Anticoagulation for non-valvular AF during chemotherapy

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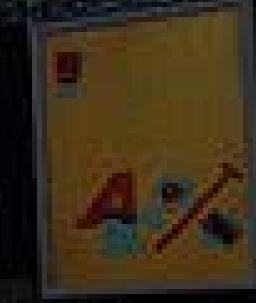

Dr J Malcolm Walker – Consultant Cardiologist UCLH

•**Conflict of Interest Statement** – ***none for this presentation***

- **Lecture Honoraria & travel support**
  - **ApoPharma**
  - **Bayer**
  - **Pfizer**
- **Advisory Boards**
  - **Pfizer - BMS**
  - **Novartis**
  - **Servier Laboratories**
- **Stocks & Directorships**
  - **None relevant**
- **Acknowledgements**
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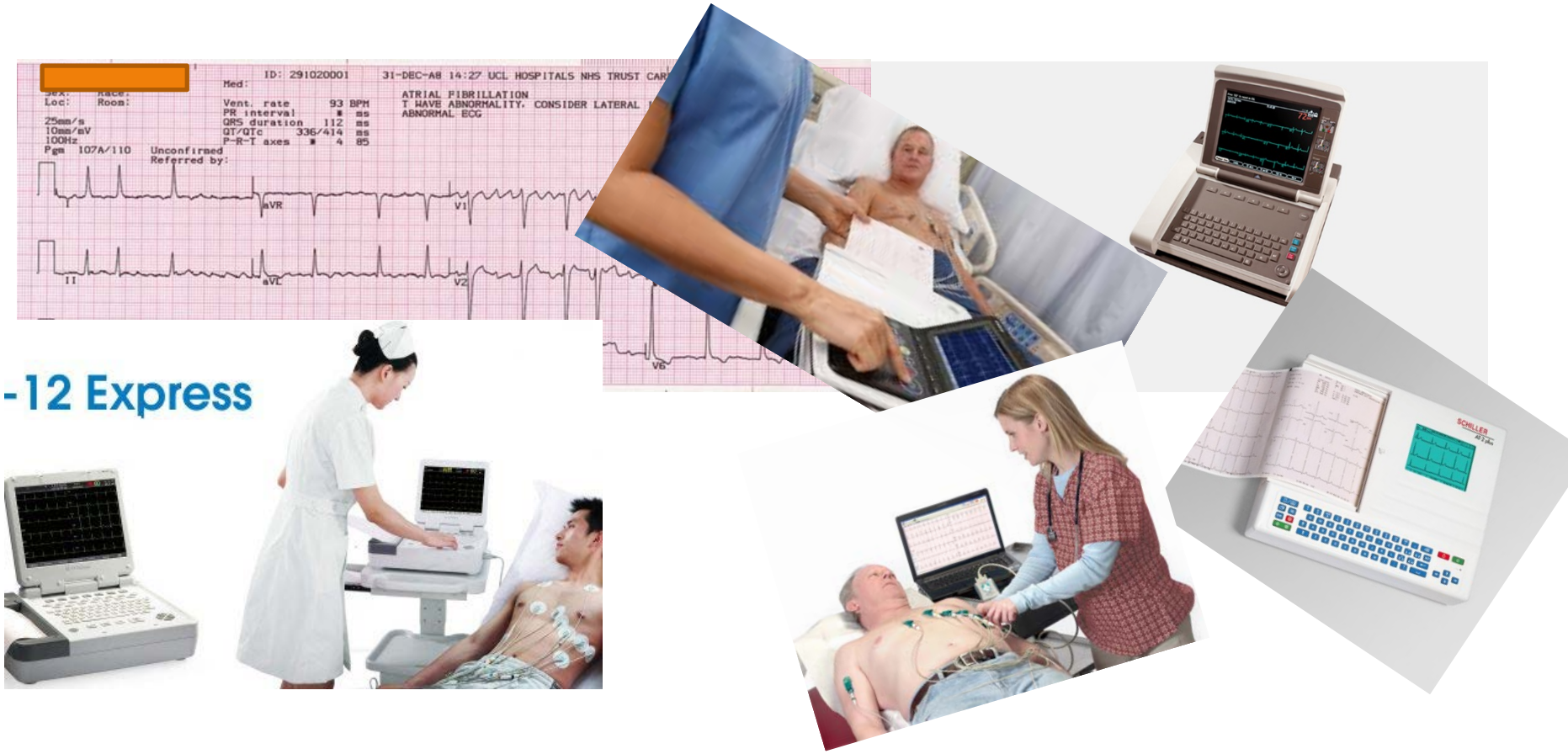
Anticoagulation for non-valvular AF during chemotherapy

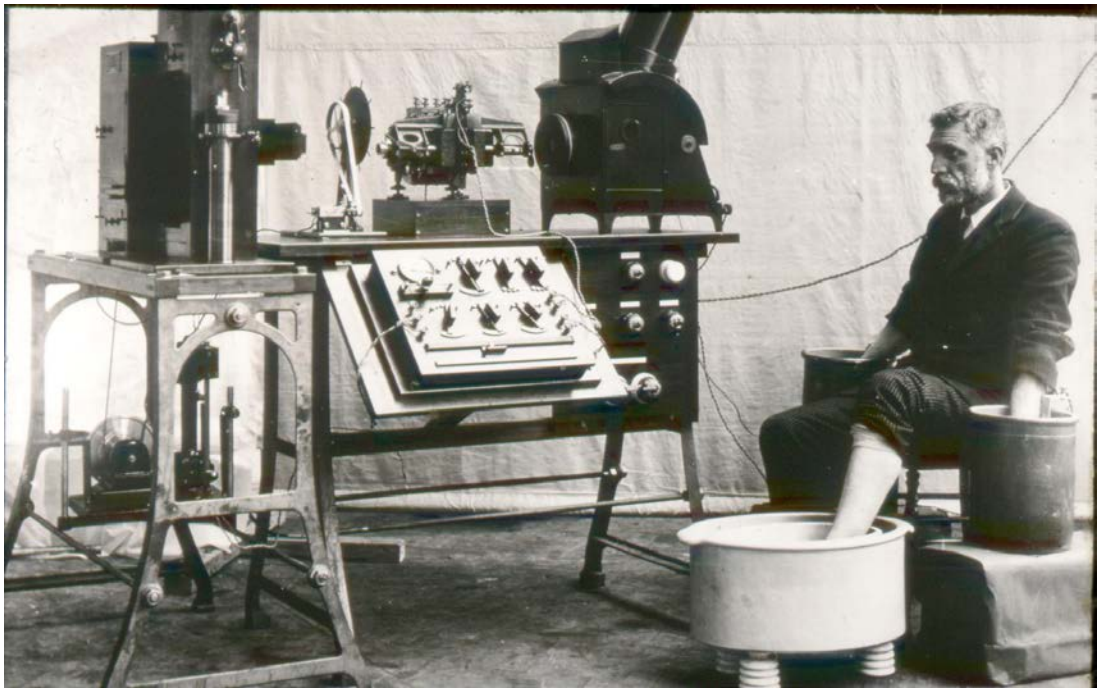
- History
- AF and its complications
- Cancer therapies and AF
- Cancer and Stroke
- Anti-thrombotic therapy
- Conclusions

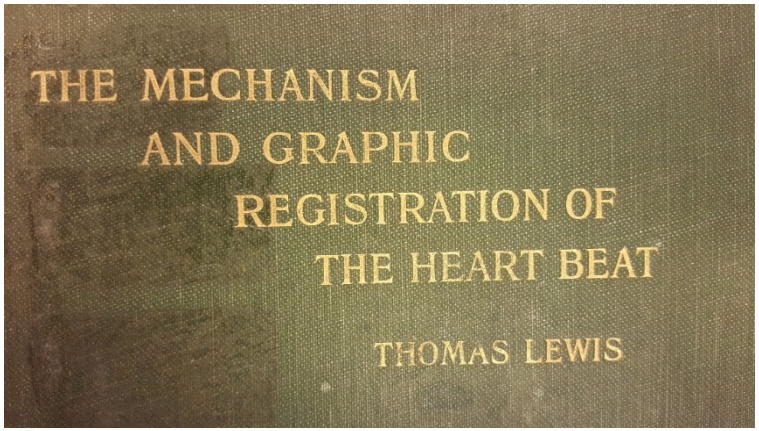
Modern cardiology is born with the ECG

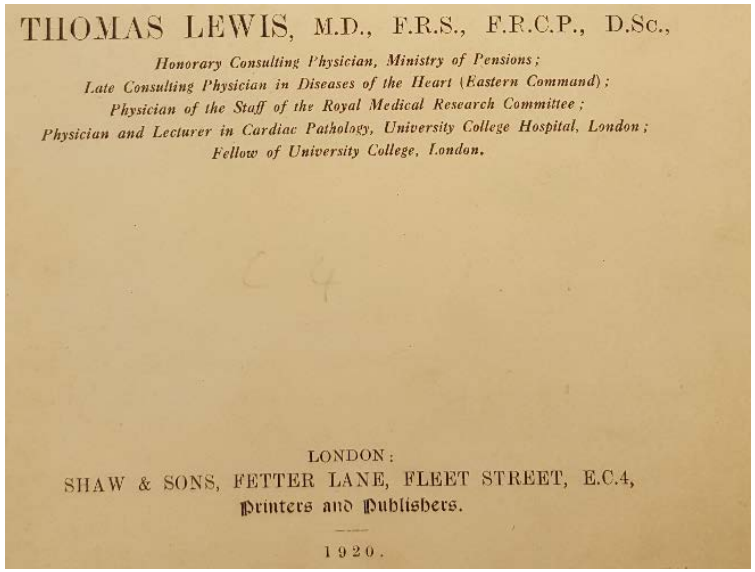


- EKG developed in Leiden(1901) by Willem Einthoven
  - Won Nobel prize for medicine in 1924

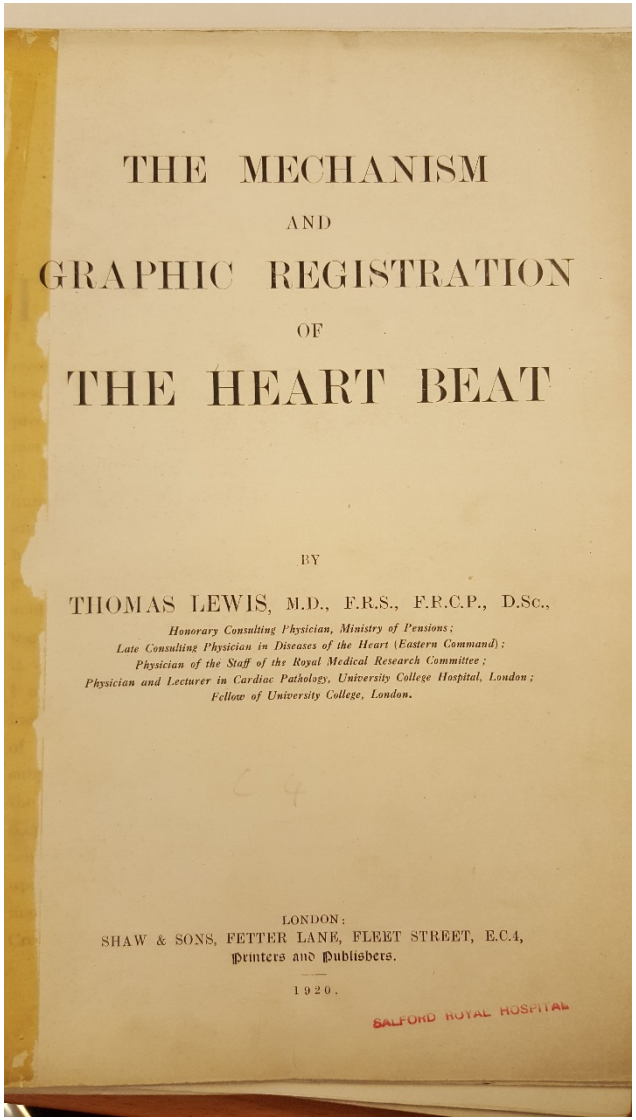
(Sir) Thomas Lewis: Pioneered use of ECG in patients at UCH from 1908







Atrial fibrillation



THE MECHANISM

AND

GRAPHIC REGISTRATION

OF

THE HEART BEAT

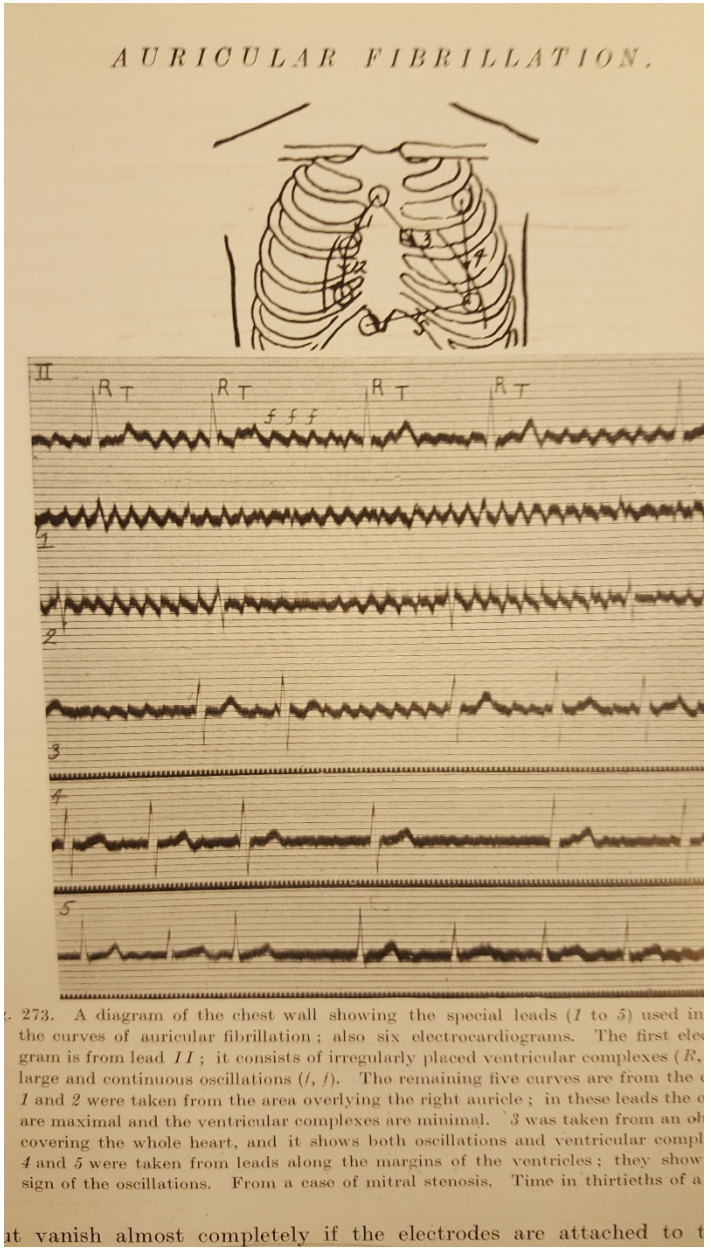
BY

THOMAS LEWIS, M.D., F.R.S., F.R.C.P., D.Sc.,

Honorary Consulting Physician, Ministry of Pensions;
Late Consulting Physician in Diseases of the Heart (Eastern Command);
Physician of the Staff of the Royal Medical Research Committee;
Physician and Lecturer in Cardiac Pathology, University College Hospital, London;
Fellow of University College, London.

LONDON:
SHAW & SONS, FETTER LANE, FLEET STREET, E.C.4,
Printers and Publishers.

1920.



