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DOACs: Practicalities & Cases from Clinic

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Overview

Use case studies to illustrate a variety of practical issues and how to address them

- Choosing an anticoagulant
- Switching anticoagulants
- Getting the dose right
- Managing interactions (drug & non-drug)
- Reviewing antiplatelet therapy
- Use of plasma drug levels

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Warm up

1. Mrs RD, 81yo, AF, HF, smoker, HTN, COPD, Cr 140, Wt 85kg, CrCl = 30-37ml/min; Rx apixaban
   a) 5mg BD or
   b) 2.5mg BD

2. Mr GF, 73yo, PE, CKD, minimal other PMHx, Cr 190, Wt 65kg, CrCl=28ml/min; Rx rivaroxaban

   15mg BD 21/7 then:
   a) 20mg OD or
   b) 15mg OD

Warm up

3. Miss AD, 76yo, PAF, HTN, T2DM, Cr 97, Wt 66kg, CrCl=48ml/min, on amiodarone, Rx dabigatran:
   a) 150mg BD or
   b) 110mg BD or
   c) 75mg BD

4. Mr JB, 68yo, DVT 1992 and 2001, lifelong warfarin, Cr 83, Wt 93kg, CrCl=85-99ml/min, switch to apixaban
   a) 5mg BD or
   b) 2.5mg BD

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Dosing in NVAF

	Dabigatran[1]	Apixaban[2]	Edoxaban[3]	Rivaroxaban[4]
Standard dose	150mg BD	5mg BD	60mg OD	20mg OD
Reduced dose	110mg BD	2.5mg BD	30mg OD	15mg OD
Criteria for dose reduction	1. Age≥80 2. On verapamil 3. Consider ↓dose: •Reflux/gastritis •Age75-80 •CrCl 30-50ml/min •"Bleed risk"	**≥2 of:** Age ≥80 Body wt ≤60kg Cr ≥133µmol/L **Or** CrCl 15-29ml/min	CrCl 15-50ml/min ---- Body wt≤60kg ---- Specific p-gp inhibitors	CrCl 15-49ml/min
CI (renal)	CrCl <30ml/min	---------- CrCl <15ml/min ----------		

1. Dabigatran SmPC. Available at www.medicines.org.uk;
2. Apixaban SmPC. Available at www.medicines.org.uk;
3. Edoxaban SmPC. Available at www.medicines.org.uk;
4. Rivaroxaban SmPC. Available at www.medicines.org.uk.

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Dosing in VTE

	Dabigatran[1]	Apixaban[2]	Edoxaban[3]	Rivaroxaban[4]
Acute	LMWH ≥ 5/7	10mg BD 7/7	LMWH ≥ 5/7	15mg BD 21/7
Standard dose	150mg BD	5mg BD	60mg OD	20mg OD
Reduced dose	110mg BD	2.5mg BD	30mg OD	15mg OD
Criteria for dose reduction	1. Age≥80 2. On verapamil 3. Consider ↓dose: •Reflux/gastritis •Age75-80 •CrCl 30-50ml/min •"Bleed risk"	Prevention of recurrent VTE following completion of 6 months of treatment for VTE	CrCl 15-50ml/min ---- Body wt≤60kg ---- Specific p-gp inhibitors	"Bleed risk"
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Dosing in VTE

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Criteria for dose reduction	1. Age≥80 2. On verapamil 3. Consider ↓dose: •Reflux/gastritis •Age75-80 •CrCl 30-50ml/min •"Bleed risk"	**Prevention of recurrent VTE following completion of 6 months of treatment for VTE**	CrCl 15-50ml/min ---- Body wt≤60kg ---- Specific p-gp inhibitors	**"Bleed risk"**
CI (renal)	CrCl <30ml/min	---------- CrCl <15ml/min ----------		

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Risk of underdosing

- Danish registry – reduced dose DOAC vs standard VKA[1]
- SSE
  - NS increase with apixaban
  - NS decrease with rivaroxaban/dabigatran
- Unable to confirm off/on-label dose reduction
- Significant selection bias, even after adjusting for confounding
  - E.g. overall mean age=73: lowest mean age = warfarin (71), highest mean age = apixaban (83)

