

New oral anticoagulants: key messages for clinicians

Matteo Giorgi-Pierfranceschi,¹ Chiara Cattabiani,¹ Francesco Dentali²

¹Emergency Department, Hospital of Val d'Arda, Piacenza, Italy; ²Internal Medicine Department, University of Insubria, Varese, Italy

ABSTRACT

New oral anticoagulants are an effective and safe alternative to vitamin K antagonists in many fields of clinical practice. The use of the direct inhibitors of activated Factor II (dabigatran) and activated Factor X (apixaban and rivaroxaban), both in patients with non-valvular atrial fibrillation (NVAF) and those with acute venous thromboembolism (VTE), is of great interest for internal medicine physicians. This paper aims to give practical guidance on management (starting therapy, follow up and bleeding complications) of patients treated with dabigatran, rivaroxaban or apixaban for NVAF or acute VTE providing practical tables concerning the phases of therapy, management of complications, drug interaction and dose adjustment if renal impairment occurs.

Introduction

Vitamin K antagonists (VKA) interfere with the coagulation cascade through inhibition of Factors II-VII-IX-X. VKA have a slow onset of anticoagulant action, a long half-life, multiple food and drug interactions, and a very narrow therapeutic window outside of which the thrombotic and bleeding risk increases exponentially. These characteristics mean that VKA require periodical monitoring of the international normalized ratio (INR) for dose adjustments. These features have determined the exclusion of a large portion (approx. 50%) of all eligible subjects from anticoagulant therapy.

New oral anticoagulants (NOAC) have been stud-

ied in several randomized controlled trials, enrolling over 100,000 patients.¹⁻¹⁵ Potential indications for NOAC include primary and secondary prevention of arterial and venous thromboembolic events. So far, these drugs (or some of them) have proven their effectiveness and safety in the prevention of venous thromboembolism (VTE) in major orthopedic surgery,¹⁴ in the secondary prevention of acute coronary syndromes (ACS),¹⁵ non-valvular atrial fibrillation (NVAF)¹⁻⁴ and VTE⁵⁻¹⁰ (Tables A1 and A2). In particular, NVAF and VTE are frequently encountered in clinical practice by clinicians and these will receive particular attention in this paper.

The most attractive features of NOAC concern the direct and selective inhibition of a single coagulation factor (thrombin or Factor X), the fast onset of anticoagulant activity, the predictable effect, the few food and drug interactions, and the short plasma half-life. Thanks to these characteristics, the NOAC can be used at fixed dose, and they do not usually need to be monitored.

Thanks to these characteristics, and to the favorable results of phase III clinical trials, in particular in patients with NVAF and VTE, the prescription of NOAC in clinical practice is expected to increase.

This paper provides a summary of the information provided in the papers that make up this monographic issue in order to give some practical advice on management of patients treated with these new agents.

Correspondence: Matteo Giorgi-Pierfranceschi, Emergency Department, Hospital of Val d'Arda, via Roma 35, 29017 Fiorenzuola d'Arda (PC), Italy.
Tel.: +39.0523.989799.
E-mail: m.giorgi@ausl.pc.it

Key words: new oral anticoagulants, internal medicine, management checklist.

Conflict of interests: the authors declare no potential conflict of interests.

Received for publication: 11 November 2013.

Revision received: Not required.

Accepted for publication: 4 December 2013.

This work is licensed under a Creative Commons Attribution NonCommercial 3.0 License (CC BY-NC 3.0).

©Copyright M. Giorgi-Pierfranceschi et al., 2013
Licensee PAGEPress, Italy
Italian Journal of Medicine 2013; 7(s8):74-84
doi:10.4081/ijm.2013.s8.74

Initial treatment

Before introducing a treatment with NOAC, clinicians should check the following factors (Table A3).

- Clinical indications (NVAF, VTE): evaluation of the thromboembolic risk in patients with atrial fibrillation (with the CHADS-VASC2 score) (Table A4).

