Anticoagulation for non-valvular AF during chemotherapy

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

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• Advisory Boards
  Pfizer - BMS
  Novartis
  Servier Laboratories

• Stocks & Directorships
  None relevant

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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

THOMAS LEWIS

... convincing 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 has been demonstrated that this disturbance of ventricular rhythm 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

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

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 LA 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

![ECG waveform](image)

<table>
<thead>
<tr>
<th><strong>CHA₂DS₂-VASc scoring</strong></th>
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<tr>
<td>Congestive heart failure (inc Left Ventricular Dysfunction)</td>
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# AF and Stroke Risk

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<th>Risk</th>
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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?
AF and Stroke Risk (Stroke/TE/TIA)
from Danish National Registry: 1997-2011; n=> 3x10^6

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• 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 CHA₂DS₂-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 CHA₂DS₂-VASC risk factor.
## AF and Stroke Risk

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**CAUTION — PREVIOUS CANCER or CURRENT CANCER/ CHEMOTHERAPY NOT INCLUDED**
AF and cancer – complicated relationships

![Diagram showing the complicated relationships between AF and cancer](image-url)
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.

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0102861
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.

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

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

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


- 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?

---

**Risk factors for AF**
- Old age
- Preexisting diastolic / systolic dysfunction
- Weight gain > 7% especially in the peri-transplant period
- Cardiotoxic chemotherapeutic agents such as melphalan, adriamycin etc
- Elevated creatinine levels
- h/o mediastinal radiation
- Coexisting cardiac disorders such as CAD, valvular heart disease, cardiac amyloidosis, dilated LA

**Atrial fibrillation**

**Increased length of stay, increased intensive care unit admission, increased cardiovascular related mortality**
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)
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)
Stroke and cancer


**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

1. Person with new-onset atrial fibrillation presenting acutely

2. Emergency treatment for life-threatening haemodynamic instability

3. Treatment for haemodynamic instability that is not life-threatening

4. Cardioversion and rate and rhythm control

5. Anticoagulation

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

nice.org.uk/guidance/cg180
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

http://pathways.nice.org.uk/pathways/atrial-fibrillation
Management of AF complicating cancer
an algorithm for anti-thrombotic Rx

Cancer-related atrial fibrillation

Assess bleeding risk: cancer-related high bleeding-risk features*, HAS-BLED score†
Assess thromboembolic risk: CHA₂DS₂-VASc score‡

No High bleeding-risk features
CHA₂DS₂-VASc ≥1 and HAS-BLED <3
Antithrombotic therapy

High bleeding-risk features
CHA₂DS₂-VASc =0 or HAS-BLED ≥3
Optional antithrombotic therapy§

No antithrombotic therapy

(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 thromboembolism targets
  - Experience from PCI
# Unresolved questions

## Table 4

### Open Issues Concerning AF in Cancer Patients

<table>
<thead>
<tr>
<th>Area</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>Prevalence of AF in different types of cancer based on large cohorts or registries</td>
</tr>
<tr>
<td></td>
<td>Occurrence of AF in relation to various cancer modalities, particularly novel targeted therapies</td>
</tr>
<tr>
<td></td>
<td>Risk factors of AF</td>
</tr>
<tr>
<td></td>
<td>Impact of AF on cancer prognosis and outcome</td>
</tr>
<tr>
<td></td>
<td>Impact of AF on therapeutic decisions concerning cancer management</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Mechanisms of AF induction</td>
</tr>
<tr>
<td>Diagnosis and assessment</td>
<td>Evaluation of classic and novel biomarkers for AF prediction</td>
</tr>
<tr>
<td></td>
<td>Use of established thromboembolic risk assessment scores (i.e., CHADS(_2) or CHA(_2)DS(_2)-VASc)</td>
</tr>
<tr>
<td></td>
<td>Evaluation of the need for cancer-specific scores</td>
</tr>
<tr>
<td>Management</td>
<td>Evaluation of available strategies for stroke prevention</td>
</tr>
<tr>
<td></td>
<td>Use of novel anticoagulants for stroke prevention (dabigatran, rivaroxaban, apixaban)</td>
</tr>
<tr>
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<td>Use of available pharmacological therapies and other strategies for AF prevention</td>
</tr>
<tr>
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<td>Use of available pharmacological and interventional therapies for AF management</td>
</tr>
</tbody>
</table>
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
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\textsuperscript{a}, Wei-Hsi Chen\textsuperscript{b},
Yeh Tang\textsuperscript{a}, Kun-Ming Rau\textsuperscript{a}, Yeng-Yang Chen\textsuperscript{a},
Tai-Lin Huang\textsuperscript{a}, Jia-Shou Liu\textsuperscript{b}, Cheng-Hua Huang\textsuperscript{a,}\textsuperscript{*}

\textsuperscript{a} Department of Internal Medicine, Chang Gung Memorial Hospital, 123 Ta-Pei Road, Niaosung Hsiang, Kaohsiung Hsien, Taiwan, ROC
\textsuperscript{b} Department of Neurology, Chang Gung Memorial Hospital, Kaohsiung, Taiwan, ROC

Received 20 December 2004; received in revised form 22 March 2005; accepted 29 March 2005
The number of cycle of chemotherapy in the occurrences of ischemic stroke
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

Ablation of Focus  →  Electrical Isolation:
                             (circumferential, segmental)  →  Substrate Isolation:
                             linear/wide-area ablation targeting complex signals, targeting autonomic ganglia,
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*
AF: acute presentation

1. Person with new-onset atrial fibrillation presenting acutely
   - 2. Emergency treatment for life-threatening haemodynamic instability
   - 3. Treatment for haemodynamic instability that is not life-threatening
     - 4. Cardioversion and rate and rhythm control
     - 5. Anticoagulation

http://pathways.nice.org.uk/pathways/atrial-fibrillation
AF & Stroke

1. Adult with atrial fibrillation
   2. Assessing stroke risk
   3. Assessing bleeding risk
   4. Preventing stroke
      5. Anticoagulation
         6. Anticoagulation treatment
         7. Assessing anticoagulation control with vitamin K antagonists
         8. Reviewing anticoagulation
      9. No anticoagulation
         10. Left atrial appendage occlusion
         11. Reviewing stroke and bleeding risks

Controlling heart rate and rhythm

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