EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

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EUROPEAN Heart Rhythm ASSOCIATION
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EUROPEAN SOCIETY OF CARDIOLOGY®

EHRA Practical Guide on the use of new oral anticoagulants (NOAC) in patients with non-valvular atrial fibrillation

- This slide set is based on the following full text paper:

  European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvularatrial fibrillation.
  H. Heidbuchel; P. Verhamme; M. Alings; M. Antz; W. Hacke; J. Oldgren; P. Sinnaeve; A.J. Camm; P. Kirchhof.

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  http://www.ncbi.nlm.nih.gov/pubmed/23625942

- An executive summary was published in:

  European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Executive Summary.
  H. Heidbuchel; P. Verhamme; M. Alings; M. Antz; W. Hacke; J. Oldgren; P. Sinnaeve; A.J. Camm; P. Kirchhof.

  European Heart Journal 34: 2094-106 (2013)

  Published by Oxford University Press, April 26, 2013

  http://www.ncbi.nlm.nih.gov/pubmed/23625209

- Updated information, downloadable anticoagulation cards, and possibility for feedback are available via : www.NOACforAF.eu

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The EHRA writing committee collaborated with medical experts from the different companies to assure data accuracy and completeness.

Advantages of new oral anticoagulants (NOACs) over vitamin K antagonists (VKAs) for thromboembolic prevention in patients with non-valvular AF

- predictable effect without need for monitoring
- fewer food and drug interactions
- more predictable half-life/elimination
- improved efficacy/safety ratio

Need for a practical guide

- 2010 ESC Guidelines (and the 2012 Update) do not detail the NOAC in specific clinical situations.[1,2]
- Multiple physician tools supplied with each drug may be confusing.
- EHRA has now produced a practical guide to supplement AF guidelines.

1. Camm et al, Europace 2010;12:1360-420

2. Camm et al, Eur Heart J 2012; 33:2719-47

NOACs approved or under evaluation for prevention of systemic embolism or stroke in patients with non-valvular AF

	Dabigatran	Apixaban	Edoxaban *	Rivaroxaban
Action	Direct thrombin inhibitor	Activated factor Xa (FXa) inhibitor	Activated factor Xa (FXa) inhibitor	Activated factor Xa (FXa) inhibitor
Dose	150 mg BID 110 mg BID	5 mg BID 2.5 mg BID	60 mg QD 30 mg QD 15 mg QD	20 mg QD 15 mg QD
Phase III clinical trial	RE-LY [1]	ARISTOTLE [2] AVERROES [3]	ENGAGE-AF [4]	ROCKET-AF [5]

* not yet approved by EMA

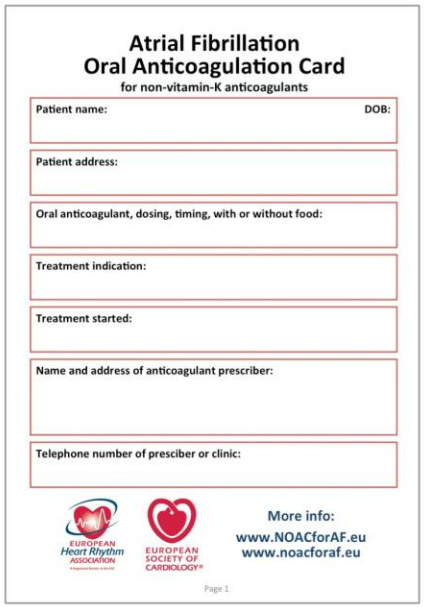
1. Connolly et al, N Engl J Med 2009; 361:1139-51
2. Granger et al, N Engl J Med 2011; 365:981-92
3. Connolly et al, N Engl J Med 2011; 364:806-17
4. Ruff et al, Am Heart J 2010; 160:635-41
5. Patel et al, N Engl J Med 2011;365:883-91

1. Practical start-up and follow-up scheme for patients on NOACs

- Risk/benefit analysis: is a NOAC indicated?
- When choosing a NOAC, consider co-medications taken by patient.
- Consider co-medications such as PPI to reduce risk for gastro-intestinal bleeding.
- Carry information card: generic card could serve for all NOACs.
- Need to educate patient on importance of strict adherence to regimen – discontinuation is dangerous.

EHRA proposal for a universal NOAC anticoagulation card

Card can be downloaded in a printer-ready form or in a ppt format that can be configured to the local language from www.NOACforAF.eu



Atrial Fibrillation
Oral Anticoagulation Card
for non-vitamin-K anticoagulants

Patient name: DOB:

Patient address:

Oral anticoagulant, dosing, timing, with or without food:

Treatment indication:

Treatment started:

Name and address of anticoagulant prescriber:

Telephone number of presciber or clinic:

More info:
www.NOACforAF.eu
www.noacforaf.eu

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Planned or unplanned visits

Date (or date range):	Site (GP; clinic; cardiologist; ...):	To do / findings:

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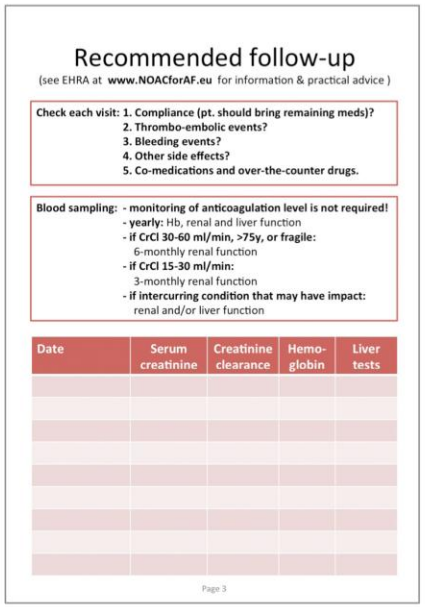

Recommended follow-up
(see EHRA at **www.NOACforAF.eu** for information & practical advice)

Check each visit: 1. Compliance (pt. should bring remaining meds)?
2. Thrombo-embolic events?
3. Bleeding events?
4. Other side effects?
5. Co-medications and over-the-counter drugs.

Blood sampling: - **monitoring of anticoagulation level is not required!**
- **yearly:** Hb, renal and liver function
- **if CrCl 30-60 ml/min, >75y, or fragile:** 6-monthly renal function
- **if CrCl 15-30 ml/min:** 3-monthly renal function
- **if intercurring condition that may have impact:** renal and/or liver function

Date	Serum creatinine	Creatinine clearance	Hemo-globin	Liver tests

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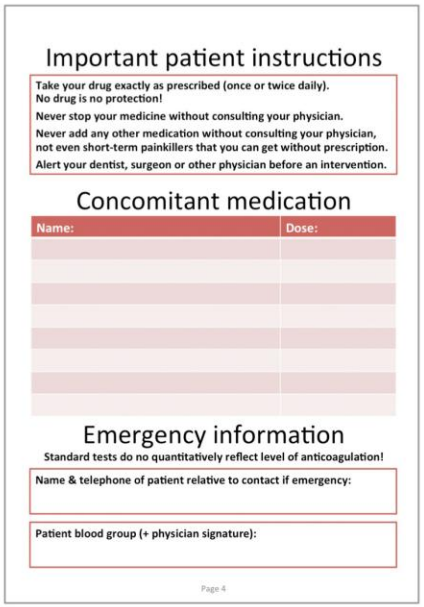

Important patient instructions

Take your drug exactly as prescribed (once or twice daily).
No drug is no protection!
Never stop your medicine without consulting your physician.
Never add any other medication without consulting your physician, not even short-term painkillers that you can get without prescription.
Alert your dentist, surgeon or other physician before an intervention.

