# New oral anticoagulants. Surveillance and follow-up

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# Disclosures

| | **Laurent Fauchier:** |
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EHRA PRACTICAL GUIDE

# European Heart Rhythm Association practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

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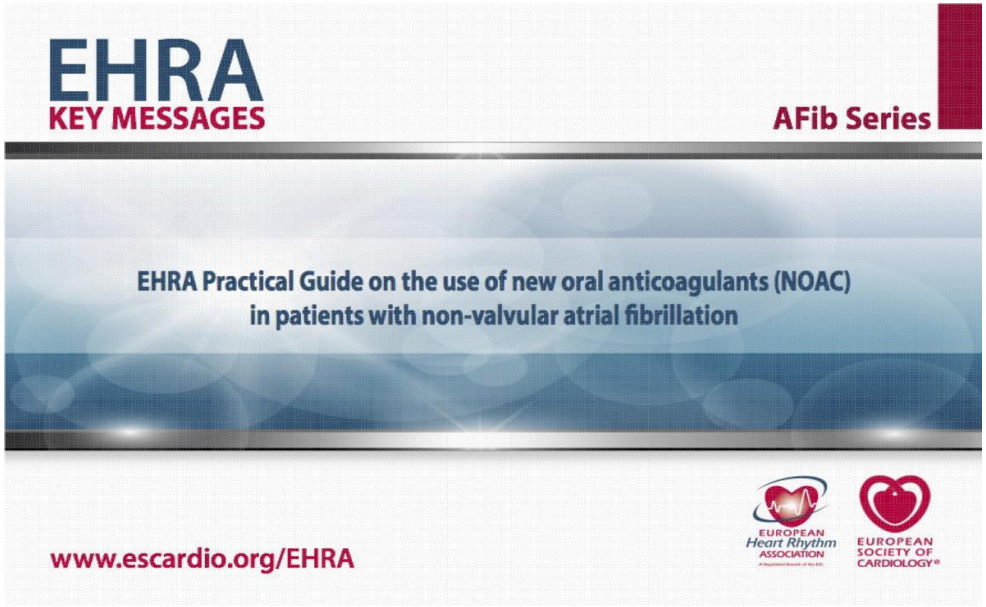


