Anticoagulation
Prescribing options & considerations
Reversal agents

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Oxford University Hospitals NHS Foundation Trust
Safety nets
whether national rail or anticoagulation

• Queue to vote in local elections at 7am
• Roadworks
• New carpark payment
  – APCO rather than RingGo
• ‘Technical problems’ on second train
## Safety analysis of pooled DOAC data vs VKA in VTE treatment

<table>
<thead>
<tr>
<th></th>
<th>Pooled DOAC (n/N)</th>
<th>Pooled VKA (n/N)</th>
<th>Risk ratio (95% CI)</th>
<th>P value</th>
<th>ARR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intracranial bleeding</strong></td>
<td>15/13477 (0.1%)</td>
<td>43/13481 (0.3%)</td>
<td>0.37 (0.21-0.68)</td>
<td>0.001</td>
<td>-0.17% (-0.30% to -0.03%)</td>
</tr>
<tr>
<td><strong>Fatal bleeding</strong></td>
<td>7/13477 (0.1%)</td>
<td>22/13481 (0.2%)</td>
<td>0.35 (0.15-0.84)</td>
<td>0.02</td>
<td>-0.08% (-0.16% to -0.01%)</td>
</tr>
<tr>
<td><strong>Major GI bleeding</strong></td>
<td>63/13477 (0.5%)</td>
<td>76/13481 (0.6%)</td>
<td>0.78 (0.47-1.31)</td>
<td>0.35</td>
<td>-0.12% (-0.37% to 0.13%)</td>
</tr>
<tr>
<td><strong>CRNM bleeding</strong></td>
<td>854/13477 (6.3%)</td>
<td>1103/13481 (8.0%)</td>
<td>0.73 (0.58-0.93)</td>
<td>0.01</td>
<td>-1.88% (-3.24% to -0.52%)</td>
</tr>
</tbody>
</table>

ARR: absolute risk reduction; CRNM: clinically relevant nonmajor; GI: gastrointestinal; NOAC: non-VKA oral anticoagulant; RR: relative risk; VKA: vitamin K antagonist.

There are no head-to-head studies between these agents. There are limitations such as differing patient populations, designs and outcomes, and caution should therefore be exercised when interpreting these findings. No conclusions about the relative efficacy or safety of any of these agents should be drawn from these data. Please refer to individual product SmPCs for further information.

*Adapted from Van Es et al. 2014.*
<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>DOACs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Dosing</td>
<td>Variable, once a day</td>
<td>Fixed, od or bd</td>
</tr>
<tr>
<td>Monitoring required</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Drug interaction</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Food interaction</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Reversibility</td>
<td>Yes – vit K and PCC</td>
<td>Dabigatran – Idarizizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AntiXas – no direct antidote in UK</td>
</tr>
<tr>
<td>Range of effect</td>
<td>Yes, ie target 2.5 v 3.5</td>
<td>No</td>
</tr>
<tr>
<td>Dossette box</td>
<td>Occasionally</td>
<td>Yes, except dabigatran</td>
</tr>
</tbody>
</table>
# Pharmacology/dosing of the DOACs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode of Action</strong></td>
<td>Factor II</td>
<td>Factor X</td>
<td>Factor X</td>
<td>Factor X</td>
</tr>
<tr>
<td><strong>Time to peak</strong></td>
<td>2 hours</td>
<td>2-4 hours</td>
<td>1-3 hours</td>
<td>1-2 hours</td>
</tr>
<tr>
<td><strong>T 1/2</strong></td>
<td>12-14 hrs</td>
<td>7-11 hrs</td>
<td>12 hrs</td>
<td>10-14 hours</td>
</tr>
<tr>
<td><strong>Dosing (AF)</strong></td>
<td>BD</td>
<td>OD</td>
<td>BD</td>
<td>OD</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Esterase catalysed hydrolysis</td>
<td>CYP3A4 dependent and independent mechanisms</td>
<td>CYP 3A4</td>
<td>Esterase catalysed hydrolysis CYP3A4/5 &lt;10%</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>85% Renal</td>
<td>33% Renal</td>
<td>27% Renal</td>
<td>50% renal</td>
</tr>
<tr>
<td><strong>Dose (AF)</strong></td>
<td>150mg</td>
<td>20mg</td>
<td>5mg</td>
<td>60mg</td>
</tr>
<tr>
<td></td>
<td>110mg (&gt;80yrs, verapamil or increased bleed risk)</td>
<td>15mg (CrCL 30-49ml/min)</td>
<td>2.5 (2 or more: &gt;80yr, weight &lt;60kg, Cr &gt;133um/l) or CrCl15-39</td>
<td>30mg (CrCl 15-50ml/min, weight &lt;60kg, or erythromycin/cyclosporin/ketaconazole/drondarone)</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Metal valves</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Antidote</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
GP survey (n=76)

