

New developments in rhythm medicine

Equity and excellence:

Liberating the
NHS

Mark Earley

St Bartholomew's Hospital

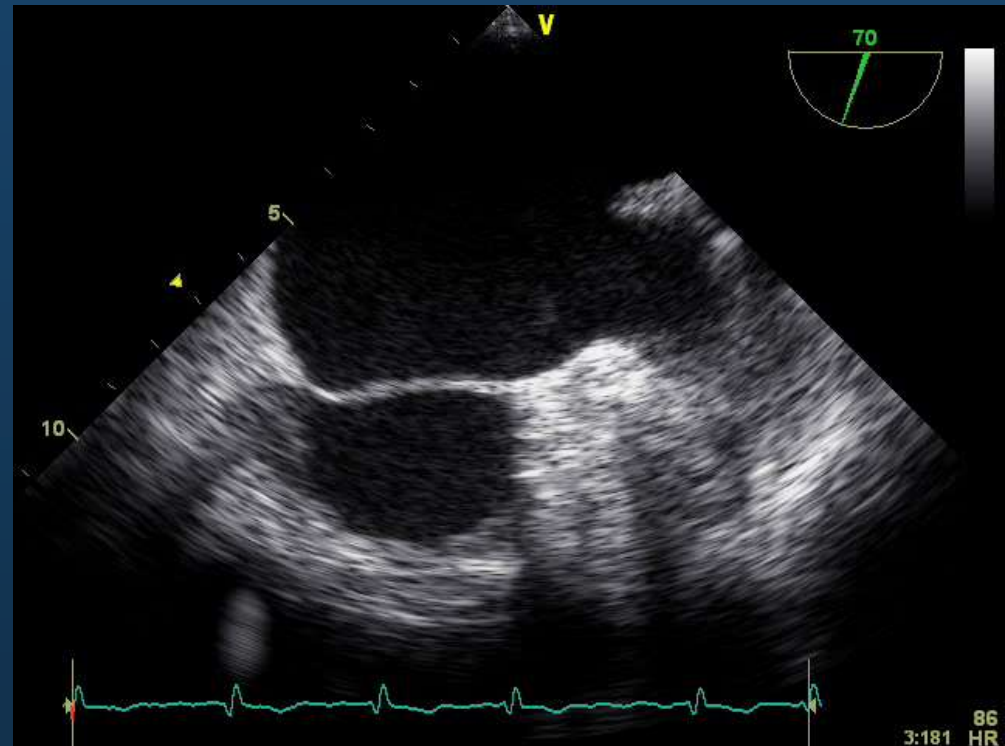
5th October 2010

New developments

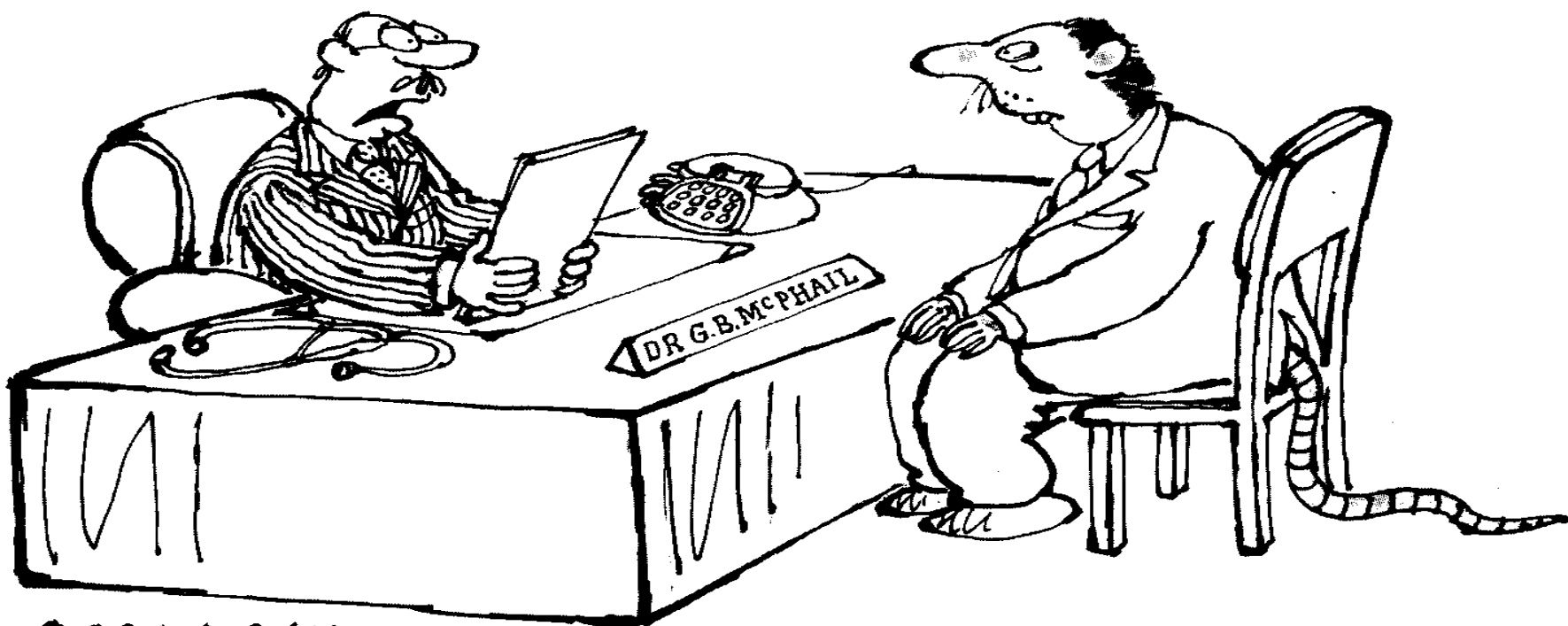
- Atrial fibrillation
 - Stroke prevention
 - Novel antiarrhythmic agents
 - AF ablation established therapy
- Genetic insights into arrhythmia
- Device therapy
 - Expanding indications for CRT
 - New technology
 - *Multipolar leads*
 - *Subcutaneous ICDs*
 - *MRI safe pacemakers*
 - Home monitoring

Stroke prevention in AF

- Stroke in AF
 - ↑ mortality
 - ↑ hospitalisation
 - ↑ disability
- Emboli from LAA



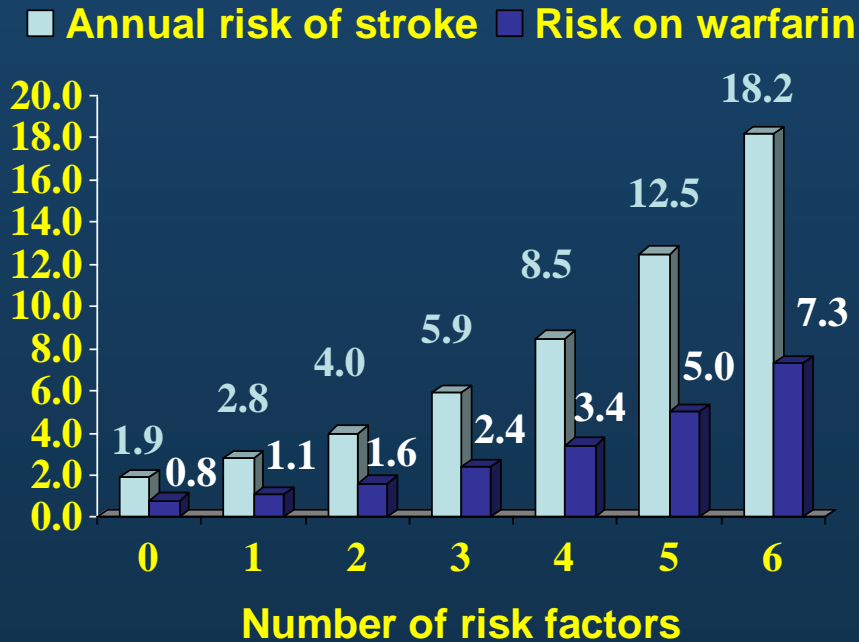
CARDIAC
&
VASCULAR
UNIT



McLACHLAN

'I did warn you that there might be some side effects with the Warfarin treatment, Mr Gadwall.'

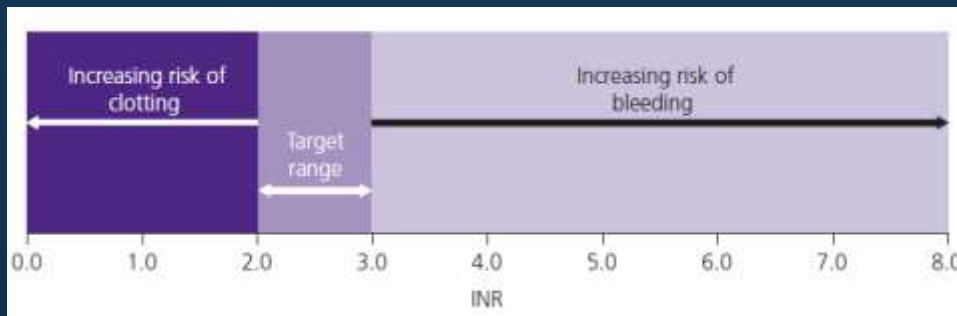
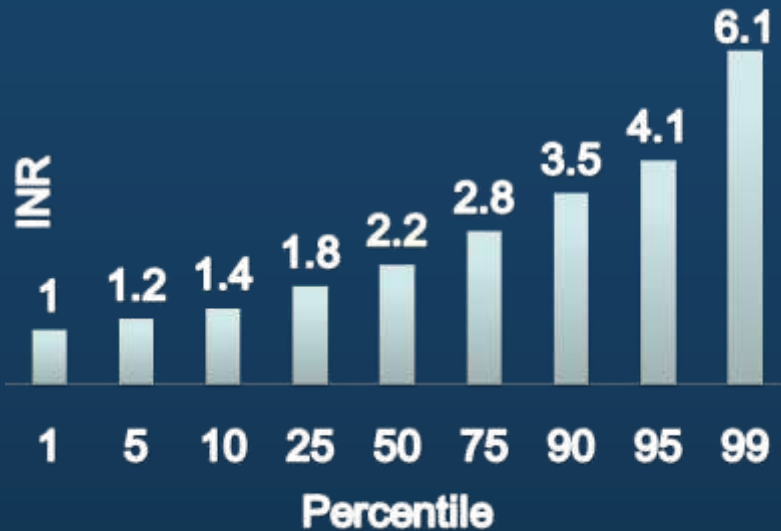
Stroke prevention - warfarin



CHADS₂ risk factors

- Congestive Heart Failure
- Hypertension
- Age > 75
- Diabetes
- Previous stroke (score 2)

