

New drugs, new trials

How does LAA occlusion fit?

Dr David Begley
Papworth Hospital, Cambridge
Device Based Stroke Prophylaxis
Heart Rhythm Congress 2011

Overview

- New drugs
 - Novel antithrombotic agents
- New trials (and some old ones)
 - Oral anticoagulation
 - Left atrial appendage occlusion

Heparin (unfractionated)

- Introduced in 1935
- Poly-saccharide chains of varying lengths
- Binds and activates antithrombin III (AT)
- Activated AT inactivates thrombin
(and other proteases – incl. Factor Xa)
- Intravenous or subcutaneous administration

Low-molecular weight heparin (fractionated)

- Introduced in the 1990s
- Short poly-saccharide chains
- Binds and activates antithrombin III
- Activated AT inactivates Xa
(lesser direct effect on thrombin)
- More predictable pharmacokinetics/dynamics
- Subcutaneous administration

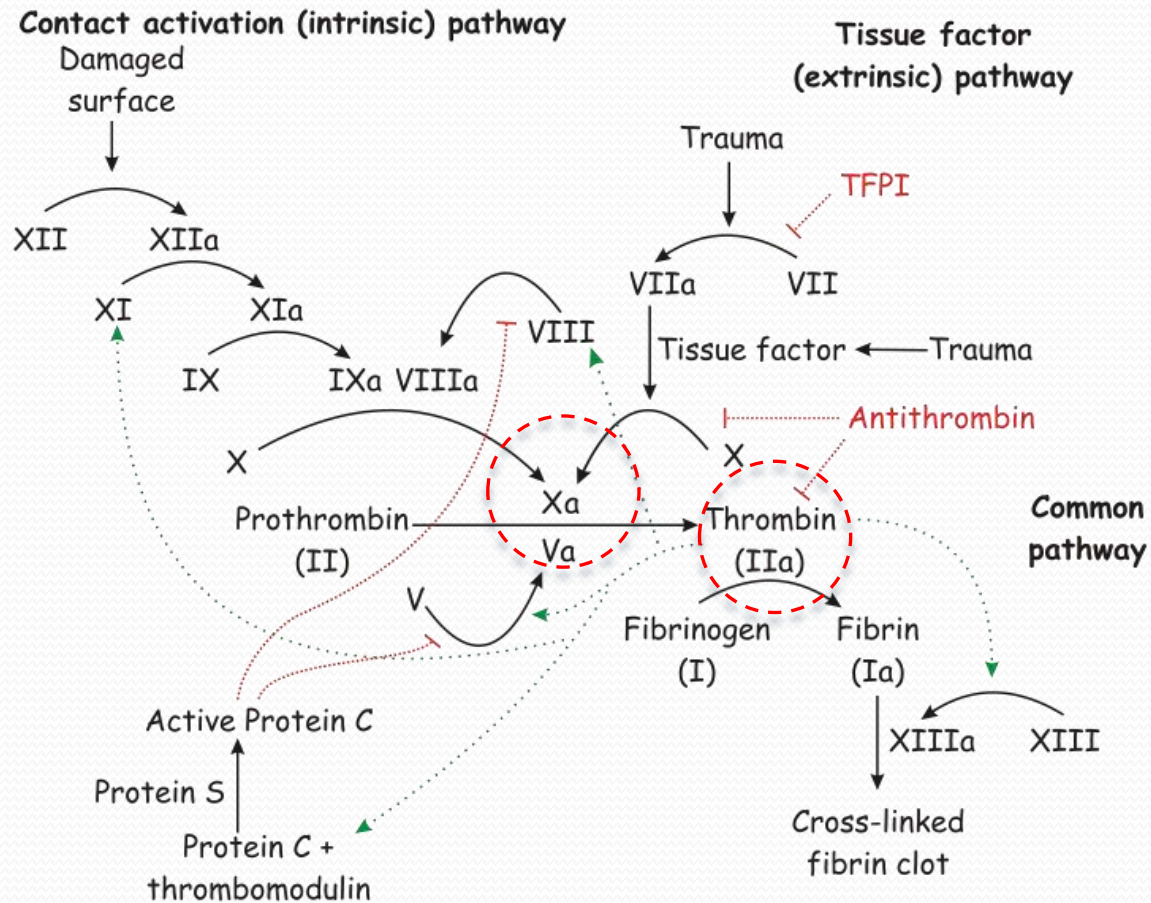
Vitamin K Antagonists

- Introduced in early 1950s
- Inhibits synthesis of calcium dependent clotting factors
 - II, VII, IX and X
- Orally active
- Many limitations
 - Variable metabolism
 - Drug-drug interactions
 - Drug-food interactions
 - Narrow therapeutic window (frequent monitoring)