Concomitant medication

Name:	Dose:

Emergency information
Standard tests do no quantitatively reflect level of anticoagulation!

Name & telephone of patient relative to contact if emergency:

Patient blood group (+ physician signature):

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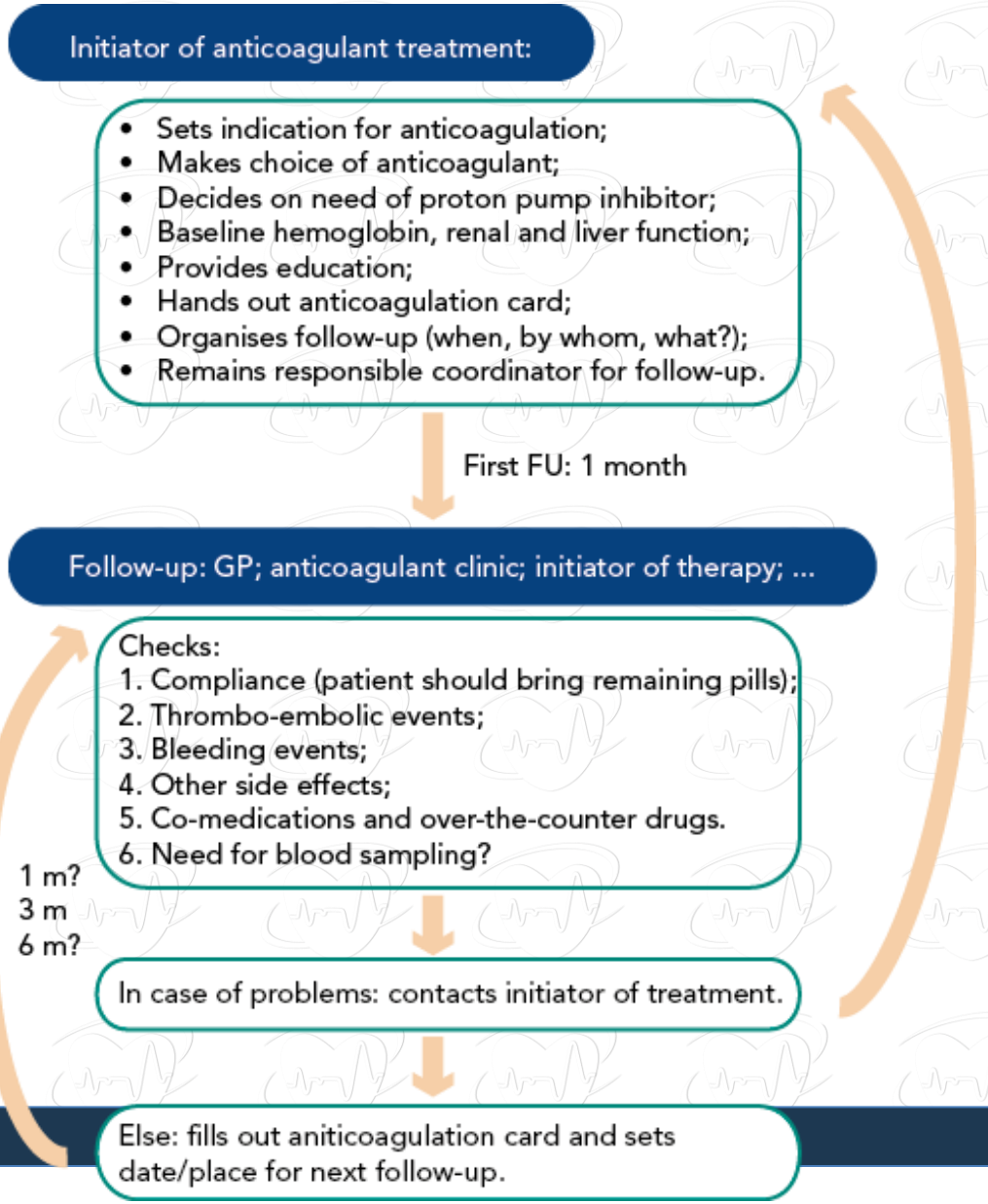
Need for structured follow-up

- All NOACs are anticoagulants and hence can cause serious bleeding.
- All NOACs have some drug-drug interactions (DDIs).
- AF population is a fragile patient population.
- Patients should return for ongoing review according to a predetermined schedule.
- Follow-up can be undertaken by specialist or GP with experience in the field and/or appropriate secondary care physicians.
- Nurse co-ordinated AF clinics may be used. [1]

1. Berti et al, Eur Heart J, 2013 (Epub ahead of print)

Suggested structured follow-up



Checklist during follow-up of AF patients on NOACs

	Interval	Comments
Compliance	Each visit	Inspect remaining medication Stress importance of compliance Inform about compliance aids
Thrombo-embolism	Each visit	Cerebral, systemic and pulmonary circulation
Bleeding	Each visit	"Nuisance" bleeding – prevention possible? Bleeding with risk or impact on QoL – prevention possible? Need to revise dose?
Side effects	Each visit	Continuation? Temporary cessation with bridging? Change of anticoagulant drug?
Co-medications	Each visit	Prescription or over-the counter drugs? Even temporary use can be risky
Blood sampling	Yearly 6-monthly 3-monthly on indication	Haemoglobin, renal, liver function Renal function if CrCl 30-60 ml/min or if on dabigatran and aged >75 years or fragile If CrCl 15-30 ml/min If intercurring condition may impact renal or hepatic function.

Follow-up: considerations

- Renal function: impaired renal function increases plasma levels and hence anticoagulant effect of all NOACs, especially dabigatran. Dose reduction may be indicated.
- Minor bleeding: most is temporary and classified as ‘nuisance’. Discontinuation or dose reduction should not be considered unless frequent and impacting on patient’s QoL.