1. Nielson PB, Skjøth F, Søgaard M et al. BMJ 2017;256:j510

Risk of underdosing

- ORBIT II AF registry (US) – 1 in 8 patients on wrong dose[1]
  - Overdose = ↑risk of death (HR 1.91 95%CI 1.02 to 3.60),
  - Underdose (9.4% of all pts) = ↑ risk of CV hospitalisation (HR 1.26 95%CI 1.07 to 1.50)

1. Yao X et al. J Am Coll Cardiol 2017;69(23):2779-2790

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Cases from the anticoagulation clinic

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Case 1 – The overmanaged old

- Mrs EE – 93yo
- Warfarin for stroke prevention – NVAF
- BG: T2DM, stroke, hyperthyroidism
- DH:
  - AM: metformin, carbimazole
  - PM: citalopram, warfarin

- CHA_2DS_2-VASc = ….

  a) 4 **b) 5** **c) 6**

- HAS-BLED = ….

  a) 1 **b) 2** **c) 3**

Case 1 – The overmanaged old

- Making warfarin work
- Wheelchair bound – requires DNs
- Unstable INRs – over last 6 months:
  - 3 failed samples (poor veins)
  - Six INRs >3 (four >5), nine INRs <2
  - Admission for INR >10 (Sept 2015)
  - retest every 7-14 days
  - **TTR = 37%**
- Daughter refills dosette box weekly to include warfarin

Time in Therapeutic Range (TTR)

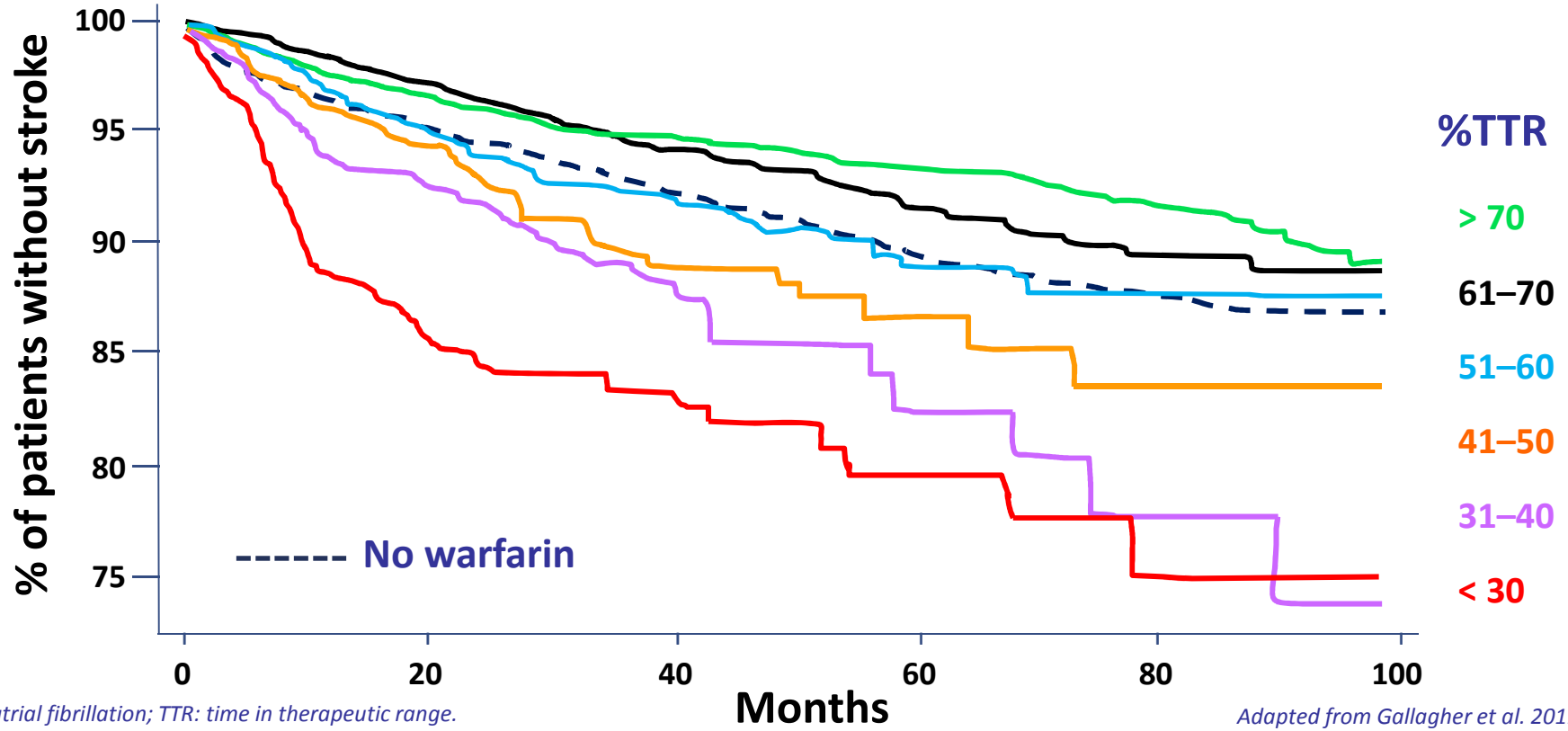
Q: What is a good TTR, who should be switched?