Anti-Platelet Agents

- Aspirin
- Clopidogrel

Coagulation Cascade



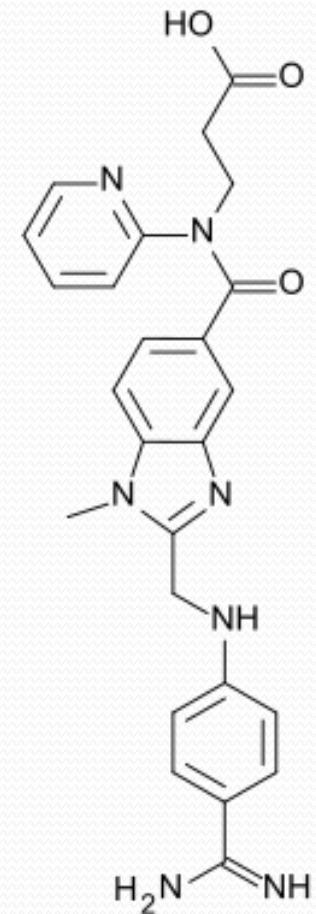
Novel Agents

- Direct thrombin inhibitors
 - Ximelagatran
 - Dabigatran etexilate
 - AZD0837
- Oral factor Xa inhibitors
 - Rivaroxaban
 - Apixaban
 - Edoxaban
 - Betrixaban
 - YM150
 - etc

Direct Thrombin Inhibitors

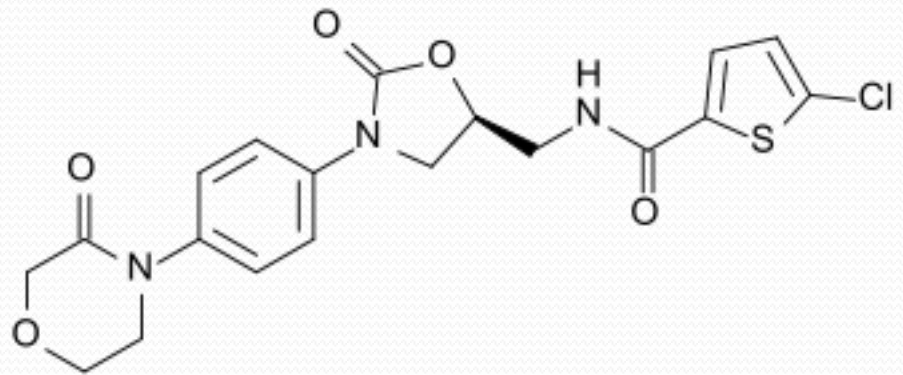
- Dabigatran (Pradaxa)
 - Similar to benzamidine-base thrombin inhibitors
- Orally active
- Short shelf life (humidity)