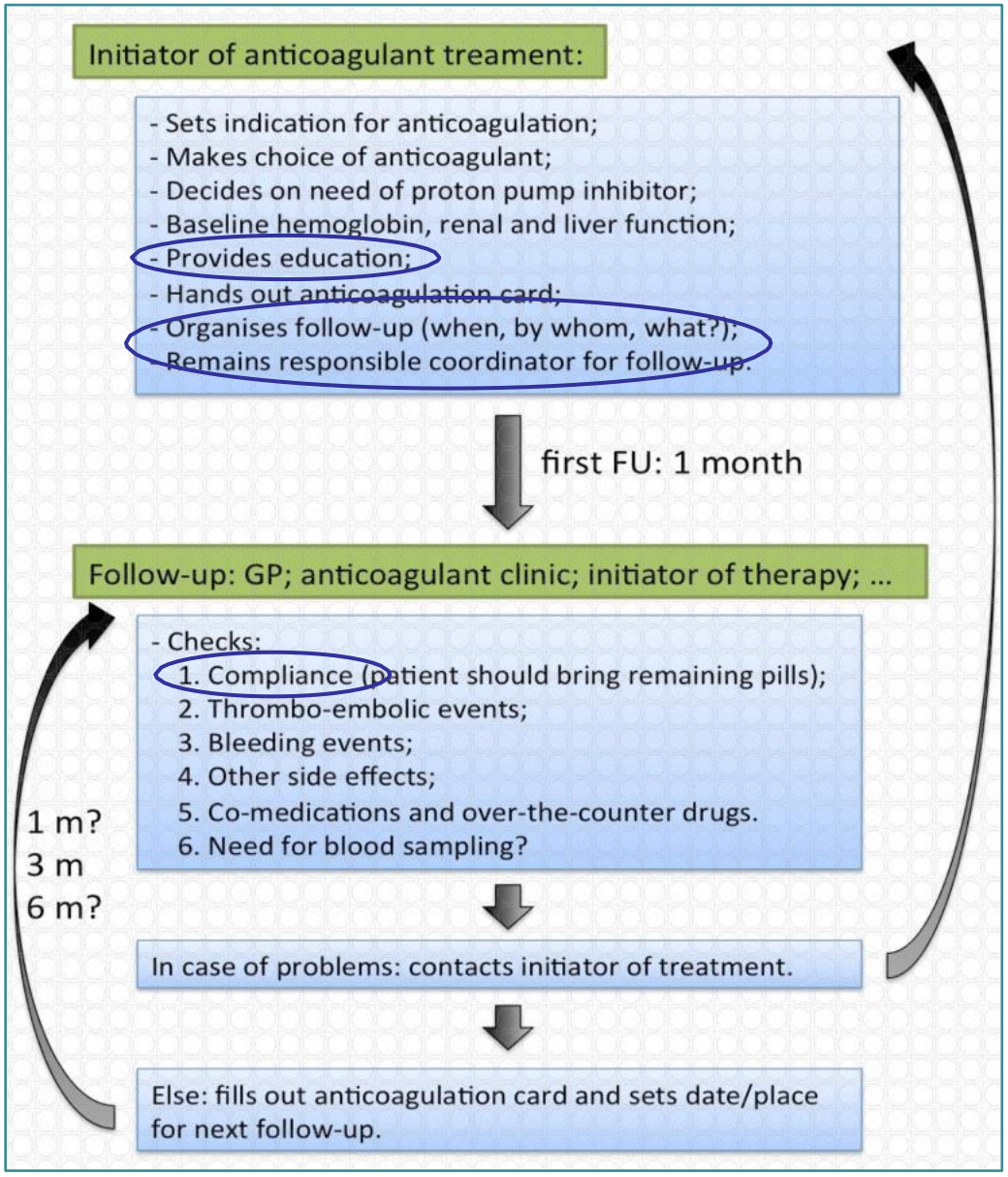

Heidbuchel et al, EHRA Practical Guide for use of NOAC in AF, Eur Heart Journal & EP Europace 2013

# New oral anticoagulant (NOAC) drugs

## New possibilities = new responsibilities

1. Start-up and follow-up.
2. How to interpret coagulation tests?
3. Drug-drug interactions and pharmacokinetics of NOAC.
4. Switching between anticoagulant regimens.
5. Ensuring compliance of NOAC intake.
6. How to deal with dosing intake errors?
7. Patients with chronic kidney disease.
8. What to do if (suspected) overdose without bleeding?
9. Management of bleeding complications.
10. Planned surgical intervention or ablation.
11. Urgent surgical intervention.
12. Patients with both AF + coronary artery disease.
13. Cardioversion in a NOAC treated patient.
14. Patients presenting with acute stroke while on NOAC.
15. NOAC vs. VKA in AF patients with a malignancy.

