

NOAC: “NO Anticoagulation without Consideration”

Typical scenarios of stroke prevention in patients with AF
An article from the series «Atrial fibrillation – update 2014»

Nicole R. Bonetti^a, Eva S. Laube^a, Jürg H. Beer^{a,b}

^a Department of Internal Medicine, Cantonal Hospital of Baden, Switzerland

^b Laboratories for Platelet Research, Center of Molecular Cardiology, University of Zurich, Switzerland

Summary

Novel Oral Anticoagulants (NOACs) target factors IIa and Xa specifically, thereby significantly changing the landscape of thromboembolic prophylaxis in patients with Atrial Fibrillation (AF).

In large phase III trials they have proven to be at least as effective as routine therapy (i.e., Vitamin K Antagonists (VKAs) and heparins) in preventing thromboembolic events with a favourable risk benefit profile (i.e., significantly less major and intracerebral bleeding events).

Fixed dosing and no need for therapeutic monitoring are among their practical advantages, making them an attractive alternative in long term anticoagulation for patients and doctors alike.

However, further data concerning specific patient subgroups (e.g., oncological / paediatric patients), specific bleeding management and specific NOACs in different scenarios are awaited. Therefore a non-critical use of these substances is to be discouraged.

Key words: direct factor Xa inhibitors; direct thrombin inhibitors; atrial fibrillation; stroke; anticoagulant therapy

Introduction

Atrial fibrillation as the most common cardiac arrhythmia is of great health and economic relevance, as thromboembolic events due to atrial fibrillation result in significant morbidity and mortality (two-fold increased risk of dying, five-fold increased risk of stroke) [1, 2].

For 50 years Vitamin K Antagonists have been the only anticoagulant option in preventing thromboembolic events in patients with atrial fibrillation.

Though these drugs are very effective, well known, established and accepted, as well as cost efficient, they are subject to numerous limitations, such as drug-drug or drug-food interactions, a narrow

therapeutic range and the need for anticoagulant monitoring [3, 4].

Thus novel oral anticoagulants (NOACs) have been introduced, changing the landscape of oral cardioembolic prophylaxis in patients with non-valvular atrial fibrillation.

These agents specifically target the factors IIa (dabigatran etexilate) and Xa (rivaroxaban, apixaban, edoxaban).

In large scale clinical trials – ROCKET-AF (rivaroxaban) [5], ARISTOTLE (apixaban) [6], RE-LY (dabigatran) [7] and ENGAGE-TIMI (edoxaban) [8] – these substances have proven to be at least non inferior to standard therapy in preventing ischaemic cerebrovascular events with a favourable risk benefit profile, i.e., significantly lower intracranial and major bleeding rates [9–12]. Dabigatran (150 mg bid) and apixaban (5 mg bid) were even shown to be superior to VKAs in preventing ischaemic stroke.

Moreover, the predictable pharmacokinetics with no need for therapeutic monitoring – among other aspects – has led to wide acceptance with patients and doctors alike.

However, certain aspects e.g., renal dysfunction, age, comorbidities and drug-drug interactions should be taken into consideration on a case-by-case basis when prescribing NOACs.

Therefore, the use of these agents should be well considered.

The following article aims to present an overview of typical scenarios and support individualised clinical decision making.

Funding / potential competing interests:

No financial support and no other potential conflict of interest relevant to this article were reported.

Correspondence:

Professor Jürg H. Beer, MD
Department of Internal Medicine
Cantonal Hospital of Baden
CH-5404 Baden
hansjuerg.beer[at]ksb.ch

Clinical scenario 1: Compliance, frail elderly, impaired renal function

A 79-year-old female patient is newly diagnosed with atrial fibrillation in the course of a syncope evaluation. She qualifies for oral anticoagulation.

She lives by herself and treatment compliance according to her general practitioner is difficult. Her BMI is low at 17. Apart from this she presents with moderate renal impairment (CrCl (Cockcroft) 37 ml/min, Crea 133 µmol/l). Which therapeutic option to choose?

Patients with renal dysfunction and atrial fibrillation represent a complex population, since they are at a substantially higher risk for both bleeding and thromboembolic events (3.9% vs 2.9% annually for ischaemic stroke, 0.8% vs 0.5% annually for intracranial bleeding) [13–17].

Due to a lack of clinical outcome data in patients with severe renal impairment (CrCl <30 ml/min) current ESC Guidelines discourage the use of NOACs in this population, although some (apixaban, rivaroxaban) are approved for a CrCl >15 ml/min [18].

In patients with mild to moderate renal impairment (CrCl 30–50 ml/min) FXa inhibitors in reduced dosing – i.e., 15 mg qd for rivaroxaban and 2.5 mg bid for apixaban – show similar concentrations as in patients with higher dosing and normal renal function [18], therefore presenting a reasonable alternative to VKA in those patients – apixaban perhaps more so than rivaroxaban (table 1).