- 43% not confident to **assess** anticoagulation control on warfarin
- 67% not confident in **knowledge** of DOACs
- 53% not confident to **prescribe** the DOACs

Price …Shapiro, 2018, BJHaem 181; S1
Community pharmacist survey

• 38% not confident in **knowledge** of DOACs

• 43% not confident to **counsel** about DOACs

• 30% not confident to **undertake NMS or MUS**
  
  (NMS= New Medicines Service & MUS= Medicines Use Review)
Safer prescribing of Direct Oral Anticoagulants (DOACs)

Background
Anticoagulants remain a key patient safety issue across the Trust.
From April 2017 - March 2018, there were 258 anticoagulation-related safety incidents reported. Twenty-four of these incidents were associated with patient harm: 22 minor harm, 3 moderate harm and 1 major harm. Many of these incidents were associated with the Direct Oral Anticoagulants (DOACs).

Aim
To determine the knowledge and confidence of hospital doctors in prescribing DOACs and to ascertain how best to target educational support.

Method
A survey was emailed to all the prescribers in the Trust in March 2018.
108 doctors completed the survey. 57% of respondents were Consultants.
The pie graphs below show the proportion of responses by clinical grade and clinical speciality.

Results
Only 44% of respondents felt confident in their knowledge of DOACs.
Only 52% of respondents felt confident to prescribe DOACs.
FYs and CTs were overall more confident than Consultants.
Doctors in surgical specialities and anaesthetics were less confident than those in medical specialities.

How do you access support?
Of survey respondents:
- 62% rely on the expertise of other members of the clinical team
- 57% use Medicine Information Leaflets (MILs)
- 42% blood haematology
- 12% refer to non-OOH specific guidelines
FYs were more likely to access MILs or senior support and consultants were more likely to book or email haematology

How would you like help?
Of survey respondents:
- 58% would like further teaching in the form of an e-learning module or workbook
- 30% would like small group teaching.

What steps have we taken?
Many resources (including those requested additionally in the survey) are already available:
1. E-learning module - titled 'VTE prevention and safe anticoagulation for doctors and pharmacists' - introduced in 2017 and is now part of statutory and mandatory training.
2. Medicine Information Leaflets (MILs) - these are available on the Intranet.
3. Inpatient Anticoagulation Nurse Specialist and Anticoagulation Specialist Pharmacists - these team members are available on bleep 5035 and bleep 4511 respectively.

Additional plan:
4. Safety alert - we plan to feedback the survey results via a 'safety alert' on the Trust website. This alert will highlight the available resources already available and provide contacts for additional support.
5. Small group teaching - we are offering teaching during mandatory teaching programmes (e.g. Foundation, Core) and in Departmental Meetings.