Problems with warfarin – therapeutic index

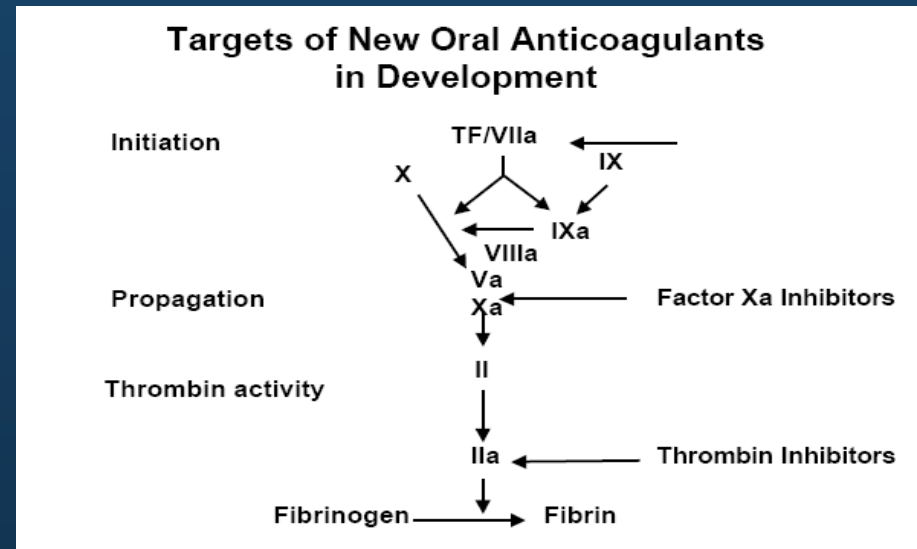


- n=13000
- Median INR = 2.2
- 1/5 INR 2-3 100% of time
- 1/3 INR 2-3 <20% of time
- INR <2 RR stroke = 2.4
- INR >3 RR IC haemorrhage = 2.1

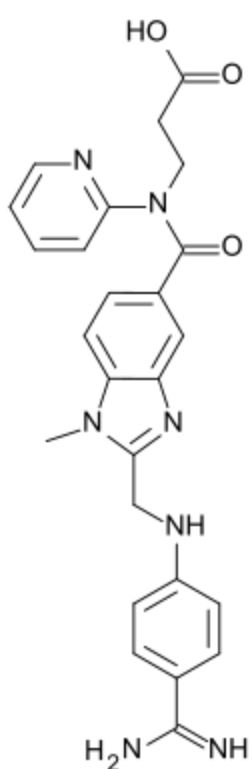
Walker et al Heart Rhythm 2008;5:1365–1372

New era for stroke prevention

- Vitamin K antagonist (VKA)
 - Warfarin
- Direct Thrombin Inhibitors (DTI)
 - Dabigatran (*RE-LY*)
- Anti Factor Xa
 - Rivaroxaban (*Rocket AF*)
 - Apixaban (*Aristotle*)
- LA appendage occlusion



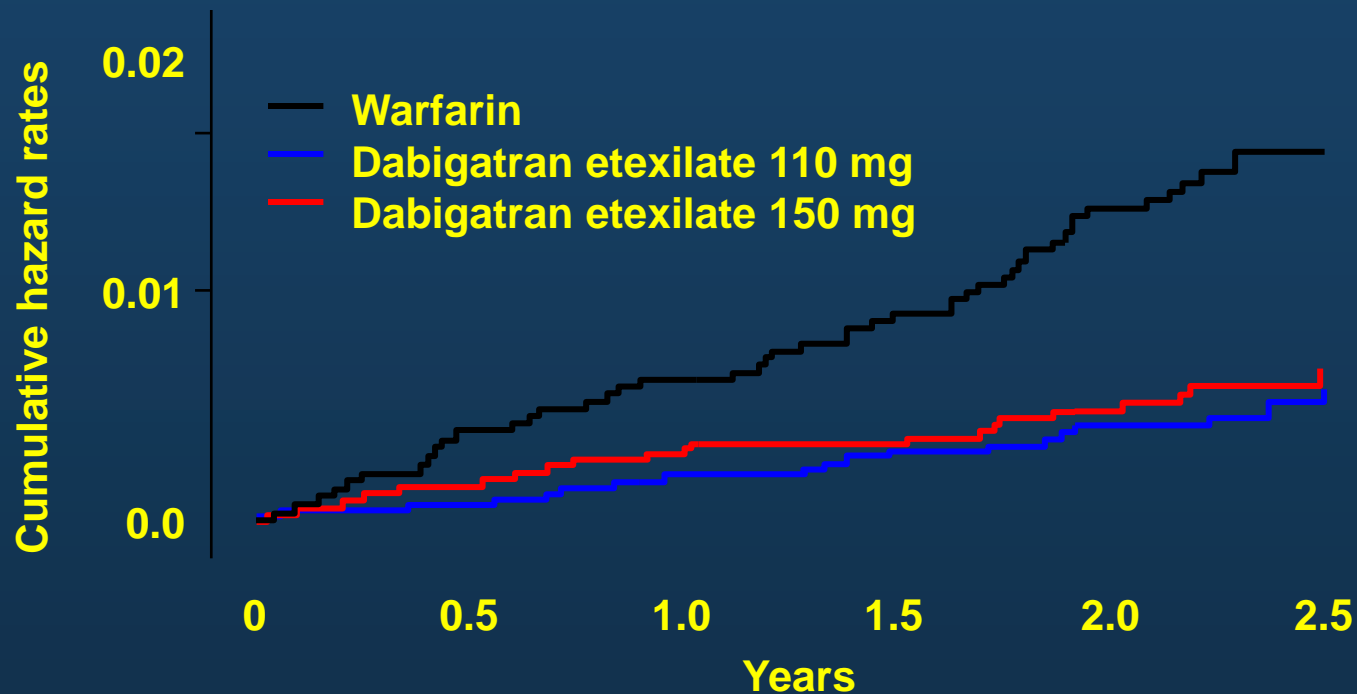
Dabigatran



RE-LY	Warfarin	Dabigatran 110mg bd	Dabigatran 150mg bd
Stroke or embolism	1.69	1.31	1.11
Major bleed	3.36	2.71	3.11
Event rate - % pa			

Connolly et al N Engl J Med. 2009 Sep 17;361(12):1139-51

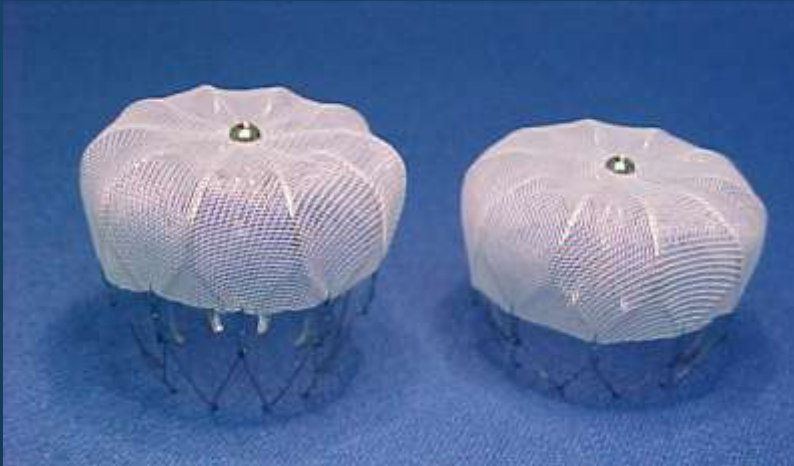
Dabigatran: Time to first intracranial bleed