2. How to measure the anticoagulant effect of NOACs

Routine monitoring of coagulation not required, but quantitative assessment of drug exposure may be needed in emergency situations:

- serious bleeding and thrombotic events
- urgent surgery
- renal or hepatic insufficiency
- potential DDI
- suspected overdosing

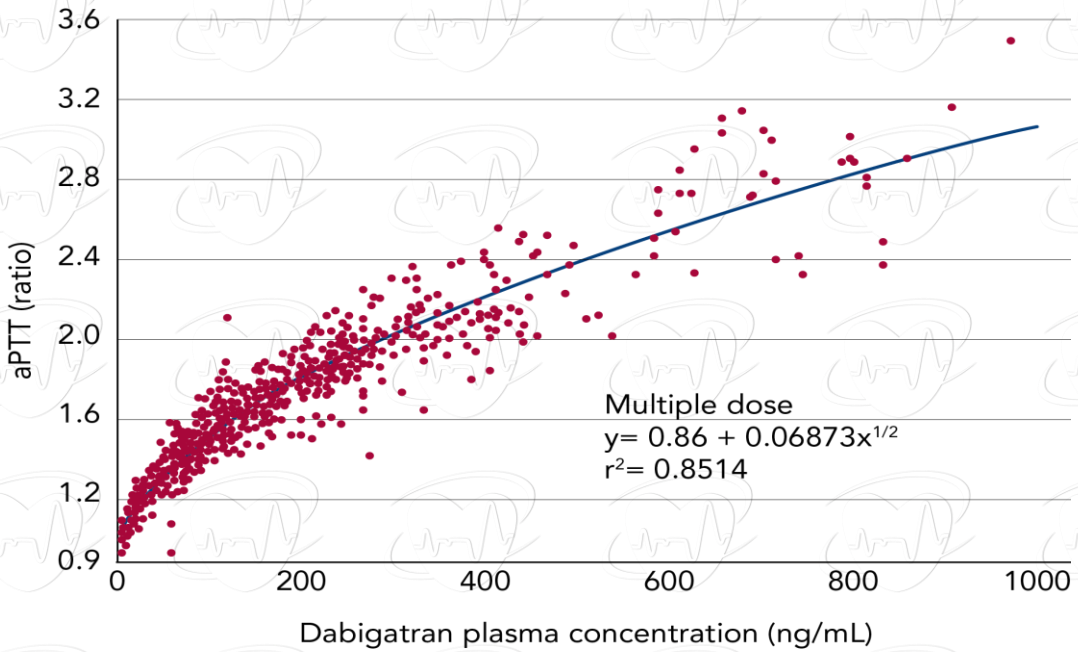
Measuring the anticoagulant effect of NOACs

- Important to know exactly when NOAC was administered relative to time of blood sampling. Maximum effect at maximum plasma concentration (~3h after administration).
- Activated thromboplastin time (aPTT): qualitative assessment of dabigatran, but sensitivity varies.
- Diluted thrombin time (DTT): Hemoclot® suitable for quantitative assessment of dabigatran but no data on cut off below which surgery is safe.
- Anti-FXa chromogenic assays: commercially available for quantitative assessment, but no data to associate level with bleeding or thrombo-embolism risk.

Measuring the anticoagulant effect of NOACs

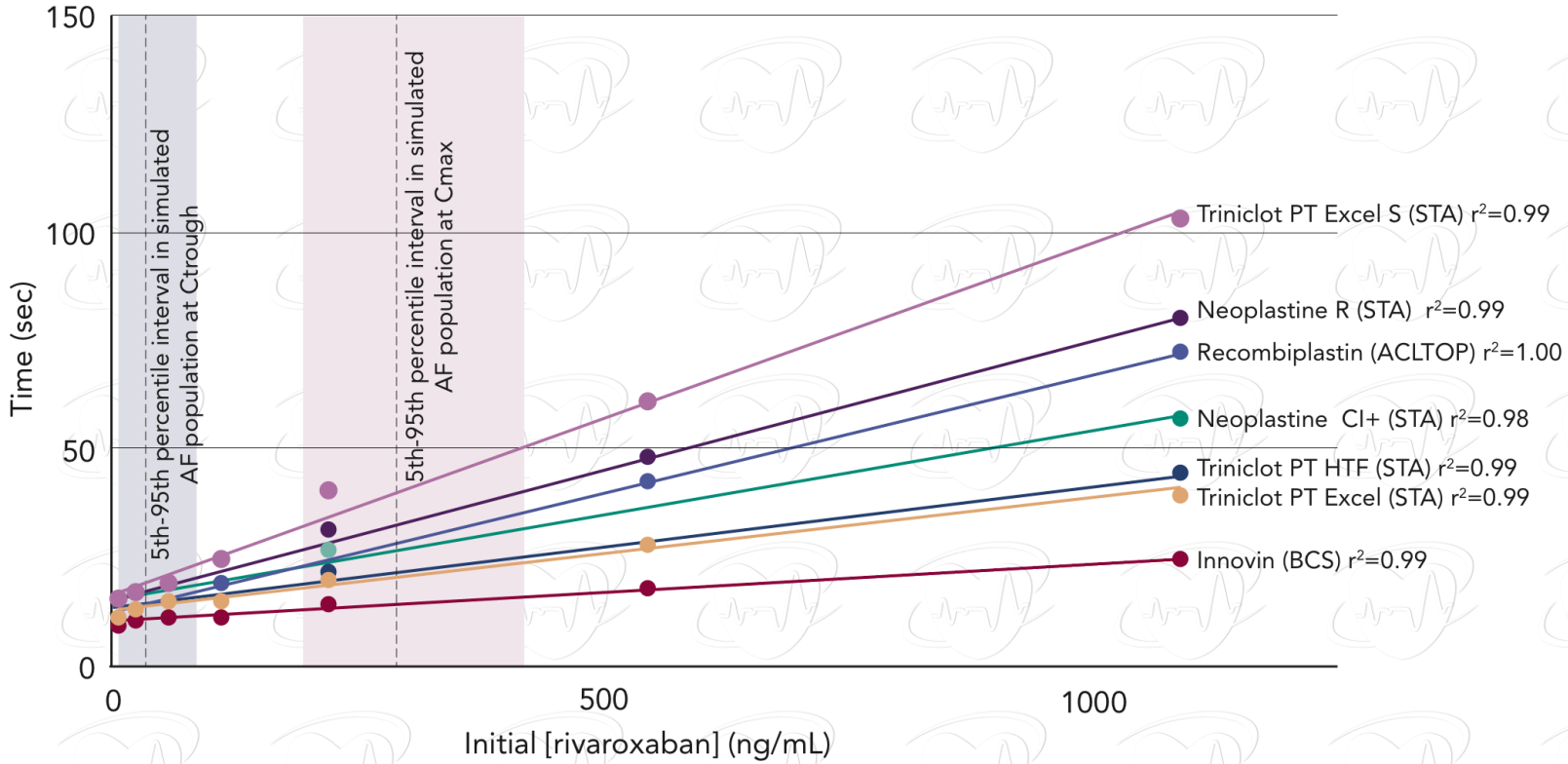
	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Plasma peak	2h after ingestion	1-4h post ingestion	1-2h after ingestion	2-4h after ingestion
Plasma trough	12-24h after ingestion	12-24h after ingestion	12-24h after ingestion	16-24h after ingestion
PT	cannot be used	cannot be used	prolonged but no known relation with bleeding risk	prolonged: may indicate excess bleeding risk but local calibration required
INR	cannot be used	cannot be used	cannot be used	cannot be used
aPTT	at trough >2x ULN suggests excess bleeding risk	cannot be used	prolonged but no known relation with bleeding risk	cannot be used
dTT	At trough >200ng/ml ≥ 65s: excess bleeding risk	cannot be used	cannot be used	cannot be used
Anti-FXa assays	n/a	no data yet	quantitative; no data on threshold values for bleeding or thrombosis	quantitative; no data on threshold values for bleeding or thrombosis
Ecarin clotting time	at trough >2x ULN: excess bleeding risk	not affected; cannot be used	not affected; cannot be used	not affected; cannot be used