Moving forward...
We plan to continue to monitor anticoagulation incidents and will consider repeating this survey in a year's time.
Practical DOACS

• Before starting
  – Indication – VTE, non-valvular AF
  – FBC, renal and LFTs, coag screen
  – Interacting medications: antiretrovirals, anti-TB, anti-epileptics

• Switching from warfarin
  – INR <2.5

• Annual check renal fn and anticoag review
DOAC pharmacokinetics v LMWH

Tinzaparin

Apixaban

4 hrs  24 hrs

4 hrs  24 hrs
The increased risk of stroke and intracranial bleeding outside a narrow therapeutic range with warfarin
Poor INR control increases stroke risk

37,907 AF patients – UK General Practice Research

% TTR

> 70
61–70
51–60
41–50
31–40
< 30

% of patients without stroke

Months

Gallagher Thromb Haemost 2011;106:968–77
NICE CG180 and QS93

• Identify patients poorly controlled on warfarin
• Over 6 month period
  – TTR <65%
  – INR >8 x1
  – INR >5 x2
  – INR <1.5 x2

• Reassess anticoag taking into account different factors eg drug interactions, compliance
How to choose which anticoagulant (shared decision)

Photo by Nathan Dumlao on Unsplash
Choice of anticoagulant (1)

• Indication
  – use as licensed
  – i.e. DOACs are an option for VTE and NVAF, but not AF with significant mitral stenosis or for patients with metal heart valves

• Guidelines
  – NICE Guidelines NVAF: If anticoagulation is appropriate, offer either warfarin or a DOAC
Choice of anticoagulant (2)

• Renal failure
  – Warfarin is preferred in those with CrCl <30ml/min

  – For most eGFR ≈ CrCl but for those at extremes of age and weight calculate CrCl
  – Apixaban, edoxaban and rivaroxaban are licensed for use with a CrCl 15-29ml/min
    BUT very limited data so use with extreme caution
  – Apixaban is the least renally cleared

  – If CrCl ≤ 60ml/min, re-check renal function at an interval of ‘CrCl/10 monthly’
  – E.g. CrCl = 40ml/min, every 4 months
Choice of anticoagulant (3)

• Previous ICH
  – DOACs have lower risk of ICH compared with warfarin

• Extracranial bleeding
  – Warfarin and dabigatran are more readily reversible
  – Major GI bleeding increased on Dabigatran (150mg dose) rivaroxaban and edoxaban
  – Increased menorrhagia reported in some women on rivaroxaban*

*Observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years – see Rivaroxaban SPC
Choice of anticoagulant (4)

- Prosthetic valves/higher range
  - No evidence for DOACs

- Poor compliance
  - Offset more rapid, no regular monitoring

- Frequent, intermittent, variable use of other drugs
  - DOACs less problematic

- Weight > 120kg
  - Consider warfarin in preference to DOACs

- Good control (TTR>65%) - patient choice
Choice of anticoagulant (5)

• Best evidence
  – Warfarin for VTE associated with triple positive APS
TRAPS
Randomized controlled trial of Rivaroxaban vs Warfarin in APS

High-risk APS patients
- LA positive
- aCL positive
- aB2GPI positive

Rivaroxaban
N=59

Warfarin
N=61

1,5 years

Events on Rivaroxaban: 19%

Events on Warfarin: 3%

Stopped early for excess of events on Rivaroxaban

Vittorio Pengo et al. Blood 2018;132:1365-1371
Safety incidents
COUNSELLING

A national patient safety alert was issued in 2017 highlighting the importance of counselling patients on anticoagulation.
INTERACTIONS WITH DOACS

Incident
76yr old male, 77kg, Cr 76 (eGFR 86)
PMH - AF and epilepsy
DHx – carbamazepine, apixaban 2.5mg bd
PC: ischaemic stroke

Problems:
1. Carbamazpeine + apixaban
2. Apixaban 2.5mg incorrect dose
→ patient is on approx. ¼ correct dose…….
STABLE ARTERIAL VASCULAR DISEASE

- COMPASS trial, Lancet, Anand et al 2018
- Multicentre double-blind randomised placebo controlled trial, 7470 patients
- Patients had history of PVD, carotid arterial disease, CAD
- Aspirin 100mg v Rivaroxaban 2.5mg bd plus aspirin 100mg v rivaroxaban 5mg bd
- Median duration 21 months
- Primary outcome: cardiovascular death, MI, stroke, major adverse limb events (including amputation)
## Stable Arterial Vascular Disease – COMPASS Trial 2018

