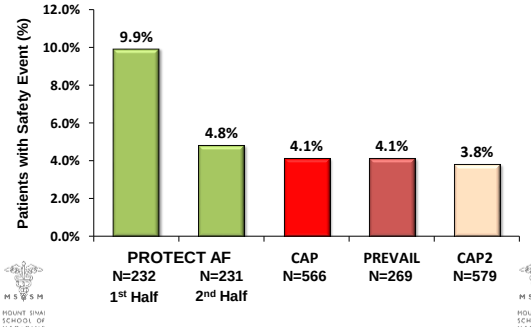
Safety Events Across Trials

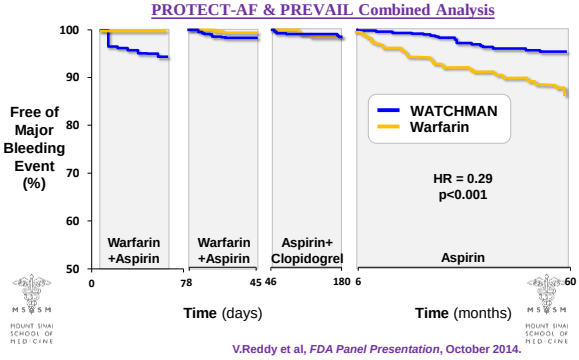
PROTECT AF, CAP, PREVAIL & CAP-1



Bleeding: A Safety Issue with OAC

Less Bleeding after 6-mo Post-Implantation

PROTECT-AF & PREVAIL Combined Analysis



V.Reddy et al, *FDA Panel Presentation*, October 2014.

Left Atrial Appendage Closure

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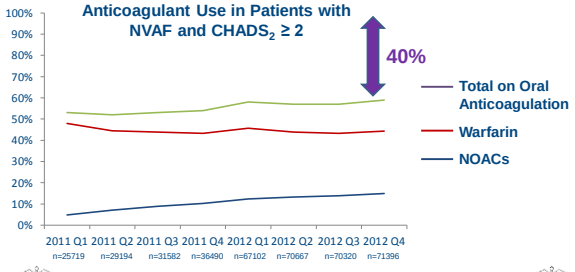
Drug Use Since the Introduction of NOACs

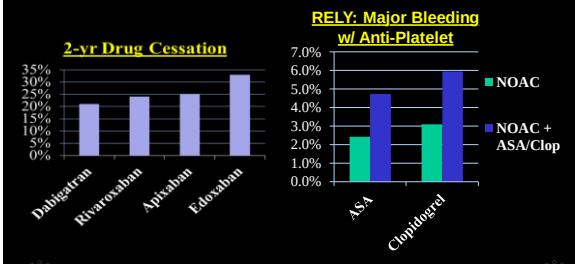
Warfarin is Still the Most Commonly Used Drug



Jani, et al. Results from the NCDR-Pinnacle Registry *ACC -2014*

NOACs are Excellent Medications

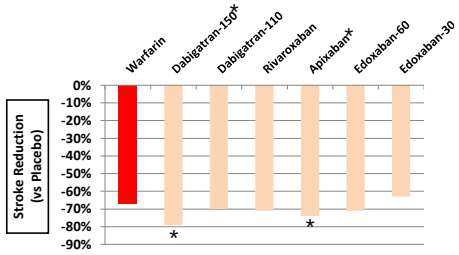
But Not for Everyone…



FDA Slide Deck. *Dabigatran FDA Review from Panel Meeting* 2010

Preventing Stroke in Non-Valvular AF

Imputed Benefit of Different Strategies (*vs* Control)



*Reached statistical superiority relative to warfarin.

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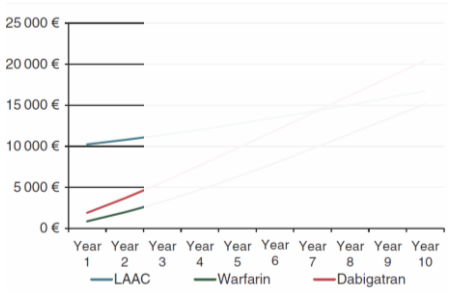
5. **How cost-effective is LAAC?**

Economic Analysis: Budget Impact

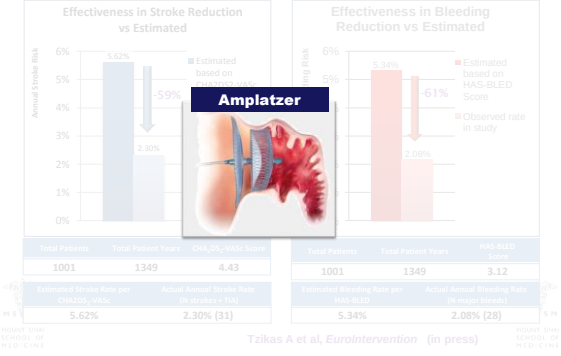
Watchman *vs* Dabigatran *vs* Warfarin



S.L.Amarosi et al, *Europace*, 16:1131 (2014)

Amplatzer Cardiac Plug Registry

Efficacy



Tzikas A et al, *EuroIntervention* (in press)

Final Thoughts

LA Appendage Closure & Stroke Prevention

- ~40% of patients are not protected against stroke w/ OACs
- "Local" therapy with LAA closure is comparable to Warfarin
  - LAAC less effective in preventing Ischemic Strokes, but balanced by fewer Hemorrhagic Strokes
  - Over 50% reduction in Disabling Strokes
  - Over 50% reduction in Cardiovascular Mortality
- Safety improves with Operator Experience
  - Tamponade Rate: 5% [PROTECT AF] → 1-2% [CAP/PREVAIL/CAP-2]

The Watchman Device
FDA Labeling

- **Watchman is indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who are:**
  1. **At increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc scores**
  2. **Are suitable for warfarin**
  3. **And have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.**

Watchman: FDA Labeling
Device Patient Selection Considerations

Rationale for seeking an alternative to warfarin:

- A history of major bleeding while taking therapeutic anticoagulation therapy
- The patient's prior experience with oral anticoagulation (if applicable)
- A medical condition, occupation, or lifestyle placing the patient at high risk of major bleeding secondary to trauma

Factors to consider for Watchman implantation:

- The presence of indication(s) for long-term warfarin use, other than non-valvular atrial fibrillation
- Overall medical status
- Suitability for percutaneous, trans-septal procedures
- Ability to comply with the recommended post-Watchman device implant pharmacologic regimen

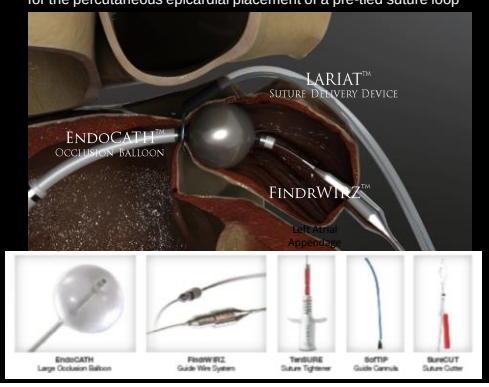
VuMedi CME Webinar: LAA closure in 2015
London – 16 June 2015