For dabigatran with 80% renal excretion a dose reduction to 110 mg bid seems advisable in patients with a CrCl <50 ml/min in the presence of additional bleeding risks (i.e., age ≥80 y, HAS-BLED Score ≥3).

For these reasons, dabigatran may not be the NOAC of first choice in patients with chronic kidney disease if further fluctuations in renal function are to be anticipated [18].

Generally we recommend being cautious and restrictive in chronic kidney disease with CrCl <40 ml/min. Furthermore, at least six monthly controls of renal function are recommended for patients on NOACs; however we suggest more frequent clinical and laboratory

controls in this vulnerable population. Moreover, additional controls are in order in presence of possibly aggravating factors, such as acute illness (infections, acute heart failure, co-medications (NSAIDs), dehydration).

Clinical decision: In this case a VKA was chosen in light of the impaired and possibly fluctuating renal function and questionable adherence to daily dosing. If TTR (Time in Therapeutic Range) should not develop satisfactorily, apixaban could be considered.

Clinical scenario 2: Interactions

A 67-year-old male patient with atrial fibrillation is to be put on rhythm controlling medication with amiodarone. He is currently orally anticoagulated with dabigatran 2 × 150 mg. Renal function is normal, CHA2DS2-VASc Score 3, HAS-BLED Score 2. Are changes in medication required?

Although NOACs are known for fewer interactions than VKAs, prescribing physicians need to take pharmacokinetics of co-administered drugs into consideration (table 2).

An important interaction mechanism for all NOACs with possible exception of rivaroxaban is a significant intestinal re-secretion via a P-glycoprotein transporter (P-gp).

Therefore, inhibition of this mechanism results in higher plasma levels. Plenty of drugs, often employed in patients with atrial fibrillation, are substrates of this pathway (e.g., quinidine, amiodarone, dronedarone, verapamil) and should therefore be used with caution, especially in combination with dabigatran.

Furthermore, CYP3A4 type hepatic elimination is of significance in the clearance of rivaroxaban and apixaban, less so for edoxaban. Thus combinations with strong inhibitors (clarithromycin, erythromycin, ritonavir, ketoconazole, fluconazole) or inducers (rifampicin, St. John's wort, carbamazepine, phenytoin, phenobarbital) of this pathway should be avoided.

NOACs themselves do not impact these pathways and can be combined with further substrates such as midazolam, atorvastatin and digoxin without risk of elevating plasma levels of these substances.

Table 1
NOACs in renal dysfunction [20].

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban*
Fraction of renal excretion	80%	27%	35%	50%
Approved for CrCl ≥ ...	≥30 ml/min	≥15 ml/min	≥15 ml/min	Not available
Dosing in CKD	– 150 mg bid / 110 mg bid if high risk of bleeding	2.5 mg bid if 2 out of 3 factors present:	– 15 mg qd	Not available
– CrCl 30–49 ml/min	– Not recommended	– Serum crea ≥133 µmol/l	– Not recommended	
– CrCl 15–29 ml/min	– Not recommended	– age ≥80 y	– Not recommended	
– CrCl ≤15 ml/min		– weight ≤60 kg		

* no EMA approval yet

Table 2

Drug – drug interactions and recommendations toward dosing according to EHRA practical guide [20].

	Via	Dabigatran	Apixaban	Rivaroxaban
Atorvastatin	P-Gp competition and CYP 3A4 inhibition	+ 18% (AUC)	Minor increase	No effect
Digoxin	P-Gp competition	No effect	No effect	No effect
Verapamil	P-Gp competition (weak CYP3A4 inhibition)	+ 12 – 180%	Moderate increase	Minor increase → Cave if CrCl 15–50 ml/min
Diltiazem	P-Gp competition und CYP3A4 inhibition	No effect	+ 40%	Minor increase → Cave if CrCl 15–50 ml/min
Quinidine	P-Gp competition	+ 50 %	Moderate increase	+50 %
Amiodarone	P-Gp competition	+ 12 – 60%	Moderate increase	Minor increase → Cave if CrCl 15–50 ml/min
Dronedarone	P-Gp and CYP3A4 inhibition	+ 70 – 100%	Moderate increase	Moderate increase
Ketoconazole; itraconazole; voriconazole	P-Gp competition, CYP3A4 inhibition	+ 140 – 150%	+ 100%	+ 160%
Fluconazole	CYP3A4 inhibition	No data yet	Moderate increase	+ 42%
Cyclosporin	P-Gp competition	Strong increase	Moderate increase	+ 50%
Clarithromycin; erythromycin	P-Gp competition and CYP3A4 inhibition	+ 15 – 20%	Strong increase	+ 30–54%
HIV protease inhibitors	P-Gp competition and CYP3A4 inhibition	Strong increase	Strong increase	+ 153%
Rifampicin; St John's wort; phenytoin; carbamazepine	P-Gp and CYP3A4/CYP2J2 inducers	– 66%	– 54%	– 50%
Antacids (PPI, H2B)	GI absorption	– 12–30%	No effect	No effect
Age ≥80 y.	Increased plasma level			
Age ≥75 y.	Increased plasma level			
Weight ≤60 kg	Increased plasma level			