# Suggested structured follow-up

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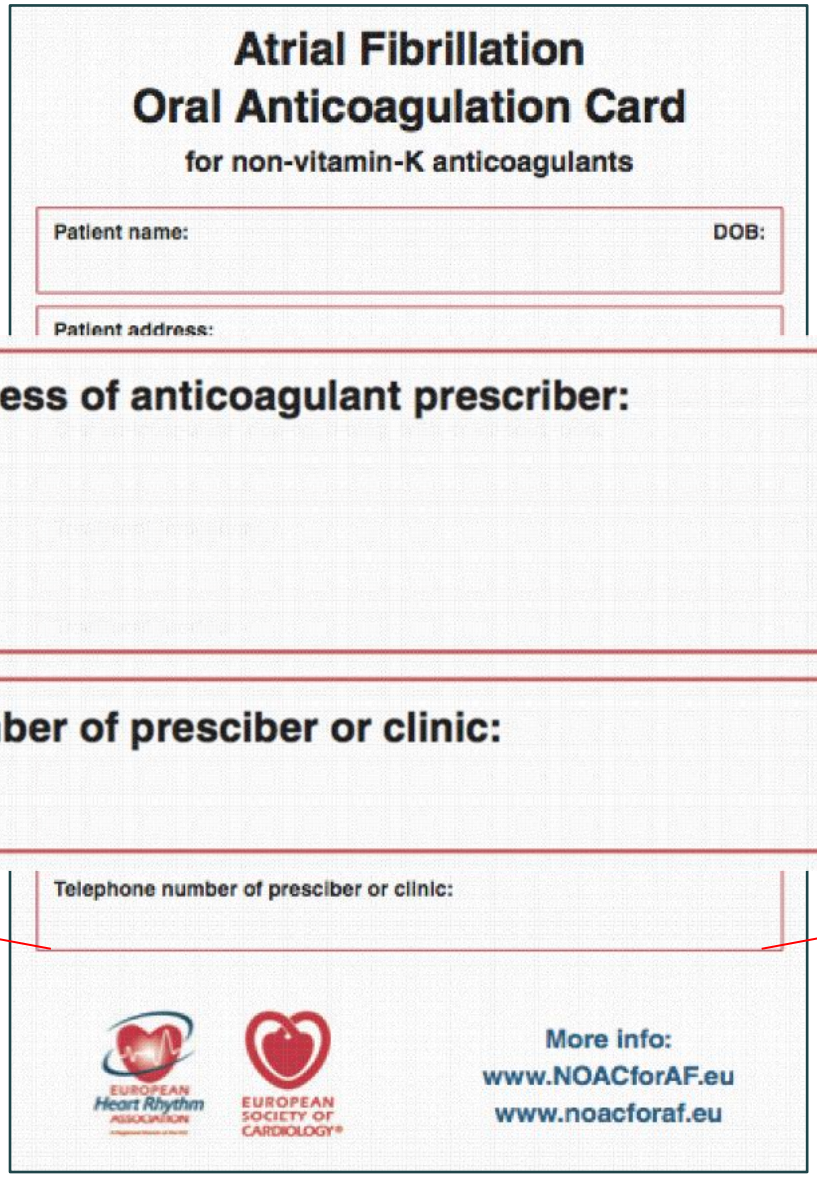
# EHRA proposal for a universal
## Anticoagulation Patient Card /1