LAA Closure: The Epicardial Approach

Dr John P Foran
Consultant Cardiologist
Royal Brompton Hospital – London, GB

Components of the Lariat LAA closure device

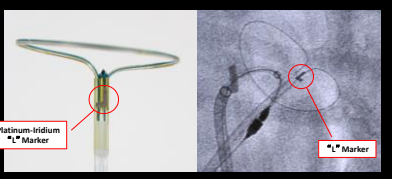
for the percutaneous epicardial placement of a pre-tied suture loop



Lariat LAA closure animation

The Next Generation LARIAT + Device

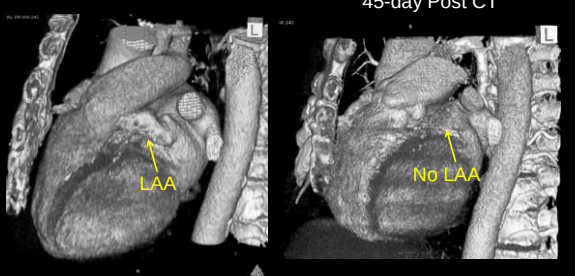
Lariat +
snare width increased from
40 mm → 45 mm



Lariat LAA ligation closure may result in a permanent transmural lesion

Pre CT

45-day Post CT



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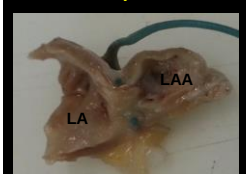
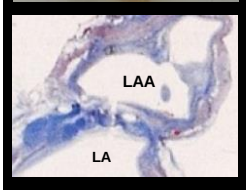
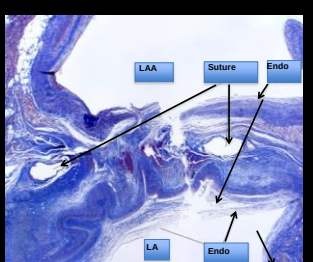


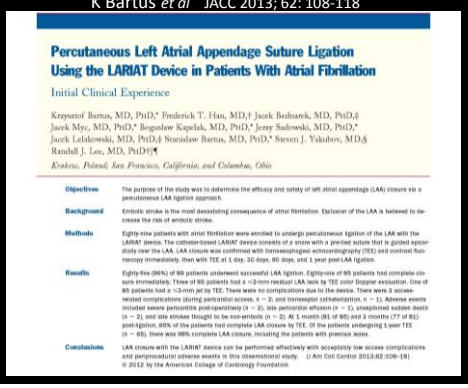




Bartus *et al* Circ Arrhythmia 2014; 7: 764-767

Lariat Device – Initial clinical experience

K Bartus *et al* JACC 2013; 62: 108-118



Percutaneous Left Atrial Appendage Suture Ligation Using the LARIAT Device in Patients With Atrial Fibrillation

Initial Clinical Experience

Krzysztof Bartus, MD, PhD,* Frederick T. Han, MD,† Jacek Bednarek, MD, PhD,‡ Jacek Myc, MD, PhD,* Bogusław Kapelak, MD, PhD,* Jerzy Sadowski, MD, PhD,* Jacek Lelakowski, MD, PhD,‖ Stanisław Bartus, MD, PhD,* Steven J. Yakubov, M.D.§ Randall J. Lee, MD, PhD†¶

Kraków, Poland; San Francisco, California; and Columbus, Ohio

Objectives The purpose of the study was to determine the efficacy and safety of left atrial appendage (LAA) closure via a percutaneous LAA ligation approach.

Background Embolic stroke is the most devastating consequence of atrial fibrillation. Exclusion of the LAA is believed to decrease the risk of embolic stroke.

Methods Eighty-nine patients with atrial fibrillation were enrolled to undergo percutaneous ligation of the LAA with the LARIAT device. The catheter-based LARIAT device consists of a snare with a pre-tied suture that is guided epicardially over the LAA. LAA closure was confirmed with transesophageal echocardiography (TEE) and contrast fluoroscopy immediately, then with TEE at 1 day, 30 days, 90 days, and 1 year post-LAA ligation.

Results Eighty-five (96%) of 89 patients underwent successful LAA ligation. Eighty-one of 85 patients had complete closure immediately. Three of 85 patients had a >2-mm residual LAA leak by TEE color Doppler evaluation. One of 85 patients had a >3-mm jet by TEE. There were no complications due to the device. There were 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). 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.

Conclusions LAA closure with the LARIAT device can be performed effectively with acceptably low access complications and periprocedural adverse events in this observational study. (J Am Coll Control 2013;62:108–18) © 2013 by the American College of Cardiology Foundation

Micropuncture telescopic 2-piece needle pericardial access technique

LAA Closure: The Epicardial Approach

Discussion points:

- Truly OAC contraindicated patients
- Planning CTLA
- Novel µ-puncture telescopic 2-piece needle
- Third generation Lariat + device
- Initial European Experience with Lariat + (n=86)
  86/86 acute closure / n=2 (2.3%) complications / 97% (30/31) complete closure at 3/12 f/u
- No device related concerns

VuMedi Webinar

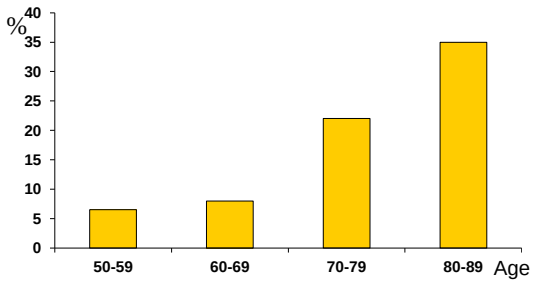
Endocardial Devices

Sameer Gafoor, Horst Sievert, Patrick Böhm,
Ilona Hofmann, Laura Vaskelyte, Stefan Bertog
CardioVascular Center Frankfurt - CVC
Frankfurt, Germany

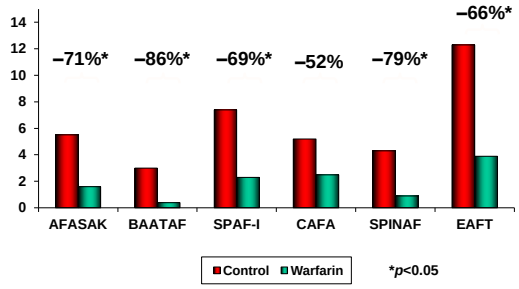
Indications and indications

Atrial fibrillation is one of the most important stroke causes, especially in the elderly

Framingham Study, Wolf, 1991



Anticoagulation in AF
Randomised Trials



Anticoagulation is effective, …

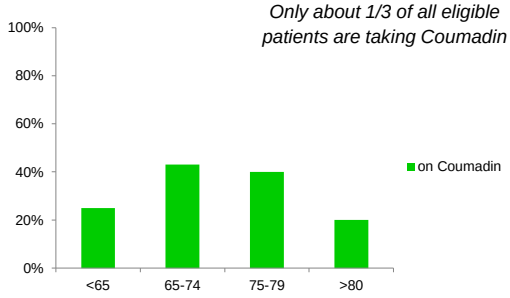
… but unfortunately it does not always work in clinical practice…