- Half life 12-17 hours
- Low bio-availability



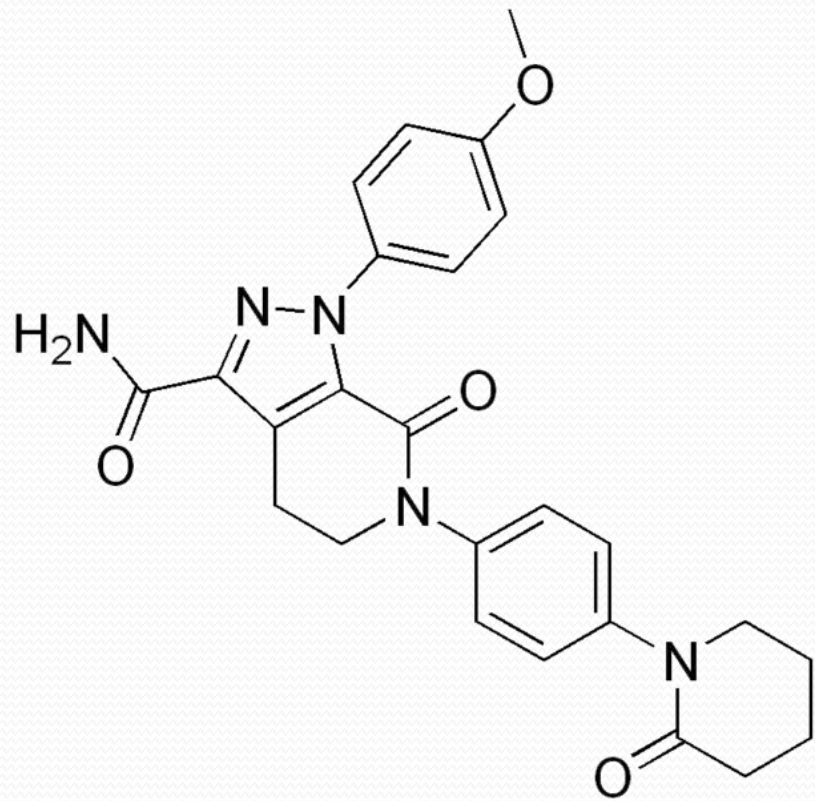
Oral Factor Xa Inhibitors

- Rivaroxaban (Xarelto)
 - Oxazolidinone derivative
- Orally active
- Flat dose response curve
- Half life 7-11 hours
- Excretion 2/3 hepatic



Oral Factor Xa Inhibitors

- Apixaban (Eliquis)
- Orally active
- Half life 9-14 hours
- Excretion
 - 75% biliary
 - 25% renal



Vitamin K agonist versus control

- 5 large randomized studies
- Relative risk reduction 64%
 - 67% including only ischaemic strokes
 - 2.7% absolute annual risk reduction (similar for both primary and secondary prevention)
- 26% reduction in all cause mortality
- Low rate of intra-cranial haemorrhage

Antiplatelet therapy versus control

- 8 randomized studies
- Aspirin resulted in 19% reduction in stroke (not significant)
 - 21% including only ischaemic strokes
 - 0.8% absolute annual risk reduction primary prevention
 - 2.5% absolute annual risk reduction secondary prevention
- Variable dose of aspirin used
- Higher bleeding rates with higher dose (300mg)

Vitamin K agonists versus antiplatelet therapy

- 9 randomized studies
- VKA superior with 39% relative risk reduction
- Increase in bleeding complications with VKA

Oral Anticoagulation

- Narrow therapeutic range
 - Requires frequent monitoring
- Drug – drug interactions
 - Dose adjustment required when adding/removing other drugs
- Drug – food interactions
 - Diet may cause INR to be out of therapeutic range
- Compliance
- 50% of patients who might benefit from OAC may remain untreated or sub-optimally treated¹

RE-LY

- Randomized Evaluation of Long-term anticoagulation therapy
 - Dabigatran versus VKA
 - Dose of dabigatran blind or unblinded adjusted does warfarin
 - 18,113 patients
 - 110mg bd
 - Non-inferior
 - Lower rates of major bleeding
 - 150mg bd
 - Lower rates of stroke
 - Similar rates of major bleeding

ROCKET -AF

- Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
 - Rivaroxaban 20mg od versus warfarin
 - Double blind
 - 14,264 patients
 - Non-inferior to warfarin in terms of stroke or embolism
 - Similar risk of major
 - Intracranial and fatal bleeding less frequent with rivaroxaban

AVERROES

- Apixaban VERsus acetylsalicylic acid to pRevent strOkES study
 - Apixaban 5mg bd versus aspirin 81-324mg od
 - Double blind
 - 5599 patients
 - High risk patients unsuitable for warfarin
 - Stopped early due to clear reduction in stroke
 - Stroke rate 1.9% (Apixaban) versus 3.9% (Aspirin)
 - Similar rates of bleeding complications
 - Major haemorrhage 1.4% (Apixaban) versus 1.2% (Aspirin)

ARISTOTLE

- Apixaban for the prevention of stroke in subjects with atrial fibrillation
 - Apixaban 5mg bd versus warfarin
 - Double blind
 - 18,201 patients
 - AF and one additional risk factor for stroke
 - Superior to warfarin in terms of stroke and embolism
 - Lower rates of major bleeding and death

Guidance and Recommendations

- Licensing in UK
 - Patients >75 years with non-valvular AF and previous stroke/TIA or heart failure
 - Patients >65 years with AF and DM, CAD or hypertension
- NICE
 - Requested further information from manufacturers
 - Have not recommended dabigatran for prevention of stroke in patients with AF
 - Further guidance due in December

