



Modern flimmer behandling

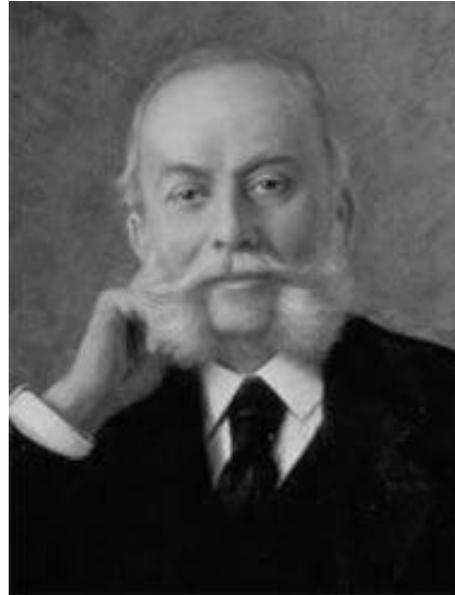
Viste ni att !!!

Peter Linde

2012



Sponsor Pfizer



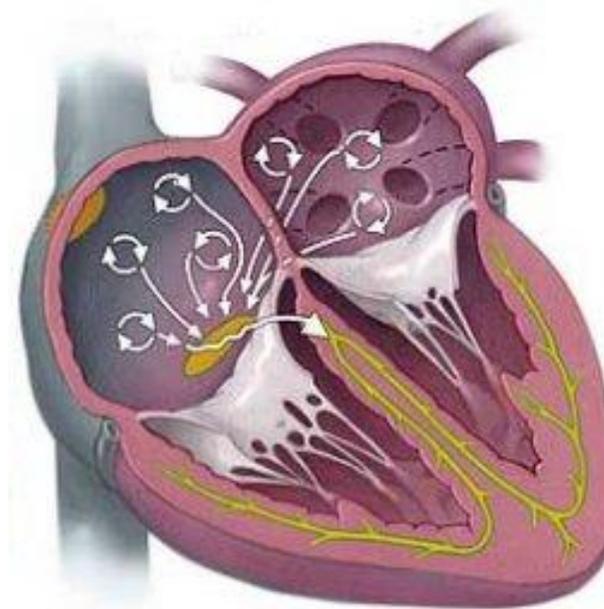
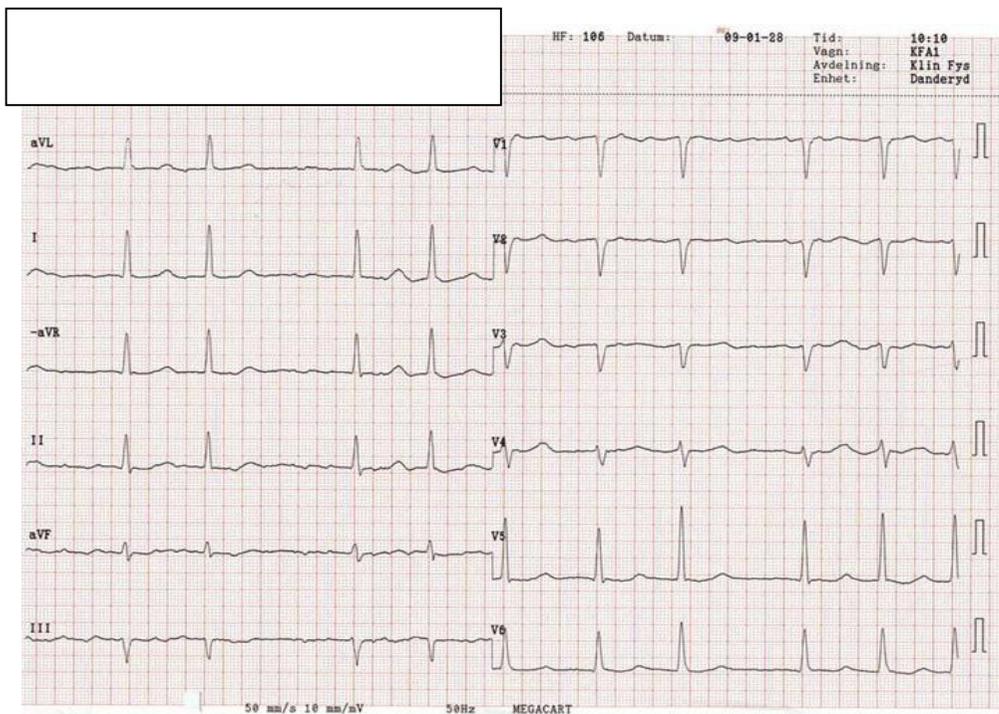
FALL

- Elsa är en 66 årig kvinna som nyliggen vårdats för en hjärtinfarkt. Man gjorde en PCI mot LAD. Akut inga tecken på hjärtsvikt.

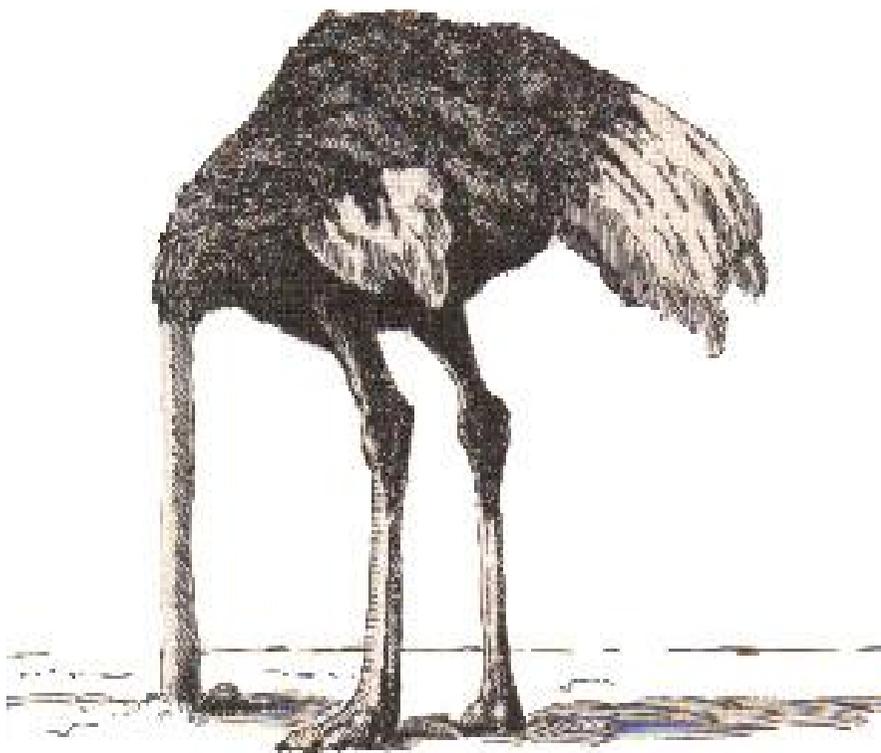
Kommer på 1 månades besök med EKG.



EKG



Vad gör du??



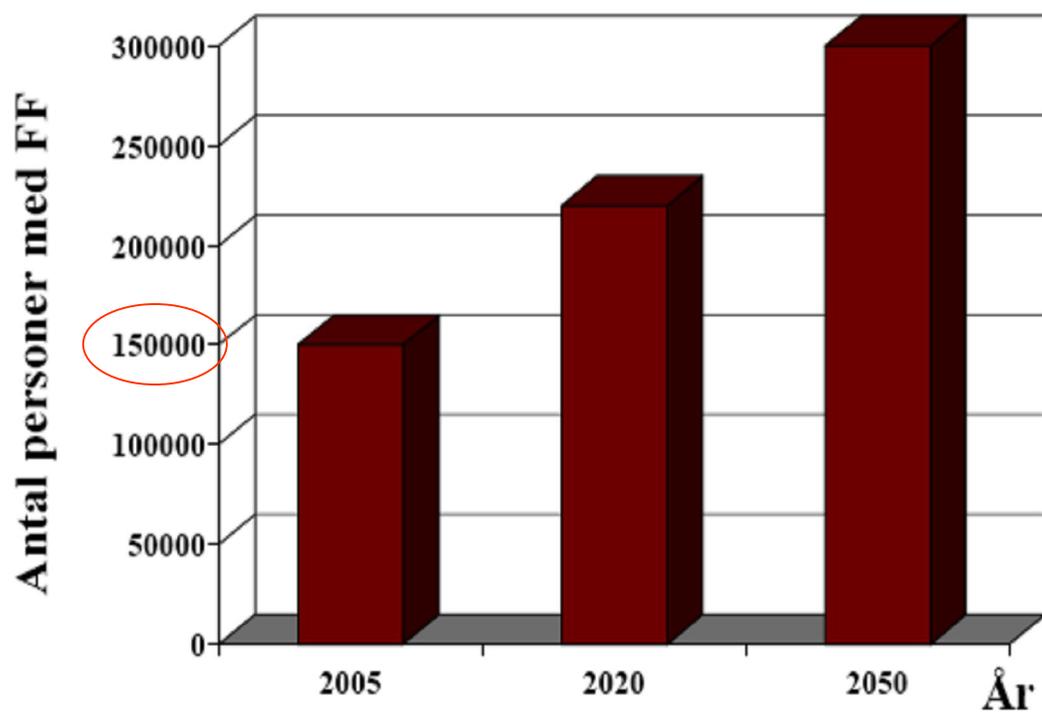
- Visar läkaren som säger att hon mår ju bra så vi gör inget.
- Tänker att det går nog över av sig själv?
- Kaster EKG så att ingen ser?

Kampen mot förmaksflimmer





Vad betyder detta för Sverige?





Förmaksflimmer

TABLE I: TYPES AND CLASSIFICATION OF ATRIAL FIBRILLATION**

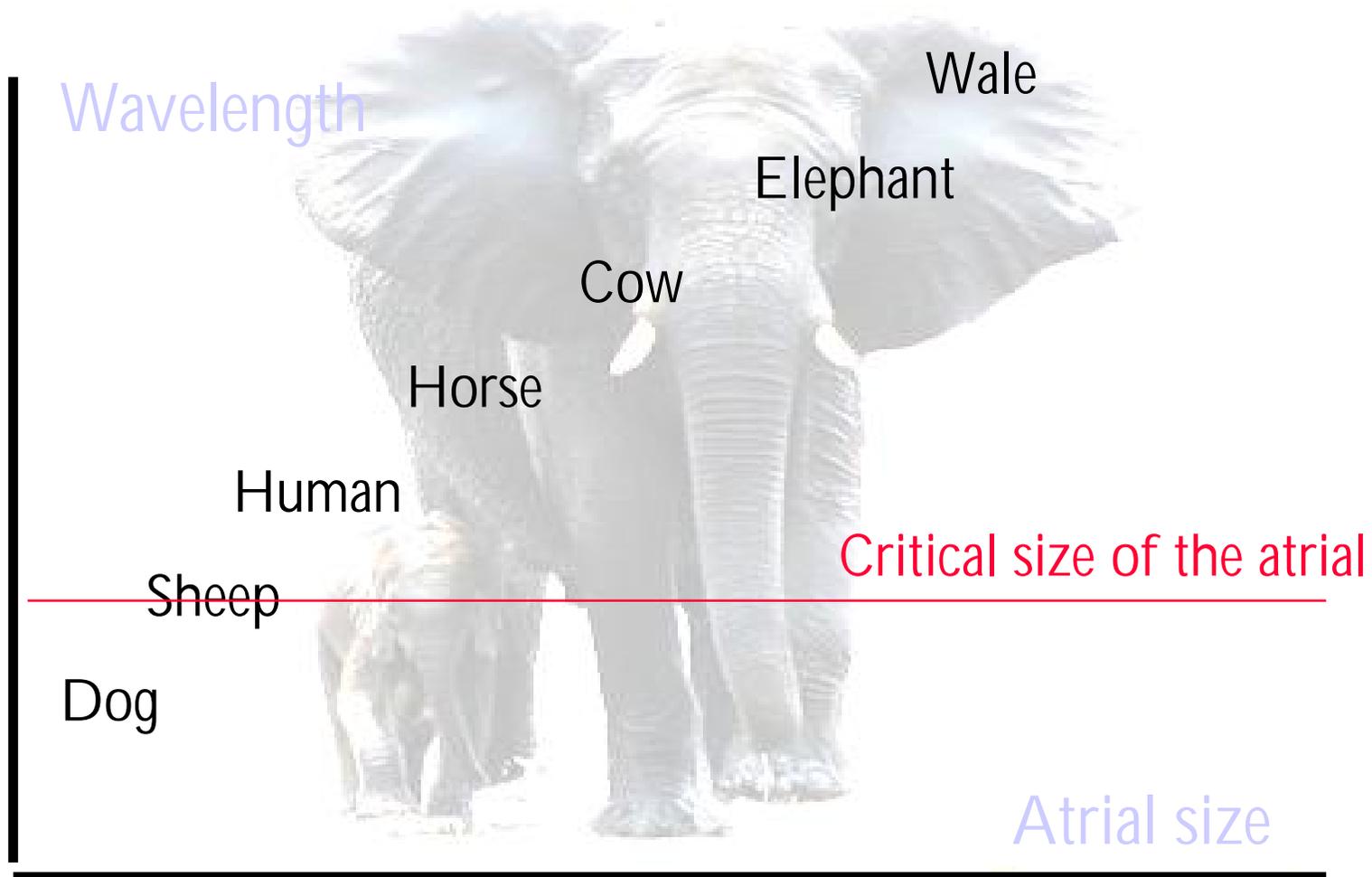
Atrial Fibrillation Episode	An atrial fibrillation episode is defined as AF which is documented by ECG monitoring and has a duration of at least 30 seconds, or if less than 30 seconds, is present continuously throughout the ECG monitoring tracing. The presence of subsequent episodes of AF requires that sinus rhythm be documented by ECG monitoring between AF episodes.
Paroxysmal AF*	Paroxysmal AF is defined as recurrent AF (\geq two episodes) that terminates spontaneously within 7 days. Episodes of AF of \leq 48 hours' duration that are terminated with electrical or pharmacologic cardioversion should also be classified as paroxysmal AF episodes.
Persistent AF*	Persistent AF is defined as continuous AF that is sustained beyond seven days. Episodes of AF in which a decision is made to electrically or pharmacologically cardiovert the patient after \geq 48 hours of AF, but prior to 7 days, should also be classified as persistent AF episodes.
Longstanding Persistent AF	Longstanding persistent AF is defined as continuous AF of greater than 12 months' duration.
Permanent AF	The term permanent AF is not appropriate in the context of patients undergoing catheter or surgical ablation of AF, as it refers to a group of patients for which a decision has been made not to restore or maintain sinus rhythm by any means, including catheter or surgical ablation. If a patient previously classified as having permanent AF is to undergo catheter or surgical ablation, the AF should be reclassified.

* It is recognized that patients may have both paroxysmal and persistent AF. A patient's AF type should be defined as the most frequent type of AF experienced within six months of an ablation procedure. Continuous AF is AF that is documented to be present on all ECG monitoring performed during a defined period of time.

** We recommend that the term "chronic AF" not be used in the context of patients undergoing ablation of AF as it is ambiguous, and there is no standardized definition of this term.