… not with warfarin and not with newer drugs

- Any localized or general physical condition in which the hazard of hemorrhage might be greater than the potential clinical benefits of anticoagulation
- Any personal circumstance in which the hazard of hemorrhage might be greater than the potential clinical benefits of anticoagulation
- Pregnancy
- Hemorrhagic tendencies
- Blood dyscrasias.
- Recent or contemplated surgery of central nervous system
- Recent or contemplated surgery of the eye
- Recent or contemplated traumatic surgery resulting in large open surfaces
- Gastrointestinal bleeding
- Genitourinary tract bleeding
- Respiratory tract bleeding
- Cerebrovascular hemorrhage
- Cerebral aneurysms
- Dissecting aorta
- Pericarditis
- Pericardial effusions
- Bacterial endocarditis
- Threatened abortion
- Eclampsia
- Preeclampsia
- Inadequate laboratory facilities
- Unsupervised patients
- Senility
- Alcoholism
- Psychosis
- Lack of patient cooperation
- Spinal puncture
- Other diagnostic procedures with potential for uncontrollable bleeding
- Therapeutic procedures with potential for uncontrollable bleeding
- Major regional anesthesia
- Lumbar block anesthesia
- Malignant hypertension

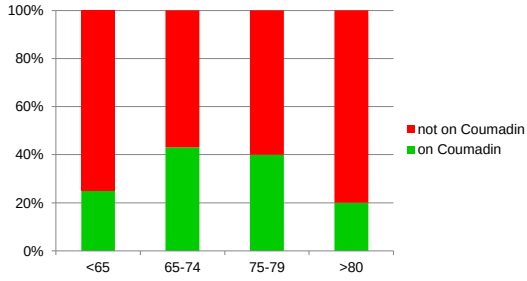
Lone Atrial Fibrillation

Only about 1/3 of all eligible patients are taking Coumadin



Stafford and Singer, Arch Int Med, 1996

Lone Atrial Fibrillation



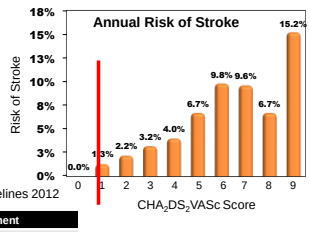
Stafford and Singer, Arch Int Med, 1996

CHA_2DS_2VASc

- CHA_2DS_2VASc, developed by Lip et al, is a refinement of the older $CHADS_2$ Score which includes additional stroke risk factors and puts greater emphasis on age as a risk factor[1]

	Condition/Risk Factor	Points
C	Congestive heart failure	1
H	Hypertension	1
A_2	Age ≥75 years	2
D	Diabetes Mellitus	1
S_2	Previous stroke or TIA	2
V	Vascular disease	1
A	Age 65-74 years	1
Sc	Sex (female gender)	1

European Society of Cardiology Guidelines 2012



CHA_2DS_2-VASc Score	Treatment
0 or 1 and female	none
≥ 1	Coumadin or NOAC

1. Lip GY et al, *Chest* 2010;137(2):263-72

Is there another option to reduce this?

Where do thrombi form?

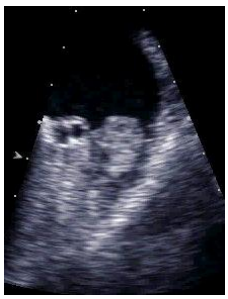
Setting	N	Appendage	Percent	LA Body	Percent	Reference
TEE	317	66	21	1	0.3	Stoddard; JACC, 1995
TEE	233	34	15	1	0.4	Manning; Circ, 1994
Autopsy	506	35	7	12	2.4	Aberg; Acta Med Scan, 1969
TEE	52	2	4	2	3.8	Tsai; JFMA, 1990
TEE	48	12	25	1	2.1	Klein; Int J Card Image, 1993
TEE & Operation	171	8	5	3	1.8	Manning; Circ, 1994
SPAF III TEE	359	19	5	1	0.3	Klein; Circ, 1994
TEE	272	19	7	0	0.0	Leung; JACC, 1994
TEE	60	6	10	0	0.0	Hart; Stroke, 1994
Total	**2018**					

Total Thrombus	222	201	90.5	21	9.5	

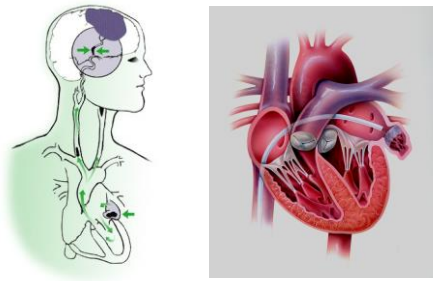
Blackshear and Odell, Ann Thoracic Surgery 1996

Who among us has not seen this?

Or at least been tested on it?



Stroke Prophylaxis: LAA Closure



Blackshear and Odell, Ann Thoracic Surgery 1996

Where is the evidence?

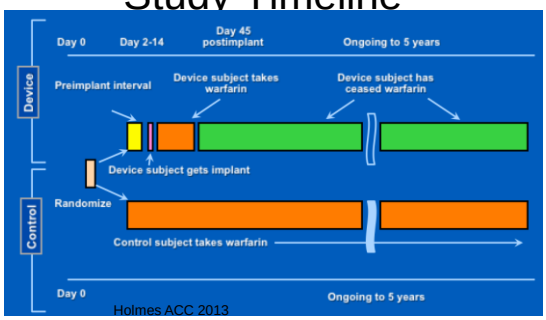
Trials to know…

- PROTECT AF
- CAP
- PREVAIL
- ASAP

PROTECT AF Trial

- Prospective, randomized study of WATCHMAN LAA Device vs. Long-term Warfarin Therapy
- 2:1 allocation ratio device to control
- 800 Patients enrolled from Feb 2005 to Jun 2008
  - Device Group (463)
  - Control Group (244)
  - Roll-in Group (93)
- 59 Enrolling Centers (U.S. & Europe)
- Follow-up Requirements
  - TEE follow-up at 45 days, 6 months and 1 year
  - Clinical follow-up biannually up to 5 years
  - Regular INR monitoring while taking warfarin

PROTECT-AF Trial Study Timeline



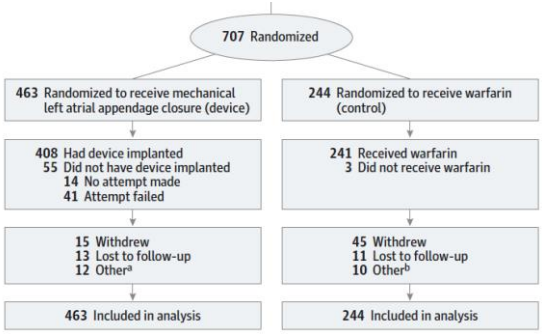
Holmes ACC 2013

PROTECT-AF Study Endpoints

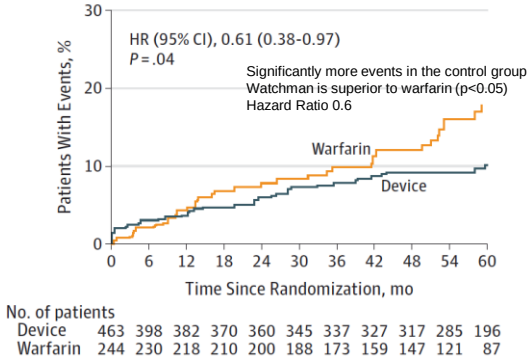
- Efficacy endpoint
  - All stroke – ischemic or hemorrhagic
    - Deficit with symptoms more than 24 hours
    - Symptoms less than 24 hours confirmed by CT or MRI
  - CV and unexplained death
    - includes sudden death, MI, CVA, arrhythmia, and heart failure
  - Systemic Embolization