Red: Contraindicated/not recommended
Orange: Reduce dose (dabigatran 2 x 110 mg; apixaban 2 x 2.5 mg; rivaroxaban 1 x 15 mg)
Yellow: Consider dose reduction in presence of another "yellow" factor

Concomitant use of all NOACs with platelet inhibitors and NSAIDs elevates bleeding risk by at least 60% and should therefore be balanced against the potential benefit individually. Since food intake results in an increased bioavailability of almost 100% in rivaroxaban, it should be taken with meals, whereas no significant food interaction exists for apixaban, dabigatran and edoxaban. Table 2 (according to the EHRA's practical guide) gives an overview of the most relevant interactions [19, 20].

Clinical decision: In this case – in absence of further risk factors for elevated plasma levels – the therapy with dabigatran in the presence of amiodarone was continued in a lower dose regimen of 2 x 110 mg.

Clinical scenario 3: NOACs and triple anticoagulation

A 66-year-old male patient with atrial fibrillation under oral anticoagulation with rivaroxaban has been experiencing stable angina pectoris and in the course is newly diagnosed with a two vessel coronary artery disease. In an elective PCI the ACD and RIVA are treated with 2 DES (-olimus). How to fare with triple antico-

agulation?

The combination of coronary heart disease and atrial fibrillation presents a common and complex clinical scenario, associated with significantly elevated mortality rates [21]. Concomitant use of oral anticoagulants (VKAs, NOACs) and dual antiplatelet therapy results in an at least two fold increase of major bleeding events after an ACS [22–25] and should be avoided or kept as short as possible. To date, there are no clinical data on the combination of NOACs with ASA and clopidogrel apart from a small number of patients in the RE-LY trial for dabigatran. Moreover, data concerning the combination with the newer P2Y12 inhibitors prasugrel and ticagrelor are lacking, therefore current guidelines advise against such combinations (exceptions being clopidogrel allergy and in-stent thrombosis under clopidogrel therapy).

In case of an ACS, NOACs should be discontinued on admission. Patients presenting with a STEMI should receive additional parenteral periprocedural anticoagulation, with no regard to the last dose of NOAC, preferably with bivalirudin due to its short half life and lower bleeding risk [20].

If a coronary intervention is not pressing, discontinuation of the NOAC is recommended for at least 24 h be-

fore PCI and periprocedural anticoagulation should be used according to local practice.

The recently published WOEST trial [26] demonstrated that the combination of VKAs and a single antiplatelet agent (clopidogrel) is superior to triple therapy (VKA, ASA, clopidogrel) when it comes to bleeding, whereas rates of ischemic complications did not differ between the groups (any bleeding 19.4% vs 44.4%, HR 0.36, 95% CI 0.26–0.50).

Therefore, duration of triple anticoagulation is frequently shortened according to clinical practice.

In light of lacking clinical data, adhering to ESC Guidelines recommending VKA, ASA and clopidogrel seems reasonable, however shortened durations of triple anticoagulation are likely to be implemented in the near future (table 3) [27, 28].

Clinical decision: In this case the patient was put on triple anticoagulation (VKA & clopidogrel & ASA) for 3–6 months with 3-monthly re-evaluation, followed by clopidogrel and VKA for another 6 months. Thereafter, a monotherapy with OAC could be considered.

Clinical scenario 4: NOACs and cardioversion

A 58-year-old female patient with atrial fibrillation under oral anticoagulation with apixaban for eight weeks is bothered by palpitations and presents for elective cardioversion. Can this be safely performed?

According to ESC guidelines [20] patients with atrial fibrillation of >48 h duration (or unknown) undergoing cardioversion should receive adequate anticoagulation for at least three weeks or a prior TEE to rule out left atrial thrombi.

Prospective data regarding the safety of cardioversion under NOACs are not available.

Observational data from the RE-LY trial (n = 1270 patients) have documented a comparatively low rate of ischaemic stroke after cardioversion in patients treated with dabigatran (0.77% for dabigatran 110 mg bid, 0.30%

for dabigatran 150 mg bid & 0.60% for warfarin) [29].

Analysis of the subgroup data from the ARISTOTLE (apixaban, n = 540 patients) and ROCKET-AF (rivaroxaban, n = 285 patients) trials, although on a smaller patient population, suggests similar findings.

Since there are no available coagulation assays for NOACs providing information on effectiveness of anticoagulation over the past few weeks, compliance is of utmost importance. If it can be reliably confirmed a cardioversion on NOAC therapy seems acceptable [20]. If in doubt, a prior TEE is advisable.

Clinical decision: In this case, as strict adherence/compliance to therapy was doubtful, a prior TEE was performed, not detecting intracardial thrombus formation.