Curvilinear relationship between aPTT and dabigatran plasma levels



Van Ryn et al Thrombosis and haemostats 2010;103:1126-7

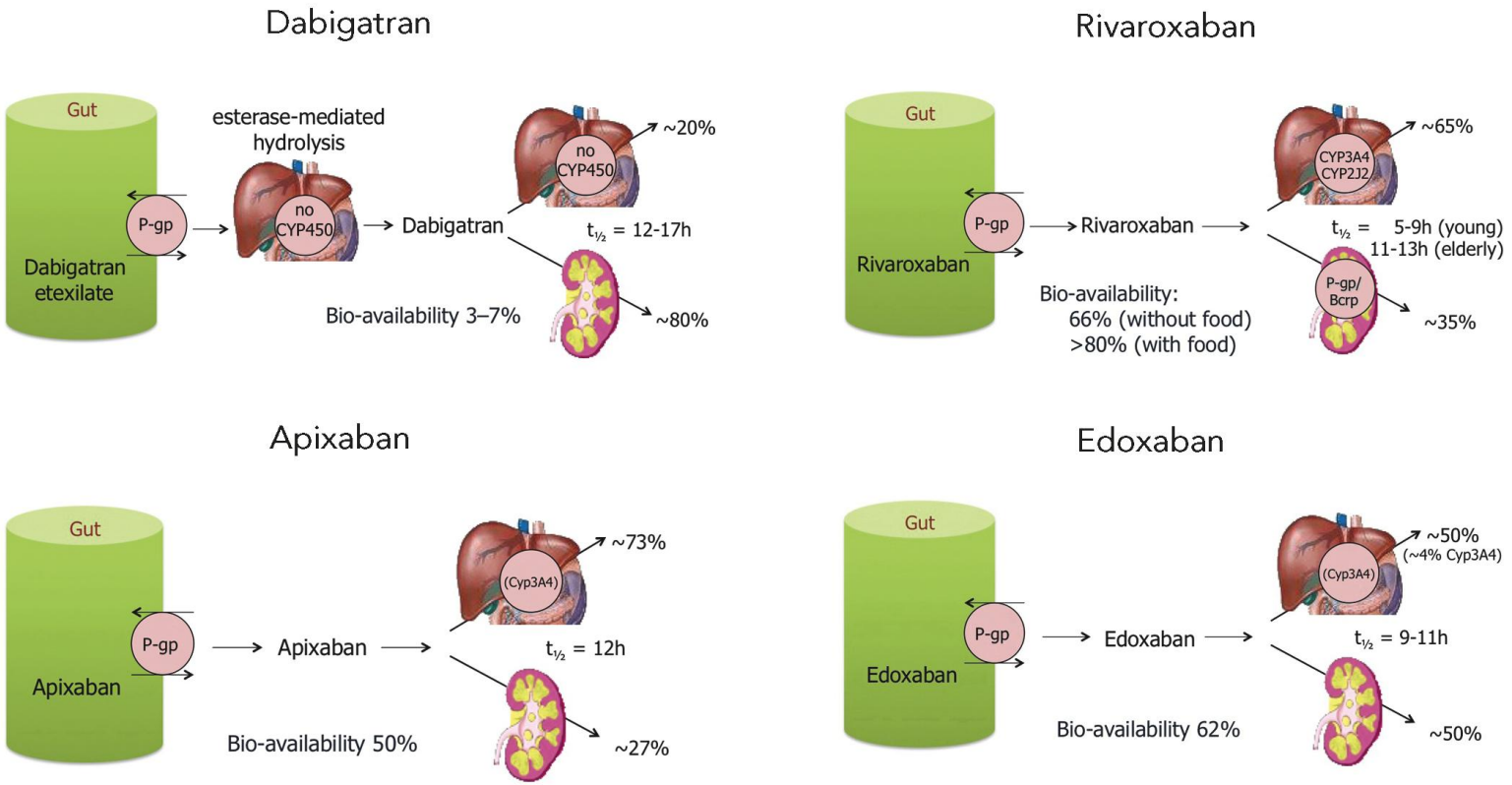
Relation between PT and FXa inhibitor (rivaroxaban) plasma levels



Douxfils et al Thromb Res. 2012;130:956-66

3. Drug-drug interactions and pharmacokinetics of NOACs

Absorption and metabolism of NOACs



Absorption and metabolism of NOAC

	Dabigatran	Apixaban	Edoxaban *	Rivaroxaban
Bioavailability	3-7%	50%	62%	66% (w/o food) ~100% with food
Prodrug	yes	no	no	no
Clearance: non-renal/renal of adsorbed dose if normal renal function	20%/80%	73%/27%	50%/50%	65%/35%
Liver metabolism: CYP3A4	no	yes (elimination; minor CYP3A4)	minimal (<4% of elimination)	yes (elimination)
Absorption with food	no effect	no effect	6-22% more	+39%
Intake with food?	no	no	no official recommendation yet	mandatory
Absorption with H2B/PPI	plasma level -12 to -30%	no effect	no effect	no effect
Asian ethnicity	plasma level +25%	no effect	no effect	no effect
GI tolerability	dyspepsia 5-10%	no problem	no problem	no problem
Elimination half-life	12-17h	12h	9-11h	5-9h (young)/11-13h (elderly)

* not approved yet

Mechanisms underlying DDIs in NOACs

- P-glycoprotein transporter involved in absorption and renal clearance – plasma levels may be affected by P-gp inducers or inhibitors[1]
- Cytochrome P450 CYP3A4 involved in hepatic clearance of rivaroxaban and apixaban – plasma levels may be affected by CYP3A4 inducers of inhibitors[2]

1. Gnoth et al, J Pharmacol Exp Ther 2011;338:372-80
2. Mueck et al, Br J Clin Pharmacol 2013

Action to be taken in case of DDIs

Three levels of alert:

- Red – contraindicated/not recommended for use
- Orange – adapt NOAC dose
  - dabigatran: 150 mg to 110 mg BID
  - rivaroxaban: 20 mg to 15 mg QD
  - apixaban: 5 mg to 2.5 mg BID
- Yellow – consider dose reduction if two concomitant yellow interactions
- Where no data available, NOACs not recommended yet

Possible drug-drug interactions – Effect on NOAC plasma levels part 1

		Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Atorvastatin	P-gp/ CYP3A4	+18%		no effect	no effect
Digoxin	P-gp	no effect		no effect	no effect
Verapamil	P-gp/ wk CYP3A4	+12–180%		+ 53% (slow release)	
Diltiazem	P-gp/ wk CYP3A4	no effect	+40%		
Quinidine	P-gp	+50%		+80%	+50%
Amiodarone	P-gp	+12–60%		no effect	
Dronedarone	P-gp/CYP3A4	+70–100%			
Ketoconazole; itraconazole; voriconazole; posaconazole;	P-gp and BCRP/ CYP3A4	+140–150%	+100%		up to +160%

Red – contraindicated; orange – reduce dose; yellow – consider dose reduction if another yellow factor present; hatching – no data available; recommendation made from pharmacokinetic considerations