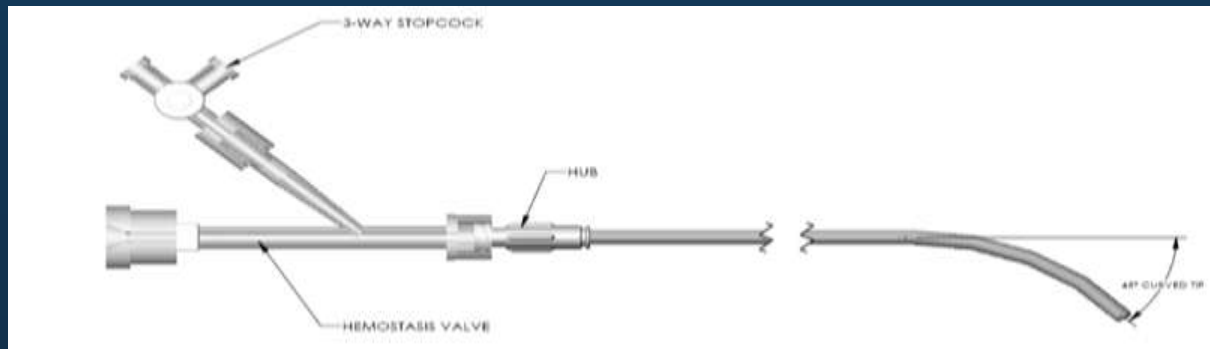
New anticoagulants

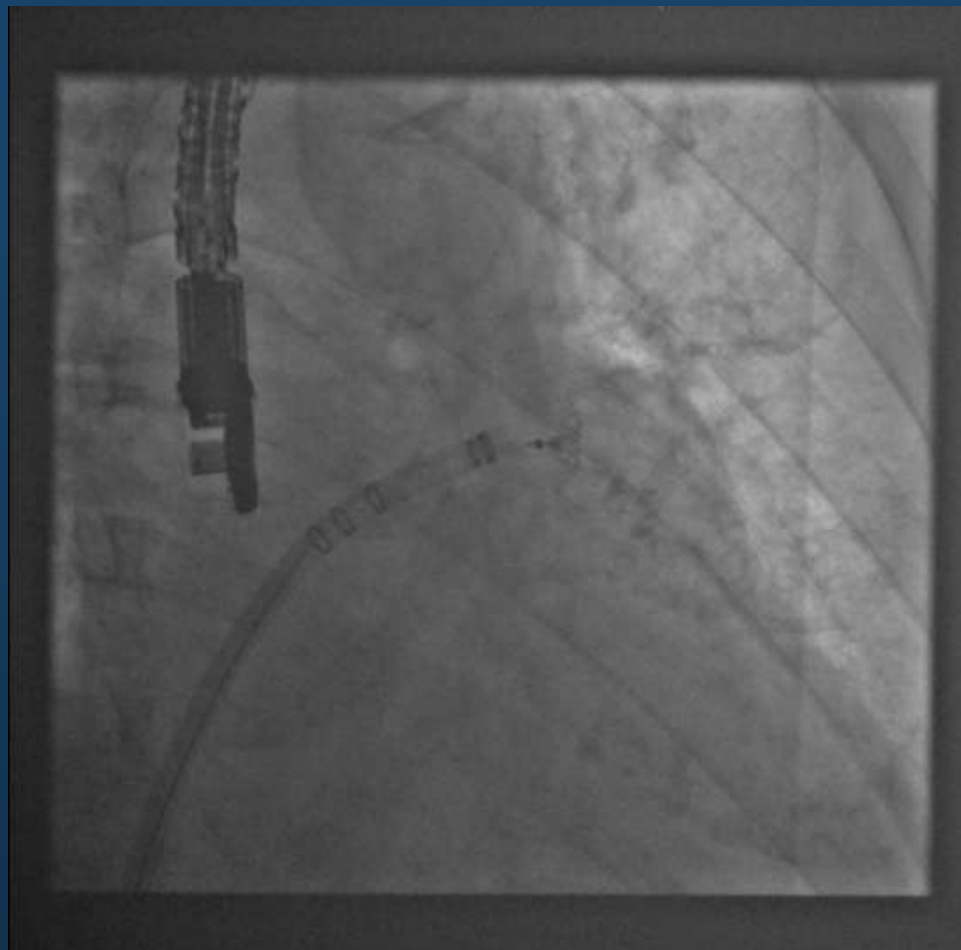
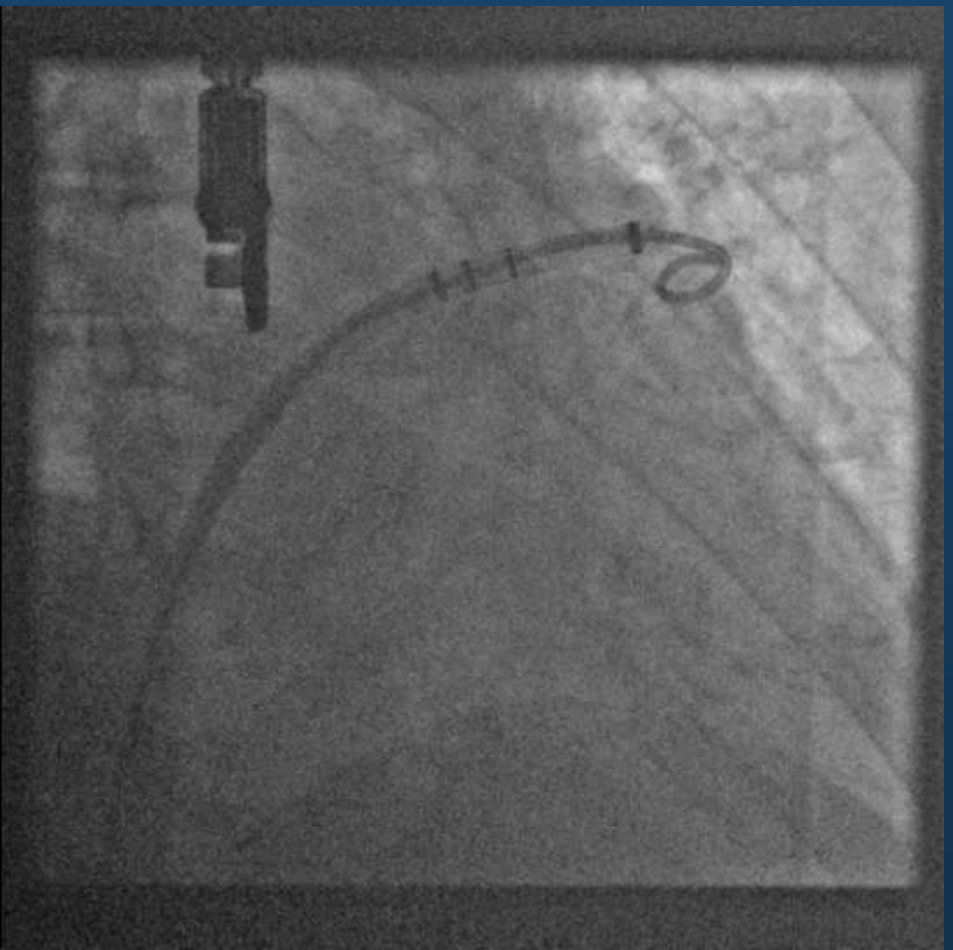
Properties	Warfarin	Dabigatran	Rivaroxaban
Orally active	Yes	Yes	Yes
Rapid onset	No (days)	Yes (peak 1.5h)	Yes (peak 2-4h)
Half life	40hrs	7-16h	5-9h
No food/drug interactions	No	+/-	Yes
Predictable anticoagulant effect	No	Yes	Yes
Extra-renal clearance	Yes	No	Not sig.
Rapid offset	No	No	No
Antidote	Yes	No	No

Watchman™

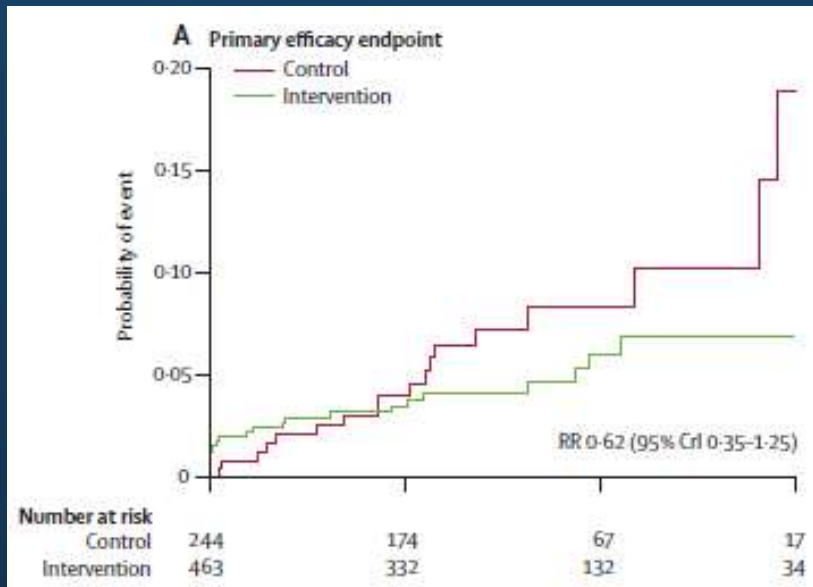


- Nitinol frame + fixation barbs
- 21-33mm diameter
- Catheter delivery via transeptal approach
- GA
- TOE + fluoroscopic guidance





Protect AF - efficacy



	Watchman	Warfarin
Primary End Point	3.0	4.9
Ischaemic stroke	2.2	1.6
Haemorrhagic stroke	0.1	1.6
Death	0.7	2.7
Systemic embolism	0.3	0
PEP successfully treated	1.9	4.6
Event Rate per 100 patient years follow up		

Holmes et al Lancet 2009; 374: 534-42

Protect AF - safety

	Watchman	Wafarin
Primary safety event rate (Per 100 year follow up)	7.4	4.4
If successfully treated (Per 100 year follow up)	1.4	4.4
Tamponade	22 (4.8)	0
Major bleed	16 (3.5)	10 (4.1)
Procedural 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
N (%)		

Holmes et al Lancet 2009; 374: 534–42

NICE guidance (IPG 349) June 2010

- Efficacy established and low risk
- Multidisciplinary team to review and consider all options
- Cardiac surgery on site
- Technically challenging – need appropriate training
- Report problems to MHRA

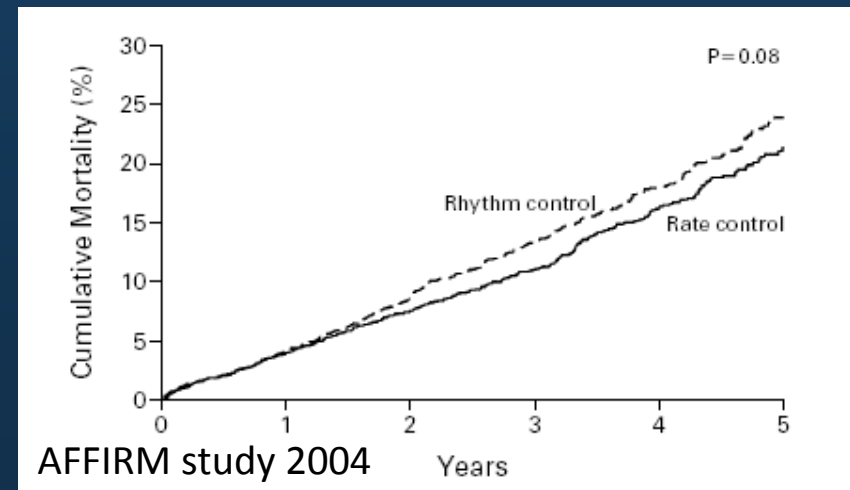
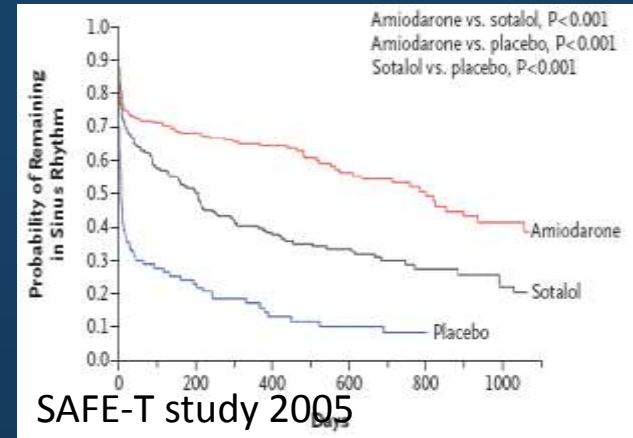
New strategies for stroke prevention in AF

- Dabigatran is better than warfarin
- New agents currently under evaluation
- LAA occlusion is a viable alternative to warfarin

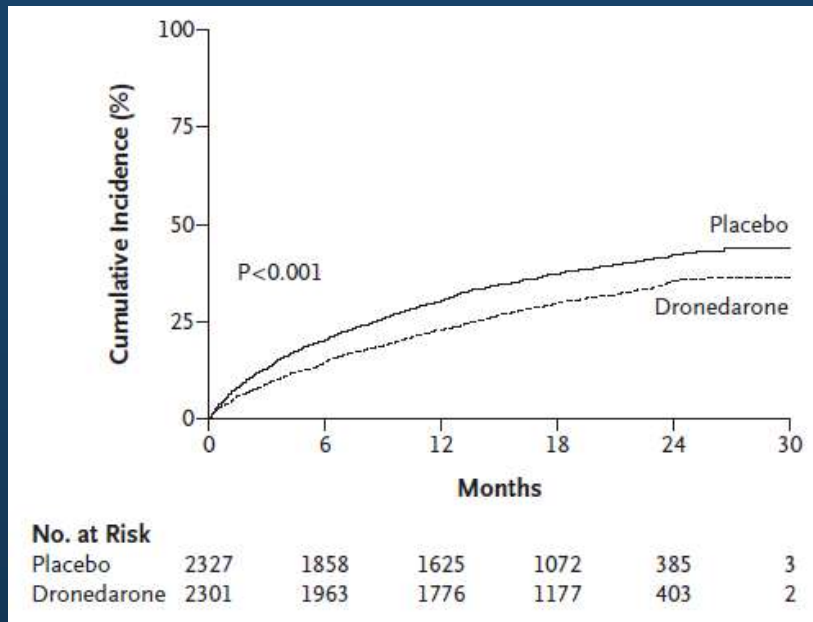
Are they cost efficient?