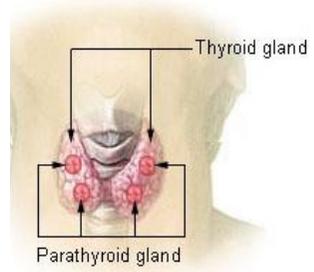


The cause of Atrial fibrillation





Thyroid and Parathyroid Glands



Electrophysiological Mechanisms

Inflammation

Microreentrant circuits

PV foci

Haissaguerre
NEJM 1998

LOM

Hwang
Circulation 2000

Gener

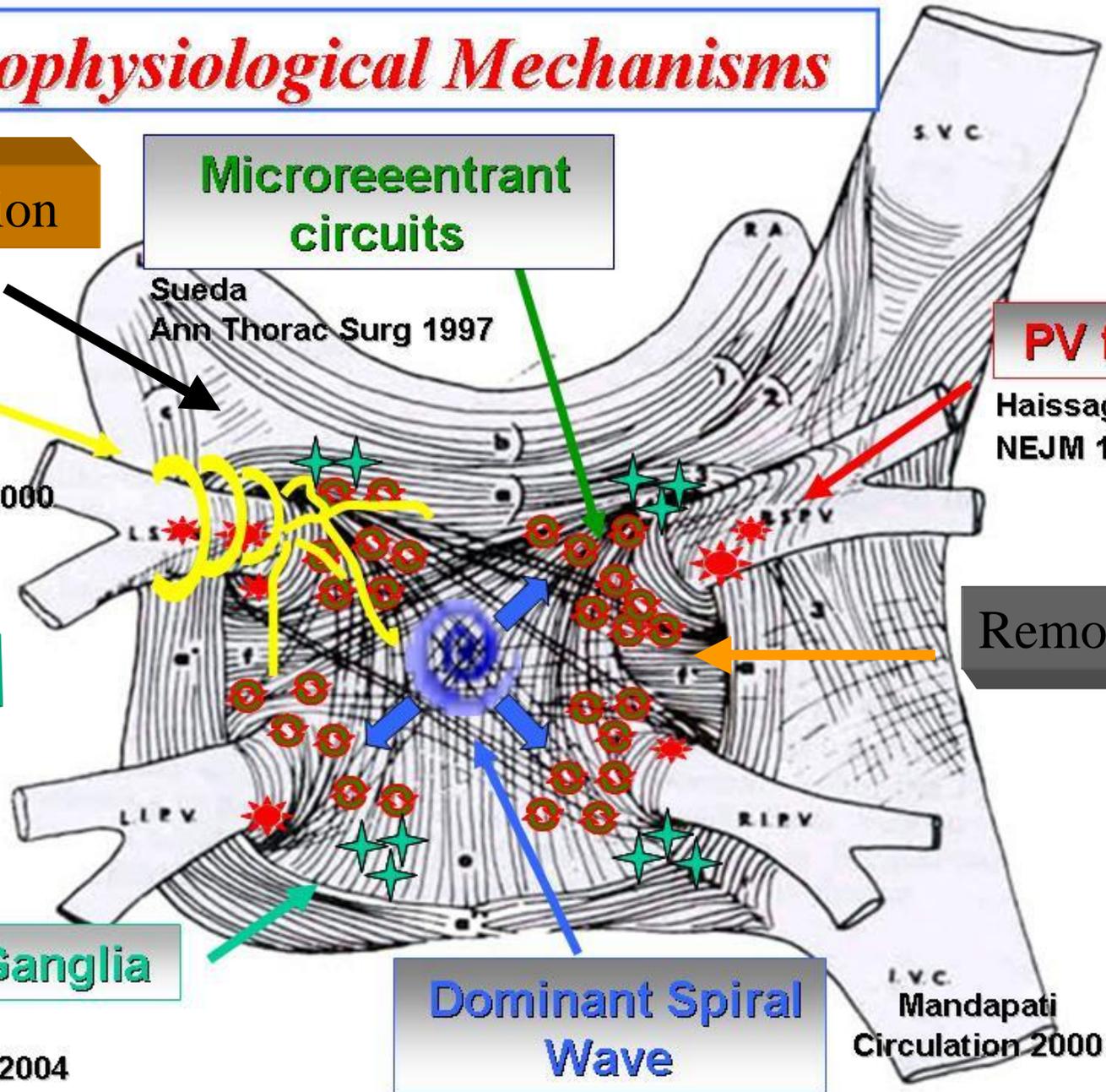
Remodeling

Vagal Ganglia

Pappone
Circulation 2004

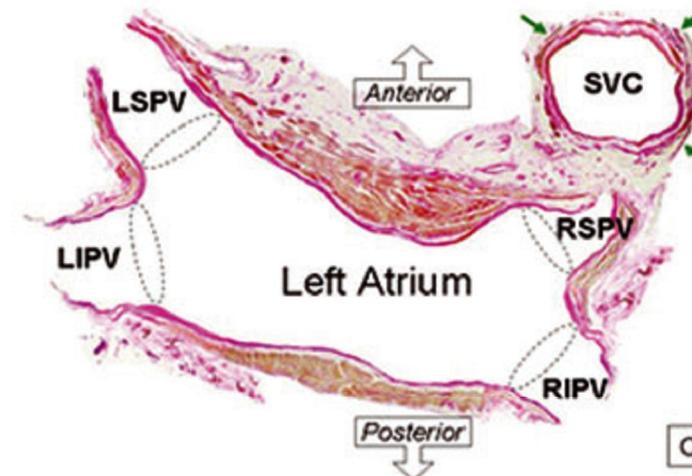
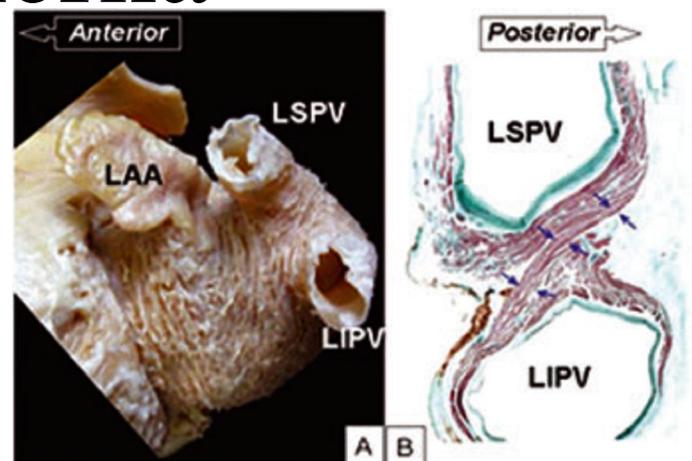
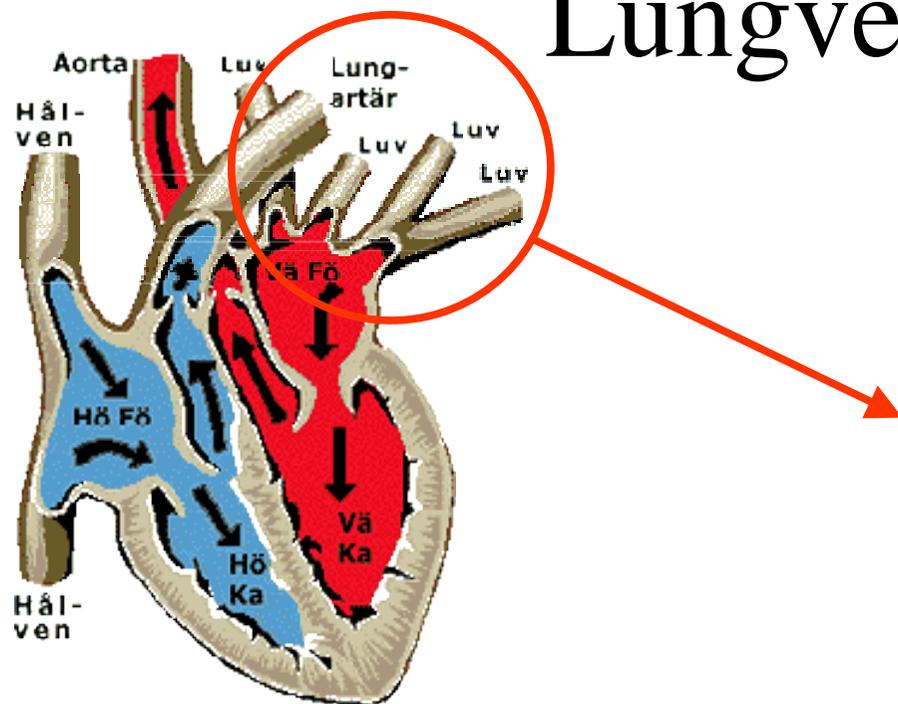
Dominant Spiral Wave

I.V.C.
Mandapati
Circulation 2000



Sueda
Ann Thorac Surg 1997

Anatomi Lungvenerna



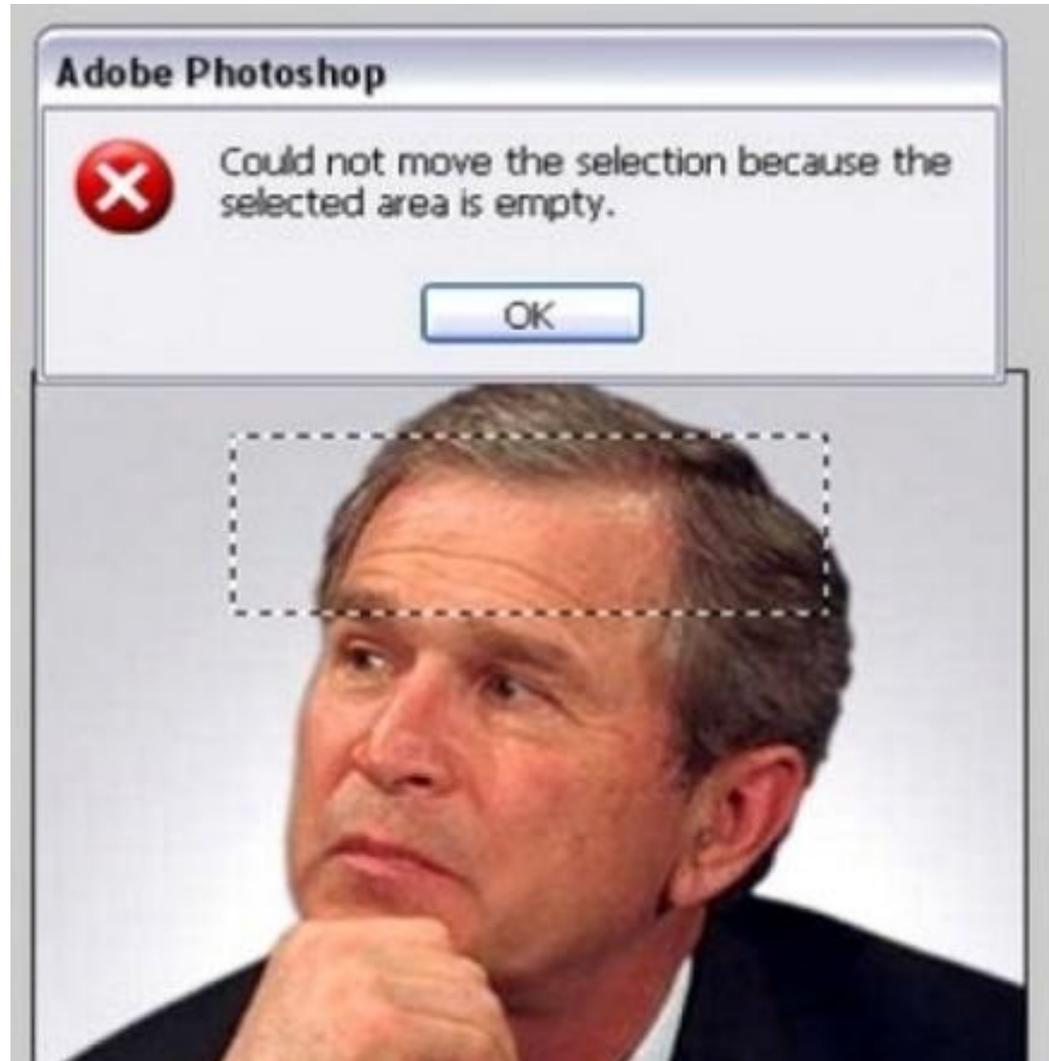
Venice Chart International Consensus Document on Atrial

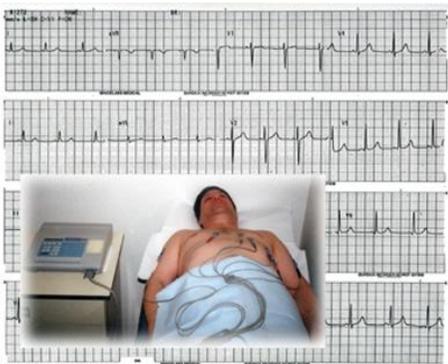
Fibrillation Ablation: 2011 Update J Cardiovasc Electrophysiol, Vol. 23,
pp. 890-923, August 2012



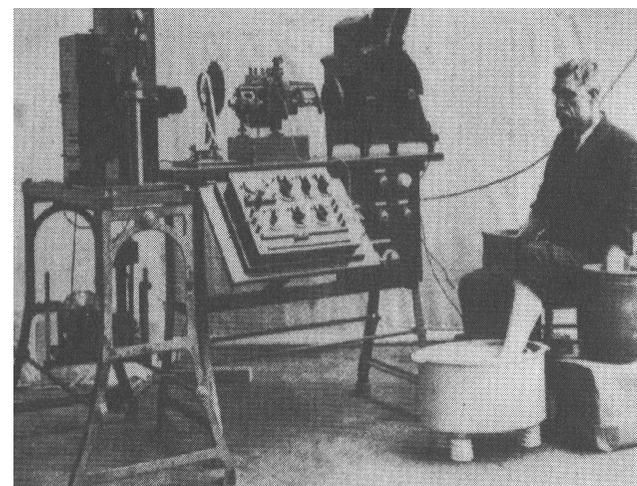
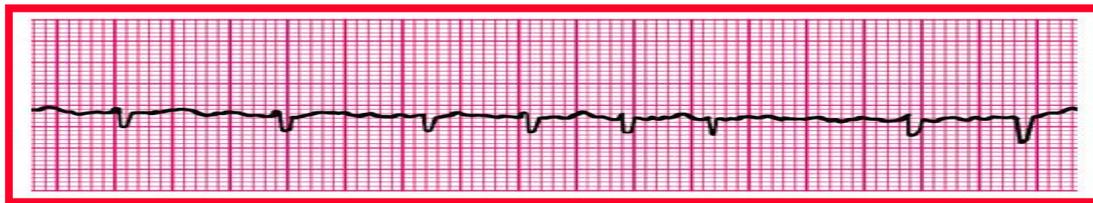
Diagnostik

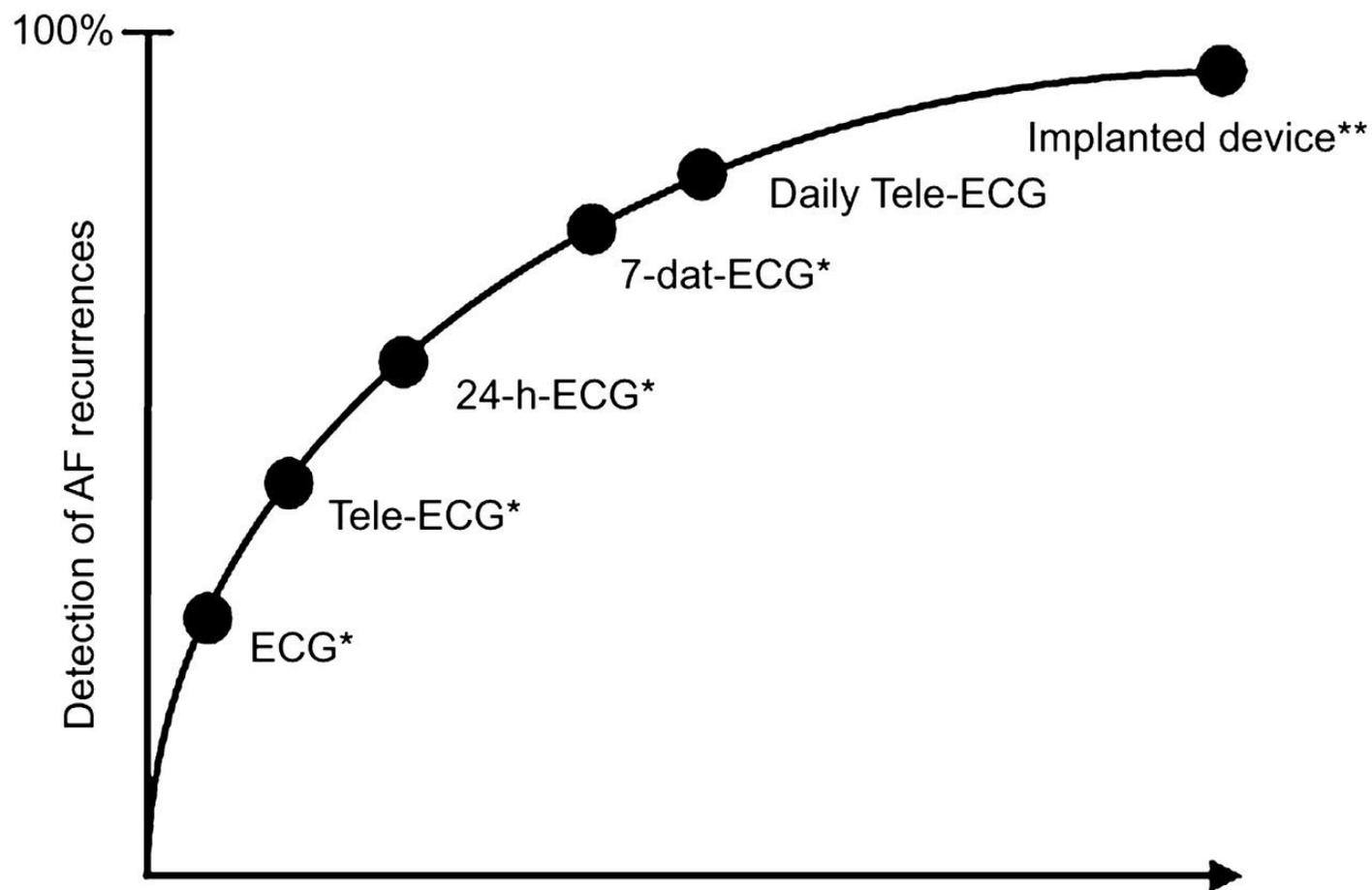
Att hitta förmaksflimmer





Hitta förmaksflimmer





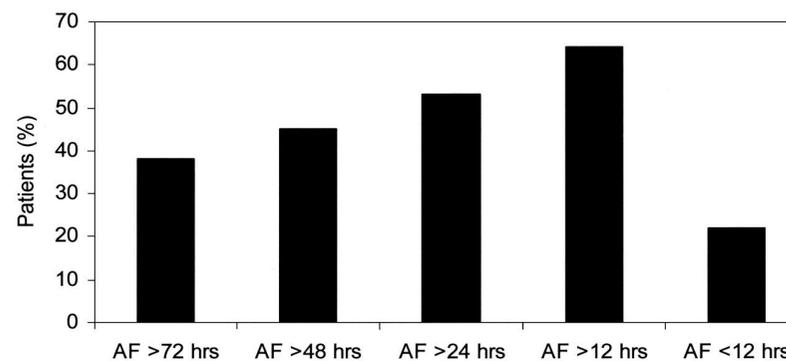
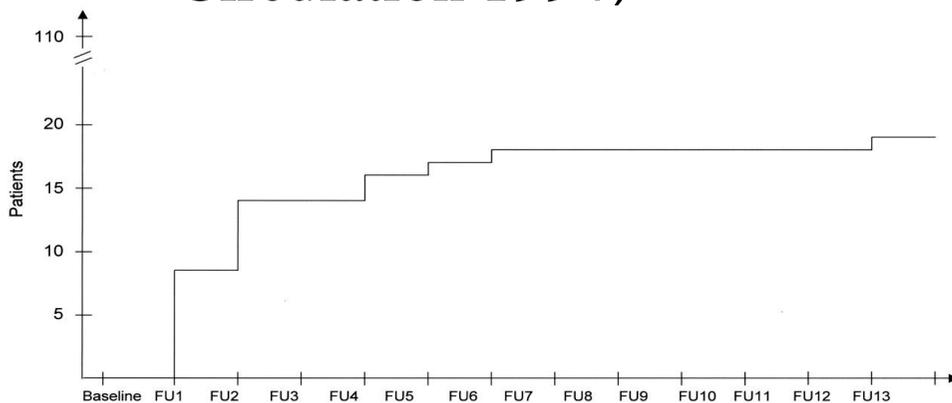
*During the three months follow ups

** As the *theoretic* gold standard

et al. *Europace* 2009;11:671-687

Inga flimmersymptom betyder inte flimmerfri

- Hos patienter med paroxysmalt FF är asymptomatiska FF-episoder betydligt vanligare än symptomatiska (Page et al Circulation 1994)



Israel, C. W. et al. J Am Coll Cardiol
2004;43:47-52

Kumulativ incidence av asymtomatisk FF > 48 timmar

38% asymtomatiska

Fall



- Man beställde ett hjärt-EKO, tog TSH,T4 samt optimerade hennes BT mediciner.
- ER visade rikligt med flimmer i skurar på några timmar. De flesta av dessa episoder kände hon inte av.
- Hon var ganska tjatig så du frågar nu din läkare om vi kan släppa henne till PV?