Possible drug-drug interactions – Effect on NOAC plasma levels part 2

	Interaction	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fluconazole	CYP3A4	no data	no data	no data	+42%
Cyclosporin; tacrolimus	P-gp	no data	no data	no data	+50%
Clarithromycin; erythromycin	P-gp/ CYP3A4	+15–20%	no data	no data	+30–54%
HIV protease inhibitors	P-gp and BCRP/ CYP3A4	no data	strong increase	no data	up to +153%
Rifampicin; St John's wort; carbamezepine; phenytoin; phenobarbital	P-gp and BCRP/ CYP3A4/CYP2J2	-66%	-54%	-35%	up to -50%
Antacids	GI absorption	-12-30%	no data	no effect	no effect

Red – contraindicated; orange – reduce dose; yellow – consider dose reduction if another yellow factor present; hatching – no data available; recommendation made from pharmacokinetic considerations

Factors associated with raised plasma levels of NOACs part 3

		Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Aged ≥ 80 years	Increased plasma level			no data	
Aged ≥ 75 years	Increased plasma level			no data	
Weight ≤ 60 kg	Increased plasma level				
Renal function	Increased plasma level				

Other increased bleeding risk

Pharmacodynamic interactions – antiplatelet drugs, NSAIDs
Systemic steroid therapy
Other anticoagulants

Recent surgery on critical organ (brain, eye)

Thrombocytopenia (e.g. chemotherapy)

HAS-BLED ≥ 3

Orange – reduce dose; yellow – consider dose reduction if another yellow factor present;
hatching – no data available; recommendation made from pharmacokinetic considerations

4. Switching between anticoagulant regimens

VKA to NOAC	INR <2.0: immediate INR 2.0–2.5: immediate or next day INR >2.5: use INR and VKA half-life to estimate time to INR <2.5
Parenteral anticoagulant to NOAC: Intravenous unfractioned heparin (UFH) Low molecular weight heparin (LMWH)	Start once UFH discontinued (t½=2h). May be longer in patients with renal impairment Start when next dose would have been given
NOAC to VKA	Administer concomitantly until INR in appropriate range Measure INR just before next intake of NOAC Re-test 24h after last dose of NOAC Monitor INR in first month until stable values (2.0–3.0) achieved
NOAC to parenteral anticoagulant	Initiate when next dose of NOAC is due
NOAC to NOAC	Initiate when next dose is due except where higher plasma concentrations expected (e.g. renal impairment)
Aspirin or clodiprogel to NOAC	Switch immediately, unless combination therapy needed

5. Ensuring compliance with NOAC intake

Important – anticoagulant effect drops rapidly after 12-24 h

- QD better adherence than BID for cardiovascular drugs in general, but no data on superior dosing scheme for NOAC in clinical practice.
- Patient education crucial: leaflets and instruction at initiation, patient safety card, group sessions.
- Involve family members.

Ensuring compliance with NOAC intake

- Nurse-co-ordinated AF centres to focus on compliance?
- Technological aids – medication boxes, smartphone apps.
- INR monitoring not needed/not useful.
- Involve pharmacy?
- If low compliance despite these, consider VKAs.

6. How to deal with dosing errors

Missed dose:	BID: take missed dose up to 6 h after scheduled intake. If not possible skip dose and take next scheduled dose. QD: take missed dose up to 12 h after scheduled intake. If not possible skip dose and take next scheduled dose.
Double dose:	BID: skip next planned dose and restart BID after 24 h. QD: continue normal regimen.
Uncertainty about intake:	BID: continue normal regimen. QD: take another dose then continue normal regimen.
Overdose:	Hospitalization advised.

7. Patients with chronic kidney disease

Estimated t½ and AUC NOAC plasma concentrations compared to healthy controls

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
CrCl ≥ 60 ml/min CKD Stage I & II	~ 14 h [1]	no data	~ 8.6 h [2]	~ 8.5 h [3] (+44%)
CrCl 30–60 ml/min CKD Stage III	~ 18 h [1]	no data	~ 9.4 h [2]	~ 9 h [3] (+52%)
CrCl 15–30 ml/min CKD Stage IV	~ 28 h [1]	no data	~ 16.9 h [2]	~ 9.5 h [3] (+64%)
CrCl ≤ 15 ml/min CKD Stage V	no data	no data	no data	no data

1. Stangier et al, Clinical pharmacokinetics 2010;49:259-68
2. Ridout et al, J Clin Pharmacol 2009:49:1124
3. Kubitza et al, Br J Clin Pharmacol 2010:70:703-2

NOACs in renal dysfunction – Approved European labels

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
% of absorbed dose renally excreted	80%	27%	50%[1]	35%
Bio-availability	3-7%	50%	62%[2]	66% without food ~ 100% with food
% of administered dose renally excreted	4%	14%	37%	33%
Approved for CrCl	≥30 ml/min	≥15 ml/min	not available	≥15 ml/min
Label dosing recommendation	CrCl ≥15 ml/min, no adjustment (i.e. 150 mg BID)	Serum creatinine ≥1.5 ml/dl, no adjustment (i.e. 5 mg BID)		CrCl ≥ 50 ml/min, no adjustment (i.e. 20 mg QD)

1. Ogata et al J Clin Pharmacol 2010;50:743-53

2. Matsushima et al The AAPS Journal 2011;13:S2

NOACs in renal dysfunction – Practical recommendations for dosing in chronic kidney disease

Dabigatran	Apixaban	Edoxaban *	Rivaroxaban
When CrCl 30-49 ml/min, 150 mg BID is possible (SmPC) but 110 mg BID if 'high risk of bleeding' (SmPC) or 'recommended' (GL update)[1] Note: 75 mg BID approved in US only ** -if CrCl 15-30 ml/min - if CrCl 30-49 ml/min -and other orange factor (e.g. verapamil)	CrCl 15-29 ml/min: 2.5 mg BID is possible Serum creatinine ≥ 1.5 mg/dl in combination with age ≥80 years or weight ≤60 kg (SmPC) or with other yellow' factor: 2.5 mg BID	not available	15 mg OD when CrCl 15-49 ml/min

* No EMA approval yet. Needs update after finalisation of SmPC ** No EMA indication. FDA recommendation based on pharmacokinetics. Carefully consider benefits and risks of this approach Note that 75 mg capsules are not available in Europe for AF indication.