<table>
<thead>
<tr>
<th></th>
<th>Aspirin 100mg</th>
<th>Aspirin 100mg and rivaroxaban 2.5mg bd</th>
<th>Rivaroxaban 5mg bd</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular death, MI, stroke</strong></td>
<td>7%</td>
<td>5%</td>
<td>6% HR 0.86 (0.69-1.08)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR 0.72 (CI 0.57-0.90)</td>
<td></td>
</tr>
<tr>
<td><strong>Major limb events including amputation</strong></td>
<td>2%</td>
<td>1%</td>
<td>2% HR 0.67 (0.45-1.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR 0.54 (CI 0.35-0.82)</td>
<td></td>
</tr>
<tr>
<td><strong>Major bleeding</strong></td>
<td>2%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>NB mainly GI, fatal bleeding not increased</td>
<td></td>
<td>HR 1.61 (1.12-2.31)</td>
<td>HR 1.68 (1.17-2.40)</td>
</tr>
</tbody>
</table>

*Hazard ratios compared to aspirin 100mg od*
Reversal

Elective
Emergency
## Pre-op management of DOACs

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Renal function (GFR/min)</th>
<th>Low bleeding risk</th>
<th>High bleeding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>≥80</td>
<td>24 hrs</td>
<td>48 hrs</td>
</tr>
<tr>
<td></td>
<td>≥50–&lt;80</td>
<td>24-48 hrs</td>
<td>48-72 hrs</td>
</tr>
<tr>
<td></td>
<td>≥30–&lt;50</td>
<td>48-72 hrs</td>
<td>96 hrs</td>
</tr>
<tr>
<td>Apixaban, edoxaban and rivaroxaban</td>
<td>≥30</td>
<td>24 hrs</td>
<td>48 hrs</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td>48 hrs</td>
<td>72 hrs</td>
</tr>
</tbody>
</table>
Bleeding and Reversal
## Risk of thrombosis in absence of anticoagulation

<table>
<thead>
<tr>
<th></th>
<th>Annualised Thrombosis risk%</th>
<th>Daily %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lone AF</td>
<td>1</td>
<td>0.003</td>
</tr>
<tr>
<td>Average risk AF</td>
<td>5</td>
<td>0.014</td>
</tr>
<tr>
<td>High risk AF</td>
<td>12</td>
<td>0.033</td>
</tr>
<tr>
<td>AVR (St Jude)</td>
<td>11</td>
<td>0.03</td>
</tr>
<tr>
<td>AVR (B-Shiley)</td>
<td>23</td>
<td>0.06</td>
</tr>
<tr>
<td>MVR (St Jude)</td>
<td>22</td>
<td>0.06</td>
</tr>
<tr>
<td>Multiple VR</td>
<td>91</td>
<td>0.25</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>4</td>
<td>0.01</td>
</tr>
<tr>
<td>VTE in last month</td>
<td>-</td>
<td>1.6</td>
</tr>
</tbody>
</table>

ACCP 2004
Managing bleeding on DOAC

• Bleeding no more frequent than with warfarin
• Half life is relatively short (10-15 hours)

• FBC, PT, APTT, fibr, +/- DOAC level + renal fn

• Resuscitate
• Apply direct measures
• IV tranexamic acid
• Reversal agents:
  – Specific antidote available for dabigatran
  – PCC or APCC for apixaban, rivaroxaban, edoxaban (specific antidote not yet available in UK)
Idarucizumab

- High affinity monoclonal antibody to dabigatran
- 1x5g dose
- Idarucizumab-dabigatran complexes are renally cleared
- No known increased thrombosis risk
- Licensed and NICE approved
Andexanet a specific antidote to Xa inhibitors

- A truncated inactive recombinant FXa expressed in CHO cells that avidly binds Xa inhibitors.
- Lacks the GLA domain and is catalytically inactive because of a mutation (S419A) in the catalytic triad.