- Reduction in major bleeding significantly higher for DOACs vs VKA when TTR<66% (vs TTR>66%)
- Efficacy benefits heterogeneous: unable to compare
- Not identified TTR where warfarin > DOAC (efficacy or safety)

Ruff C et al. *Lancet 2014;383:955-62*

TTR Correlates with Stroke

Stroke survival in 37,907 AF patients – UK General Practice Research Database (27,458 warfarin users and 10,449 not treated with an antithrombotic)[1]



AF: atrial fibrillation; TTR: time in therapeutic range.

Adapted from Gallagher et al. 2011[1].

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1. Gallagher et al. *Thromb Haemost* 2011;106:968–977.

Case 1 – The overmanaged old

- Cr 71, CrCl = 47.3ml/min
- 68.5kg

- Apixaban 5mg twice daily

1. Which drug?
2. Does it matter?
3. How to decide?

AF – Efficacy & Safety: 4-Trial Meta-analysis

Measure	Pooled DOAC Events /Total	Pooled Warfarin Events /Total	Risk Ratio	95% CIs	p	Outcome
Efficacy						
Ischaemic Stroke	665 /29292	724 /29221	0.92	0.83-1.02	0.10	
Hemorrhagic stroke	130 /29292	263 /29221	0.49	0.38-0.64	<0.0001	
Myocardial Infarction	413 /29292	432 /29221	0.97	0.78-1.20	0.97	
All-cause mortality	2022 /29292	2245 /29221	0.90	0.851-0.95	0.0003	
Safety						
Intracranial hemorrhage	204 /29287	425 /29211	0.48	0.39-0.59	<0.0001	
Gastrointestinal bleeding	751 /29287	591 /29211	1.25	1.01-1.55	0.043	

0.25 Favours DOAC 1 2

Ruff C, et al. Lancet 2014;383:955-62

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Estimating Renal Function

- Use Cockcroft – Gault equation as per pivotal studies
  - Avoid MDRD
- What weight?
  - No consensus or evidence!
  - Actual weight used in trials
  - Extremes of weight poorly represented
  - Avoid IBW –risk of underdose
  - Consider adjusted body weight in extreme of weight

http://www.lambethccg.nhs.uk/news-and-publications/meeting-papers/south-east-london-area-prescribing-committee/Documents/Cardiovascular%20Disease%20Guidelines/Creatinine%20clearance%20guidance%20July%202017.pdf

https://www.sps.nhs.uk/articles/what-factors-need-to-be-considered-when-dosing-patients-with-renal-impairment-2/

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Any other factors to help decide?