1. Camm et al, Eur Heart J 2012;33:2719-47

NOACs in chronic kidney disease – Clinical evidence

- CKD a risk factor for both thrombo-embolic events and bleeding[1,2]
- CrCl <60 ml/min may predict increased stroke and systemic embolism[3]
- In Phase III trials, similar AUCs for reduced doses in patients with decreased renal function as for higher dose in patients with normal renal function[4]
- Rivaroxaban approved for people with CKD stage IV, with lower dose regimen, but should be used with caution: no trial data available in patients with CrCl 15-30 ml/min
- Low dose dabigatran (75 mg BID) approved by FDA but not EMA for patients with severe renal insufficiency

1. Olesen et al, N Engl J Med 2012;367:625-35
2. Hohnloser et al, Eur Heart J 2012;33:2821-30
3. Piccini et al, Circulation 2013;127:169-71
4. Mueck et al Clin Pharmacol 2011;50:675-86

NOACs in chronic kidney disease – Practical suggestions

- CKD should be considered an additional risk factor for stroke in AF but CKD also increases bleeding risk
- NOACs are a reasonable choice for anticoagulant therapy in AF patients with mild or moderate CKD
- NOACs similar benefit/risk ratio to VKAs with rivaroxaban (15 mg QD) in renal impairment (CrCl <50 ml/min).[1]
  With apixaban, there may be a lower relative bleeding risk [2]

1. Fox et al, Eur Heart J 2011;32:2387-94

2. Hohnloser et al, Eur Heart J 2012;33:2821-30

NOACs in chronic kidney disease – Practical suggestions

- Dabigatran may not be first choice as primarily cleared renally but may be used in stable patients.
- FXa inhibitors have 25-50% renal clearance therefore may be preferred
- Consider dose reductions in patients with CrCl <50 ml/min: apixaban 2.5 mg BID,[1] rivaroxaban 15 mg/day[2]
- Avoid NOACs in AF patients on haemodialysis: consider VKAs

1. Fox et al, Eur Heart J 2011;32:2387-94

2. Connolly et al N Engl J Med 2011; 364:806-17

NOACs in chronic kidney disease – Practical suggestions

- Monitor renal function regularly and adapt the dose accordingly
- Monitor renal function at the following intervals:

yearly	stage I-II (CrCl ≥ 60 ml/min)
6-monthly	stage III, elderly (>75 yrs) or frail patients on dabigatran (CrCl 30–60 ml/min)
3-monthly	stage IV (CrCl ≤ 30 ml/min)

8. What to do if there is a (suspected) overdose without bleeding, or a clotting test is indicating a risk of bleeding

- Acute recent ingestion of overdose: activated charcoal to reduce absorption (standard dosing scheme for adults of 30 to 50 g).
- Consider coagulation tests to assess possible bleeding risk.
- In absence of bleeding, wait-and see approach.

9. Management of bleeding complications
Possible measures to take in case of bleeding part 1

Non life-threatening

Dabigatran	FXa inhibitors
Inquire last intake + dosing regimen	Inquire last intake + dosing regimen
Estimate normalization of haemostasis	Normalisation of haemostasis: ±24h
Normal renal function: ±24h	
CrCl 50-80 ml/min: 24-36h	
CrCl 30-50 ml/min: 36-48h	
CrCl <30 ml/min: ≥48h	
Maintain diuresis	
Local haemostatic measures	Local haemostatic measures
Fluid replacement (colloids if needed)	Fluid replacement (colloids if needed)

Possible measures to take in case of bleeding part 2

Non life-threatening

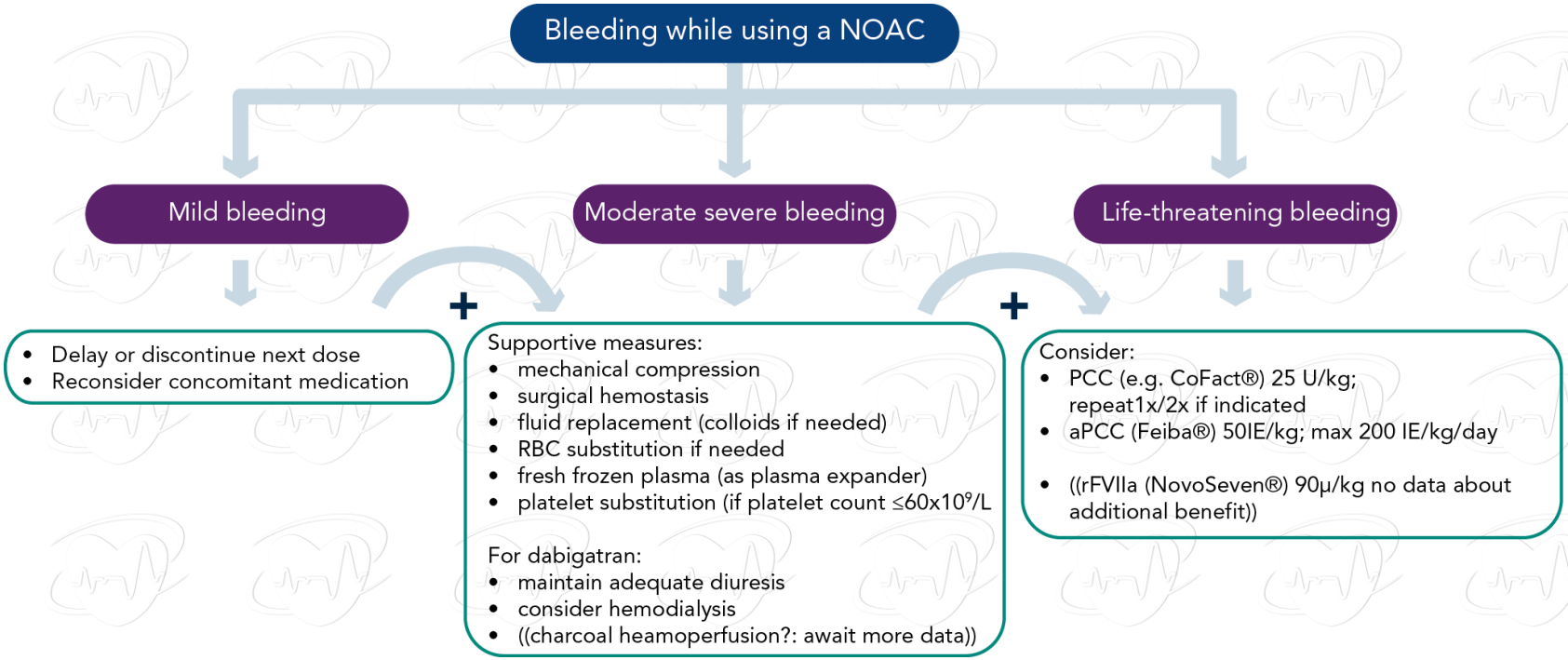
Dabigatran	FXa inhibitors
RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤ 60 x 10^9 /L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans Desmopressin can be considered in special cases (coagulopathy or thrombopathy) Consider dialysis (primary evidence: - 65% after 4h) Charcoal haemoperfusion not recommended (no data)	RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤ 60 x 10^9 /L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans Desmopressin can be considered in special cases (coagulopathy or thrombopathy)

Possible measures to take in case of bleeding part 3

Life-threatening

Dabigatran	FXa inhibitors
All of the above	All of the above
Prothrombin complex concentrate (PCC) 25 U/g (may be repeated once or twice but no clinical evidence)	Prothrombin complex concentrate 25 U/kg (may be repeated once or twice but no clinical evidence)
Activated PCC 50IE/kg; max 200 IE/day: no strong data about additional benefit over PCC. Can be considered before PCC if available	Activated PCC 50IE/kg; max 200 IE/day: no strong data about additional benefit over PCC. Can be considered before PCC if available
Activated factor VII (rFVIIa; 90μg/kg); no data about additional benefit + expensive (only animal evidence)	Activated factor VII (rFVIIa; 90μg/kg); no data about additional benefit + expensive (only animal evidence)