PROTECT-AF Study Endpoints

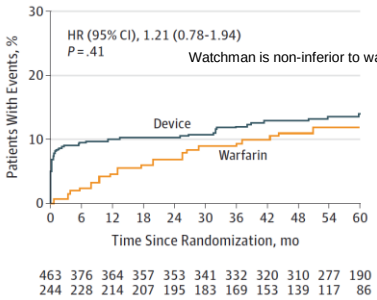
- Safety Endpoint
  - Device embolization requiring retrieval
  - Pericardial effusion requiring intervention
  - Cranial bleeds and GI bleeds
  - Any bleed requires more than 2U PRBC

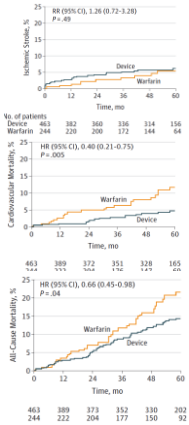


Primary efficacy endpoint



Primary safety endpoint





Ischemic stroke — RR 1.26, p=NS

CV Mortality — RR 0.40 p=0.005

All-cause mortality — RR 0.66 p=0.04

Safety endpoint

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

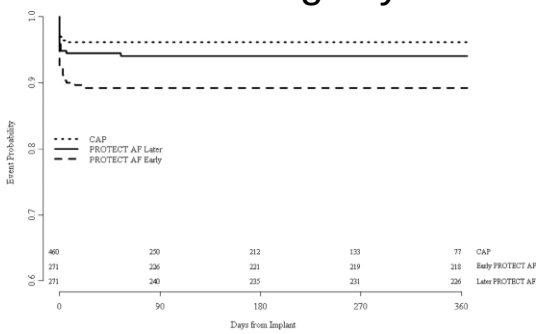
Issues with the PROTECT-AF trial

- PROTECT-AF had low risk patients (34% of subjects had CHADS2 score of 1
- Adjunctive antiplatelet therapy with aspirin and clopidogrel enrolled in the trial
- Acute safety events: 56% of primary safety events in device group occurred on day of procedure

Continued Access Registry

- Continued access to the Watchman device for a subset of the PROTECT-AF study investigators
- Nonrandomized
- Same inclusion and exclusion criteria as PROTECT AF
- 460 patients at 26 centers between August 2008-April 2010

CAP Registry



CAP Registry results

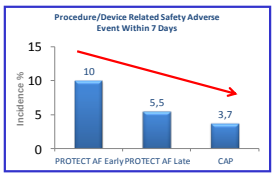
- Serious pericardial effusion rate down to 2.2%
- No procedure –related stroke
- Relative risk reduction of 56% (p=0.002) in procedure or device-related safety events
- Relative risk reduction of 58% (p=0.014) in serious pericardial effusions

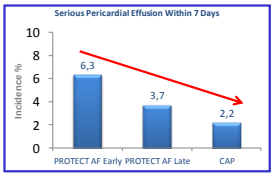
PROTECT-AF early vs. late

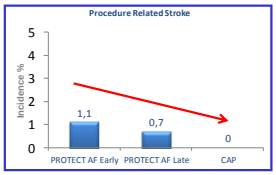
	PROTECT AF	PROTECT AF		PROTECT AF		CAP	P*	P†	P‡
	PROTECT AF	Early	Late	First 3 Patients	Other Patients	CAP	P*	P†	P‡
Procedure time, mean±SD, min	62±34	67±36	58±33	82±40	55±29	50±21	<0.001	<0.001	<0.001
Implant success, n/total (%)	485/542 (89.5)	239/271 (88.2)	246/271 (90.8)	133/154 (86.4)	352/388 (90.7)	437/460 (95.0)	0.001	0.001	0.136
Procedure/device-related safety adverse event within 7 d, n/total (%)	42/542 (7.7)	27/271 (10.0)	15/271 (5.5)	19/154 (12.3)	23/388 (5.9)	17/460 (3.7)	0.007	0.006	0.012
Serious pericardial effusion within 7 d, n/total (%)	27/542 (5.0)	17/271 (6.3)	10/271 (3.7)	10/154 (6.5)	17/388 (4.4)	10/460 (2.2)	0.019	0.018	0.308
Procedure-related stroke, n/total (%)	5/542 (0.9)	3/271 (1.1)	2/271 (0.7)	1/154 (0.7)	4/388 (1.0)	0/460 (0)	0.039	0.039	0.675

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

Reasons for PREVAIL study

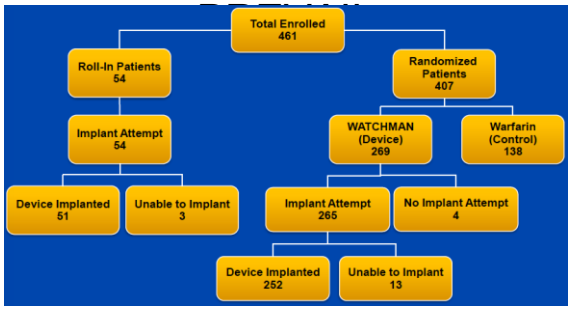
- Concerns for early PROTECT-AF stafety
  - Many pericardial effusions and procedure related strokes
  - Many Watchman patients did not receive assigned treatment
  - Not tested with new operators
- Second randomized trial needed to confirm late PROTECT-AF and CAP results
- More warfarin compliance needed
- Change the noninferiority margin

PREVAIL study

- Prospective multicenter 2:1 randomized study
- Faster time from randomization to implant
- More new implanters
- Different primary endpoints
  - 1st primary endpoint – same as PROTECT AF
  - 2nd primary endpoint
    - Ischemic stroke and systemic embolism >7 days post randomization

PREVAIL inclusion criteria

- CHADS2 criteria – calculated score of 2 or greater
- Took people that would not be candidates for aspirin therapy alone, i.e.,
  - CHADS1 criteria of 1 or greater if
    - Age >75 or older
    - Baseline LVEF 30-35%
    - Age 65-74 and has diabetes or CAD
    - 65 or greater with documented CHF