- Ongoing treatment with other antithrombotic agents (VKA unfractionated heparin (UFH), low molecular weight heparins (LMWH), fondaparinux, warfarin, NOAC) or antiplatelet drugs and concomitant treatment with drugs that may alter the efficacy and safety of NOAC.
- Presence of absolute or relative contraindications to anticoagulant therapy: inherited or acquired bleeding disorders, severe uncontrolled hypertension, active or recent gastrointestinal ulcers, vascular retinopathy, recent intracranial or intracerebral hemorrhage, vascular abnormalities of the central nervous system (CNS), recent neurosurgery or ophthalmic surgery, bronchiectasis, or a history of pulmonary hemorrhage.
- Presence of absolute or relative contraindications to NOAC therapy: prosthetic heart valves, pulmonary emboli (PE) hemodynamically instable candidates for thrombolysis.
- Evaluation of the bleeding risk (HAS-BLED score in patients with AF) (Table A5).
- Evaluation of routine laboratory tests: coagulation (aPTT, PT) complete blood cell count (BCC), hepatic function (excluding patients with severe hepatic impairment, defined as bilirubin >2 times upper limit of normal (ULN), in association with AST/ALT/ALP >3 times ULN) and renal function (Cockcroft method to calculate creatinine clearance) (Table A6).
- Identification of the appropriate dosage (Tables A7 and A8) according to the data sheet for the selected drug, patient characteristics and disease type. For patients with VTE, only Xa-inhibitors (rivaroxaban and apixaban) have been approved for acute treatment with a dual intensity approach (Table A8). Elderly subjects (>80 years of age) represent a particular population in which both cardioembolic and bleeding risk are increased, but few data are currently available regarding the use of NOAC in this kind of patients (data transferability).

The systematic assessment of all these points could help the internist to identify those patients who could benefit from NOAC treatment.

Monitoring

The pharmacological characteristics of NOAC allow the use of standardized dosages without the need for routine monitoring with coagulation tests. In general, only complete BCC, renal (plasma creatinine, creatinine clearance, Cockcroft-Gault method), and hepatic function (indexes of hepatic cytolysis) are useful for monitoring patients on NOAC therapy.

According to current guidelines,^{16,17} these tests should be performed before initiation of therapy, after the first three months of therapy, and then every six

months. Monitoring should be planned more frequently in subjects with risk factors such as age over 80 years or altered renal function (Table A9).

Furthermore, at each visit the following points should be considered.

- Concomitant administration of drugs that can increase or decrease the anticoagulant effect of these drugs or that contraindicate NOAC co-administration.
- Adherence to the therapy (drug compliance): calculating the number of tablets taken in the period between two consecutive prescriptions and checking the boxes of medication used.
- Occurrence of bleeding or thromboembolic events during treatment.
- Reevaluation of indication to continue anticoagulant therapy and of the patient's risk of bleeding.

Management of bleeding events

Bleeding events are certainly the most feared complication of anticoagulant treatment. An appropriate clinical approach is mandatory according to the bleeding severity (*e.g.* minor, major, life-threatening). In case of any bleeding complications, it may be useful to collect information on dosage and time of last intake of the drug. Furthermore, in all the major and life-threatening bleeding complications, the clinician should collect information on concomitant pharmacotherapy, paying particular attention to any new therapies that have been introduced that may interfere with the NOAC, such as macrolide antibiotics, antifungal agents, antiarrhythmics, antidepressants, antiepileptics, non-steroid anti-inflammatory drugs (NSAIDs) etc. (Table A10). Evaluation of renal function with creatinine clearance calculation (in particular in patients receiving dabigatran), hepatic function and complete BCC should be performed. Finally, local measurement for assessment of hemostasis failure should be considered.

Minor bleeding

These are hemorrhagic adverse event without the characteristics of major and life-threatening bleedings. In this case, drug intake may be postponed or one dose of the drug may be skipped.

Major bleeding

According to the widely accepted International Society on Thrombosis and Hemostasis (ISTH) definition, bleeding is classified as major if it was overt and associated with a decrease in the hemoglobin level of 2 g/dL or more, required the transfusion of 2 or more units of blood, occurred into a critical site (retroperitoneal, intraocular, hemoperitoneum, hemothorax,

spinal hematoma, hematemesis and melena, hemo-pericardium, hemarthrosis of the large joints), or contributed to death¹⁸ (Table A11).

In addition to standard supportive measurements (such as mechanical compression, surgical hemostasis, fluid replacement, and other hemodynamic support), when a major bleeding complication occurs, the clinician must withhold anticoagulant therapy. Blood volume repletion and restoration of normal platelet count (in case of thrombocytopenia $\leq 60 \times 10^9/L$ or thrombopathy) should be considered. Furthermore, since dabigatran is potentially dialyzable (although clinical experience is limited), dialysis should be considered in patients treated with this drug (Table A12).