Clinical scenario 5: NOACs and acute stroke

A 72-year-old female patient with atrial fibrillation currently treated with rivaroxaban (20 mg) presents with acute onset of right-sided somatosensory paresis. She is diagnosed with left hemispheric ischaemic stroke. Can a thrombolytic therapy be evaluated?

Currently, guidelines approve of thrombolytic therapy with recombinant tissue plasminogen activator (rtPA) within a 4.5 h timeframe after first manifestation of stroke symptoms [30].

It is, however, recommended against in patients under anticoagulant therapy.

Thrombolysis cannot be administered within 48 h (representing 4 plasma half lives) after the last dose of NOAC (cave: No experience with NOACs, recommendation in analogy to VKAs).

In case of uncertainty concerning the last dose of NOAC the use of thrombolytics should be discouraged.

In case of haemorrhagic stroke NOACs – by analogy to VKAs – can be re-established after 10–14 days if cardioembolic risk is deemed to be high and bleeding risk respectively relatively low.

Table 3

Antithrombotic therapy in patients with coronary heart disease and atrial fibrillation.

	Low bleeding risk (HAS-BLED 0–2)	High bleeding risk (HAS-BLED ≥ 3)
ACS & PCI	Radial approach recommended BMS or DES Month 0–6: VKA & clopidogrel & ASA Month 7–12: VKA & clopidogrel Month 13 +: OAC monotherapy	Radial approach recommended Primarily BMS Month 0–1: VKA & clopidogrel & ASA Month 2–12: clopidogrel & VKA Month 13 +: OAC monotherapy
Elective BMS	Month 0–1: VKA & clopidogrel & ASA Month 2–12: VKA & clopidogrel Month 13 +: OAC monotherapy	Month 0–1: VKA & clopidogrel & ASA Month 2 +: OAC monotherapy
Elective DES (-olimus)	Month 0–3: VKA & clopidogrel & ASA Month 4–12: VKA & clopidogrel Month 13 +: OAC monotherapy	Not recommended
Elective DES (paclitaxel)	Month 0–6: VKA & clopidogrel & ASA Month 7–12: VKA & clopidogrel Month 13 +: OAC monotherapy	Not recommended

ACS: Acute Coronary Syndrome; PCI: Percutaneous Coronary Intervention; BMS: Bare Metal Stent; DES: Drug Eluting Stent

The contraindication against any form of anticoagulation in patients with a history for spontaneous intracerebral bleed is to be taken into consideration, unless the cause has been resolved. The decision to reconstitute anticoagulation in patients after intracerebral haemorrhage will remain a difficult one, best addressed multidisciplinary considering aetiology, the balance between bleeding and thromboembolic risk, as well as personal preferences.

In case of ischaemic stroke continuation of NOACs depends on stroke size. By analogy to VKAs some advocate the 1–3–6–14 day rule, which re-implements anticoagulant therapy in patients with TIA after 1 day, with small ischaemia after 3 days, with moderate infarct after 6 days and not before 14 days in large strokes [20].

Clinical decision: In this scenario it was decided against a thrombolytic therapy, instead local therapy was considered, however, due to excellent clinical progress rejected.

Clinical scenario 6: Surgical procedure

A 64-year-old female patient with atrial fibrillation on apixaban is scheduled for a routine colonoscopy. CHA₂DS₂-VASc Score 3, HAS-BLED Score 2. Is it necessary to discontinue anticoagulation, and if so, when?

Due to the rapid onset of action of NOACs, periprocedural bridging therapy is no longer necessary. The timing of discontinuation and restarting the drug bases on patient characteristics (kidney function, age, concomitant medication) as well as surgical factors (surgical site, type of surgery, bleeding risk).

Especially for dabigatran renal function has to be taken into account (table 4) [20]. In interventions posing no clinically important bleeding risk, such as dermatological, dental and ophthalmological procedures or endoscopy without surgical intervention, the intervention can take place at trough concentration (i.e., 12 or 24 h after the last intake, for bid or qd dosing respectively) with restart of anticoagulation 6 h after haemostasis.

In procedures carrying higher bleeding risks (i.e., PM-implantation, atrial fibrillation ablation procedures, spinal/epidural anaesthesia...) discontinuation is recommended for at least 48 h prior (table 4) [31,32].

In treatments with complete haemostasis, NOACs may be re-established 6–8 h after the procedure. However, many surgical treatments require a longer discontinuation period. In those cases a transient venous thromboprophylactic therapy with low molecular weight heparin could be considered 6–8 h after surgery and achieved haemostasis [20].

Clinical decision: In this case the procedure (endoscopy without biopsy) posed a small bleeding risk and was performed at trough concentration (i.e., 12 h after last dose). Apixaban was re-started 6 h after the intervention. If biopsies had been taken, an OAC free interval of up to 7 days with LMWH prophylaxis could be considered and discussed with the responsible gastroenterologist.

Clinical scenario 7: Bleeding management, monitoring and therapy reversal

A 72-year-old male patient with atrial fibrillation on rivaroxaban presents with lower gastrointestinal bleeding. Haemodynamics are stable; Hb remains stable at 12.5 g/dl. A specific coagulation assay does not suggest overdosing. Should special measures be taken?

