ANMCO Position Paper: the use of non-vitamin K dependent new oral anticoagulant(s) in pulmonary embolism therapy and prevention

Iolanda Enea (Coordinator)1*, Loris Roncon (Coordinator)2, Michele Massimo Gulizia, FACC, FESC (Coordinator)3*, Michele Azzarito (Coordinator)4, Cecilia Becattini5, Amedeo Bongarzoni6, Franco Casazza7, Claudio Cuccia8, Carlo D’Agostino9, Matteo Rugolotto10, Marco Vatrano11, Eugenio Vinci12, Paride Fenaroli13, Dario Formigli14, Paolo Silvestri14, Federico Nardi, FACC, FESC15, Maria Cristina Vedovati16, and Marino Scherillo14

1 Emergency Care Department, S. Anna e S. Sebastiano Hospital, Via G. Tescione, 1. 81100 Casert, Italy
2 Cardiology Department, S. Maria della Misericordia Hospital, Rovigo, Italy
3 Cardiology Department, Garibaldi-Nesima Hospital, Azienda di Rilievo Nazionale e Alta Specializzazione “Garibaldi”, Catania, Italy
4 Cardiology Unit, San Carlo di Nancy Hospital, Rome, Italy
5 Department of Internal and Vascular Medicine, Perugia General Hospital, Perugia, Italy
6 Cardiology Department, San Carlo Borromeo Hospital, Milano, Italy
7 Moscati Foundation, Buccinasco, Milan, Italy
8 Cardiology Unit, Poliambulanza Foundation Hospital, Brescia, Italy
9 Cardiology Department, University General Hospital, Bari, Italy
10 Cardiology Department, Ca’ Foncello Hospital, Treviso, Italy
11 CCU-Hemodynamics and Interventional Cardiology Department, Civili Pugliese Hospital, Catanzaro, Italy
12 Cardiology-CCU Department, Umberto I Hospital, Siracusa, Italy
13 Nephrology and Dialysis Unit, Salvatore Maugeri Foundation, University of Pavia, Pavia, Italy
14 Interventional Cardiology-CCU Department, G. Rummo Hospital, Benevento, Italy
15 Cardiology Department, Castelli Hospital, Verbano, Italy
16 Department of Internale and Vascular Medicine, S. Maria della Misericordia Hospital, University of Perugia, Perugia, Italy

Revised by: Maria Gabriella Carmina, Maria Paola Cicini, Anna Maria Costante, Giuseppe Favretto, Adriano Murrone, and Pietro Zonzin.

Consensus Document Approval Faculty in appendix

*Corresponding author. Tel: +393402369289, Email: i_enea@hotmail.com

© The Author 2017. Published on behalf of the European Society of Cardiology. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Introduction

Pulmonary embolism (PE) remains the third leading cause of cardiovascular death after myocardial infarction (MI) and stroke.\(^1\) The introduction of new oral anticoagulants, or ‘Non vitamin K Oral Anticoagulants’ (NOACs) have changed the way we treat PE patients during and after hospital stay as well as throughout long-term period.\(^2\)–\(^10\) The purpose of this document is to provide cardiologists with the opinion of experts on emerging topics related to the use of NOACs for PE. The authors will describe: (i) the role of the NOACs in the treatment of acute PE, according to the latest European Society of Cardiology (ESC) Guidelines (GL); (ii) the meaning of innovation of the NOACs compared with the traditional therapy; (iii) an update on their use in ‘frail patient’, in cancer patients and obesity; (iv) a practical follow-up (FU) scheme for PE patients treated with the NOACs; and (v) drug-drug interactions, management of bleeding risk and relative complications.

Pulmonary embolism after the European Society of Cardiology guidelines 2014: diagnostic flow-charts, prognostic stratification, and treatment options

Over the years the ‘anatomic’ definition of massive or non-massive PE has been replaced by the ‘functional’ one of the ‘high-risk’ PE or ‘not-high-risk’ PE.\(^11\) In order to identify patients at higher risk of death in not-high-risk group, 2008 ESC GL\(^12\) underlined the importance of the measurement of the right ventricular to left ventricular diastolic diameter ratio (RVDD/LVDD) on echocardiography or computed tomographic angiography (CTA) and the assessment of markers of myocardial injury, like troponins, or of right heart overload, like brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-pro-BNP). According to the current ESC GL, a further risk stratification has to be considered for stable patients, using some validated clinical scores as PE severity index (PESI) or its simplified version (sPESI), to decide whether or not to perform echocardiography and troponin assessment.\(^1\)

At presentation, a simple cardiovascular evaluation is enough to plan the most appropriate diagnostic and therapeutic works-up for patients with suspected PE.\(^7\) According to systolic blood pressure, two different paths are proposed to obtain the final diagnosis: rapid times and simplified procedure in ‘high-risk patients’, longer time and well-constructed procedure in ‘not-high-risk patients’.

The high-risk group constitutes about 5–10% of all patients with PE and includes patients with a wide range of mortality risk, from 17% in patients with blood pressure < 90–63% in patients with early cardiac arrest.\(^13,14\) European Society of Cardiology guidelines emphasize the role of echocardiography as a rapid bed-side examination in this setting, because high-risk PE is a life-threatening event and echocardiographic features of right ventricular dysfunction (RVD) are believed to be sufficient to perform an immediate reperfusion therapy, without further testing.\(^13,15\)

In not-high-risk patients, ESC GL suggest a stepwise approach based on the pre-test clinical probability and D-dimer determination, to avoid the early performance of CTA or scintigraphy.\(^16\) Today, to the original Wells’ score of 3 levels of probability (low, intermediate, and high), we prefer the simplified one involving only two levels of probability, namely ‘PE unlikely’ and ‘PE likely’.\(^17,18\) If the score is compatible with a ‘PE unlikely’, a D-dimer test should be performed, due to its high negative predictive value: if normal, it excludes a current thrombotic process, if abnormally high a CTA should be performed. To give D-Dimer a greater specificity and to reduce the high number of false positives, a cut-off value adjusted for the age (age \(\times\) \(10\) \(\mu\)L/L for age \(\geq\)50 years) was introduced.\(^21\) If PE is ‘likely’ the D-dimer dosage can be omitted since a normal value does not exclude PE. Regarding the sub-segmental defects at CTA, single defects should be interpreted with caution.\(^22\)

As for the prognostic stratification, the ESC GL 2014 proposed the PESI score\(^13\) and its simplified version sPESI.\(^24\) The aim of these scores is to better stratify not-high-risk category. We believe that sPESI is a simpler and friendly tool for the prognostic stratification of PE patients, because it takes into account only 6 variables, instead of 11, commonly assessed at admission.
The spESI score stratifies not-high-risk patients into two groups:

1. Low-risk patients, with \( spESI = 0 \), who do not require further testing and are candidates for early discharge;
2. Intermediate-risk patients, with a \( spESI \) greater than or equal to 1 point. This group requires a further stratification into two sub-groups by means of imaging and laboratory tests: ‘intermediate-high’ are those patients in whom both RVD and troponin increase are present and a monitoring appears needed; ‘intermediate-low’ are those patients in whom only one test, either imaging or laboratory, is abnormal: they do not seem to require special attention, when anticoagulant therapy is started.

In conclusion, PESI and spESI may be considered useful tools for the initial evaluation of PE patients, although we believe in agreement with other authors, that further studies are probably required to improve the risk profile of patients at intermediate risk. It is possible that the wide-spread use of high-sensitivity troponin will increase the number of positive results at presentation and improve its prognostic value.

Patients who can benefit from non-vitamin K dependent new oral anticoagulant(s) treatment

Anticoagulation therapy is the cornerstone in the treatment of venous thromboembolism (VTE) because it can reduce mortality in the acute phase and recurrence in both the short and long periods. According to the current clinical practice, the treatment of VTE generally consists of three phases: an acute phase of 5-7 days, a short-term phase, up to 3 months after the acute event and a long-term phase with undefined duration which must be reserved for those patients at higher risk for recurrence.

High-risk patients must be treated with a drug able to reperfuse the lung and reduce the right ventricle overload as soon as possible. For this purpose, the systemic thrombolysis with Actilyse is recommended, Tenecteplase, tested in Peitho study in intermediate-risk patients, is not approved. Surgical embolectomy (Grade I recommendation and evidence C) or a percutaneous embolectomy (recommendation IIa degree and evidence C) are currently recommended in case of absolute and/or relative contraindications to thrombolysis or if thrombolytic treatment has failed.

In not-high-risk patients, anticoagulation is the therapy of choice and often the only therapy to practice. The traditional anticoagulation therapy consists of low molecular weight heparins (LMWHs) or fondaparinux. The indication to start parenteral anticoagulation therapy in patients with PE likely, without waiting for the definitive diagnostic confirmation, appears clinically relevant; equally the early initiation of therapy with vitamin K inhibitors (VKAs) to achieve adequate international normalized ratio (INR) within a reasonable time, for the purpose of early discharge is useful.

The use of NOACs should be reserved for patients at low or intermediate-low risk, both in the form of ‘single drug approach’ or, instead of Warfarin, as ‘double drug single dose approach’ after few days of parenterally anticoagulation with heparin.