Life-threatening bleeding

Intracranial hemorrhage or other bleeding events characterized by a decrease in hemoglobin of 5 g/dL or more, requiring transfusion of 4 units or more of packed red blood cells, and bleeding events associated with shock and hypoperfusion or requiring surgery should be considered potentially life-threatening. In this case, in addition to the standard supportive measures, it is mandatory to restore normal blood coagulation as soon as possible using, if available, (four factors) intravenous (i.v.) prothrombin concentrates (PCCs) at a dose of 50 IU/kg.^{19,20}

In case of treatment failure, administration of activated prothrombin concentrate (FEIBA, Baxter) containing Factors II, VII, IX, X in inactive and active forms at a dose of 50 IU/kg (up to 200 IU/kg/day) or administration of recombinant activated Factor VII (rFVIIa: Novo Seven; 90-100 $\mu\text{g}/\text{kg}$) should be considered, although use of these compounds may be associated with a high risk of thromboembolic complications.^{18,21}

Tranexamic acid at a dose of 10-30 mg/kg (i.v.) may be considered as a supportive measure, although there are no clinical data on the use of this compound in patients receiving NOAC²² (Table A13).

In the future, since an increase in the use of NOAC is expected, protocols for the management of adverse bleeding events (periodically revised in consideration of new information from literature) should be established in each hospital. Strategies for switching to and from NOAC should also be put in place (Table A14).^{17,23}

Conclusions

New oral anticoagulants are a new treatment option particularly favorable for the management of patients with NVAf and acute VTE. Risk of thromboembolic and hemorrhagic complication should be evaluated in each patient before the intro-

duction of an NOAC. Due to their relatively short half-life, compliance to therapy appears to be crucial, and an incorrect drug intake may result in therapeutic failure or in the occurrence of severe and potentially life-threatening adverse events. Clinician expertise in treating and monitoring acute and chronic diseases may be central to the management of these new anticoagulant drugs, helping to increase the benefits and to reduce complications of this therapy.

References

1. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-92.
2. Connolly SJ, Eikelboom J, Joyner C, et al. Apixabanin patients with atrial fibrillation. *N Engl J Med* 2011;364:806-17.
3. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51.
4. Patel MR, Mahaffey KW, Garg J. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-91.
5. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. *New Engl J Med* 2013;368:699-708.
6. Schulman S, Kakkar AK, Schellong SM, et al. A Randomized trial of dabigatran versus warfarin in the treatment of acute venous thromboembolism (RE-COVER II). *ASH Annual Meeting*, San Diego, CA, USA, 2011.
7. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *New Engl J Med* 2009;361:2342-52.
8. Buller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *New Engl J Med* 2012;366:1287-97.
9. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *New Engl J Med* 2010;363:2499-510.
10. Romualdi E, Donadini MP, Ageno W. Oral rivaroxaban after symptomatic venous thromboembolism: the continued treatment study (EINSTEIN-Extension study). *Expert Rev Cardiovasc Ther* 2011;9:841-4.
11. Goldhaber SZ, Leizorovicz A, Kakkar AK, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med* 2011;365:2167-77.
12. Cohen AT, Spiro TE, Büller HR, et al. Extended-duration rivaroxaban thromboprophylaxis in acutely ill medical patients: MAGELLAN study protocol. *J Thromb Thrombolysis* 2011;31:407-16.
13. Cohen AT, Spiro TE, Büller HR, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med* 2013;368:513-23.
14. Galanis T, Merli GJ. New oral anticoagulants: prevention of VTE in phase III studies in total joint replacement surgery and the hospitalized medically-ill patients. *J Thromb Thrombolysis* 2013;36:141-8.
15. Mega JL, Braunwald E, Mohanavelu S, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised,