. 273. A diagram of the chest wall showing the special leads (*1* to *5*) used in the curves of auricular fibrillation; also six electrocardiograms. The first ele gram is from lead *II*; it consists of irregularly placed ventricular complexes (*R*, large and continuous oscillations (*f*, *f*). The remaining five curves are from the *1* and *2* were taken from the area overlying the right auricle; in these leads the are maximal and the ventricular complexes are minimal. *3* was taken from an ob covering the whole heart, and it shows both oscillations and ventricular compl *4* and *5* were taken from leads along the margins of the ventricles; they show sign of the oscillations. From a case of mitral stenosis. Time in thirtieths of a

ıt vanish almost completely if the electrodes are attached to t

THE MECHANISM AND GRAPHIC REGISTRATION OF THE HEART BEAT

THOMAS LEWIS

vincing evidences were at length obtained as to the true nature of this important disorder of the human heart.

As we now recognise it in man it is characterised by a single chief quality, namely, the absence of all signs of normal auricular contraction; further it is responsible in the great majority of patients in whom it is found

irregularity of the ventricular action and of the arterial pulse.

The irregularity, which is one of the chief features of the condition, is the commonest persistent irregularity exhibited by the human heart, constituting as it does approximately 50 per cent. of all such cases. It was

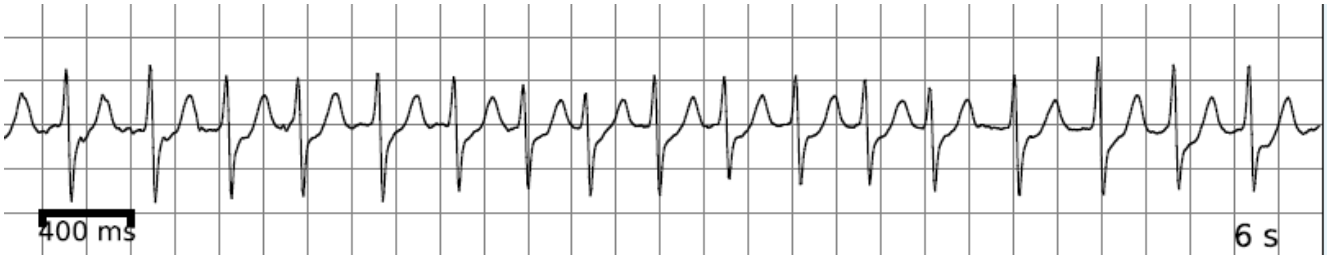
be demonstrated that this disturbance of ventricular rhythm is t

chamber. This conclusion and our detailed knowledge of the condition is

due to the work of a very large body of men. Fully possessed of the facts, we may now trace the earlier work along two independent paths. Observations were undertaken upon the arterial pulse; others were carried out upon the venous system; each series being distinct and for very many years unassociated with the other. The two paths of investigation converged and finally met in modern times.

On the one hand, a conspicuously irregular arterial pulse, especially associated with mitral disease in its later stages, was the subject of study

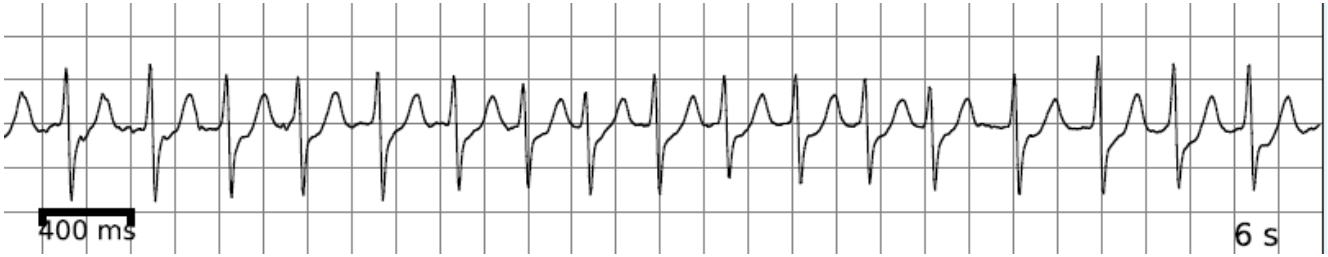
Atrial Fibrillation – clinical features



- **Prevalence**
  - 1.8% of population
  - 6% in > 65yr
  - 12% of patients with AF are 75 to 84 yr.
- **Classification**
  - Paroxysmal: Self-terminating AF generally <7 days (majority <24hr)
  - Persistent: Lasting > 7 days; generally need DCC or chemical cardioversion
  - Long-standing persistent: AF present for > 1 yr.
  - Permanent
- **Some clinical Features**
  - Increasing prevalence with age
  - Men > women
  - White > Black
  - Some familial forms & some genetic associations (Chinese families with K+ channel defect)

Atrial Fibrillation – Substrates

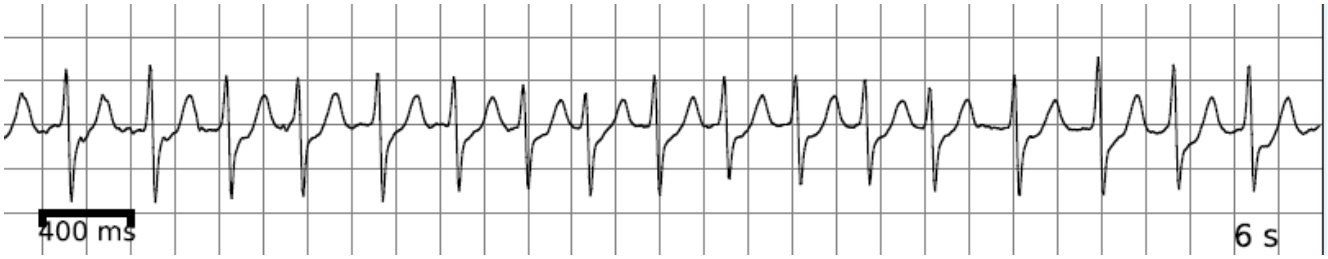
AF developed during Sinus rhythm – remodelling of atria related to stretch/ dilatation



DISEASES	ANATOMIC	CELLULAR	ELECTROPHYSIOLOGIC
Hypertension	Atrial Dilatation	Myolysis	Conduction abnormalities
Heart Failure	Pulmonary Vein dilatation	Apoptosis/ necrosis	ERP dispersion
Coronary disease	Fibrosis	Channel expression change	Ectopic activity
Valve Disease	*Not for this presentation*		
Hyperthyroidism, HFE, alcohol, obesity…….			Thyroid induced EP change; Fe toxicity?

Adapted from Prytowski et al Hurst's "The Heart" 2017

Effects of AF



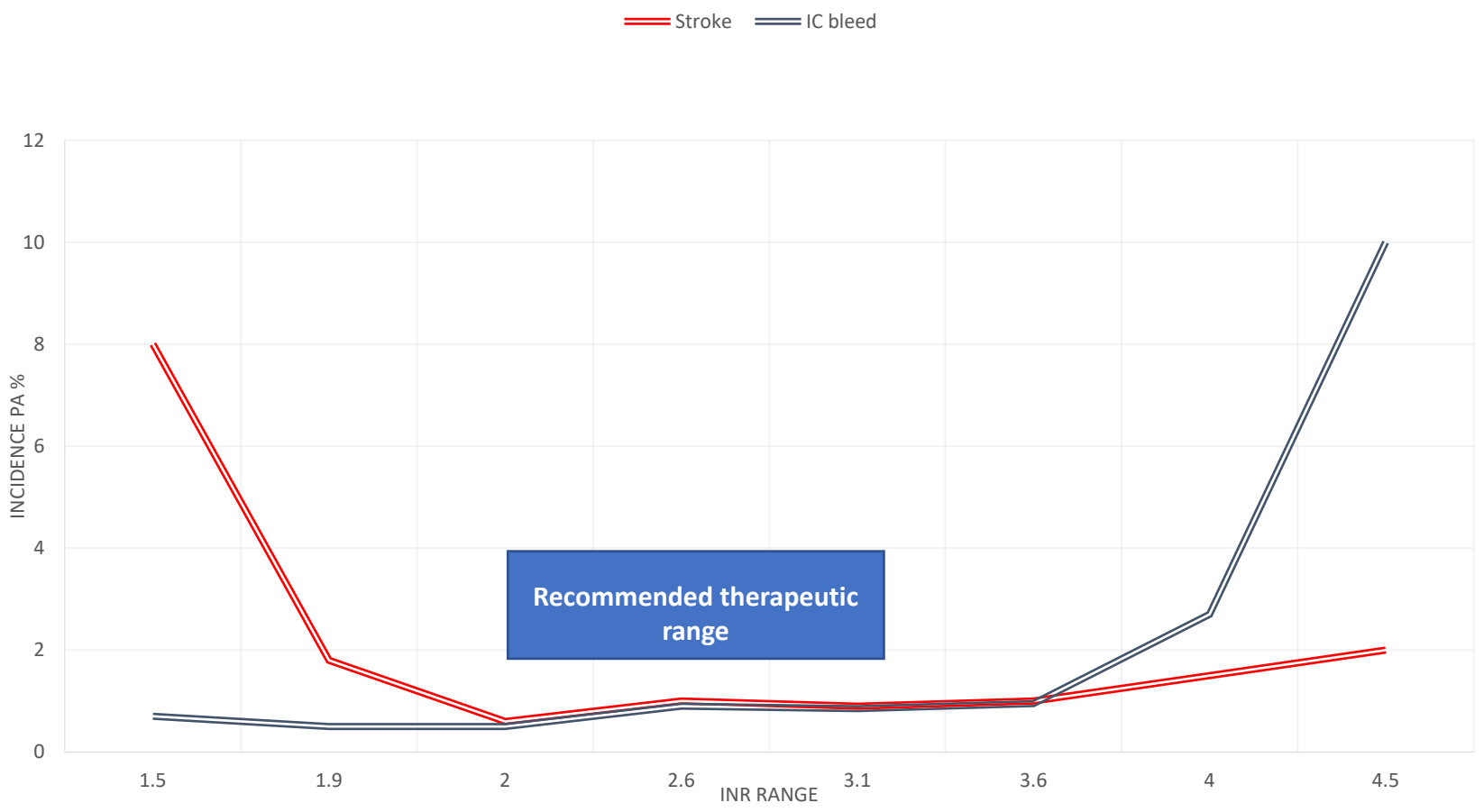
- **Haemodynamic**
  - **Loss of chronotropic competence**
    - Resting heart rate is high
    - Excessive rise in heart rate in response to exertion/ increased demand

    Palpitations, exercise limitation, decompensation (acute heart failure), collapse
  - **Fall in cardiac output**
    - 10 to 15% reduction in cardiac efficiency – *at least*
    - Rise in mean L A pressure – pulmonary oedema – especially in restrictive LV physiology
    - Reduced coronary blood flow
- **Stroke/ TIA/ Thrombo-embolism**

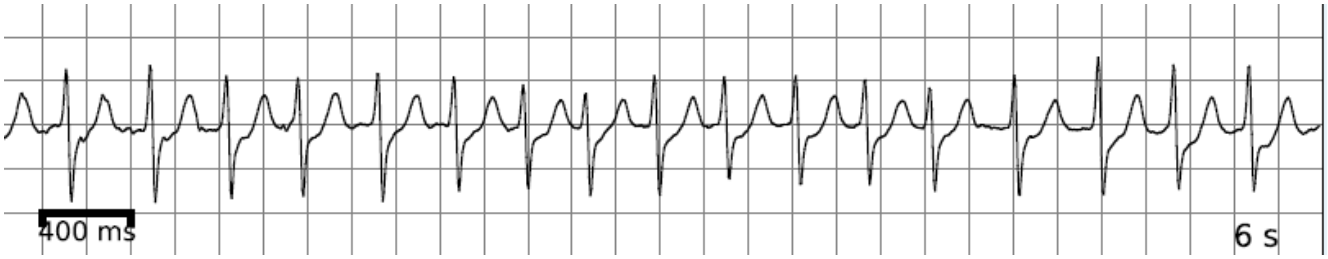
1. Not ***all*** are at risk
2. **Anticoagulation reduces the risk of stroke**

AF: reduction in ischaemic stroke vs IC haemorrhage according to INR range

(adapted from Hart et al. Ann Int Med 1999)



AF and Strokes

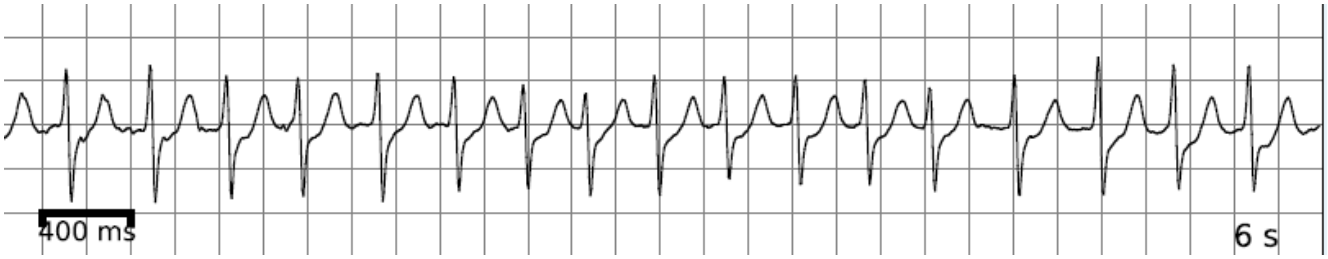


- Cardio-emboli arise in the left atrium
  - Generally these are “red” thrombi
  - “Red” thrombi – may be prevented by anti-coagulation

  (cf. “White” thrombi formed in high flow situations eg. Arteries - prevented by anti-platelet Rx)
  - AF patients: 60% **ischaemic stroke** due to cardio-embolism
  - In non-AF patients the proportion is 20%; *(Dulli et al. Neuroepidemiology 2003).*

  (NB. 80% of ischaemic strokes occur in patients without AF – look for other causes)
- Epidemiology
  - Registry data on >64 yr olds (n=4.3 million), AF increases relative risk of embolic stroke by 5.8 x vs 1.4 x for non-embolic stroke (adjusted for age, sex & CV co-morbidities); *(Yuan et al. Am J Pub Health 1998).*

AF and Stroke Risk



CHA_2DS_2-VASc scoring	Score
Congestive heart failure (inc Left Ventricular Dysfunction)	1
Hypertension	1
Aged 75 or more	2
Diabetes	1
Stroke/TIA/thromboembolism	2
Vascular disease (prior Myocardial Infarction, Peripheral Artery Disease or aortic plaque)	1
Aged 65-74	1
Sex category: female	1