Alternatives to Anticoagulation

- Surgical excision or exclusion of left atrial appendage
- Endovascular occlusion

Surgical

- Excision
 - Since 1930s
 - Part of mitral valve surgery
 - Recently component of Maze procedure
- Exclusion
 - Linear stapling
 - Suturing



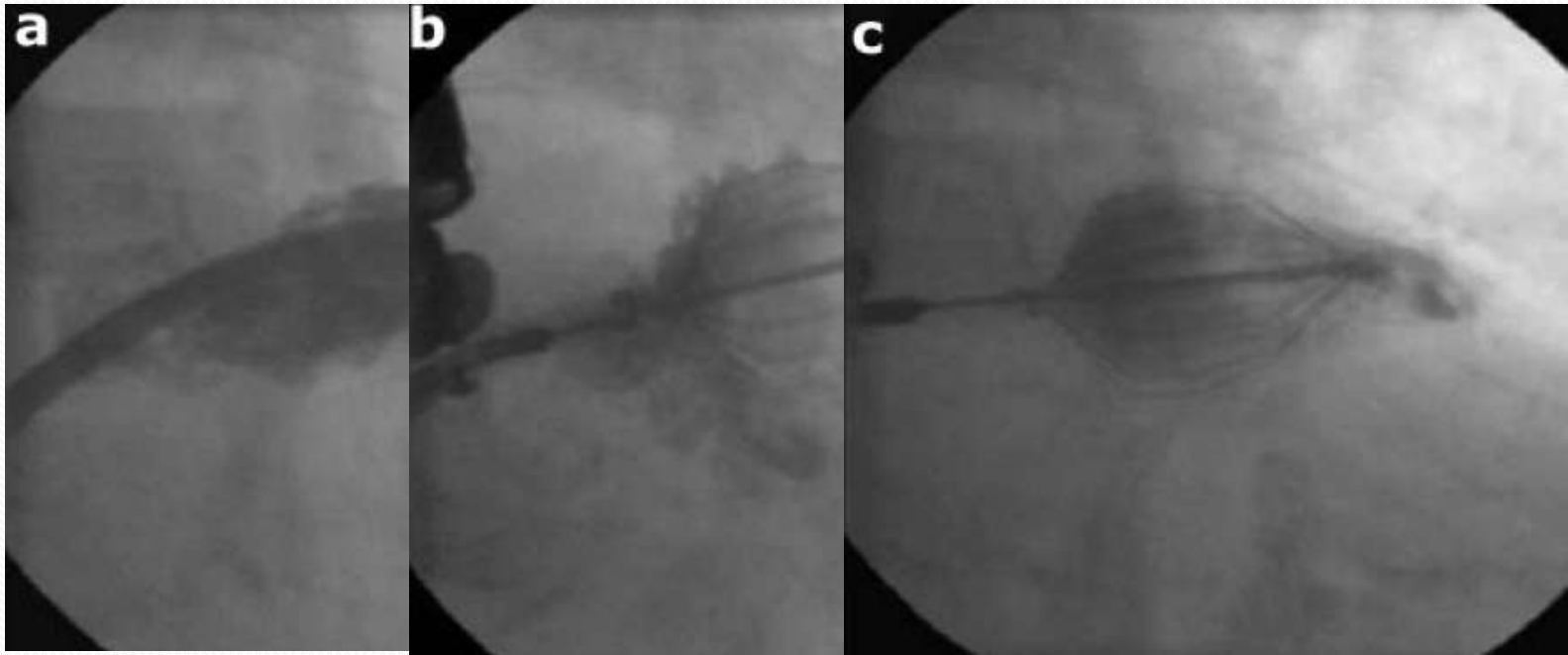
Surgical

- Results disappointing
- Variable practice
- Residual flow worse than doing nothin