- double-blind, phase II trial. *Lancet* 2009;374:29-38.
16. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. *Eur Heart J* 2012;33:2719-47.
 17. Heidbuchel H, Verhamme P, Alings M, et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *Eur Heart J* 2013;34:2094-106.
 18. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3:692-4.
 19. Eerenberg ES, Kamphuisen PW, Sijkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011;124:1573-9.
 20. Marlu R, Hodaj E, Paris A, et al. Effect of nonspecific reversal agents on anticoagulant activity of dabigatran and rivaroxaban. A randomised crossover ex vivo study in healthy volunteers. *Thromb Haemos* 2012;108:217-24.
 21. van Ryn J, Ruehl D, Priepke H, et al. 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;93:148.
 22. Shakur H, Roberts R, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010;376:23-32.
 23. Palareti G, Ageno W, Ferrari A, et al. Clinical management of rivaroxaban-treated patients. *Expert Opin Pharmacother* 2013;14:655-67.
 24. Agnelli G, Becattini C, Franco L. New oral anticoagulants for the treatment of venous thromboembolism. *Best Pract Res Clin Haematol* 2013;26:151-61.

Appendix

New oral anticoagulants: key messages for clinicians

Characteristics	ARISTOTELE		RE-LY		ROCKET -AF	
	Apixaban	Warfarin	Dabigatran	Warfarin	Rivaroxaban	Warfarin
No. patients	9120	9081	6076	6022	7131	7133
Age (years)	70 (63-76)	70 (63-76)	71.5	71.5	73 (65-78)	73 (65-78)
Gender (women)	35.5%	35%	36.8%	36.7%	39.7%	39.7%
Dose (mg)	5 mg twice	Target INR 2-3	150 twice	Target INR 2-3	20	Target INR 2-3
Follow up (days)	657	657	730	730	707	707
CHADS2 score (mean \pm SD)	2.1 \pm 1.1	2.1 \pm 1.1	2.2 \pm 1.2	2.1 \pm 1.1	3.5 \pm 0.94	3.5 \pm 0.95

Table A1. Randomized controlled trials comparing NOACs and vitamin K antagonists in patients with non-valvular atrial fibrillation.

NOAC	Dabigatran	Rivaroxaban	Apixaban
Phase III study	RE-COVER RE-COVER II	EINSTEIN DVT EINSTEIN PE	AMPLIFY
Treatment	Enoxaparin/dabigatran vs enoxaparin/warfarin	Rivaroxaban vs enoxaparin/VKAs	Apixaban vs enoxaparin/warfarin
Design	Double blind	Open-label	Double blind double-dummy
No. patients	RECOVER no. 2539 RECOVER II no. 2589	EINSTEIN DVT no. 3449 EINSTEIN PE no. 4832	AMPLIFY 5395
Dose (mg)	LWMH (100U/kg bid) Days 1-7 Dabigatran 150 bid from Day 8	Rivaroxaban 15 mg bid Days 1-21 and 20 mg bid from Day 22	Apixaban 10 mg bid Days 1-7 and 5 mg bid from Day 8
Duration	RE-COVER 6 months RE-COVER II 6 months	EINSTEIN DVT 3-6 or 12 months EINSTEIN PE 3-6 or 12 months	AMPLIFY 6 months

Table A2. Randomized controlled trials comparing NOACs and vitamin K antagonists in patients with acute venous thromboembolism. Modified from Agnelli et al., 2013.²⁴

<p>Patient evaluation</p> <ul style="list-style-type: none"> • Check indication to anticoagulation (CHA2DS2VASC in AF patients) • Assess bleeding risk stratification (HAS BLED) • Calculate creatinine clearance • Choice of anticoagulant and dosing regimen • Concomitant medications • Patient education • Assess risk stratification in PE patients 	<p>Lab. tests</p> <ul style="list-style-type: none"> • CBC (platelets count included) • Renal function • Liver function • Coagulation tests
<p>DO NOT consider NOACs if:</p> <ul style="list-style-type: none"> • Rheumatic mitral valve disease • Severe left ventricular dysfunction • Left ventricular aneurysm • Left ventricular thrombus • Mechanical valve prosthesis • Hemodynamically instable PE candidate for thrombolysis • Severe impaired renal function or hemodialysis • Stable INR with warfarin • High TTRs • Poorly compliant patient • Concomitant contraindicated medications 	<p>Consider NOACs if:</p> <ul style="list-style-type: none"> • Strong preference expressed by the patient • Compliant patient • HAS BLED at high risk • Low TTRs • Labile INR • Inability to monitor INR • Dual antiplatelet therapy • Patient undergoing AF electrical cardioversion • Patient with VKA therapy contraindication

Table A3. Initial treatment.