Hur farligt är förmaksflimmer?

- Ökar riskerna för stroke 3—6 ggr¹
- Risken för död ökad 1,5- 1,9 ggr
- Dubblerar mortalitet vid och efter hjärtinfarkt³
- 30% av FF har dålig VK-funktion

¹ Wolf et al. Neurology. 1978; 28:973-977

² Benjamin et al Circ.1998; 98: 946-952

³ Goldberg et al Am Heart J 2002;143:519



Behandling

Besvär !



Inga Besvär



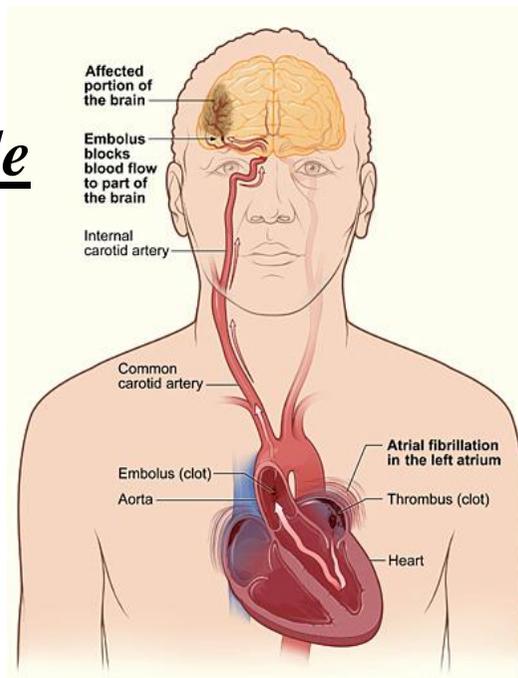
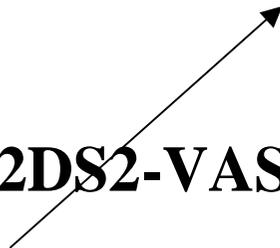
KONTROLL

Blodförtunnade

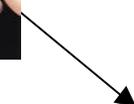
Besvär eller inte



CHA2DS2-VAS

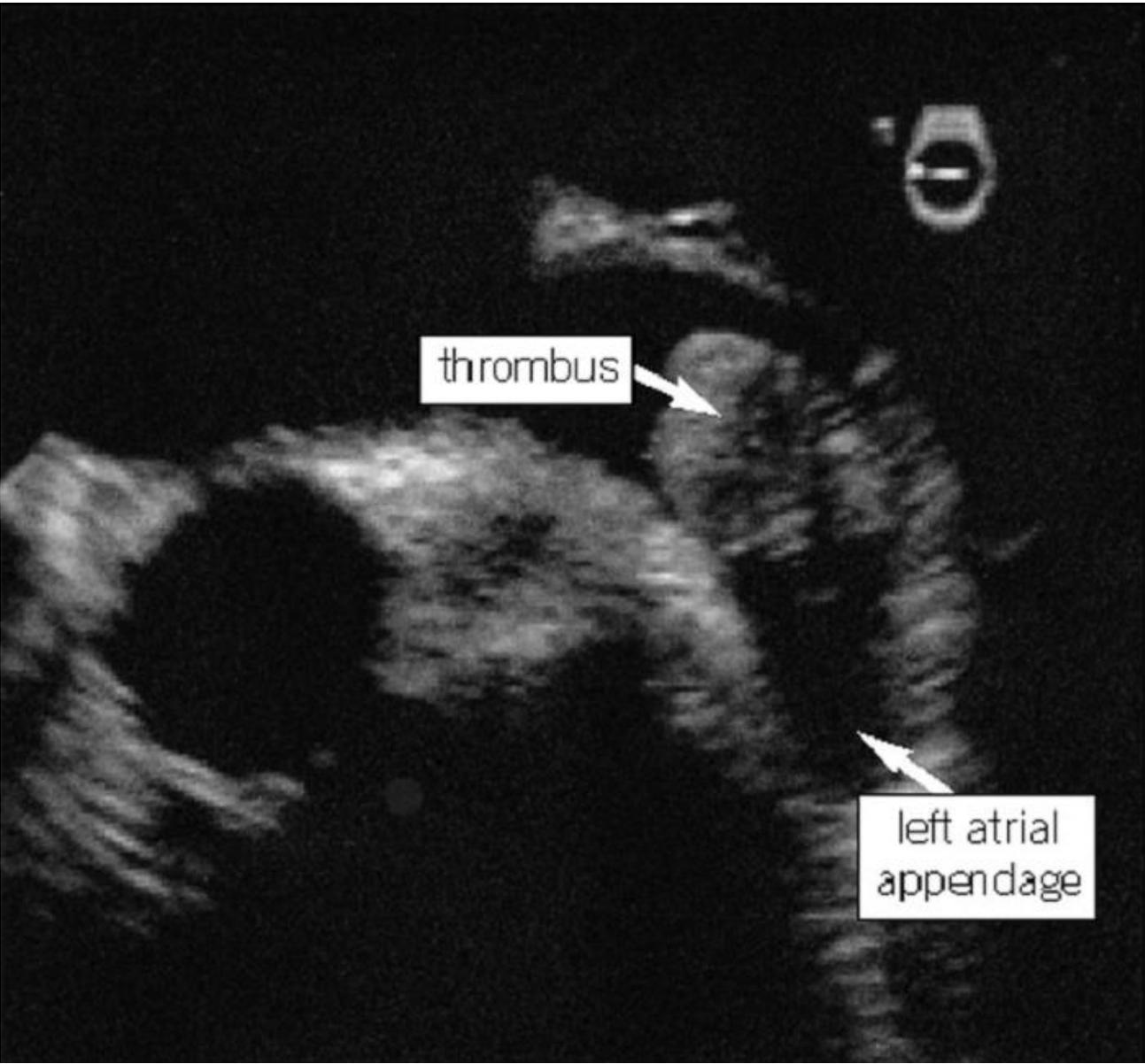


Förebygga stroke och död.



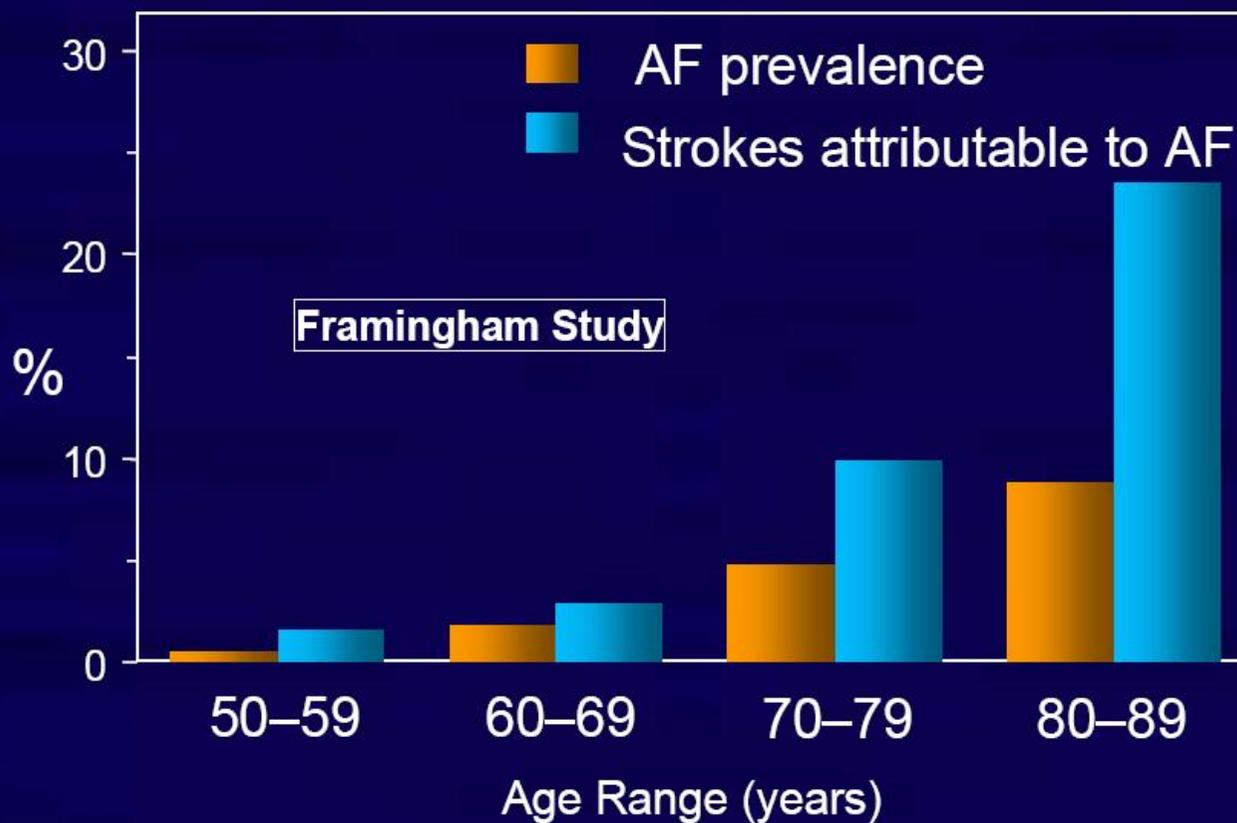
Frekvensreglering







1/6 of All Strokes Attributable to AF



Wolf et al. Stroke 1991;22:983-988.

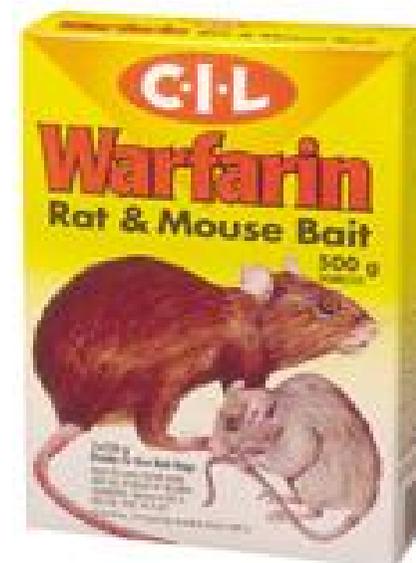
(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA₂DS₂-VASc

(Note: maximum score is 9 since age may contribute 0, 1, or 2 points)

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease ^a	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	9

CHA₂DS₂-VASc score	Adjusted stroke rate (%/year)^b
0	0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

Waran



Historien bakom warfarin

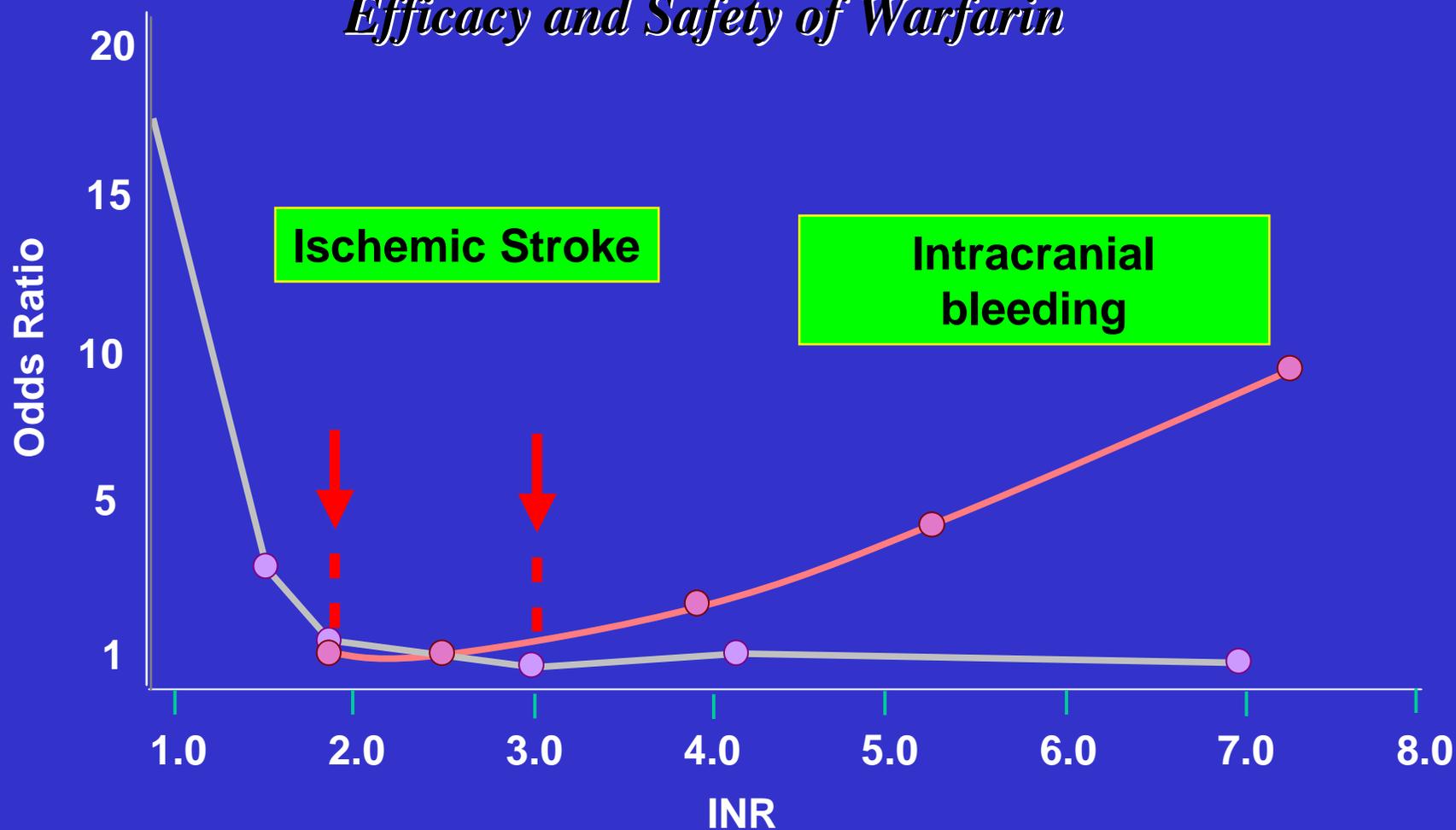
- n 1930-talet: Wisconsin
- n Kor dog av indre blödningar uten någon känd orsak
- n "Sweet clover disease"
- n Bönder blev rekommenderad att inte gje korna möjligt sötklöver hö.
- n Rottgift 1948, medicin 1954





INR at the Time of Stroke or Bleeding

Efficacy and Safety of Warfarin



(Hylek and Singer, 1994; Hylek et al, 1996)

ASA ineffektivt vid FF



Fall



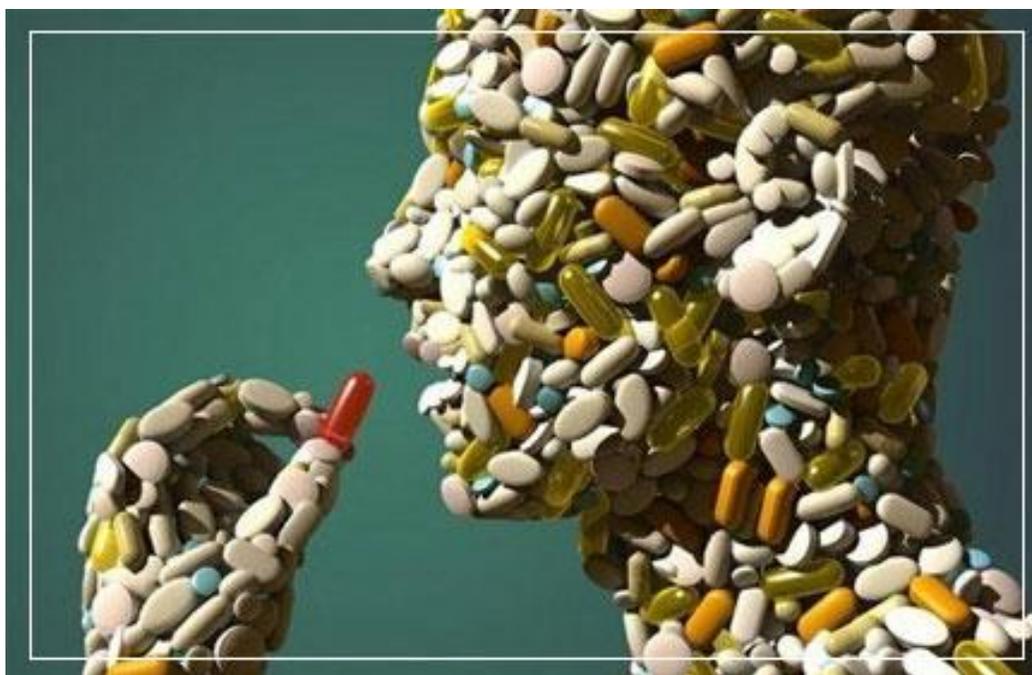
- Hon har nu tagit Waran i ett år och hon tycker inte om det.
- Hon är surare än någonsin och har hört av en väninna att det finns nya mediciner där man inte behöver ta prover.