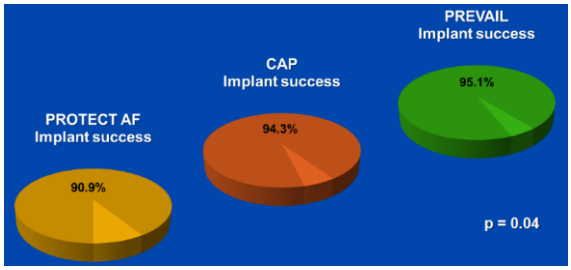


PREVAIL patients were different

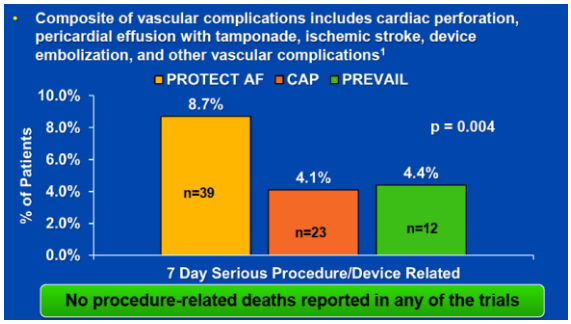
Characteristic	PROTECT AF N=463	CAP N=566	PREVAIL N=269	P value
Age, years	71.7 ± 8.8 (463) (46.0, 95.0)	74.0 ± 8.3 (566) (44.0, 94.0)	74.0 ± 7.4 (269) (50.0, 94.0)	<0.001
Gender (Male)	326/463 (70.4%)	371/566 (65.5%)	182/269 (67.7%)	0.252
CHADS$_2$ Score (Continuous)	2.2 ± 1.2 (1.0, 6.0)	2.5 ± 1.2 (1.0, 6.0)	2.6 ± 1.0 (1.0, 6.0)	<0.001
CHADS$_2$ Risk Factors				
CHF	124/463 (26.8%)	108/566 (19.1%)	63/269 (23.4%)	
Hypertension	415/463 (89.6%)	503/566 (88.9%)	238/269 (88.5%)	
Age ≥ 75	190/463 (41.0%)	293/566 (51.8%)	140/269 (52.0%)	
Diabetes	113/463 (24.4%)	141/566 (24.9%)	91/269 (33.8%)	
Stroke/TIA	82/463 (17.7%)	172/566 (30.4%)	74/269 (27.5%)	

Most notable differences:
Age, Diabetes, and Prior Stroke/TIA

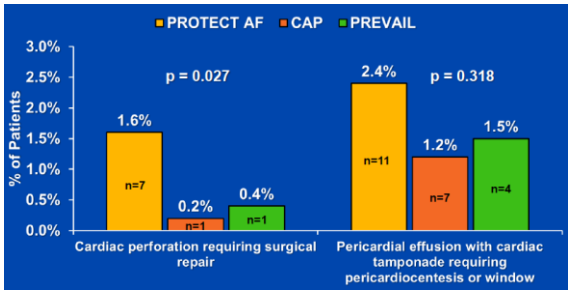
Implant success improved



Vascular complications decreased



Pericardial effusions requiring intervention decreased



Endpoints

- Primary endpoint: 7 day death ischemic stroke, systemic embolism and procedure or device-related complications requiring major cv endovascular intervention
  - Improved procedural implant success
  - Decreased composite vascular complications
  - Decreased procedural stroke rate
  - Decreased perforations requiring surgical repair
  - Little difference in outcome between new and old operators

Endpoints

- 2 endpoint: composite endpoint of stroke, systemic embolism and CV death
  - Control group had low event rates compared to past
  - Similar low event rate
  - Although event rates similar, did not meet non-inferiority criterion

In addition, improved warfarin discontinuation

New PREVAIL WATCHMAN Subjects	45 Days Post-Implantation	6 months Post-Implantation
Rate of Warfarin Discontinuation	92.3% (227/246)	98.3% (235/239)

PROTECT WATCHMAN Subjects	45 Days Post-Implantation	6 months Post-Implantation
Rate of Warfarin Discontinuation	86.8% (348/401)	92.2% (355/385)

FDA Approval for

- Nonvalvular atrial fibrillation
- Increased risk for stroke and systemic embolism based on CHADS2 or CHADS2VASc score AND
- Deemed by physicians to be suitable for warfarin AND
- Have appropriate rationale to seek a non-pharmacologic alternative to warfarin

That's nice, except for a slight intercontinental difference

European Heart Journal (2012) 33, 2719–2747
doi:10.1093/eurheartj/ehs253

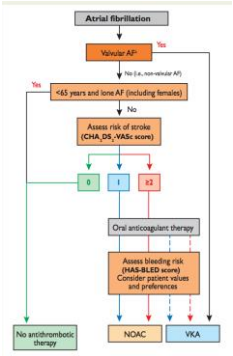
ESC GUIDELINES

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

Authors/Task Force Members: A. John Camm (Chairperson) (UK)*, Gregory Y.H. Lip (UK), Raffaele De Caterina (Italy), Irene Savelieva (UK), Dan Atar (Norway), Stefan H. Hohnloser (Germany), Gerhard Hindricks (Germany), Paulus Kirchhof (UK)

Camm EHJ 2012



Camm EHJ 2012

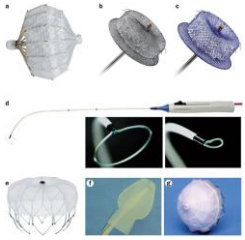
So what did they recommend?

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

Camm EHJ 2012 ESC 2012 Update Afib Guidelines

Why did they do that?

- There are more devices available in Europe than in the US



Yu Nature Reviews Cardiology 2013

Why did they do that?

- More studies available in Europe with more patients, mostly for contraindicated for anticoagulation

Observed and expected events at 1 year in different studies in LAA occlusion patients contraindicated for OAC

Study name	Number of patients	CHA_2DS_2-VASc	Follow-up (months)	Total stroke/TIA follow-up	Stroke %/year	% Reduction	Death patient/year	Antithrombotic therapy
Spanish Unicentre (ACP)[14]	35	3.94±1.89	21.14±10.1	2.85% (1/35)	0% versus 5.45%		5.04%	3–6 m DAPT 3 m indefinite ASA
Partial ACP European postmarket	145	3.7±1.7	24	2.12% (1/47)	1.24% versus 5.33%	65%	NA	3 m DAPT 3 m ASA
USA-European ASAP (Watch)[13]	150	4.4±1.7	14.4±8.6	2.6% (4/150)	1.7% vs 7.3%	77%	5%	6 m DAPT
Canadian (ACP)[15]	52	5 (4–6)	20±5	5.7% (3/52)	1.1% vs 8.6%	87%	5.8%	1–3 or 1–6 m
Iberian multicentre (current)	167	4 (3–6)	22±8.3	4.2% (7/167)	2.4% vs 9.6%	75%	5.8%	3–6 m DAPT 6 m indefinite ASA
Average of figures or percentages	549	4.2	20.38	3.54% (16/451)	1.28% vs 7.25%	76%	5.41%	

ACP, Amplatzer Cardiac Plug; ASA, aspirin; DAPT, double antiplatelet therapy; LAA, left atrial appendage; OAC, oral anticoagulant; TIA, transient ischaemic attack.