AF and Stroke Risk

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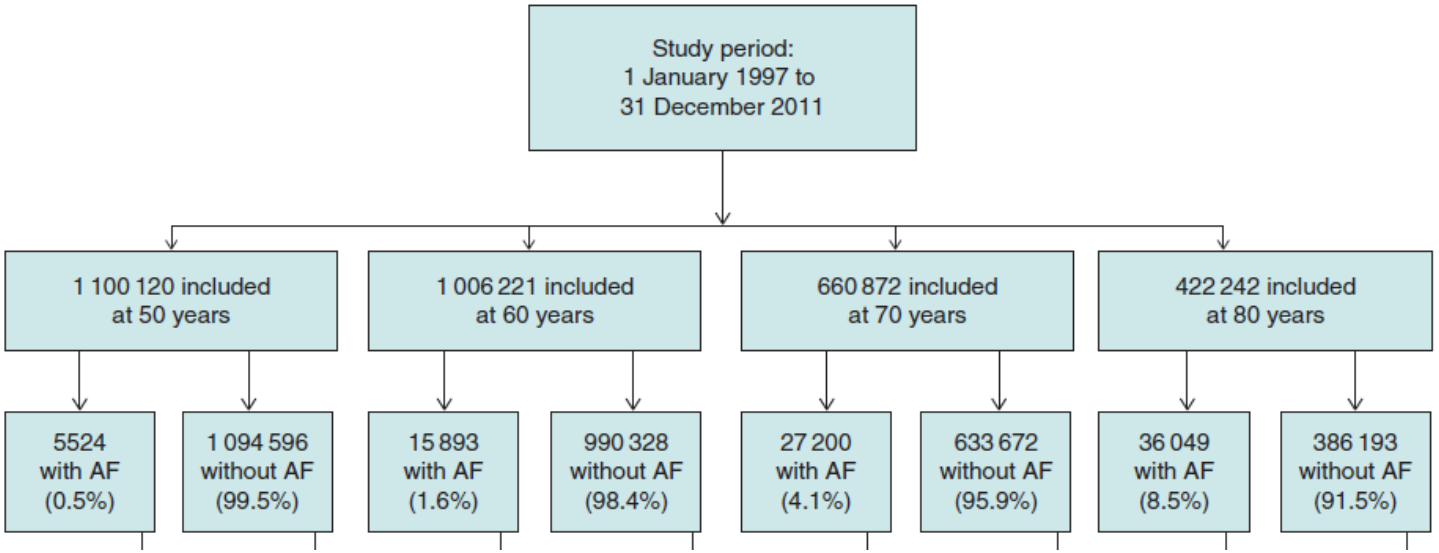
Risk	$CHADS_2$ score	Annual stroke rate (%)
LOW	0	1.9
INTERMEDIATE	1	2.8
		4.0
HIGH	3	5.9
	4	8.5
	5	12.5
	6	18.2

AF and Stroke Risk (Stroke/TE/TIA)

from Danish National Registry: 1997-2011; n=> 3x10^6

- Cardio-embolism source of Stroke in 16 to 30% of cases
- 80% ischaemic strokes occur in persons without AF
- **Question?**
  - **Is it the components of the risk score that determine risk of Stroke**
  - **Or are the components only important in the setting of AF?**



Europace (2016) **18**, 1689–1697
doi:10.1093/europace/euv401

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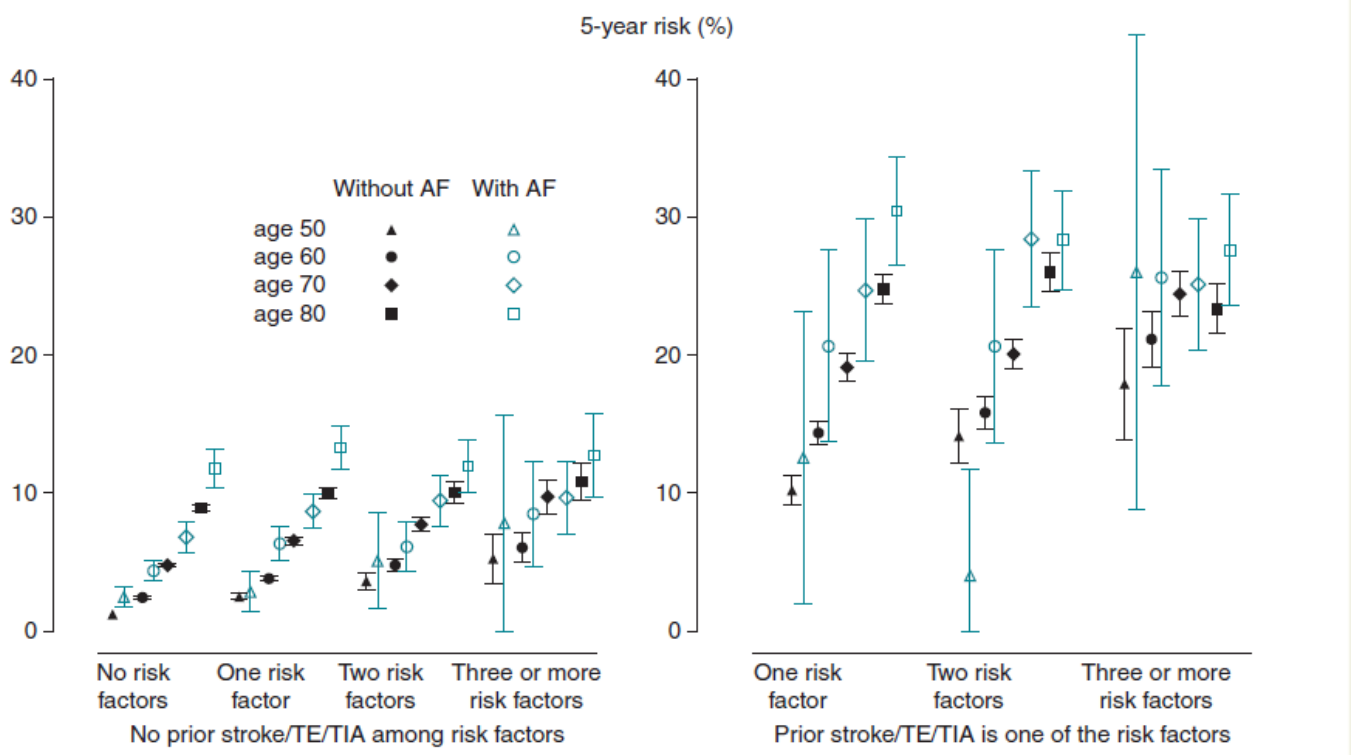

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from Danish National Registry: 1997-2011; n=> $3x10^6$

- **Question?**
  - **Is it the components of the risk score that determine risk of Stroke**
  - **Or are the components only important in the setting of AF?**

- **Conclusion**
  1. **In presence of CHA_2DS_2-VASC risk factors AF is associated with a *modest increase in risk of stroke***
  2. ***In most cases, AF increases stroke risk less than an age increase of 10yr and equivalent to 1* CHA_2DS_2-VASC risk factor.**

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AF and Stroke Risk

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Sex category: female	1

CAUTION – PREVIOUS CANCER or CURRENT CANCER/ CHEMOTHERAPY NOT INCLUDED

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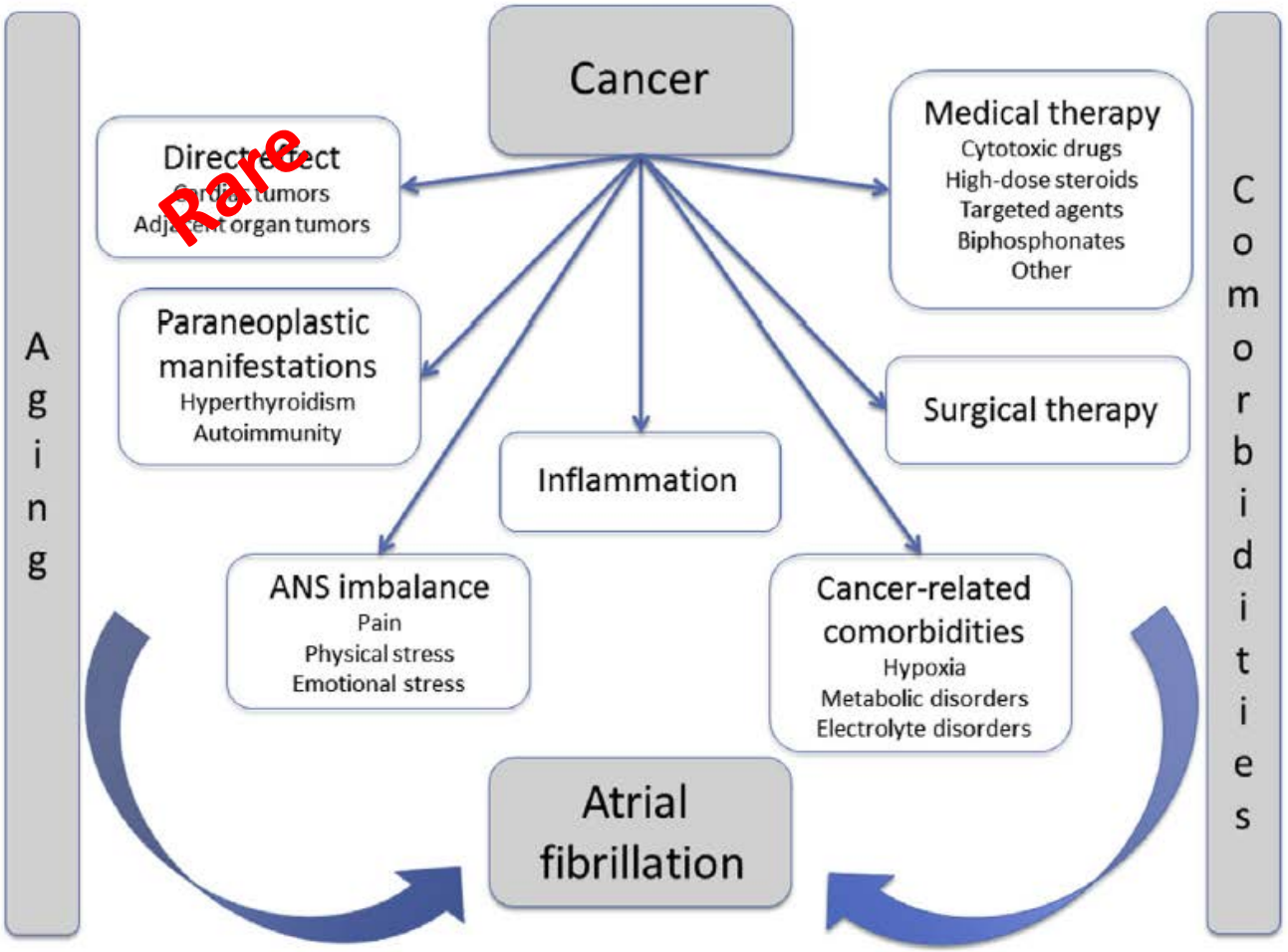
AF and cancer – *complicated relationships*

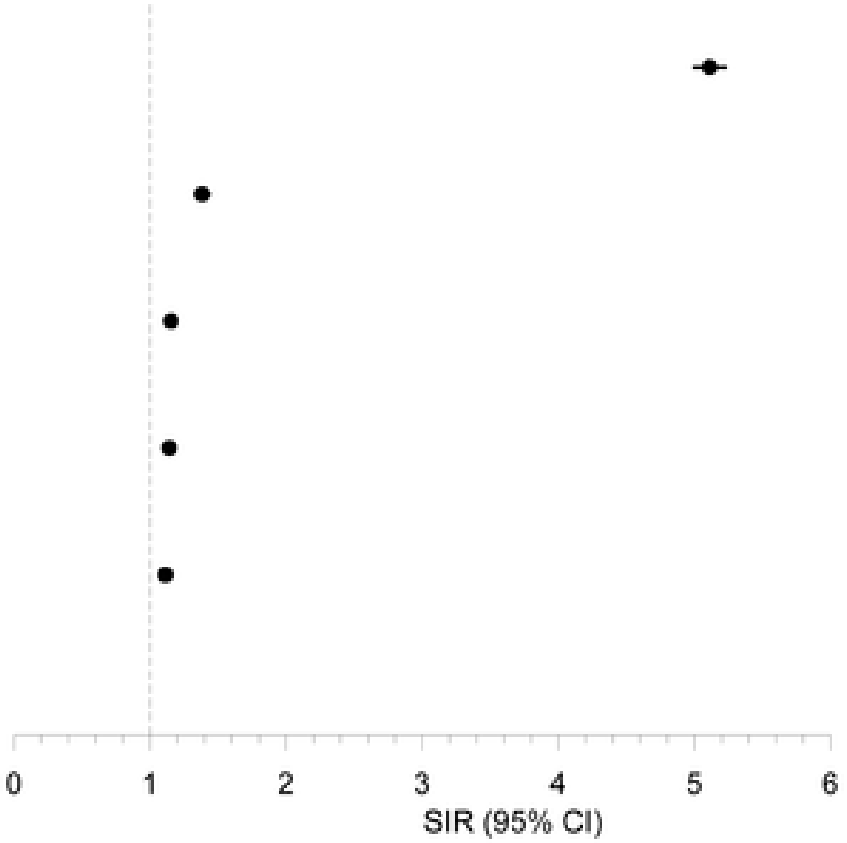


(J Am Coll Cardiol 2014;63:945–53)

Recent onset AF may be a marker for occult cancer

Figure 1. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for all cancer sites following atrial fibrillation by follow-up period, Denmark, 1980–2011.

Follow-up (months)	Observed/expected number of cancers	SIR (95% CI)
0-3	6656/1302	5.11 (4.99-5.24)
4-6	1664/1203	1.38 (1.32-1.45)
7-12	2589/2242	1.15 (1.11-1.20)
13-24	4531/3966	1.14 (1.11-1.18)
>24	22 429/20 151	1.11 (1.10-1.13)



Ostenfeld EB, Erichsen R, Pedersen L, Farkas DK, Weiss NS, et al. (2014) Atrial Fibrillation as a Marker of Occult Cancer. PLOS ONE 9(8): e102861. https://doi.org/10.1371/journal.pone.0102861
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0102861

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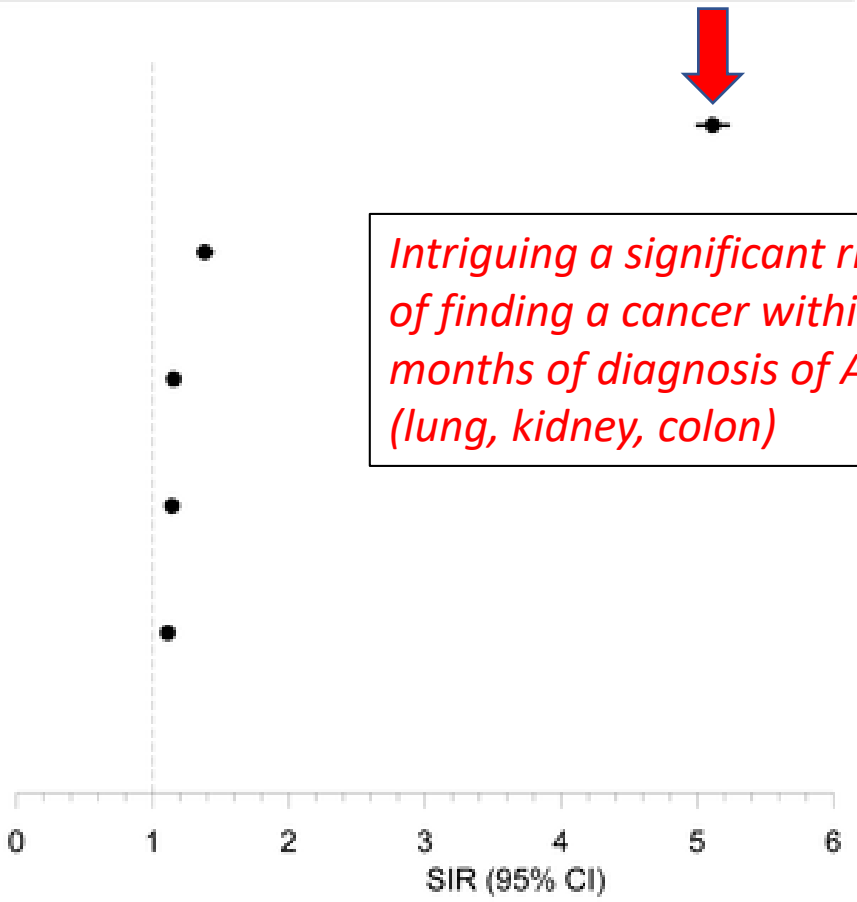


