The New Oral Anticoagulants (Direct Oral Anticoagulants - DOACs)

Dr Francis Matthey, FRCP, FRCPath
Consultant Haematologist
Chelsea and Westminster Hospital

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The New Anticoagulants

Novel Oral Anti-Coagulants (NOACs) = Direct Oral Anti-Coagulants (DOACs)
Our drugs before DOACs

- Warfarin
- Heparin
- LMW heparin

narrow therapeutic index
require monitoring

Beware renal failure
s/c injection
osteoporosis
The Ideal Anticoagulant

- Oral and once daily
- Fixed, predictable dose
- No interactions with food
- No monitoring required
- Easily reversible
- Not retained in renal failure
- No placental transfer
- Not immunogenic
Currently available DOACs (NOACs)

Dabigatran (Pradaxa)
Rivaroxaban (Xarelto)
Apixaban (Eliquis)
Edoxaban (Lixiana)
<table>
<thead>
<tr>
<th></th>
<th>Oral</th>
<th>Predictable response</th>
<th>Fixed dosing</th>
<th>No routine monitoring</th>
<th>No food / drug interactions</th>
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</thead>
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<td>Ideal</td>
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<td>VKA</td>
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<td>Fondaparinux</td>
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<td>Lepirudin</td>
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<td>Dabigatran</td>
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<td>Rivaroxaban</td>
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<td>Apixaban</td>
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<td>No HITT</td>
<td>Reversible</td>
<td>No placental transfer</td>
<td>Not immunogenic</td>
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<td>Lepirudin</td>
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<td>Dabagatran</td>
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<td>Rivaroxaban</td>
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<td>Apixaban</td>
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<tr>
<td></td>
<td>Warfarin</td>
<td>NOAC / DOAC</td>
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<tr>
<td>Established</td>
<td>Decades</td>
<td>Last 5 years</td>
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<tr>
<td>Interactions</td>
<td>Multiple interactions with foods and drugs</td>
<td>Minimal number of interactions with only a few drugs (exercise care with antifungals [e.g. ketoconazole, voriconazole] and some antivirals [e.g. ritonavir, atazanavir].)</td>
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<tr>
<td>Dosage</td>
<td>Variable dose, according to patient's size, metabolism, state of health, diet, and other medications</td>
<td>Fixed dose independent of size, provided that kidney function is normal.</td>
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<tr>
<td>Time within therapeutic range</td>
<td>At best – about 70%</td>
<td>In theory, 100% of the time assuming no missed doses</td>
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<tr>
<td>Need for blood test monitoring</td>
<td>Required regularly to assess that the INR is within the therapeutic range and modification of the warfarin dose made in the light of the INR result</td>
<td>No routine blood test monitoring required.</td>
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<tr>
<td>Major side effects</td>
<td>Risk of haemorrhage (bleeding)</td>
<td>Risk of haemorrhage (bleeding)</td>
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<tr>
<td>Reversal agent (antidote) in event of bleeding</td>
<td>Yes – Prothrombin Complex Concentrate and intravenous / oral vitamin K</td>
<td>No specific antidote (reversal agent) available yet but DOACS have a short biological half life and are quickly eliminated from the circulation. PCC (Prothrombin Complex Concentrate) partially reverses the effect of DOACS</td>
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<tr>
<td>Bleeding incidence</td>
<td>Around 2% per year</td>
<td>Around 2% per year. Gastrointestinal bleeding slightly more common than with warfarin but fatal intracranial bleeding occurs less frequently than with warfarin</td>
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DOACs – Major Indications

- Thromboprophylaxis in large joint orthopaedic surgery (hip and knee replacement).

- Prevention of systemic embolism in non-valvular atrial fibrillation (NVAF) with one of more risk factors:
  - Prior stroke or TIA
  - Age 75 yrs +
  - Hypertension
  - Diabetes
  - Symptomatic heart failure

- Treatment and prevention of venous thromboembolism
<table>
<thead>
<tr>
<th>Indication</th>
<th>NICE approval</th>
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</thead>
<tbody>
<tr>
<td>Post-op thromboprophylaxis (hip/knee replacement)</td>
<td>Dabigatran (approved Sept 2008)</td>
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<tr>
<td></td>
<td>Rivaroxaban (approved Apr 2009)</td>
</tr>
<tr>
<td></td>
<td>Apixaban (approved Dec 2011)</td>
</tr>
<tr>
<td>Medical inpatient thromboprophylaxis</td>
<td>Apixaban (appraisal in progress)</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban (not seeking approval)</td>
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<tr>
<td>Atrial fibrillation</td>
<td>Dabigatran (approved Nov 2011)</td>
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<tr>
<td></td>
<td>Rivaroxaban (approval May 2012)</td>
</tr>
<tr>
<td></td>
<td>Apixaban (approval Feb 2013)</td>
</tr>
<tr>
<td></td>
<td>Edoxaban (approval Sept 2015)</td>
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<tr>
<td>DVT / PE treatment</td>
<td>Rivaroxaban (approved July 2012)</td>
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<tr>
<td></td>
<td>Dabigatran (approved Dec 2014)</td>
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<td></td>
<td>Apixaban (approved March - June 2015)</td>
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<td></td>
<td>Edoxaban (approved August 2015)</td>
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</table>
Mechanism of Action