Choosing the oral anticoagulant drug to fit the patient profile	
Recurrent stroke, systemic embolic event, or transient ischaemic attack despite good anticoagulation control (TTR >70%)	Dabigatran 150 mg BID
Moderate-to-severe renal impairment (CrCl 15–49 mL/min)	Apixaban 5 mg BID*, rivaroxaban 15 mg once daily, dabigatran (if CrCl 30–49 mL/min)†, or edoxaban 30 mg once daily‡
High risk of gastrointestinal bleeding	Apixaban 5 mg BID* or dabigatran 110 mg BID§
Gastrointestinal symptoms or dyspepsia	Apixaban 5 mg BID*, rivaroxaban 20 mg once daily¶, or edoxaban 60 mg once daily‖
High risk of bleeding (HAS-BLED ≥3)	Dabigatran 110 mg BID§, apixaban 5 mg BID*, or edoxaban 60 mg once daily‖
Once daily dosing or preference to have a lower pill burden	VKA, rivaroxaban 20 mg once daily¶, or edoxaban 60 mg once daily‖
Asian patients (consider drugs with reduced risk of intracranial haemorrhage and major bleeding in Asian subgroups)	Apixaban 5 mg BID*, dabigatran†, or edoxaban 60 mg once daily‖
Less likely to do well on VKA with good TTR (SAMe-TT_2R_2 score >2)	VKA with additional education and more regular follow-up, dabigatran†, rivaroxaban 20 mg once daily¶, apixaban 5 mg BID*, or edoxaban 60 mg once daily‖

Freedman, Potpara, Lip. Lancet 2016;388:806-817

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Reviews & Prescribing Decision Aids

- Freedman B, Potpara TS, Lip GY. Lancet 2016;388:806-817
- Savelieva I, Camm AJ. Clin Cardiol 2014;37(1):32-47
- Shields AM, Lip GY. J Internal Medicine 2015;278(1):1-18
- Millar CM, Laffan MA. Clinical Medicine 2017;17(3):233-244

Switching – complicated?

- SPC:

When converting patients from vitamin K antagonist (VKA) therapy to Eliquis, warfarin or other VKA therapy should be discontinued and Eliquis started when the international normalised ratio (INR) is < 2

- Stop & check every 24/48hrs until INR < 2?

- In practice
  - Maintenance patients
  - INR ↓ 1.0 for every 24 hours omitted
  - Simple instruction
  - e.g. INR 2.4: stop warfarin, leave 1 day & commence DOAC

Case 1 – The overmanaged old

- Tolerated well
- No venepuncture (& thus no DNs) required
- Dosette from pharmacy; alleviate daughter's commitment to weekly refill

- Reduce burden on health service
- Reduce burden on daughter
- Improve quality of life for pt (↓venepuncture)

Case 2 – Pharmacokinetics! [1]

29yo male

- PMH: isolated calf DVT, and 2 episodes SVT since 2011

PE – Given rivaroxaban 15mg bd 21/7 then 20mg od.

- Negative comprehensive malignancy screen.
- FVL heterozygote on thrombophilia screen.