Nya mediciner mot proppar

Dabigatran

Pradaxa®



Apixaban

Eliquis®

Rivaroxaban

Xarelot®

Betrixaban

EXPLORE-Xa (2010)

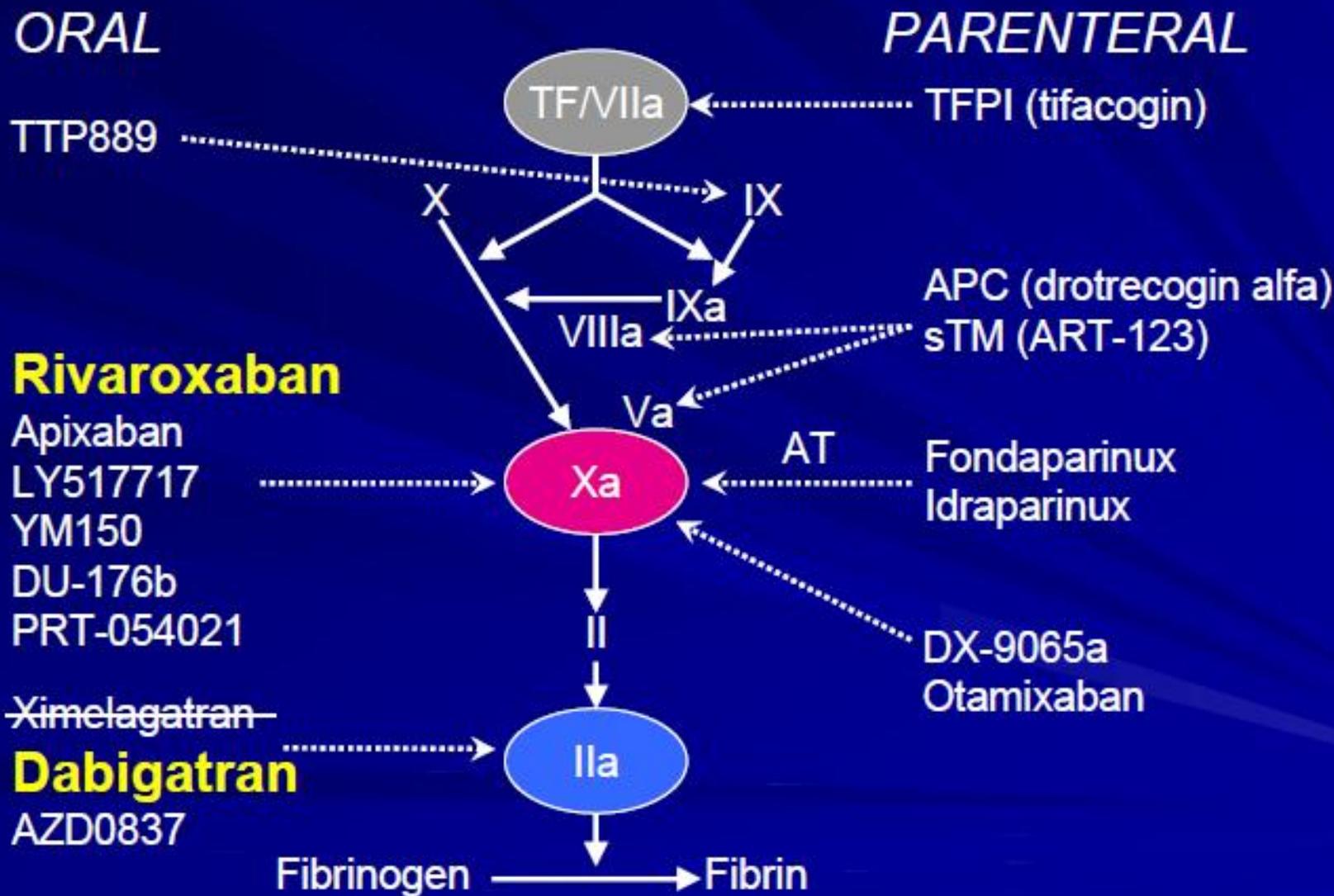
Edoxaban

Ximelagatran

Exanta®

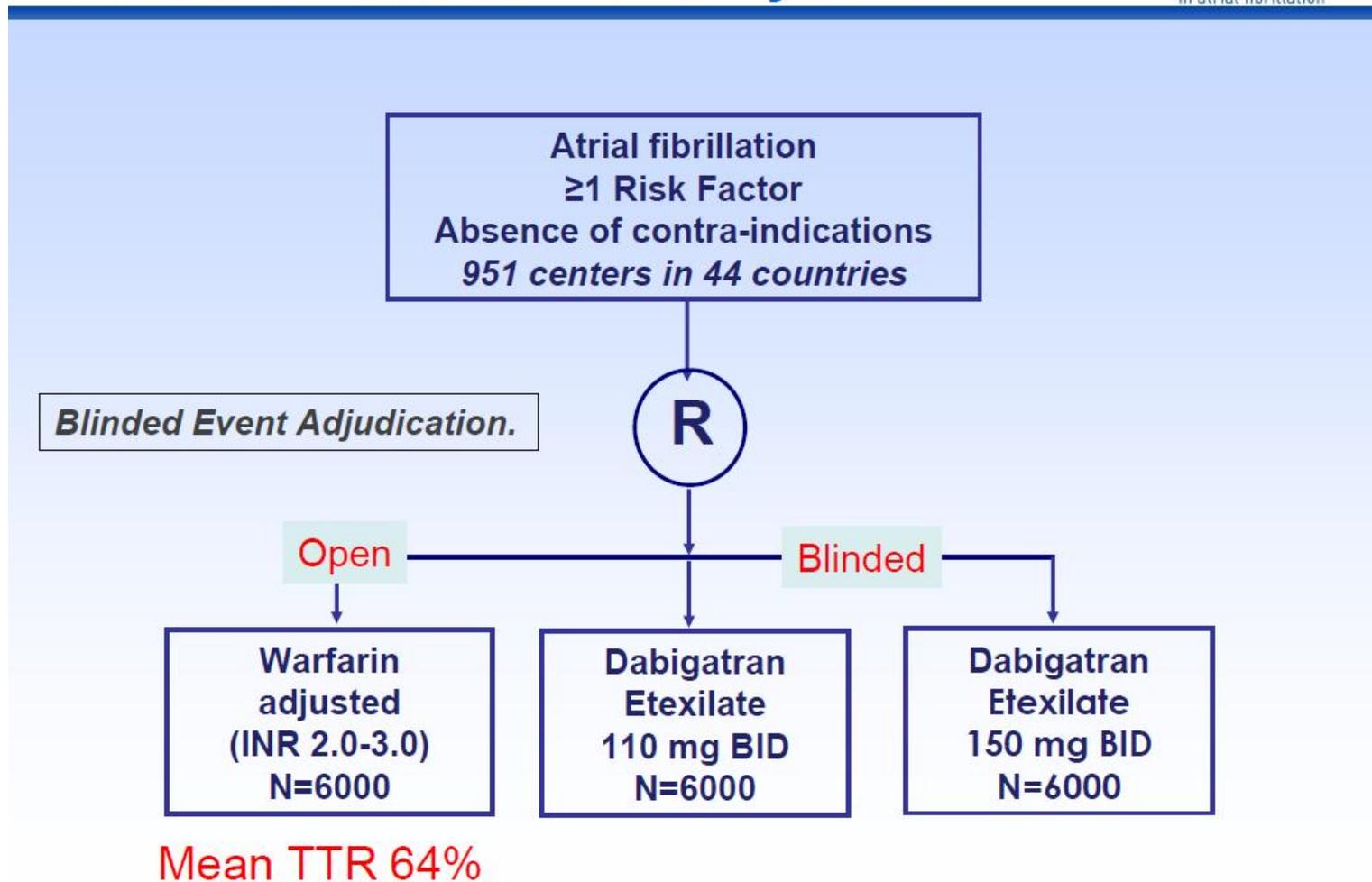


New anticoagulants





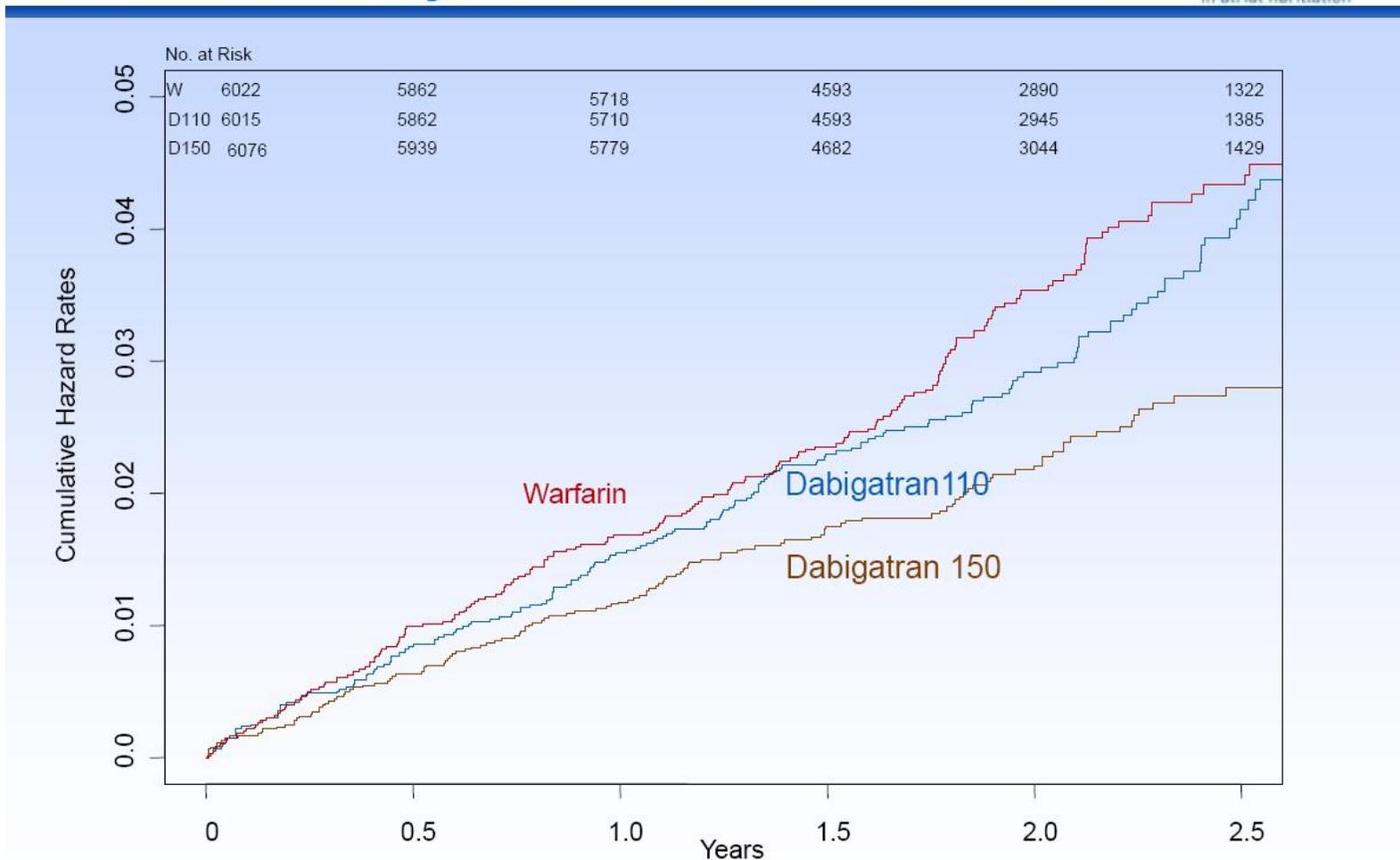
RE-LY: A Non-inferiority Trial



Nejm.org september 17, 2009



Stroke or Systemic Embolism



Nejm.org september 17, 2009



Conclusions

- For the primary efficacy and safety results, the main RELY study results are consistent showing reductions in stroke and major bleeding with Dabigatran compared Warfarin irrespective of centre based INR control
- For secondary outcomes such as all vascular events and mortality the advantages of Dabigatran may be greater at sites with poorer INR control



Atrial Fibrillation with At Least One Additional Risk Factor for Stroke

ARISTOTLE

Randomize
Double blind
(n = 15,000)

- Age \geq 75 years
- Prior stroke, TIA or SE
- CHF or LVEF \leq 40%
- Diabetes mellitus
- Hypertension

Apixaban 5 mg oral twice daily
+
Warfarin placebo

Apixaban placebo twice daily
+
Warfarin (target INR 2-3)

Warfarin/warfarin placebo adjusted by INR/sham INR
based on encrypted point-of-care testing device

Primary outcome: stroke and systemic embolism

Other outcomes: Death, MI, bleeding

Stratified by warfarin-naïve status

448 events over anticipated 2 year median follow-up;
>90% power to show non-inferiority
(apixaban vs warfarin upper bound of 95% CI <1.38)



Summary



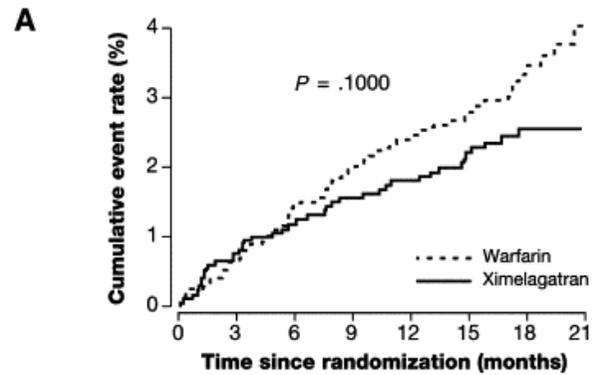
Treatment with apixaban as compared to warfarin in patients with AF and at least one additional risk factor for stroke:

- Reduces stroke and systemic embolism by 21% ($p=0.01$)
- Reduces major bleeding by 31% ($p<0.001$)
- Reduces mortality by 11% ($p=0.047$)

with consistent effects across all major subgroups and with fewer study drug discontinuations on apixaban than on warfarin, consistent with good tolerability.

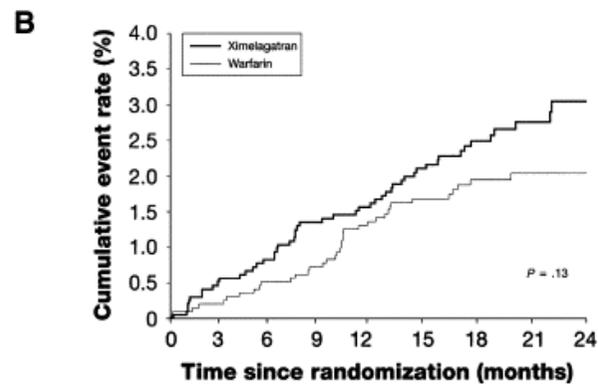


Sportif III-V



Patients at risk

Warfarin	1703	1633	1576	864	318
Ximelagatran	1704	1630	1575	865	358



Patients at risk

Ximelagatran	1960	1900	1596	848	243
Warfarin	1962	1910	1624	867	240

[Am Heart J.](#) 2003 Sep;146(3):431-8.