Intriguing a significant risk of finding a cancer within 3 months of diagnosis of AF (lung, kidney, colon)

Ostenfeld EB, Erichsen R, Pedersen L, Farkas DK, Weiss NS, et al. (2014) Atrial Fibrillation as a Marker of Occult Cancer. PLOS ONE 9(8): e102861. https://doi.org/10.1371/journal.pone.0102861
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0102861

AF epidemiology in cancer

taken from: (J Am Coll Cardiol 2014;63:945–53)

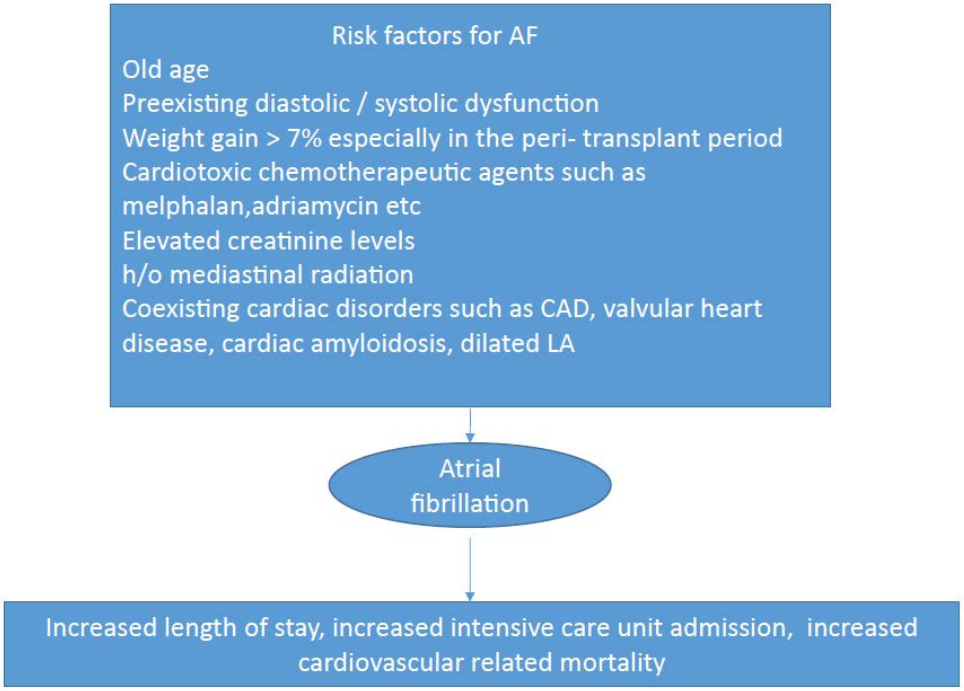
- Recent onset cancer (n=24,125)
  - AF in 2.4% at outset plus developed in further 1.8%
  - 2x increase in Thrombo-embolic risk; **adjusted HR 1.98 p<0.001**
  - 6x increase in risk of Heart failure; **adjusted HR 6.3 (p<0.001)**

- Most frequent association is post-operative AF (pulmonary resection)
  - 12.6% to 60% occurrence
  - Increases post-op mortality: 6.7% vs 1.0% AF vs no AF (P<0.024)
    - Risk factors for post-op AF
      - Advanced cancer; BP or pAF history; physical status; post-op tachycardia
      - Increased BNP; ectopy on ECG; E/e' > 8; low mean HR
      - Long surgery; blood Tx
- Cytotoxic chemotherapy
  - Cisplatin, 5 flouro-uracil, anthracycline, paclitaxel/docetaxel, ifosfamide, gemcitabine, and mitoxantrone; high-dose corticosteroids, antiemetic agents such as ondansetron; targeted therapies; and bisphosphonates

Haematological cancers – especially complicating AHSCT

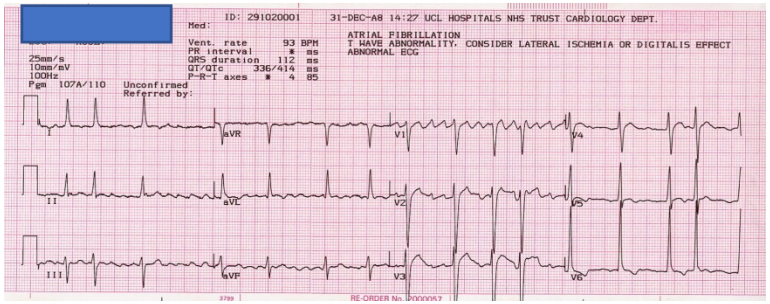
adapted from: Mathur et al . *Clinical Lymphoma, Myeloma & Leukemia,* Vol. 16, No. 2, 70-5 © 2016

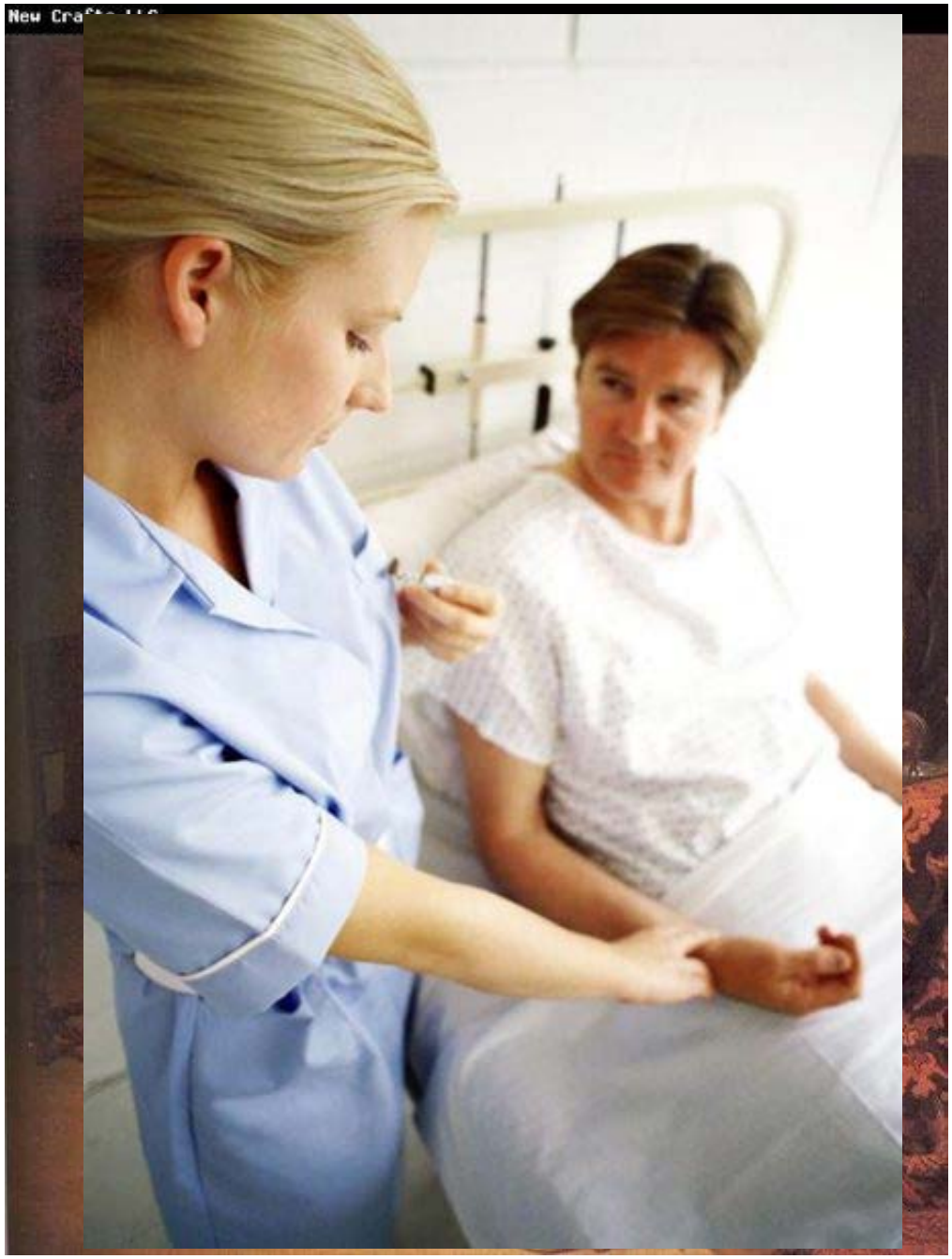
- Recognised early that AHSCT associated with AF
  - Plasma cell malignancies predominate
  - 27% in one study @ 14.8 days, but most were out-patients & true incidence higher?



Detecting AF

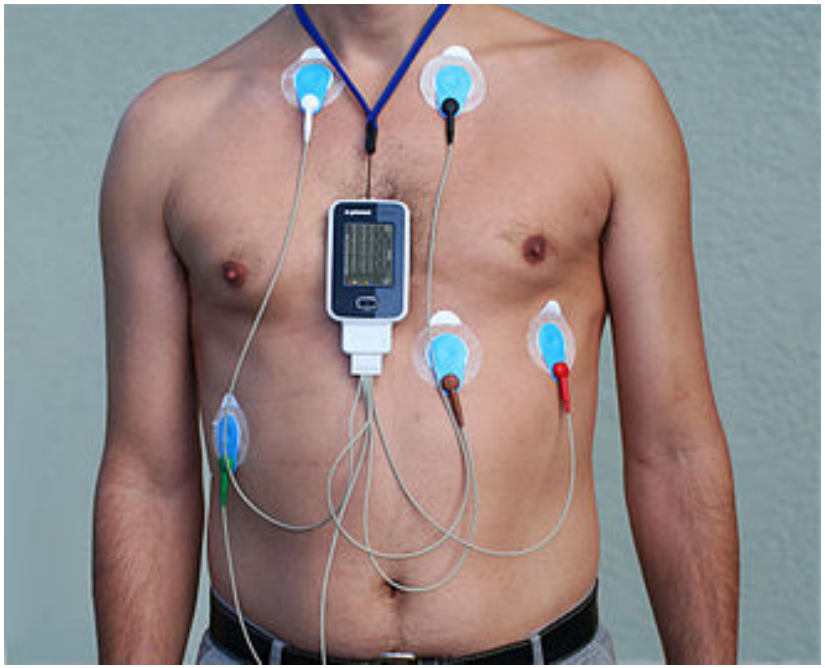
- Clinical, at the bedside
  - The irregularly irregular pulse
- The ECG

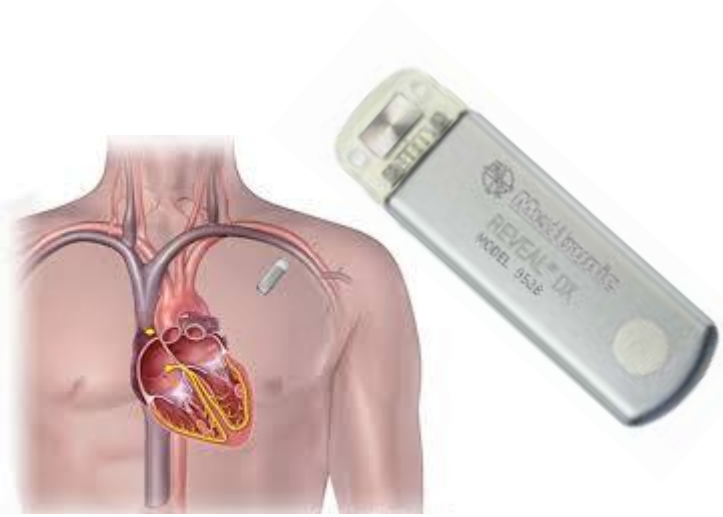


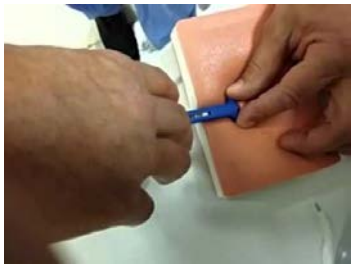


Detecting AF

- Holter ECG 24 hr increases detection rates
- Longer sampling intervals increase detection further
  - Implantable loop recorders

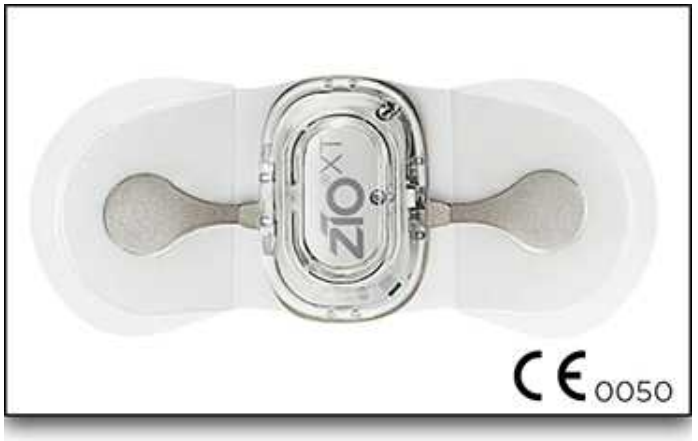


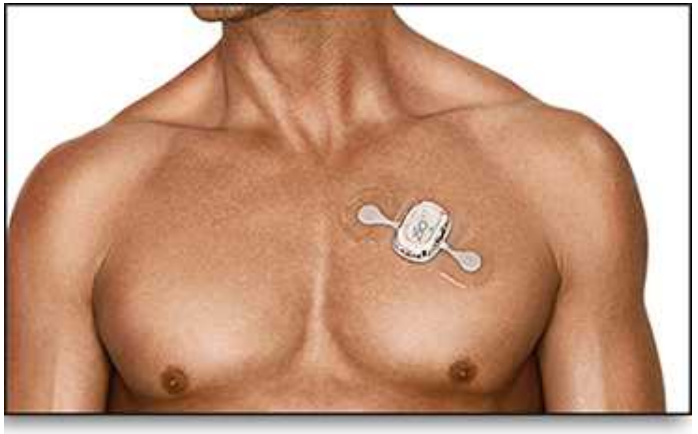




Detecting AF

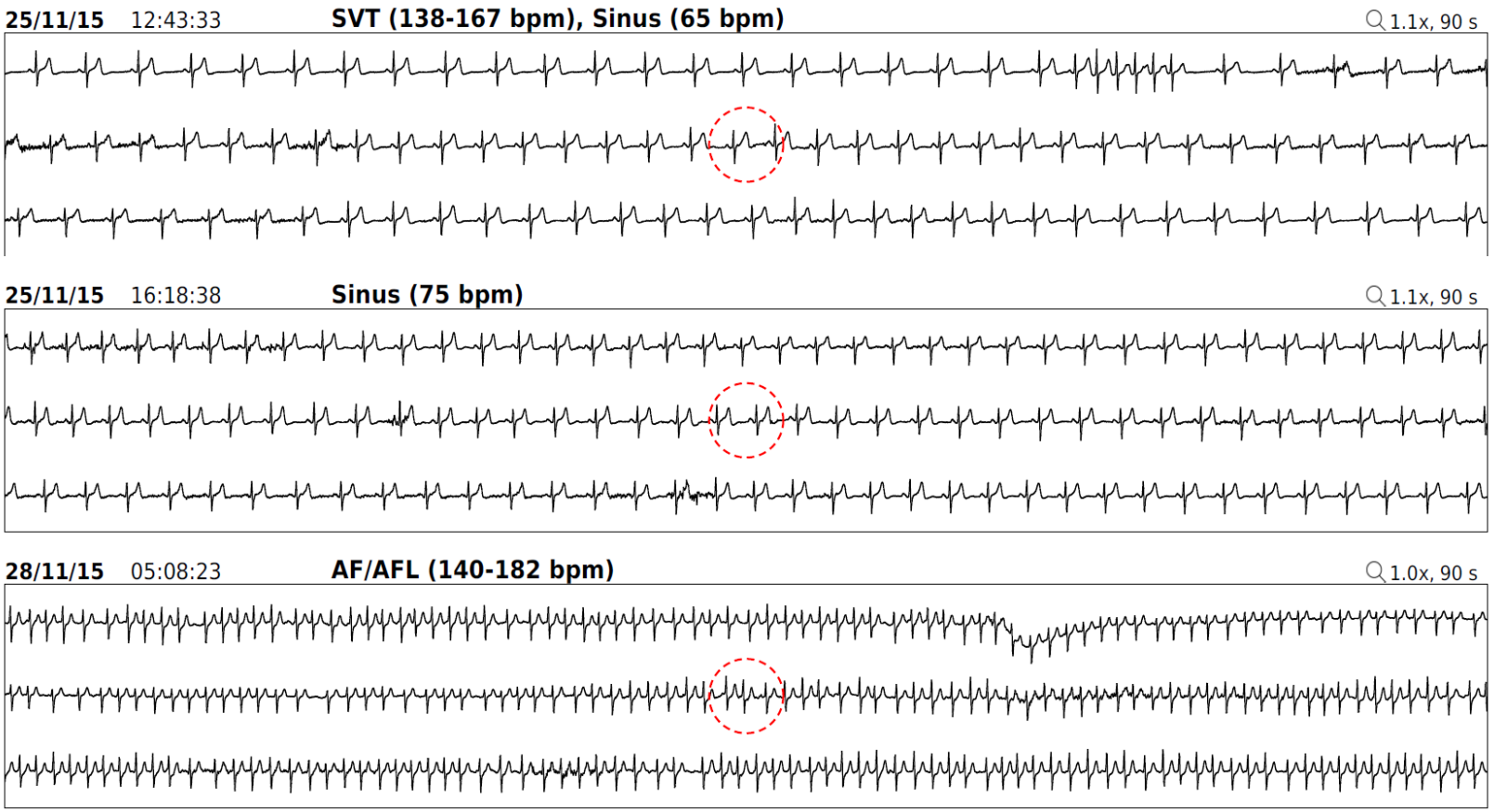
- Holter ECG 24 hr increases detection rates
- Longer sampling intervals increase detection further
  - Wearable Patch recorders, eg. Zio x 14 day, or Bardy x 7 day