For intermediate-risk patients, the GL suggest hospitalization in wards with monitoring just to observe the haemodynamic evolution according to the ‘wait and watch’ strategy, reserving ‘rescue’ thrombolysis to the ones who evolve towards hypotension or shock. In these cases, when thrombolysis is contraindicated, alternative procedures, such as surgery (IIb-C recommendation) or percutaneous embolectomy (IIb-B), should be considered.

In intermediate-high risk patients with PESI class III-V or spESI \( \geq 1 \), in the presence of positive troponin and of RVD, the possibility of using thrombolysis precludes NOACs therapy; even if after the acute phase, if there is right ventricular function improvement, we envisage the therapy with NOACs, waiting for definitive clinical evidence in this population and using, if necessary, a ‘safe dose’ of thrombolysis.

In not-high-risk patients the use of NOACs cannot be administered in the presence of severe renal failure (RF); in the presence of a systolic blood pressure \( > 180 \) mmHg or diastolic \( > 100 \) mmHg; in pregnancy or breastfeeding; in cancer patients requiring anticoagulant treatment by LMWHs; patients with liver failure associated with coagulopathy and increased risk of bleeding; patients with moderate or severe chronic liver cirrhosis (Child Pugh B or C) in the case of Rivaroxaban and Edoxaban, severe chronic liver cirrhosis (Child Pugh C) in the case of Apixaban and Dabigatran.

From the traditional therapy to non-vitamin K dependent new oral anticoagulant(s): the meaning of innovation compared with traditional therapy

The availability of NOACs represents a significant achievement for the treatment of VTE in terms of feasibility. Conventional anticoagulation for VTE includes initial parenteral anticoagulant treatment with: (i) unfractionated heparin (UFH) by intravenous bolus followed by continuous infusion based on the coagulation response, got by monitoring the activated partial thromboplastin time (aPTT) (the use of calcic heparin is no more used in clinical practice); (ii) LMWHs; (iii) fondaparinux, a synthetic pentasaccharide factor X activated (FXa) inhibitor; the initial therapy has to be overlapped with Warfarin from 3 to 5 days, until therapeutic INR is obtained. Thanks to their rapid onset of action (\( T_{max} 1-4 \) h), NOACs do not require to be overlapped with heparin, so it is a helpful treatment in reducing the duration of hospitalization and it seems to be associated with a lower risk of bleeding. Furthermore, while Warfarin requires laboratory monitoring for dose adjustment, NOACs are administered orally in fixed doses without the need for periodical laboratory monitoring, reducing medical examinations and long-term costs.

Therapeutic scheme’s innovation

The clinical development of NOACs in two different regimes allows the choice of the most adequate regimen for different clinical settings. In the Dabigatran vs. Warfarin in the treatment of acute venous thromboembolism (RE-COVER)
studies and in the HOKUSAI study. Dabigatran and Edoxaban were used for the acute and long-term treatment of VTE after initial treatment with heparin or fondaparinux. In the Apixaban for Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First Line Therapy.

In oral Apixaban for the treatment of acute venous thromboembolism study (AMPLIFY), in oral Rivaroxaban for the treatment of acute deep vein thrombosis study (EINSTEIN DVT) and in oral Rivaroxaban for the treatment of acute pulmonary embolism (EINSTEIN PE) studies, Apixaban and Rivaroxaban were used according to the ‘single drug’ approach and no parenteral pre-treatment was required. The single-drug approach consists of an initial higher dosage of the drug, lasting 1 week for Apixaban and 3 weeks for Rivaroxaban, followed by a maintenance dose of the same drug to be continued for the long-term treatment of VTE. The rationale for the increased initial doses of oral anticoagulants are the high risk of recurrence in the early period after diagnosis of VTE and the results of previous studies showing potential lower efficacy of idraparinux and ximelagatran at maintenance doses as compared with conventional treatment in the acute phase.

These different regimens facilitate the management of anticoagulant therapy in different clinical scenarios of acute PE. The safety of NOACs in the prolonged treatment can induce a further innovation of the therapeutic approach in intermediate-risk patients where the extension of a potentially dangerous therapy often induces an inopportune withdrawal of anticoagulant treatment.

Home treatment
The NOACs can facilitate home treatment of VTE. Approximately 52% and 90% of patients included in the EINSTEIN DVT and EINSTEIN PE studies were hospitalized, respectively. Specifically, the proportion of patients with PE hospitalized for five days or less was 45% in those who received Rivaroxaban and 33% in those who received conventional anticoagulation. The use of the NOACs with the ‘single drug’ approach is of particular interest in patients with PE at low risk of death (sPESI = 0). One hundred and six patients with low risk VTE, including 35 with PE, were treated as outpatients with Rivaroxaban according to the ‘single drug’ approach. No recurrence of VTE or major bleeding or clinically relevant non-major bleeding was observed during anticoagulant treatment (0%, 95% CI 0–3.4%). A final remark on the health facilities is dedicated to patients on anticoagulant therapy. To date, the patients taking anticoagulant treatment need to be followed by the centres dedicated to monitor the activity of the drug. Now it becomes necessary to implement outpatients’ clinics dedicated to the clinical disorder where the patient is followed globally. Here anticoagulant treatment is simply one aspect of the management of the disease, rather than the only one.

Acute phase therapy: are the NOACs all the same?

Six randomized phase III studies on the treatment of VTE showed the non-inferiority of NOACs as compared with conventional therapy in terms of efficacy, with potential advantage in terms of safety (Table 1).

A meta-analysis, including 11,539 patients with PE, confirmed the improved safety profile of NOACs compared with conventional treatment: OR 0.30 (95% CI 0.10–0.95) for major bleeding and OR 0.89, 95% CI 0.77–1.03 for clinically relevant bleeding. Concerning the type of bleeding, pooled data from phase III studies on the treatment of VTE have shown a significant reduction of intracranial bleeding [risk ratio (RR) 0.37 95% CI 0.21–0.68] and fatal bleeding (RR 0.36 95% CI 0.15–0.84). A trend toward reduction in major gastrointestinal bleeding was observed with NOACs as compared with conventional treatment, but further evidence is needed on this issue (RR 0.78, 95% CI 0.47–1.31). The net clinical benefit defined as a first episode of a patient-relevant outcome (recurrence of VTE, VTE related mortality or major bleeding), was in favour of NOACs as compared with conventional treatment (3.2% vs. 4.0%, RR 0.79, 95% CI 0.70–0.90), while similar rates of all-cause death were observed in the two treatment groups (RR 0.98, 95% CI 0.84–1.14). It is hard to give an indication of the preference of one over the other new oral anticoagulants in the acute phase of PE because the primary outcome of non-inferiority for the efficacy and the safety were brilliantly achieved by all the NOACs.

As we analyse the profiles of the patients enrolled in the different trials, we discover that the degree of PE haemodynamic commitment, the definition of its anatomic extent, the degree of RVD, its own genesis (provoked or unprovoked), the presence of co-morbidities and the applied therapeutic approach are different; not to mention the type of the study (open-label vs. double-blind). These are the reasons preventing us from the choice of the suitable NOAC. The practical use might make the difference: Rivaroxaban and Apixaban have the advantage of not requiring a preliminary parenteral therapy, even if their dosage has to be adjusted after one (Apixaban) or 3 weeks’ (Rivaroxaban) initial ‘intensive’ anticoagulation phase that is useful for the prevention of embolic recurrence, observed in previous studies. It is difficult to think that the definition of the patient’s risk profile takes place in a single transit in an emergency room. Who has analysed the predictive goodness of PESI and sPESI scores in post hoc analyses in the NOACs trials says that low-risk patients so identified will nevertheless be treated ‘in a clinical decision unit or by a closely monitored outpatient strategy’. European Society of Cardiology guidelines suggest the possibility of treating these patients as outpatients and always by a close monitoring strategy. It is necessary to have the time to reflect on the certainty of the diagnosis of embolic disease, during the screening of other diseases. Finally, in situations where it is not immediately certain to be faced with a patient with PE at low risk, we have to make a prudent observation, perhaps to avoid the risk of a thrombolytic therapy or an invasive strategy when the patient has assumed a NOAC. Just for this reason, we suggest a period of 48 h hospitalization also for the lowest risk patient. We have to consider also the fact that the patients enrolled in the trials are younger (average 56 years) than the ones we meet in the common clinical practice (average 70 years). The NOACs are more than just an alternative to
Table 1  The non-vitamin k dependent new oral anticoagulant(s) in the acute phase of venous thromboembolism