Endovascular Exclusion

- PLAATO, ev3 Inc

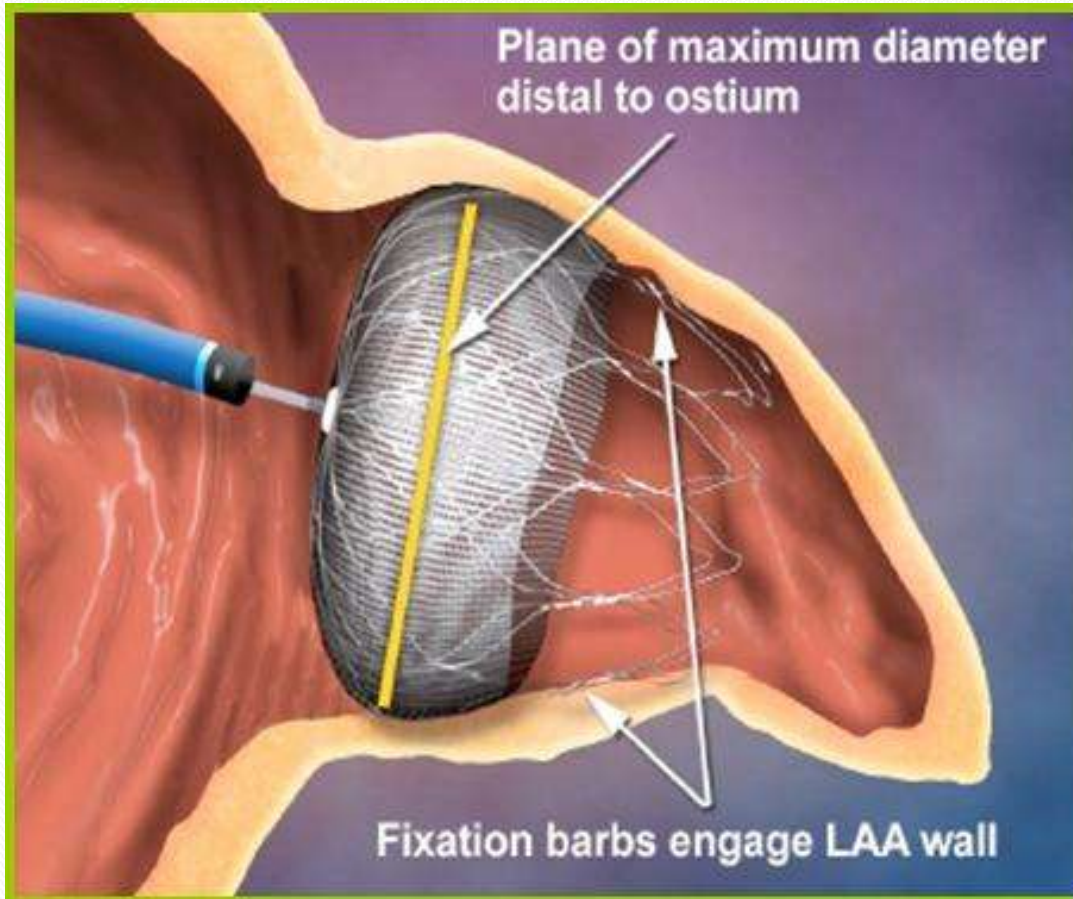




Endovascular Exclusion

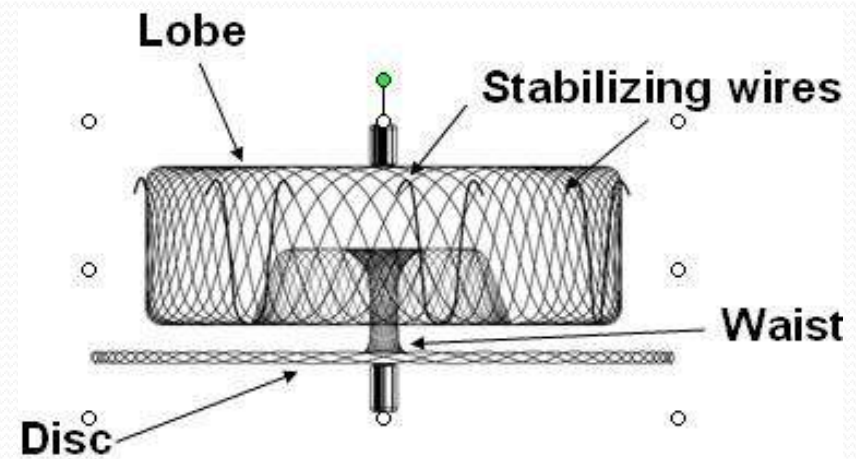
- Watchman, Atritech



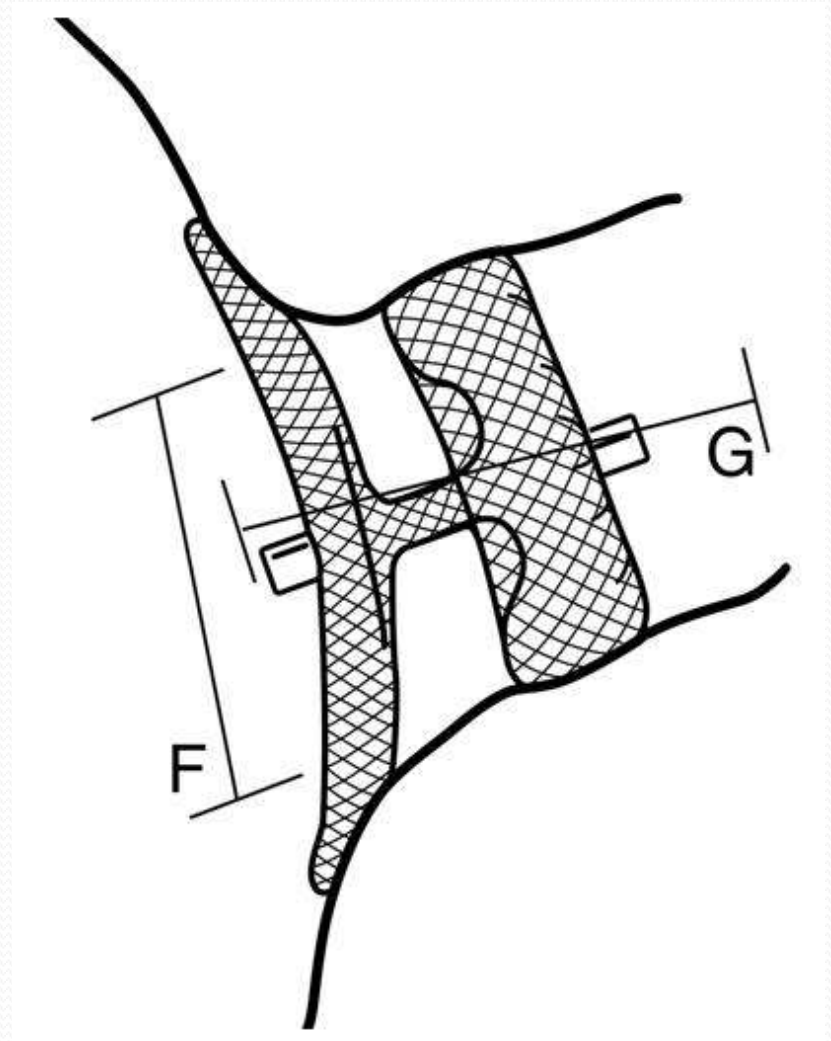


Endovascular Exclusion

- Amplatzer Cardiac Plug, AGA Medical



The AMPLATZER[®] Cardiac Plug is a percutaneous transcatheter device intended for cardiac structures not involving the septal wall, which require closure or occlusion. One intended use is the nonsurgical closure of the left atrial appendage.



Endovascular Exclusion

- Feasibility
- Efficacy

Feasibility

- Sievert et al. *Circulation* 2002
 - 15 patients underwent implantation of PLAATO device
 - Devices implanted successfully in all patients
 - 1 patients had tamponade from accessing the appendage
 - One month follow-up TOE
 - Stable position, smooth atrial surface, no thrombus

Feasibility

- Sick et al. *JACC* 2007
 - 66 patients underwent implantation of the Watchman device
 - 2 device embolizations
 - 2 cardiac tamponades
 - 1 air embolism
 - Mean follow-up 740 ± 341 days
 - 2 transient ischaemic attacks
 - 2 deaths (not device related)

Feasibility

- Meier B et al. *Catheter Cardiovasc Interv* 2003
 - 16 patients underwent implantation of the Amplatzer Septal Occluder
 - 1 device embolization requiring surgery
 - 5 year follow-up
 - No embolic events
 - No thrombus

Efficacy

- Block et al. *JACC* 2009
 - 64 patients with contra-indication to warfarin and high risk for stroke underwent PLAATO implant
 - 5 year follow-up
 - 1 tamponade related to device implantation
 - Stroke rate 3.8% lower than predicted by CHADS₂
 - Almost half that predicted