In general, bleeding complications, namely major and intracranial bleeds, are significantly less frequent in patients on NOACs compared to VKAs.

However, the gastrointestinal bleeding risk, especially on rivaroxaban and dabigatran is elevated. This may be due to anticoagulatory active metabolites in the gut, which are not present in VKAs.

Specific antidotes are not yet available, though phase II trials are ongoing (as of May 2014). Current recommendations based on in vitro and scarce experimental data and suggest the administration of procoagulatory substances in major bleeds only [33–36], whereas for minor to moderate bleeding the usual measures apply, as half-lives are short (fig. 1) [20].

Routine use of specific coagulation assays for therapeutic monitoring is not recommended, as rapidly changing concentrations and short half-lives of NOACs render them hard to interpret.

Clinical decision: In this case no special measures (i.e., treatment with procoagulant substances) were ta-

Table 4
Periprocedural management of NOACs [20]

Clearance (ml/min)	Dabigatran		Apixaban		Rivaroxaban	
	Low risk	High risk	Low risk	High risk	Low risk	High risk
≥ 80	≥ 24 h ‡	≥ 48 h	≥ 24 h	≥ 48 h	≥ 24 h	≥ 48 h
50 – 80	≥ 36 h	≥ 72 h	≥ 24 h	≥ 48 h	≥ 24 h	≥ 48 h
30 – 50	≥ 48 h	≥ 96 h	≥ 24 h	≥ 48 h	≥ 24 h	≥ 48 h
15 – 30	Not recommended (ESC guidelines 2010/2012)					

‡ Timing of last dose before surgical procedure

High bleeding risk procedures: Pulmonary vein isolation; VT ablation; spinal or epidural anaesthesia, lumbar puncture; thoracic surgery, abdominal surgery, liver biopsy, kidney biopsy

Low bleeding risk procedures: Endoscopy with biopsy, prostate biopsy, angiography, PM- or ICD implantation

ken (fig. 1). Were the bleeding more severe, PCC (Prothrombin Concentrate Complex) would be considered.

Clinical scenario 8: Prosthetic heart valves

A 58-year-old female patient who receives anticoagulation with phenprocoumon because of a mechanical aortic valve and atrial fibrillation asks her GP about the possibility of switching therapy to a NOAC since she's tired of anticoagulant monitoring. What will the answer be?

The RE-ALIGN trial compared dabigatran to warfarin in patients with mechanical heart valves. The trial had to be prematurely terminated in phase II due to a significant increase in thromboembolism (5% vs 0%) and bleeding events (4% vs 2%; HR 1.76, 95% CI 0.37–8.46) [37]. This observation may be due to coagulation activation on contact (FIX) or via tissue damage (FVII) which is both targeted by VKAs, not however by NOACs. Therefore VKAs currently represent the only form of oral anticoagulation applicable to patients with mechanical heart valves, which thus represent an important limitation for the use of NOACs.

Clinical decision: The therapy with VKA was continued.

Clinical scenario 9: Compliance – forgotten dose(s)

A 62-year-old female patient with atrial fibrillation on dabigatran calls her GP at 11 A.M. because she has for-

gotten to take the morning dose at 07:00 A.M. What should the recommendation be and how to fare with dosing errors in general?

As NOACs have a predictable therapeutic effect, its monitoring is not necessary to guide therapy. As the therapeutic effect however fades rapidly after 12–24 h strict drug adherence is crucial and should be regularly addressed by the treating physician.

In case of a missed dose of NOACs with a bid regimen (i.e., every 12 h), like dabigatran and apixaban, a forgotten dose should still be taken up to 6 h after scheduled intake. For NOACs with a qd dosing regimen (i.e., rivaroxaban, edoxaban), up to 12 h after scheduled intake. If the mistake lays further back, the next scheduled dose should be taken.

In case of accidental double dosing of NOACs with a bid regimen, skipping the next planned dose (i.e., after 12 h) is advisable. In NOACs with a qd intake, the regimen should be continued as planned, since at 24 h a major part of the drug will have been eliminated.

In case of uncertainty concerning dose intake, one could advise patients with a bid regimen to continue as planned without taking another pill. In case of qd dosing it seems recommendable taking another pill, as the next dose is scheduled after 24 h with a longer potential period without sufficient anticoagulant effect [20].

Clinical decision: In this case, the patient was advised to still take the missed dose at this delayed point of time.

Figure 1
Absorption and metabolism of NOACs.