Rhythm control for AF

- Old drugs
 - Amiodarone
 - Flecainide/Propafenone
 - Sotalol
- New drugs
 - Dronaderone
 - Vernakalant
- Catheter ablation

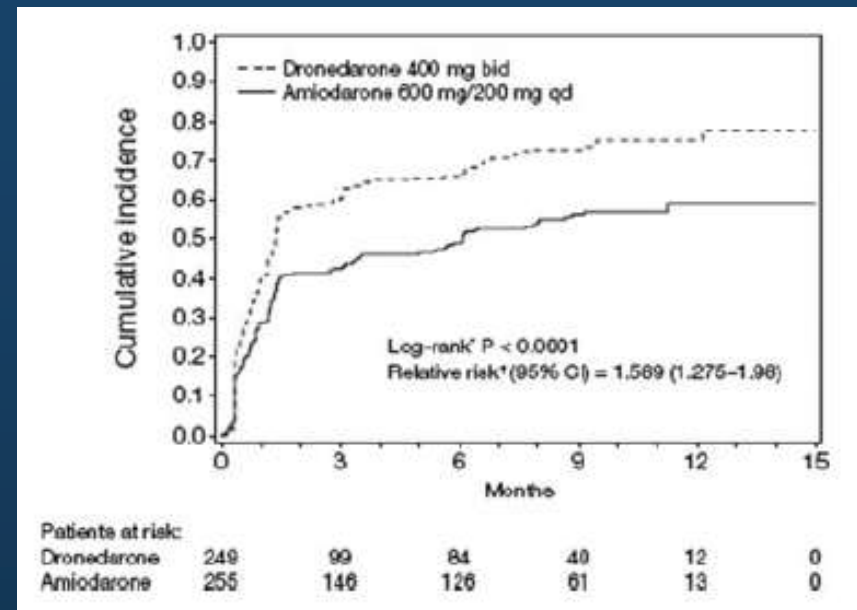


Dronedarone (Multaq)



ATHENA v placebo

- PEP: Death or first admission 31.9 v 39.4%
- 30% drug discontinued
- Annual stroke risk 1.8 v 1.2%



DIONYSOS v amiodarone

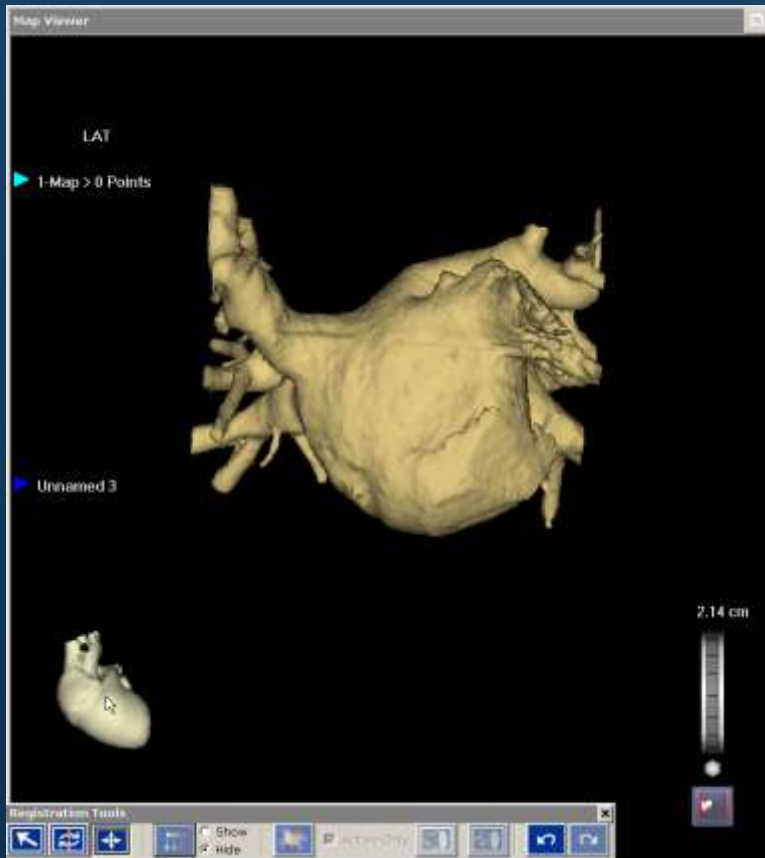
- Failure to CV or AF recurrence + drug discontinuation 75.1 v 58.8%
- AF recurrence 36.5 v 24.3%
- Major Safety 39.3 v 44.5%

NICE – TA 197 (Aug 2010)

Dronedarone may be considered an option in non permanent AF when:

- First line (BBBlockers) failed *and*
- 1 other CV risk factors
 - Hypertension needing 2 drugs
 - Diabetes
 - TIA/stroke/embolism
 - LA >50mm
 - Age > 70
- *Not* NYHA III or IV

Catheter ablation of AF



ESC RECOMMENDATIONS 2010

Ablation of paroxysmal AF **should be considered** in symptomatic patients who have failed a trial of antiarrhythmic medication.

IIa A

Ablation of paroxysmal AF **may be considered** prior to antiarrhythmic drug therapy in symptomatic patients despite adequate rate control and no significant underlying heart disease.

IIb B

Persistent symptomatic AF that is refractory to antiarrhythmic therapy **should be considered a treatment option**.

IIa B

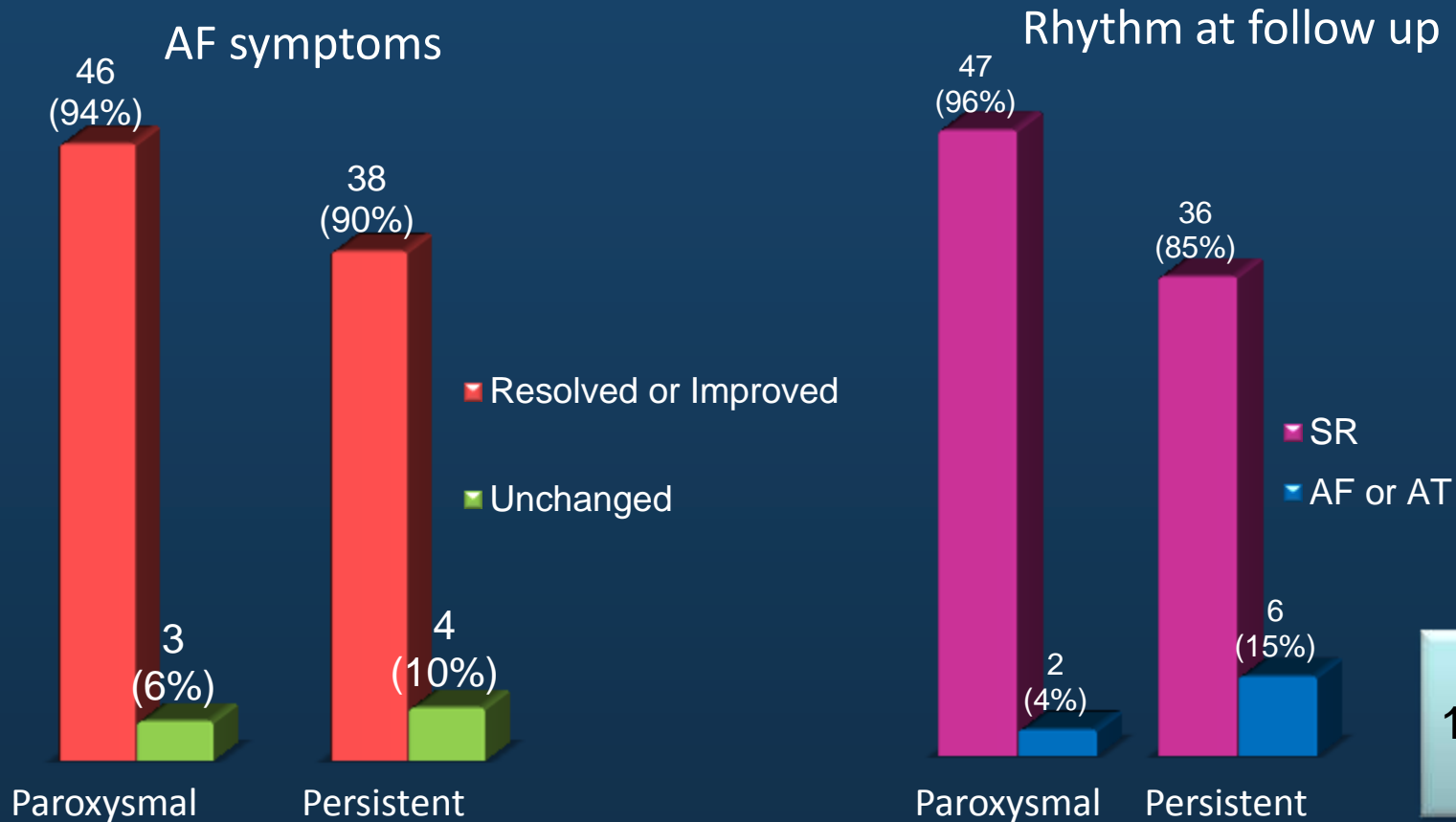
Ablation of AF in patients with heart failure **may be considered** when antiarrhythmic medication, including amiodarone, fails to control symptoms.

IIb C

Ablation of symptomatic long-standing persistent AF **may be considered** in patients refractory to antiarrhythmic drugs.