PROTECT-AF

- Holmes et al. *Lancet* 2009
 - Multi-centre randomized trial
 - Comparing LAA occlusion with the Watchman device to warfarin in patients high risk for stroke
 - 2:1 randomization ratio
 - Non-inferiority design

PROTECT-AF

- Composite primary efficacy endpoint
 - Stroke
 - Cardiovascular death
 - Systemic embolism
- Composite primary safety endpoint
 - Excessive bleeding
 - Procedure related complication

PROTECT-AF

- 4998 patients screened
 - 4291 ineligible
 - 707 randomized
- Excluded patients
 - 845 refusals
 - 360 DCC or ablation
 - 343 lone AF
 - 283 EF <30%
 - 275 CHADS₂ 0
 - 240 unable to take warfarin
 - 1945 Echo reason

PROTECT-AF

- 463 assigned to LAAO
- 449 implants attempted
- 408 devices implanted
 - 349 stopped warfarin at 45 days
- 244 assigned to warfarin
- 241 started warfarin

	Intervention (n=463)	Control (n=244)
Age	71.7	72.7
Male	326 (70.4%)	171 (70.1%)
CHADS ₂		
1	157 (33.9%)	66 (27%)
2	158 (34.1%)	88 (36.1%)
3	88 (19%)	51 (20.9%)
4	37 (8.0%)	24 (9.8%)
5	19 (4.1%)	10 (4.1%)
6	4 (0.9%)	5 (2.0%)
CCF	124 (26.8%)	66 (27.0%)
Hypertension	413 (89.2%)	220 (90.2%)
Age greater than 75 years	190 (41.0%)	115 (47.1%)
Diabetes	113 (24.4%)	72 (29.5%)
Previous stroke/TIA	82 (17.7%)	49 (20.1%)

	Intervention (n=463)	Control (244)
Atrial fibrillation		
Paroxysmal	200 (43.2%)	99 (40.6%)
Persistent	97 (21.0%)	50 (20.5%)
Permanent	160 (34.6%)	93 (38.1%)
Unknown	6 (1.3%)	2 (0.8%)
Atrial fibrillation onset		
Less than 1 year	69 (14.9%)	50 (20.5%)
1 year or more	360 (77.8%)	182 (74.6%)
No estimate	34 (7.3%)	12 (4.9%)
LV ejection fraction	57.3%	56.7%

PROTECT-AF

- Aggregate follow-up 1065 patient years
- Average 18 months per patient

PROTECT-AF

- Primary efficacy endpoint event rate
 - 3.0 per 100 patient years in intervention group
 - 4.9 per 100 patient years in control group
- Probability of non-inferiority >99.9%

PROTECT-AF

- Primary safety endpoint event rate
 - 7.4 per 100 patient years in intervention group
 - 4.4 per 100 patient years in control group
- High proportion of safety events occurred on day of procedure in intervention group (mainly pericardial effusion)

	Intervention (n=463)	Control (n=244)
Pericardial effusion	22 (4.8%)	0
Major bleeding	16 (3.5%)	10 (4.1%)
Procedure related stroke	5 (1.1%)	0
Device embolization	3 (0.6%)	0
Haemorrhagic stroke	1 (0.2%)	6 (2.5%)
Other	2 (0.4%)	0

PROTECT-AF

- LAA occlusion is non-inferior to warfarin
- Higher initial safety event rate
 - Most without long-term sequelae

PROTECT-AF

- Criticism
 - Small numbers included
 - High complication rate by experienced operators (learning curve)
 - Predominantly low risk patients enrolled
 - Poor warfarin control (target INR achieved 66% of time)

Indications for LAA Closure

- **2.1 *Indications and current treatments***
- 2.1.1 Atrial fibrillation is the irregular and rapid beating of the atria. Patients with AF may be asymptomatic or may have symptoms such as fatigue, palpitations, chest pain, shortness of breath and fainting. They also have an increased risk of thromboembolic stroke. In non-rheumatic AF, thrombi largely develop in the LAA.
- 2.1.2 Patients with AF who are considered to be at a high risk of thromboembolic stroke are often treated with warfarin anticoagulation therapy. Surgical intervention may involve obliteration of the LAA through an open or thoracoscopic approach.

Indications for LAA Closure

- Patients with non-rheumatic atrial fibrillation at high risk for stroke
- Absolute or relative contra-indication to oral anticoagulation (but will require short period of anticoagulation)
- Suitable left atrial appendage anatomy