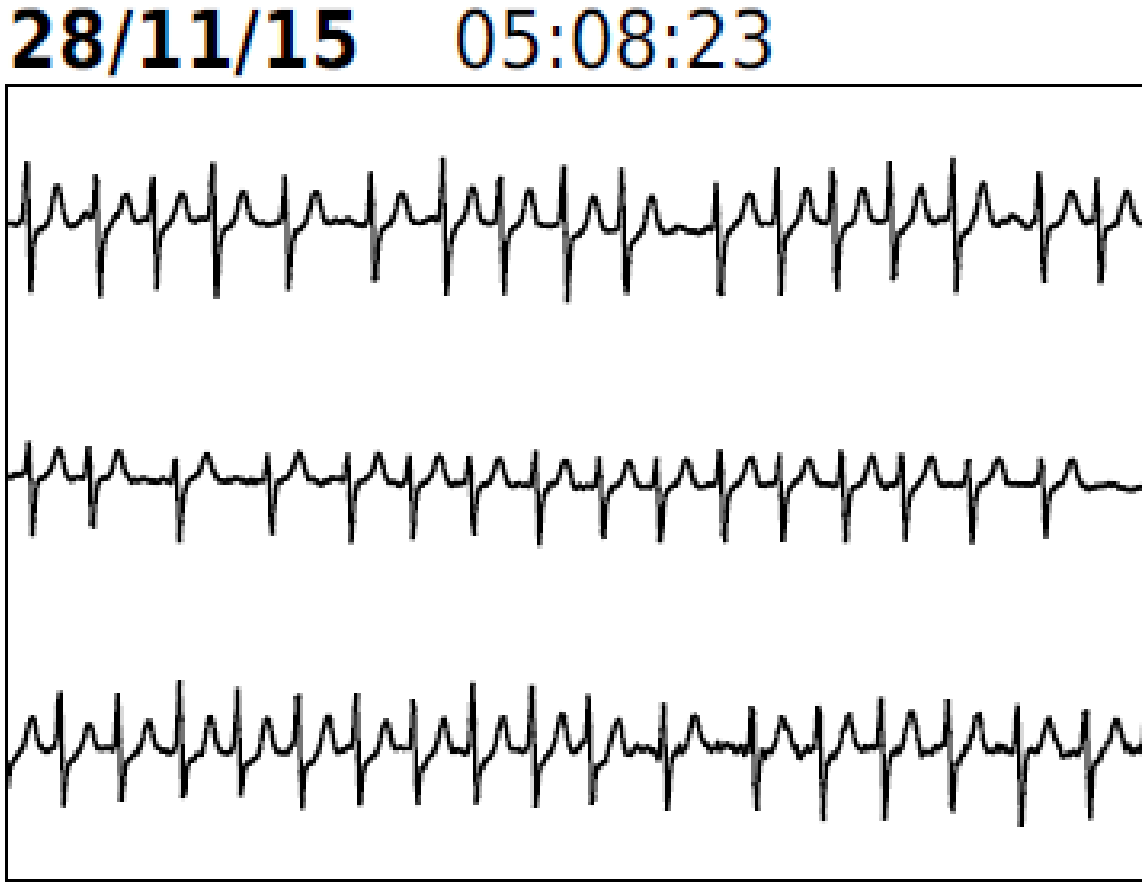




Wearable continuous ECG monitoring:
ZIO 14 day Holter ECG:

Male 42, myeloma (no cardiac amyloid), BP history, dizzy spells, multiple normal 12l ECG



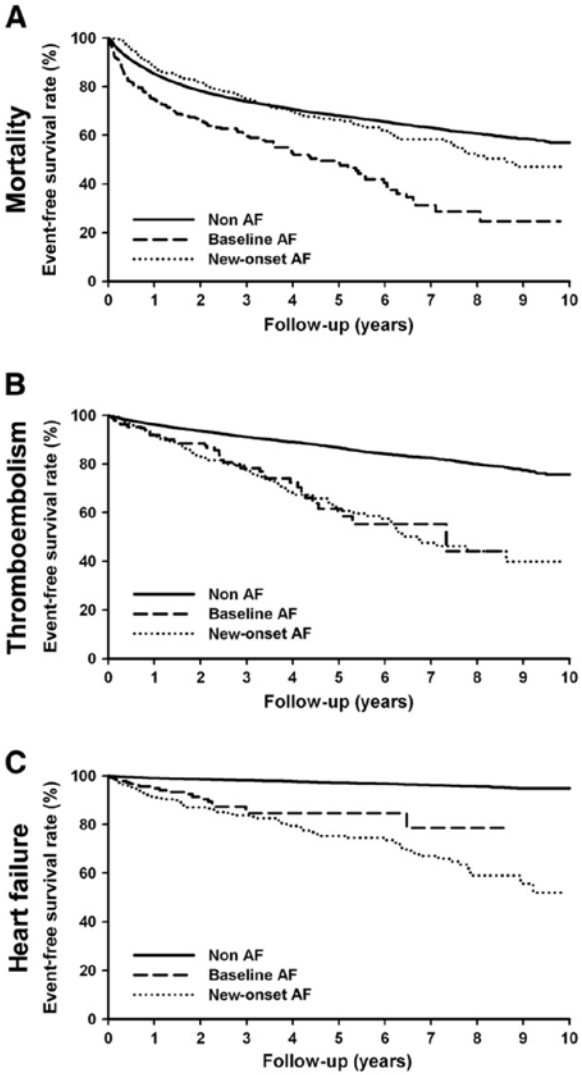


13 days of recording; 11 hours of AF on day 4 (asymptomatic)

Thromboembolism and cancer

(Hu et al. Int J Cardiol 2013 165)

- Retrospective study of cancer in Taiwan, n=24,125
- AF present at diagnosis 2.4% - **baseline AF (n=584)**
- AF developed during cancer Rx – 1.8%; **new onset AF (n=423)**



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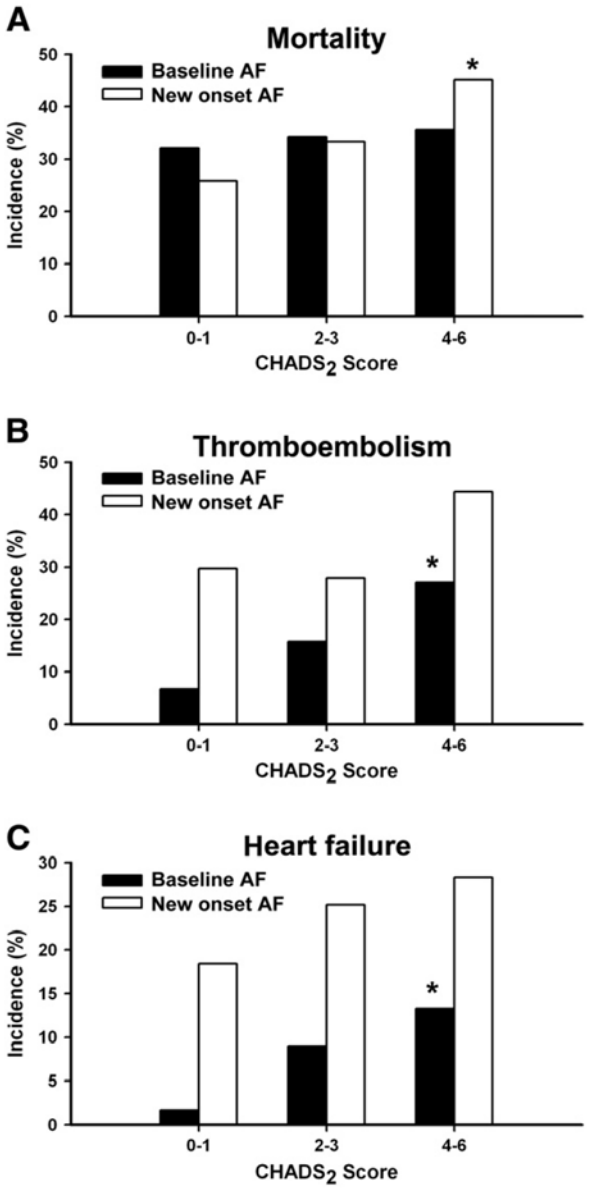
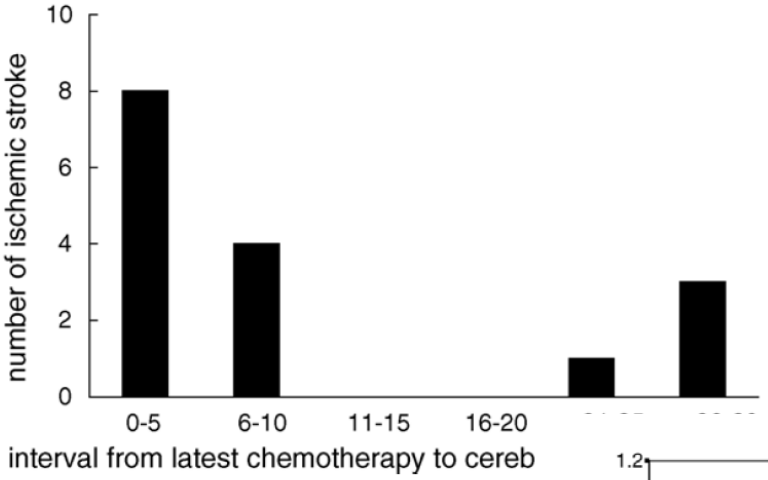
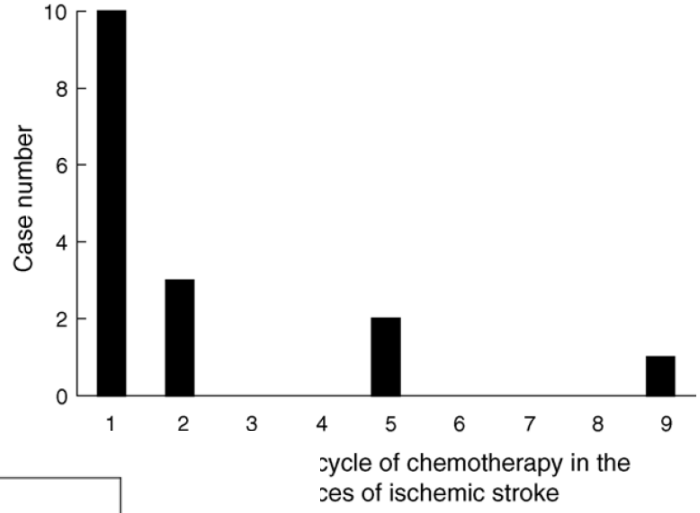


Stroke and cancer

from Clinical Neurology and Neurosurgery 108 (2006) 150–156



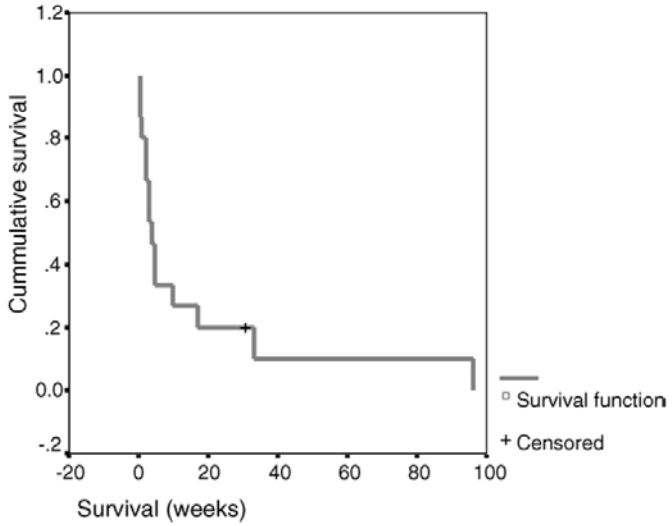


From Taiwan

Retrospective study on 11,000 patients,1993-2004 multiple cancers.