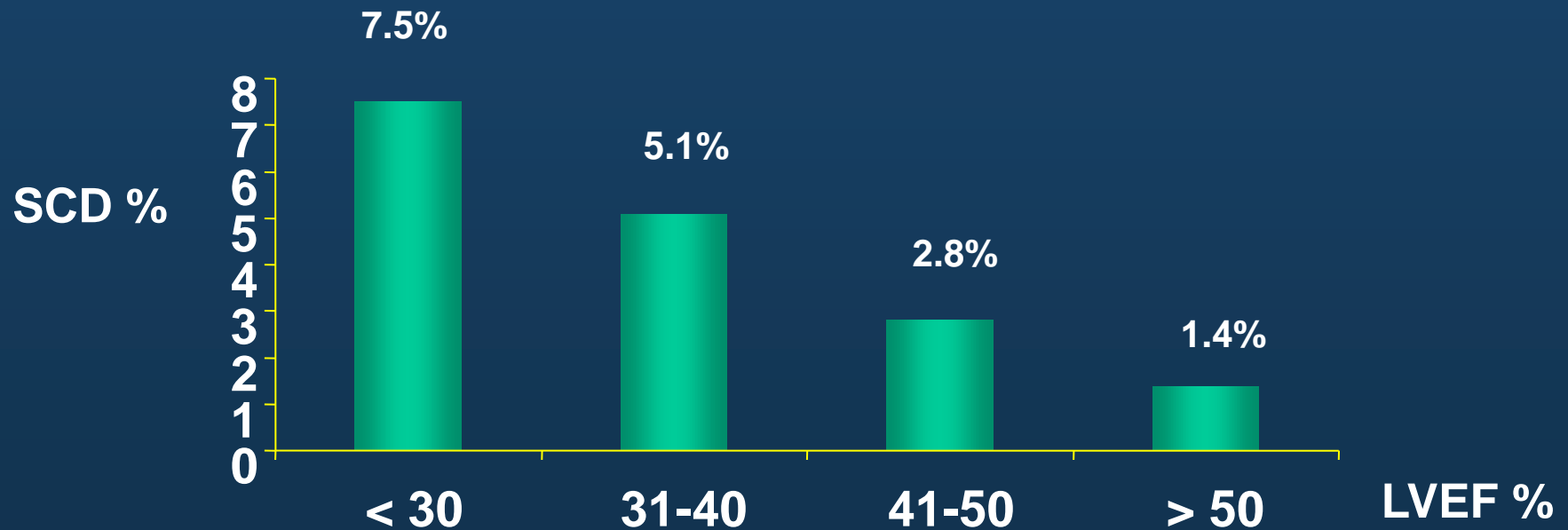
IIb C

Catheter ablation



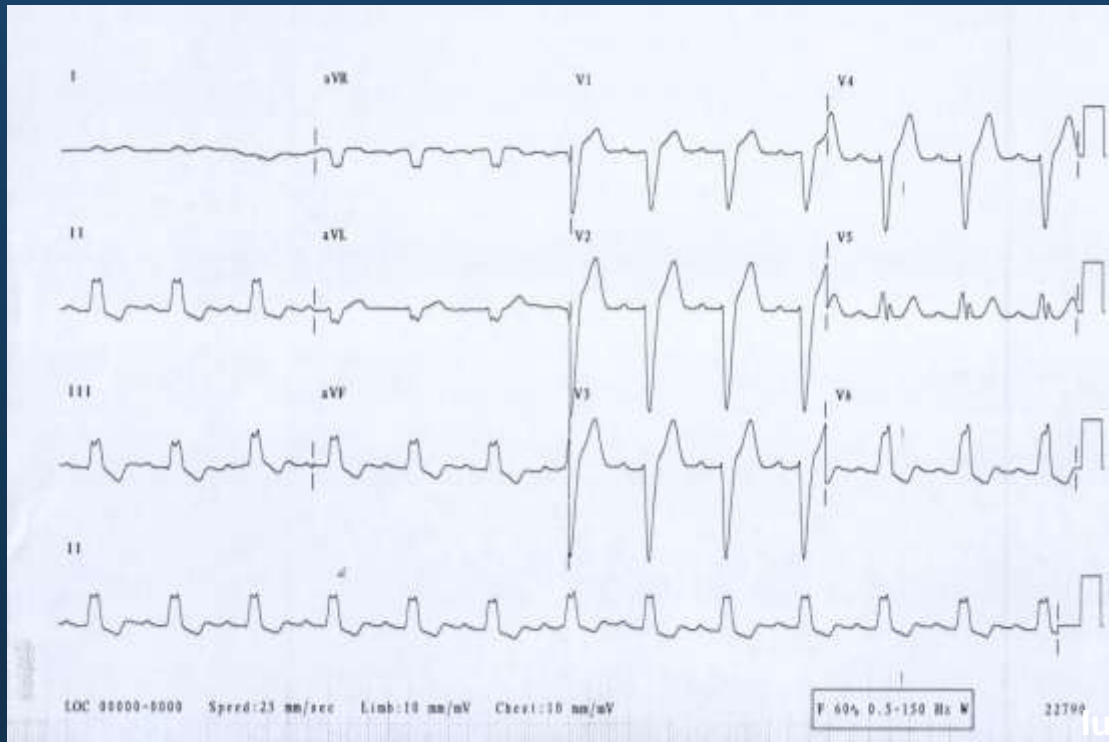
Complications
16 of 493 cases
3.2%

Heart failure and sudden death

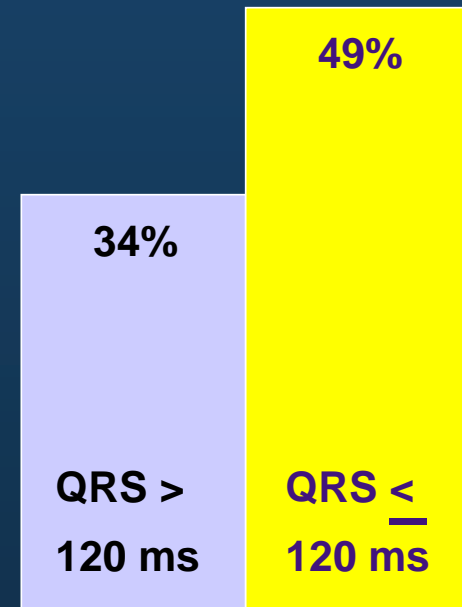


Gorgels PMA. *European Heart Journal*. 2003;24:1204-1209.

Dysynchrony leads to worse outcomes

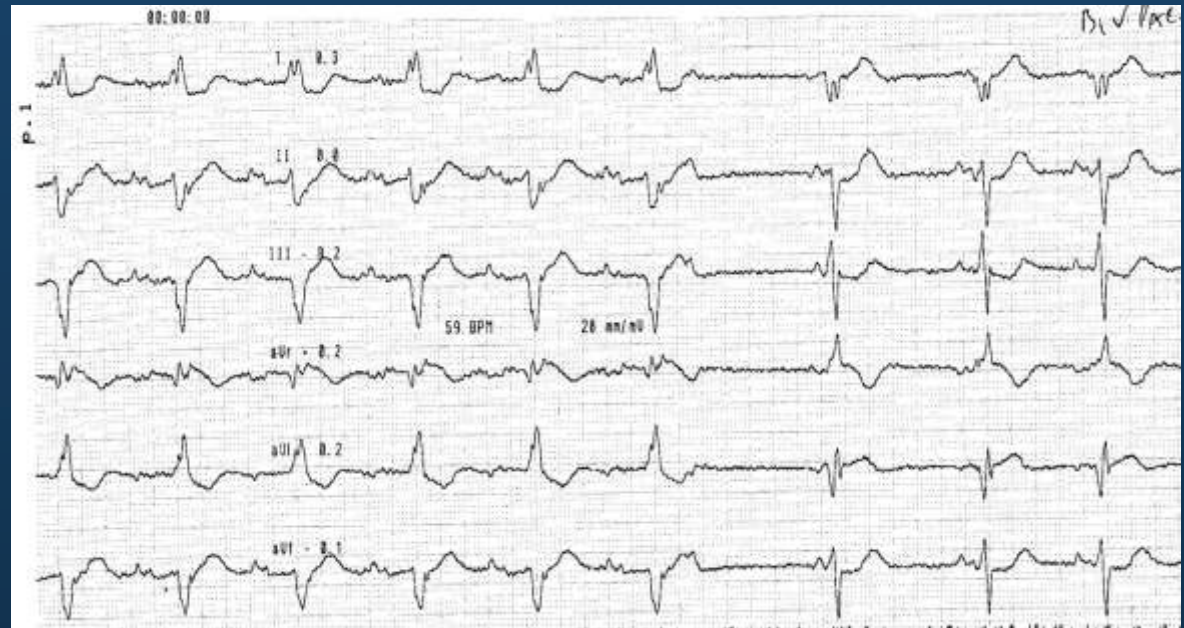
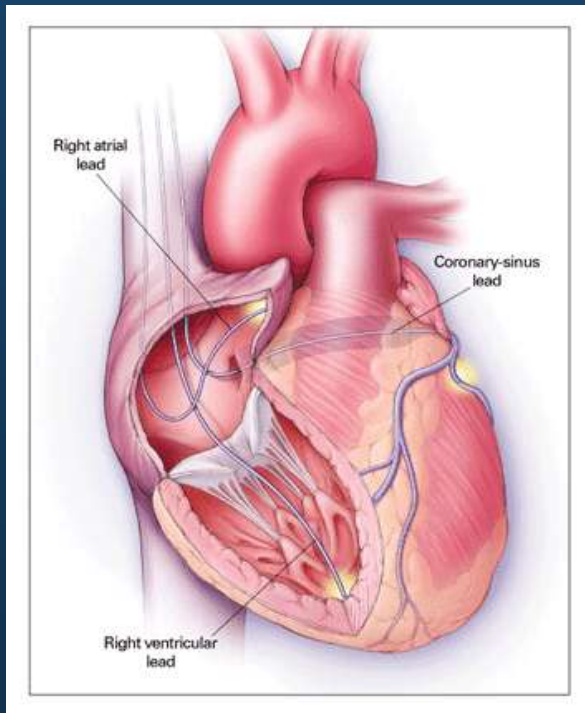


Long-term (45 Mo) Survival



Juliano et al. AHJ 2002;143:1085-91

Cardiac Resynchronisation



No pacing

BiV pacing

CRT – evidence base



CRT Indications:

- LBBB
- EF < 35%
- NYHA > 2

Expanding the indications for CRT

NICE 2007

1. NYHA III-IV

2. Sinus rhythm

- Either – QRS>150
- Or-QRS130-149 + mechanical dysynchrony

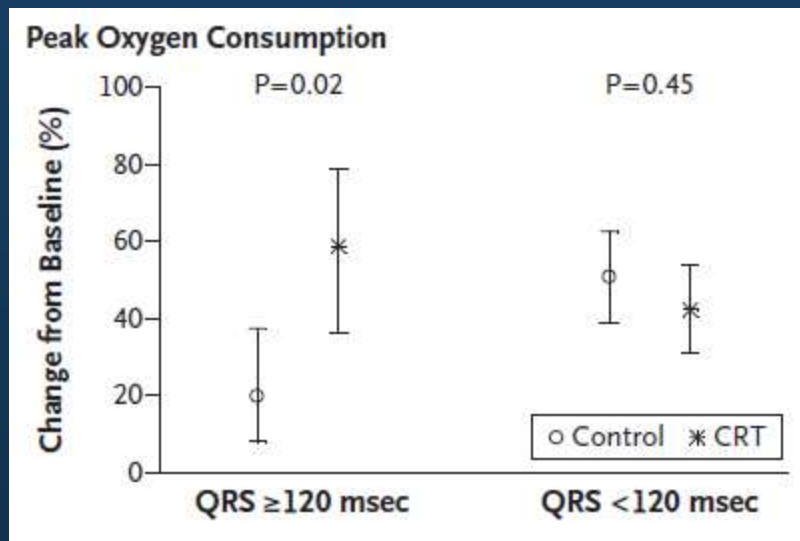
3. LVEF <35%

4. Receiving OPT

- Narrow QRS with mechanical dysynchrony?
- Wide QRS but NYHA 1-2?

CRT if only mechanical dysynchrony present?

- RethinQ (NEJM 2007)



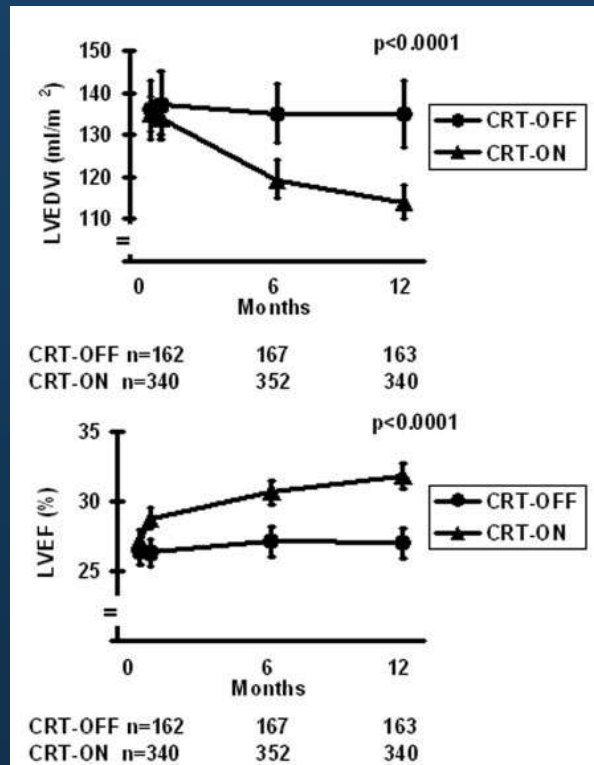
- Prospect (Circ 08)