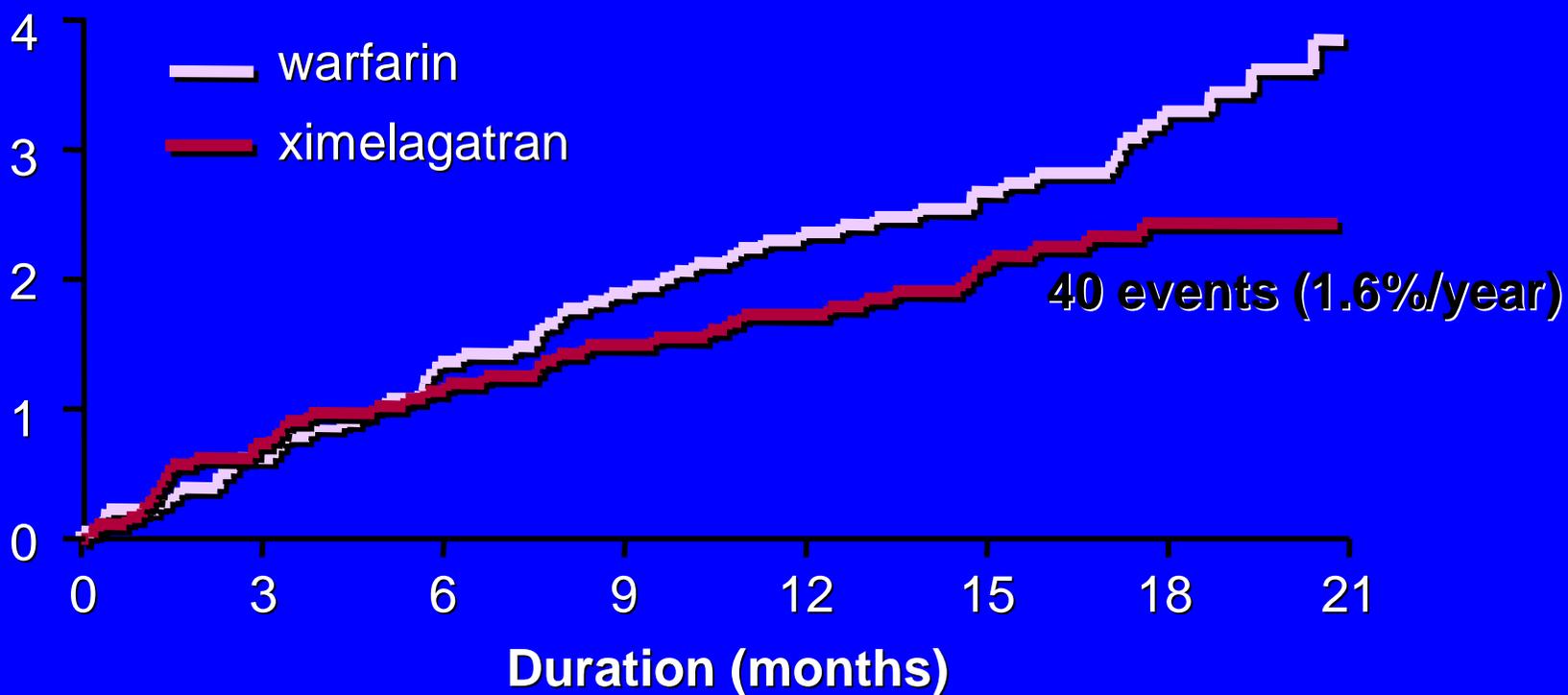


Primary events: stroke and SEE

Intention-to-treat analysis

Cumulative event rate (%)

56 events (2.3%/year)



Halperin JL. executive (SPORTIF III and V) Am Heart J. 2003;146:431-438.



Study Design

Atrial Fibrillation

Risk Factors

- CHF
- Hypertension
- Age \geq 75
- Diabetes

At least 2 or 3 required*

OR

- Stroke, TIA or Systemic embolus

Rivaroxaban

20 mg daily
15 mg for Cr Cl 30-49 ml/min

Randomize
Double Blind /
Double Dummy
(n ~ 14,000)

Warfarin

INR target - 2.5
(2.0-3.0 inclusive)

Monthly Monitoring
Adherence to standard of care guidelines

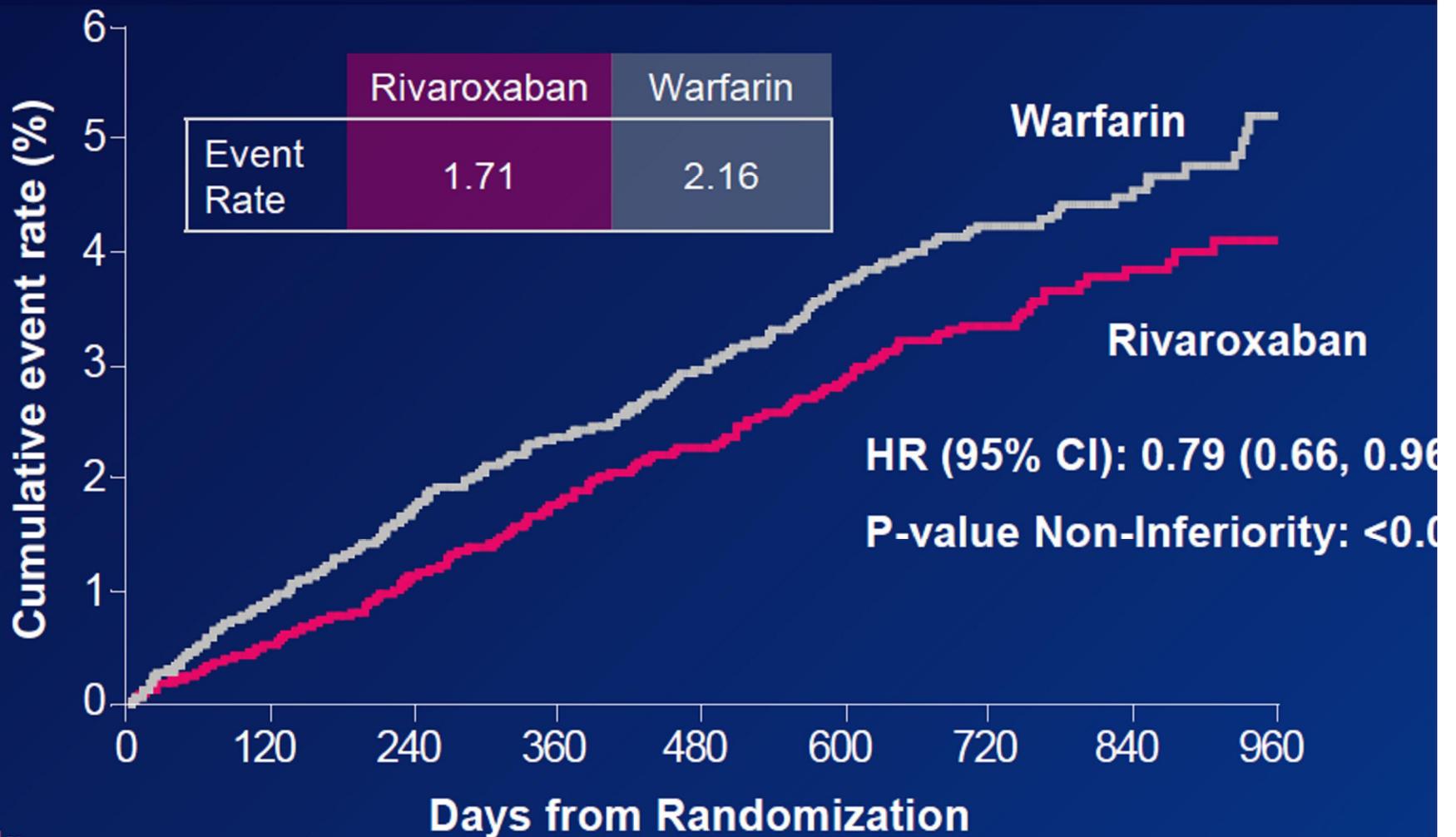
Primary Endpoint: Stroke or non-CNS Systemic Embolism

* Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%



Primary Efficacy Outcome

Stroke and non-CNS Embolism



No. at risk:

Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655



AVERROES Design

36 countries, 522 centres

AF and ≥ 1 risk factor, and demonstrated or expected unsuitable for VKA

Apixaban 5 mg BID

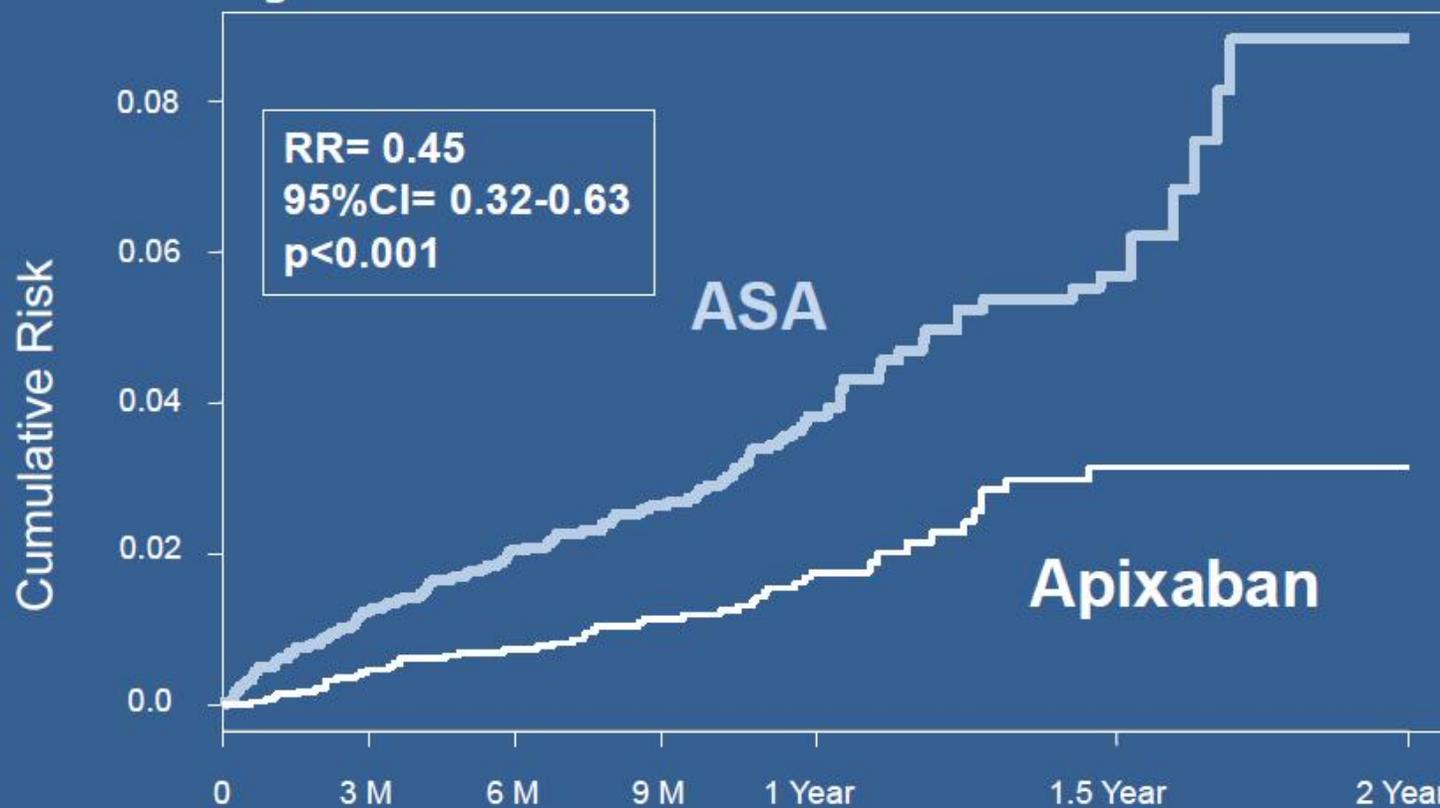
2.5 mg BID in selected patients



Primary Outcome: Stroke or Systemic Embolic Event (SEE)



Stroke or Systemic Embolic Event



No. at Risk							
ASA	2791	2694	2451	2058	1347	533	78
Apix.	2809	2744	2489	2064	1335	530	83



Ref:

- 1. Connolly S et al NEJM 2009 & NEJM 2011.
- 2. Patel M et al NEJM 2011.
- 3. Granger C et al NEJM 2011.
- 4. EMA
- 5. TLV

	Dabigatran 110mg (Pradaxa)	Dabigatran 150mg (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaba (Lixiana)
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Godkänd indikation FF

✓

✓

✓

Stroke/SE (non-inferior)

✓

✓

✓

✓

↓ Stroke/SE (superior, ITT)

✓

✓

↓ Ischemic stroke

✓

↓ Mortalitet

(✓)

✓

↓ Större blödning

✓

✓

↓ IC blödning

✓

✓

✓

✓

↑ GI blödning

✓

✓

↑ Hjärtinfarkt

?

?

↑ Säkerhet vid måttlig nedsatt njurfunktion

✓

Färre behandlingsavbrott

✓

Validering mot ASA

✓

Nya mediciner

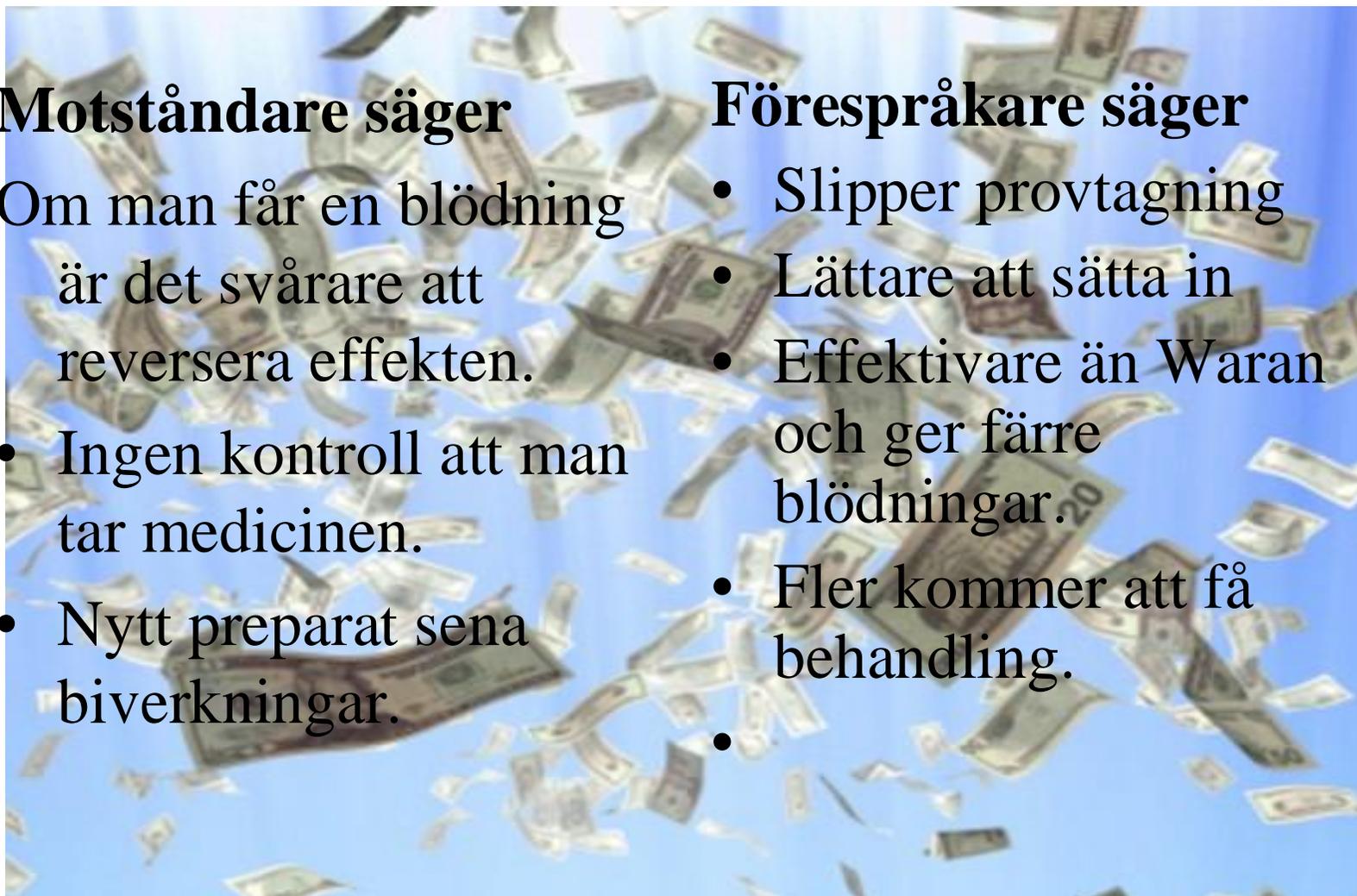
Motståndare säger

Om man får en blödning är det svårare att reversera effekten.

- Ingen kontroll att man tar medicinen.
- Nytt preparat sena biverkningar.

Förespråkare säger

- Slipper provtagning
- Lättare att sätta in
- Effektivare än Waran och ger färre blödningar.
- Fler kommer att få behandling.