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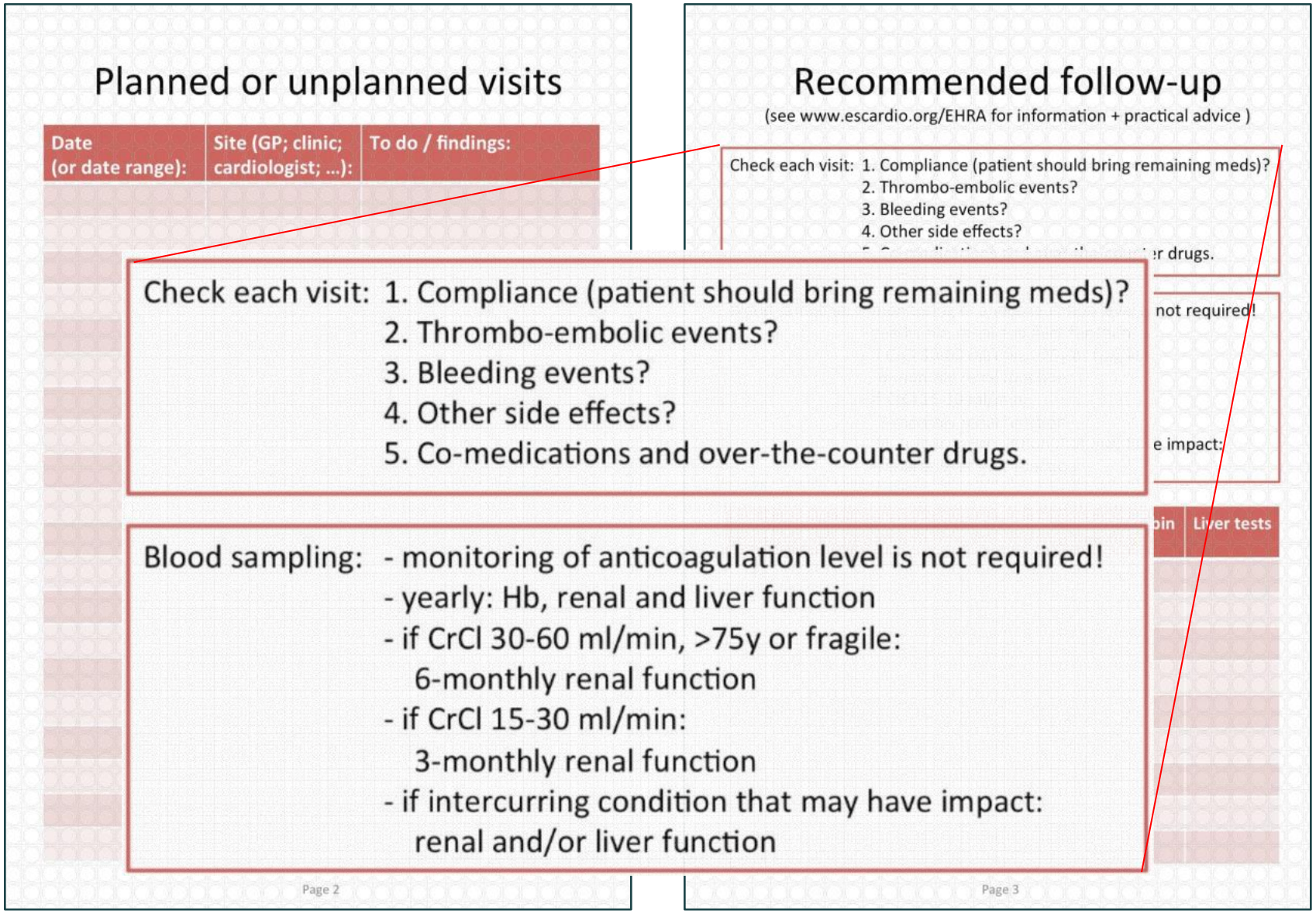