| Drug       | Trial          | Design          | Treatment and dosage                                                                 | Duration | Patients                  | Effectiveness NOACs vs. VKA (recurrent VTE or fatal PE) | Safety NOACs vs. VKA (major bleeding ± CRNM) |
|------------|----------------|-----------------|--------------------------------------------------------------------------------------|----------|---------------------------|--------------------------------------------------------|---------------------------------------------|
| Dabigatran | RE-COVER       | Double-blind parallel-group placebo | Enoxaparin/Dabigatran (150 mg b.i.d.) vs. Enoxaparin/Warfarin                        | 6 months | 2539 patients with VTE    | VTE recurrence or fatal PE: 2.5% Dabigatran vs. 2.1% Warfarin (P < 0.001) | Major Bleeding 1.6% Dabigatran vs. 1.9% Warfarin (±CRNM; P = ns) |
|            | RE-COVER II    | Double-blind parallel-group placebo | Enoxaparin/Dabigatran (150 mg b.i.d.) vs. Enoxaparin/Warfarin                        | 6 months | 2589 patients with VTE    | VTE recurrence or fatal PE: 2.3% Dabigatran vs. 2.2% Warfarin (P < 0.001) | Major Bleeding 15 patients Dabigatran vs. 22 patients Warfarin (±CRNM; P = ns) |
| Rivaroxaban | EINSTEIN DVT   | Open-label      | Rivaroxaban (15 mg b.i.d. × 3 weeks followed by 20 mg/day) vs. Enoxaparin/Warfarin | 3.6 or 12 months | 3449 patients with DVT | VTE Recurrence or fatal PE: 2.1% Rivaroxaban vs. 3% Warfarin (P < 0.001) | Major Bleeding 8.1% Rivaroxaban vs. 8.1% Warfarin (±CRNM; P = ns) |
|            | EINSTEIN-PE    | Open-label      | Rivaroxaban (15 mg b.i.d. × 3 weeks followed by 20 mg/day) vs. Enoxaparin/Warfarin | 3.6 or 12 months | 4832 patients with PE     | VTE Recurrence or fatal PE: 2.1% Rivaroxaban vs. 1.8% Warfarin (P < 0.03) | Major Bleeding or CRNM 10.3% Rivaroxaban vs. 11.4% Warfarin (±CRNM; P = ns) |
| Apixaban   | AMPLIFY        | Double-blind parallel-group placebo | Apixaban (10 mg b.i.d. × 7 dd. followed by 5 mg b.i.d.) vs. Enoxaparin/Warfarin     | 6 months | 5395 patients DVT: 3532 PE: 1836 | VTE recurrence or fatal EP: 2.3% Apixaban vs. 2.7% Warfarin (P < 0.001) | Major Bleeding 0.6% Apixaban vs. 1.8% Warfarin (±CRNM; P < 0.001) |
| Edoxaban   | Hokusai-VTE    | Double-blind parallel-group placebo | LMWH/Edoxaban (60 mg/day or 30 mg/day if Cr Cl < 30-50 mL/h or weight < 60 Kg × 3 weeks vs. UFH or LMWH/Warfarin | 3-12 months | 8240 patients DVT: 4921 PE: 3319 | VTE recurrence or fatal EP: 3.2% Edoxaban vs. 3.5% Warfarin (P < 0.001) | Major Bleeding or CRNM 8.5% vs. 10.3% Warfarin (±CRNM; P = ns) |

Results in terms of efficacy and safety of the phase III clinical trials for the treatment in the acute phase of pulmonary embolism or deep vein thrombosis.

CRNM, clinically relevant non-major bleeding; NOACs, non-vitamin K dependent new oral anticoagulant(s); VTE, venous thromboembolism; PE pulmonary embolism; VKA, vitamin K antagonist; DVT, deep vein thrombosis study; UFH, unfractionated heparin.
the standard in the treatment of patients with PE.49 We have to prescribe them after understanding the risk of the disease, the origin of the acute embolic event and the vulnerability of our patient. So we can draw a tailored therapy, wise, not hasty.

**Disputes about using non-vitamin K dependent new oral anticoagulant(s): the cancer patient, the fragile patient, the patient with renal failure, the obese patient**

Despite a cost-effectiveness ratio more favourable than traditional therapy, NOACs still have some areas of uncertain use, which mainly refers to those categories of patients who are normally under represented in clinical trials: cancer, RF, obesity and the so-called ‘frail’ patient.

The ‘frailty’ refers to elderly patients, generally >75 years old, with co-morbidities, an increased risk of adverse events and/or poor prognosis.50 It is not ‘static’ condition but often ‘dynamic’. In clinical trials about VTE, patients >75 years are defined ‘frail’ if they have RF and reduced body weight. In fact, the risk of VTE in patients >85 years is 100 times higher than in patients <45 years, while the risk of recurrent VTE increases of 15-20% for each decade of age. About 25% of patients hospitalized for VTE present RF from moderate to severe.51 Unfortunately, in clinical trials the percentage of the elderly >75 years is only 10-17% with exclusion of patients with creatinine clearance (Cr Cl) < 30 and 25 mL/min (Table 2). It is difficult to extend the results of the trials to the ‘real’ frail patients. In any case, the results of some analyses in the frail patients, showed equivalent effectiveness of Dabigatran, Rivaroxaban and Apixaban and statistically significant superiority of Edoxaban (P = 0.0408). Regarding the major bleeding events, no significant difference was observed for Apixaban and Edoxaban, a tendency to higher risk of bleeding in patients >85 years treated with Dabigatran vs. placebo and a good safety profile was documented for Rivaroxaban (1.3% vs. 4.5% of major bleeding events; HR 0.27; 95% CI 0.13 to 0.54). However, the inclusion criteria showed some differences among trials.3,7,10,52 Regarding chronic RF, due to the different pharmacokinetics of the molecules, that have a specific elimination, an increased incidence of VTE events and bleeding complications during anticoagulant therapy has been documented.53 Patients with chronic RF have been excluded from the recruitment in the clinical trials evaluating the NOACs. As a result, the current recommendation about the use of NOACs in these groups of patients comes from the analysis of subgroups and from previous pharmacokinetic studies.53 In short, while in patients with severe RF (Cr Cl < 25-30 mL/min) the NOACs are contraindicated, in patients with moderate RF (Cr Cl 30-50 mL/min) they can be used.54 It would be prudent to use a FXa inhibitor with a subsequent dose adjustment. For Apixaban, dose reduction is recommended when at least two of the following factors are present: age >80 years, weight <60kg, and serum creatinine >1.5 mg/dl, co-exist; Rivaroxaban does not require a dosage reduction in moderate renal impairment and it is not recommended in severe RF; Dabigatran should not be used with a Cr Cl < 50 mL/min; finally, the recommended dose of Edoxaban in moderate RF is 30 mg/day. A close follow-up of renal function in these patients is mandatory.

**Obesity**, body mass index (BMI) >30 kg/m², is a known risk factor for VTE events.55 In the major trials, it was not an exclusion criterion and it did not provide dose modifications. The percentage of obese patients enrolled was small. In the subgroup studies, the efficacy and the safety of the NOACs in obese patients53 were good, although the RE-COVER study showed a non-significant trend towards a higher incidence of VTE events in patients with

---

**Table 2 The subgroups of fragile patients in the great trials**

| Drug       | EINSTEIN DVT/PE (pooled) | RECOVER I-II (pooled) | AMPLIFY | Hokusai-VTE |
|------------|--------------------------|-----------------------|----------|-------------|
| Number of patients | 8281 | 5107 | 5244 | 8240 |
| Average age | 55 | 57 | 57 | 55 |
| Cr Cl < 30 mL/min | 22 (0.4%) | 15 (0.4%) | 6 (0.1%) | 29 (0.5%) |
| Renal excretion | 33% | 80% | 27% | 50% |
| Cancer | >5.2% | >5% | >3% | >9% |
| Recommended dose in the presence of moderate Cr Cl 30-50 mL/min kidney failure () | 15 mg/b.i.d. for 3 weeks followed by 20 mg/day | 150 mg/b.i.d. | 2.5 mg/b.i.d. | 30 mg/day |
| Pre-specified subgroups | | | | |
| Age > 75 aa | 1283 (15.5%) | 529 (10.4%) | 749 (14.3%) | 1104 (13.4%) |
| Kidney Failure | | | | |
| Cr Cl > 50 mL/min | 654 (7.9%) | - | 1388 (26.5%) | 541 (6.6%) |
| Cr Cl < 80 mL/min | 1373 (26.9%) | | | |
| Weight | | | | |
| Weight < 50 Kg | 108 (1.3%) | 57 (1.1%) | | 457 (8.7%) |
| Weight > 60 Kg | | | | 1043 (12.7%) |

Main epidemiological data on frail patients in the trials with the NOACs.

n.a., not applicable; DVT, deep vein thrombosis study; PE, pulmonary embolism; VTE, venous thromboembolism; Cr Cl, Creatinine Clearance.
BMI > 30 kg/m², these data seem to be in contrast with the results of the Randomized Evaluation of Long-term anticoagulant Therapy (RE-LY). 36

Cancer and VTE are closely associated. From ‘Registro Informatizado de la Enfermedad Tromboembólica Venosa’ (RIETE) observations, VTE event occurs in 20% of patients with cancer and in patients with VTE cancer was present in 20% of cases. 57 Moreover, VTE is a negative prognostic factor in patients with cancer. 58 Currently, the LMWHs are the first-line therapy in patients with cancer and VTE due to their better efficacy and safety profile compared to Warfarin with respect to the reduction of VTE recurrences. The potential benefits of the NOACs can also be extended to patients with cancer, especially in the medium to long-term therapies. Unfortunately, there is no randomized trial specifically designed for cancer patients. The scientific data available derived from the analysis of subgroups in which the NOACs were compared with the combination therapy of LMWHs/VKAs showed for all the NOACs a safety and efficacy comparable to non-cancer patients. 58 These observations were confirmed by three recent meta-analyses and systematic reviews. 59–61 In each observation, the risk of VTE and/or VTE-related death was comparable with the traditional therapy as well as the safety profile. These data, however, should be carefully interpreted because of the small number of very selected cancer patients randomized and the lack of direct confrontation with LMWHs, first-line therapy.