Possible measures to take in case of bleeding



Van Ryn et al Am J Med 2012;125:417

10. Patients undergoing a planned surgical intervention or ablation

Classification of surgical interventions according to bleeding risk

Interventions not necessarily requiring discontinuation of anticoagulant

Perform procedures at 'through' levels of NOAC. Consider scheduling intervention 18-24 h after last intake and then restart 6 h later (i.e. skipping 1 dose with BID NOAC)

- Dental interventions
  - Extraction of 1 to 3 teeth
  - Paradontal surgery
  - Incision of abscess
  - Implant positioning
- Ophthalmology
  - Cataract or glaucoma intervention
- Endoscopy without surgery
- Superficial surgery (e.g. abscess incision, small dermatological excision)

Classification of surgical interventions according to bleeding risk

Low risk

- Endoscopy with biopsy
- Prostate or bladder biopsy
- Electrophysiological study or radiofrequency catheter ablation for supraventricular tachycardia (including left sided ablation via single transseptal puncture)
- Angiography
- Pacemaker or ICD implantation (unless complex anatomical setting e.g. congenital heart disease)

High risk

- Complex left-sided ablation: pulmonary vein isolation, VT ablation
- Spinal or epidural anaesthesia; lumbar diagnostic puncture
- Thoracic surgery
- Abdominal surgery
- Major orthopedic surgery
- Liver biopsy
- Transurethral prostate resection
- Kidney biopsy

When to stop NOACs before a planned surgical intervention

Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban		Edoxaban *		Rivaroxaban	
	No important bleeding risk and/or local haemostasis possible: perform at trough level (i.e. ≥12h or 24h after last intake)							
	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24h	≥48h	≥24h	≥48h	no data yet	no data yet	≥24h	≥48h
CrCl 50–80 ml/min	≥36h	≥72h	≥24h	≥48h	no data yet	no data yet	≥24h	≥48h
CrCl 30–50 ml/min §	≥48h	≥96h	≥24h	≥48h	no data yet	no data yet	≥24h	≥48h
CrCl 15–30 ml/min §	not indicated	not indicated	≥36h	≥48h	no data yet	no data yet	≥36h	≥48h
CrCl <15 ml/min	no official indication for use							

*no EMA approval yet.; Low risk: surgery with low risk of bleeding. High risk: surgery with high risk of bleeding § many of these patients may be on the lower dose of dabigatran (i.e. 2x110 mg/d) or apixaban (i.e. 2x2.5 mg/d), or have to be on the lower dose of rivaroxaban (15 mg/d).

When to restart NOACs after a planned surgical intervention

Procedures with immediate and complete haemostasis: Atraumatic spinal/epidural anethesia Clean lumbar puncture	Resume 6–8 h after surgery
Procedures associated with immobilization: Procedures with post-operative risk of bleeding:	Initiate reduced venous or intermediate dose of LMWH 6–8 h after surgery if haemostasis achieved. Restart NOACs 48–72h after surgery upon complete haemostasis Thromboprophylaxis (e.g. with LMWH) can be initiated 6-8 h after surgery

Recommendations for stopping and starting NOACs after AF ablation procedures

- Limited available data. [1-5]
- Recommend strategy of bridging (with well-timed preoperative discontinuation, as above: slide 40) and restarting of NOACs.
- A too aggressively shortened periprocedural cessation of NOACs and/or no bridging may be less safe when compared to continued VKA administration and ablation under an INR between 2.0 and 3.0, both concerning bleeding and cardioembolic complications.

1. Kakkireddy et al, J Am Coll Cardiol 2012; 59:1168-74
2. Kaseno et al, Circ J 2012; 76:2337-42
3. Snipelisky et al, J Interv Card Electrophysiol 2012; 35:29-33
4. Winkle et al J Card Electrophysiol 2012; 23:264-8
5. Kim et al, Heart Rhythm, 2013 (ePub ahead of print)

11. Patients undergoing an urgent surgical intervention

- Discontinue NOAC.
- Try to defer surgery at least 12 h and ideally 24 h after last dose.
- Urgent surgery associated with much higher rates of bleeding than elective procedures, but lower than VKA-treated patients. [1]
- Coagulation tests can be considered (classical test or specific tests) but strategy based on these results has never been evaluated. Therefore such strategy cannot be recommended and should not be used routinely.

1. Healey et al, Circulation 2012:126;343-8

12. Patients with AF and coronary heart disease Clinical evidence part 1

- AF with ST-elevation (STE) or non ST-elevation (NSTE) ACS is associated with higher mortality rates. [1]
- Thrombotic vs bleeding risk in published trials and cohorts influenced by comorbidities and local practice.
- Triple therapy with VKA doubles risk of bleeding complications compared with clopidogrel +VKA. [2,3]
- Triple therapy with double antiplatelet drug therapy (DAPT) and NOACs at least doubles bleeding risk after ACS. [4]
- Data from RE-LY trial suggests that the advantages of NOAC over VKA in dual or triple therapy are preserved, but no comparative trial data to recommend one over the other. [5]

1. Lopes et al Eur Heart J 2009;30:2019-28
2. Sorensen et al, Lancet 2009; 374:1967-74
3. Lamberts et al Circulation 2012:126:1185-93
4. Mega et al, N Engl J Med 2012;366:9-19
5. Dans et al Circulation 2013;127:634-40

Patients with AF and coronary heart disease Clinical evidence part 2

- No Phase III trial data available for evaluation of NOACs in patients with recent ACS.
- In a meta-analysis of dabigatran trials, small but significant increased rate of MIs with dabigatran vs VKA (OR 1.33, 95% CI 1.03–1.71, p=0.03) but without impact on overall net clinical survival benefit [1,2] No excess MI observed in AF trials assessing FXa inhibitors.
- After ACS, DAPT with apixaban increases major bleeding risk. [3]
- Low-dose rivaroxaban with DAPT improves ischemic outcome after ACS but increased major bleeding risk.

1. Uchino et al, Arch Intern Med 2012;172:397-402
2. Hohnloser et al Circulation 2012;125:669-76
3. Alexander et al, N Engl J Med 2011;365:699-7082

Scenario 1. Recommendations concerning management of AF patients on NOACs who present with an acute coronary syndrome (ACS) part 1

- Temporarily discontinue NOACs upon presentation
- Initiate DAPT therapy unless frail with high bleeding risk
- Administer low-dose aspirin (150–300 mg loading; 75–100 mg later) on admission, preferably combined with ADP receptor inhibitor (ticagrelor or prasugrel preferred over clopidogrel)
- Initiate paraenteral anticoagulation (fondaparinux preferred)

Scenario 1. Recommendations concerning management of AF patients on NOACs who present with an acute coronary syndrome (ACS) part 2

In case of STEMI:

use primary PCI (radial approach) over fibrinolysis

- avoid UFH or enoxaparin until NOAC effect disappeared

In case of NSTE-ACS:

if not urgent, delay coronary angiography until waning of NOAC effect

- peri-procedural anticoagulation (UFH or bivalirudin preferred)

1. Uchino et al, Arch Intern Med 2012;172:397-402; 2. Alexander et al, N Engl J Med 2011;365:699-708

Scenario 1. Recommendations concerning management of AF patients on NOACs who present with an acute coronary syndrome (ACS) part 3

In case of PCI:

- use radial approach
- if indicated, balloon angioplasty without stenting
- use bare metal stents
- use additional paraenteral anticoagulation
- periprocedural bivalirudin preferred. Discontinue immediately after PCI
- avoid glycoprotein IIb/IIIa inhibitors unless bail-out situations

Scenario 1. Recommendations concerning management of AF patients on NOACs who present with an acute coronary syndrome (ACS) part 4

- In patients requiring revascularization, bypass surgery may be preferred in selected patients.
- When restarting NOAC consider dose reduction according risk and aim for shortest necessary duration of dual/triple therapy.
- Newer platelet inhibitors prasugrel and ticagrelor have not been evaluated for NOACs. Recommend awaiting further data before combining these with NOACs.