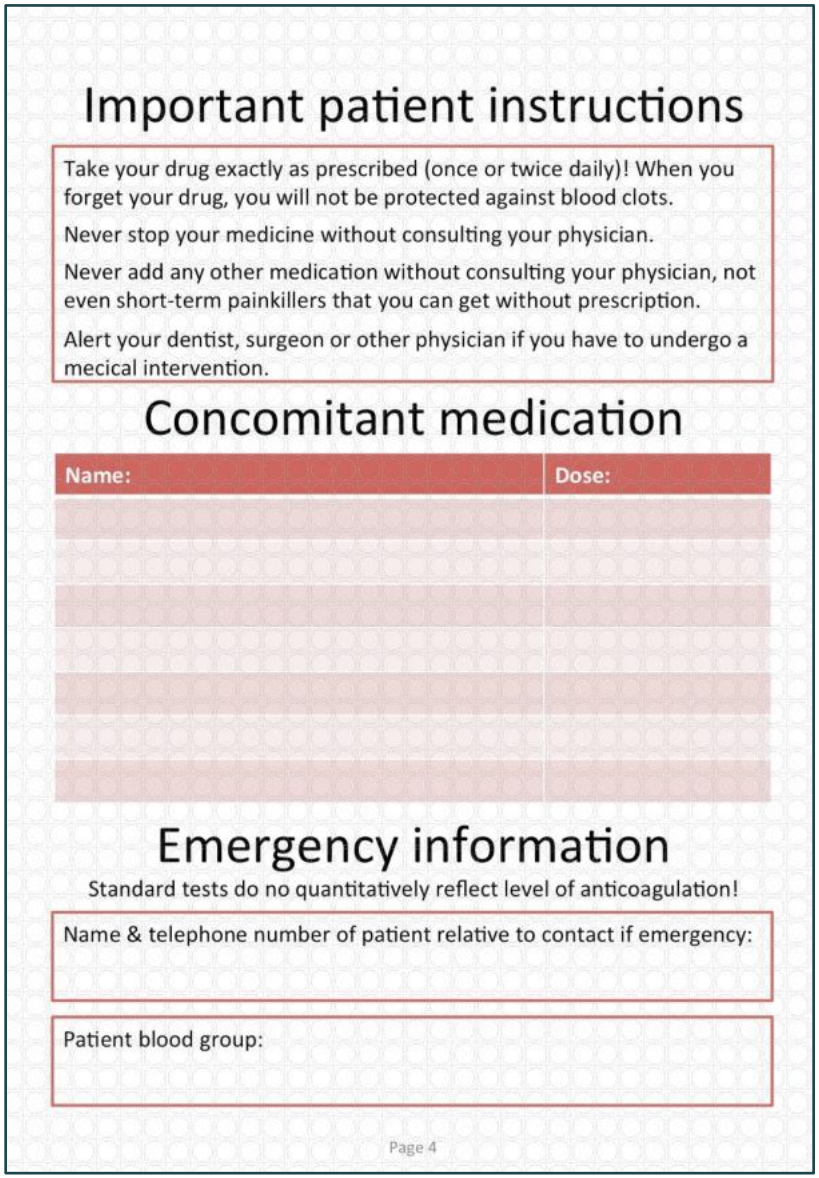
# EHRA proposal for a universal
## Anticoagulation Patient Card /2