ANNEXA-A phase III results (part 1): andexanet bolus dose

- Near complete normalization of all coagulation parameters within 2 minutes of infusion completion
- These effects lasted 1–2 hours with the bolus dose tested
- No SAEs, premature treatment discontinuations, thrombotic events or antibodies to factor X/Xa

Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Mark Crowther, M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., John H. Lawrence, M.D., Patrick Yue, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Andrew M. Demchuk, M.D., Daniel J. Pallin, M.D., Mauricio Concha, M.D., Shelly Goodman, B.S.N., R.N., Janet Leeds, Ph.D., Sonia Souza, Ph.D., Deborah M. Siegal, M.D, Elena Zotova, Ph.D., Brandi Meeks, M.Sc., Sadia Ahmad, M.B., B.S., Juliet Nakamya, Ph.D., Truman J. Milling, Jr., M.D., for the ANNEXA-4 Investigators

N Engl J Med
Volume 380(14):1326-1335
April 4, 2019
Study Overview

• In a single-group trial, 352 patients with acute major bleeding while taking a factor Xa inhibitor were treated with andexanet.

• Andexanet markedly reduced anti–factor Xa activity, and 82% of the patients had excellent or good hemostatic efficacy at 12 hours.
Conclusions

• In patients with acute major bleeding associated with the use of a factor Xa inhibitor, treatment with andexanet markedly reduced anti–factor Xa activity, and 82% of patients had excellent or good hemostatic efficacy at 12 hours
Case

• Call from Haematology Consultant at DGH
  – 15 yr old girl
  – Overdose of thirty-fifty 150mg dabigatran tablets 4 hours previously
    – Minor gum bleeding only, haemodynamically stable
    – PTR 9.1, APTTR 4.8
    – Repeat: PTR 8.7, APPR 5.1, fibrinogen 2.6g/L, TT 53s
    – Normal FBC, renal and liver function (Cr 46umol/L)
    – Previous normal coag screen

• What do you think? What is your advice?
# DOACs and coag tests

Effect of DOACs is dependent on reagent

<table>
<thead>
<tr>
<th></th>
<th>PT</th>
<th>APTT</th>
<th>TT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td>Minimal prolongation in usual treatment range</td>
<td>Prolonged APTT suggests dabigatran level within or above usual treatment range</td>
<td>Normal TT = little or no dabigatran present</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>Often prolonged but normal PT does not exclude therapeutic anticoagulation</td>
<td>Not useful</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>Not useful</td>
<td>Not useful</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
<td>Often prolonged but normal PT does not exclude therapeutic anticoagulation</td>
<td>Not useful</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Initial advice

- 10mg/kg tranexamic acid IV
- 10mg vitamin K IV
- Send coag tube to tertiary centre
- Prothrombin complex concentrate (PCC) was to be used ONLY if the patient developed significant bleeding
- Request idarucizumab on site
Idarucizumab

Dabigatran level (ng/ml)

Time post-dabigatran ingestion (h)

Shapiro et al. BJHaem 2016
# Usual DOAC levels

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Usual trough (ng/ml)</th>
<th>Usual peak (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban 5 mg bd</td>
<td>103 (41-230)</td>
<td>171 (91-321)</td>
</tr>
<tr>
<td>Dabigatran 150 mg bd</td>
<td>90 (31-225)</td>
<td>184 (64-443)</td>
</tr>
<tr>
<td>Edoxaban 60 mg od</td>
<td>36 (19-62)</td>
<td>-</td>
</tr>
<tr>
<td>Rivaroxaban 20mg od</td>
<td>22 (4-96)</td>
<td>223 (160-360)</td>
</tr>
</tbody>
</table>

These ranges are for guidance only and vary considerably between patients and between studies. Trough and peak anticoagulant levels presented as 90% confidence intervals except for edoxaban which is presented as median (interquartile range).
Summary
Choice of anticoagulant and reversal

• Basics of anticoagulants
• Highlight safety issues
• Factors in choosing
• Reversal

• Effective but high risk medicines
• Safety - education and safety nets
Thank you

susie.shapiro@ouh.nhs.uk