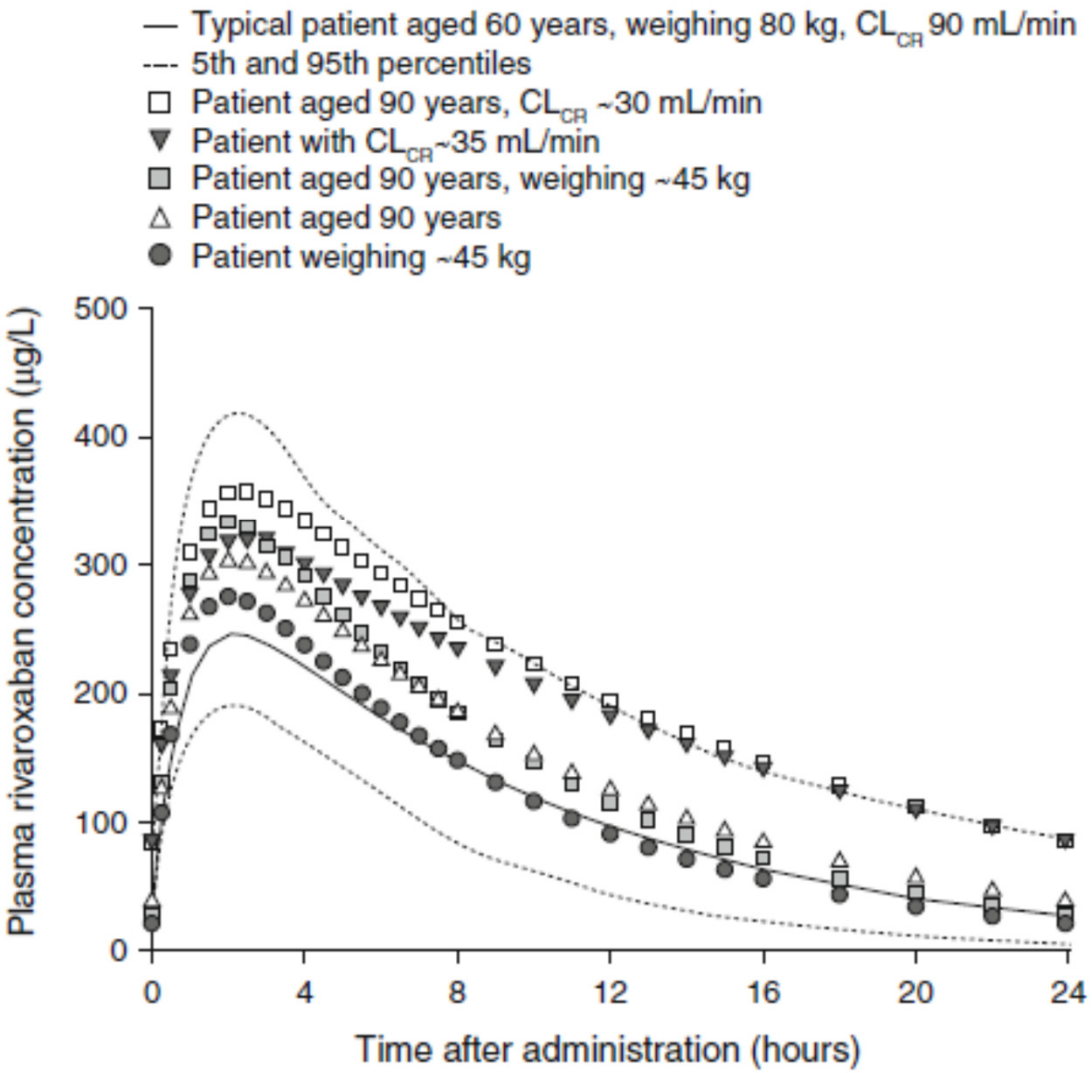
5 months later…

- A&E – acute dyspnoea, palpitations
- d-dimer raised, CTPA – new PE.
- Anti-Xa assay on admission approx. 5 hrs post dose, low 40mg/L.

What went wrong?

1. Modified case, original presented by Prof J Beyer-Westendorf ISTH Berlin 2017

Rivaroxaban PK



Mueck et al. *Clin Pharmacokinet* 2014;53:1-16

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Case 2 – Pharmacokinetics!

- Acute Management
  - Split dose LMWH
  - 79kg, CrCl = 115ml/min
  - Dalteparin 7,500units BD

- Thrombosis Clinic 3 weeks later
  - Switch back to rivaroxaban 20mg od
  - Commence rivaroxaban when next LMWH dose due
  - Further investigation…

Case 2 – Pharmacokinetics!