# EHRA proposal for a universal Anticoagulation Patient Card /3



## Important patient instructions

Take your drug exactly as prescribed (once or twice daily)! When you forget your drug, you will not be protected against blood clots.

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 if you have to undergo a mecical intervention.

## Concomitant medication

| Name: | Dose: |
|---|---|
| | |
| | |
| | |
| | |
| | |
| | |
| | |

## Emergency information

Standard tests do no quantitatively reflect level of anticoagulation!

Name & telephone number of patient relative to contact if emergency:

Patient blood group:

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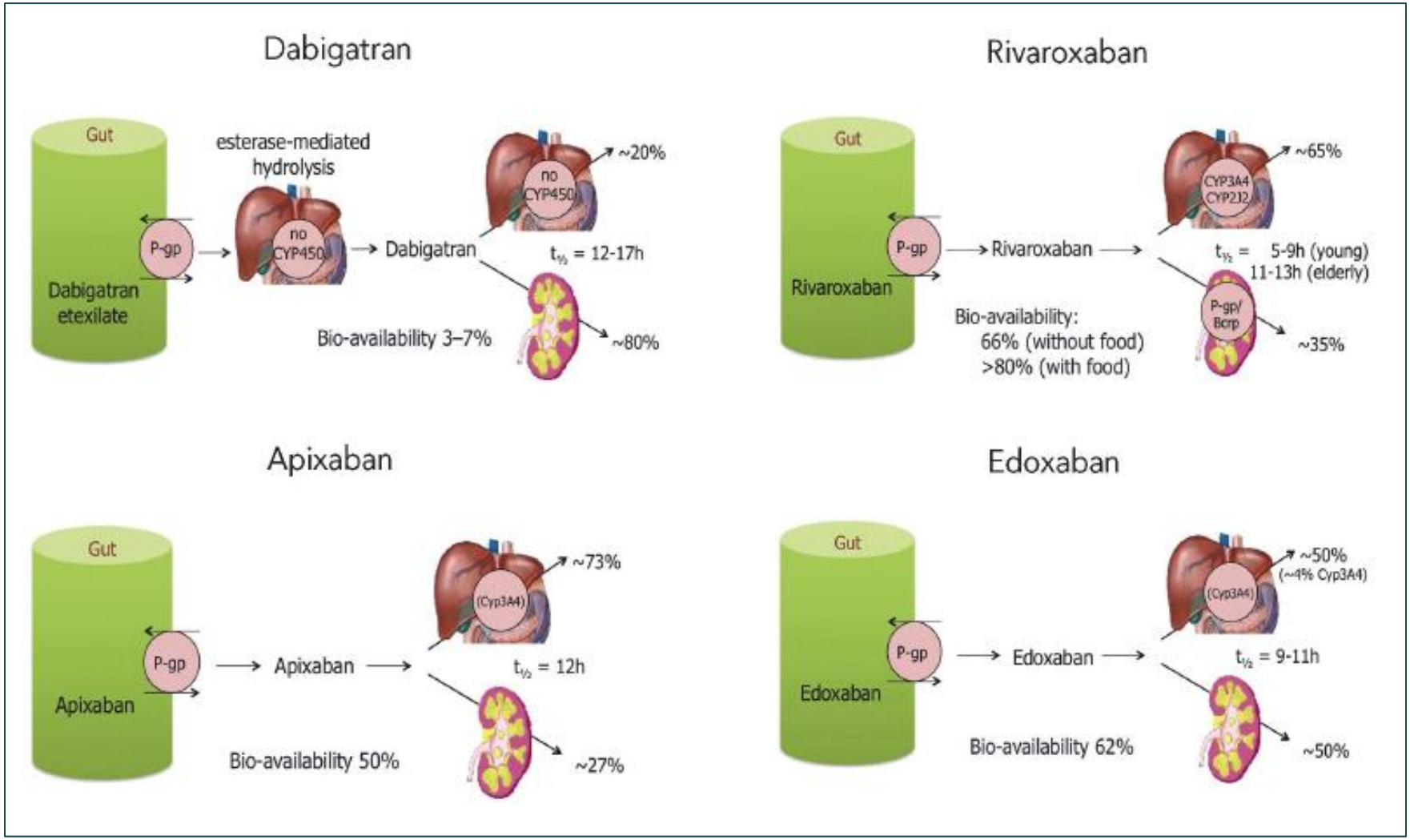
# NOACs: Agenda for Out-patient Visits

| Points | Interval | Comments |
|---|---|---|
| Compliance | Each visit | Patient to bring medication – note and calculate adherence; re-educate re strict schedule; consider and inform about compliance aids |
| Thromboembolism | Each visit | Systemic (stroke, TIA, systemic embolus)<br>Pulmonary embolus |
| Bleeding | Each visit | Nuisance bleeds: PPIs, haemorrhoidectomy, etc.<br>Motivate patient to be diligent with NOAC<br>Bleeding with impact on QoL, or with risk: prevention if possible, or change of NOAC |
| Other side effects | Each visit | ? relationship to NOAC; if necessary consider temporary discontinuation with bridging or change to other NOAC |
| Co-medications | Each visit | Prescription and OTC drugs (when, for how long?) |
| Blood sampling | 12 monthly | Renal, haemoglobin and liver function tests |
| | 6 monthly | Renal: if CrCl 30 – 60 ml/min, on dabigatran, ≥75 years, or frail |
| | 3 monthly | Renal: if CrCl 15 - 30 ml/min |