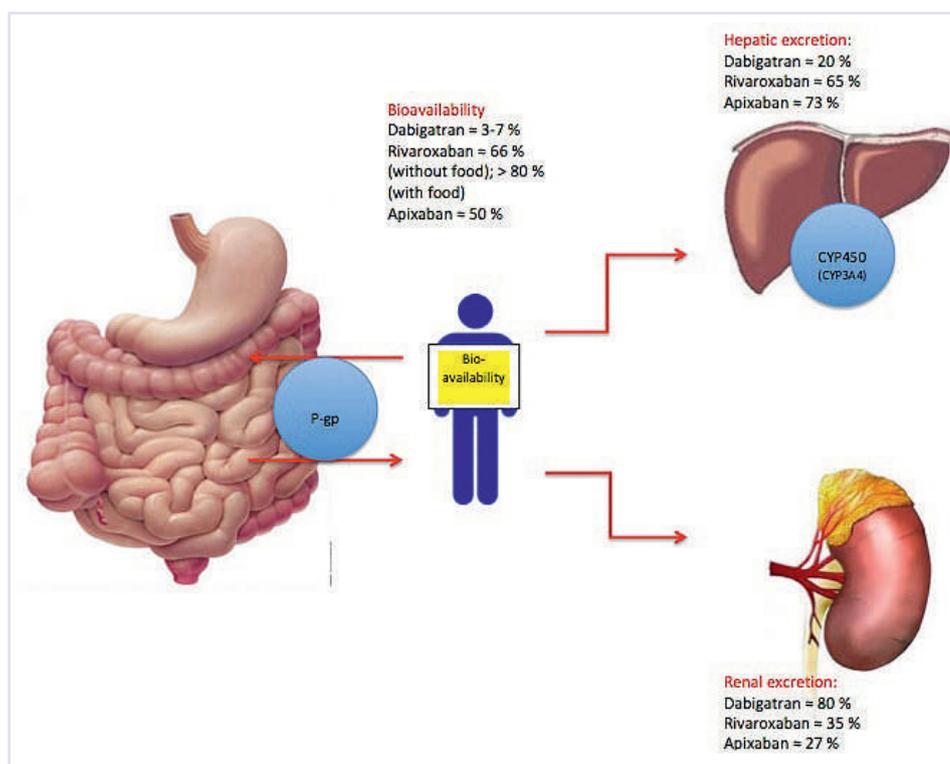
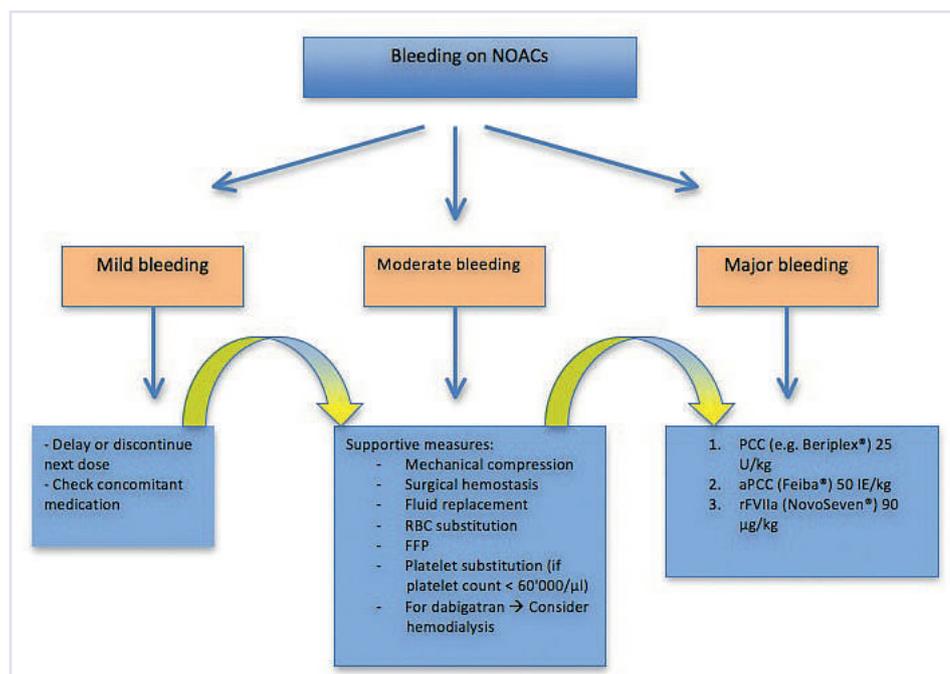


Figure 2

Management of bleeding in patients taking NOACs. From: Heidbuchel H, Verhamme P, Alings M, Kichhof P, et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2013;15(5): 625–51 [20], reprinted with permission.



Clinical scenario 10: Liver cirrhosis

A 67-year-old male patient is newly diagnosed with atrial fibrillation (CHA₂DS₂-VASc Score 1, HAS-BLEED 5). As a concomitant disease he suffers from alcoholic liver cirrhosis Child C with a spontaneous INR of around 1.7. Can NOACs be (safely) introduced?

Ever since the first oral thrombin inhibitor (ximelagatran) was withdrawn from the market due to liver toxicity this has been a concern.

In the phase III trials for dabigatran and rivaroxaban, patients with significant liver disease (acute or chronic hepatitis, cirrhosis or asymptomatic elevation of aminotransferases >3× upper limit) were excluded. Monitoring of liver function did not suggest significant toxicity however [5, 7].