Thrombosis OPD: Supervised dosing & serial anti-Xa plasma rivaroxaban levels

	Baseline (trough)	2hrs post dose	6hrs post dose
Rivaroxaban plasma level by anti-Xa	<25mg/L	115mg/L	39mg/L
PK from VTE studies[1]	25.6mg/L (5.93-86.9)	259mg/L (180-405)	191mg/L (123-311)

- **Now what's wrong?**

On discussion: eating habits irregular (shift work) – didn't know to take with food

	2 hrs post dose
Rivaroxaban plasma level with full breakfast	318mg/L
Rivaroxaban plasma level with dinner	418mg/L

1 Mueck et al. Thromb J 2013;11:10

Case 3 – Drug-Drug Interactions

75 yo male Asian-Pakistani

- Jan 2017: GP - new PAF on 24hr Holter (16hr AF)
- Seen 24/1/17 in anticoag clinic

PMH:

- ESRD 1989 - yellow fever
- Previous tuberculosis peritonitis
- Living related renal transplant 1989 (failed 2000)
- Bronchiectasis
- IHD: MI 2000, 2001: 3xCABG
- 2004 2nd cadaveric renal transplant
- OA
- Hiatus hernia & gastritis
- Hyperlipidaemia

DHx:

- Aspirin 75mg od
- Neoral (ciclosporin) 50mg BD
- mycophenolate 500mg BD
- bisoprolol 5mg OD
- atorvastatin 10mg OD
- ranitidine 150mg BD
- Ferrous sulphate 200mg BD
- colecalciferol 800units od
- co-codamol prn

nil herbal nil supplements
NKDA

Case 3 – Drug-Drug Interactions

Weight 96.4kg Cr 89 (18/1/17) CrCl = 70.3ml/min

CHA_2DS_2-VASc = 4 HAS-BLED = 2 (on aspirin!)

Plan:

1. Stop Aspirin
2. Start apixaban 5mg bd (24/1/17)
3. Check CNI & apixaban levels (both trough)

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Aspirin for SPAF

- 20% RRR (vs placebo) in stroke[1]
- AVERROES: Apixaban = 55% RRR versus aspirin[2]
  - 50% increase MB (NS)
  - Identical fatal bleeds, ICH
- Negative net clinical benefit[3]
- NICE CG 180 (2014): not recommended
- ESC AF Guideline (2016): DO NOT USE – risk of harm

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1. Hart et al. *Ann Intern Med* 2007;146:857-867
2. Connolly SJ et al. NEJM 2011;364:806-817
3. Fauchier et al. Stroke 2016;47(7):1831-6