**Heidbuchel H, et al. *Europace*. 2013;15:625-651.**[31]

# Absorption and metabolism of NOACs

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# NOAC and kidney disease

| | Dabigatran | Apixaban | Edoxaban* | Rivaroxaban |
|---|---|---|---|---|
| **Fraction of absorbed dose renally excreted** | 80% | 27% | 50% | 35% |
| **Approved for CrCl ≥ …** | ≥30 ml/min | ≥15 ml/min | not available | ≥15 ml/min |
| **Dosing recommendation** | CrCl ≥50 ml/min: no adjustment (i.e. 2 x 150 mg/d) | serum creatinine ≥1.5 mg/dl: no adjustment (i.e. 2 x 5 mg/d) | not available | CrCl ≥50 ml/min: no adjustment (i.e. 1 x 20 mg/d) |
| **Dosing if CKD** | When CrCl 30-49 ml/min: 150 mg BID is possible (SmPC) but 110 mg BID if 'high risk of bleeding' (SmPC) or 'recommended' (AF GL Update 2012)<br><br>Note: 75 mg BID approved in US only:<br>- if CrCl 15-30 ml/min<br>- if CrCl 30-49 ml/min and other orange factor Table 5 (e.g. verapamil) | Serum creatinine ≥ 1.5 mg/dl or CrCl 15-49 ml/min: no adjustment by itself;<br><br>reduce to 2.5 mg BID in combination with ≤60 kg or with ≥80 year old | not available | 15 mg OD recommended when CrCl 15-49 ml/min (caution if 15-30 ml/min) |
| **Not approved for** | CrCl <30 ml/min | CrCl <15 ml/min | not available | CrCl <15 ml/min |

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*: no EMA approval yet. Needs update after finalisation of SmPC

# Drug-drug interactions
## and other dosing considerations /1

| | via | Dabigatran | Apixaban | Edoxaban* | Rivaroxaban |
|---|---|---|---|---|---|
| **Atorvastatin** | P-gp competition and CYP3A4 inhibition | +18% | no data yet | no effect | no effect |
| **Digoxin** | P-gp competition | no effect | no effect | no effect | no effect |
| **Verapamil** | P-gp competition (and weak CYP3A4 inhibition) | +12-180% (reduce dose and take simultaneously) | no data yet | +53% (SR) (Reduce dose by 50%)* | minor effect (use with caution if CrCl 15-50 ml/min) |
| **Diltiazem** | P-gp competition and weak CYP3A4 inhibition | no effect | +40% | no data yet | minor effect (caution if CrCl 15-50 ml/min) |
| **Quinidine** | P-gp competition | +50% | no data yet | +80% (Reduce dose by 50%)§ | +50% |
| **Amiodarone** | P-gp competition | +12-60% | no data yet | no effect | minor effect (caution if CrCl 15-50 ml/min) |
| **Dronedarone** | P-gp and CYP3A4 inhibitor | +70-100% (US: 2 x 75 mg) | no data yet | +85% (Reduce dose by 50%)* | no data yet |
| **Ketoconazole; itraconazole; voriconazole; posaconazole** | P-gp and BCRP competition; CYP3A4 inhibition | +140-150% (US: 2 x 75 mg) | +100% | no data yet | up to +160% |
| **fluconazole** | weak CYP3A4 inhibition | no data yet | no data yet | no data yet | +40% (if systemically administered) |
| **Cyclosporin; tacrolimus** | P-gp competition | no data yet | no data yet | no data yet | +50% |

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# Drug-drug interactions
## and other dosing considerations /2

| | via | Dabigatran | Apixaban | Edoxaban* | Rivaroxaban |
|---|---|---|---|---|---|
| **Clarithromycin; erythromycin** | P-gp competition and CYP3A4 inhibition | +15-20% | no data yet | no data yet | +30-50% |
| **HIV protease inhibitors (e.g. ritonavir)** | P-gp and BCRP competition or inducer; CYP3A4 inhibition | no data yet | Strong increase | no data yet | up to +150% |
| **Rifampicin; St. John's wort; carbamazepine; phenytoin; phenobarbital** | P-gp/ BCRP and CYP3A4/CYP2J2 inducers | -66% | -54% | -35% | up to -50% |
| **Antacids (H2B; PPI; Al-Mg-hydroxide)** | GI absorption | -12-30% | no effect | no effect | no effect |
| **Other factors:** | | | | | |
| **Age ≥ 80 years** | Increased plasma level | | | no data yet | |
| **Age ≥75 years** | Increased plasma level | | | no data yet | |
| **Weight ≤ 60 kg** | Increased plasma level | | | | |
| **Renal function** | Increased plasma level | See Table Renal Function | | | |
| **Other increased bleeding risk (especially if HAS-BLED ≥3)** | | Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history or active GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy) | | | |

