VIA MEDICA

POSITION PAPER

Cardiology Journal
2018, Vol. 25, No. 4, 423–440
DOI: 10.5603/CJ.2018.0080

ISSN 1897–5593

Use of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation — Messages from the 2018 EHRA

Anna Tomaszuk-Kazberuk[1, 2], Łukasz Kołtowski[1, 3], Paweł Balsam[1, 3], Marek Koziński[1, 4], Agnieszka Kapłon-Cieślicka[1, 3], Karolina Kupczyńska[1, 5], Justyna Domienik-Karłowicz[1, 6], Anna Budaj-Fidecka[1, 3], Piotr Buszman[1, 7, 8], Maciej Wybraniec[1, 9], Paweł Burchardt[1, 10, 11], Błażej Michalski[1, 5], Miłosz J. Jaguszewski[1, 12]

[1]Club 30, Polish Cardiac Society, Poland
[2]Department of Cardiology, Medical University of Bialystok, Poland
[3]First Department of Cardiology, Medical University of Warsaw, Poland
[4]Department of Principles of Clinical Medicine, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[5]Department of Cardiology, W. Bieganski Hospital, Medical University of Lodz, Poland
[6]Department of Internal Medicine and Cardiology with the Center for Diagnosis and Treatment of Venous Thromboembolism, Medical University of Warsaw, Poland
[7]Center for Cardiovascular Research and Development, American Heart of Poland, Katowice, Poland
[8]Third Clinical Department of Cardiology, Silesian Center for Heart Diseases, Medical University of Silesia, Zabrze, Poland
[9]First Department of Cardiology, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland
[10]Department of Biology and Lipid Disorders, Poznan University of Medical Sciences, Poznan, Poland
[11]Department of Cardiology, J. Strus Hospital, Poznan, Poland
[12]First Department of Cardiology, Medical University of Gdansk, Poland

Introduction

Non-vitamin K antagonist oral anticoagulants (NOACs) were developed and approved as substitutes for vitamin K antagonists (VKAs) [1–3]. NOACs have become the preferred treatment strategy in patients with eligible atrial fibrillation (AF) based on their favorable efficacy/safety profile, predictable effect without the need for routine coagulation monitoring together with fewer food and drug interactions when compared with VKAs [1, 4–6]. As the results of new clinical trials are released and clinical experience with NOACs expands, new recommendations in this field are published [1, 3, 4]. Recently, the 2018 European Heart Rhythm Association (EHRA) Practical Guide on the use of NOACs in the setting of AF, the second update of this clinical practice-guiding document, has been published [1].

This review aims to present highlights of the recent update of the Practical Guide, with a particular emphasis on changes and new aspects when compared with its previous versions [1–3]. This manuscript, similarly to the discussed expert consensus, considers several key clinical scenarios for which evidence-based recommendations were framed.

Use of NOACs in valvular heart disease: Eligibility for NOACs

In patients with AF, NOACs are recommended in the prevention of stroke and systemic thromboembolism in a vast majority of patients at risk, excluding only patients who underwent implanta-

Address for correspondence: Dr. Łukasz Kołtowski, First Department of Cardiology, Medical University of Warsaw, ul. Banacha 1a, 02–097 Warszawa, Poland, tel: +48 22 599 19 51, fax: +48 22 599 19 50, e-mail: lukasz@koltowski.com

tion of a mechanical prosthetic valve and those with moderate to severe mitral stenosis, usually due to rheumatic heart disease [4, 7]. The former AF patients with valvular heart disease (VHD) are classified as functional EHRA (Evaluated Heartvalves, Rheumatic or Artificial) type 1 and require therapy with a VKA [4, 6, 7]. On the other hand, the EHRA type 2 category includes patients with all other types of VHD, after mitral valve repair, bioprosthetic valve replacement and transcatheter aortic valve implantation (TAVI) [7]. Such AF patients were at least to some extent enrolled in landmark NOAC trials (e.g. valvular regurgitations or stenoses other than moderate- to severe mitral stenosis, patients > 3 months after bioprosthetic valve implantation or mitral valve repair) or there is no rationale against therapy with NOAC (e.g. patients after TAVI procedures) [8–12]. Therefore, the EHRA experts conclude that these patients may be treated either with a VKA or with a NOAC [1, 4, 7]. One exception are AF patients with a biological mitral prothesis implanted for rheumatic stenosis. Due to typical enlargement and structural changes of atria in this setting, VKAs may be the preferred option over NOACs (Table 1) [1]. Additionally, despite few data supporting such management [13, 14], the EHRA experts believe that AF patients with hypertrophic cardiomyopathy and indications for anticoagulation may benefit from NOACs [1].

Use of EHRA NOAC card, careful dose reduction criteria: Pre-specified follow-up schedule for patients on NOACs

Anticoagulation therapy in AF patients should be initiated ensuring a balance between the risk and benefit [4]. Subsequently, the choice of particular anticoagulant (NOAC or VKA) should be advocated by guidelines of professional societies and indications approved by regulatory authorities [1]. European guidelines generally prefer NOACs over VKAs in majority AF patients **(class I, level of evidence A)** [4]. However, before initiation of any anticoagulant kidney function should be assessed and then monitored if NOAC therapy is started. Additionally, all product characteristics, patient-related factors, and patient preferences should be considered when choosing a particular treatment strategy [15, 16].

Importantly, EHRA experts emphasize that standard NOAC doses, tested in large randomized trials, should be used in clinical practice [1]. In fact, only in RE-LY and ENGAGE-AF were adequately powered to test both lower and higher NOAC doses [3, 9, 17]. Thus, in the clinical practice, we should follow the dose reduction criteria investigated in the fully powered randomized clinical trials (RCTs) [1, 4].

Notably, proton pump inhibitors are proposed in the EHRA guide as protective agents aimed to reduce the event rates of gastrointestinal (GI) bleeding related to NOAC therapy [1]. In particular, they may be considered in patients with known ulcer or previous GI bleeding, as well as those on concomitant dual antiplatelet therapy [18–22]. However, data on this gastroprotective effect in patients treated with NOACs are limited [1].

Education of patients on NOACs at each visit is critically important [23, 24]. Crucial aspects of education comprise: i) intake modalities, i.e. once daily or twice a day, intake with food in case of rivaroxaban, ii) the key role of rigorous adherence to the prescribed therapy, iii) how to deal with any lapse in dosing, and iv) to be careful not to leave their medication behind when travelling. NOAC-treated patients, similarly to those on VKAs, should possess an anticoagulation card [1, 4, 16]. The updated NOAC card proposed by EHRA experts will be available soon in different languages at www.NOACforAF.eu. This uniform card contains information on the used NOAC regimen (e.g. name of anticoagulant, dosing, timing, with or without food), treatment indication, date when treatment was started, concomitant medications, name and address of physician coordinating NOAC treatment, emergency situations (e.g. contact to patient relatives, patient blood group), planned or unplanned visits, recommended follow-up with a checklist, results of hemoglobin concentration as well as kidney and liver tests [1–3].

The follow-up of patients on NOACs has to be cautiously planned, specified and communicated among the different caregivers [4, 25–27]. Medical therapy of NOAC users should be regularly reviewed, preferably the first time 1 month after drug initiation and then at least every 3 months. A structured follow-up of NOAC-treated patients proposed by EHRA experts is shown in Figure 1. The authors of the recent EHRA Practical Guide also updated and expanded the recommended checklist during the follow-up contacts of AF patients on anticoagulation (Table 1) [1, 3].

Adherence to prescribed therapy: Strict adherence plays a key role

NOAC's anticoagulant effect diminishes after 12–24 hours which makes strict adherence to drug intake a critical issue [28]. Importantly, NOAC plasma concentrations and general coagulation tests

Table 1. Checklist during follow-up contacts of atrial fibrillation patients on anticoagulation. Reprinted with permission from: Eur Heart J. 2018; 39(16): 1330–1393.

	Interval	Comments
1. Adherence	Each visit	• Instruct patient to bring NOAC card and complete list of medication: make note and assess average adherence • Re-educate on importance of strict intake schedule • Inform about adherence aids (e.g. special boxes; smartphone applications). Consider specific adherence measuring interventions (e.g. review of pharmacy refill data; electronic monitoring; special education session)
2. Thromboembolism	Each visit	• Systemic circulation (TIA, stroke, peripheral) • Pulmonary circulation
3. Bleeding	Each visit	• 'Nuisance' bleeding: preventive measures possible? Motivate patient to diligently continue anticoagulation • Bleeding with impact on quality-of-life or with risk: prevention possible? Need for revision of anticoagulation indication, dose or timing?
4. Other side effects	Each visit	Carefully assess relation with NOAC: decide for continuation (and motivate), temporary cessation, or change of anticoagulant drug
5. Co-medications	Each visit	• Prescription drugs; over-the-counter drugs • Careful interval history: also temporary use can be risky
6. Blood sampling (incl. hemoglobin, renal and liver function)	Yearly	Patients other than those specified below
	6-monthly	≥ 75 years (especially if on dabigatran) or frail
	x-monthly	If renal function CrCl ≤ 60 mL/min: recheck interval = CrCl/10
	If needed	If intercurrent condition that may impact renal or hepatic function
7. Assessing and minimizing modifiable risk factors for bleeding	Each visit	• As recommended by current guidelines • Particularly: uncontrolled hypertension (systolic > 160 mmHg), medication predisposing for bleeding (e.g. ASA, NSAIDs), labile INR (if on VKA), excessive alcohol intake)
8. Assess for optimal NOAC and correct dosing	Each visit	Especially based on the above, re-assess whether • The chosen NOAC is the best for the patient • The chosen dose is correct

ASA — acetylsalicylic acid; CrCl — creatinine clearance (preferably measured by the Cockcroft-Gault method); INR — international normalized ratio; NOACs — non-vitamin K antagonist oral anticoagulans; NSAIDs — non-steroidal anti-inflammatory drugs; TIA — transient ischemic attack; VKAs — vitamin K antagonists

reflect drug intake over the last 24–48 hours and therefore they cannot be considered tools to monitor adherence to therapy [29]. Regular follow-up assessment with a pre-specified schedule together with education of patients and their families is the preferred strategy to facilitate adherence to NOAC therapy [15, 16, 23, 24, 28, 30]. Other possible tools potentially improving adherence are the use of pharmacy databases to monitor adherence, implementation of technological aids (e.g. medication boxes, smartphone/watchOS applications) [31–33], and preference of once daily dosing regimens over BID regimens [34–36].

Switching between anticoagulant regimens

Appropriate switching between anticoagulants aims at balancing between both thrombotic and bleeding risks. Six clinical scenarios may be considered: 1) switching from a VKA to a NOAC; 2) switching from a NOAC to a VKA; 3) switching from a NOAC to parenteral anticoagulants; 4) switching from a parenteral anticoagulant to a NOAC; 5) switching from one NOAC to another NOAC; and 6) switching from an antiplatelet drug to a NOAC (Fig. 2) [1]. All recommendations are based on the current knowledge regarding pharmacokinetics and pharmacodynamics of anticoagulants. Regarding the above listed situations:

1. NOAC should be initiated immediately when international normalized ratio (INR) value is < 2.0. In patients with INR 2.0–2.5, NOAC may be started immediately or (preferentially) the next day. For INR values exceeding 2.5, INR should be re-checked within 1–3 days.