	Risk factors	Score	Score	Cardioembolic risk %/year (CI)
CHADS2	C Congestive heart failure	1	0	1.9 (1.2-3.0)
	H Hypertension	1	1	2.8 (2.0-3.8)
	A Age ≥ 75	1	2	4.0 (3.1-5.1)
	D Diabetes mellitus	1	3	5.9 (4.6-7.3)
	S Stroke or TIA	2	4	8.5 (6.3-11.1)
				5
			6	18.2 (10.5-27.4)

	Risk factors	Score	Score	Cardioembolic risk %/year (CI)
CHA2DS2-VASC SCORE	C Congestive heart failure	1	0	0.78 (0.58-1.04)
	H Hypertension	1	1	2.01 (1.70-2.36)
	A Age ≥ 75	2	2	3.71 (3.36-4.09)
	D Diabetes mellitus	1	3	5.92 (5.53-6.34)
	S Stroke or TIA	2	4	9.27 (8.71-9.86)
	V Vascular disease (AMI, ACS, PAD)	1	5	15.26 (14.35-16.24)
	A Age 65-74 year	1	6	19.74 (18.21-21.41)
	Sc Gender category	1	7	21.50 (18.75-24.64)
			8	22.38 (16.29-30.76)
			9	23.64 (10.62-52.61)

Table A4. Cardioembolic risk stratification.

HAS-BLED SCORE	Risk factors	Score	Total Score	Bleeding risk %/year
	Stroke/TIA	1	0	1.13
	Age > 65 years	1	1	1.02
	Prior major bleeding or predisposition to bleeding	1	2	1.88
	Hypertension	1	3	3.74
	Medication usage predisposing to bleeding	1	4	8.70
	History of alcohol use	1	5	12.50
	Labile INR	1	6	...
	Liver disease	1	7	...
	Renal disease	1	8	...
			9	...

Table A5. Bleeding risk stratification.

	CrCl mL/min	DABIGATRAN	APIXABAN	RIVAROXABAN
Fraction renal excretion of absorbed dose		80%	27%	35%
APPROVED FOR		CrCl ≥ 30 mL/min	CrCl ≥ 15 mL/min	CrCl ≥ 15 mL/min
NOT RECOMMENDED IF		CrCl < 30 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min
DOSING ADJUSTMENT		<ul style="list-style-type: none"> - CrCl ≥ 50 mL/min No adjustment: 150 mg/bid - CrCl 30-49 mL/min 150 mg bid is possible or 110 mg bid if recommended or high risk of bleeding 	<ul style="list-style-type: none"> - Serum Creatinine < 1.5 mg/dL No adjustment: 5 mg bid CrCl 15-29 mL/min 2.5 mg bid Serum creatinine ≥ 1.5 mg/dL in combination with at least one of: <ul style="list-style-type: none"> - age ≥ 80 years - weight ≤ 60 Kg - concomitant diltiazem 2.5 mg bid 	<ul style="list-style-type: none"> CrCl ≥ 50 mL/min No adjustment: 20 mg qd CrCl 15-49 mL/min 15 mg qd
ESTIMATED DRUG HALF-LIVES IN DIFFERENT STAGES OF CKD (I-V)	CrCl ≥ 60 Stage I-II	14 h	No data	8.5 h (+44%)
	CrCl 30-60 Stage III	18 h	No data	9 h (+52%)
	CrCl 15-30 Stage IV	28 h	No data	9.5 h (+64%)
	CrCl ≤ 30 Stage V	No data	No data	No data

Table A6. NOACs and chronic kidney disease. Modified from Heidbuchel et al., 2013.¹⁷

	DABIGATRAN	APIXABAN	RIVAROXABAN
ACTION	DIRECT THROMBIN INHIBITOR (prodrug)	ACTIVATED FACTOR Xa INHIBITOR	ACTIVATED FACTOR Xa INHIBITOR
DOSE	150 mg bid 110 mg bid	5 mg bid 2.5 mg bid	20 mg qd 15 mg qd
PLASMA PEAK LEVEL AFTER INGESTION	2 h	1-4 h	2-4 h
PLASMA TROUGH LEVEL AFTER INGESTION	12-24 h	12-24 h	16-24 h
ELIMINATION HALF LIFE	12-17 h	12 h	5-9 h young 11-13 h elderly
RENAL/NON-RENAL CLEARANCE OF ABSORBED DOSE	20/80%	73/27%	65/35%
ABSORPTION WITH FOOD	NO EFFECT	NO EFFECT	INTAKE WITH FOOD MANDATORY
ABSORPTION WITH H2B or PPI	-12-30%	NO EFFECT	NO EFFECT
GASTRIC TOLERABILITY	DYSPEPSIA	NO PROBLEM	NO PROBLEM

Table A7. NOACs approved for prevention and treatment of stroke and systemic embolism in non-valvular atrial fibrillation.