Briefly, the profile of efficacy and safety of the NOACs and their favourable pharmacokinetic and pharmacodynamic characteristics together with the preliminary results of the subgroups support the use of the NOACs even in elderly and frail patients, obesity, or moderate renal impairment. The absence of trials built on these patients and the ‘nuanced’ differences in the criteria of analysis among subgroups makes it difficult to do a direct comparison among NOACs.

On the other hand, the complexity of the patients that occur in clinical practice, where multiple co-morbidity rather than ‘isolated factors of frailty’ often co-exist, does not allow to provide simple formulas to guide medical therapy. It will be the correct assessment of the patients’ complexity and their risk benefit ratio that will lead us to choose the best treatment for each patient. As far as the cancer patients are concerned, on the contrary, the potential benefit of the NOACs will be supported by dedicated clinical trials. Today it is not possible to recommend their widespread use in this setting.

The use and the duration of the non-vitamin K dependent new oral anticoagulant(s) in the extended phase

After the first episode of PE the existing guidelines recommend at least 3 months’ anticoagulant therapy in all patients. 1,48 They give no precise details concerning on how to conduct FU and anticoagulant therapy duration. Follow-up generally ceases with the suspension of anticoagulant therapy even though, after a PE episode, the patients have a higher overall mortality than the control population and may experience MI, stroke, PE recurrence, and seldom develop a chronic pulmonary hypertension. 62

Stages and duration of treatment

The extended phase (> 3 months) of anticoagulant therapy is aimed at reducing the risk of PE recurrence if not related to acute episode. 48 The duration of treatment depends on the risk of PE recurrence, on the bleeding risk, on the preference of the individual patient. In cases of unprovoked PE, various predictive models for identifying patients at low risk of recurrence have been proposed 63–65 but none of them has been validated in prospective studies.

The annual incidence of major bleeding during anticoagulant therapy varies from 0.8 to over 6%, and the annual incidence of fatal bleeding is between 0.1 and 0.5%. 66–68 While, the rate of major bleeding during the first 3 months’ anticoagulant therapy is about 3%. The American College of Chest Physicians GL proposed a score of bleeding risk based on a number of variables derived from the literature. 48

Extended therapy: traditional anticoagulant therapy limits

With regard to LMWHs, the limits are represented by the route of administration, the risk of thrombocytopenia, the reduced excretion in RF, and the possible risk of osteoporosis in prolonged use. The use of Fondaparinux is limited by parenteral administration, moderate RF or severe RF and there are also poor security data in the event of extended use. Vitamin K inhibitors have several limitations such as a narrow therapeutic window, an unpredictable response, an action to slow onset and cessation, the need for monitoring, and the interactions with food and drugs.

Extended therapy: the non-vitamin K dependent new oral anticoagulant(s)

They present some substantial advantages: a rapid onset of action, a short half-life, the absence of an important interactions with food or other drugs, less risk of brain bleeding and they don’t require a routine monitoring. The disadvantages include: the unavailability of a laboratory test standard for a quantitative evaluation of the effect of drugs in case of major bleeding, emergency surgical procedure; they are also contraindicated if Cl Cr < 30 mL/min, 69,70 lastly, for their use, a good reliability in the regular drug assumption by patients is necessary.

Clinical trials and the extended phase

The studies so far published on the NOACs have dealt with the extended phase but not the indefinite one; in just one study, secondary prevention of venous thromboembolism twice-daily oral direct thrombin inhibitor Dabigatran etexilate in the long-term prevention of recurrent symptomatic VTE (RE-MEDY) 4 there was a direct comparison with Warfarin while in others the comparison was placebo.

In the RE-MEDY study 6 Dabigatran was found to be not inferior to Warfarin in secondary prevention of VTE, the study showed less major haemorrhagic or clinically relevant events in the Dabigatran group compared to Warfarin; an increased incidence of acute coronary events in the
Dabigatran group was also observed, as already shown in RE-LY study. This increase was not detected in the placebo-control study, Secondary Prevention of venous thromboembolism twice-daily oral direct thrombin inhibitor Dabigatran etexilate in the long-term prevention of recurrent symptomatic VTE, RE-SONATE and this suggested that the Dabigatran does not increase acute coronary events but it prevents them less than Warfarin.

In the EINSTEIN-Extension study the Rivaroxaban group had a significant recurrence reduction of VTE compared to placebo; similar to the findings with Dabigatran, major and clinically relevant bleedings were more frequent in the Rivaroxaban group than in the placebo group; Rivaroxaban has not been compared in the extended phase with the VKAs.

Venous thromboembolism recurrence and death were found significantly reduced by both dosages of Apixaban vs. placebo in the AMPLIFY-Extension study. Both 2.5 and 5 mg Apixaban dosages showed no major or clinically relevant bleeding increase compared to placebo. These latest dosages make the use of Apixaban in the extended phase of VTE therapy attractive. Apixaban was also not compared with the VKAs in the extended phase (Table 3).

When to prefer non-vitamin K dependent new oral anticoagulant(s) and when vitamin K inhibitors

In randomized clinical trials younger patients, with low risk of bleeding, no strong indication to continue the anticoagulant therapy and with less comorbidity compared with real life, were enrolled; underweight patients, obese people were poorly represented. The data coming from the use of the NOACs in the real world are of some concern as they appear to highlight major bleeding fourfold more than the ones reported from clinical studies. Possible clarifications regarding the current limitations on the use of the NOACs may come from ad hoc trials. As for efficacy, NOACs have given excellent results in the extended phase of the VTE treatment. Compared with traditional therapy, they showed less bleeding events. It is likely that, as it was said, their use can be particularly advantageous, compared with traditional therapy in patients at higher risk of recurrence of VTE who require protracted prophylactic therapy.

Non-vitamin K dependent new oral anticoagulant(s) are to be preferred: in presence of logistical problems for VKAs monitoring; if time in the therapeutic range (TTR) is <60%; in patients with a history of cerebral haemorrhage; at the express request of patients, if they are proved to be reliable.

On the contrary the preference falls on VKAs if the TTR is >60%, in the presence of low risk of bleeding or severe RF, CI Cr < 30 mL/min and finally in likely poor compliance in regular intake of NOACs.

Clinical and laboratory follow-up in the non-vitamin K dependent new oral anticoagulant(s) patient

The NOACs are drugs that, for their pharmacological and pharmacodynamic profile, guarantee a rapid mechanism of

### Table 3: The main trials in long-term treatment of pulmonary embolism

| Drug     | Trial          | Comparison | Design     | Expected treatment | Expected reduction | VTE in the check | Reduced risk of VTE recurrence | Major bleeding or CRNM in the active group | Reduced risk of VTE recurrence in the active group |
|----------|----------------|------------|------------|--------------------|--------------------|------------------|-------------------------------|--------------------------------------------|---------------------------------------------------|
| Dabigatran | RE-SONATE     | Placebo    | Superiority| 150 b.i.d.          | 70%                | 5.6%             | 92%                           | 5.3% vs. 1.8% (+CRNM; P = 0.001) | 0.0% vs. 10.2% (+CRNM; P < 0.001) |
| Warfarin  | RE-MEDY       | Dabigatran | Non-inferiority | 150 b.i.d. | 18-36 months | 2856 | 1.3% | 0.38% vs. aVK |
| Placebo   | AMPLIFY Ext   | Placebo    | Superiority| 5 mg bid           | 41%                | 8.8%             | 80%                           | 3.0% vs. 7.7% (+CRNM; P = 0.001) | 3.0% vs. 1.2% (+CRNM; P < 0.001) |
| Rivaroxaban| EINSTEIN-Ext | Placebo    | Superiority| 20 mg             | 50%                | 1197             | 7.1%                          | 6.0% vs. 1.2% (+CRNM; P < 0.001) |

Results in terms of reduced risk of VTE recurrence and major bleeding or CRNM, clinically relevant non-major bleeding.
action, efficacy stable in time and a short half-life useful in the case of preparation of such surgery (Table 4). The administration of fixed doses of the drugs is useful to avoid oscillations of the effectiveness in terms of anticoagulant effect and to avoid the need of periodic blood sampling; finally, the minimal interaction with foods and/or with other drugs makes more favourable their pharmacokinetic characteristics and pharmaco-dynamics.76

As regards the principal pharmacological features, the direct thrombin inhibitors are small synthetic molecules that bind to the active sites of the thrombin inhibiting both free thrombin and the bound one.77,78