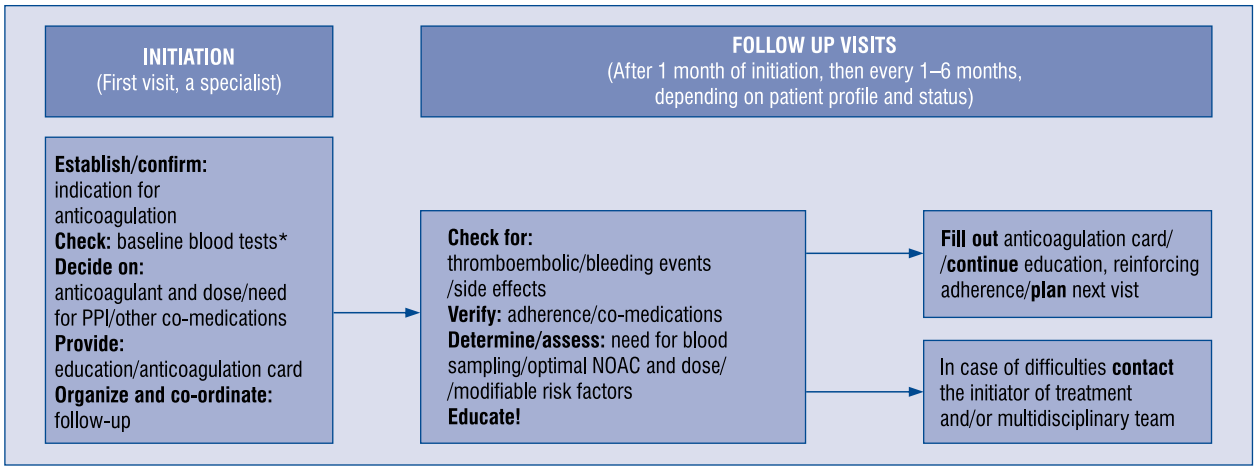

Figure 1. Initiation and follow-up visits of patients on non-vitamin K antagonist oral anticoagulants (NOACs) — a simplified scheme. Dependent on local situation, follow-up may be performed by general practitioners or specialists. *hemoglobin, liver/renal function, coagulation panel; PPI — proton pump inhibitor. Adapted from: Eur Heart J. 2018; 39(16): 1330–1393.

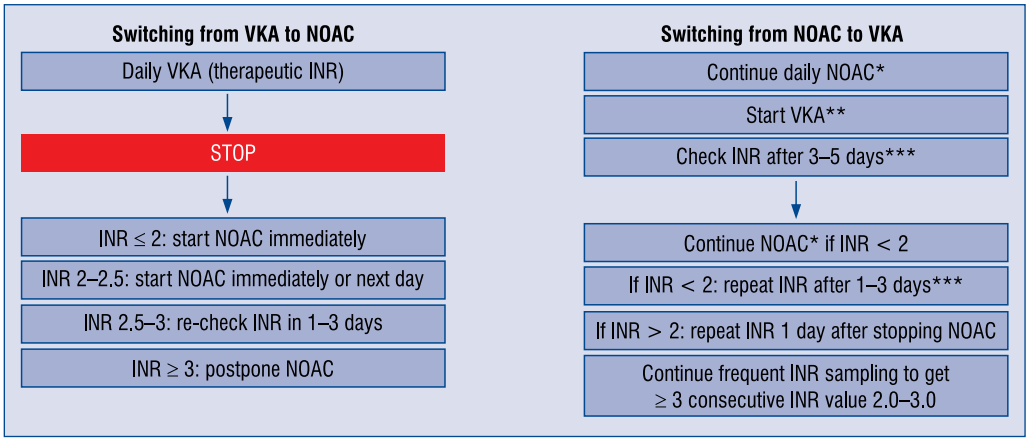

Figure 2. Switching between anticoagulant regimes; *half dose for edoxaban; **loading dose for phenprocoumon; ***before NOAC intake; INR — international normalized ratio; NOAC — non-vitamin K antagonist oral anticoagulant; VKA — vitamin K antagonist. Adapted from: Eur Heart J. 2018; 39(16): 1330–1393.

The estimated time when INR drops below this threshold depends on the current INR and the half-life of the VKA (half-lives for acenocoumarol, warfarin and phenprocoumon are 8–24 h, 36–48 h and 120–200 h, respectively) [1].

2. Due to the delayed onset of VKA action, it may take 5–10 days until INR achieves the therapeutic range. Therefore, both drugs should be used concomitantly until therapeutic INR values are obtained. Loading doses are recommended neither for acenocoumarol nor for warfarin but remain appropriate for phenprocoumon [1, 37–39].
3. Both unfractionated heparin (UFH) and low molecular weight heparin (LMWH) can be started at the time of next scheduled dose of NOAC [1].
4. NOACs can be initiated 2–4 hours after intravenous infusion of UFH is stopped. NOACs can be started when the next dose of LMWH is scheduled [1].
5. An alternative NOAC can be started when the following dose of the initial NOAC is planned unless overdose of the initial NOAC is expected. In such case, a longer interval between doses of NOACs is recommended [1].
6. NOAC may be initiated immediately when either acetylsalicylic acid (ASA) or clopidogrel

is stopped. However, in some AF patients (e.g. undergoing percutaneous coronary intervention [PCI] with stent implantation) combination therapy is required [1].

Pharmacokinetics and drug–drug interactions of NOACs: Check drug–drug interactions

Detailed description of pharmacokinetics of different NOACs remains beyond the scope of the present review. Despite fewer food and drug–drug interactions of NOACs vs. VKAs, pharmacokinetic interactions of the former agents with other drugs and comorbidities should be considered by the treating physicians [1]. Absorbtion, metabolism, distribution, as well as excretion of NOACs have been described in detail previously [3]. An essential mechanism responsible for drug–drug interactions involving NOACs is GI re-secretion over a P-glycoprotein (P-gp) transporter after absorption in the gut. Competitive inhibitors of this pathway, i.e. verapamil, dronedarone, amiodarone, and quinidine, increase plasma levels of NOACs [40, 41]. Notably, hepatic clearance of rivaroxaban and apixaban depends on CYP3A4-type cytochrome P450-mediated elimination. Therefore, strong inhibition or induction of CYP3A4 may affect plasma concentrations of these NOACs [42–44]. In principle, NOACs should not be administered in combination with CYP3A4 and P-gp inhibitors, i.e. dronedarone, itraconazole, ketoconazole, voriconazole [45, 46]. On the other hand, strong inducers of P-gp and/or CYP3A4, i.e. rifampicin or carbamazepine, substantially decrease NOAC levels in plasma and such combinations should be avoided or used carefully [1, 47–49].

Importantly, rivaroxaban for stroke prevention in AF should be administered with food. Otherwise its bioavailability is substantially impaired [44]. Nevertheless, no food interactions were documented with other NOACs exposure as tablet formulation [50–52]. Last but not least, dabigatran capsules must not be opened since it may result in a considerable increase in its bioavailability [51, 53].

In summary, potential drug–drug interactions, especially in combination with other clinical risk factors, influencing NOAC levels in plasma are crucial for selecting the most appropriate NOAC-therapy and/or a 'reduced dose' for a specific patient [41, 42, 54, 55]. More detailed information on NOAC interactions is provided in the recent update of the Practical Guide and in summaries of product characteristics [1].

NOACs in patients with chronic kidney disease or advanced liver disease: Assess kidney function, creatinine clearence!

Both kidneys and liver are substantially involved in the metabolism and elimination of NOACs. Kidney function should be assessed at least once a year in patients on NOACs in order to adapt the drug dose if necessary. In patients with reduced creatinine clearance (CrCl), i.e. ≤ 60 mL/min, it is recommended to assess kidney function more frequently. Importantly, CrCl should be preferably assessed by using the Cockroft-Gault method and the minimum frequency of kidney function evaluation in months may be calculated by dividing CrCl by 10 [1, 4].

All four NOACs demonstrated comparative efficacy and safety in patients with mild to moderate chronic kidney disease (CKD), i.e. **CrCl ≥ 30 mL/min**, when compared with warfarin [56–61]. In cases with CrCl 30–50 mL/min, dosing of NOACs should be adapted as follows:

- dabigatran — 150 mg BID or 110 mg BID in patients at high risk of bleeding;
- rivaroxaban — 15 mg QD;
- edoxaban — 30 mg QD;
- apixaban — 2.5 mg BID if at least two out of three criteria are fulfilled: age ≥ 80 years, body weight ≤ 60 kg, creatinine ≥ 1.5 mg/dL.

Rivaroxaban, apixaban, and edoxaban, but not dabigatran, are approved in Europe in cases with severe CKD, i.e. **CrCl of 15–29 mL/min**, at reduced doses:

- rivaroxaban — 15 mg QD;
- edoxaban — 30 mg QD;
- apixaban — 2.5 mg BID.

In contrast, all NOACs are contraindicated in patients with a **CrCl of ≤ 15 mL/min** and on dialysis (Table 2) [1].

Advanced liver disease is associated with impaired blood coagulation resulting in increased bleeding risk. However, it may also lead to thrombotic complications [62]. Additionally, severe liver dysfunction can strongly affect hepatic clearance and drug metabolism [63]. Contraindications to NOACs include coagulopathy associated with hepatic disease and clinically relevant bleeding risk [1, 17, 64–66]. Rivaroxaban is contraindicated in patients with Child-Turcotte Pugh B cirrhosis [67]. Finally, initiation of NOAC therapy in cases with advanced liver disease and their follow-up is recommended at a specialized center in a multidisciplinary team, including a hepatologist and a hematologist [1].

Table 2. Non-vitamin K antagonist oral anticoagulants and renal function. Adapted from: Eur Heart J. 2018; 39: 1330–1393.

Creatinine clearance	Dabigatran	Rivaroxaban	Edoxaban	Apixaban
> 95 mL/min	2 × 150 mg	20 mg	60 mg	2 × 5 mg or 2 × 2.5 mg***
50–95 mL/min	2 × 150 mg	20 mg	60 mg**	2 × 5 mg or 2 × 2.5 mg***
30–50 mL/min	2 × 150 mg or 2 × 110 mg*	15 mg	30 mg	2 × 5 mg or 2 × 2.5 mg***
15–30 mL/min	No	15 mg	30 mg	2 × 2.5 mg
Dialysis	No	No	No	No

*2 × 110 mg in patients at high risk of bleeding. **consider additional dose reduction criteria (body weight ≤ 60 kg, concomitant use of P-glycoprotein inhibitor). ***2 × 2.5 mg if 2 out of 3 fulfilled: age ≥ 80 years, body weight ≤ 60 kg, creatinine > 1.5 mg/dL. Pink backgrounds = cautionary use.