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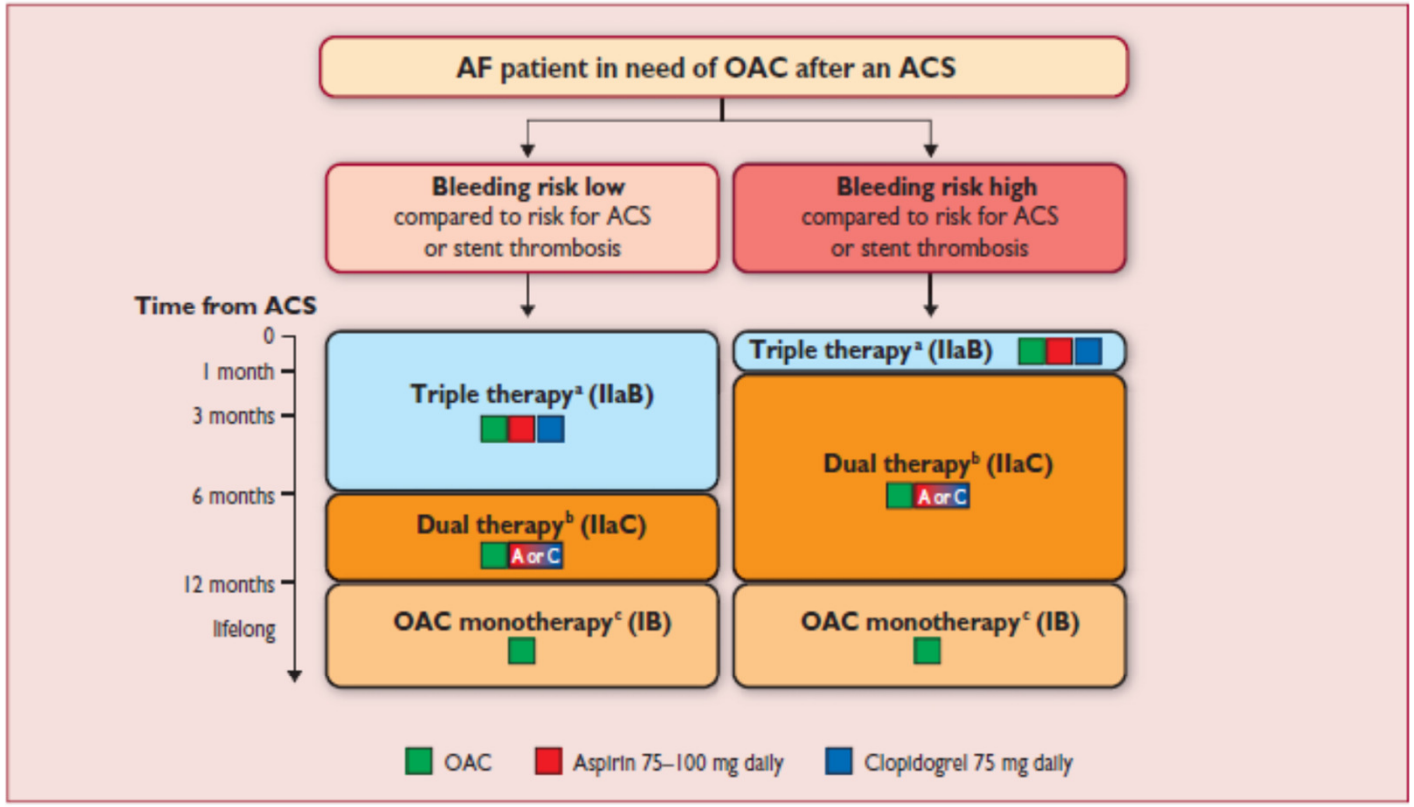
Aspirin for CVD in AF

- Stable arterial disease
- No acute events <12 months
- = OAC monotherapy

- But what if ACS/PCI etc within the last 12 months…

Aspirin for CVD in AF



ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.

[a]Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients, especially those not receiving a stent or patients at a longer time from the index event.

[b]OAC plus single antiplatelet.

[c]Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events.

Figure 12 Antithrombotic therapy after an acute coronary syndrome in atrial fibrillation patients requiring anticoagulation.

Kirchhof et al. Eur Heart J 2016;37:2893-2962

Is there an interaction?

- Ciclosporin:
  - Strong inhibitor p-gp , Moderate inhibitor CYP3A
  - Dependant on both pathways for metabolism/excretion
- DOACs
  - Not inhibitor/inducer but competition for shared pathways
- PK studies:
  - Not all DOACs quantified. Tested or predicted >50% ↑ AUC
  - 20% ↑ AUC of CNI[1]
  - "Narrow window" drugs

1 Vanhove T et al. *Ter Drug Monit* 2017;13(9):77-82

Case 3 – Drug-Drug Interactions

Pre-DOAC Ciclosporin A levels (mcg/L):

- 11/2016: **61**
- 12/2016: **66**
- 01/2017: **72**

Follow up 3/2/17:

- Taken apixaban at 8:30am and 8:30pm
- Reports no missed doses
- Anti-Xa trough level 67.5mg/L (reference 23-109mg/L)
- Ciclosporin A level 65mcg/L (target 50-75mcg/L)

Case 3 – Drug-Drug Interactions

Follow up 8/8/17

- Well, no bleeding, no medication changes
- Ciclosporin July = 65mcg/L; no ciclosporin dose change
- No need to recheck anti-Xa-linked apixaban levels

Alternative strategy?

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Immunosuppressive					
Cyclosporin; Tacrolimus	P-gp competition	Not recommended	No data yet	+73%	Extent of increase unknown

- Edoxaban 30mg once daily – PK of edoxaban + ciclosporin already investigated with dosing recommendation[1]

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1. Parasrampuria DA et al. Br J Clin Pharmacol. 2016;82(6):1591-1600

I thought we weren't testing?