Lopes-Minguez Heart 2015

ASAP trial for Watchman

- 150 patients with Afib at 4 centers
- Not candidates for oral anticoagulation

Left Atrial Appendage Closure With the Watchman Device in Patients With a Contraindication for Oral Anticoagulation

The ASAP Study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology)

Vivek Y. Reddy, MD,* Sven Möbius-Winkler, MD,† Marc A. Miller, MD,* Petr Neuzil, MD, PhD,‡ Gerhard Schuler, MD,† Jens Wiebe, MD,§ Peter Sick, MD,‖ Horst Sievert, MD§

New York, New York; Leipzig, Frankfurt, and Regensburg, Germany; and Prague, Czech Republic

Reddy JACC 2013

ASAP trial

Table 3 Procedure and Device-Related Serious Adverse Events (N = 150)

Device embolization	2 (1.3%)
Pericardial effusion with tamponade (percutaneous drainage)	2 (1.3%)
Pericardial effusion, no tamponade (no intervention required)	3 (2.0%)
Device thrombus with ischemic stroke*	1 (0.7%)
Femoral pseudoaneurysm (surgically repaired)	1 (0.7%)
Femoral hematoma/bleeding	2 (1.3%)
Other†	3 (2.0%)
Total patients with procedure- and device-related SAEs	13 (8.7%)

Values are n (%). *Device thrombus and stroke occurred in a single patient, but is counted as 2 adverse events. †Oral bleeding, n = 1, and intraprocedural hypotension, n = 2.
SAE = serious adverse event(s).

Reddy JACC 2013

ASAP trial

Table 4 Clinical Outcomes

	Entire Cohort Events/Patient-Years*
Primary efficacy	8/175.0 (4.6%)
Death, all cause	9/180.0 (5.0%)
All stroke	4/176.0 (2.3%)
Ischemic stroke	3/176.9 (1.7%)
Hemorrhagic stroke	1/179.1 (0.6%)

The primary efficacy endpoint was defined as the combined events of ischemic stroke, hemorrhagic stroke, systemic embolism, and cardiovascular/unexplained death. *Events per 100 patient-years.

Expected rate with CHADS2 7.3%

Expected rate if use aspirin and clopidogrel 5.0%

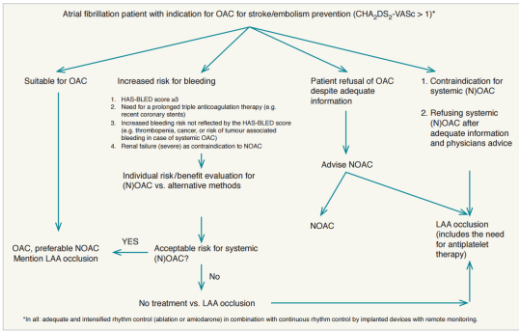
Actual seen rate of ischemic stroke 1.7%

Reddy JACC 2013

Other possible/(upcoming) indications

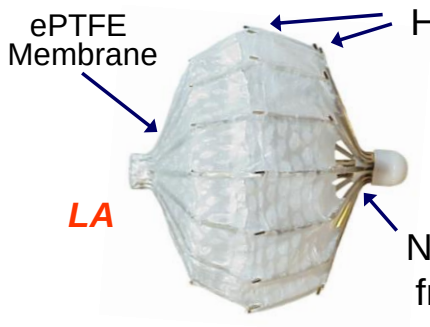
- Patients with contraindication to anticoagulation
- As complement to anticoagulation (e.g., patient now requires PCI)
- As adjunct to ablation of atrial fibrillation

Meier, Sievert et al. Eurointerv 2014

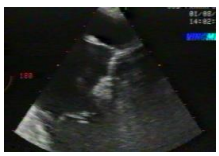


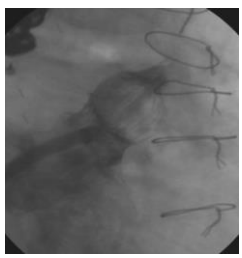
Meier, Sievert et al. Eurointerv 2014

PLAATO™ Occluder



First LAA closure Aug 30, 2001





- Procedure time 85 min
- Coumadin off since 2001
- Had his 84th birthday in Jan 2013
- Zero bleeding
- Zero embolic events

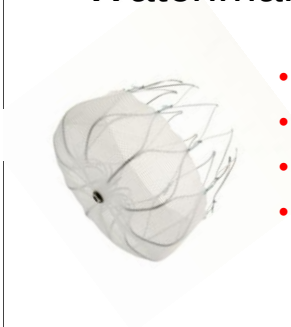
PLAATO

- Technical success rate 94%
- Periprocedural MAE 5%
- No device related complications beyond 30 days
- Stroke risk reduction 65%
- FU up to 11 yrs

LAA Closure

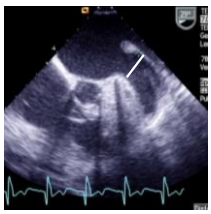
Endocardial	Epicardial
• PLAATO	• SentreHeart
• Watchman	• AEGIS
• ACP → Amulet	• AtriCure
• Coherex	• Medtronic
• Sideris Patch	
• Occlutech	
• pfm Medical	
• Lifetech	
• Cardia	

Watchman Occluder

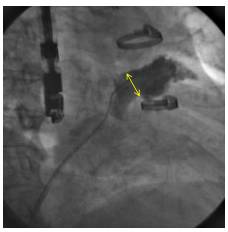


- Nitinol
- PET membrane
- Hooks
- 21, 24, 27, 30, 33 mm

Watchman Implantation

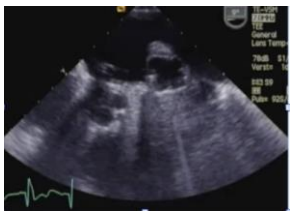


- LAA diameter in TEE 19 mm



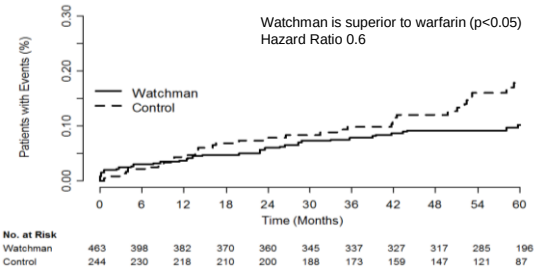
Watchman Implantation

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

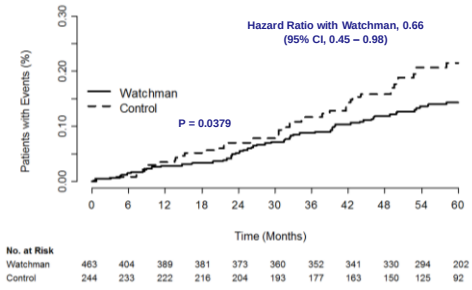


- device selection according to measurements
- Implantation of 21mm Watchman Occluder

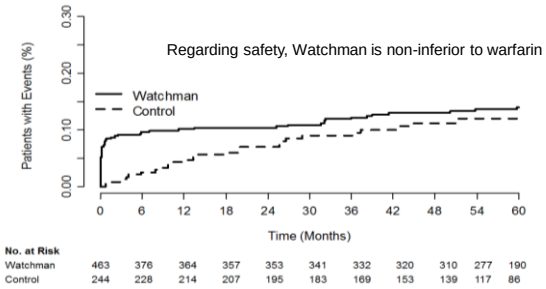
PROTECT AF:
Primary Efficacy Endpoint:
Stroke, Death, Systemic Embolization