How to measure the anticoagulant effect of NOACs? No need for routine plasma levels assessment

Although the results of standard coagulation tests, including prothrombin time (PT) and activated partial thromboplastin time (aPTT), are affected by NOACs, these tests generally do not accurately reflect NOAC anticoagulant effects. Nevertheless, specific coagulation assays are available to quantify NOAC levels in plasma [29, 68, 69]. Hospitals should consider 24/7 availability of these particular assays, especially in emergency situations. Most routine coagulometers are capable of measuring NOAC plasma levels within 30 minutes [1]. Anti-FXa chromogenic assays reliably measure plasma concentrations of FXa inhibitors. Importantly, unmeasurable anti-Xa activity rules out clinically relevant drug levels. Both, ecarin chromogenic assay (ECA) and diluted thrombin time (dTT) test are proportional to dabigatran blood concentrations and can be used for quantitative assessment [1]. When interpreting the result of a coagulation assay in a patient on NOAC, it is critical to know the time of NOAC administration and its relation to blood sampling. Importantly, the most pronounced effect of a NOAC on the clotting test takes place simultaneously with its peak plasma concentration, i.e. 1–3 hours after NOAC intake [44, 70–75].

NOAC plasma level measurements may be considered in emergencies/complex patient profiles and under expert guidance: Rare indications, precautions and potential pitfalls

As mentioned above, the routine measurement of plasma NOAC concentration to guide therapy is discouraged and should be performed **in particular situations** of potentially essential interactions or specific scenarios, including emergencies. Additionally, these tests should be done in centers with vast experience in the interpretation and performance of such measurements [1].

Emergencies

In emergencies, i.e. bleeding, acute stroke, suspected overdosing, intoxication or in patients undergoing urgent procedures, routine coagulation tests provide a quick information on recent exposure, while specific assays inform us on accurate assessment of plasma NOAC levels [29, 68, 69, 76].

Information on drug exposure may determine the optimal timing of procedure in case of urgent surgery or in planned surgery in patients at high-bleeding risk. Furthermore, coagulation assays may guide thrombolytic therapy, for instance, in cases with acute ischemic stroke [68, 72, 77–79].

Elective procedures

The current EHRA Guide does not recommend routine measurement of NOAC anticoagulant activity before elective procedures [1]. Potential exceptions to this role include: i) situations when the time from the last dose is unknown or uncertain, or ii) in case of potential drug–drug interactions or change in renal/hepatic function, based on concerns on the clearance of the drug [1, 80, 81].

Factors influencing pharmacokinetics

Measurement of plasma NOAC concentration may be also considered in patients at high risk, i.e. very lean or obese patients, uncontrolled cancer patients receiving therapy for malignancies, especially in case of unclear/unknown pharmacokinetic interactions [44, 70–75, 77].

Problem solving: Dosing errors, overdose without bleeding or potential risk of bleeding

Overdose without bleeding

Overdose of NOAC can be a significant clinical problem. In patients with a suspected NOAC overdose, coagulation tests are suitable to set its degree and potential risk of bleeding [29, 68, 69]. Notably, aPTT result within limits of normal practically excludes high levels of dabigatran [72]. A normal PT excludes high levels of edoxaban and rivaroxaban [68]. However, these widely available coagulation tests should not be used for a quantitative estimation of high NOAC concentrations [1]. If a more aggressive normalization of plasma levels is necessary, or rapid normalization is not expected because of major renal failure the measures used in the management of bleedings may be considered (e.g. administration of a specific reversal agent) [1, 2, 82–85].

Management of bleeding under NOACs: Nuisance bleeding, minor bleeding and non-life-threatening major bleeding

Nuisance and minor bleeding

Nuisance bleedings are very often disregarded both by cardiologists and general practitioners, although they are a frequent cause of interruptions of treatment. Majority of these bleeds can be managed conservatively, i.e. by delaying NOAC intake or withholding its dose. Minor bleedings frequently require more aggressive management focused on the cause of bleeding. Epistaxis and gum bleeds should be managed using local anti-fibrinolytics. Recurrent minor bleeding events without causal therapeutic options should be treated using other NOAC with a potentially different bleeding profile, although we have no solid data on this subject [1, 4].

Non-life-threatening major bleeding

In case of a non-life-threatening major bleeding the use of antifibrinolytics, i.e. tranexamic acid, 1 g i.v., repeated every 6 hours if needed or desmopressin 0.3 g/kg i.v. infusion with a maximal dosing of 20 g — especially in specific scenarios with associated coagulopathy or thrombopathy — may be considered. Tranexamic acid is efficacious to support hemostasis, particularly in trauma-induced bleeding, with a favourable safety profile [86–88].

Patients on dabigatran with life-threatening bleedings: The role of idarucizumab

Life-threatening bleedings

The most relevant changes have been introduced in measures concerning life-threatening bleedings. Patients on NOACs with such type of bleeding benefit from its reversal. In the REVERSE-AD study, fragment of humanized monoclonal antibody, idarucizumab was successfully implemented in patients on dabigatran with life-threatening bleedings, or with the necessity of a major life-saving emergency surgery [82, 83, 89]. Since anticoagulant effect of dabigatran can be fully reversed by idarucizumab within minutes, the use of 5 g idarucizumab administered intravenously in two bolus doses of 2.5 g no more than 15 minutes apart, is recommended as first choice of therapy in case of life-threatening bleeding. After 24 hours dabigatran can be effectively re-initiated if clinically indicated (Fig. 3) [82, 83, 89, 90].

Recently, new data were reported on the possibility of direct reversal of apixaban, edoxaban, or rivaroxaban. Andexanet alpha, based on the ANNEXA-4 study [83, 84] may become the first line therapy in life-threatening bleeding under FXa-inhibitor therapy. Although approved in USA, its regulatory approval and availability are pending in Europe. Thus, the direct reversal of FXa-inhibitors remains unavailable in clinical settings [91]. In the ANNEXA-4 study, which includes exclusively patients with major or life-threatening bleeding, the drug is given as a bolus over 15–30 minutes, followed by a 2-hour infusion. The dosing depends on the kind of NOAC-therapy and on the timing since last intake [84]. Nevertheless, anticoagulant activity may re-appear after stopping the infusion. Thus, it is actually unknown at which point in time and with which anticoagulant effect FXa inhibitors or heparin should be re-administered following andexanet alpha use.

Data coming from RCTs and registries investigating NOACs have demonstrated that administration of coagulation factors such as prothrombin complex concentrate (PCC) or activated PCC (aPCC) are rarely needed [91, 92]. Antagonizing the effect of NOAC has to be considered very carefully because of possible prothrombotic effect [93–99]. On the other hand, in cases with severe/life-threatening bleedings with no clear secondary/reversible/treatable cause the potential risks of re-initiating anticoagulation may outweigh the

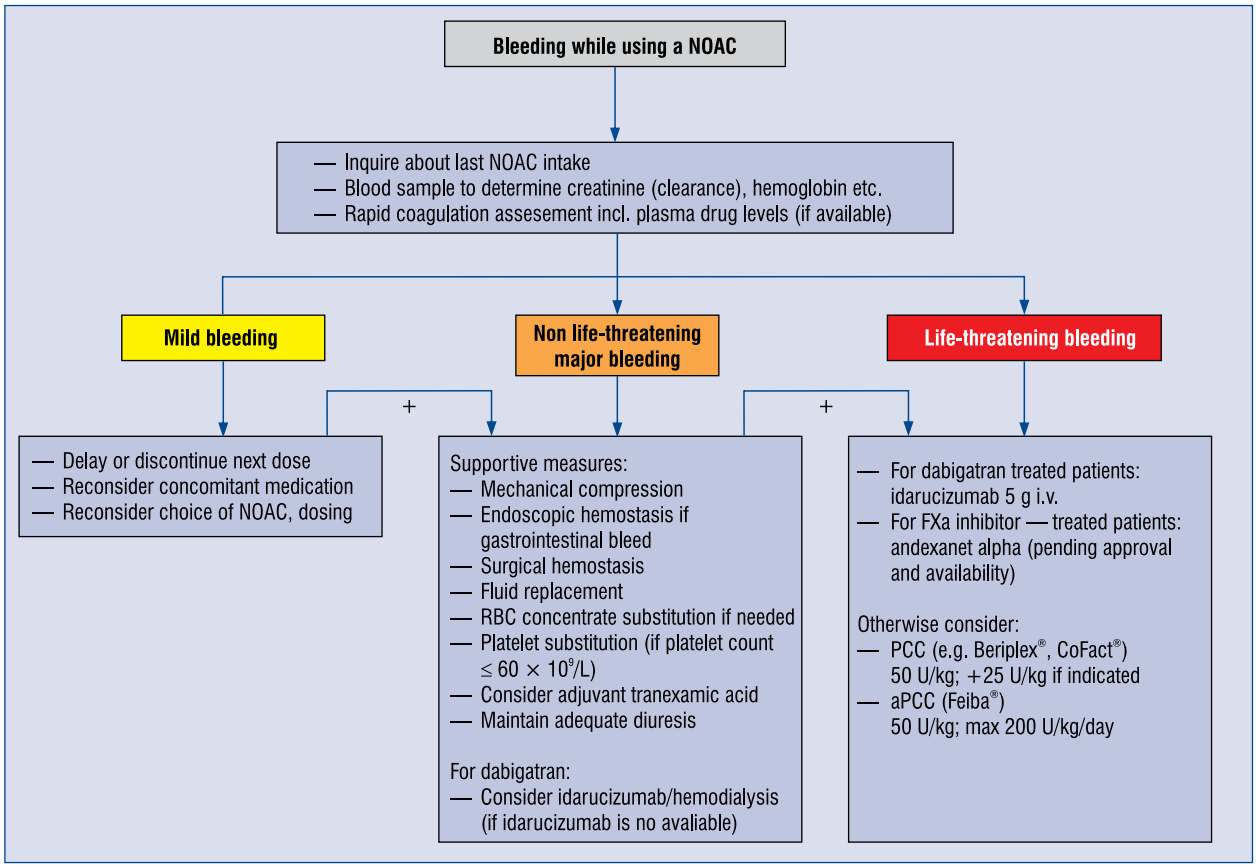

Figure 3. Management of bleeding in patients on non-vitamin K antagonist oral anticoagulants (NOACs); aPCC — activated prothrombin complex concentrate; PCC — prothrombin complex concentrate; RBC — red blood cell. Reprinted with permission for: Eur Heart J. 2018; 39(16): 1330–1393.

benefits of NOAC therapy [1]. In such situations, percutaneous or surgical left atrial appendage occlusion may be considered as a valuable option instead of long-term anticoagulation [1, 4, 100]. Finally, whether the use of PCC or aPCC is useful in NOAC-related intracranial bleeding is still hotly debated [101–104] since a multicentre analysis did not reveal a significant benefit on hematoma enlargement [105]. In patients with intracranial bleeding caused by dabigatran, reversal of the anticoagulant effect is possible by infusion of reversal agent, idarucizumab. Hematoma growth was observed in 2 out of 12 patients with intracranial bleeding treated with dabigatran receiving idarucizumab on hospital admission [106].

Patients presenting with acute stroke: Use of endovascular thrombectomy is a 'first-line treatment' in selected cases

The incidence of stroke ranges from 1% to 2% in the subset of AF under anticoagulation therapy. Both assessment of adherence to NOAC therapy and measurement of anticoagulant plasma level on admission remains crucial to optimize the secondary prevention strategy [107].