**Direct FXa inhibitors** work by blocking both free FXa, and the one that is incorporated into the prothrombin complex. The FXa block has several theoretical advantages: the production of thrombin is inhibited both by the intrinsic and extrinsic pathway.79

As known, current guidelines recommend evaluating Cr Cl before starting NOACs. Inpatients with normal renal function or mildly impaired, the reassessment will be performed annually, while inpatients with moderate renal impairment (30 < Cr Cl < 60 mL/min) every 3-6 months and in presence of worsening. About the liver function, NOACs are contraindicated in patients with severe hepatic impairment or hepatic disease associated with coagulopathy. The NOACs don’t require a routine monitoring of coagulation parameters. However, particular clinical situations need measurement of laboratory values to rule out an underlying bleeding tendency and/or the absence of contraindications to continued treatment.79 For the Dabigatran, the prothrombin time (PT) is not a sensitive indicator to evaluate the anticoagulant effect while the determination of the aPTT, according to most authors80 allows hypothesizing, qualitatively, the presence or absence of therapeutic effect. The blood concentration of Dabigatran may be quantified by the ecarin aggregation time (ECT) and the diluted thrombin time (TT).81 The INR during therapy with Dabigatran shows false positives.82 Regarding the direct inhibitors of FXa it is known that Apixaban83 does not change the aPTT, while Rivaroxaban84 and Edoxaban85 are associated with increased values both aPTT and PT. The use of chromogenic calibrated test on the specific molecule shows a good sensitivity to the estimation of the NOACs concentration.86 However, to date, the food and drug administration (FDA) have been approved no kits. Without specific laboratory tests, the most important clinical information to be verified, during control visits, are adherence and persistence to therapy. At each FU examination it will be important to collect a set of information systematically concerning:

- the degree of adherence to treatment;
- the occurrence of adverse reactions (thrombotic and/or haemorrhagic events);
- the concomitant risk of drug interactions;
- some laboratory parameters (Table 5), when necessary;

Recently, the results of the study reverse effect of idarucizumab on active Dabigatran (RE-VERSE AD)87 have led to the approval of the first specific reversal agent, the idarucizumab, which specifically binds the molecules of Dabigatran. Other antidotes, PER977,88 andexanet-alpha89 are currently under investigation.

**Non-vitamin K dependent new oral anticoagulant(s) in everyday clinical practice: drug-drug interactions, protocol for the treatment of bleeding and perioperative management**

**Drug-drug interactions**

Despite the lower number of drug-drug interactions compared with VKAs, a careful assessment of patients’ comorbidities and of concomitant therapies is required when prescribing NOACs. The characteristics of the individual NOACs in terms of absorption, metabolism, elimination, and known interactions should be considered. An important mechanism of interaction common to all the NOACs is the significant re-secretion over a P-glycoprotein transporter after absorption in the intestines. Therefore, competitive inhibition of this pathway will result in increased plasma levels of NOACs.90 Many commonly used drugs, especially in

---

**Table 4** Mechanism of action and main pharmacological characteristics of the non-vitamin K dependent new oral anticoagulant(s)

| Target               | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|----------------------|------------|-------------|----------|----------|
| Reaching peak dose   | 1.25-3 h   | 2.4 h       | 3.4 h    | 1.2 h    |
| Prodrug              | Yes        | No          | No       | No       |
| Metabolism via CYP   | No         | 32%         | 15%      | <4%      |
| Transport            | P-gp       | P-gp        | P-gp     | P-gp     |
| Bioavailability      | 6%         | 80%         | 60%      | 62%      |
| Absorption with food | No Effect  | +39%        | No Effect| +6-22%   |
| Taking with food     | With or without food | With or without food | With or without food | With or without food |
| Protein binding      | 35%        | 93%         | 87%      | 50%      |
| Half-life            | 14-17 h (BID) | 7-11 h (QD/BID) | 8-15 h (BID) | 10-14 h (QD) |
| Renal excretion      | 80%        | 33%         | 25%      | 35%      |
| Absorption H2B/PPI   | 12-30%     | No          | No       | No       |
| Gastrointestinal tolerability | Dyspepsia (5-10%) | No Effect | No Effect | No Effect |
patients with atrial fibrillation as verapamil, dronedarone and amiodarone are inhibitors of P-glycoprotein and their concomitant use can increase plasma levels of NOACs.91 The inducers of the P-glycoprotein can significantly reduce plasma levels of NOACs. Whether the change in plasma levels is clinically significant in terms of increased bleeding or thrombotic risk depends on the degree of interaction. Rivaroxaban and Apixaban have hepatic metabolism by CYP3A4 (P450). The induction or inhibition of this cytochrome may influence the plasma levels of these drugs substantially and therefore their use is not recommended concomitantly with strong inducers/inhibitors such as rifampicin92 or carbamazepine. Only a small proportion of Edoxaban is metabolized by CYP3A4, while this type of metabolism is not described for Dabigatran. NOACs are also contraindicated in patients receiving antiretroviral therapy; no clinical data are currently available on potential interactions with other drugs such as anticancer therapies (Table 6).

Management of bleeding complications
Current GL recommend the use of prothrombin complex concentrates (PCC) to restore the levels of clotting factors in patients who experience major bleeding during treatment with VKAs.93 A rapid normalization or otherwise a significant reduction of the clotting times is observed early after infusion of PCC. However, no definitive data are currently available on the clinical benefit associated with the use of these agents. With regard to the NOACs, the administration of PCC led to the complete and rapid normalization of coagulation time in healthy volunteers treated with Rivaroxaban, but no effect was observed in healthy volunteers treated with Dabigatran.94 Therefore, the use of the PCC is recommended in patients experiencing major bleeding during treatment with anti-Xa agents but not with Dabigatran. Promising results are currently available on the role of specific agents, antidotes, designed to reverse the anticoagulant effect of NOACs. Idarucizumab, an antibody fragment developed to block the anticoagulant effect of Dabigatran, obtained a complete normalization of coagulation within minutes when given as a single intravenous bolus in 90 patients with severe bleeding or need for invasive procedures in emergency.95,96 Andexanet alfa, a recombinant molecule of human FXa modified to be catalytically inactive but to retain high binding affinity for

| Follow-up | Check | Parameter | Drug |
|-----------|-------|-----------|------|
| Baseline  | lab test | Haemoglobin | Dabigatran, Rivaroxaban, Apixaban, Edoxaban |
|           |       | Creatininemia |     |
|           |       | ALT, AST |     |
| First month and each visit | Events Adherence Interaction | Thrombosis and/or bleeding Remaining drug P-gp e CYP3A4 |     |
| Third month (Only if creatinine clearance 30-60 mL/min) | Events Adherence Interaction lab test | Thrombosis and/or bleeding Remaining drug P-gp e CYP3A4 Haemoglobin Creatininemia ALT, AST |     |
| Sixth month (Only if creatinine clearance 30-60 mL/min) | Events Adherence Interaction lab test | Thrombosis and/or bleeding Remaining drug P-gp e CYP3A4 Haemoglobin Creatininemia ALT, AST |     |
| Every 12th month (long-term therapy) | Events Adherence Interaction lab test | Thrombosis and/or bleeding Remaining drug P-gp e CYP3A4 Haemoglobin Creatininemia ALT, AST |     |
| Specific indication (Thromboembolic events, acute bleeding, surgery, etc.) | Lab test | INR PT aPTT Diluted TT Chromogenic anti-FXa ECT |     |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; P-gp, P-glycoprotein; CYP3A4, CytochromeP450A4; QD, once a day; BID, twice a day; PPI, Proton Pomp Inhibitors; INR, international normalized ratio; PT, prothrombin time; aPTT, activated partial thromboplastin time; TT, thrombin time; aFX, Activated Factor X; ECT, ecarin aggregation time; ULN, above the upper limit. Green, in favour literature data; Red, negative literature data; Yellow, inconclusive literature data.
indirect FXa inhibitors, reversed the anticoagulant effect of Apixaban in 34 volunteers. The clinical development of small molecules capable of antagonizing the effect of several parenteral and oral anti Xa agents has started. However, given the short half-life of the NOACs, the clinical value of antidotes in real life remains to be determined. Activated charcoal should be used in all patients who had last dose of NOACs in the previous 2 h (Figure 1).