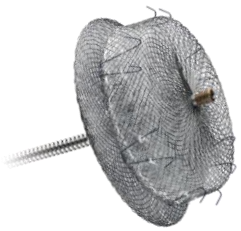
Intention-to-Treat:
All-Cause Mortality

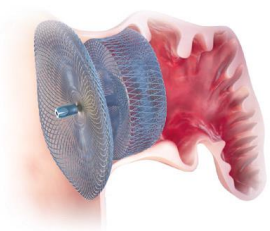


Primary Safety Endpoint:
device embolization, pericardial effusion, severe bleeding



Amplatzer Cardiac Plug



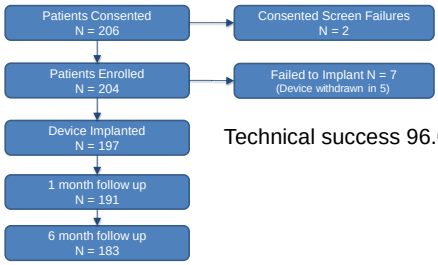


- Lobe diameter 16-30mm
- Lobe length 6.5mm
- Disk diameter 20-36mm
- 9, 10 or 13F sheath

Amplatzer Cardiac Plug
Post-Market EU Registry

- Prospective study
- 100 % monitored
- Independent adjudication of AEs
- 15 European centers
- N = 204
- Follow-up: 1214 patient months

Amplatzer Cardiac Plug
Post-Market EU Registry



Technical success 96.6%

Device/Procedure Related Safety Events

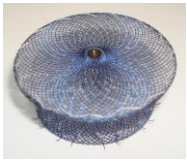
	≤7 Days Post Procedure	>7 days Post Procedure	Total
Peri-procedural Stroke / TIA*	0 (0.0%)	0 (0.0%)	0 (0.0%)
Serious Pericardial Effusion	3 (1.5%)	0 (0.0%)	3 (1.5%)
Device Embolization	3 (1.5%)	0 (0.0%)	3 (1.5%)
Device Related Thrombus	0 (0.0%)	5 (2.4%)	5 (2.4%)
Total Safety Events	**6 (2.9%)**	**5 (2.4%)**	**11 (5.4%)**

* The stroke/TIA is reference to device or procedure related strokes as adjudicated by the AE Review Committee.

N=204

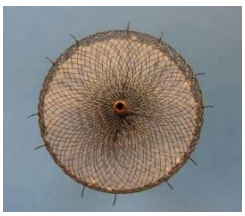
Amulet

- Pre-loaded
- Recessed end screw
- Larger disc diameter
- Longer lobe length
- Longer waist length
- Larger sizes up to 34mm
- Stiffer stabilizing wires (.0065)
- More stabilizing wires on larger devices



Increased Stability

- More stabilizing wires in larger devices
  - ➢ increased stability

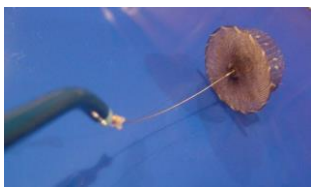


ACP

Amulet

Flexible Delivery Cable

- Delivery cable includes an 0.014" inner wire
- Enables visualization of final device placement prior to release

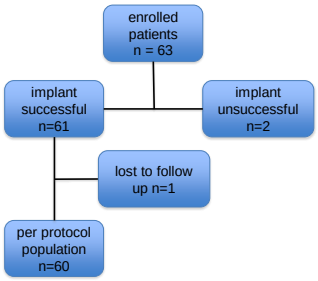


Coherex WaveCrest

- **Retractable anchors**
- ePTFE occluder material is **occlusive** and non-thrombogenic
- Distal contrast injection
  - to assess stability
  - to assess occlusion
- 3 sizes (22, 27, 32mm)

CE mark Aug 2013

The Coherex WAVECREST I Trial Gen 1.3



The Coherex WAVECREST I Trial

Primary Efficacy Endpoint

	intent to treat (n = 63)	per protocol[1] (n=60)
45 day closure[2]	58 (92%)	58 (97%)

1) *per protocol: successful device implant & 45 day transesophageal echo suitable for interpretation by echo core lab*
2) *closure: no residual flow >3 mm*

The Coherex WAVECREST I Trial

Primary Safety Endpoint

MAEs through 45 Days

Enrolled population	N = 63
Device embolization	0
Pericardial effusion	0
Stroke or TIA	0
Device associated thrombus	0

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Future of LAA Closure

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

VuMedi Webinar
June 2015

Presenter Disclosure Information

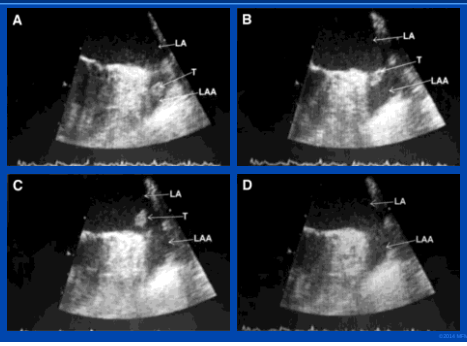
David R. Holmes, Jr., M.D.

"Future of LAA Closure"

The following relationships exist related to this presentation:

Both Mayo Clinic and I have a financial interest in technology related to this research. That technology has been licensed to Boston Scientific.

Disappearing LAA Thrombus Resulting in Stroke



Parekh A, Ezekowitz M et al: Circ 114:e513, 2006

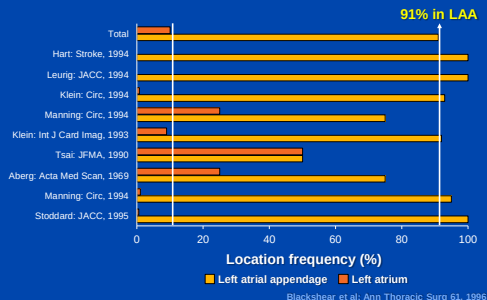
LAA Occlusion and Stroke Prevention
What are the Issues

- Stroke risk
- Pathophysiology of stroke
- Bleeding and drug discontinuation remains a problem with OAC therapies (new and old)
- Site specific therapy makes intuitive sense
- Does it work?
- Which patients

How Big is the Problem?

- AF is the most common arrhythmia
  - Affects more than 3 million individuals in the U.S.
  - Projected to increase to 16 million by 2050
- Lifetime risk in men and women >40 is 1 in 4
- Patients with AF have a 5-fold higher risk of stroke
  - Over 87% of strokes are thromboembolic
  - Cardioembolic strokes result in highest morbidity and mortality
  - Recurrence rates are high
  - Both AF and Stroke increase as we grow older

Location of Thrombi in Left Atrium



Blackshear et al: Ann Thoracic Surg 61, 1996

Nonvalvular Atrial Fibrillation
Stroke Prevention

- Warfarin most commonly used
  - Reduces stroke by 64%
- Severely underutilized
  - Even after AF stroke only 30-70% of patients are anticoagulated
- At 3 years after initiation of warfarin ~ 50% of patients discontinue therapy
- Clinical reality
  - "VKA therapy only achieves a fraction of its evidence-based potential"

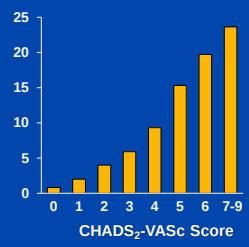
Lewalter T et al: Europace 16:626-630, 2014