Thrombolytic therapy after NOAC

Revolutionary data were shown on management of the acute course of ischemic stroke in AF patients treated with NOAC. According to the nowadays recommendations thrombolytic therapy with the use of recombinant tissue plasminogen activator (rt-PA) cannot be given on full anticoagulation and/or within 24 hours (or longer in case of renal insufficiency, in elderly, etc.) after the last dose of a NOAC due to their plasma half-lives and the risk of uncontrolled bleedings [108]. This recommendation does not apply to dabigatran because of the availability of idarucizumab [83]. According to the REVERSE-AD trial, idarucizumab acts instantly, completely and durably. After reversal and assessment of coagulation status, thrombolysis i.v. within 4.5 hours of onset of moderate to severe stroke seems feasible and safe [106, 109]. It is unknown yet if the same approach will be safe and

effective also for Xa-inhibitors once andexanet alpha becomes available [1]. Last but not least, the use of rt-PA may be considered after NOAC intake when NOAC specific coagulation measurement is performed and/or time frame of the last dose is known [110–112]. Thus, as mentioned above, the easy-to-use point-of-care testing should be available 24/7 for emergency situations (currently possible in a minority of labs) [1].

Endovascular thrombectomy

The benefits of endovascular thrombectomy performed within 7.3 hours from symptom onset have been documented in non-anticoagulated patients having occlusion of a distal portion of internal carotid artery or proximal middle cerebral artery [113]. The eventual effect of present anticoagulation on reperfusion related risk of bleeding must be considered in patients on NOACs presenting with ischemic stroke. An alarmingly high rate of asymptomatic hemorrhagic transformation was reported in a recent registry including 28 patients with stroke on NOACs undergoing mechanical recanalization [114]. Currently, although endovascular thrombectomy is set as a 'first line strategy' in a subset with contraindication for thrombolytic therapy by the European Stroke Organization [115], the American Heart Association provided no recommendation in this regard [108], thus, more prospective studies are warranted to support mechanical recanalization.

No need for bridging: Planned invasive procedures, surgery, or ablations

Minor bleeding risk

In most minor surgical procedures, i.e. dental interventions, cataract or glaucoma intervention, endoscopy without biopsy, superficial surgery, and procedures with controllable bleeding, oral anticoagulation should not be interrupted. Above-mentioned procedures may be performed 12–24 hours after the last NOAC intake and restarted 6 hours after the procedure [1].

Low bleeding risk

In case of low-bleeding-risk-procedures, i.e. cardiac device implantations, endoscopy with biopsy, prostate or bladder biopsy, electrophysiological study or catheter ablation, excluding complex procedures, performed in patients with normal kidney function, it is recommended to take the last NOAC dose of 24 hours before the elective procedure [1, 116]. It is important to check the kidney function and to adapt the time of NOAC withdrawal.

High bleeding risk

In high-risk major bleeding invasive procedures, i.e. spinal or epidural anaesthesia, lumbar diagnostic puncture, thoracic surgery, abdominal surgery, major orthopedic surgery, liver or kidney biopsy, transurethral prostate resection, it is recommended to take the last NOAC dose 48 hours or longer before surgery [1].

Importantly, preoperative bridging with LMWHs or UFH is not recommended in patients treated with NOACs [1, 117, 118]. In case of immediate and complete hemostasis, NOACs can usually be resumed 6–8 hours after the end of the intervention. Notably, restarting full dose anticoagulation within the first 48–72 hours after the procedure is associated with substantial bleeding risk and in individual patients this risk may exceed the prothrombotic risk. In general, initiation of post-operative thromboprophylaxis 6–8 hours after surgery and resuming a NOAC 48–72 hours after operation, but as soon as possible, can be considered (Table 3) [1].

Anticoagulation in the setting of AF ablations remains a difficult problem. On one hand, an increased risk of thromboembolic complications exists in these patients, on the other there is a substantial risk of bleeding during the procedure [119, 120]. The last NOAC dose should be administered 12 hours before AF ablation, especially if transseptal puncture is to be performed without periprocedural imaging. The results of the ongoing Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study are awaited. This large prospective cohort study (n = 3291) aims to determine how to optimally manage NOAC-treated AF patients undergoing elective surgical or interventional procedures (PAUSE; NCT02228798) [121].

Urgent surgical intervention

All patients requiring urgent surgery should stop NOAC immediately. Three categories of intervention have been proposed: 1) immediate procedures, 2) urgent procedures, and 3) expedite procedures [1]. In case of dabigatran-treated patients, who require life-, limb-, organ-saving procedure (immediate procedure) within minutes, it is recommended to consider reversal with idarucizumab [83, 122]. If dedicated agent is not available, administration of PCC or aPCC is advised despite lack of evidence [102, 117, 123]. Urgent and expedite procedures should be deferred, if pos-

Table 3. Non-vitamin K antagonist oral anticoagulant (NOAC) treatment strategy before atrial fibrillation (AF) ablation. Rule out left atrium/left atrial appendage thrombus prior to ablation if ≥ 36 hours without NOAC, if there is doubt about compliance, or in high thromboembolic risk. Target activated clotting time during ablation: 300–350 s. Adapted from: Europace 2018; 20(8): 1231–1242.

Last intake of NOAC	(–)24 to (–)12 hours	Prior to planned AF ablation
Factors to shorten interruption	— High CHA_2DS_2-VASc score ≥ 3 — No heparin i.v. prior to 1st TSP — Operator experience — Imaging for transseptal puncture — Large left atrium	
Factors to lenghten interruption	— Low CHA_2DS_2-VASc score ≤ 2 — Heparin i.v. prior to 1st TSP — Limited operator experience — No imaging for transseptal puncture — Normal size left atrium — Reduced renal function	
Reasumption	3 to 5 hours after the procedure	Rule out tamponade and other major bleeding prior to restarting

TSP — transeptal puncture

sible, until 12–24 hours after last dose [1]. Routine coagulation tests cannot exclude drug levels for all of the NOACs, though normal aPTT for dabigatran and normal PT for rivaroxaban exclude high levels of these drugs. Plasma levels and specific coagulation tests (dTT/ECA for dabigatran and anti-FXa for factor Xa inhibitors) provide close understanding of coagulation status [1].

Use of NOACs in combination with antiplatelet therapy as a preferred strategy: Patients with AF and coronary artery disease

So far there was lack of large outcome trials comparing VKAs and NOACs in patients with AF undergoing PCI for acute coronary syndromes or for stable coronary artery disease, in particular subset treated with single- or dual-antiplatelet therapy [124]. New data coming from randomized clinical trials on NOACs post-PCI have emerged. There are two large studies addressing this topic, namely PIONEER AF-PCI [125] and RE-DUAL PCI [126]. The first one compared two rivaroxaban dosages to VKA and double antiplatelet therapy for 12 months (n = 2124), and showed that rivaroxaban lowered the risk of clinically relevant bleeding complications compared to VKA, irrespective of double antiplatelet therapy combination. The limitation of this trial were the dosages of rivaroxaban (i.e. 2.5 mg and 15 mg) that have not been validated for stroke prevention in the Caucasian population [125]. The RE-DUAL PCI evaluated two doses of dabigatran (110 mg and 150 mg BID) in combination with clopidogrel or ticagrelor (dual therapy) vs. standard triple therapy with VKA, ASA and clopidogrel or ticagrelor in a subset of AF undergoing PCI with stent implantation (n = 2725). Dual therapy strategy with of both doses of dabigatran reduced non-major and major bleeding events compared to triple therapy, and was non-inferior (110 mg) or superior (150 mg) to VKA for prevention of cerebral ischemic events [126].

There is no more support for using bare metal stent in coronary artery disease to shorten the duration of $P2Y_{12}$ therapy in patients on NOACs [1, 4, 18]. The use of new $P2Y_{12}$ inhibitors (ticagrelor, prasugrel) in triple therapy is discouraged (**class III, level of evidence C**) [4, 18]. However, it is possible to use antiplatelet agents in combination with NOAC in dual therapy (without ASA) in patients with high thrombotic risk, acute coronary syndromes, or previous stent thrombosis [1]. Shortening of triple therapy is now the preferred strategy. In patients with high ischemic risk, triple therapy should be continued for 1–6 months (depending on bleeding risk) with subsequent dual therapy until 1 year [127, 128]. There is a general agreement among the EHRA experts not to extend triple therapy beyond 6 months [1].

Cardioversion in patients treated with NOACs

In patients with AF lasting > 48 hours (or of unknown duration) undergoing cardioversion, effec-

tive oral anticoagulation needs to be fixed for at least 3 weeks before the procedure or transesophageal echocardiography (TEE) has to be performed to rule out left atrial thrombi [4, 129, 130]. After cardioversion, oral anticoagulation is mandatory for at least another 4 weeks for all patients [1, 4, 130].

Single NOAC dose ≥ 4 hours before cardioversion (≥ 2 h after apixaban loading dose) is safe and effective in patients with AF of ≥ 48 hours duration, provided that TEE is performed prior to cardioversion [1]. A similar strategy of initiating a NOAC before cardioversion, with a TEE dependent on institutional policy or patient-related stroke risk, is applicable to those with AF of ≥ 48 hours duration [131–133].

Patients with thrombus on TEE cardioversion should be postponed. Treatment with VKA is standard management in this scenario. However, NOACs may be also considered an option, especially in patients in whom VKAs are poorly tolerated or adequate INR control cannot be achieved [9, 134].

Frail and elderly patients should not be undertreated: NOACs in special clinical scenarios

NOACs in frail and older patients

A meta-analysis that included data for all four NOACs investigated in the phase 3 RCTs suggests the lack of age influence on the NOAC efficacy/safety profile [135]. In older patients, higher absolute risk resulted in the larger absolute risk reduction when using NOACs instead of VKA. Additionally, there was a lower number needed to treat compared to younger patients [136]. Although bleeding rate was higher in elderly patients, the overall pattern of bleedings comprising reduced intracranial and increased GI bleeding showed no difference between NOACs and VKA. The rate of intracranial bleedings is lower with all NOACs vs. VKA [135].

Frailty and falls

According to the EHRA experts frailty should not exclude patients from treatment with anticoagulants. Of note, frail and older patients are at an increased risk of stroke and have the biggest benefit from oral anticoagulation [1, 137]. In this particular patient subset, the benefit of NOACs vs. VKA has best been documented for edoxaban and apixaban [138, 139]. To improve the situation, all falling patients on oral anticoagulant should be carefully assessed by multidisciplinary team assessment to address the risks and remediable pathology to minimize the risk of further falls [1, 140].

Dementia and anticoagulation

Dementia should not be an exclusion exclusion criterion to anticoagulation therapy [141, 142].

Obesity

There is very scarce data with respect to anticoagulation therapy in extreme obesity, thus, the use of VKA in patients with a body mass index ≥ 40 kg/m^2 or weight > 120 kg should be considered [143, 144]. In cases when a NOAC is required in obese patients, specific measurements of drug trough levels should be considered [1].