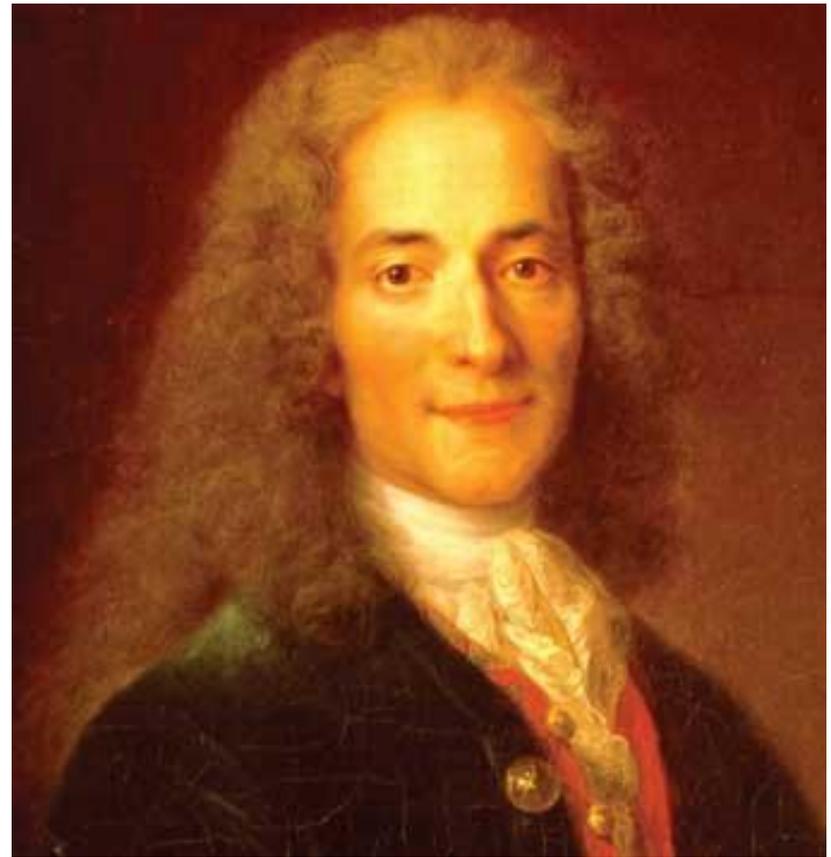




”Doktorer är personer som skriver ut medicin som det vet lite om, för att bota sjukdomar de vet mindre om , till människor de inte vet något om.”

Voltaire 1694-1778

”Ett fyndigt ord bevisar ingenting”





Indikation för antikoagulation vid FF

- In patients with a CHA₂DS₂-VASc score = > 2, OAC therapy with:
adjusted-dose VKA (INR 2–3); or
a direct thrombin inhibitor (dabigatran); or
an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)
is recommended, unless contraindicated.

Klass Ia rekommendation.

European Heart

Journaldoi:10.1093/eurheartj/ehs253



Guidelines for the management of atrial fibrillation

The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)

European Heart Journal (2010) 31, 2369–2429



Mediciner

Recidiv profylax

- B-blockare
 - Metoprolol, Seloken,
 - Bisoprolol, Tenormin.
- **Speciella mediciner**
 - Tambocor©
 - Rytmonorm©
 - Sotalol©
 - Durbis©
 - **Multaq©**
 - Cordarone©

Frekvens reglering

- B-blockare
- Digitalis
- Ca blockare
 - Verapamil©
 - Cardizem©





Fall

- Hon har nu fått allt mer besvär av sitt flimmer och vill ha behandling.
- Hon har nu varit på akuten ett flertal gånger men tar nu kontakt med dig eftersom hon inte uppfattar sig omhändertagen.



Tabletter och studier.



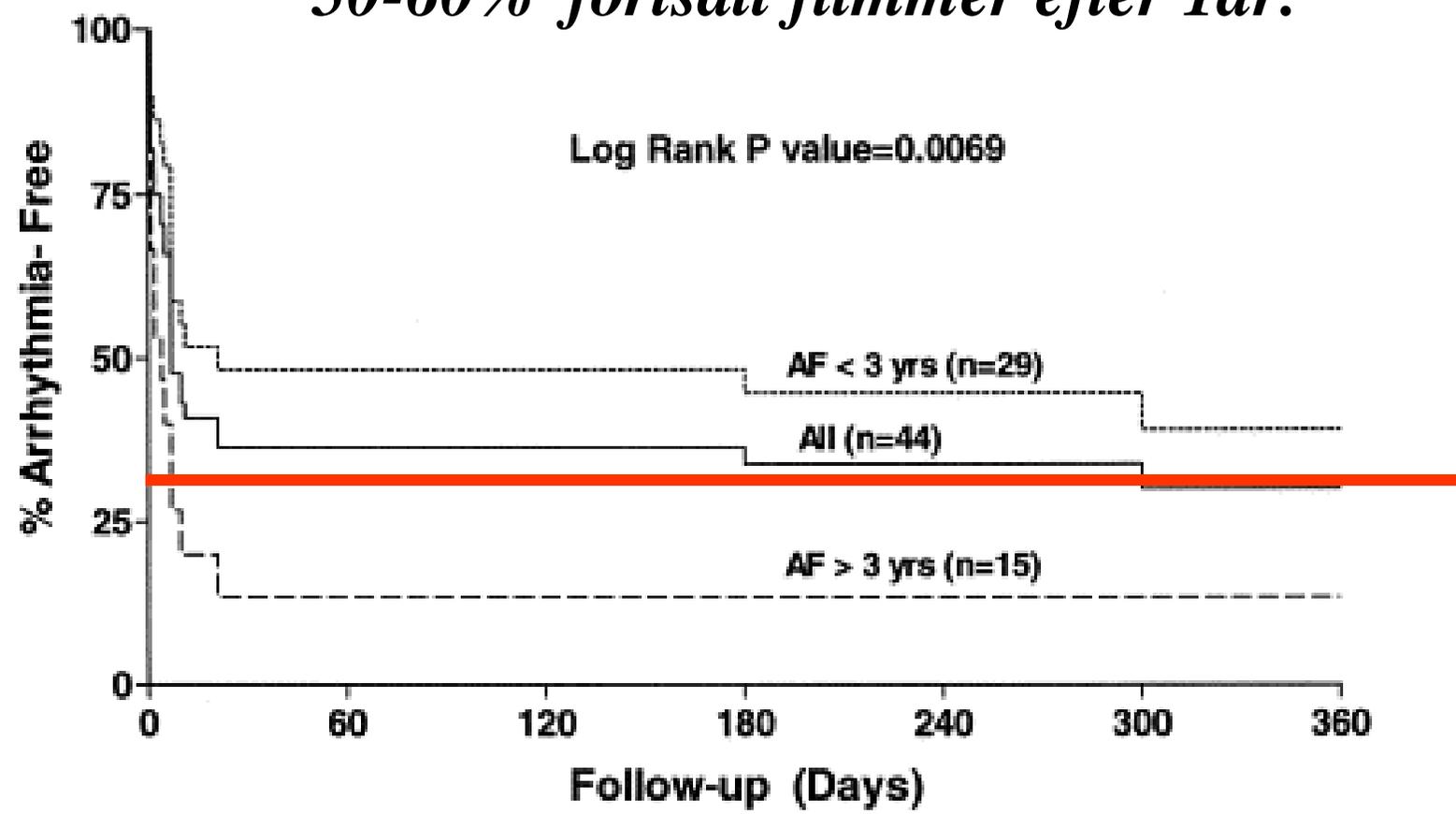
Patient No.	Drug 1	Drug 2	Drug 3	Drug 4	Final Therapy
1	Sotal	Prop + Ver	Amio		Amio
2	Flecain + Aten	Sotal	Amio	Aten	Aten
3	Dig + Prop	Amio			Amio
4	Sotal	Prop + Ver	Amio	Ver + Dig	Ver + Dig
5	Prop + Aten				Prop + Aten
6	Flecain + Dig	Procain + Dig	Sotal	Amio	Amio
7	Procain + Dig	Prop + Dig	Amio	Ver + Dig	Ver + Dig
8	Sotal	Amio			Amio
9	Flecain + Aten	Sotal	Amio	Aten + Dig	Aten + Dig
10	Flecain + Dig	Procain + Dig			Procain + Dig
11	Procain + Dig	Flecain + Dig	Sotal	Amio	RF Abl
12	Amio	Quinid + Dig	Prop + Aten	Aten + Dig	Aten + Dig
13	Procain + Dig	Prop + Aten	Amio	Dilt + Dig	Dilt + Dig
14	Sotal	Prop + Ver	Amio	Metop	Metop
15	Sotal	Amio	Dilt + Dig		Dilt + Dig
16	Procain + Dig	Prop + Dig	Sotal	Amio	AV node Abl + PPM
17	Sotal	Flecain + Aten	Amio	Ver + Dig	Ver + Dig
18	Prop + Dig	Sotal	Flecain + Aten	Amio	Amio
19	Flecain + Aten	Sotal	Amio	Procain + Dig	Aten + Dig
20	Sotal	Prop + Dig	Amio	Ver + Dig	Ver + Dig
21	Sotal	Prop + Dig	Amio	Dig	Dig
22	Amio	Sotal	Prop + Aten		RF Abl
23	Procain + Dig				Procain + Dig
24	Amio	Sotal	Prop + Dig	Metop	Metop
25	Sotal	Prop + Aten	Procain + Dig	Amio	Amio
26	Quinid + Dig	Prop + Ver	Amio	Aten	Aten
27	Flecain + Dig	Sotal	Amio	Dilt + Dig	Dilt + Dig
28	Sotal	Prop + Aten	Amio		Amio
29	Amio	Prop + Aten	Sotal	Dig	Dig
30	Amio				Amio

Amio = amiodarone; Aten = atenolol; AV = atrioventricular; Dig = digoxin; Dilt = diltiazem; Flecain = flecainide; Metop = metoprolol; PPM = permanent pacemaker following AV node ablation; Procain = procainamide; Prop = propafenone; Quinid = quinidine; RF Abl = catheter ablation of atrial flutter; Sotal = sotalol; Ver = verapamil.



Långtidseffekt

50-60% fortsatt flimmer efter 1år.



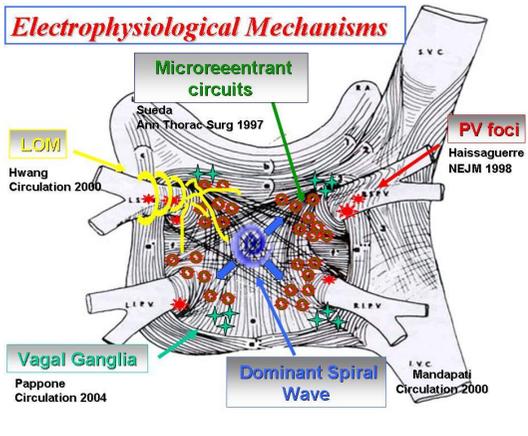


Ablationer

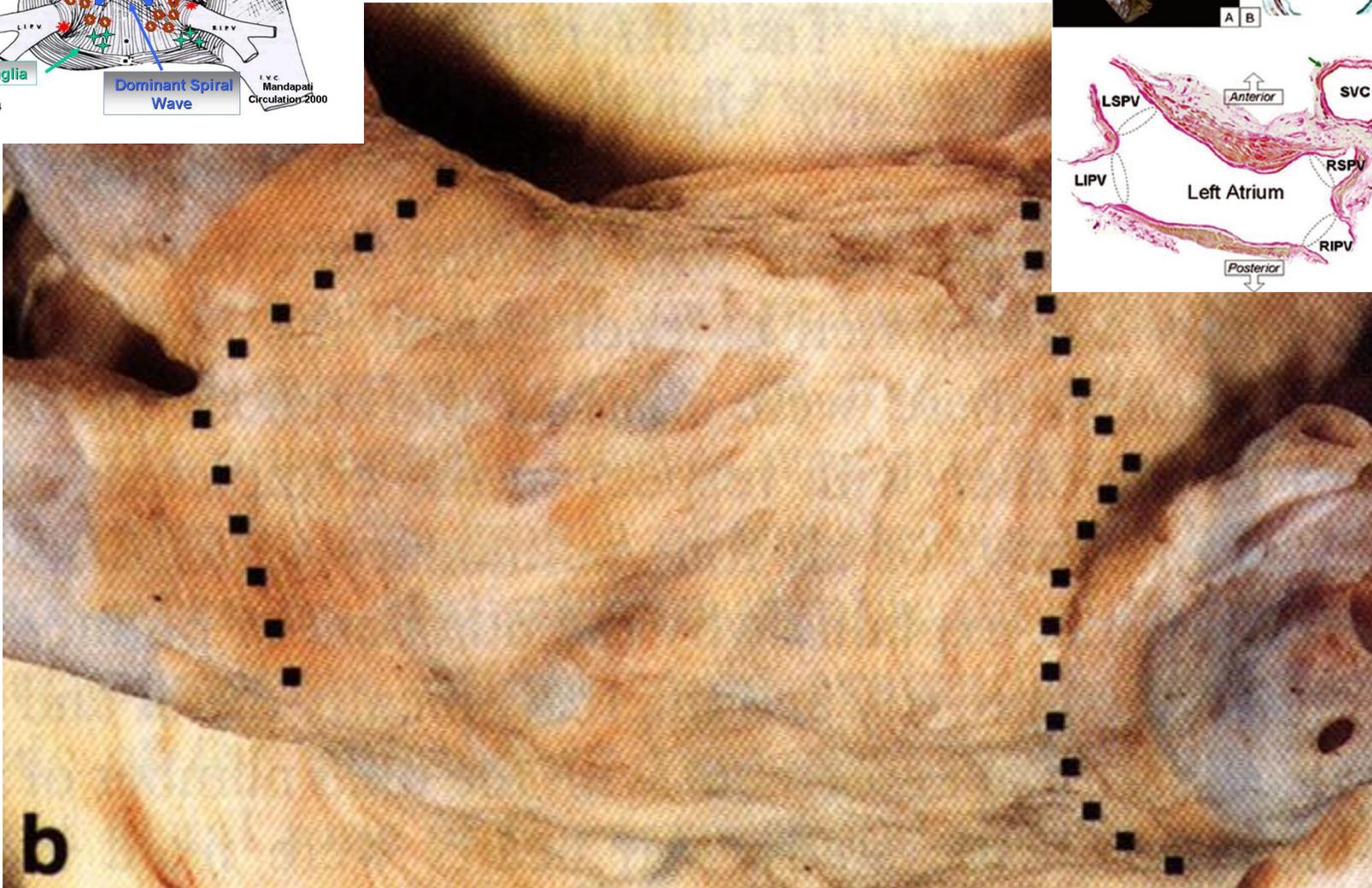
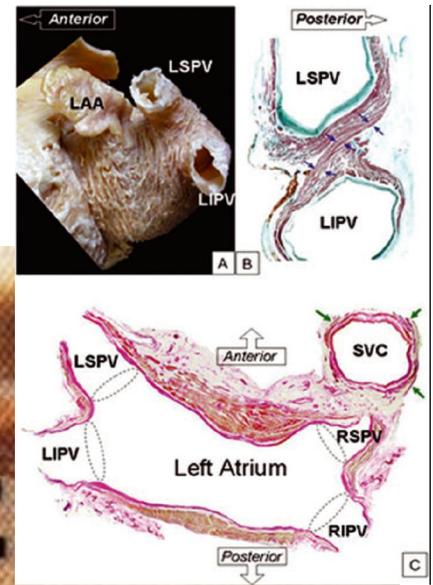


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Electrophysiological Mechanisms