CHA_2DS_2-VASc Refines Stroke Risk Determination in AF Patients

CHA_2DS_2-VASc Risk Criteria

Risk Factor	Score
Prior stroke or TIA	2
Age ≥75	2
Age 65-74	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1
Vascular disease	1
Female sex	1

One Year Stroke Risk



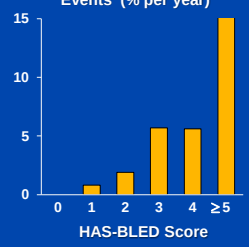
Mason PK: Am J Medicine, 2012

HAS-BLED Stratifies Bleeding Risk on Warfarin

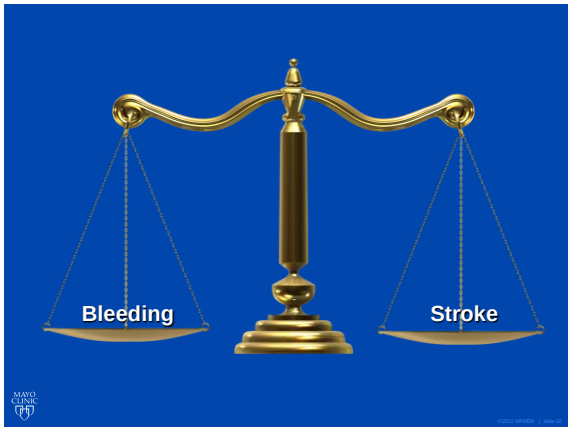
HAS-BLED

Condition	Points
Hypertension	1
Abnormal liver and renal function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INR	1
Age >65	1
Drugs or alcohol (1 point each)	1 or 2

Incidence of Major Bleeding Events (% per year)



Roldan V: Chest, 2013



Nonvalvular Atrial Fibrillation
Stroke Prevention

- NOACS have been widely tested as an alternative to warfarin
- Found to have less ICH than warfarin
- Still not widely adopted
  - Cost
  - Lack of antidotes
  - Dosing
  - Bleeding hazard – GI bleeding may even be increased

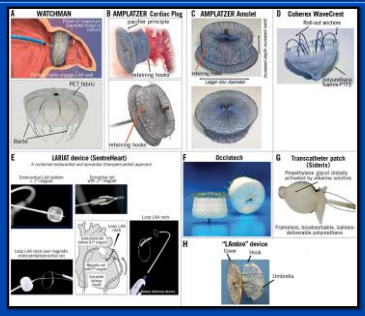
Lewalter T et al: Europace 16:626-630, 2014

NOACS versus Warfarin

- NOACS:
  - Significant ↓ in all cause mortality
    - RR 0.90, 95% CI 0.85-0.95
  - Significant ↓ in ICH
    - RR 0.48, 95% CI 0.39-0.59
  - Significant ↑ in GI bleeding
    - RR 1.25, 95% CI 1.01-1.55

Ruff et al: Lancet 383:955-62, 2014

LAA Closure for Stroke Prevention in Non-Valvular AF



Bergmann MW et al: EuroIntervention 2014;10:497-504

PROTECT AF: Long-Term Efficacy Results (2,621 Patient-Years of Follow-Up)

	Event rate (per 100 pt-yr)			Posterior probabilities	
	WATCHMAN n=463	Control n=244	Rate ratio (95% CrI)	Non-inferiority	Superiority
Primary efficacy	2.3	3.8	0.60 (0.41, 1.05)	>0.999	0.960
Stroke (all)	1.5	2.2	0.68 (0.42, 1.37)	0.999	0.825
Ischemic	1.4	1.1	1.26 (0.72, 3.28)	0.779	0.147
Hemorrhagic	0.2	1.1	0.15 (0.03, 0.49)	0.999	0.999
Systemic embolism	0.2	0.0	NA	NA	NA
Death (CV & unexplained)	1.0	2.4	0.40 (0.23, 0.82)	>0.999	0.995

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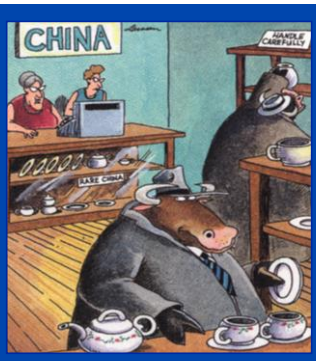
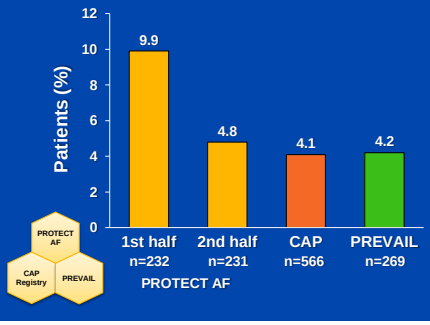
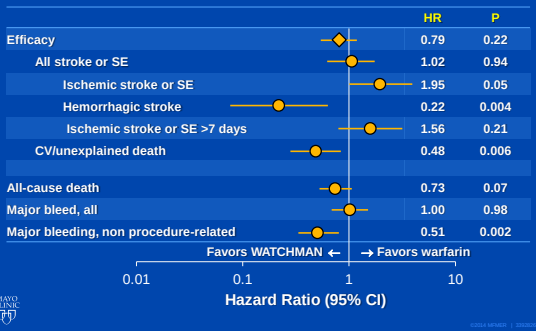


"I got a bad feeling about this, Harriet."

Safety Events: PROTECT AF, CAP, PREVAIL



PROTECT AF/PREVAIL Meta-Analysis: WATCHMAN Comparable to Warfarin



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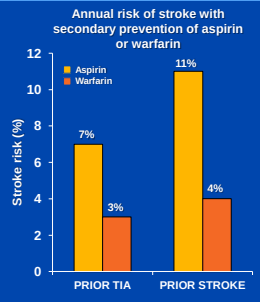
- Does it work?
- Which patients

Aspirin and Plavix® Registry (ASAP)

The ASAP registry is a non-randomized feasibility study designed to evaluate if the WATCHMAN® Device is a safe and effective treatment for people unable to take warfarin

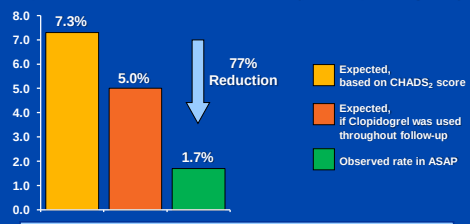
- AF patients who are contraindicated or intolerant of warfarin have few options for thromboembolic prophylaxis
- Patients may be treated with aspirin and/or clopidogrel; this treatment paradigm has a higher stroke risk than warfarin



The WATCHMAN Device is not approved for patients contraindicated to OACs

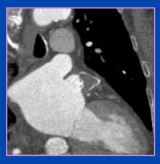
Results

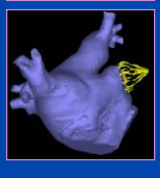
Expected and Observed Stroke Rates (per 100 patient-years)



Observed rate of ischemic stroke represents a 77% reduction from the expected event rate

Stroke and Atrial Fibrillation
Alternative to Warfarin or NOACS





- Patients who could be treated with warfarin/NOACS
- Patients who choose not to be treated with warfarin/NOACS
- Contraindications to warfarin/NOACS

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