Low body weight

Severely underweight patients, i.e. < 50 kg, were underrepresented in large RCTs. Even for apixaban and edoxaban that were dose-adjusted based on body weight, data are limited for this particular subset [1]. On the other hand, VKA therapy may substantially increase bleeding risk in underweight patients [145]. If therapy with a NOAC is warranted in these individuals, measurement of trough levels may be considered to check for drug accumulation [146].

Women of reproductive age

All cases of abnormal uterine bleeding on anticoagulation require assessment for underlying structural problems and potential local hormonal therapy or surgical procedures to reduce the risk of recurrence of abnormal uterine bleeding. Importantly, due to the lack of data on their safety, all NOACs are contraindicated in pregnancy as well as during breastfeeding [1].

NOACs in athletes

Undoubtedly, athletes on anticoagulation should avoid contact sports. Limited evidence exists on the use of NOACs in such patients. Theoretically, the use of an once daily agent administered in the evening may be advantageous in athletes. Such a regimen allows to avoid high NOAC concentrations during the actual exercise [1].

Epilepsy

Epilepsy is a relatively frequent disease especially in population after stroke. Patients who suffer generalized seizures are particularly vulnerable to head trauma. Notably, tongue biting is a risk of bleeding [147, 148]. Since anticoagulation is strongly affected by antiepileptic drugs [48], in some scenarios, NOACs may not be the preferred choice [1].

Anticoagulation in patients with a malignancy

Anticoagulation therapy in population with cancer stands for a very important clinical problem. Nevertheless, the data is scarce. Of note, HOKUSAI-VTE Cancer trial comparing edoxaban with LMWH targeted cancer patients with venous thromboembolic disease (VTE) but not AF [149]. Edoxaban was non-inferior with regard to the primary endpoint of recurrent VTE and major bleeding. Recurrent VTE tended to be reduced with edoxaban, major bleeding — due to elevated event rates of GI bleeding in patients with GI cancer — was higher [149]. Also several meta-analyses including VTE trials reported similar or better efficacy of NOACs in comparison to VKA or LMWH for VTE prevention in small cancer populations, although major bleeding rates were higher [150]. Further research is required to investigate the application of these findings to AF subset with malignancy. Furthermore, drug–drug interactions between NOACs and specific chemotherapeutic agents are still not fully understood [1, 151].

Summary: New EHRA guide highlights and take home messages

Although NOACs have emerged as the preferred choice, many unresolved questions remain. Herein, we present several key messages provided by an updated "EHRA Practical Guide" essentially improving our knowledge and confidence in the clinical routine:

1. The strategy with NOACs can be used in patients with VHD. NOACs are not recommended in patients after mechanical valve implantation or mitral stenosis of rheumatic origin.
2. The EHRA NOAC card should be distributed to patients on NOACs both at initiation and during follow-up.
3. Proper education by improvement of knowledge and implementation of technological aids should be used to optimize adherence to the prescribed NOACs, including dedicated mobile applications with decision support systems.
4. Tested standard doses of NOACs should be recommended to provide optimal benefit for the patient. Dose reduction of NOACs should be carefully discussed and based on the dose reduction criteria used in the large phase 3 RCTs.
5. Drug–drug interactions should be carefully checked in every patient before the strategy with NOAC is recommended.
6. Renal function should be assessed using CrCl preferably estimated by the Cockroft-Gault formula. The minimum frequency of renal function testing in months may be calculated by dividing CrCl by 10.
7. Routine assessment of NOAC plasma levels is not obligatory and should be limited to particular situations like emergencies (severe bleeding, urgent surgery, and stroke) or complex patient profiles (e.g. multiple relevant drug–drug interactions, severe over-/ /underweight or reduced kidney function) and should be performed under the guidance of a coagulation expert.
8. The use of NOACs with antiplatelet therapy is feasible, safe and preferred over VKA, however triple therapy with potent $P2Y_{12}$ inhibitors should be avoided (prasugrel, ticagrelor).
9. Endovascular thrombectomy is the 'first line strategy' in a subjects with contraindications to thrombolysis by the European Stroke Organization.
10. Thrombolysis with rt-PA can be used when no NOAC effect can be assumed by specific coagulation assays or after NOAC effect reversal.
11. Frail and elderly patients should not be undertreated. NOACs are safe and efficient in high-risk subsets

Conflict of interests/Disclosure: Anna Tomaszuk-Kazberuk — received speaking fees from Boehringer Ingelheim; Advisory Boards: Bayer, Boehringer Ingelheim outside the submitted work; Łukasz Kołtowski — received institutional research grants from Reva Medical Inc., personal fees from Abbott, Boston Scientific, travel grants from Boehringer Ingelheim outside the submitted work; Paweł Balsam — received institutional research grants from Bayer AG, personal fees from Boehringer Ingelheim, Bayer AG, Pfizer outside the submitted work; Marek Koziński — received speaking fees from Abbott Laboratories, travel grant from Boehringer Ingelheim outside the submitted work; Agnieszka Kapłon-Cieślicka — received speaking fees and/or travel grants from: Abbott Laboratories, Bayer, Boerhringer Ingelheim, Boston Scientifc, MSD, Pfizer, Sandoz, Servier, Viventum outside the submitted work; Piotr Buszman — institutional research grants: Balton, Merill Lifesciences, Abbott, Medtronic, speaker fees: Balton, Meril Lifesciences, Boston Scientific, AstraZeneca outside the submitted work; Maciej Wybraniec — research grant from Adamed Group under the auspices of Polish Cardiac Society, travel grants from Bayer, Pfizer, Orion Pharma outside the submitted work; Miłosz J. Jaguszewski — received speaking fees and travel grants from

Boheringer Ingelheim, Biotronic, St. Jude Medical, Abbott, Servier, AstraZeneca, Sandoz, Pfizer, and Egis outside the submitted work. The other authors report no conflicts of interest.

References

1. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018; 39(16): 1330–1393, doi: 10.1093/eurheartj/ehy136, indexed in Pubmed: 29562325.
2. Heidbuchel H, Verhamme P, Alings M, 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.
3. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2015; 17(10): 1467–1507, doi: 10.1093/europace/euv309, indexed in Pubmed:26324838.
4. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016; 37(38): 2893–2962, doi: 10.1093/eurheartj/ehw210.
5. Barnes GD, Ageno W, Ansell J, et al. Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH. J Thromb Haemost. 2015; 13(6): 1154–1156, doi: 10.1111/jth.12969.
6. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017; 38(36): 2739–2791, doi: 10.1093/eurheartj/ehx391., indexed in Pubmed: 28886619.
7. Lip G, Collet J, Caterina R, et al. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). EP Europace. 2017; 19(11): 1757–1758, doi: 10.1093/europace/eux240.
8. Avezum A, Lopes RD, Schulte PJ, et al. Apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease: findings from the apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial. Circulation. 2015; 132(8): 624–632, doi:10.1161/CIRCULATIONAHA.114.014807, indexed in Pubmed: 26106009.
9. Ezekowitz MD, Nagarakanti R, Noack H, et al. Comparison of dabigatran and warfarin in patients with atrial fibrillation and valvular heart disease: the RE-LY trial (randomized evaluation of long-term anticoagulant therapy). Circulation. 2016; 134(8): 589–598, doi: 10.1161/CIRCULATIONAHA.115.020950, indexed in Pubmed: 27496855.
10. Breithardt G, Baumgartner H, Berkowitz SD, et al. Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial. Eur Heart J. 2014; 35(47): 3377–3385, doi:10.1093/eurheartj/ehu305, indexed in Pubmed: 25148838.
11. De Caterina R, Renda G, Carnicelli AP, et al. Valvular heart disease patients on edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. J Am Coll Cardiol. 2017; 69(11): 1372–1382, doi: 10.1016/j.jacc.2016.12.031, indexed in Pubmed: 28302288.
12. Pan KL, Singer DE, Ovbiagele B, et al. Effects of non-vitamin k antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and valvular heart disease: a systematic review and meta-analysis. J Am Heart Assoc. 2017; 6(7), doi: 10.1161/JAHA.117.005835, indexed in Pubmed:28720644.
13. Noseworthy PA, Yao X, Shah ND, et al. Stroke and bleeding risks in NOAC- and warfarin-treated patients with hypertrophic cardiomyopathy and atrial fibrillation. J Am Coll Cardiol. 2016; 67(25): 3020–3021, doi: 10.1016/j.jacc.2016.04.026, indexed in Pubmed: 27339501.
14. Dominguez F, Climent V, Zorio E, et al. Direct oral anticoagulants in patients with hypertrophic cardiomyopathy and atrial fibrillation. Int J Cardiol. 2017; 248: 232–238, doi: 10.1016/j.ijcard.2017.08.010, indexed in Pubmed: 28811092.
15. Lane D, Aguinaga L, Blomström-Lundqvist C, et al. Cardiac tachyarrhythmias and patient values and preferences for their management: the European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). Europace. 2015; 17(12): 1747–1769, doi:10.1093/europace/euv233.
16. Heidbuchel H, Berti D, Campos M, et al. Implementation of non-vitamin K antagonist oral anticoagulants in daily practice: the need for comprehensive education for professionals and patients. Thromb J. 2015; 13: 22, doi: 10.1186/s12959-015-0046-0, indexed in Pubmed: 26124699.
17. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013; 369(22): 2093–2104, doi:10.1056/NEJMoa1310907, indexed in Pubmed: 24251359.
18. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). , 2018. Eur Heart J. 2018; 39(3): 213–260, doi: 10.1093/eurheartj/ehx419, indexed in Pubmed:28886622.
19. Scarpignato C, Gatta L, Zullo A, et al. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. BMC Med. 2016; 14(1): 179, doi: 10.1186/s12916-016-0718-z, indexed in Pubmed: 27825371.
20. Ray WA, Chung CP, Murray KT, et al. Association of proton pump inhibitors with reduced risk of warfarin-related serious upper gastrointestinal bleeding. Gastroenterology. 2016; 151(6): 1105–1112.e10, doi: 10.1053/j.gastro.2016.08.054, indexed in Pubmed: 27639805.
21. Di Minno A, Spadarella G, Spadarella E, et al. Gastrointestinal bleeding in patients receiving oral anticoagulation: Current treatment and pharmacological perspectives. Thromb Res. 2015; 136(6): 1074–1081, doi: 10.1016/j.thromres.2015.10.016, indexed in Pubmed: 26508464.
22. Chan E, Lau W, Leung W, et al. Prevention of dabigatran-related gastrointestinal bleeding with gastroprotective agents: a popu-