15 strokes (0.137%)

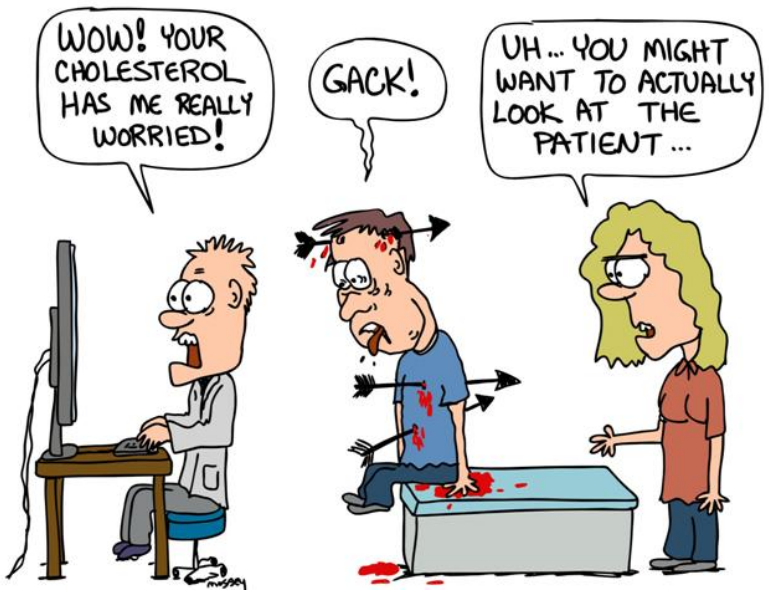
No. 1 = Platinum based chemo; gemcitabine #2



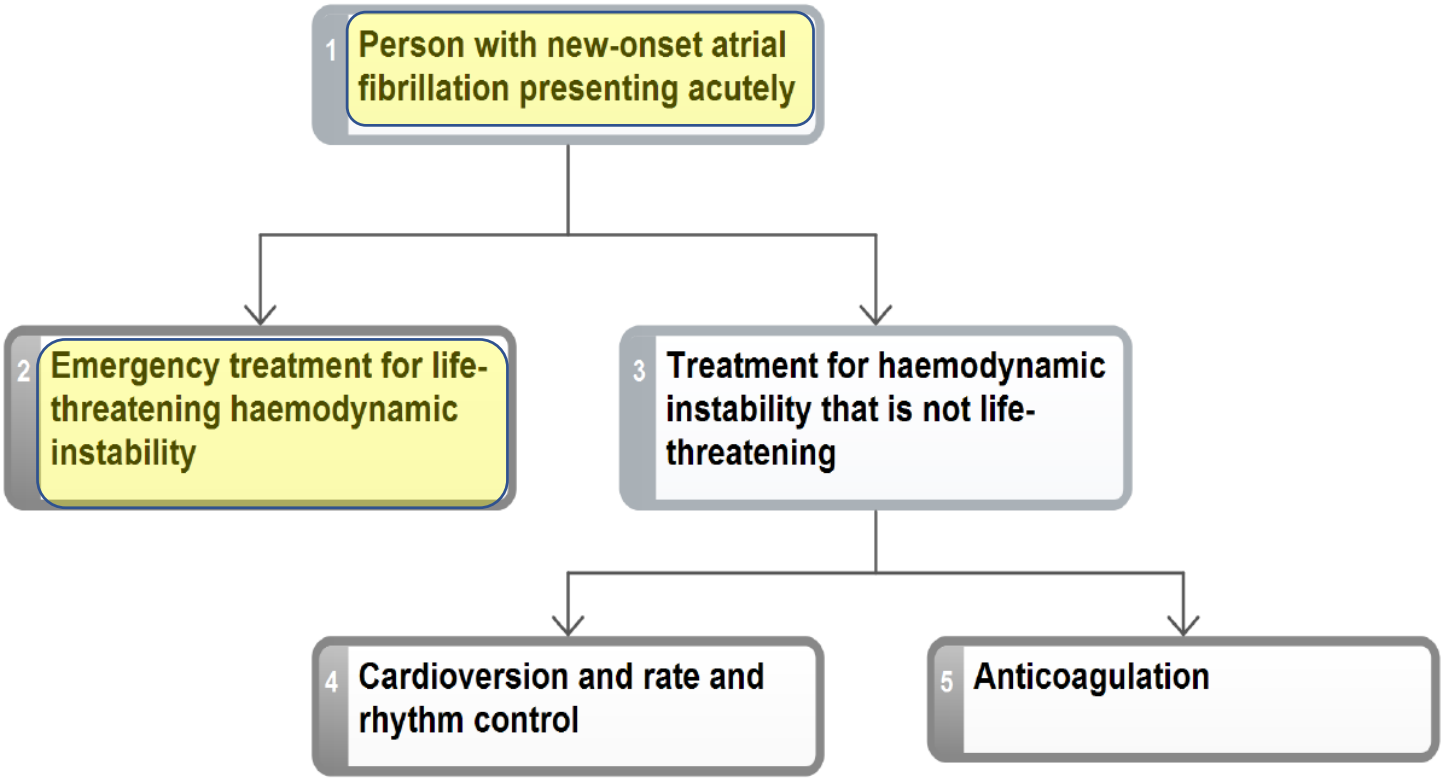
AF does not feature in this retrospective series

Treatment of AF – in cancer patients

- The principles are similar to other AF patients
  - Evidence presented so far suggests risks from AF in cancer reflect underlying “conventional” cardiovascular issues
    - ***Would expect higher cardio-embolic potential than non-cancer group***
      - *eg. Pancreatic, ovarian, primary liver & lung cancers*
      - *eg. Cisplatin, gemcitabine, 5 fluorouracil, erythropoietin, gcsf*
  - Prospective, trial data are not available
  - Personalised medicine



AF: acute presentation

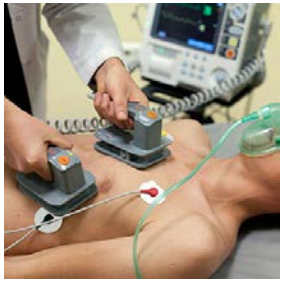


http://pathways.nice.org.uk/pathways/atrial-fibrillation

AF: acute presentation – person with new-onset AF

Life threatening haemodynamic instability

- Cardioversion
  - TOE guided in some cases
- "Pharmacological" cardioversion
  - Amiodarone or Flecainide



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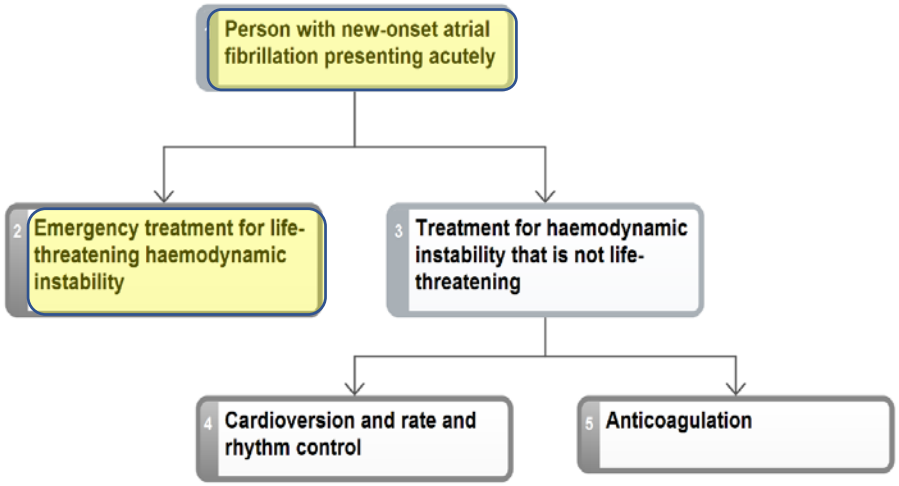
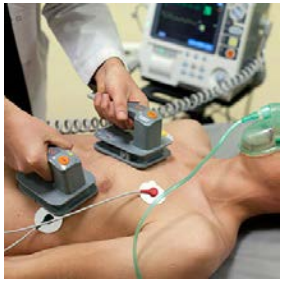


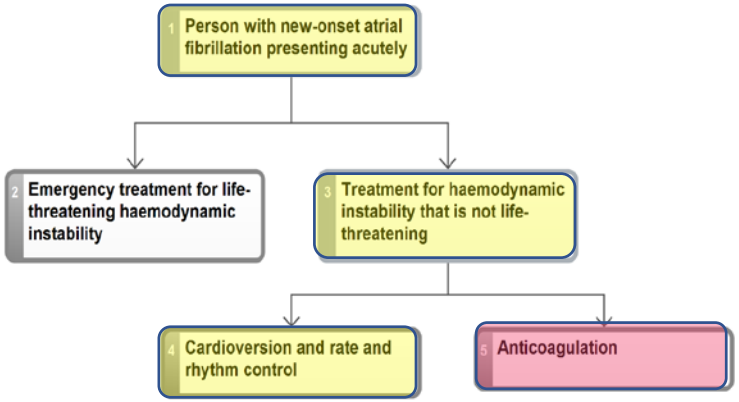
AF: acute presentation – person with new-onset AF

Haemodynamic instability that is *not* life threatening

- Cardioversion & rate
  - Preferably TOE guided
  - “Pharmacological” cardioversion
  - Amiodarone or Flecainide
  - Beta-blockers for rate control

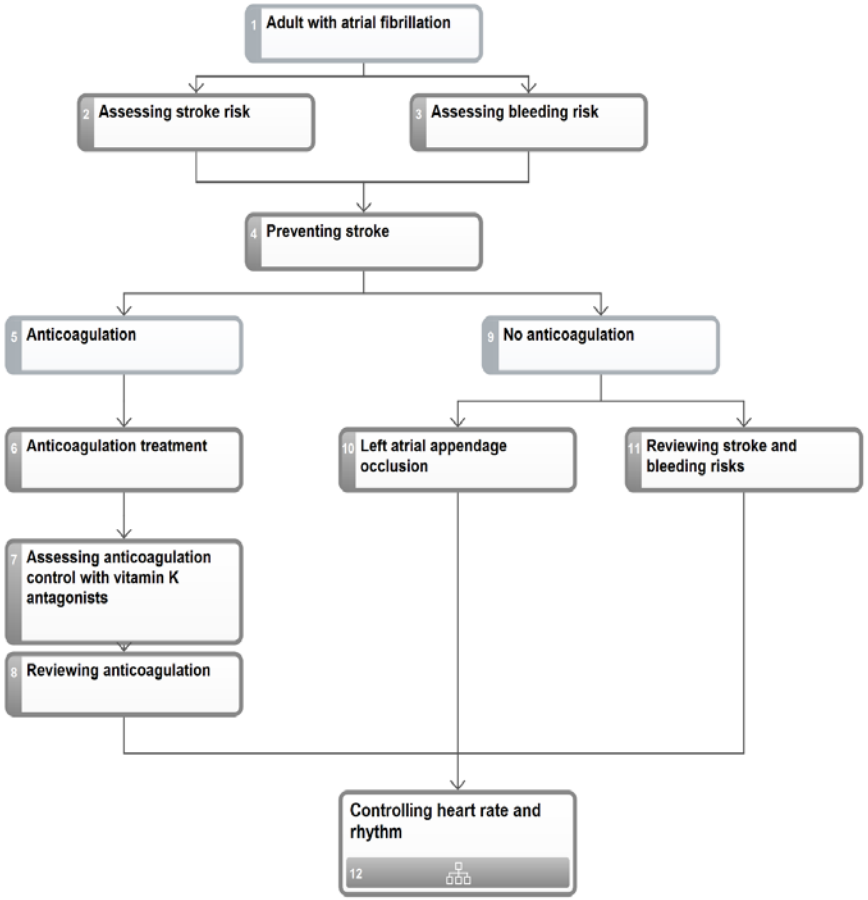


- Anti-coagulation
  - LMWH in first instance
  - Risk : benefit assessment



AF in cancer patients

- Stroke prevention
  1. Assessing the risk of stroke
  2. Assessing the risk of bleeding



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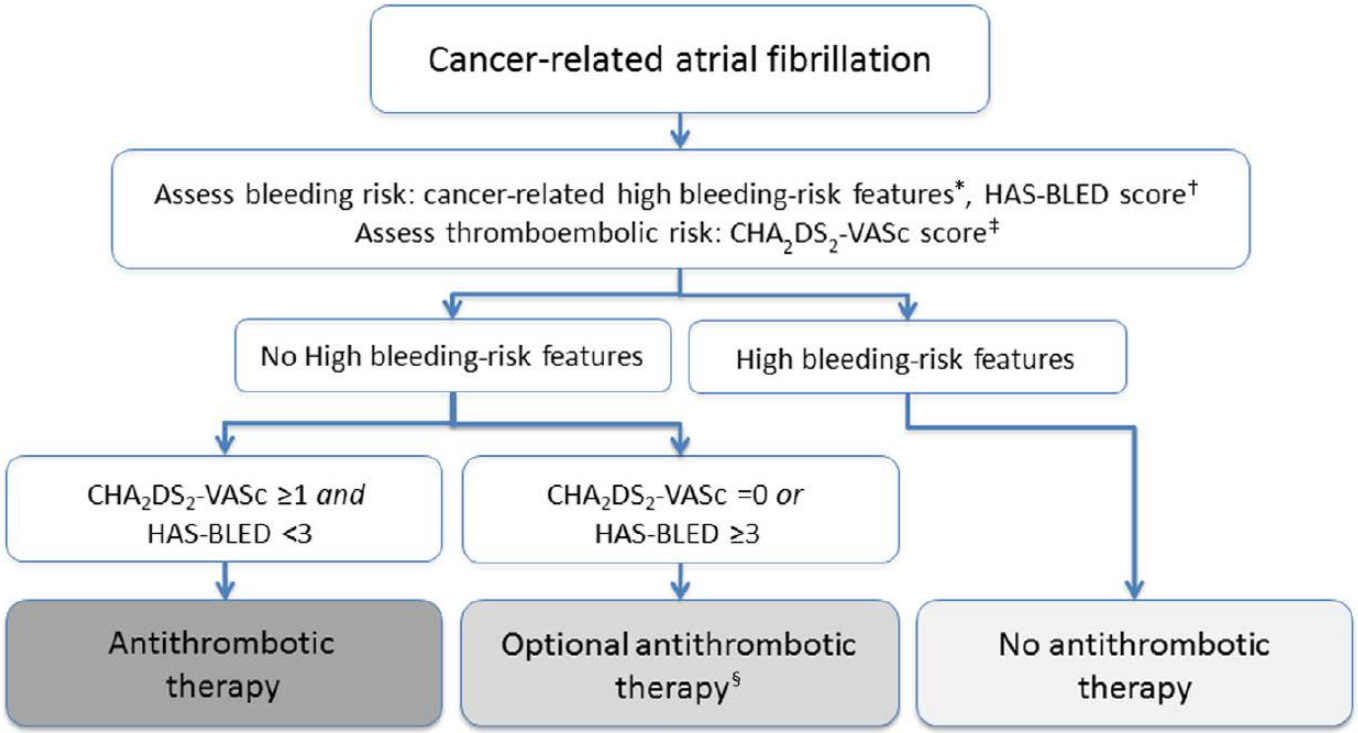
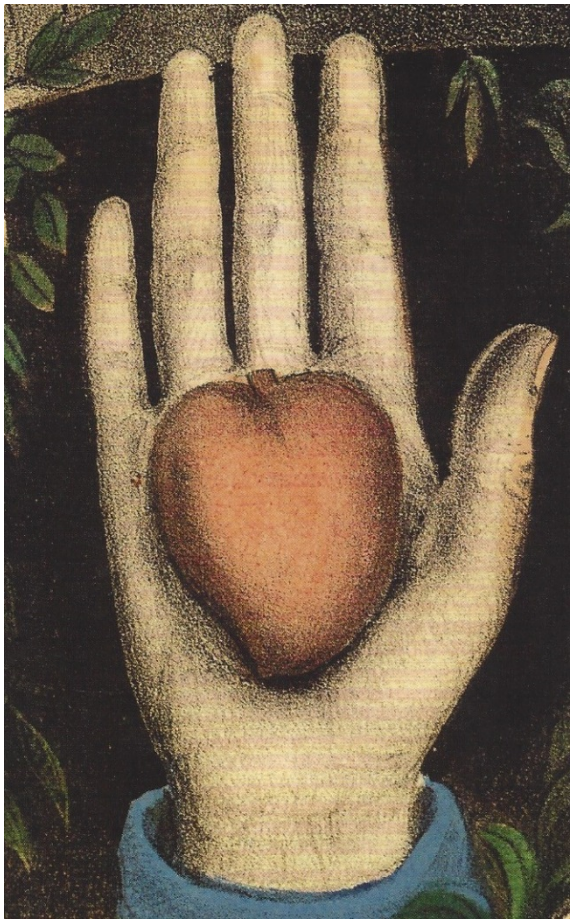
Management of AF complicating cancer
an algorhythm for anti-thrombotic Rx



(J Am Coll Cardiol 2014;63:945–53)

What anti-thrombotic therapy?