- Role of DOAC plasma level testing = controversial
  - Probable role where PK-related changes anticipated
  - Not linked to clinical outcomes (thrombosis/bleed or coag)
- Aims
  - Exploratory
  - Has the intervention 'worked'
- Outcomes
  - Dose adjust?
  - Alternative treatment

I thought we weren't testing?

- Possible scenarios
  - **A**: GI disease/surgery, malabsorption syndromes
  - **D**: Extremes of weight
  - **M**: Drug-drug interactions (select few)
  - **E**: Severe renal impairment

- Then what?

Case 4 - Obesity

- 62yo male, PAF, HTN, T2DM
- switched from warfarin to rivaroxaban 20mg once daily

DH:

- Atorvastatin
- Metoprolol
- Metformin
- Candesartan
- Omeprazole
- Amlodipine
- Humulin I
- Beconase nasal

Assessments:

- CHA_2DS_2-VASc = 2
- HAS-BLED = 0
- **Wt 143kg** Ht 180cm
- Cr 100
- CrCl(adj)=98ml/min
- Hb:146 ALT:26

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Can we use a DOAC?

ISTH[1]

- Avoid DOACs if BMI >40 or Wt >120kg
  - Available evidence suggests peaks may be reduced & clearance may be increased; risk of underdosing
- If using DOACs in above, check drug-specific plasma peak & trough
  - by anti-Xa (a/r/e) or dTT (d), or mass spec (any).
  - If out of range, change to VKA rather than dose adjust

1. Martin K, Beyer-Westendorf J, Davidson BL et al. J Thromb Haemost 2016;14:1308-1313

Why Rivaroxaban?

- Review paper[1] of
  - Subanalysis of pivotal studies (AF, VTE, pVTE)
  - PK studies

- Suggests no dose adjustment necessary in obesity, including >120kg

1. Moore KT and Kröll D. Am J Med 2017;130(9):1024-1032

Case 4 - Obesity

- Taking rivaroxaban 20mg in the morning with breakfast
- Trough anti-Xa linked plasma level
  - 1 month after starting
  - 25 hours post dose
- Result = 120mg/L
- Reference ranges:
  - Trough 19-60mg/L
  - Peak 175-360mg/L

- What should we do? What did we do?

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FAQs – But what about…

- EFT / poor swallow
- Counselling re: “no antidote”
- Missed doses
- Impact of food/drink
- Addition to MCAs
- Pregnancy/breastfeeding

Case 5…..

Don't climb a ladder drunk when you're anticoagulated

Fatal consequences of climbing a ladder under apixaban and drunken.

Stöllberger C[1], Finsterer J[2].

Author information

Abstract

BACKGROUND: Apixaban, a factor-Xa-inhibitor, is one of the non-vitamin-K-antagonist oral anticoagulants (NOACs) which are increasingly used in atrial fibrillation (AF). In real life even patients with contraindications to vitamin K antagonists (VKAs) receive NOAC because NOAC are considered as "safer" than VKAs.

CASE DESCRIPTION: In a 61-years-old man with hypertension, heart failure and paroxysmal AF apixaban was started. Despite advices from his physicians, he continued alcohol abuse and suffered from recurrent falls. After 9 months he fell from a ladder and suffered from extensive subarachnoidal and intraparenchymal hemorrhages, subdural hematoma, brain edema with midline shift and a left-sided skull fracture. Because of the inability to reverse the anticoagulant therapy, no neurosurgical intervention was carried out and the patient died without regaining consciousness.

CONCLUSIONS: Patients with recurrent falls or chronic alcohol abuse should not be considered as candidates for NOACs. If anticoagulation is deemed necessary, VKA with its potential for prompt reversibility should be favored.

Stöllberger C, Finsterer J. Neurol Neurochir Pol 2016;50(3):200-202

Thank you for listening

London SCN AF Toolkit

http://www.londonscn.nhs.uk/wp-content/uploads/2017/06/detect-protect-perfect-london-af-toolkit-062017.pdf

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