lation-based study. Gastroenterology. 2015; 149(3): 586–595.e3, doi: 10.1053/j.gastro.2015.05.002.
23. Lane DA, Barker RV, Lip GYH. Best practice for atrial fibrillation patient education. Curr Pharm Des. 2015; 21(5): 533–543, indexed in Pubmed:25175094.
24. Lane DA, Wood K. Cardiology patient page. Patient guide for taking the non-vitamin K antagonist oral anticoagulants for atrial fibrillation. Circulation. 2015; 131(16): e412–e415, doi: 10.1161/CIRCULATIONAHA.114.012808, indexed in Pubmed: 25901074.
25. Gallagher C, Elliott AD, Wong CX, et al. Integrated care in atrial fibrillation: a systematic review and meta-analysis. Heart. 2017; 103(24): 1947–1953, doi:10.1136/heartjnl-2016-310952, indexed in Pubmed: 28490616.
26. Carter L, Gardner M, Magee K, et al. An Integrated Management Approach to Atrial Fibrillation. J Am Heart Assoc. 2016; 5(1), doi:10.1161/JAHA.115.002950, indexed in Pubmed: 26811169.
27. Kirchhof P. The future of atrial fibrillation management: integrated care and stratified therapy. Lancet. 2017; 390(10105): 1873–1887, doi:10.1016/S0140-6736(17)31072-3, indexed in Pubmed: 28460828.
28. Raparelli V, Proietti M, Cangemi R, et al. Adherence to oral anticoagulant therapy in patients with atrial fibrillation. Focus on non-vitamin K antagonist oral anticoagulants. Thromb Haemost. 2017; 117(2): 209–218, doi: 10.1160/TH16-10-0757, indexed in Pubmed: 27831592.
29. Douxfils J, Ageno W, Samama CM, et al. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. J Thromb Haemost. 2018; 16(2): 209–219, doi: 10.1111/jth.13912, indexed in Pubmed: 29193737.
30. Vinereanu D, Lopes RD, Bahit MC, et al. A multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation (IMPACT-AF): an international, cluster-randomised trial. Lancet. 2017; 390(10104): 1737–1746, doi: 10.1016/S0140-6736(17)32165-7, indexed in Pubmed: 28859942.
31. Shore S, Ho PM, Lambert-Kerzner A, et al. Site-level variation in and practices associated with dabigatran adherence. JAMA. 2015; 313(14): 1443–1450, doi: 10.1001/jama.2015.2761, indexed in Pubmed: 25871670.
32. Santo K, Richtering SS, Chalmers J, et al. Mobile phone apps to improve medication adherence: a systematic stepwise process to identify high-quality apps. JMIR Mhealth Uhealth. 2016; 4(4): e132, doi: 10.2196/mhealth.6742, indexed in Pubmed: 27913373.
33. Guo Y, Chen Y, Lane DA, et al. Mobile health technology for atrial fibrillation management integrating decision support, education, and patient involvement: mAF app trial. Am J Med. 2017; 130(12): 1388–1396.e6, doi: 10.1016/j.amjmed.2017.07.003, indexed in Pubmed: 28847546.
34. Laliberté F, Nelson WW, Lefebvre P, et al. Impact of daily dosing frequency on adherence to chronic medications among nonvalvular atrial fibrillation patients. Adv Ther. 2012; 29(8): 675–690, doi: 10.1007/s12325-012-0040-x, indexed in Pubmed: 22898791.
35. Weeda ER, Coleman CI, McHorney CA, et al. Impact of once- or twice-daily dosing frequency on adherence to chronic cardiovascular disease medications: A meta-regression analysis. Int J Cardiol. 2016; 216: 104–109, doi: 10.1016/j.ijcard.2016.04.082, indexed in Pubmed: 27144286.
36. Bae JP, Dobesh PP, Klepser DG, et al. Adherence and dosing frequency of common medications for cardiovascular patients. Am J Manag Care. 2012; 18(3): 139–146, indexed in Pubmed: 22435907.
37. Ruff CT, Giugliano RP, Braunwald E, et al. Transition of patients from blinded study drug to open-label anticoagulation: the ENGAGE AF-TIMI 48 trial. J Am Coll Cardiol. 2014; 64(6): 576–584, doi: 10.1016/j.jacc.2014.05.028, indexed in Pubmed: 25104527.
38. Patel MR, Helkamp AS, Lokhnygina y, et al. Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: analysis from the ROCKET AF trial (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation). J Am Coll Cardiol. 2013; 61(6): 651–658, doi: 10.1016/j.jacc.2012.09.057, indexed in Pubmed:23391196.
39. Granger CB, Lopes RD, Hanna M, et al. Clinical events after transitioning from apixaban versus warfarin to warfarin at the end of the apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial. Am Heart J. 2015; 169(1): 25–30, doi:10.1016/j.ahj.2014.09.006, indexed in Pubmed: 25497244.
40. Gnoth MJ, Buetehorn U, Muenster U, et al. In vitro and in vivo P-glycoprotein transport characteristics of rivaroxaban. J Pharmacol Exp Ther. 2011; 338(1): 372–380, doi: 10.1124/jpet.111.180240, indexed in Pubmed: 21515813.
41. Mendell J, Zahir H, Matsushima N, et al. Drug-drug interaction studies of cardiovascular drugs involving P-glycoprotein, an efflux transporter, on the pharmacokinetics of edoxaban, an oral factor Xa inhibitor. Am J Cardiovasc Drugs. 2013; 13(5): 331–342, doi: 10.1007/s40256-013-0029-0, indexed in Pubmed: 23784266.
42. Mueck W, Kubitza D, Becka M. Co-administration of rivaroxaban with drugs that share its elimination pathways: pharmacokinetic effects in healthy subjects. Br J Clin Pharmacol. 2013; 76(3): 455–466, doi: 10.1111/bcp.12075, indexed in Pubmed: 23305158.
43. Wang L, Zhang D, Raghavan N, et al. In vitro assessment of metabolic drug-drug interaction potential of apixaban through cytochrome P450 phenotyping, inhibition, and induction studies. Drug Metab Dispos. 2010; 38(3): 448–58, doi: 10.1124/dmd.109.029694, indexed in Pubmed: 19940026.
44. Mueck W, Stampfuss J, Kubitza D, et al. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clin Pharmacokinet. 2014; 53(1): 1–16, doi: 10.1007/s40262-013-0100-7, indexed in Pubmed: 23999929.
45. Frost CE, Byon W, Song Y, et al. Effect of ketoconazole and diltiazem on the pharmacokinetics of apixaban, an oral direct factor Xa inhibitor. Br J Clin Pharmacol. 2015; 79(5): 838–846, doi: 10.1111/bcp.12541, indexed in Pubmed: 25377242.
46. Parasrampuria DA, Mendell J, Shi M, et al. Edoxaban drug-drug interactions with ketoconazole, erythromycin, and cyclosporine. Br J Clin Pharmacol. 2016; 82(6): 1591–1600, doi: 10.1111/bcp.13092, indexed in Pubmed: 27530188.
47. Vakkalagadda B, Frost C, Byon W, et al. Effect of rifampin on the pharmacokinetics of apixaban, an oral direct inhibitor of factor xa. Am J Cardiovasc Drugs. 2016; 16(2): 119–127, doi: 10.1007/s40256-015-0157-9, indexed in Pubmed: 26749408.
48. Stöllberger C, Finsterer J. Interactions between non-vitamin K oral anticoagulants and antiepileptic drugs. Epilepsy Res. 2016; 126: 98–101, doi:10.1016/j.eplepsyres.2016.06.003, indexed in Pubmed: 27450623.
49. Stöllberger C. Drug interactions with new oral anticoagulants in elderly patients. Expert Rev Clin Pharmacol. 2017; 10(11): 1191–1202, doi:10.1080/17512433.2017.1370369, indexed in Pubmed: 28825849.

50. Blech S, Ebner T, Ludwig-Schwellinger E, et al. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. Drug Metab Dispos. 2008; 36(2): 386–399, doi: 10.1124/dmd.107.019083, indexed in Pubmed: 18006647.
51. Stangier J, Stähle H, Rathgen K, et al. Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor dabigatran in healthy elderly subjects. Clin Pharmacokinet. 2008; 47(1): 47–59, doi: 10.2165/00003088-200847010-00005, indexed in Pubmed: 18076218.
52. Mendell J, Tachibana M, Shi M, et al. Effects of food on the pharmacokinetics of edoxaban, an oral direct factor Xa inhibitor, in healthy volunteers. J Clin Pharmacol. 2011; 51(5): 687–694, doi: 10.1177/0091270010370974, indexed in Pubmed: 20534818.
53. Liesenfeld KH, Lehr T, Dansirikul C, et al. Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial. J Thromb Haemost. 2011; 9(11): 2168–2175, doi: 10.1111/j.1538-7836.2011.04498.x, indexed in Pubmed:21972820.
54. Frost C, Shenker A, Gandhi MD, et al. Evaluation of the effect of naproxen on the pharmacokinetics and pharmacodynamics of apixaban. Br J Clin Pharmacol. 2014; 78(4): 877–885, doi: 10.1111/bcp.12393, indexed in Pubmed: 24697979.
55. Ruff CT, Giugliano RP, Braunwald E, et al. Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial. Lancet. 2015; 385(9984): 2288–2295, doi: 10.1016/S0140-6736(14)61943-7, indexed in Pubmed: 25769361.
56. Bohula EA, Giugliano RP, Ruff CT, et al. Impact of renal function on outcomes with edoxaban in the ENGAGE AF-TIMI 48 trial. Circulation. 2016; 134(1): 24–36, doi: 10.1161/CIRCULATIONAHA.116.022361, indexed in Pubmed: 27358434.
57. Hijazi Z, Hohnloser SH, Oldgren J, et al. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. Circulation. 2014; 129(9): 961–970, doi:10.1161/CIRCULATIONAHA.113.003628, indexed in Pubmed: 24323795.
58. Fox KAA, Piccini JP, Wojdyla D, 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(19): 2387–2394, doi: 10.1093/eurheartj/ehr342, indexed in Pubmed: 21873708.
59. Hohnloser SH, Hijazi Z, Thomas L, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J. 2012; 33(22): 2821–2830, doi: 10.1093/eurheartj/ehs274, indexed in Pubmed: 22933567.
60. Hijazi Z, Hohnloser SH, Andersson U, et al. Efficacy and safety of apixaban compared with warfarin in patients with atrial fibrillation in relation to renal function over time: insights from the ARISTOTLE randomized clinical trial. JAMA Cardiol. 2016; 1(4): 451–460, doi: 10.1001/jamacardio.2016.1170, indexed in Pubmed: 27438322.
61. Fordyce CB, Piccini JP, Patel MR, et al. On-Treatment outcomes in patients with worsening renal function with rivaroxaban compared with warfarin: insights from ROCKET AF. Circulation. 2016; 134(1): 37–47, doi: 10.1161/CIRCULATIONAHA.116.021890, indexed in Pubmed: 27358435.
62. Khoury T, Ayman AR, Cohen J, et al. The complex role of anticoagulation in cirrhosis: an updated review of where we are and where we are going. Digestion. 2016; 93(2): 149–159, doi: 10.1159/000442877, indexed in Pubmed: 26745654.
63. Lauschke VM, Ingelman-Sundberg M. The importance of patient-specific factors for hepatic drug response and toxicity. Int J Mol Sci. 2016; 17(10), doi:10.3390/ijms17101714, indexed in Pubmed: 27754327.
64. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009; 361(12): 1139–1151, doi:10.1056/NEJMoa0905561, indexed in Pubmed: 19717844.
65. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011; 365(10): 883––891, doi:10.1056/NEJMoa1009638, indexed in Pubmed: 21830957.
66. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011; 365(11): 981–992, doi:10.1056/NEJMoa1107039, indexed in Pubmed: 21870978.
67. Kubitza D, Roth A, Becka M, et al. Effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of a single dose of rivaroxaban, an oral, direct Factor Xa inhibitor. Br J Clin Pharmacol. 2013; 76(1): 89–98, doi: 10.1111/bcp.12054, indexed in Pubmed: 23294275.
68. Douxfils J, Mullier F, Loosen C, et al. Assessment of the impact of rivaroxaban on coagulation assays: laboratory recommendations for the monitoring of rivaroxaban and review of the literature. Thromb Res. 2012; 130(6): 956–966, doi: 10.1016/j.thromres.2012.09.004, indexed in Pubmed: 23006523.
69. Douxfils J, Mullier F, Robert S, et al. Impact of dabigatran on a large panel of routine or specific coagulation assays. Laboratory recommendations for monitoring of dabigatran etexilate. Thromb Haemost. 2012; 107(5): 985–997, doi: 10.1160/TH11-11-0804, indexed in Pubmed: 22438031.
70. Ogata K, Mendell-Harary J, Tachibana M, et al. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. J Clin Pharmacol. 2010; 50(7): 743–753, doi: 10.1177/0091270009351883, indexed in Pubmed: 20081065.
71. Kubitza D, Becka M, Voith B, et al. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. Clin Pharmacol Ther. 2005; 78(4): 412–421, doi: 10.1016/j.clpt.2005.06.011, indexed in Pubmed: 16198660.
72. van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate--a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost. 2010; 103(6): 1116–1127, doi: 10.1160/TH09-11-0758, indexed in Pubmed: 20352166.
73. Ezekowitz MD, Reilly PA, Nehmiz G, et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). Am J Cardiol. 2007; 100(9): 1419–1426, doi: 10.1016/j.amjcard.2007.06.034, indexed in Pubmed: 17950801.
74. Douxfils J, Chatelain C, Chatelain B, et al. Impact of apixaban on routine and specific coagulation assays: a practical laboratory guide. Thromb Haemost. 2013; 110(2): 283–294, doi: 10.1160/TH12-12-0898, indexed in Pubmed: 23765180.
75. Cuker A, Husseinzadeh H. Laboratory measurement of the anticoagulant activity of edoxaban: a systematic review. J Thromb