	DABIGATRAN	APIXABAN	RIVAROXABAN
ACTION	DIRECT THROMBIN INHIBITOR (pro-drug)	ACTIVATED FACTOR Xa INHIBITOR	ACTIVATED FACTOR Xa INHIBITOR
PROPHYLACTIC DOSE (THR-KHR)	220 mg od	2.5 mg bid	10 mg od
THERAPEUTIC DOSE (DVT-PE)	NA	10 mg bid Day 1-7 5 mg bid from Day 8	15 mg bid Day 1-21 20 mg from Day 22
PLASMA PEAK LEVEL AFTER INGESTION	2 h	1-4 h	2-4 h
PLASMA TROUGH LEVEL AFTER INGESTION	12-24 h	12-24 h	16-24 h
ELIMINATION HALF LIFE	12-17 h	12 h	5-9 h young 11-13 h elderly
RENAL/NON RENAL CLEARANCE OF ABSORBED DOSE	20/80%	73/27%	65/35%
ABSORPTION WITH FOOD	NO EFFECT	NO EFFECT	INTAKE WITH FOOD MANDATORY
ABSORPTION WITH H2B or PPI	-12-30%	NO EFFECT	NO EFFECT
GASTRIC TOLERABILITY	DYSPEPSIA	NO PROBLEM	NO PROBLEM

Table A8. NOACs approved for prevention and treatment of venous thromboembolism.

Patient interview	<ul style="list-style-type: none"> • Compliance • Thromboembolic events • Bleeding events • Side effects • Hospitalization • Concomitant medication • Consider PPI • Re-assess bleeding and thrombotic risk score 	1-year lab. test	Normal renal function <ul style="list-style-type: none"> • BCC (platelet count included) • Liver function • Renal function • Creatinine clearance
Patient education	<ul style="list-style-type: none"> • Daily intake and adherence to therapy • Consult physician before adding medication • Alert dentist/surgeon or other physician before an intervention 	6-month lab test	Moderate renal failure (CrCl 30-60 mL/min) <ul style="list-style-type: none"> • Renal function • Creatinine clearance
		3-month lab test	Severe renal failure (CrCl 15-30 mL/min) <ul style="list-style-type: none"> • Renal function • Creatinine clearance

Table A9. Monitoring.

	DRUGS/NOACS	DABIGATRAN	APIXABAN	RIVAROXBAN
Antimycotics agents	Ketoconazole	CI	DR	CI
	Voriconazole			CI
	Itraconazole	CI	DR	CI
	Posaconazole	NR		CI
	Fluconazole			*
Antiarrhythmic drugs	Verapamil	DR		
	Dronedaron	CI		CI
	Amiodaron	DR		
	Chinidin	DR		
Antibiotics	Erytromycin			*
	Clarithromycin	W	W	*
	Rifampicin	CI	CI	CI
Anti-platelet agents	Ticagrelor	W		
	Asa			W
	Clopidogrel			W
Anti-epileptics	Fenobarbital			CI
	Fenitoin	CI		CI
	Carbamazepine	CI		CI
OTHERS	Ritonavir	NR	DR	CI
	St. John wort (hypericum)	CI	CI	CI
	SSRI E SNRI	DR		
	NSAD	W		W
	Ciclosporin	CI		
	Tacrolimus	CI		

CI, contraindicated; W, warning on safety; DR, dose reduction; *not clinically relevant rise in rivaroxaban activity.

Table A10. Drug interactions.

- Fatal bleeding *and/or*
- Symptomatic bleeding in a critical area or organ:
 - intracranial
 - intraspinal
 - retroperitoneal
 - intraocular
 - intrarticular
 - intrapericardial
 - intramuscular with compartment syndrome
- and/or*
- Bleeding causing:
 - fall in hemoglobin level of 2g/dl or more or leading to transfusion of 2 or more units of whole blood or red cells

Table A11. Major bleeding definition.