- Anti-vit K
  - INR control poor in cancer
  - Haemorrhagic risk increased
- LMWH
  - Potential benefits
- New oral anti-coagulants?
  - Dabigatran
  - Rivaroxaban & Apixaban
    - No data
- Anti-platelet agents?
    - No data
- Combination therapies?
  - Venous & arterial thrombo-embolism targets
  - Experience from PCI



Unresolved questions

Table 4 **Open Issues Concerning AF in Cancer Patients**

Epidemiology	Prevalence of AF in different types of cancer based on large cohorts or registries Occurrence of AF in relation to various cancer modalities, particularly novel targeted therapies Risk factors of AF Impact of AF on cancer prognosis and outcome Impact of AF on therapeutic decisions concerning cancer management
Pathogenesis	Mechanisms of AF induction
Diagnosis and assessment	Evaluation of classic and novel biomarkers for AF prediction Use of established thromboembolic risk assessment scores (i.e., $CHADS_2$ or CHA_2DS_2-VASc) Evaluation of the need for cancer-specific scores
Management	Evaluation of available strategies for stroke prevention Use of novel anticoagulants for stroke prevention (dabigatran, rivaroxaban, apixaban) Use of available pharmacological therapies and other strategies for AF prevention Use of available pharmacological and interventional therapies for AF management

(J Am Coll Cardiol 2014;63:945–53)

Conclusions

There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know. Donald Rumsfeld

Conclusions

- AF is commonly seen in the context of cancer and its treatment
- Stroke appears to be relatively uncommon, but data is scant

  might expect this complication of AF to be more frequently seen
- Risk of complications from anti-thrombotic therapy higher than in non-cancer groups
- Very careful individualised decisions need to be made
- Underlying risk nearly as important as presence or absence of AF


Thanks for listening
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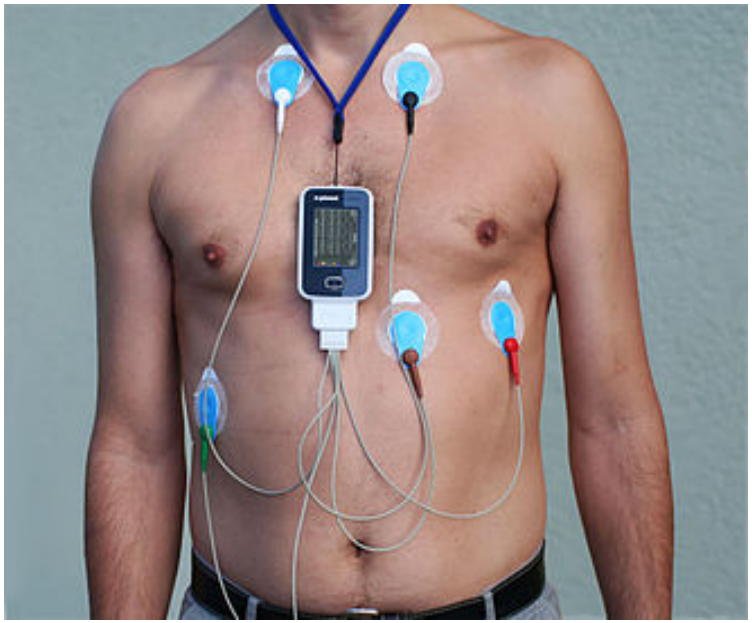
ERIC-ONC arrhythmia

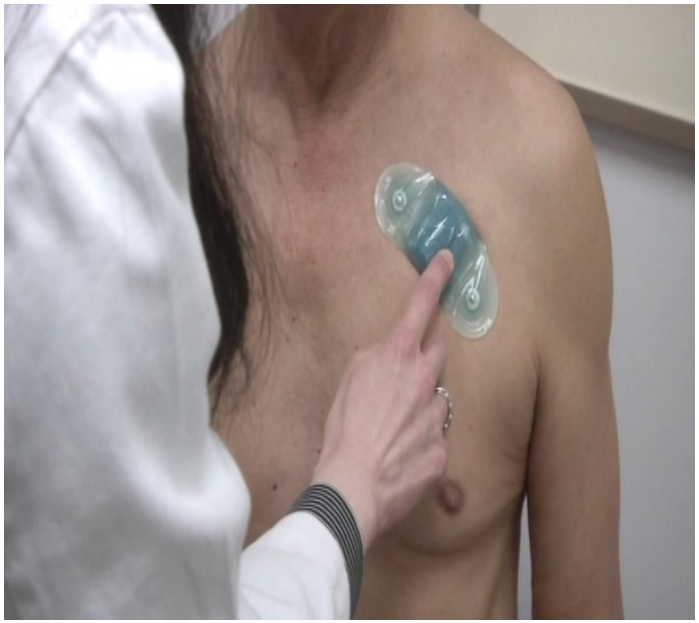
Conventional Holter

48hr, expensive equipment, 2 visits



Zio XT patch

14 days, disposable, one-stop



Incidence of ischemic stroke post-chemotherapy: A retrospective review of 10,963 patients

Shau-Hsuan Li [a], Wei-Hsi Chen [b], Yeh Tang [a], Kun-Ming Rau [a], Yeng-Yang Chen [a], Tai-Lin Huang [a], Jia-Shou Liu [b], Cheng-Hua Huang [a,*]

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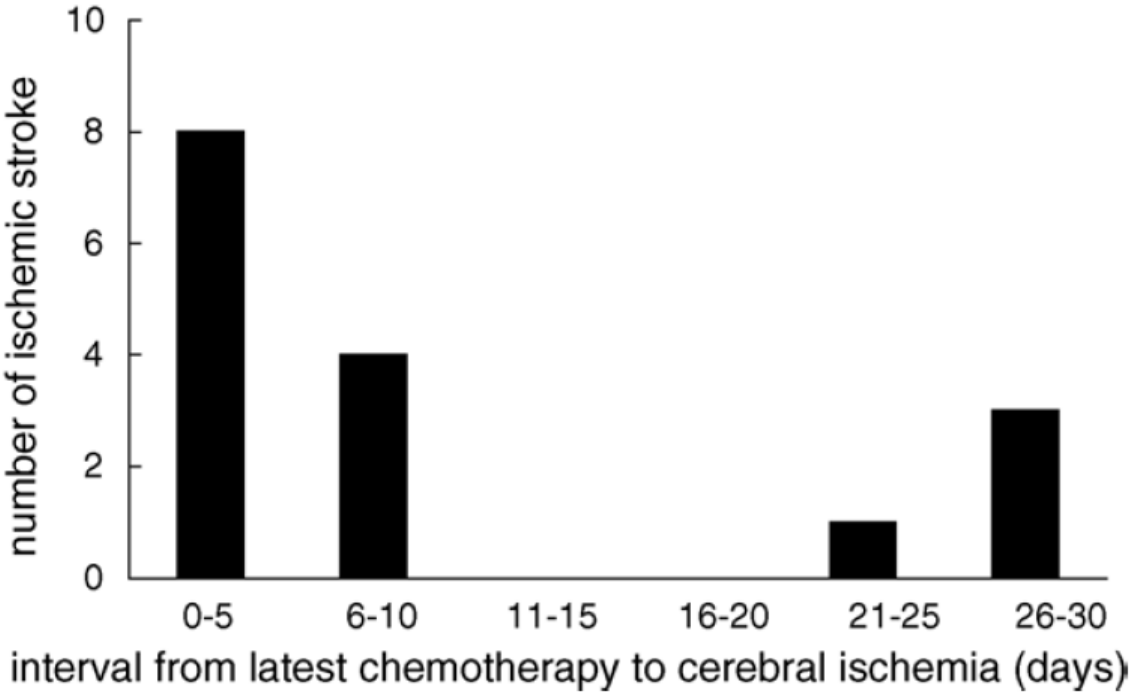

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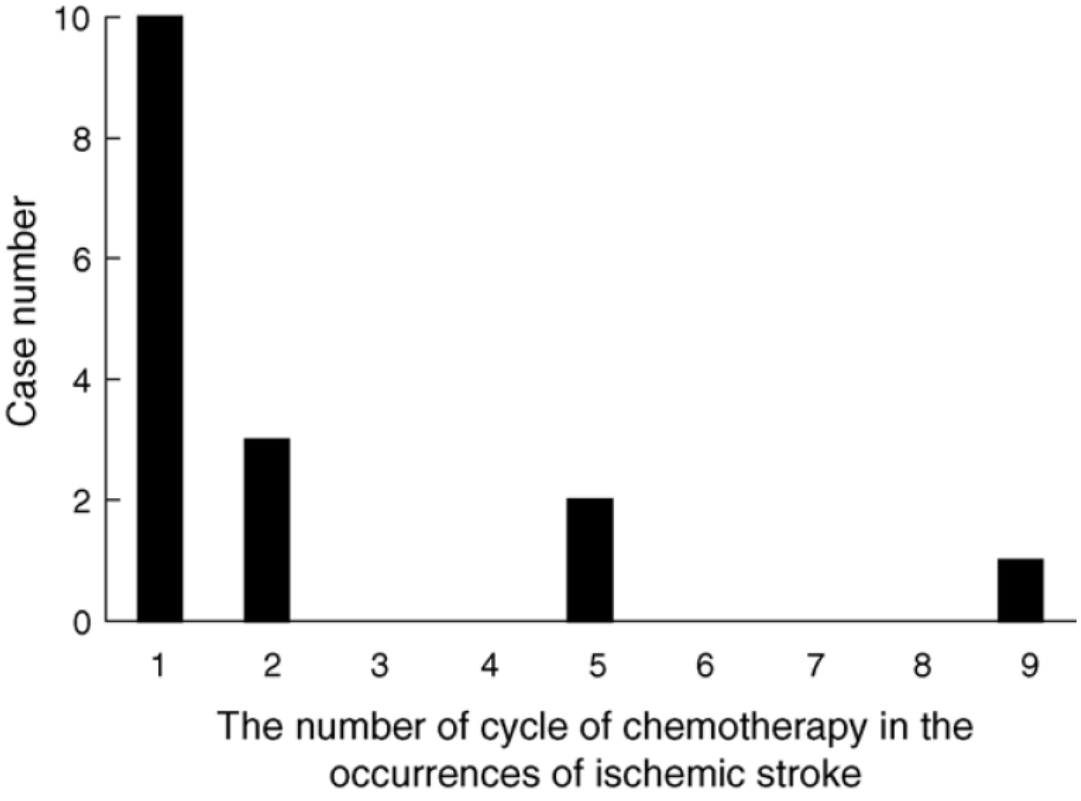
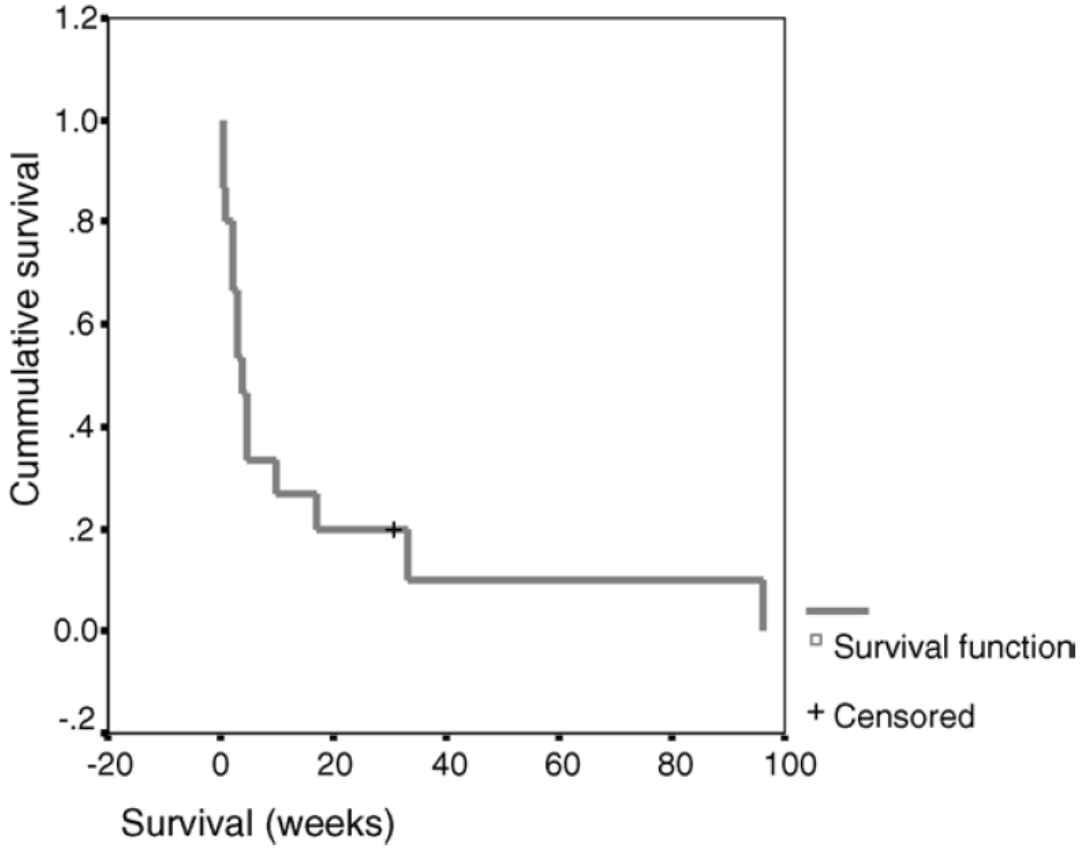

Case number
10
8
6
4
2
0
1
2
3
4
5
6
7
8
9
The number of cycle of chemotherapy in the occurrences of ischemic stroke


1.2
1.0
.8
.6
.4
.2
0.0
-.2
Cummulative survival
-20
0
20
40
60
80
100
Survival (weeks)
Survival function
Censored

Clinical aspects of arrhythmia in thalassaemia

- Management requires
  1. Diagnosis of the arrhythmia causing the symptoms
     - ECG
     - Holter ambulatory monitor – 24 hr or longer
     - Event recorders
- Techniques which may be useful
     - Implantable loop recorder – “Reveal” device

Clinical aspects of arrhythmia in thalassaemia

- Management requires
  1. Precise diagnosis
  2. Knowledge of underlying cardiac status
     - Ventricular function & cardiac structure by ECHO
     - Iron burden (T2*) by cMR