Thrombolysis. 2015; 39(3): 288–294, doi: 10.1007/s11239-015-1185-7, indexed in Pubmed: 25669624.
76. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017; 70(24): 3042–3067, doi: 10.1016/j.jacc.2017.09.1085, indexed in Pubmed: 29203195.
77. van Ryn J, Baruch L, Clemens A. Interpretation of point-of-care INR results in patients treated with dabigatran. Am J Med. 2012; 125(4): 417–420, doi:10.1016/j.amjmed.2011.10.017, indexed in Pubmed: 22306274.
78. Kaess BM, Ammar S, Reents T, et al. Comparison of safety of left atrial catheter ablation procedures for atrial arrhythmias under continuous anticoagulation with apixaban versus phenprocoumon. Am J Cardiol. 2015; 115(1): 47–51, doi: 10.1016/j.amjcard.2014.10.005, indexed in Pubmed:25456870.
79. Mani H, Herth N, Kasper A, et al. Point-of-care coagulation testing for assessment of the pharmacodynamic anticoagulant effect of direct oral anticoagulant. Ther Drug Monit. 2014; 36(5): 624–631, doi: 10.1097/FTD.0000000000000064, indexed in Pubmed: 24577124.
80. Godier A, Dincq AS, Martin AC, et al. Predictors of pre-procedural concentrations of direct oral anticoagulants: a prospective multicentre study. Eur Heart J. 2017; 38(31): 2431–2439, doi: 10.1093/eurheartj/ehx403, indexed in Pubmed: 28821169.
81. Auer J, Huber K, Granger CB. Interruption of non-vitamin K antagonist anticoagulants in patients undergoing planned invasive procedures: how long is long enough? Eur Heart J. 2017; 38(31): 2440–2443, doi: 10.1093/eurheartj/ehx416, indexed in Pubmed: 28821168.
82. Peetermans M, Pollack C, Reilly P, et al. Idarucizumab for dabigatran overdose. Clin Toxicol (Phila). 2016; 54(8): 644–646, doi:10.1080/15563650.2016.1187737, indexed in Pubmed: 27224445.
83. Pollack CV, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal - full cohort analysis. N Engl J Med. 2017; 377(5): 431–441, doi:10.1056/NEJMoa1707278, indexed in Pubmed: 28693366.
84. Connolly SJ, Milling TJ, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor xa inhibitors. N Engl J Med. 2016; 375(12): 1131–1141, doi: 10.1056/NEJMoa1607887, indexed in Pubmed: 27573206.
85. Ansell JE, Bakhru SH, Laulicht BE, et al. Use of PER977 to reverse the anticoagulant effect of edoxaban. N Engl J Med. 2014; 371(22): 2141–2142, doi:10.1056/NEJMc1411800, indexed in Pubmed: 25371966.
86. Levi M, Eerenberg E, Kamphuisen PW. Bleeding risk and reversal strategies for old and new anticoagulants and antiplatelet agents. J Thromb Haemost. 2011; 9(9): 1705–1712, doi: 10.1111/j.1538-7836.2011.04432.x, indexed in Pubmed: 21729240.
87. Shakur H, Roberts I, 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(9734): 23–32, doi: 10.1016/S0140-6736(10)60835-5, indexed in Pubmed: 20554319.
88. Poeran J, Rasul R, Suzuki S, et al. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. BMJ. 2014; 349: g4829, indexed in Pubmed: 25116268.
89. Tomaszuk-Kazberuk A, Łopatowska P, Młodawska E, et al. Successful use of idarucizumab as a reversal agent for dabigatran in a patient with acute dissected aortic aneurysm. Pol Arch Intern Med. 2017; 127(1): 68–70, doi: 10.20452/pamw.3918, indexed in Pubmed: 28146465.
90. Pruszczyk P, Tomaszuk-Kazberuk A, Słowik A, et al. Management of bleeding or urgent interventions in patients treated with direct oral anticoagulants: 2017 recommendations for Poland. Pol Arch Intern Med. 2017; 127(5): 343–351, doi: 10.20452/pamw.3995, indexed in Pubmed: 28400546.
91. Beyer-Westendorf J, Förster K, Pannach S, et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. Blood. 2014; 124(6): 955–962, doi: 10.1182/blood-2014-03-563577, indexed in Pubmed: 24859362.
92. Healey JS, Eikelboom J, Douketis J, et al. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. Circulation. 2012; 126(3): 343–348, doi:10.1161/CIRCULATIONAHA.111.090464, indexed in Pubmed: 22700854.
93. Zhou W, Schwarting S, Illanes S, et al. Hemostatic therapy in experimental intracerebral hemorrhage associated with the direct thrombin inhibitor dabigatran. Stroke. 2011; 42(12): 3594–3599, doi: 10.1161/STROKEAHA.111.624650, indexed in Pubmed: 21998060.
94. Pragst I, Zeitler SH, Doerr B, et al. Reversal of dabigatran anticoagulation by prothrombin complex concentrate (Beriplex P/N) in a rabbit model. J Thromb Haemost. 2012; 10(9): 1841–1848, doi: 10.1111/j.1538-7836.2012.04859.x, indexed in Pubmed: 22812619.
95. Godier A, Miclot A, Le Bonniec B, et al. Evaluation of prothrombin complex concentrate and recombinant activated factor VII to reverse rivaroxaban in a rabbit model. Anesthesiology. 2012; 116(1): 94–102, doi: 10.1097/ALN.0b013e318238c036, indexed in Pubmed: 22042412.
96. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation. 2011; 124(14): 1573–1579, doi: 10.1161/CIRCULATIONAHA.111.029017, indexed in Pubmed: 21900088.
97. Song Y, Wang Z, Perlstein I, et al. Reversal of apixaban anticoagulation by four-factor prothrombin complex concentrates in healthy subjects: a randomized three-period crossover study. J Thromb Haemost. 2017; 15(11): 2125–2137, doi: 10.1111/jth.13815, indexed in Pubmed: 28846831.
98. Levi M, Moore KT, Castillejos CF, et al. Comparison of three-factor and four-factor prothrombin complex concentrates regarding reversal of the anticoagulant effects of rivaroxaban in healthy volunteers. J Thromb Haemost. 2014; 12(9): 1428–1436, doi: 10.1111/jth.12599, indexed in Pubmed:24811969.
99. Zahir H, Brown KS, Vandell AG, et al. Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor prothrombin complex concentrate. Circulation. 2015; 131(1): 82–90, doi: 10.1161/CIRCULATIONAHA.114.013445, indexed in Pubmed: 25403645.
100. Gorczyca-Michta I, Wożakowska-Kapłon B. Percutaneous left atrial appendage occlusion: New perspectives for the method. Cardiol J. 2017; 24(5): 554–562, doi: 10.5603/CJ.a2017.0029, indexed in Pubmed: 28281734.