**Perioperative management**

The perioperative management of patients on NOACs for the treatment of VTE should take into account the time since the acute thromboembolic event (Table 7). Invasive procedures should be delayed beyond 3 months from acute thromboembolism whenever it is possible. Non-vitamin K dependent new oral anticoagulant(s) should be discontinued at least 48 h before surgery (a longer time is needed in patients with concomitant kidney failure). Antithrombotic prophylaxis of VTE should be started as soon as possible after surgery and anticoagulant therapy resumed as soon as adequate haemostasis is obtained. If surgery is required in the first 3 months from acute VTE, the insertion of a vena cava filter should be considered and the interruption of anticoagulant treatment should be as short as possible.

| Table 6 | Main drug-drug interactions |
|---------|-----------------------------|
| Apixaban | HIV Protease Inhibitors |
|         | Rifampicin |
|         | Itraconazole |
|         | Ketoconazole |
|         | Posaconazole |
|         | Voriconazole |
|         | Carbamazepine |
|         | Phenoxypraline |
|         | Phenoxypraline |
|         | St. John’s wort |
|         | Cyclosporin |
|         | Tacrolimus |
|         | Dronedarone |
|         | — |
| Reduced dose | Clarithromycin |
| of NOACs suggested | Erythromycin |
|                   | Itraconazole |
|                   | Ketoconazole |
|                   | Posaconazole |
|                   | Amiodarone |
|                   | Fluconazole |
|                   | Cyclosporin |
|                   | Tacrolimus |
|                   | Quinidine |
|                   | Diltiazem |
|                   | Fluconazole |
|                   | — |

The use of non-vitamin K dependent new oral anticoagulant(s) in pulmonary embolism

Table derived from EHRA 2015 recommendation.

NOACs, non-vitamin K dependent new oral anticoagulant(s).

a If 2 drugs in this category, or if 1 drug and one among age ≥ 75 years or body weight ≤ 60 kg or Creatinine clearance ≤ 50 mL/min consider conventional therapy (no data available on the efficacy and safety of NOACs in the treatment of venous thromboembolism except for Apixaban 2.5 mg twice daily during extended treatment and Edoxaban 30 mg once daily).
Practical suggestions
(1) In suspected PE, a blood pressure measurement allows us to define the haemodynamic stability, and thus 'high risk' or 'not-high risk' PE.
(2) Prognostic stratification of PE patients based on clinical, through PESI or sPESI score that is added to the assessment of bio-markers of myocardial damage and the function of the right ventricle at echocardiography allow us to distinguish intermediate mortality risk patients in intermediate-high risk and intermediate-low risk.
(3) The NOACs can be used as an alternative to traditional therapy both in low-intermediate and in low risk patients.
(4) The NOACs envisage the evenience of short hospitalizations for the lowest risk patients for whom we suggest a 48 h observation.
(5) In intermediate-high risk patients with PESI class III-V or sPESI ≥1, in the presence of positive troponin and of right ventricular dysfunction, we recommend a 'wait and watch' strategy and the possibility of using thrombolysis precludes, at the time, NOACs therapy; even if after the acute phase, if there is right ventricular function improvement, we envisage the therapy with NOACs, waiting for definitive clinical evidence in this population.
(6) Therapeutic innovation of the NOACs consists in the way of the therapy administration, with 'double drug single dose therapy’, for Dabigatran (150 mg twice daily) and Edoxaban (60 mg daily mono-administration), or a ‘single drug therapy’ with Rivaroxaban (15 mg × 2x daily for 21 days, then 20 mg daily) or Apixaban (10 mg × 2x twice daily for 7 days, then x2.5 mg twice daily).
(7) In step 'extended' the use of the NOACs exceeds the limits of traditional therapy but all the studies with NOACs have not dealt with the indefinite phase and, also, in only one study, they were compared with Warfarin. So, to date, patients, who we feel may benefit from treatment with the NOACs in the extended phase, are all naive.

Table 7 Periprocedural management in patients on treatment with non-vitamin K dependent new oral anticoagulant(s)

| Procedure Type                     | Management                                                                                          |
|------------------------------------|-----------------------------------------------------------------------------------------------------|
| Elective major surgery             | <3 months since last acute venous thromboembolism Delay surgery ≥3 months since acute venous thromboembolism, if possible |
|                                   | Stop NOACs ≥48 h before surgery                                                                     |
|                                   | Consider pre-operative vena cava filter insertion (post-operative insertion if contraindications for resumption of anticoagulation ≤5 days from surgery) |
|                                   | Start antithrombotic prophylaxis as soon as possible as in non-NOACs patients                        |
|                                   | In the absence of vena cava filter resume anticoagulant treatment <5 days from surgery               |
|                                   | Surgery ≥3 months since last acute venous thromboembolism                                             |
|                                   | Stop NOACs ≥48 h before surgery                                                                     |
|                                   | Start antithrombotic prophylaxis as soon as possible as in non-NOACs patients                        |
|                                   | If indicated, resume anticoagulant treatment ≥5 days from surgery                                   |
|                                   | Stop NOACs and assess time of last intake and regimen                                                |
| Urgent surgery/invasive procedure  | Assess blood cells count and renal function. Consider coagulation tests                            |
|                                   | activated charcoal (30-50 g) if last NOAC intake <2 h                                                 |
|                                   | consider pre-operative vena cava filter insertion                                                    |
|                                   | if <3 months since last acute venous thromboembolism,                                               |
|                                   | Administration if intra- or peri-operative unexpected bleeding                                         |
|                                   | Give red blood cells if needed                                                                       |
|                                   | Delay surgery ≥12 h since last NOAC intake, if possible                                               |
|                                   | surgery required <12 h since last NOAC intake:                                                        |

NOACs, non-vitamin K dependent new oral anticoagulant(s).
patients with idiopathic VTE intermediate-low, low risk, and among patients already on treatment with VKAs, those with logistical problems for the monitoring of VKAs, if the TTR is <60%; in patients with a history of cerebral haemorrhage. Patients, being treated with VKAs, continue this therapy if the TTR is >60%; preference instead fall back on VKAs if patients with severe RF, Cr Cl < 30 mL/min or likely poor compliance in the regular intake of NOACs.

(8) With regard to efficacy and safety in special populations of patients: there are no dosage adjustments up to BMI 30; severe RF (Cr Cl < 25-30 mL/h) contraindicates the use of the NOACs; in regard to cancer patients, missing a dedicated clinical trial and a study by comparison with LMWHs, it is not yet possible to advise, based on available data, their widespread use in this area and LMWHs remain the therapy of choice in patients with cancer;

(9) We point out the need for clinical-laboratory monitoring, in elderly patients with renal and/or hepatic insufficiency according to criteria specified in the text.

(10) As regards the bleeding risk the FDA has approved the use of idarucizumab monoclonal antibody for Dabigatran; the andexanet alpha is being tested; the use of idarucizumab monoclonal antibody for the text.

Lastly we indicate a practical ‘table’ for the peri-operative management of patients on NOACs.

Consensus Document Approval Faculty

Abrignani Maurizio Giuseppe, Alunni Gianfranco, Amico Antonio Francesco, Amodeo Vincenzo, Angeli Fabio, Aspromonte Nadia, Audo Andrea, Battistoni Ilaria, Bianca Innocenzo, Bisceglia Irma, Bonvicini Marco, Cacciavillani Luisa, Calculi Giacinto, Caldara Paola, Capocasa Marco, Ceraletta Giorgio, Casolo Giancarlo, Cassin Matteo, Casu Gavino, Cemin Roberto, Chiara Giarman, Chiarriale Francesco, Chiariello Mario, Cibinel Gian Alfonso, Ciccone Marco Matteo, Clerico Aldo, Chiaranda Giacomo, Chiarella Francesco, Chiaro Mario, Cimin Vavmane, Friedman J, Misrsmenti P, Goldhaber SZ, for the RE-MEDY and the RE-SONATE Trials Investigators. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013;368:709-718.

Bauersachs R, Berkowit SD, Brenner B, Bülter HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, Segers A, Verhamme P, Wells P, Agenlli G, Bounaumes H, Cohen A, Davidson BL, Povella F, Schollong S, Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-2510.

Büller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, Chilmsky J, Verhamme P, Wells P, Agenlli G, Cohen A, Berkowit SD, Bounaumes H, Davidson BL, Misselwitz F, Gallus AS, Raskob GE, Schollong S, Segers A. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287-1297.

Agenlli G, Bülter HR, Cohen A, Curto M, Gallus AS, Johnson M, Masuiwicz U, Pak K, Thompson J, Raskob GE, Weitz JI, for the AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369:799-808.

Agenlli G, Bülter HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI, Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368:699-708.

Raskob G, Bülter H, Prins M, Segers A, Shi M, Schwocho L, Van Kranen R, Mercari M, and the HOKUSAY VTE Investigators. Edoxaban for the long-term treatment of the venous thromboembolism: rationale and design of the Hokusai-venous thromboembolism study—methodological implicactions for clinical trials. Journal of Thrombosis and Haemostasis 2013;11:1287-1294.

Büller HR, Decousus H, Gross AM, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schollong SM, Schwocho L, Segers A, Shi M, Verhamme P, Wells P, Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013;369:1406-1415.

Torbicki A, van Beek EJR, Charbonnier B, Meyer G, Morpurgo M, Palla A, Perrier A; Task force on pulmonary Embolism of European society of Cardiology. Task force report: guidelines on diagnosis and management of acute pulmonary embolism. Eur Heart J 2000;21:1301-1336.

Torbicki A, Perrier A, Kantzinitides S, Agenlli G, Galile N, Piersczek P, Bengel F, Brady A, Ferreira D, Janssen U, Kelpritho W, Mayer E, Remy-Jardine M, Bassan JP: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society
of Cardiology (ESC). Guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2008;29:2276-2315.