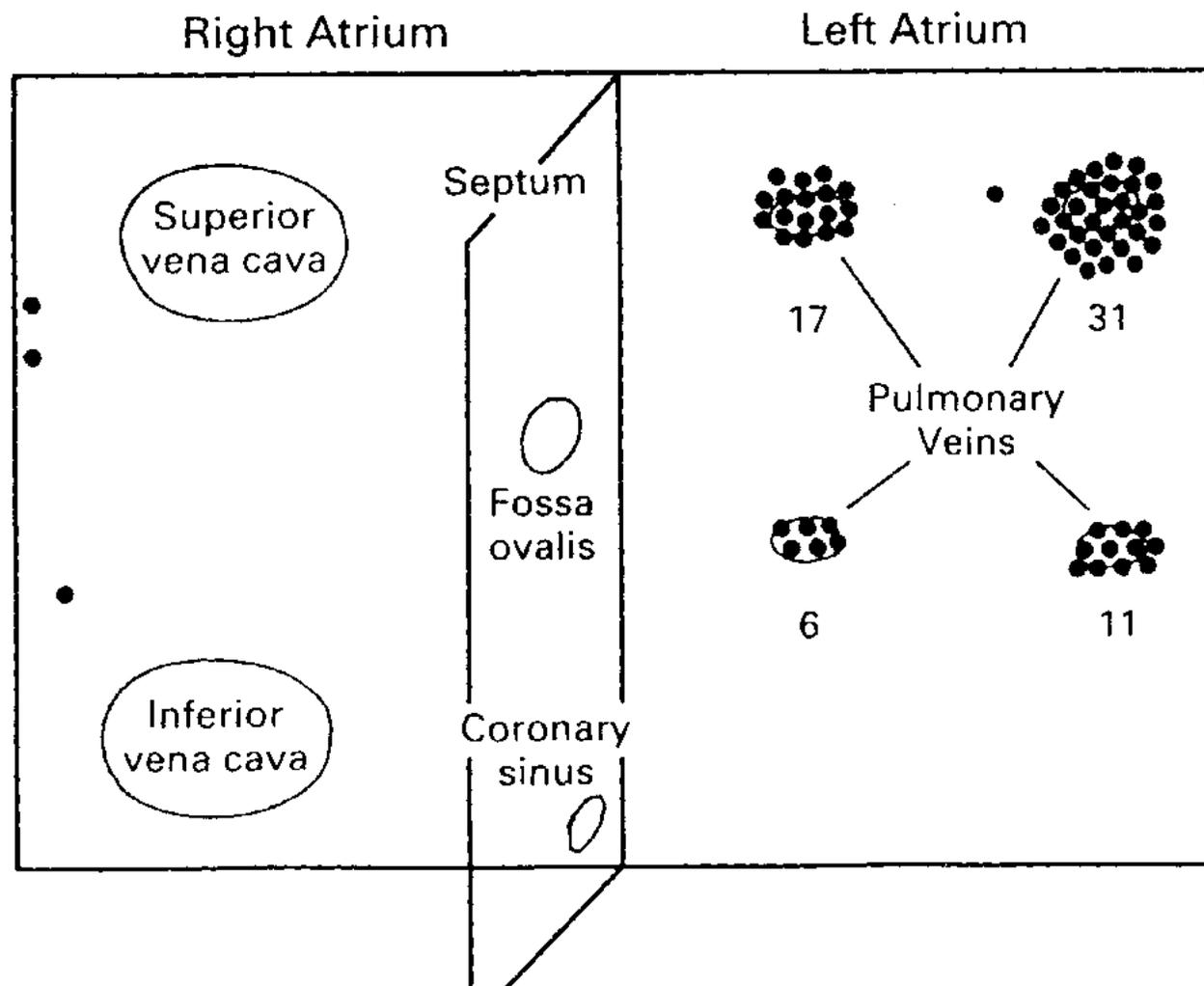


Lungvener

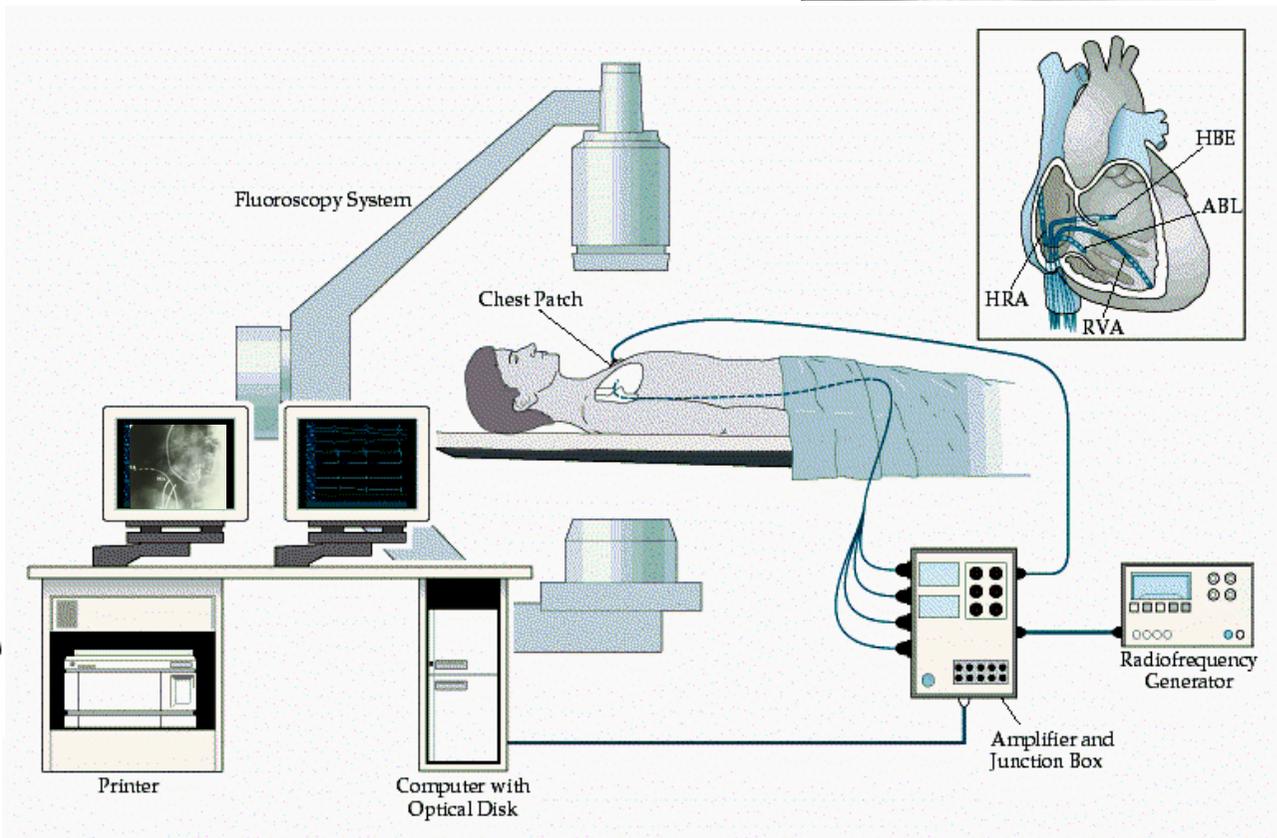
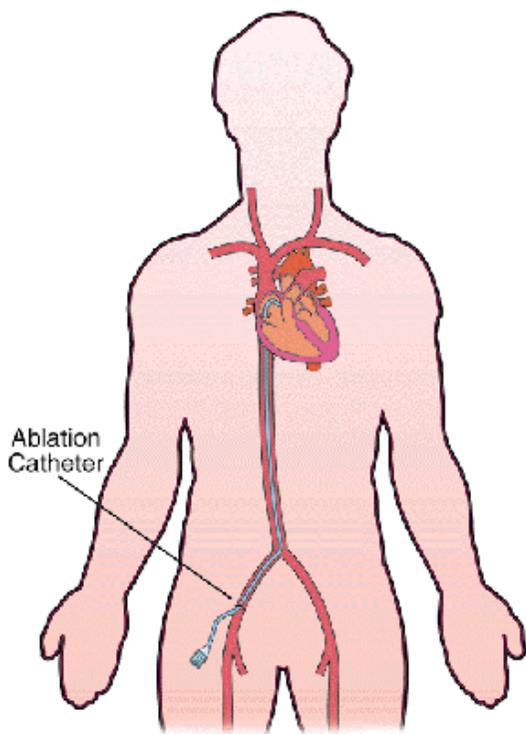
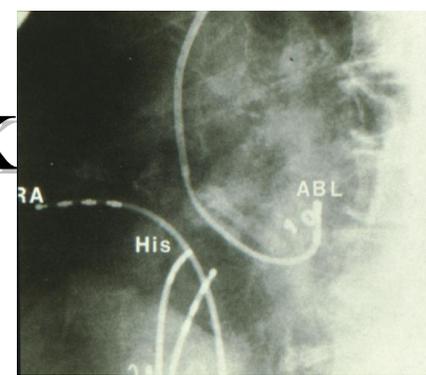




Lokalisation av SVES



Elektrofysiologisk undersökning





Ablations Lab T5



H

C: 640 W: 246.0
SAPESUM
LAO/RAO -170
CRAN/CAUD 17

Kontrast:
Gantry: °
FoV: mm
Tid: ms
Snitt: mm
Pos:

L



RAH
R

F:
mA
kV
Bildnr: 31
Bild 31 av 36

2012-04-30, 15:07:51

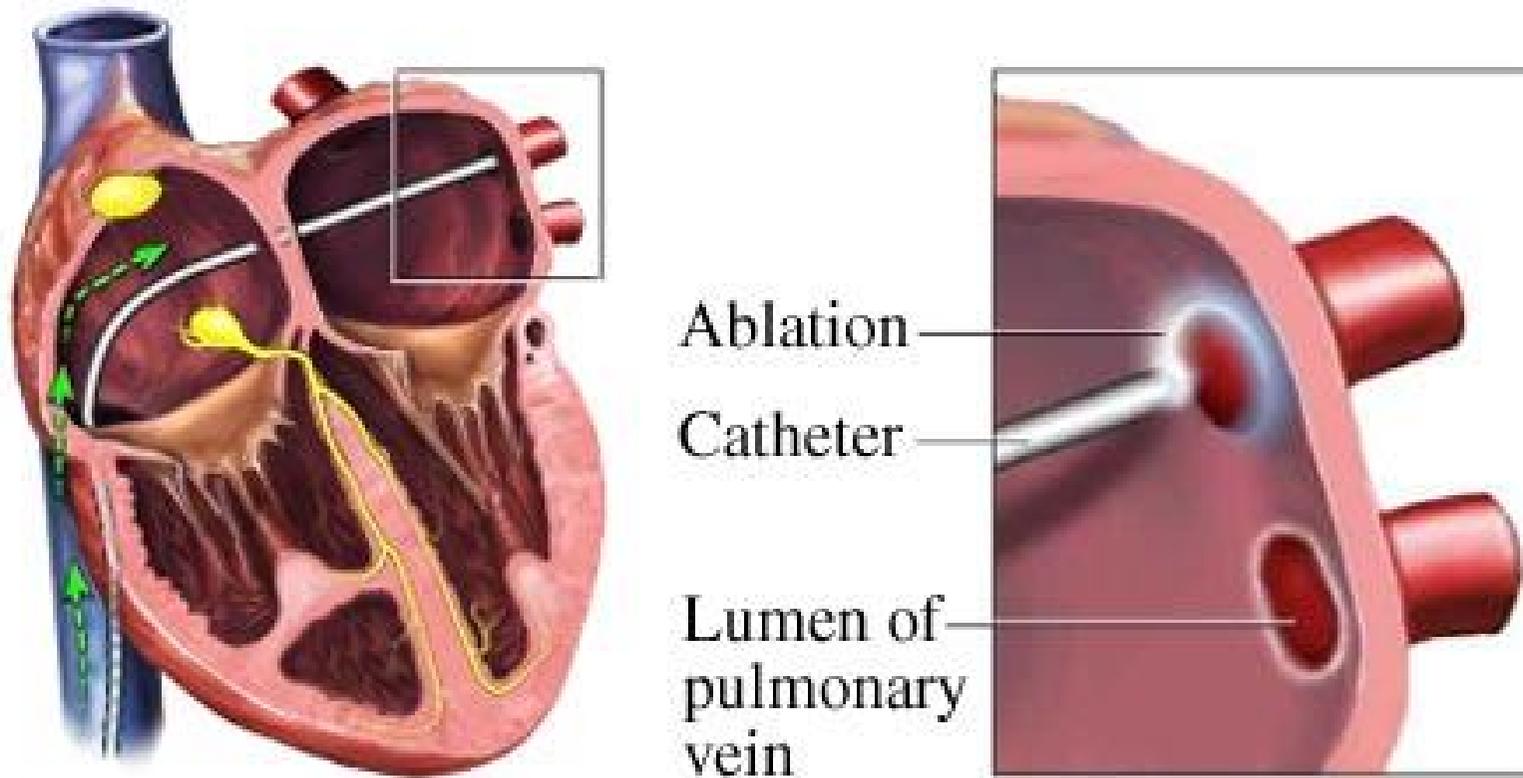
FPR



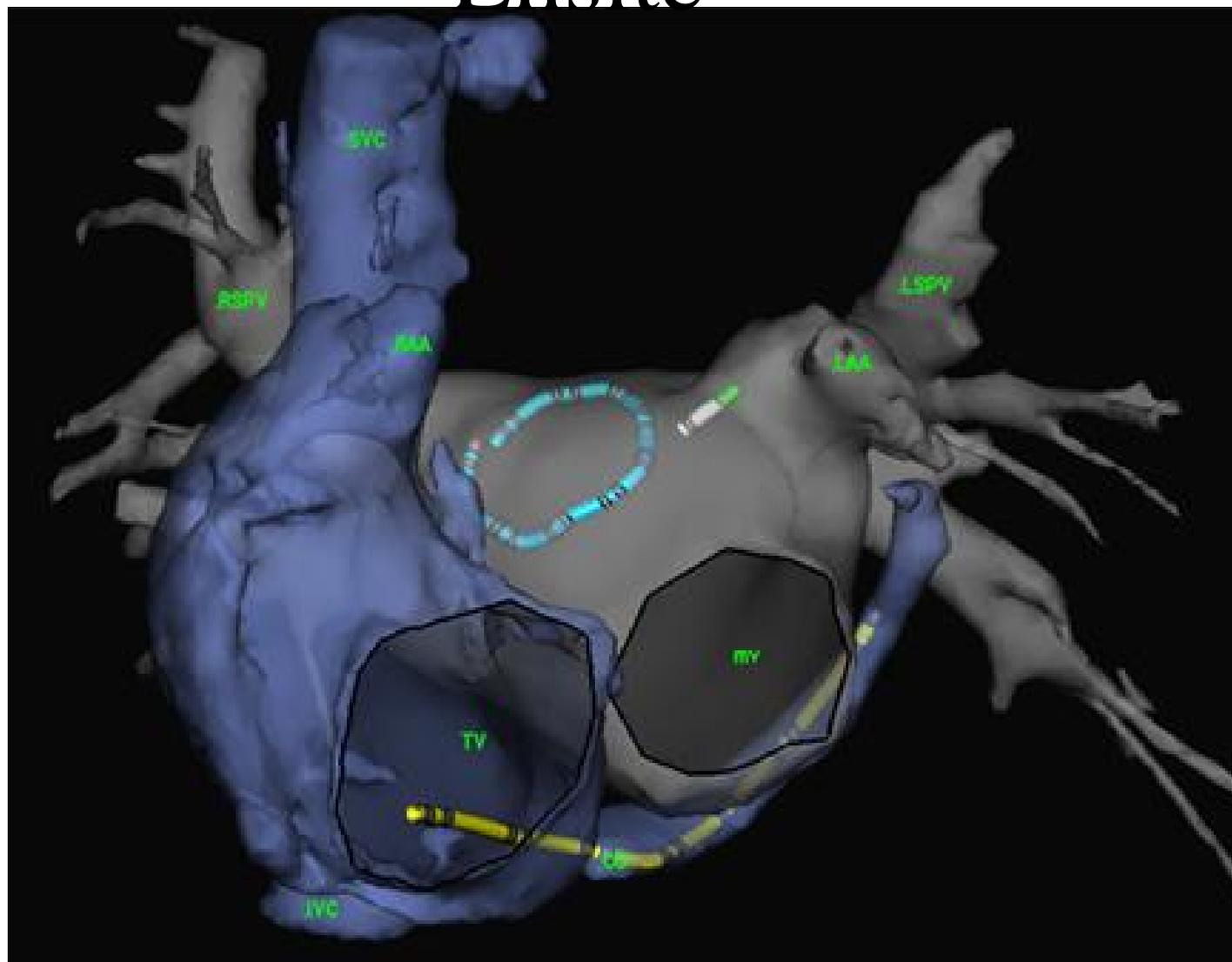
B 100 W 391
O 52 C 122

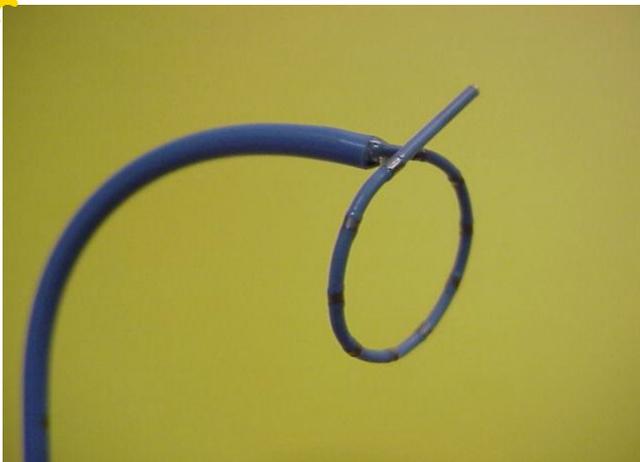
A7

Encircling

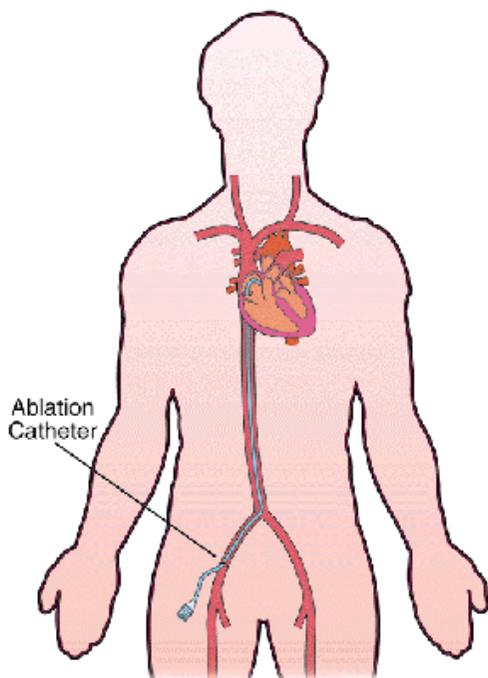


Ensite

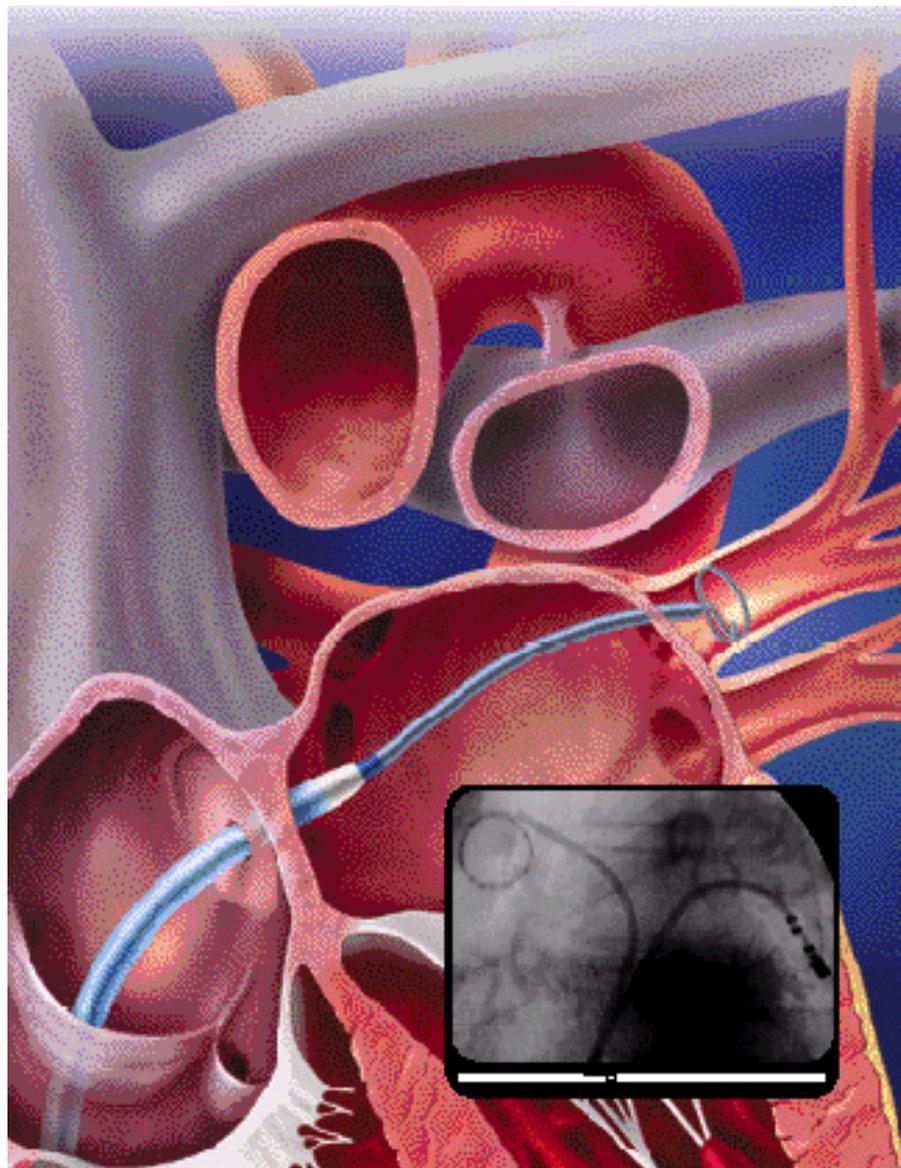




Lasso kateter



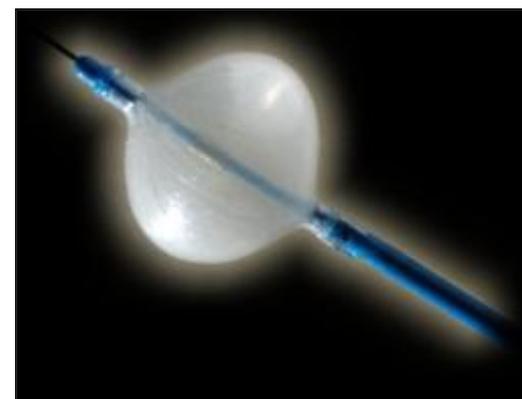
Isolering av lungvener enligt Bordeaux modellen.







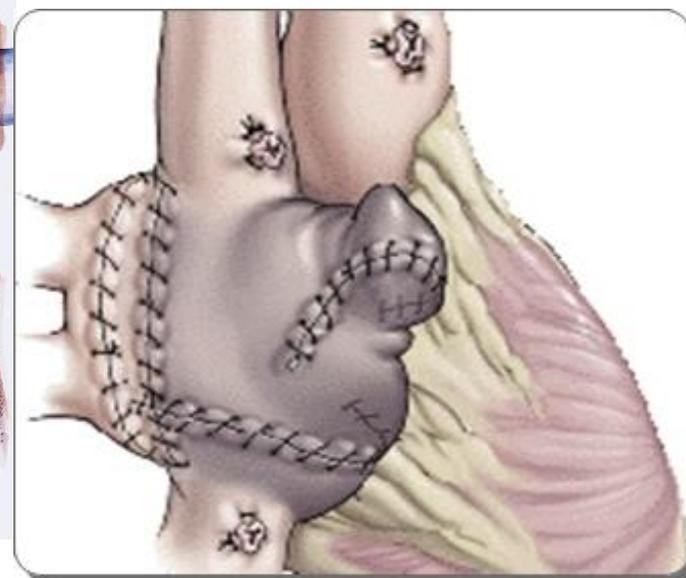
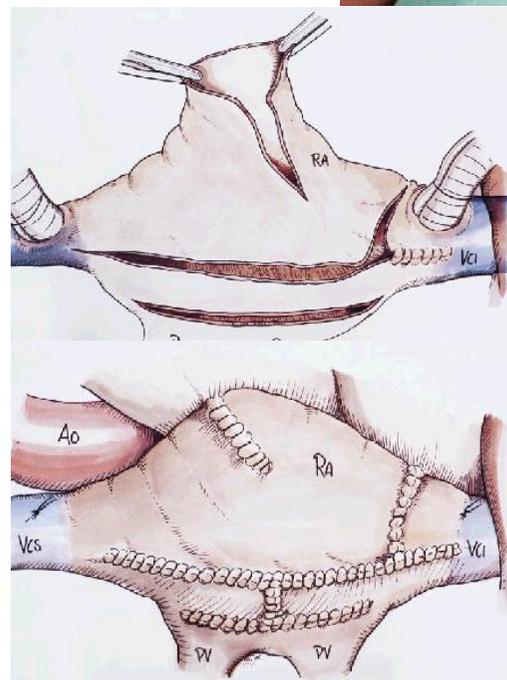
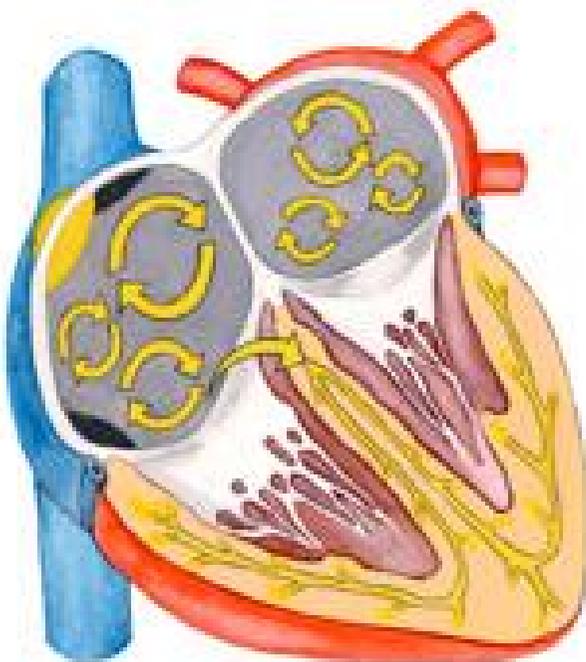
CryoCath Electrophysiology Products



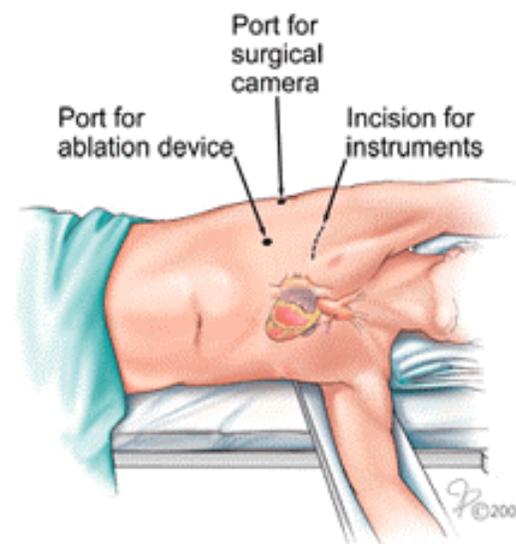
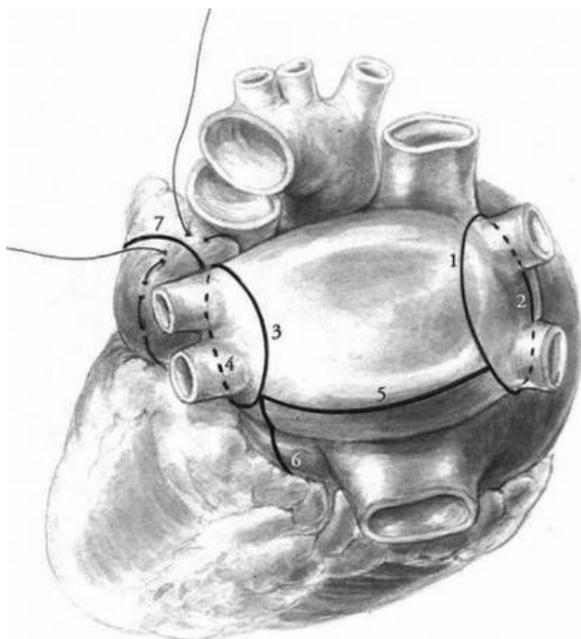
STOP AF trial,
245 patients with paroxysmal atrial fibrillation

Maze´ kirurgi

- Thorax kirurgi
- Öppen hjärtoperation

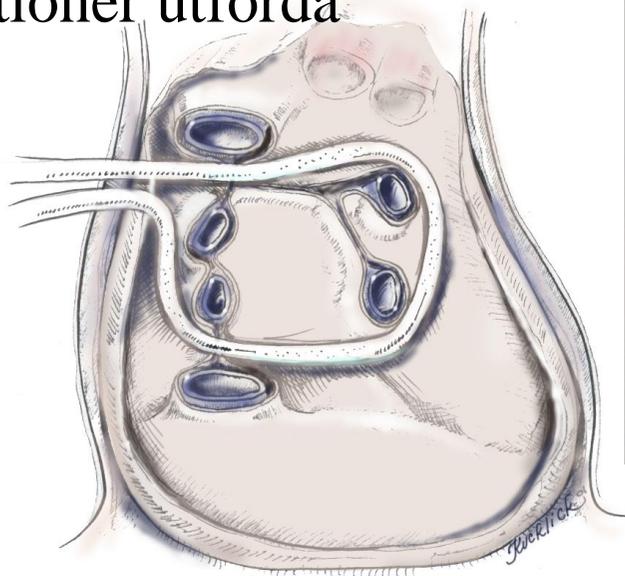


Kirurgisk ablation av förmaksflimmer Mini Maze



Endoskopisk flimmerablation USÖ

- Start maj 2007, först i Sverige
- Mikrovågsenergi – radiofrekvensenergi
- ”Box lesion” epikardiellt
- 36 ablationer utförda



Komplikationen

Table 1. Adverse Effects of Ablation for Atrial Fibrillation.*

Adverse Effect	Incidence %	Recommended Monitoring	Management
Death	0.15		
Cardiac tamponade	1.2–6.0	Blood-pressure monitoring, examination of cardiac silhouette on chest radiographic study, echocardiography	Reversal of anticoagulation, immediate pericardiocentesis, surgery if accumulation is ongoing
Stroke	0–2	Neurologic examination	Depends on center; consider thrombolysis or intervention
Pulmonary-vein stenosis	0.5–2.0	CT or MRI 3–4 mo after ablation	If stenosis is severe, with symptoms, then dilation and possible stenting of the pulmonary vein or veins
Phrenic-nerve injury	0–11	Fluoroscopy	Most patients recover without treatment
Regular atrial arrhythmia†	5–25	Transtelephonic monitoring, Holter monitoring, use of implantable loop recorder	Antiarrhythmic drugs, perform ablation again
Vascular complications (arteriovenous fistula, pseudoaneurysm)	0.5–5.0	Vascular ultrasonography	Percutaneous or open vascular surgery
Esophageal injury with ulceration	10	Esophageal temperature probe	Most patients heal without treatment
Atrioesophageal fistula	0.04	Maintain high index of suspicion for this complication (symptoms such as fever, chills, recurrent neurologic events, or sepsis occur 2–4 wk after ablation); CT or MRI	Surgery

* CT denotes computed tomography, and MRI magnetic resonance imaging.

† "Regular atrial arrhythmia" is a term used to describe both atrial tachycardia and an atypical form of atrial flutter after ablation that can occur with incomplete pulmonary-vein isolation.



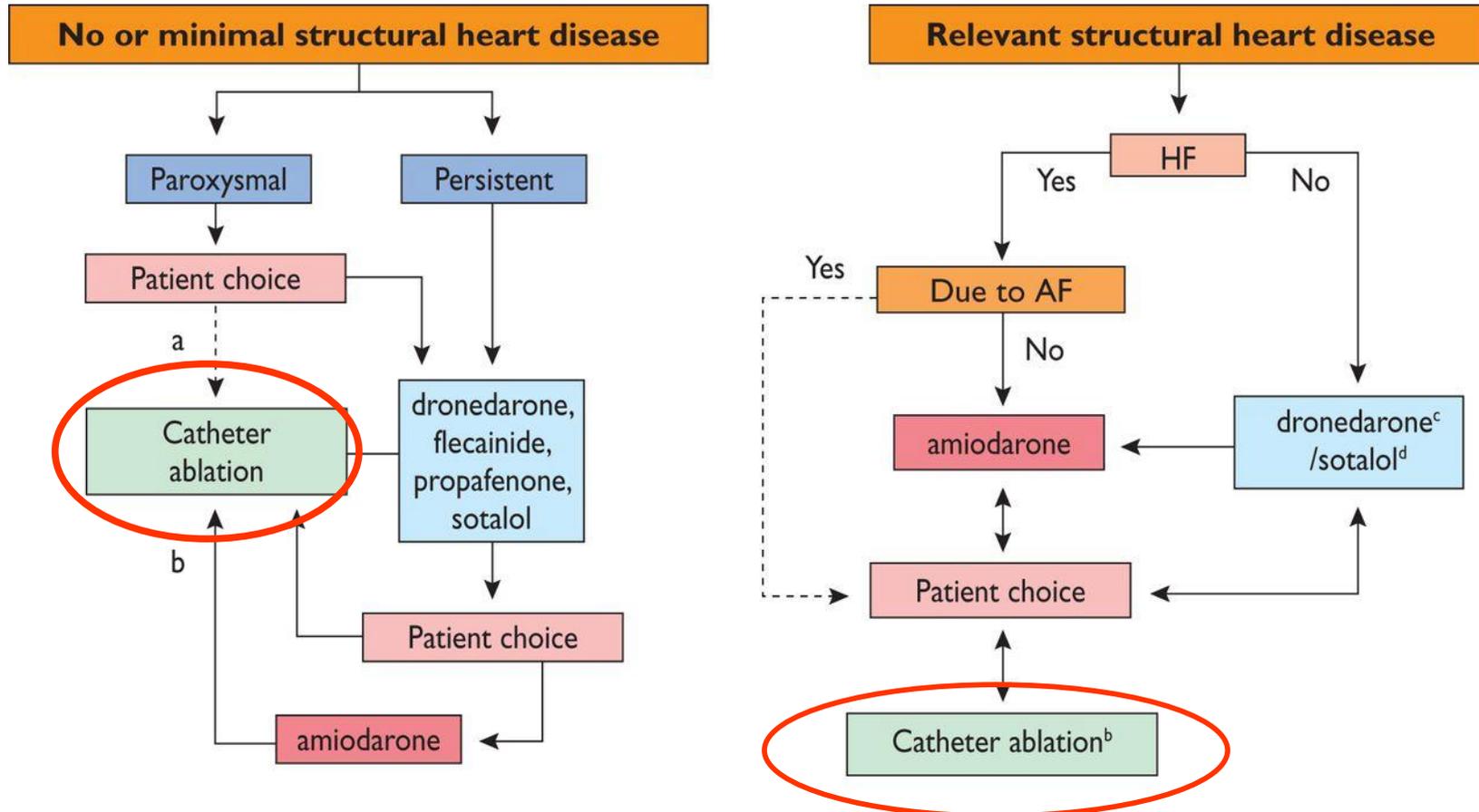


Studier

- Matthew; Meta-Analys AA mot ablation
 - 64 RF studier, och 34AA studier
 - Totalt 3,481 abladerad patienter
 - 4.3% alvarliga komplikationer
 - Lyckande frekvens med 1,4 procedurer var 77%



Antiarrhythmic drugs and/or left atrial ablation for rhythm control in AF.



AF = atrial fibrillation; HF = heart failure. ^aUsually pulmonary vein isolation is appropriate. ^bMore extensive left atrial ablation may be needed. ^cCaution with coronary heart disease. ^dNot recommended with left ventricular hypertrophy. Heart failure due to AF = tachycardiomyopathy.

**Authors/Task Force Members et al. Eur Heart J
2012;eurheartj.ehs253**



STEREOTAXIS





2015 Arytmolog





Budskap

- Sök efter flimmer det räddar hjärnceller!
- Behandla med Waran eller NOAC
- Om besvär av flimmer överväg ablation.
- ASA är ingen flimmer behandling.

NOAC (Nya antikoagulatia)

Fall

- Efter genomförd ablation känner hon sig ung och mindre gnällig. Hon slutade med Waran efter 3 månader och tar nu bara blodtrycksmediciner.





Frågor