101. Albaladejo P, Samama CM, et al. Management of severe bleeding in patients treated with direct oral anticoagulants: an observational registry analysis. Anesthesiology. 2017; 127(1): 111–120, doi: 10.1097/ALN.0000000000001631, indexed in Pubmed: 28410272.
102. Majeed A, Ågren A, Holmström M, et al. Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. Blood. 2017; 130(15): 1706–1712, doi: 10.1182/blood-2017-05-782060.
103. Hemphill JC, Greenberg SM, Anderson CS, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2015; 46(7): 2032–2060, doi:10.1161/STR.0000000000000069, indexed in Pubmed: 26022637.
104. Kuramatsu J, Gerner S, Schellinger P, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. JAMA. 2015; 313(8): 824–836, doi: 10.1001/jama.2015.0846.
105. Gerner ST, Kuramatsu JB, Sembill JA, et al. Association of prothrombin complex concentrate administration and hematoma enlargement in non-vitamin K antagonist oral anticoagulant-related intracerebral hemorrhage. Ann Neurol. 2018; 83(1): 186–196, doi: 10.1002/ana.25134, indexed in Pubmed:29314216.
106. Kermer P, Eschenfelder CC, Diener HC, et al. Antagonizing dabigatran by idarucizumab in cases of ischemic stroke or intracranial hemorrhage in Germany - A national case collection. Int J Stroke. 2017; 12(4): 383–391, doi: 10.1177/1747493017701944, indexed in Pubmed: 28494694.
107. Purrucker JC, Haas K, Rizos T, et al. Coagulation testing in acute ischemic stroke patients taking non-vitamin K antagonist oral anticoagulants. Stroke. 2017; 48(1): 152–158, doi: 10.1161/STROKEAHA.116.014963, indexed in Pubmed: 27899756.
108. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2018; 49(3): e46–e110, doi:10.1161/STR.0000000000000158, indexed in Pubmed: 29367334.
109. Tse DM, Young L, Ranta A, et al. Intravenous alteplase and endovascular clot retrieval following reversal of dabigatran with idarucizumab. J Neurol Neurosurg Psychiatry. 2018; 89(5): 549–550, doi: 10.1136/jnnp-2017-316449, indexed in Pubmed: 28986468.
110. Xian Y, Federspiel JJ, Hernandez AF, et al. Use of intravenous recombinant tissue plasminogen activator in patients with acute ischemic stroke who take non-vitamin k antagonist oral anticoagulants before stroke. Circulation. 2017; 135(11): 1024–1035, doi: 10.1161/CIRCULATIONAHA.116.023940, indexed in Pubmed: 28119380.
111. Seiffge DJ, Traenka C, Polymeris AA, et al. Intravenous thrombolysis in patients with stroke taking rivaroxaban using drug specific plasma levels: experience with a standard operation procedure in clinical practice. J Stroke. 2017; 19(3): 347–355, doi: 10.5853/jos.2017.00395, indexed in Pubmed:28877563.
112. Drouet L, Bal Dit Sollier C, Steiner T, et al. Measuring non-vitamin K antagonist oral anticoagulant levels: When is it appropriate and which methods should be used? Int J Stroke. 2016; 11(7): 748–758, doi: 10.1177/1747493016659671, indexed in Pubmed: 27412190.
113. Saver JL, Goyal M, van der Lugt A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. JAMA. 2016; 316(12): 1279–1288, doi: 10.1001/jama.2016.13647, indexed in Pubmed: 27673305.
114. Purrucker JC, Wolf M, Haas K, et al. Safety of endovascular thrombectomy in patients receiving non-vitamin K antagonist oral anticoagulants. Stroke. 2016; 47(4): 1127–1130, doi: 10.1161/STROKEAHA.116.012684, indexed in Pubmed: 26931156.
115. Wahlgren N, Moreira T, Michel P, et al. Mechanical thrombectomy in acute ischemic stroke: Consensus statement by ESO-Karolinska Stroke Update 2014/2015, supported by ESO, ESMINT, ESNR and EAN. Int J Stroke. 2016; 11(1): 134––147, doi: 10.1177/1747493015609778, indexed in Pubmed: 26763029.
116. Deharo JC, Sciaraffia E, Leclercq C, et al. Perioperative management of antithrombotic treatment during implantation or revision of cardiac implantable electronic devices: the European Snapshot Survey on Procedural Routines for Electronic Device Implantation (ESS-PREDI). Europace. 2016; 18(5): 778–784, doi: 10.1093/europace/euw127, indexed in Pubmed: 27226497.
117. Beyer-Westendorf J, Gelbricht V, Förster K, et al. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. Eur Heart J. 2014; 35(28): 1888–1896, doi: 10.1093/eurheartj/eht557, indexed in Pubmed: 24394381.
118. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. N Engl J Med. 2015; 373(9): 823–833, doi: 10.1056/NEJMoa1501035, indexed in Pubmed: 26095867.
119. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. J Interv Card Electrophysiol. 2017; 50(1): 1–55, doi: 10.1007/s10840-017-0277-z.
120. Haeusler KG, Kirchhof P, Endres M. Left atrial catheter ablation and ischemic stroke. Stroke. 2012; 43(1): 265–270, doi:10.1161/STROKEAHA.111.627067, indexed in Pubmed: 22156699.
121. Douketis JD, Spyropoulos AC, Anderson JM, et al. The Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) Study for Patients on a Direct Oral Anticoagulant Who Need an Elective Surgery or Procedure: Design and Rationale. Thromb Haemost. 2017; 117(12): 2415–2424, doi:10.1160/TH17-08-0553, indexed in Pubmed: 29212129.
122. Levy JH, Ageno W, Chan NC, et al. When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. J Thromb Haemost. 2016; 14(3): 623–627, doi: 10.1111/jth.13227, indexed in Pubmed: 26911798.
123. Albaladejo P, Bonhomme F, Blais N, et al. Management of direct oral anticoagulants in patients undergoing elective surgeries and invasive procedures: Updated guidelines from the French Working Group on Perioperative Hemostasis (GIHP) - September 2015. Anaesth Crit Care Pain Med. 2017; 36(1): 73–76, doi: 10.1016/j.accpm.2016.09.002, indexed in Pubmed: 27659969.
124. Cocco G, Amiet P, Jerie P. Anti-thromboembolic strategies in atrial fibrillation. Cardiol J. 2016; 23(2): 211–223, doi: 10.5603/CJ.a2016.0004, indexed in Pubmed: 26779967.
125. Gibson CM, Mehran R, Bode C, et al. An open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI). Am Heart J. 2015; 169(4): 472–8.e5, doi: 10.1016/j.ahj.2014.12.006, indexed in Pubmed: 25819853.
126. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J

Med. 2017; 377(16): 1513–1524, doi: 10.1056/NEJMoa1708454, indexed in Pubmed: 28844193.
127. Urban P, Meredith IT, Abizaid A, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. N Engl J Med. 2015; 373(21): 2038–2047, doi: 10.1056/NEJMoa1503943, indexed in Pubmed: 26466021.
128. Varenne O, Cook S, Sideris G, et al. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. Lancet. 2018; 391(10115): 41–50, doi: 10.1016/s0140-6736(17)32713-7.
129. Kupczynska K, Kasprzak JD, Michalski BW, et al. The impact of the latest echocardiographic chamber quantification recommendations on the prediction of left atrial appendage thrombus presence by transthoracic echocardiography. Acta Cardiol. 2018; 73(1): 91–95, doi: 10.1080/00015385.2017.1351241, indexed in Pubmed: 28799449.
130. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2014; 130(23): e199–e267, doi: 10.1161/cir.0000000000000041.
131. Hansen ML, Jepsen RM, Olesen JB, et al. Thromboembolic risk in 16 274 atrial fibrillation patients undergoing direct current cardioversion with and without oral anticoagulant therapy. Europace. 2015; 17(1): 18–23, doi: 10.1093/europace/euu189, indexed in Pubmed: 25231909.
132. Grönberg T, Hartikainen JEK, Nuotio I, et al. Anticoagulation, CHA2DS2VASc Score, and Thromboembolic Risk of Cardioversion of Acute Atrial Fibrillation (from the FinCV Study). Am J Cardiol. 2016; 117(8): 1294–1298, doi: 10.1016/j.amjcard.2016.01.024, indexed in Pubmed: 26892448.
133. Nuotio I, Hartikainen JEK, Grönberg T, et al. Time to cardioversion for acute atrial fibrillation and thromboembolic complications. JAMA. 2014; 312(6): 647–649, doi: 10.1001/jama.2014.3824, indexed in Pubmed: 25117135.
134. Lip GYH, Hammerstingl C, Marin F, et al. Left atrial thrombus resolution in atrial fibrillation or flutter: Results of a prospective study with rivaroxaban (X-TRA) and a retrospective observational registry providing baseline data (CLOT-AF). Am Heart J. 2016; 178: 126–134, doi: 10.1016/j.ahj.2016.05.007, indexed in Pubmed: 27502860.
135. Ruff CT, Giugliano RP, Braunwald E, 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. Lancet. 2014; 383(9921): 955–962, doi: 10.1016/S0140-6736(13)62343-0, indexed in Pubmed: 24315724.
136. Kato ET, Giugliano RP, Ruff CT, et al. Efficacy and safety of edoxaban in elderly patients with atrial fibrillation in the ENGAGE AF-TIMI 48 trial. J Am Heart Assoc. 2016; 5(5), doi: 10.1161/JAHA.116.003432, indexed in Pubmed: 27207971.
137. Man-Son-Hing M, Nichol G, Lau A, et al. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. Arch Intern Med. 1999; 159(7): 677–685, doi: 10.1001/archinte.159.7.677.
138. Rao MP, Vinereanu D, Wojdyla DM, et al. Clinical outcomes and history of fall in patients with atrial fibrillation treated with oral anticoagulation: insights from the ARISTOTLE trial. Am J Med. 2018; 131(3): 269–275.e2, doi: 10.1016/j.amjmed.2017.10.036, indexed in Pubmed: 29122636.
139. Steffel J, Giugliano RP, Braunwald E, et al. Edoxaban versus warfarin in atrial fibrillation patients at risk of falling: ENGAGE AF-TIMI 48 analysis. J Am Coll Cardiol. 2016; 68(11): 1169–1178, doi: 10.1016/j.jacc.2016.06.034, indexed in Pubmed: 27609678.
140. Tricco AC, Thomas SM, Veroniki AA, et al. Comparisons of Interventions for Preventing Falls in Older Adults: A Systematic Review and Meta-analysis. JAMA. 2017; 318(17): 1687–1699, doi: 10.1001/jama.2017.15006, indexed in Pubmed: 29114830.
141. Friberg L, Rosenqvist M. Less dementia with oral anticoagulation in atrial fibrillation. Eur Heart J. 2018; 39(6): 453–460, doi: 10.1093/eurheartj/ehx579, indexed in Pubmed: 29077849.
142. Dietzel J, Haeusler KG, Endres M. Does atrial fibrillation cause cognitive decline and dementia? Europace. 2018; 20(3): 408–419, doi:10.1093/europace/eux031, indexed in Pubmed: 28387847.
143. Chagnac A, Weinstein T, Korzets A, et al. Glomerular hemodynamics in severe obesity. Am J Physiol Renal Physiol. 2000; 278(5): F817–F822, doi:10.1152/ajprenal.2000.278.5.F817, indexed in Pubmed: 10807594.
144. Martin K, Beyer-Westendorf J, Davidson BL, et al. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. J Thromb Haemost. 2016; 14(6): 1308–1313, doi: 10.1111/jth.13323, indexed in Pubmed: 27299806.
145. Sandhu RK, Ezekowitz J, Andersson U, et al. The 'obesity paradox' in atrial fibrillation: observations from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. Eur Heart J. 2016; 37(38): 2869–2878, doi: 10.1093/eurheartj/ehw124, indexed in Pubmed: 27071819.
146. De Caterina R, Lip GYH. The non-vitamin K antagonist oral anticoagulants (NOACs) and extremes of body weight-a systematic literature review. Clin Res Cardiol. 2017; 106(8): 565–572, doi: 10.1007/s00392-017-1102-5, indexed in Pubmed: 28396988.
147. Stefanidou M, Das RR, Beiser AS, et al. Incidence of seizures following initial ischemic stroke in a community-based cohort: The Framingham Heart Study. Seizure. 2017; 47: 105–110, doi: 10.1016/j.seizure.2017.03.009, indexed in Pubmed: 28364691.
148. Beghi E, D'Alessandro R, Beretta S, et al. Incidence and predictors of acute symptomatic seizures after stroke. Neurology. 2011; 77(20): 1785–1793, doi:10.1212/WNL.0b013e3182364878, indexed in Pubmed: 21975208.
149. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med. 2018; 378(7): 615–624, doi: 10.1056/NEJMoa1711948, indexed in Pubmed: 29231094.
150. Brunetti ND, Gesuete E, De Gennaro L, et al. Direct oral anti-coagulants compared with vitamin-K inhibitors and low-molecular-weight-heparin for the prevention of venous thromboembolism in patients with cancer: A meta-analysis study. Int J Cardiol. 2017; 230: 214–221, doi:10.1016/j.ijcard.2016.12.168, indexed in Pubmed: 28062137.
151. Short NJ, Connors JM. New oral anticoagulants and the cancer patient. Oncologist. 2014; 19(1): 82–93, doi: 10.1634/theoncologist.2013-0239, indexed in Pubmed: 24319019.