Patient history	<ul style="list-style-type: none"> • Last intake of NOACS • Dosing regimen • New medications • New pathologies • Bleeding risk factors • Estimate drug half-life 	Laboratory tests	<ul style="list-style-type: none"> • BCC (platelet count included) • Renal function • Liver function • Coagulation tests
Standard supportive measurements	<ul style="list-style-type: none"> • Maintain diuresis (DTI) • Look for local bleeding sources • Local hemostasis • Fluid replacement • Transfusion therapy when indicated (FFP, RBC, PLT, fibrinogen) • Tranexamic acid (1g p.o. TID) • Dialysis (dabigatran) 	Next dose of NOAC	<ul style="list-style-type: none"> • Delay or discontinue the next doses of NOAC • Avoid prolonged dose reduction or treatment discontinuation if not strictly necessary

Table A12. Non-life-threatening major bleeding.

Patient history	<ul style="list-style-type: none"> Last intake of NOACS Dosing regimen New medications New pathologies Bleeding risk factors Estimate drug half-life 	Laboratory test	<ul style="list-style-type: none"> BCC (platelet count included) Renal function Liver function Coagulation tests
Standard supportive measurements	<ul style="list-style-type: none"> Maintain diuresis (DTI) Look for local bleeding sources Local hemostasis Fluid replacement Transfusion therapy when indicated (FFP, RBC, PLT, fibrinogen) Tranexamic acid (10-30 mg/kg i.v. every 6-8 h) PCCs 50 U/Kg i.v. 	If failure consider	<ul style="list-style-type: none"> aPCCs (FEIBA) 40 U/kg i.v. or rFVIIa (Novo Seven) 90-100 μg/kg i.v.
		NOAC	<ul style="list-style-type: none"> Treatment discontinuation

Table A13. Life-threatening major bleeding.

	DABIGATRAN (D)	APIXABAN (A)	RIVAROXABAN (R)
FROM LMWH or FONDAPARINUX	<ul style="list-style-type: none"> Discontinue LMWH Start D at the time the next dose of LMWH would have been administrated 	<ul style="list-style-type: none"> Discontinue LMWH Start A at the time the next dose of LMWH would have been administrated 	Start with the first dose of R 0-2 hours before prescribed next dose of parenteral anticoagulant
TO LMWH or FONDAPARINUX	<ul style="list-style-type: none"> Discontinue D Start LMWH at the time the next scheduled dose 	<ul style="list-style-type: none"> Discontinue A Start LMWH at the time the next scheduled dose 	Start with the first dose of parenteral anticoagulant when R should be administrated
FROM VKA	<ul style="list-style-type: none"> Discontinue VKA and check INR when INR < 2 start the first dose of D 	Warfarin should be discontinued and A started when INR < 2	Stop warfarin at least two days and acenocumarol at least one day before introducing R . Check INR: <ul style="list-style-type: none"> INR \leq 2 start R immediately INR 2-3 start R the day after INR > 3 re-check INR after 2 days
TO VKA	Start VKA before D is stopped. Base the warfarin initiation on the creatinine clearance (CrCl) as above: <ul style="list-style-type: none"> CrCl > 50 ml/min stop D 3 days after starting VKA CrCl 30-49 ml/min stop D 2 days after starting VKA 	Start warfarin before A is stopped. A affect INR, so INR testing should be performed just before the next intake of A . Consider also A discontinuation and start LMWH and warfarin at the time of the next dose of A . Stop LMWH when INR reaches acceptable range.	Start warfarin before R is stopped. R affect INR, so INR testing should be performed just before the next intake of R . Consider also R discontinuation and start LMWH and warfarin at the time of the next dose of R . Stop LMWH when INR reaches acceptable range.
FROM UFH	<ul style="list-style-type: none"> Discontinue infusion of UFH Start D immediately with the first dose of D 	A UHF can be initiated when the next dose of A is due	R can be started at the time of UHF discontinuation
TO UFH	<ul style="list-style-type: none"> Stop D Start UHF after 12 h from UHF discontinuation 	UHF can be initiated when the next dose of A is due	UHF can be initiated when the next dose of A is due

Table A14. Switching to- and from-NOACs. Modified from Heidbuchel et al., 2013¹⁷ and Palareti et al., 2013.²³