Tissue factor

VII → VIIa

Warfarin

X → Xa

Prothrombin

LMWH

Thrombin

Heparin

Fibrinogen → Fibrin
Mechanism of Action

Tissue factor

VII → VIIa

X → Xa

Prothrombin → Thrombin

Fibrinogen → Fibrin

Edoxaban
Apixaban
Rivaroxaban

Dabigatran

Fibrinogen
Dabigatran

- Orally active
- Direct thrombin inhibitor
- Non-inferior to enoxaparin (40 mg/day) for VTE prophylaxis in hip/knee surgery
- Twice daily dosing
- Requires initial therapeutic LMWH in setting of treatment for VTE (so 3rd line at C&W for VTE)
Rivaroxaban

- Orally active
- Inhibitor of factor Xa
- Once daily dosing
- No lab monitoring required
- Avoid in renal insufficiency or liver disease
Apixaban

- Orally active
- Inhibitor of factor Xa
- Twice daily dosing
- No lab monitoring required
- Avoid in renal impairment (CrCl < 15 mL/min) or liver disease
- Reduce dose in moderate renal impairment, age > 80 yrs, body weight < 60 kg
- Improved survival and less haemorrhagic stroke compared to warfarin (ARISTOTLE study, 2011)
Edoxaban (Lixiana)

- Licensed for NVAF and VTE
- Once daily dosing
- For VTE: requires parenteral anticoagulant for the initial 5 days (therefore not cost effective in this context)
- Inhibitor of factor Xa
- Daily cost of treatment ~ £2.10 per day
DOACs – Issue to Consider

- Specific patient characteristics
  - Bleeding risk (lowest bleeding risk with apixaban, dabigatran 110 mg, edoxaban)
  - Previous g.i. bleed – use apixaban or edoxaban
  - High risk of ischaemic CVA – dabigatran 110 mg
  - Coronary artery disease / MI – rivaroxaban (positive effect in ACS)
  - Renal impairment – apixaban, rivaroxaban, edoxaban
  - Patient preference – once daily dose – rivaroxaban, edoxaban
DOACs – Issue to Consider 2

Contraindicated in:

- Pregnancy
- Breast Feeding
- Prosthetic Heart Valves
  - The term 'non valvular AF' = not mitral stenosis or a prosthetic heart valve
- ? Cancer
DOACs – Issues to Consider 3

- **Switching between other anticoagulants (including bridging for surgery):**
  - From a VKA (warfarin) to a DOAC
  - From a DOAC to a VKA
  - From a LMWH and a DOAC (and vice-versa)

**Strategies take into account:**
- The short half-life of DOACs (≈ 6 – 14 hrs)
- The DOAC's rapid onset of action (within 2 – 4 hours)
- The slow onset of action of VKAs and time to wear off
DOACs – Issues to Consider 4

- Circumstances when measurement of DOAC may help
  - untoward bleeding
  - possible overdose
  - renal impairment
  - emergency surgery
  - to assess compliance

- Methodology to measure DOACs
  - Use of specific substrates in the laboratory.
  - Therapeutic ranges have been published
<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>aPTT</th>
<th>PT</th>
<th>Thrombin time</th>
<th>Anti-Xa</th>
<th>Ecarin time</th>
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</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>N or ↑</td>
<td>↑ ↑ ↑</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Heparin</td>
<td>↑ ↑ ↑</td>
<td>N or ↑</td>
<td>↑ ↑ ↑</td>
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<tr>
<td>LMWH</td>
<td>N or ↑</td>
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<td>N</td>
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<tr>
<td>Dabigatran</td>
<td>↑ ↑ ↑</td>
<td>N</td>
<td>↑ ↑ ↑</td>
<td>↑</td>
<td>↑ ↑ ↑</td>
</tr>
<tr>
<td>Rivaroxiban</td>
<td>N or ↑</td>
<td>↑</td>
<td>N</td>
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Reversal of Conventional Anticoagulants

- Warfarin
- Prothrombin
- X
- Xa
- LMWH
- Heparin
- Protamine
- Vitamin K
- Fibrinogen
- Fibrin