13. Casazza F, Becattini C, Bongarzoni A, Cuccia C, Roncon L, Favretto G, Zonzin P, Pignataro L, Agnelli G. Clinical features and short term outcomes of patients with acute pulmonary embolism. The Italian Pulmonary Embolism Registry. Thromb Res 2012;130:847-852.

14. Casazza F, Bongarzoni A, Guenzati G, Tassinario G, Mafrici A. Fulminant pulmonary embolism, successfully treated with thrombolysis. Analg Resusc Curr Rev 2015;4:1.

15. Stein PD, Matta F. Thrombolytic therapy in unstable patients with acute pulmonary embolism: saves lives but underused. Am J Med 2012;125:465-470.

16. Wells PS, Anderson DR, Rodger M, Ginsberg JG, Kearon C, Gent M, Turpie AG, Romanis J, Weitz J, Chamberlain M, Bowie D, Barnes D, Hirsh J. Derivation of a simple clinical model to categorize patient probability of pulmonary embolism: increasing the models utility with the Simplified D-dimer. Thromb Haemost 2000;83:416-420.

17. Gibson NS, Sohne M, Grup JN, Dick U, Gerdies VE, Bossuyt PM, Wells PS, Builier HR. Further validation and simplification of the Wells clinical decision rule in pulmonary embolism. Thromb Haemost 2008;99:229-234.

18. Le Gal G, Righini M, Roy PM, Sanchez D, Aujesky D, Bounameaux H, Perrier A. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med 2006;144:165-171.

19. Klokk FA, Mos IC, Nijkeuter M, Righini M, Perrier A, Le Gal G, Huisman MV. Simplification of the revised Geneva score for assessing clinical probability of pulmonary embolism. Arch Intern Med 2008;168:2311-2316.

20. Schouten HJ, Geersing GJ, Koek HL, Zuithoff NP, Janssen KJ, Douma RA, van Dessel PJ, Moons KG. Retracing diagnostic algorithmic conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis. BMJ 2013;346:f2492.

21. Carrier M, Righini M, Wells PS, Perrier A, Anderson DR, Rodger MA, Pleasance S, Le Gal G. Subsegmental pulmonary embolism diagnosed by computed tomography: incidence, and clinical implications. A systematic review and meta-analysis. Arch Intern Med 2008;168:2311-2316.

22. Aujesky D, Bongarzoni A, Stiell I, Dreyer JF, Barnes D, Forgie M, Kovacs G, Ward J, Kovacs MJ. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. Ann Intern Med 2001;135:98-107.

23. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, Roy PM, Fine MJ. Derivation and validation of a prognostic model for pulmonary embolism. Am J Resp Crit Care Med 2005;172:1041-1046.

24. Jimenez D, Aujesky D, Moores L, Gomez V, Lobo JL, Uresandi F, Pleasance S, Le Gal G. Age-adjusted probability of pulmonary embolism. Thromb Haemost 2006;90:1260-1264.

25. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis. BMJ 2013;346:f2492.

26. Piazza G, Hohlfelder B, Jaff MR, Ourie K, Engel Hardt TC, Sterling PM, Jones NJ, Gurlie JC, Bhatheja R, Kennedy RJ, Goswami NM. Natarran K, Rundback J, Sadig LR, Liu SK, Bhalla N, Laia Raja M, Weinstock BS, Cynamon J, Elmasri F, Garcia MJ, Kumar M, Aydery J, Soukas P, Kuo W, Yu P, Goldhaber SZ. A prospective, single arm, multicenter trial of ultrasound facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism. The Seattle II study. JACC Cardiovasc Interv 2015;8:1382-1392.

27. Kuo WT, Banerjee A, Kim PS, De Marco FJ Jr, Levy JR, Facchin M, Unver K, Bertini MJ, Sista AK, Hall MJ, Rosenberg J, De Gregorio MA. Pulmonary embolism response to fragmentation embolectomy and catheter thrombectomy (PERFECT): initial results from a prospective multicenter registry. Chest 2015;148:667-673.

28. Sharifi M, Bay C, Skrochi L, Rahimi F, Mehdipour M; for the MOPETT Investigators. Moderate pulmonary embolism treated with thrombolysis. Am J Cardiol 2013;111:273-277.

29. Dobesh PP, Fanikos J. New oral anticoagulant for the treatment of venous thromboembolism: understanding differences and similarities. Drugs 2014;74:2015-2032.

30. Quon P, Le HH, Raymond V, Mitbaa M, Mohysh A. Clinical and economic benefits of extended treatment with apixaban for the treatment and prevention of recurrent venous thromboembolism in Canada. J Med Econ 2016;19:557-567.

31. Buller HR, Cohen AT, Davodson B, Decousus H, Gallus AS, Gent M, Pillon G, Piovella F, Prins MH, Raskob G; for the van Gogh Investigators. Idraparinux versus standard therapy for venous thromboembolic disease. N Engl J Med 2007;357:1094-1104.

32. Agnelli G, Gallus A, Goldhaber SZ, Haas S, Huisman MV, Hull RD, Kakkar AK, Misselwitz F, Schellong S. Treatment of proximal deep vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAV 59-7939): The ODIN DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in patients with acute symptomatic deep Vein Thrombosis) study. Circulation 2007;116:180-187.

33. Beam DM, Kahler ZP, Kline JA. Immediate discharge and home treatment with rivaroxaban of low-risk venous thromboembolism diagnosed in two U.S. emergency departments: a one-year preplanned analysis. Acir Emerg Med 2015;22:788-795.

34. Levi M, Eerenberg E, Kamphuisen PW. Bleeding risk and reversal strategies for old and new anticoagulants and antiplatelet agents. J Thromb Haemost 2011;9:1705-1712.

35. Vedovati MC, Becattini C, Germini F, Agnelli G. Efficacy and safety of direct oral anticoagulants after pulmonary embolism: a meta-analysis. Int J Cardiol 2015;177:601-607.

36. van Es N, Coppen N, Schulman S, Midddeldorp S, Builier H. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism. N Engl J Med 2009;360:2276-2285.

37. Beyer-Westendorf J, Ageno W. Benefit-risk profile of non-vitamin K antagonist oral anticoagulants in the management of venous thromboembolism. J Thromb Haemost 2015;13:1145-1151.

38. Fiessinger JN, Huisman MV, Davidson BL, Bounameaux H, Francis CW, Eriksson H, Lundström T, Berkowitz SD, Nyström P, Thorsen M, van Deiden JJ, Moons KG, Reitsma JB. Diagnostic accuracy of studies. A systematic review and meta-analysis of the management outcome and catheter thrombolysis (PERFECT): initial results from a prospective multicenter registry. Chest 2015;148:667-673.

39. Sharifi M, Bay C, Skrochi L, Rahimi F, Mehdipour M; for the MOPETT Investigators. Moderate pulmonary embolism treated with thrombolysis. Am J Cardiol 2013;111:273-277.

40. Dobesh PP, Fanikos J. New oral anticoagulant for the treatment of venous thromboembolism: understanding differences and similarities. Drugs 2014;74:2015-2032.

41. Quon P, Le HH, Raymond V, Mitbaa M, Mohysh A. Clinical and economic benefits of extended treatment with apixaban for the treatment and prevention of recurrent venous thromboembolism in Canada. J Med Econ 2016;19:557-567.

42. Buller HR, Cohen AT, Davodson B, Decousus H, Gallus AS, Gent M, Pillon G, Piovella F, Prins MH, Raskob G; for the van Gogh Investigators. Idraparinux versus standard therapy for venous thromboembolic disease. N Engl J Med 2007;357:1094-1104.

43. Agnelli G, Gallus A, Goldhaber SZ, Haas S, Huisman MV, Hull RD, Kakkar AK, Misselwitz F, Schellong S. Treatment of proximal deep vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAV 59-7939): The ODIN DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in patients with acute symptomatic deep Vein Thrombosis) study. Circulation 2007;116:180-187.

44. Beam DM, Kahler ZP, Kline JA. Immediate discharge and home treatment with rivaroxaban of low-risk venous thromboembolism diagnosed in two U.S. emergency departments: a one-year preplanned analysis. Acir Emerg Med 2015;22:788-795.

45. Levi M, Eerenberg E, Kamphuisen PW. Bleeding risk and reversal strategies for old and new anticoagulants and antiplatelet agents. J Thromb Haemost 2011;9:1705-1712.

46. Vedovati MC, Becattini C, Germini F, Agnelli G. Efficacy and safety of direct oral anticoagulants after pulmonary embolism: a meta-analysis. Int J Cardiol 2015;177:601-607.
The use of non-vitamin K dependent new oral anticoagulant(s) in pulmonary embolism

Ginsberg JS; for the THRIVE Treatment Investigators. Ximelagatran vs low-molecular-weight heparin and warfarin for the treatment of deep vein thrombosis: a randomized trial. J Am Med Assoc 2005;293:681-689.

47. Ferrmann GJ, Erkens PM, Prins MH, Wells PS, Pasp AF, Lensing AW. Treatment of pulmonary embolism with rivaroxaban: outcomes by simplified pulmonary embolism severity index score from a post hoc analysis of the EINSTEIN PE study. Acad Emerg Med 2015;22:299-307.

48. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounaumeau H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR; American College of Chest Physicians. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141(2 Suppl):e149S-e94S.

49. Bambr L, Wang MY, Prins MH, Ciniglio C, Bauersachs R, Lensing AW, Cano SJ. Patient-reported treatment satisfaction with oral rivaroxaban versus standard therapy in the treatment of acute symptomatic deep-vein thrombosis. Thromb Haemost 2013;110:732-741.

50. Bauersachs R. Managing venous thromboembolism with novel oral anticoagulants in the elderly and other high-risk patients groups. Eur J Intern Med 2014;25:600-606.

51. Prandoni P. Treatment of patients with acute deep venous thrombo sis and/or pulmonary embolism: efficacy and safety of non-VKA oral anticoagulants in selected populations. Thrombosis Research 2014;133:227-233.

52. Prins MH, Lensing AW, Bauersachs R, van Bellen B, Bounaumeau H, Brighton TA, Cohen AT, Davidson BL, Decousus H, Raskob GE, Berkowitz SD, Wells PS; EINSTEIN Investigators. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thromb J 2013;11:21.

53. Morrill AM, De G, Willet KC. Dosing of target-specific oral anticoagulants in special populations. Ann Pharmacother 2015;49:1031-1045.

54. Lega JC, Bertoletti L, Gremilliet C, Boisser C, Mismetti P, Laporte S. Consistency of safety profile of new oral anticoagulants in patients with renal failure. J Thromb Haemost 2014;12:337-343.

55. Fein PD, Beem-Kovacs A, Olson RE. Obesity as a risk factor in venous thromboembolism. Am J Med 2005;118:978-980.

56. Connolly SJ, Ezekowitz MD, Yusuf S, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR; EINSTEIN Investigators. Oral rivaroxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:1139-1151.

57. Monreal M, Falga C, Valdez M, Suarez F, Gabriel, Tolosa C, Montes J; European Cooperative Group of Chest Physicians Evidence-based Clinical Practice Guidelines. Chest 2012;141:e445-e885.

58. Baur KA. Pros and cons of new oral anticoagulants. Hematology 2013;4:44-470.

59. Schulman S. Advantages and limitations of the new anticoagulants. J Intern Med 2014;275:1-11.

60. Prandoni P. The treatment of venous thromboembolism with novel oral anticoagulants: warnings and limitations. Blood Transfus 2015;13:178-180.

61. Stangier J, Rathgen K, Stable H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate. An open-label, parallel group, single-centre study. Clin Pharmacokinet 2010;49:259-268.

62. Westendorf JB, Förster K, Pannsch S, Ebertz F, Gelbracht V, Thieme C, Michalis F, Kühler C, Werth S, Sahin K, Tittl L, Hänsel U, Weiss N. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. Blood 2014;124:955-962.

63. Weitz JI, Bauersachs R, Beyer-Westendorf J, Bounaumeau H, Brighton TA, Cohen AT, Davidson BL, Holberg G, Kakkar A, Lensing AWA, Prins M, Haskell L, van Bellen B, Verhamme P, Wells PS, Prandoni P. Two doses of rivaroxaban versus aspirin for prevention of recurrent venous thromboembolism. Rationale for and design of the EINSTEIN CHOICE study. Thromb Haemost 2015;114:645-650.

64. van Es N, Di Nisio M, Bleker SM, Segers A, Mercuri MF, Schwocho L, Kakkar A, Weitz JI, Beyer-Westendorf J, Boda Z, Carrier M, Chlumsky J, Décosus H, Garcia D, Gibbs H, Kamphuisen PW, Monreal M, Ockelrod P, Pabinger I, Verhamme P, Grosso M, Büller HR, Raskob GE. Edoxaban for treatment of venous thromboembolism in patients with cancer. Rationale and design of the Hokusai VTE-Cancer Study. Thromb Haemost 2015;114:1268-1276.

65. Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor Xa inhibitors in development. Clin Pharmacokinet 2009;48:1-22.

66. Di Nisio M, Mittendorf S, Büller HR. Direct thrombin inhibitors. N Engl J Med 2005;353:1028-1040.

67. Bauer KA. New anticoagulants: Anti Xa vs. Anti Xa—is one better? J Thromb Thrombolyis 2006;21:67-72.

68. Heidbuchel H, Verhamme P, Alings M, Arentz M, Hacke W, Oldgren J, Sinnavee P, Camm AJ, Kirchhof P. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace 2013;15:625-651.

69. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Weising S, van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Weising S. Duration of antithrombotic therapy. J Thromb Haemost 2012;10:1116-1127.

70. Pengo V, Crippa L, Falanga A, Finazzi G, Marongiu F, Palareti G, Poli D, Tait RC, Douketis J. Predicting disease recurrence in patients with previous unprovoked venous thromboembolism. A proposed prediction score (DASH). J Thromb Haemost 2012;10:1019-1025.

71. Carrier M, Le Gal G, Wells PS, Rodger MA. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. Ann Intern Med 2010;152:578-589.

72. Ost D, Tepper J, Mihara H, Landar O, Heinzer R, Fein A. Duration of anticoagulation following venous thromboembolism: a meta-analysis. J Am Med Assoc 2005;294:706-715.

73. Algeno W, Gallus AS, Wittkowski A, Crowther M, Hylek EM, Palareti G. Oral Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e445-e885.
83. Hillarp A, Gustafsson KM, Faxälv L, Strandberg K, Baghaei F, Fagerberg Blü Baxter I, Berndtsson M, Lindahl TL. Effects of the oral, direct factor Xa inhibitor apixaban on routine coagulation assays and anti-FXa assays. J Thromb Haemost 2014;12:1545–1553.
84. Francart SJ, Hawes EM, Deal AM, Adcock DM, Gosselin R, Jeanneret C, Friedman KD, Moll S. Performance of coagulation tests in patients on therapeutic doses of rivaroxaban. A cross-sectional pharmacodynamic study based on peak and trough plasma levels. Thromb Haemost 2014;111:1133-1140.
85. Morishima Y, Kamisato C. Laboratory measurements of the oral direct factor Xa inhibitor edoxaban. Am J Clin Pathol 2015;743:241-247.
86. Barrett YC, Wang Z, Frost C, Shenker A. Clinical laboratory measurement of direct factor Xa inhibitors: Anti-Xa assay is preferable to prothrombin time assay. Thromb Haemost 2010;104:1263-1271.
87. Pollack VC, Reilly PA, Eikelboom JW, Verhamme P, Bernstein RA, Dubiel R, Huisman WM, Hylek EM, Kreuzer J, Levy JH, Selke FW, Steiniger T, Wang B, Kam CW, Weitz JI. Idarucizumab for dabigatran reversal. NE Engl J Med 2015;373:511-520.
88. Ansell JE, Bakhru SH, Laulicht BE, Steiner SS, Grosso M, Brown K, et al. Use of PER977 to reverse the anticoagulant effect of edoxaban. N Engl J Med 2014;371:2141-2142.
89. Gosselin RC, Francart SJ, Hawes EM, Moll SM, Dager WE, Adcock DM. Heparin calibrated chromogenic anti-Xa activity measurements in patients receiving rivaroxaban: can this test be used to quantify drug level? Am J Phamacoother 2015;49:777-783.
90. Yasuda K, et al. Interaction of cytochrome P450 3A inhibitors with P-glycoprotein. J Pharm Exp Ther 2002;303:323-332.
91. Nutescu E, Chuatrisorn I, Hellenbart E. Drug and dietary interactions of warfarin and novel oral anticoagulants: an update. J Thromb Thrombolysis 2011;31:326-343.
92. Kubitz A, Becka M, Voith B, et al. Safety, pharmacokinetics, and pharmacodynamics of single doses of BAY 59-7939: an oral, direct factor Xa inhibitor. Clin Pharmacol Ther 2005;78:412-421.
93. Baker RI, Coughlin PB, Galusz A, Harper PL, Salem HH, Wood EM; Warfarin Reversal Consensus Group. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. Med J Aust 2004;181:492-497.
94. Eerenberg ES, Kamphuisen PW, Slipkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation 2011;124:1573-1579.
95. Glund S, Stangier J, Schmohl M, Moschetti V, Haazen W, De Smet M, et al. Idarucizumab, a specific antidote for dabigatran: immediate, complete and sustained reversal of dabigatran induced anticoagulation in elderly and renal impaired subjects. Blood 2014;124:344.
96. Glund S, Stangier J, Schmohl M, Gansser D, Norris S, van Ryn J, et al. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, doubleblind phase 1 trial. Lancet 2015;386:680-690.
97. Crowther MKM, Lorenz T, Mathur V, et al. A phase 2 randomized, double-blind, placebo-controlled trial of PRT064445, a novel, universal antidote for direct and indirect factor Xa inhibitors. J Thromb Haemost 2013;11(Suppl 2):AS20.1.
98. Heidebuchel H, Verhamme P, Alpins M, Antz M, Diener HC, Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Klinchhof P. 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;17:1467-1507.