- Mmode
- Pulsed Doppler
- Tissue Doppler imaging

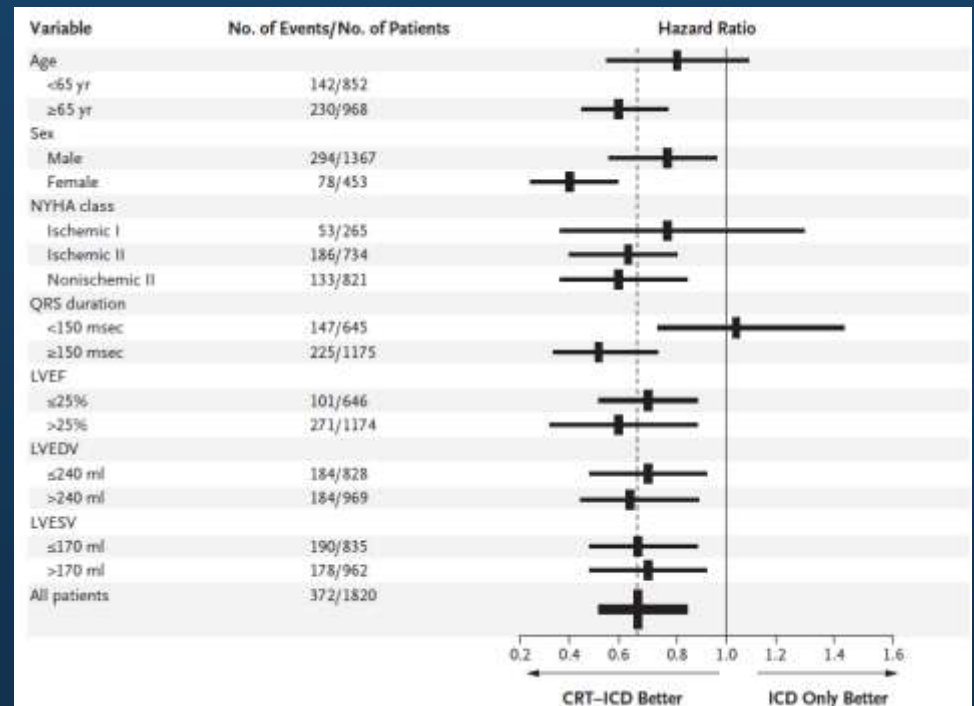
- All methods are poor predictors of response to CRT

CRT if NYHA I or II?

- REVERSE (Circ 09)



- MADIT CRT (NEJM 09)

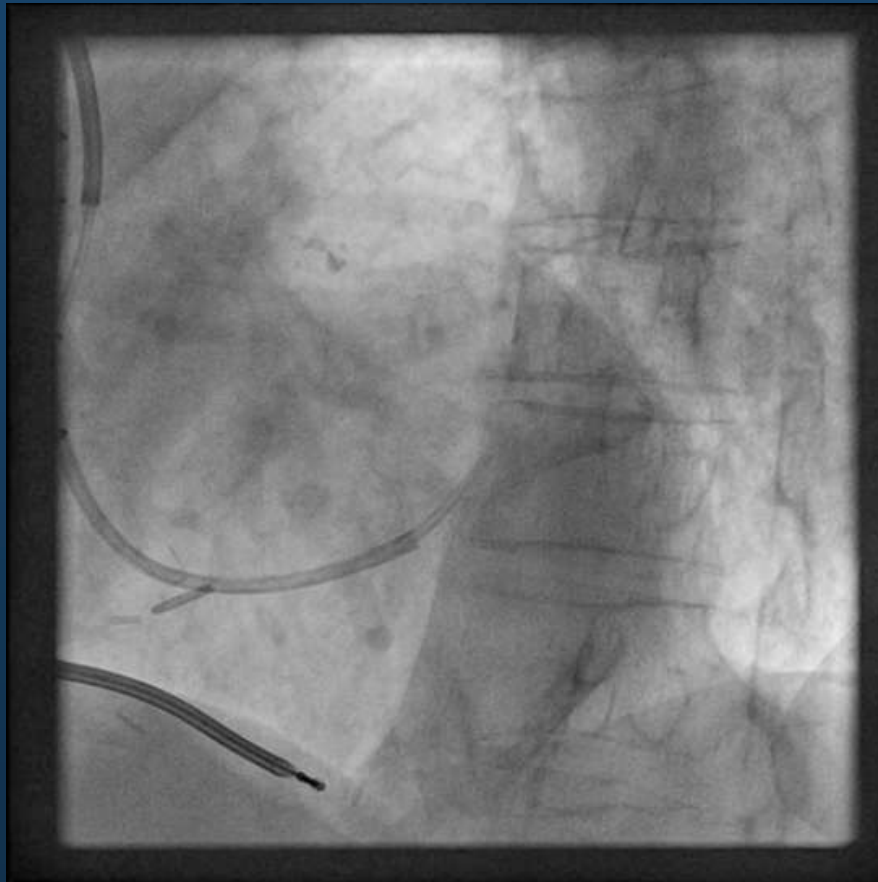


Expanding the indications for CRT

NICE 2011??

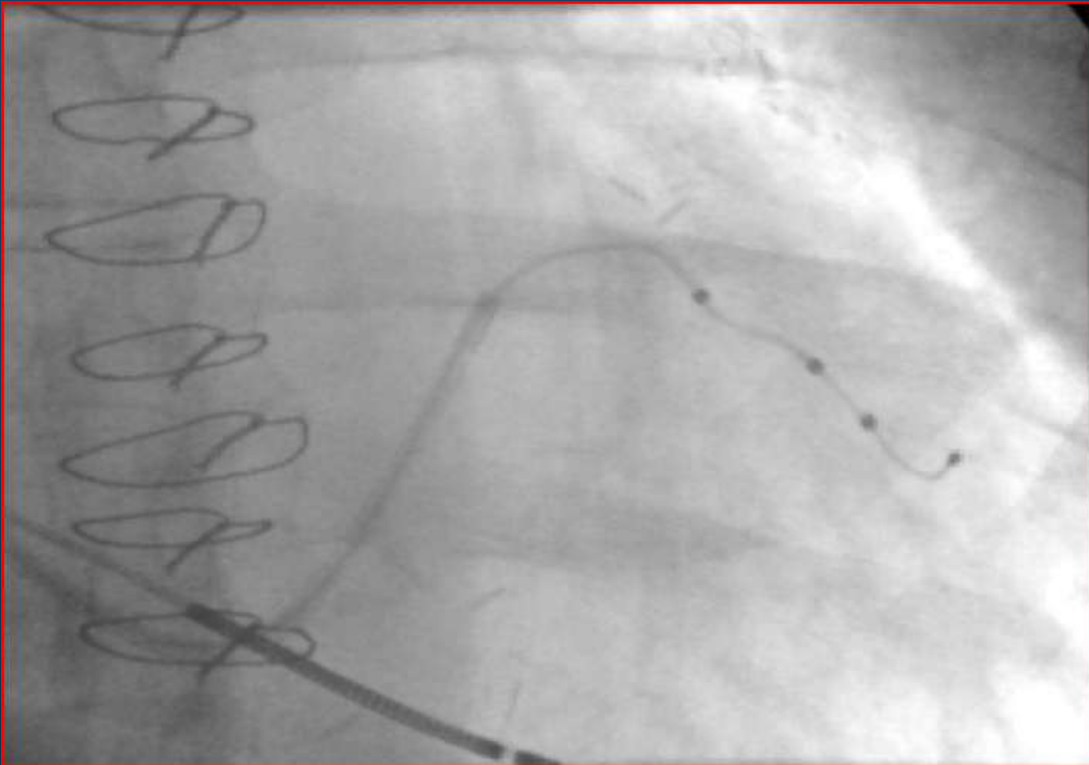
1. NYHA I-IV
2. Sinus rhythm
 - QRS >150
3. LVEF <35%
4. Receiving OPT

CRT – confined by anatomy



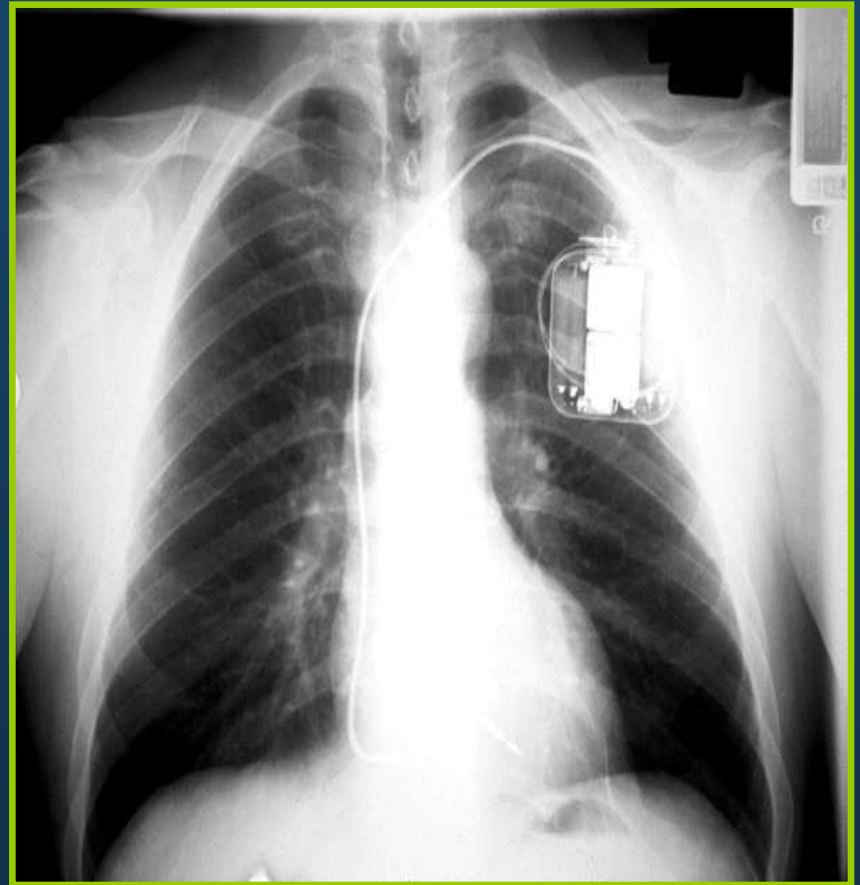
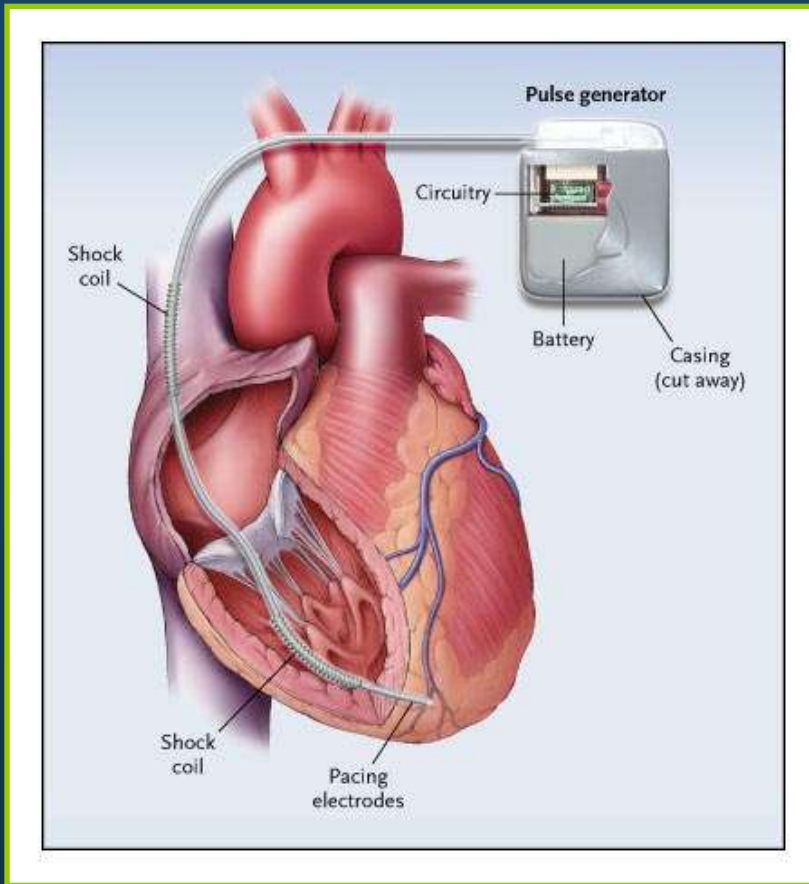
Major complications	
CS lead displacement	5.7-6%
CS dissection	0.3-4%
CS perforation	0.8-2%
Infection/erosion	1.3-2.7%
Tamponade	0.3-0.5%
Death	0.2-0.6%
Total	8.6-15.8%