PCC = Prothrombin Complex Concentrate
Reversal of DOACs

VII → VIIa

X → Xa

Prothrombin → Thrombin → Fibrinogen → Fibrin

Apixaban → Rivaroxaban → Dabigatran

PCC → aPC C

Feiba (activated prothrombin complex concentrate)

aPCC - FEIBA (activated prothrombin complex concentrate)
Specific Reversal Agents for DOACs

- **Idarucizumab** (Boehringer Ingelheim): a fragment of an antibody (Fab), which is a specific antidote to the oral direct thrombin inhibitor dabigatran

- **Andexanet alfa** (Portola Pharmaceuticals): a truncated form of enzymatically inactive factor Xa, which binds and reverses the anticoagulant action of the factor Xa inhibitors (e.g.: rivaroxaban, apixaban and edoxaban)

- **Aripazine** (Perosphere Inc.): a synthetic small molecule (~500 Da) that reverses oral dabigatran, apixaban, rivaroxaban, as well as subcutaneous fondaparinux and LMWH in vivo
Cost of Reversal

Vitamin K = pennies
FFP = ££
PCC = £££
aPCC = £££
rVIIa = £££££ (!)
DOACs = ? £££
Interpretation of Biochemical Iron Studies

- Iron is poorly absorbed from the G.I. tract
- Having passed through the gut, it is transported in the blood largely bound to transferrin, the iron-bind protein.
- The amount of iron in the blood fluctuates during the day (due to dietary intake etc.)
- It is laid down in iron stores as apoferritin – the serum ferritin is the best single blood test measure of iron stores but....
- Serum ferritin is also an acute phase reactant and can go up in liver disease.
Interpretation of Biochemical Iron Test Results

- If the serum ferritin is low then the patient is iron deficient
- **High serum ferritin:**
  - acute inflammation or liver disease (check LFTs, liver U/S)
  - iron overload
- **Low serum iron:**
  - iron deficiency
  - Anaemia of Chronic Disease (ACD)
  - recent poor dietary intake of iron (probably)
- TIBC (= transferrin or UIBC) is:
  - high in iron deficiency
  - normal or low in ACD
- **Transferrin saturation is:**
  - Low in iron deficiency
  - Low in ACD
  - High in iron overload (the most sensitive indicator of iron overload)
Ferritin, serum iron and TIBC

- Ferritin
- Iron deficiency
- Anaemia of chronic disorders
- Iron overload

<table>
<thead>
<tr>
<th>Condition</th>
<th>Female</th>
<th>Male</th>
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<tr>
<td>Ferritin</td>
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<tr>
<td>Iron deficiency</td>
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<tr>
<td>Anaemia of chronic disorders</td>
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<td></td>
</tr>
<tr>
<td>Iron overload</td>
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Microgram/L

- Serum iron
- UIBC
Biochemical Iron Studies – Some other issues

- Ideally, blood sample for iron studies (serum iron, TIBC, % saturation) should be taken fasted (diurnal variation in serum iron).
- The serum ferritin is not subject to diurnal variation
- If the serum ferritin is high and the TIBC/transferrin saturation is normal then the patient probably does not have iron overload.
  - Look for inflammation (check ESR), LFTs, liver U/S
- If the patient is iron deficient and has recently started oral iron then the serum iron may be high but the ferritin still low.
- Occasionally, a trial of oral iron therapy may be required in the setting of acute inflammation to establish if the patient is iron deficient (e.g. rheumatoid arthritis pt, high ESR, raised ferritin, low serum iron, normal TIBC)
Evaluation of anemia in the adult according to the mean corpuscular volume

Anemia detected on CBC

Evaluate MCV and look for other "flags" on CBC report for presence of abnormal RBCs, or examine peripheral smear

MCV low (<80 fl)

Minor population of microcytic RBCs present

Iron studies

- Low Fe
  - Low ferritin
  - High TIBC
  - Low ferritin

Iron deficiency: determine cause

Anemia of chronic disease: infection, inflammation, or malignancy

- Iron overload present
  - Teardrop red cells
  - Splenomegaly
  - Positive family history

Sideroblastic anemia: determine cause

MCV normal (80 to 96 fl)

Minor population of macrocytic RBCs present

- Serum B12 and folate levels
- Methylmalonate (if needed)
- Homocysteine (if needed)

Dysplastic features present

Myelodysplastic disorder

- Low B12
  - Elevated methylmalonate
  - Elevated homocysteine

B12 deficiency: determine cause

Other causes:
- Increased reticulocytes
- Liver disease
- Hypothyroidism
- Drugs

MCV increased (>100 fl)

Other causes:
- Low Fe
- Normal methylmalonate
- Normal homocysteine

Folate deficiency: determine cause

CBC: complete blood count; MCV: mean corpuscular volume; RBCs: red blood cells; Fe: iron; TIBC: total iron-binding capacity (transferrin); LDH: lactate dehydrogenase