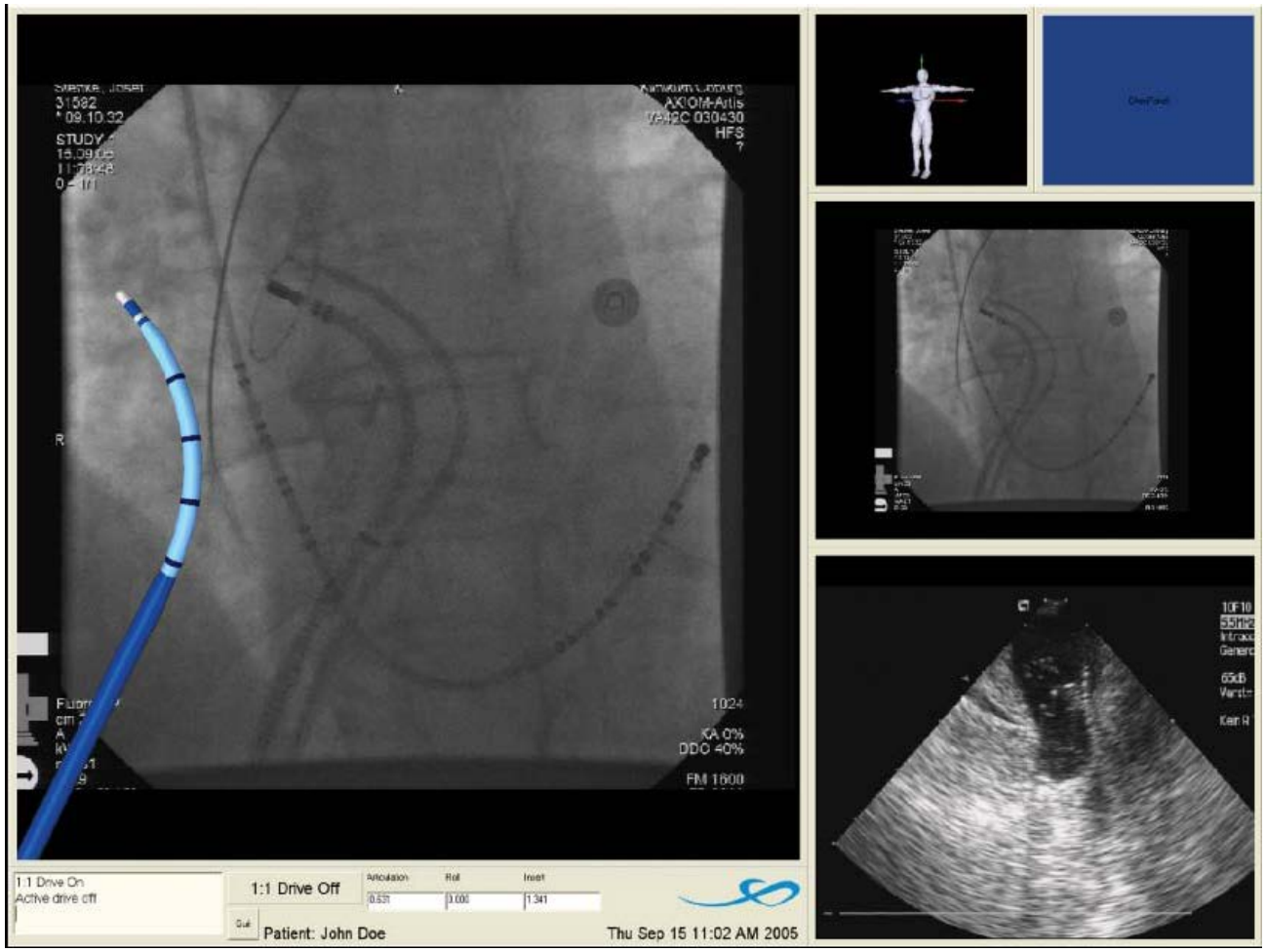
An ECHO + cMR are URGENT when

1 Ventricular arrhythmia
2 Poorly tolerated AF
3 Symptoms include loss of consciousness/ collapse/ heart failure

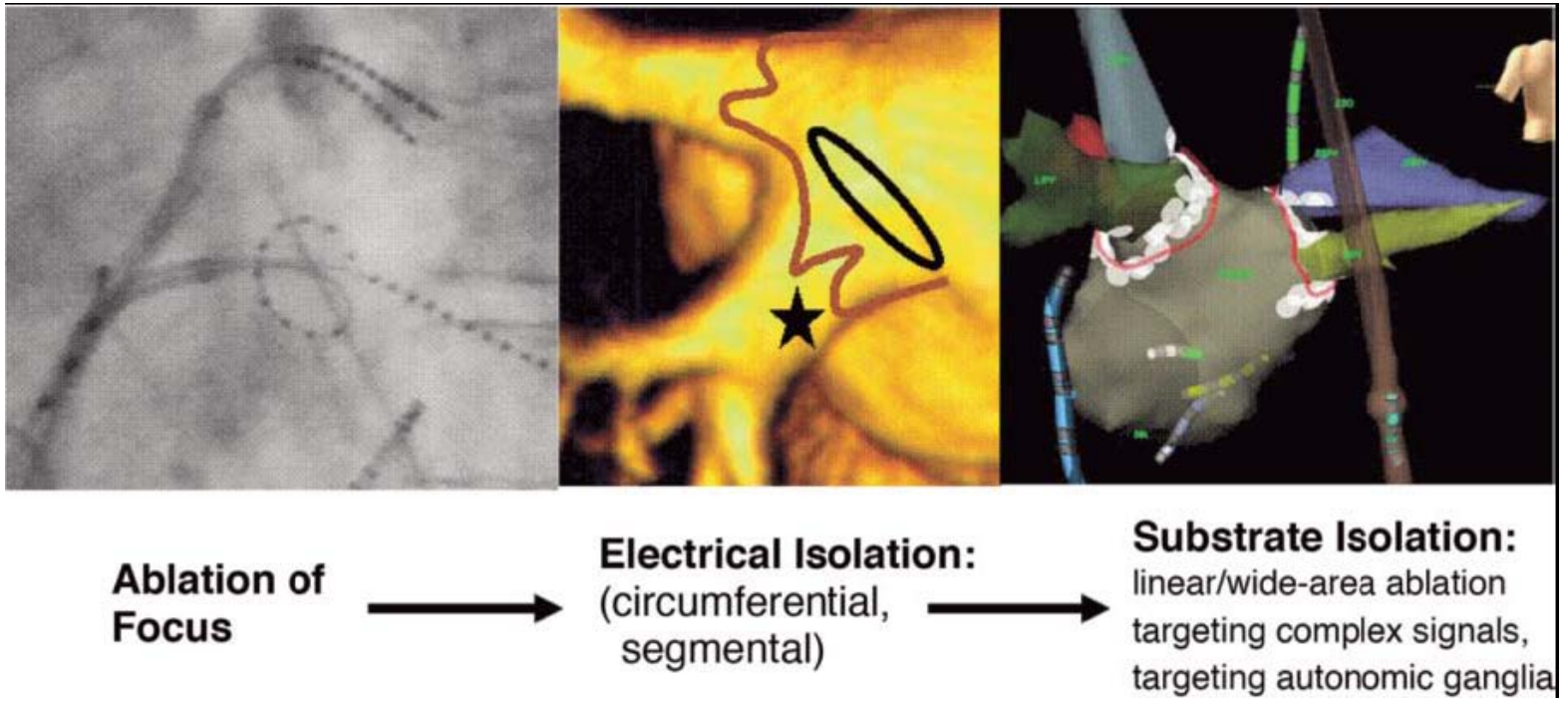
Clinical aspects of arrhythmia in thalassaemia - conclusions

- ECG
  - Necessary baseline at least every 12/12
  - At every cardiovascular assessment
    - It tells us more about the heart than just arrhythmia
- Holter 24hr ECG
  - Useful to investigate symptoms
  - Poor as a screening tool in asymptomatic well chelated TM patients with good LV function

Catheter based ablation for AF



Catheter based ablation for AF

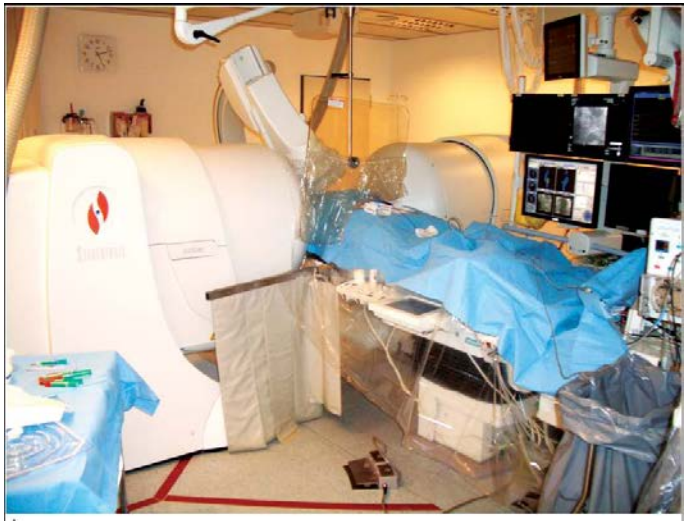


Catheter based ablation for AF

- Cardiac catheter based techniques
- Complex & time consuming (2 to 4hr)
- Often GA required
- Specialist EP cardiologists & service

- Success rates 70 to 80%
- Recurrence rates approx 15% at 1 year
- Risk of Stroke, cardiac perforation 1% to 2%

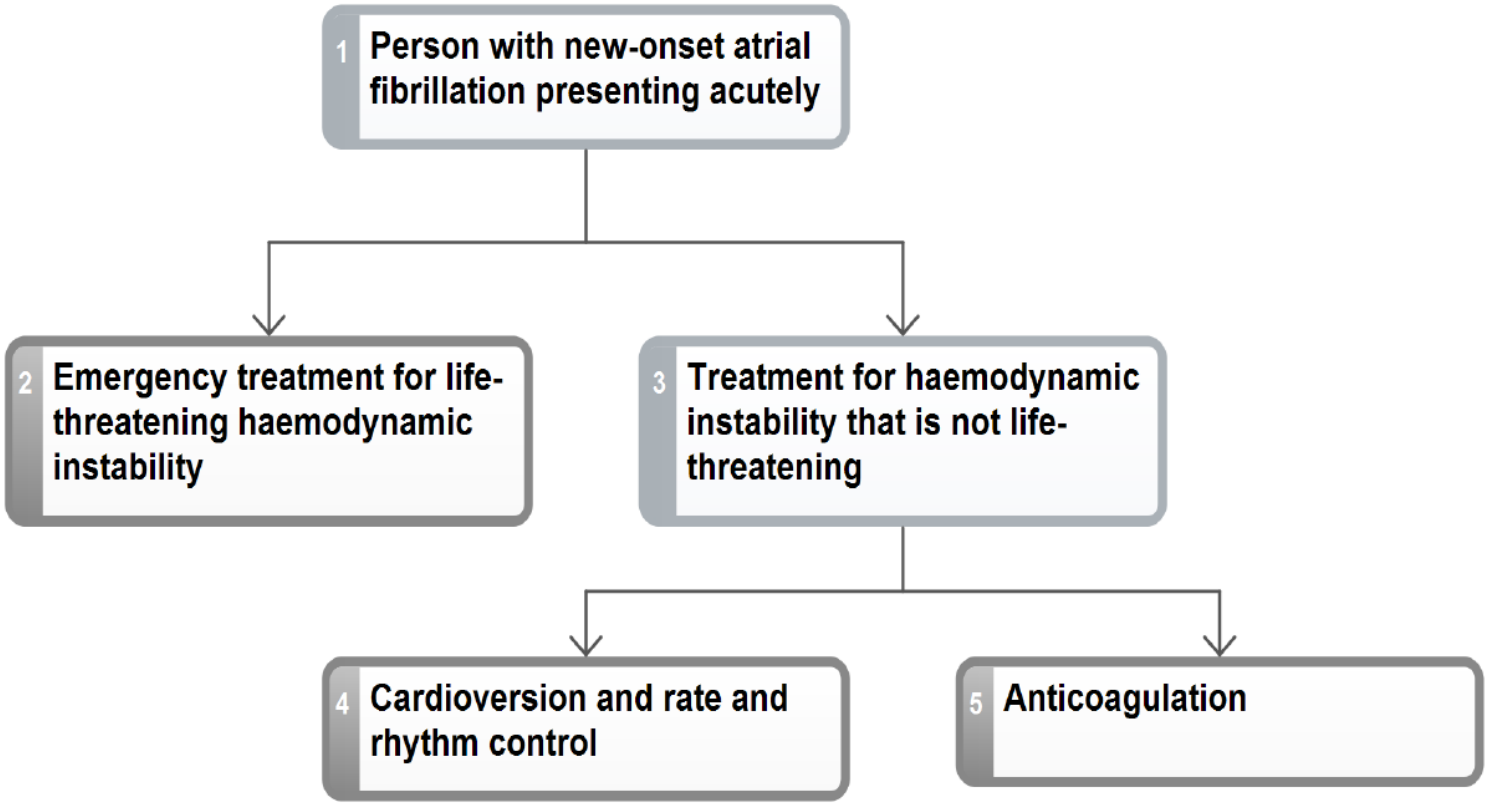
Complications and success rates may be different for thalassaemia population



A

B

AF: acute presentation



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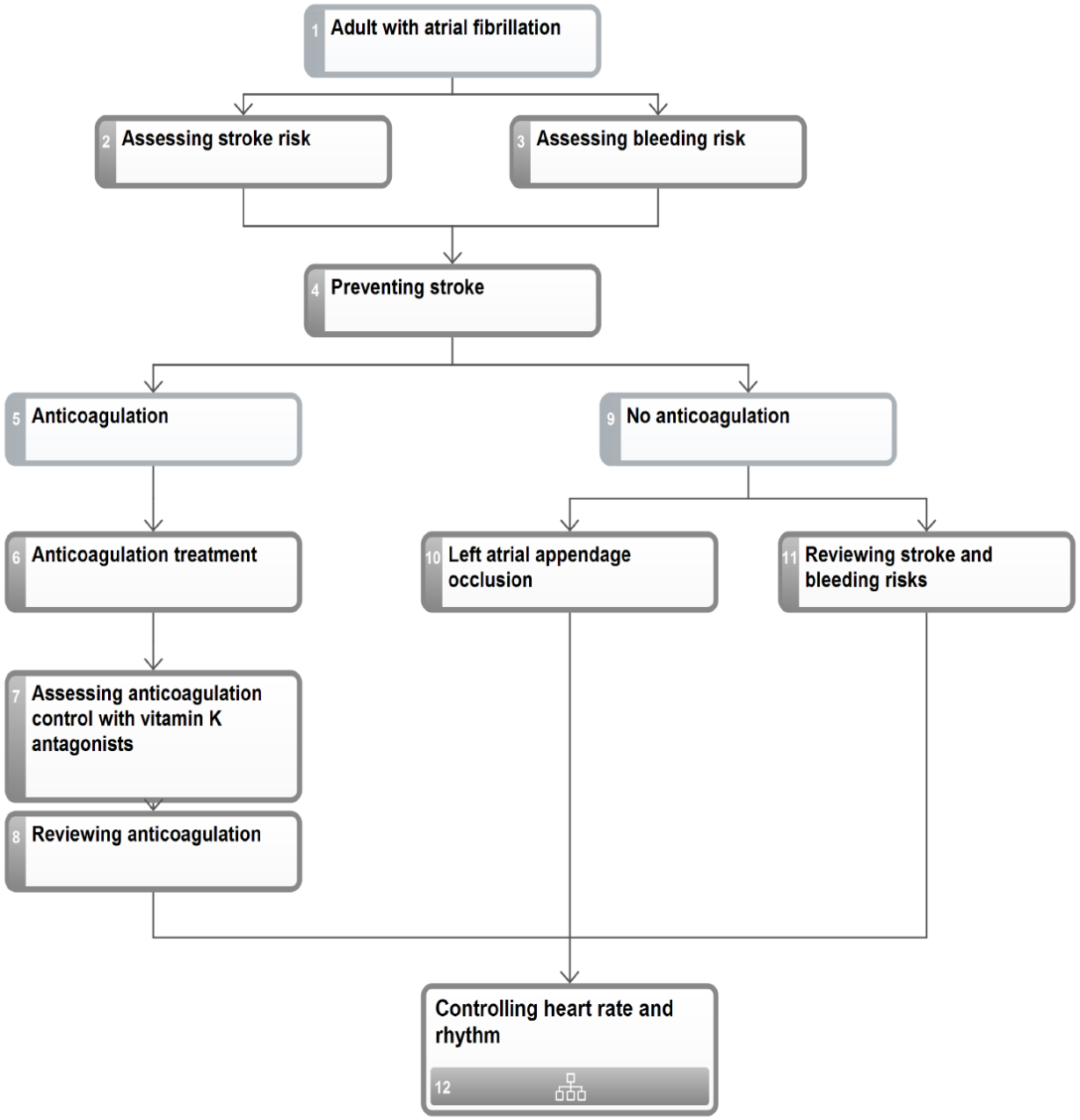
AF & Stroke



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