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# Factors increasing NOAC plasma concentration

| | Dabigatran | Apixaban | Rivaroxaban |
|---|---|---|---|
| Aged ≥80 years | | | |
| Aged ≥75 years | | | |
| Weight <60 kg | | | |
| Renal impairment | | | |
| Other risk factors | • Pharmacodynamic interactions:<br>- Antiplatelet drugs<br>- Other anticoagulants<br>- Thrombolytics<br>- NSAIDs /half-life > 12 h), systemic stroid therapy<br>- Selective serotonin (SSRIs) or serotonin-noradrenaline reuptake inhibitors (SNRIs)<br>• Recent critical organ surgery (i.e., brain, aye)<br>• Thrombocytopenia (chemotherapy)<br>• HAS-BLED score ≥3 | | |

Consider dose reduction if ≥ 2 yellow factors

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# Dosing intake errors

- Missed dose
  - no double dose to make up
  - if <50% of dosing interval has passed (i.e. 6 to 12h): still take
  - if >50% of dosing interval has passed (i.e. 6 to 12h): wait for next
- Double dose
  - for QD NOAC: continue normal dosing scheme
  - for BID NOAC: skip next dose (or take, depending on risk profile)
- Uncertainty about intake
  - for QD NOAC: take another pill; then continue planned scheme
  - for BID NOAC: do not take another pill; wait until next dose

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# Surgery bleeding risk

| Interventions not necessarily requiring discontinuation of anticoagulation |
|---|
| 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 dermatologic excisions; …) |
| **Interventions with low bleeding 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) |
| **Interventions with high bleeding risk** |
| Complex left-sided ablation (pulmonary vein isolation; VT ablation) |
| Spinal or epidural anaesthesia; lumbar diagnostic puncture |
| Thoracic, abdominal or major orthopedic surgery |
| Liver biopsy, transurethral prostate resection, kidney biopsy |

For each patient, individual factors relating to bleeding and thrombo-embolic risk need to be taken into account, and be discussed with the intervening physician.

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# Cessation before planned surgery

| | Dabigatran | | Apixaban | | Edoxaban* | | Rivaroxaban | |
|---|---|---|---|---|---|---|---|---|
| | **No important bleeding risk and/or adequate 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 | | | | | | | |

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§: many of these patients should be on the lower dose of the drug, e.g. 2x110 mg/d dabigatran or 15 mg/d rivaroxaban.

# Switching between anticoagulants

- VKA to NOAC
  - INR < 2: start NOAC
  - INR 2 – 2.5: start NOAC immediately or next day
  - INR > 2.5:estimate new INR check depending on VKA half-life
- NOAC to VKA
  - administer concomitantly until INR >2 (checked before NOAC intake!),
  - retest INR 24h after last NOAC intake,
  - monitor INR closely within first month
    (goal = 3 consecutive INRs between 2 and 3)!
- LMWH to NOAC
  - start NOAC at the time of next planned LMWH administration
- Unfractionated heparin to NOAC
  - administer NOAC at time of discontinuation i.v. heparin (cf. $t_{1/2}$ ±2h)

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# Conclusions

- Practical aspects of FU using the novel anticoagulant drugs:
  - think about education and adequate follow-up
  - ask about bleeding events
  - think about dose
  - think about possible drug interaction
  - know what to do in case of a dosing errors or bleeding
  - interrupt ‘just in time’ for a planned intervention
  - switch correctly

- If needed: consult the EHRA Practical Guide