Chelsea and Westminster Hospital
NHS Foundation Trust
Serum protein electrophoresis
## MYELOMA vs MGUS - Diagnosis

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<tr>
<th></th>
<th>Myeloma</th>
<th>MGUS</th>
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<tbody>
<tr>
<td>Bone marrow plasma cells</td>
<td>&gt; 10%</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>BJP</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Immune paresis</td>
<td>&gt; 95% of cases</td>
<td>Rare</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Often present</td>
<td>Absent</td>
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<tr>
<td>End organ damage:</td>
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<tr>
<td>Anaemia</td>
<td></td>
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</tr>
<tr>
<td>Bone lesions</td>
<td>May be present</td>
<td>Absent</td>
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<tr>
<td>Renal failure</td>
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<tr>
<td>Hypercalcaemia</td>
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</table>
Skeletal survey
Monoclonal Gammopathy of Undetermined Significance (MGUS)

- Monoclonal gammopathy found in:
  - 1% of people > 50 yrs
  - 10% of people > 80 yrs

- Clinical features of MGUS
  - No symptoms / signs
  - Incidental chance finding
  - ~ 10% will develop myeloma

- How to monitor?
  - 6 monthly FBC, U/E, calcium, protein electrophoresis and paraprotein quantitation.
  - Refer to haematology if Hb falling, urea or calcium rising, paraprotein rising, bone pain, lymphadenopathy
Assessment of Paraprotein

- Does the patient have symptoms?
- Does the patient have clinical signs (e.g. nodes)?
- How high is the paraprotein concentration?
- What sort of paraprotein is it?:
  - IgA / IgG ~ myeloma
  - IgM / IgG ~ lymphoma
- Are the other Igs suppressed?
- Is the blood count normal?
- Are the renal function and calcium normal?

Most paraproteins are discovered incidentally and do not mean that the patient has a malignancy (they usually represent MGUS)
Polyclonal Hypergammaglobulinaemia

- The finding of raised globulins without a monoclonal band is **not** an indication of myeloma.

- Causes of polyclonal $\uparrow$ $\gamma$ globulins:
  - Chronic infection
  - Chronic liver disease
    - Cirrhosis
    - Autoimmune hepatitis
  - HIV infection
  - Connective tissue disease (Sjogren’s syndrome, SLE, RA)
  - Angioimmunoblastic lymphadenopathy
  - Tropical splenomegaly syndrome
Case - neutropenia

- Mr B  60 year old African
  
  - Incidental finding of neutrophils 1.0 x 10⁹/L
Isolated neutropenia

The severity of neutropenia is categorised as:

- **Mild**: neutrophils 1.0 - 1.5 \times 10^9/L
- **Moderate**: neutrophils 0.5 – 1.0 \times 10^9/L
- **Severe**: neutrophils <0.5 \times 10^9/L
Causes of Neutropenia

- Transient
- Persistent
Transient Neutropenia

- Viral infections - neutropenia usually only lasts ≤ 2 weeks and there are seldom any clinical problems.

- Occasionally, the neutropenia may persist for months.
Persistent Neutropenia

- Benign ethnic neutropenia.
  - Neutrophil counts down to 1 x 10^9/L are a relatively common finding in individuals of African-Caribbean or Middle Eastern descent.

- Viral infections
  - EBV, HIV, hepatitis viruses

- Autoimmune disorders
  - SLE, Rheumatoid Arthritis

- Drugs
  - A long list!

- Splenomegaly (including due to liver disease)

- Haematological diseases
  - Myelodysplasia, leukaemia, lymphoma, myeloma, B12/folate deficiency etc.)
Evaluation of a patient with neutropenia

พฤษศาสตร์:
- อาการของ reccurent infection?
- ประวัติ reccurent infections
- ประวัติยา
- ประวัติครอบครัว reccurent infections
- ข้อมูล previous FBCs to establish the chronicity of the neutropenia
- ข้อมูล risk factors for HIV, TB

การตรวจ: รับผิด:
- อาการ reccurent infections ผิวหนัง, ผิวหนังรังแค, abscesses, lung infections, perianal/genital area
- Splenomegaly
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- Splenomegaly
Neutropenia
When should I seek further advice or refer to haematology?

First check:
- How severe is the neutropenia?
- Are there any other abnormalities of the blood count?
- Does the patient have any symptoms relating to the neutropenia?
- How long has the neutropenia persisted for?

Consider referral if:
- Persistent neutropenia <1.3 x 10^9/L over 6-8 weeks in Caucasian patients with no obvious cause as outlined above
- Neutropenia associated with severe and/or recurrent infection
- Neutropenia associated with other full blood count abnormalities
- Neutropenia associated with splenomegaly (NOT due to liver disease – fulfils 2 week wait criteria)
- Suspected underlying haematological disease: i.e. clinical symptoms or on blood film