Multipolar pacing leads



New device technology

Conventional ICD



Problems with transvenous system

Procedural

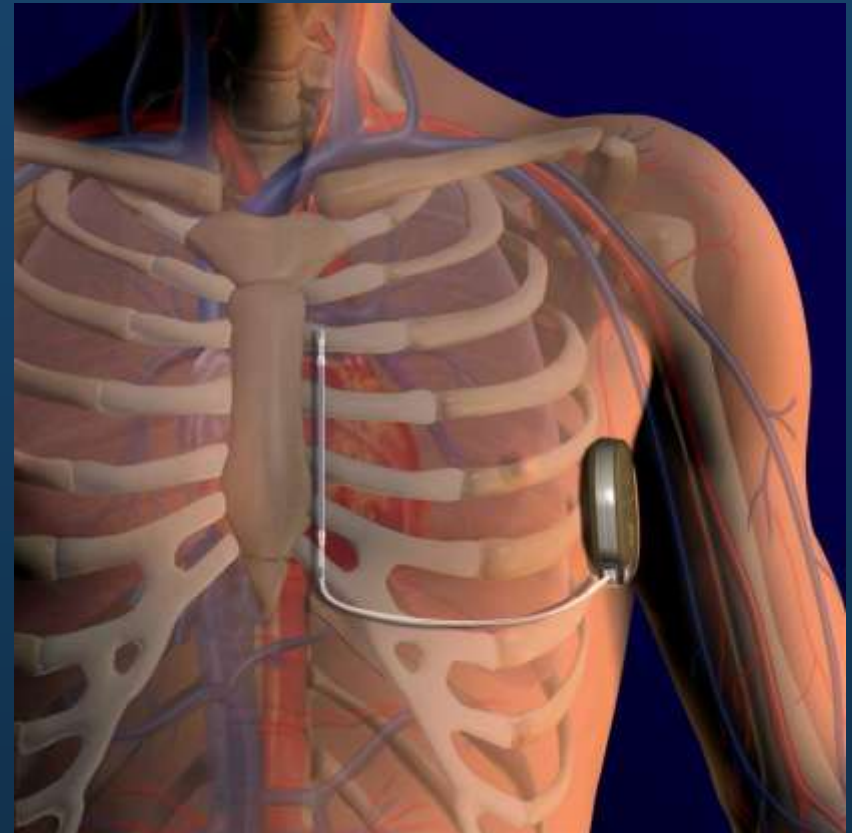
- Pneumothorax
- Haemorrhage
- Tamponade

Long term

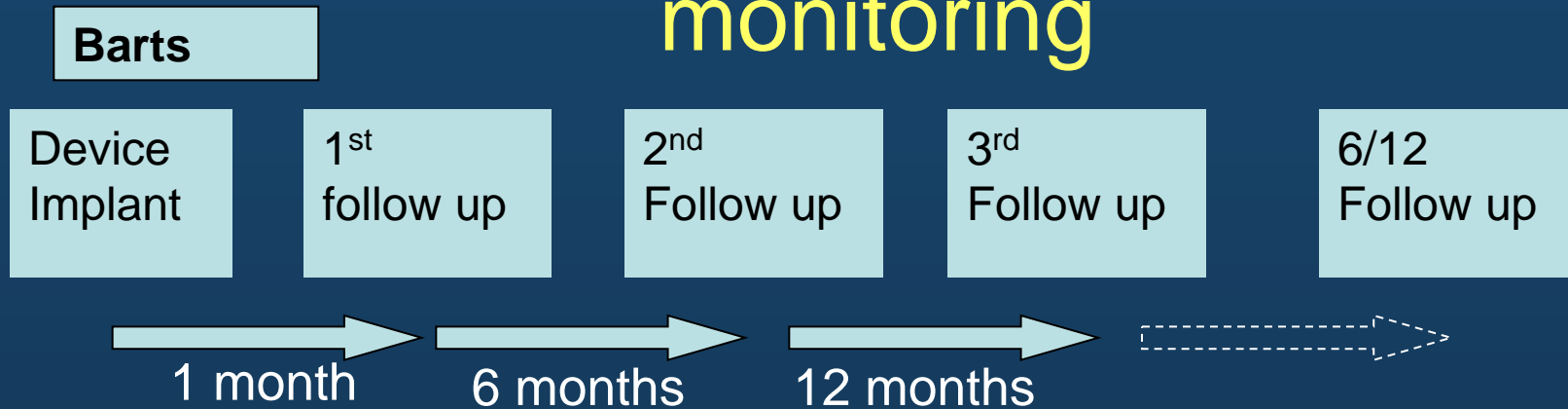
- Infection
- Lead failure
- Hazardous lead extraction

Subcutaneous ICD (Cameron Health)

- 80 joules
- 69cc, 145 grams
- 5 year longevity
- Post-shock pacing
- Single electrode connection
- Episode storage
- Growing room
- Not in vascular system



New developments – home monitoring



Home monitoring

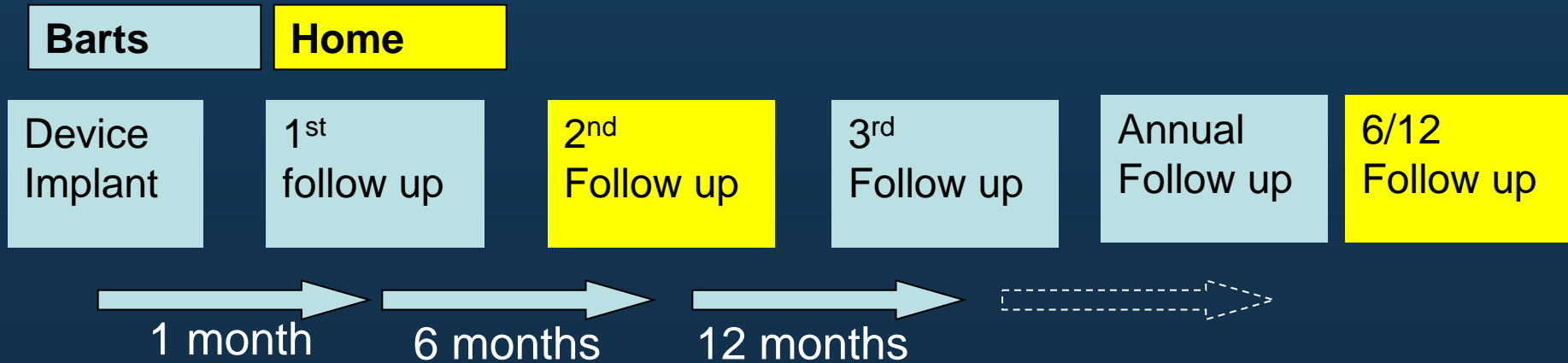
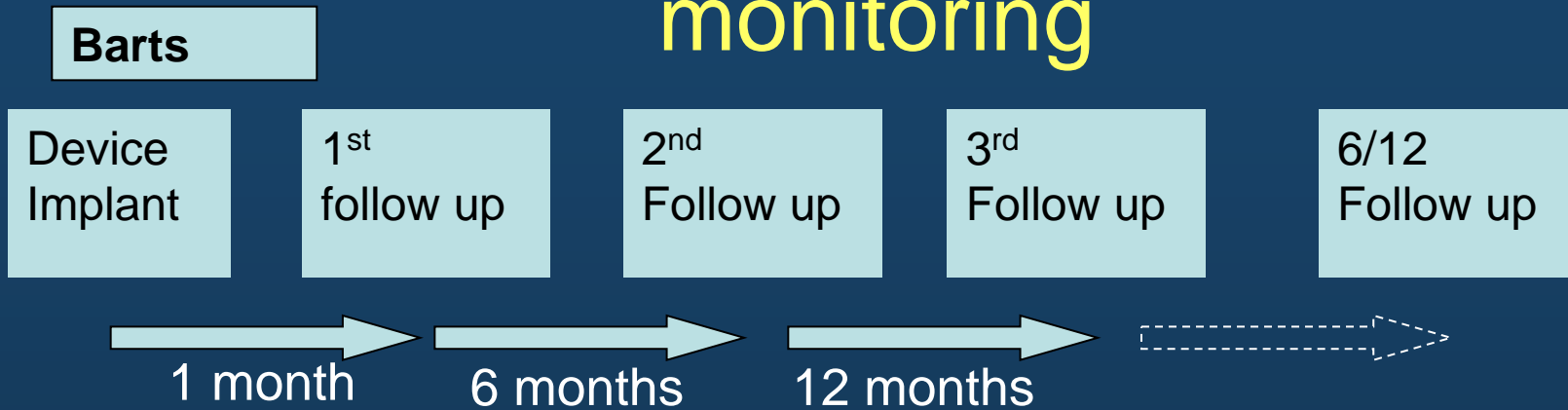
Remote clinics:



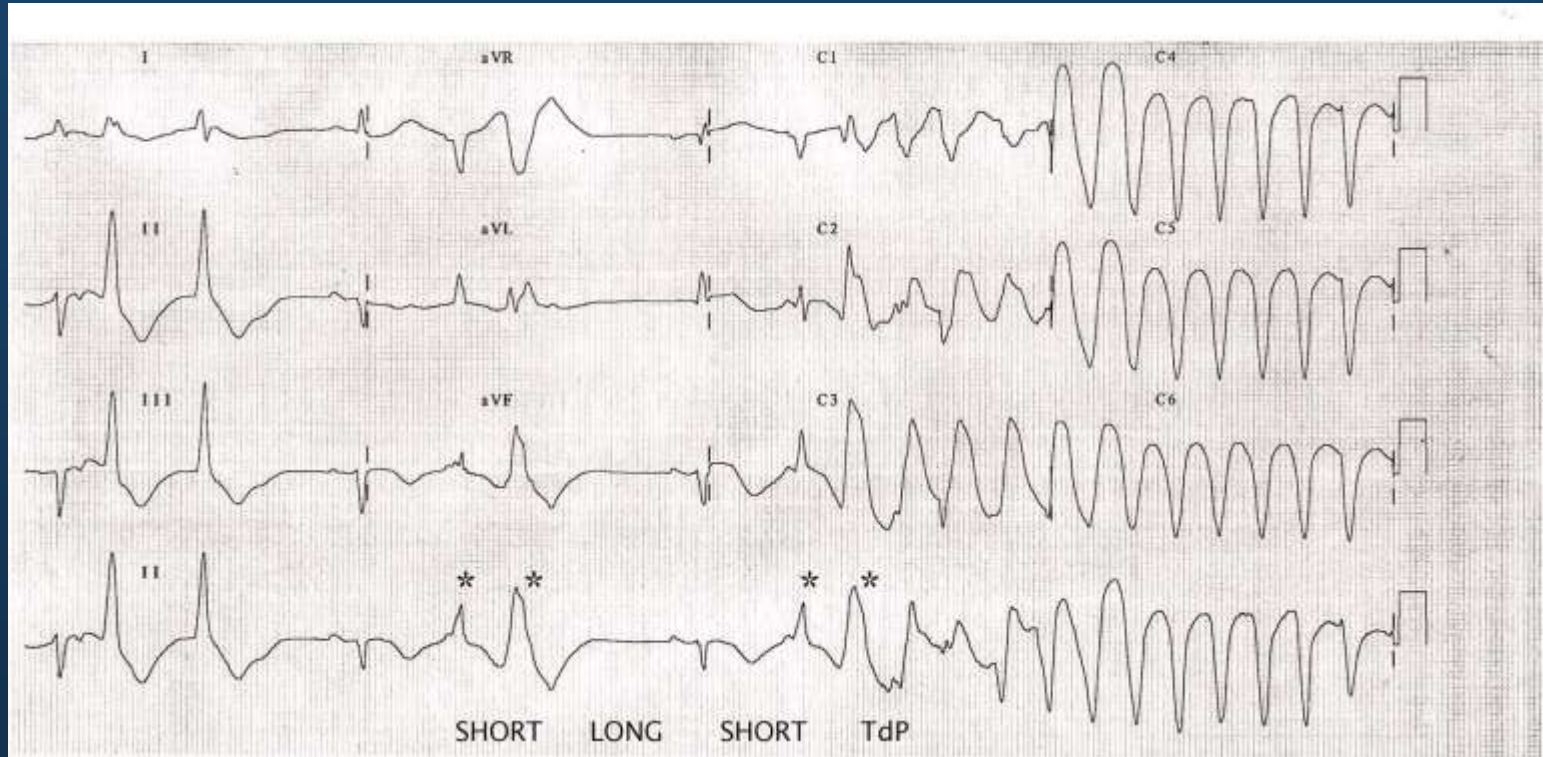
Alerts:



New developments – home monitoring



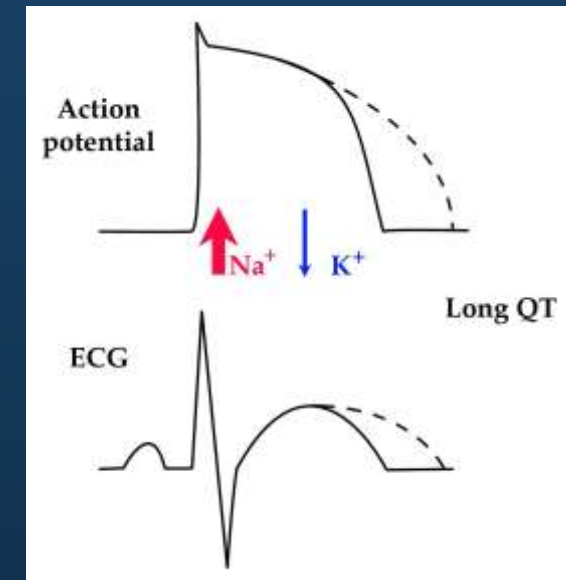
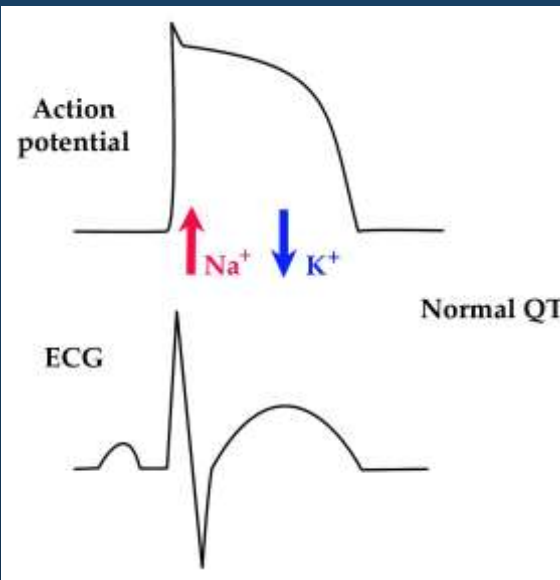
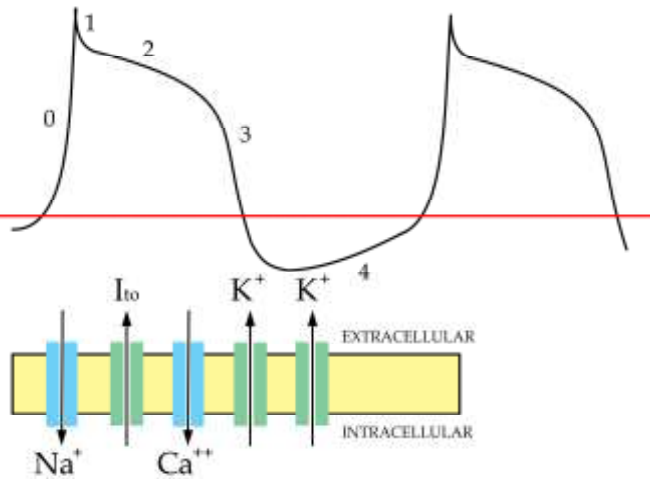
Genetic understanding of arrhythmia



Genetic understanding of arrhythmia

LQT

The cardiac action potential



Genetic understanding of arrhythmia

LQTS type	Chromosome	Gene	Protein	Ion current	Ion channel function
<i>Autosomal dominant</i>					
1	11p15.5	KCNQ1	KvLQT1	IKs	Loss
2	7q35-36	KCNH2	HERG	IKr	Loss
3	3p21-24	SCN5A	Nav1.5	INa	Gain
5	21q22	KCNE1	MinK	IKs	Loss
6	21q22	KCNE2	MiRP1	IKr	Loss

Genetic mutations can be identified in ~70% of clinically affected cases

Genetics of AF?

Gene identified	Functions	Mode	GenBank/dbSNP	No. of Cases	Race	AF Type	Method	HRD	Reference(s)
Familial AF									
No locus and gene identified									
FAF1-4	?	AD	—	4 families	Caucasian	PAF	Screen	Nil	11
Locus identified									
10q22-24	?	AD	—	3 families	Caucasian	CAF	Link	Nil	9
6q14-16	?	AD	—	1 family	Caucasian	PAF	Link	Nil	12
Gene identified									
KCNQ1 S140G	α-subunit of IK _v (KVLQT1) Gain of function	AD	NP_000209.2:p.S140G NM_000218.2:c.418A>G	1 family	Chinese	CAF	Link	Nil	13
KCNQ1 R14C	α-subunit of IK _v (KVLQT1) Gain of function under stretch	AD	NP_000209.2:p.R14C NM_000218.2:c.40C>T	50 families	Caucasian	PAF	Screen	HTN	28
KCNQ2 R27C	β-subunit of KCNQ1-KCNQ2 Gain of function	AD	NP_761961.1:p.R27C NM_172201.1:c.79C>T	2 families	Chinese	PAF	Link	Nil	18
KCNQ2 V93I	α-subunit of IK ₁ (Kir2.1) Gain of function	AD	NP_000882.1:p.V93I NM_000891.2:c.277G>A	30 kindreds	Chinese	PAF	Screen	Nil	21
KCNQ2 N588K	α-subunit of IK ₁ (HERG) Gain of function	AD	NP_000229.1:p.N588K NM_000238.2:c.1764C>A	1 family	Caucasian	PAF	Screen	Nil	20
Nonfamilial AF									
Candidate gene approach									
Ionic channels/calcium handling proteins									
KCNK1 (A112G or S38G)	β-subunit of IK _v (KVLQT1) Decreased function	Poly	rs1805127 or rs17846179	108 case-control pairs	Taiwanese	PAF + CAF	Asso	VHD, CHF, HTN	29,31
G protein beta(3)subunit (Gβ3)	Regulatory protein of IK ₁ Decreased function	Poly	rs5443	291 cases/ 292 controls	Caucasian	PAF + CAF	Asso	HTN	34
SCN5A (A1867G or H588R)	α-subunit of INa Decreased function	Poly	rs1805124	157 cases/ 314 controls	Caucasian	PAF + CAF	Asso	Nil	36
Sarcoplipin (G-66C)	Inhibitor of SERCA Functional significance unknown	Poly	rs593362	147 cases/ 92 controls	Caucasian	PAF + CAF	Screen Asso	Nil	37
Nonionic channels/calcium handling proteins									
Renin-angiotensin system									
(ACE I/D)	AngII biosynthesis pathway	Poly	rs1799752	250 case-control pairs	Taiwanese	PAF + CAF	Asso	VHD, CHF, HTN	38,42
(AGT G4A, A-20C, G-152A, and G-217A)	AngII augments ICat.	Poly	rs699 (M236T) and rs4782 (T174M)						
(AT1R A1166C)		Poly	rs1799752						
Cx40									
(-44A/+71G and -44G/+71A)	Cx40 gene promoter haplotype Decreased promoter function	Poly	—	173 cases/ 232 controls	Taiwanese	PAF + CAF	Asso	VHD, CHF, HTN	49
(P88S, M163V, G38D, and A96S)	Mutant Cx40 protein Impaired intracellular transport	S. Mut	—	15 cases	Caucasian	PAF	Screen	Nil	51
eNOS									
(T-786C, interaction with KCNE1 S38G)	Antiinflammatory pathway Functional significance unknown	Poly	—	231 cases/ 441 controls	Caucasian	PAF + CAF	Asso	HTN, CHF	51
(D894T or E298D)		Poly	rs1799989	340 patients with CHF (51 AF/289 nonAF)	Caucasian	PAF + CAF	Asso	CHF	52
MMP2 (C-1306T) and pathways	Inflammatory and fibrotic pathways	Poly	—	198 cases/ 873 controls	Japanese	CAF	Asso	Nil	53
IL10 (A-692C)	Functional significance unknown	Poly	rs1800872						
Genome-wide scan									
Bumina Hap300 BeadChip SNPs	Underlying gene uncertain			2,801 cases/ 17,754 controls (Iceland)	Caucasian	AF + AFL	Asso	Stroke, HTN	56
rs2200723	Nearby genes PITX2 and ENPP2	Poly	rs2200723	149 cases/ 738 controls (Sweden)					
rs10033464	Morphogenesis of the heart (PITX2) Breakdown of AngII (ENPP2)	Poly	rs10033464	636 cases/ 804 controls (U.S.) 333 cases/ 2,836 controls	Chinese			Stroke, diabetes mellitus	

What is new?

- New paradigm for stroke prevention in AF
- First new antiarrhythmic drug for 30years
- AF ablation as an established therapy
- Improving technology for implanting devices
- Inroads into genetics of heart rhythm ...

Prevalence of AF