Scenario 2. Recommendations concerning new onset AF in patients with a recent (<1y) ACS part 1

- In patients with low atherothrombotic risk, consider VKAs in monotherapy after 1-3 months (6 months in case of recent DES), especially where bleeding risk elevated (HAS-BLED ≥3).

- In patients with high GRACE score (> 118), use additional single antiplatelet therapy (clopidogrel preferred) in the first 6 to 12 months after the acute event.

Scenario 2. Recommendations concerning new onset AF in patients with a recent (<1y) ACS part 2

- If NOAC indicated, consider FXa inhibitor (small and insignificant increased risk of MI for dabigatran, but weigh against clinical benefit).
- If dabigatran indicated, consider low dose (110 mg BID), in combination with low-dose aspirin or with clopidogrel.
- Ultra-low dose rivaroxaban in combination with DAPT has not been evaluated in this setting and is not currently recommended.

Scenario 3. Recommendations concerning new onset AF in patients with a remote(>1 year ACS)

- Anticoagulation without additional antiplatelet agents is sufficient for most AF patients with stable CAD.
- Advantages of NOACs over VKAs likely to be preserved: NOACs may be safe and effective alternatives to VKAs. [1]
- No preference given to any of NOACs.
- If using dabigatran, consider lower dose (110 mg BID) plus low-dose aspirin (clopidogrel in case of allergy to aspirin). [2]

1. Hohnloser et al, Circulation 2012;125:669-675; 2. Dans et al Circulation 2013;127:634-40

13. Cardioversion in a NOAC treated patient

- In patients with AF >48h duration undergoing cardioversion, oral anticoagulants should have been given for at least 3 weeks before cardioversion.
- Continuous oral anticoagulation is mandatory for 4 weeks following cardioversion.
- Clinical trial data show no significant additional risk in patients treated with NOACs vs. VKAs. [1]
- If NOAC compliance can be reliably confirmed, cardioversion should be safe.
- If doubt about compliance, consider prior TEE. [2]

1. Nagarakanti et al Circulation 2011;123:131-6;

2. Piccini et al Circulation 2012;126:A19281

14. Patients presenting with acute stroke while on NOACs

Acute haemorrhagic stroke

- Discontinue NOACs.
- Limited data to support use of aspecific procoagulants e.g. PCC, aPCC and aFVII.
- Use PCC or fresh frozen plasma as discussed in slides about measures in case of major bleeding.
- Same poor prognosis as for warfarin. [1]

1. Hart et al. Stroke 2012;43:1511-7

Patients presenting with acute stroke while on NOACs

Acute ischaemic stroke

- Assess the time window since last intake of NOAC: thrombolytic therapy is associated with increased bleeding risk within 48h of last NOAC dose.
- In case of uncertainty regarding last dose, prolonged aPTT (dabigatran) or PT (FXa inhibitors) indicates that thrombolysis should not be given.
- If NOACs have been given within 48h and coagulation tests not available or abnormal, consider recanalization of occluded vessels.

Stroke patients – Management of post-acute phase

Haemorrhagic stroke

- If cardioembolic risk high and risk of new haemorrhage low, restart NOACs 10-14 days after intracerebral haemorrhage.
- For patients with low cardioembolic risk and high bleeding risk, carefully consider reinintiation of NOACs: contraindicated unless bleeding risk has been reversed.
- Consider non pharmacological strategies instead of NOACs (e.g. ablation or occlusion of the atrial appendage).
- Mechanical thrombectomy without thrombolysis: no restrictions.

Stroke patients – Management of post-acute phase

Ischaemic stroke

- If infarct size not expected to increase risk of secondary intracerebral bleeding, re-initiate:
  - in patients with TIA after 1 day
  - small, non-disabling infarct after 3 days
  - large infarcts not before 2 weeks

TIA of cardioembolic origin

- (Re)start NOACs as soon as possible.
- Bridging with LMWH not required.
- In AF patients not suitable for VKAs, apixaban is superior to aspirin in stroke prevention.[1]

1. Connolly et al, N Engl J Med 2011;364:808-17

Stroke patients – Management of post-acute phase

Ischemic stroke of cardioembolic origin

- Initiation of NAOCs depends on infarct size and risk of new embolic stroke.
- Bridging with LMHW not required.
- Aspirin is not useful in secondary stroke prevention.

Patients with AF and significant carotid stenosis

- Carotid endarterectomy and not stenting recommended to avoid triple therapy.

15. NOACs vs VKAs in AF patients with a malignancy

- Patients with malignancies are at increased risk for thromboembolic events: tumours may secrete prothrombotic factors or induce inflammatory responses.
- Cancer therapy inflicts bleeding risks through surgery, tissue damage (irradiation) or myelosuppression.
- Many malignancies are associated with increased risk of mucosal bleeding.
- Chemotherapy causes myelosuppression (leucopenia/ reduced platelet count). This also reduces red blood cells and therefore reduces safety margin in a bleeding event.

NOACs in patients with cancer – Practical suggestions part 1

- Multidisciplinary care by cardiologist and oncologist.
- When new anticoagulant initiation is needed, consider VKA over NOACs: more clinical experience and reversal options, although INR is difficult to manage.
- Malignancy in patients with AF increases stroke risk.
- If already on stable NOAC treatment: continue unless contraindications, i.e. switch to VKA not mandatory.

NOACs in patients with cancer – Practical suggestions part 2

- No additional anticoagulant therapy (e.g. LMHW) is needed if NOACs are used.
- In patients receiving moderately myelosuppressive therapies, NOACs may be continued.
- In patients undergoing tumour surgery, same principles apply as in elective surgery.
- Consider therapy-induced changes in organ function and adapt dose if indicated.

NOACs in patients with cancer – Practical suggestions part 3

- In patients undergoing myelosuppressive chemotherapy or radiation therapy, consider temporary dose reduction or cessation of NOACs.
- Monitor blood counts, bleeding signs and liver and renal function.
- Consider gastric protection with PPI or H2 blockers in all patients treated with NOACs.
- Patients on NOACs should be instructed to monitor signs of bleeding (petechiae, haemoptysis, black stools) and to contact therapy centre if these develop.

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