The results of a phase I trial evaluating apixaban in patients with mild to moderate hepatic impairment (Child-Pugh A or B), suggests that dose adjustment is not necessary in these patients, as the pharmacodynamics and – kinetics seem predictable [38].

However, adding rivaroxaban and dabigatran to plasma from patients with liver disease resulted in an enhancement of anticoagulant response compared to controls [39].

According to the manufacturers' instruction rivaroxaban and apixaban can be administered in patients with mild to moderate liver disease (Child A/B) in absence of coagulopathy, if close clinical and laboratory monitoring can be provided, whereas dabigatran is not recommended in this population.

In conclusion, NOACs should be withheld in patients with liver disease for the time being due to limited clinical

data. Alternatively LMWH or long term VKAs could be considered, however posing a challenge in therapeutic monitoring. Some authors in those cases recommend FII and FV to guide therapy [40, 41].

Clinical decision: In this case – with VKA-monitoring presenting a challenge as well – the decision was made against oral anticoagulation all together, since apart from ongoing drinking the patient also presents with oesophageal varices, therefore being at a very high bleeding risk, outweighing the risk for systemic embolism. As there are some reports pointing to a relatively safe use of VKAs in patients with cirrhosis, three monthly re-evaluations are in order.

Conclusion

NOACs have proven to be not only non-inferior to VKAs in cardioembolic prophylaxis, but even superior when it comes to intracranial and major bleeds [5–8].

Moreover, the fixed dosing regimen and rapid onset of action without therapeutic monitoring makes them a widely accepted and attractive alternative option in long-term anticoagulation.

Although they interact less with drugs and food than VKAs, combinations with CYP3A4 and P-gp inducers/inhibitors, as well as NSAIDs and platelet inhibitors (due to elevated bleeding risk), have to be carefully considered [20].

In presence of renal or hepatic dysfunction, as well as in frail and elderly patients, NOACs should be used with caution and intake tightly monitored.

Readily available (point of care) specific coagulation assays – however not recommended in routine practice –

exist, whereas antidotes in case of severe bleeding are yet to be introduced.

In light of the rapid onset and short half-lives of NOACs, strict drug adherence is of utmost importance and should be frequently addressed by the treating physician. Laboratory controls of renal and hepatic function should take place at regular intervals.

Clinical experience for many patient subgroups, such as oncological or paediatric patients is still lacking and further data evaluating different indications are urgently needed.

Therefore, a non-critical use of NOACs is discouraged in favour of a careful, individual clinical decision-making, keeping in mind that anticoagulant drugs are still among the most effective and hazardous at the same time.

References

- Benjamin EJ, Wolf PA, D'Agostino RB, Silberhatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. *Circulation*. 1998;98(10):946–52.
- Conen D, Chae CU, Glynn RJ, Tedrow UB, Everett BM, Bruing JE, et al. Risk of death and cardiovascular events in initially healthy women with new onset atrial fibrillation. *JAMA*. 2011;305(20):2080–7.
- Birman-Deych E, Radford MJ, Nilasena DS, Gage BF. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. *Stroke*. 2006;37:1070–74.
- Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S, et al. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation*. 2007;115:2689–96.
- Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in patients in non valvular atrial fibrillation. *N Engl J Med*. 2011;365:883–91.
- Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–92.
- Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–51.
- Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–14.
- Ruff CT, Antman EM, Giugliano RP, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *The Lancet*. 2014;389:955–62.
- The EINSTEIN Investigators. Oral Rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363:2499–510.
- The EINSTEIN Investigators. Oral Rivaroxaban for symptomatic pulmonary embolism. *N Engl J Med*. 2012;366:1287–97.
- Agnelli G, Buller HR, Cohen A, et al. Oral Apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369:799–808.
- Olesen JB, Lip GYH, Kamper A-L, Hommel K, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med*. 2012;367:625–35.
- Fox KA, Piccini JP, Wojyla D, Becker RC, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non valvular atrial fibrillation and moderate renal impairment. *Eur Heart J*. 2011;32:2387–94.
- Steffel J, Hindricks G, et al. Apixaban in renal insufficiency: Successful navigation between the Scylla and charybdis. *Eur Heart J*. 2012;33:2766–8.
- Friberg L, Benson L, Lip G. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. *Eur Heart J*. 2014;139.
- Steffel J. Neue orale Antikoagulanzen bei eingeschränkter Nierenfunktion und Dialyse. *Leading Opinions Nephrologie*. 2013;2:73–5.
- Camm AJ, et al. 2012 focused update of the esc guidelines for the management of atrial fibrillation: An update of the 2010 esc guidelines for the management of atrial fibrillation. Developed with the special contribution of the european heart rhythm association. *Europace* 2012;14(10):1385–413.
- Mueck W, Lensing AW, Agnelli G, Decousus H, Prandoni P, Misselwitz F. Rivaroxaban: population pharmacokinetic analyses in patients treated for acute deep vein thrombosis and exposure simulations in patients with atrial fibrillation treated for stroke prevention. *Clin Pharmacokinet*. 2011;50:675–86.
- Heidbuchel H, Verhamme P, Alings M, Kichhof P, et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* (2013) 15 (5): 625–651. doi: 10.1093/europace/eut083.
- Lopes RD, Pieper KS, Horton JR, Al-Khatib SM, Newby LK, Metha RH, et al. Short- and long term outcomes following atrial fibrillation in patients with acute coronary syndromes with or without ST-segment elevation. *Heart*. 2008;94:867–73.
- Mega JL, Braunwald E, Wiviott SD, Bassand JP, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;366:9–19.
- Alexander JH, Lopes RD, James S, Kilarus R, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med*. 2011;365:699–708.
- Lopes RD, Elliott LE, White HD, Hochman JS, et al. Antithrombotic therapy and outcomes of patients with atrial fibrillation following primary percutaneous coronary intervention: results from the APEX-AMI trial. *Eur Heart J*. 2009;30:2019–28.
- Lamberts M, Olesen JB, Runwald MH, et al. Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention: a nationwide cohort study. *Circulation*. 2012;126:1185–93.
- Dewilde WJ, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: An open label, randomised, controlled trial. *Lancet*. 2013;382:1107–15.
- Camm AJ, et al. Guidelines for the management of atrial fibrillation: The task force for the management of atrial fibrillation of the european society of cardiology. *Europace*. 2010;12:1360–420.
- Verheugt F. W.A. Antithrombotic Therapy During and After Percutaneous Coronary Intervention in Patients With Atrial Fibrillation. *Circulation*. 2013;128:2058–61.
- Nagarkani R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. *Circulation*. 2011;123:131–6.
- Jauch EC, Saver JL, Adams HP, Bruno A, Connors J, Demaerschalk B, Khatri P. Guidelines for the Early Management of Patients with Acute Ischemic Stroke. *Stroke*. 2014;44:870–947.
- Torn M, Rosendaal FR. Oral anticoagulation in surgical procedures: risks and recommendations. *Br J Haematol*. 2003;123:676–82.
- Sie P, Samama CM, Godier A, Rosencher N, Steib A, Llau JV, et al. Surgery and invasive procedures in patients on long term treatment with direct oral anticoagulants: thrombin or factor-Xa inhibitors. Recommendations of the working group on perioperative Haemostasis and the French study group on thrombosis and haemostasis. *Arch Cardiovasc Dis*. 2011;104:669–76.
- Marlu R, Hodaj E, Paris A, Albaladejo P, Crackowski JL, Pernod G. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban. A randomised crossover ex vivo study in healthy volunteers. *Thromb Haemos*. 2012;108:217–24.
- Escobar G, Arellano-Rodrigo E, Reverter JC, Villalta J, Sanz V, Molina P, et al. Reversal of apixaban induced alterations of hemostasis by different coagulation factor concentrates: studies in vitro with circulating human blood. *AHA Emerging Science Series*, June 20, 2012. *Circulation*. 2012;126:520–1.
- van Ryn J, Ruehl D, Pripke H, Huel N, Wiennen W. Reversibility of the anticoagulant effect of high doses of the direct thrombin inhibitor dabigatran, by recombinant factor VIIa or activated prothrombin complex concentrate. *Haematologica*. 2008;93(Suppl 1):148.
- Warkentin TE, Margetts P, Connolly SJ, Lamy A, Ricci C, Eikelboom JW. Recombinant factor VIIa (rFVIIa) and hemodialysis to manage massive dabigatran-associated postcardiac surgery bleeding. *Blood*. 2012;119:2172–4.
- Eikelboom J, Connolly S, Van de Werf F, et al. Dabigatran versus Warfarin in Patients with Mechanical Heart Valves. *N Engl J Med*. 2013;369:1206–14.
- Frost CE, Yu Z, Wang J, Li T, Zeigler C, Schuster A, et al. Single dose safety and pharmacokinetics of apixaban in subjects with mild or moderate hepatic impairment. *Clin Pharmacol Ther*. 2009;85:s34.
- Masood S, Van Thiel D, George M, Hoppensteadt D, Fareed J. Differential augmentation of the anticoagulant responses by newly developed oral anti-Xa and anti-IIA drugs in patients with liver disease. *FASEB J*. 2009;23(Suppl.):abstract LB383.
- Intagliata N, Henry Z, Shah N, Lisman T, Caldwell S, Northup P. Prophylactic anticoagulation for venous thromboembolism in hospitalized cirrhosis patients is not associated with high rates of gastrointestinal bleeding. *Liver*. 2014;34:26–32.
- Kinjo N, Kawanaka H, Akahoshi T, Matsumoto Y, Kamori M, Nagao Y, Hashimoto N, Uehara H, et al. Portal vein thrombosis in liver cirrhosis. *World J of Hepatology*. 2014;6:64–71.