New Oral Anticoagulants for Acute and Long-Term Treatment of Haemodynamically Stable Pulmonary Embolism

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Abstract: Historically, standard treatment of haemodynamically stable pulmonary embolism (PE) in the acute phase consists in parenteral anticoagulants overlapped with oral anticoagulants vitamin K antagonists (VKAs) for at least 5-7 days followed by VKAs alone when their therapeutic range is reached and prolonged for at least three-six months (long term phase). However standard treatment has many pharmacological and practical limitations. For overcoming these limitations, new anticoagulant drugs with better pharmacological profile and easier to use, have been manufactured and tested in pre-clinical and clinical trials with the aim to reach at least non inferiority compared to standard treatment.

In the setting of PE, new oral anticoagulants (NOACs), direct inhibitors of thrombin (dabigatran) or activated factor X (apixaban, edoxaban, rivaroxaban) have been tested in the acute and long-term phases of treatment in phase III randomized clinical trials (RCTs). Rivaroxaban (EINSTEIN-PE study) and apixaban (AMPLIFY study) have been tested directly from diagnosis, dabigatran (RE-COVER I and II studies) and edoxaban (HOKUSAI study) starting after 7-10 days of standard treatment. Overall, these trials have demonstrated that NOACs are effective and safe at least as standard treatment, promising a revolutionary approach to PE treatment in acute/sub-acute PE based on single drug approach or rapid switch from parenteral to oral anticoagulation.

In this paper the Authors focus on phase III RCTs on NOACs in the acute and long-term phases of PE treatment, highlighting the first two weeks of treatment.

Keywords: Pulmonary embolism, new oral anticoagulants, apixaban, dabigatran, edoxaban, rivaroxaban, bleedings, efficacy, safety.

BACKGROUND

Pulmonary embolism (PE) represents one of the leading cause of mortality and morbidity in cardiovascular settings. The mortality burden of acute PE remains severe, two weeks and three months mortality rate being respectively 11.4% and 17.4% [1]. Early mortality of PE is strongly influenced by haemodynamic status at clinical presentation. In fact, PE patients presenting with shock die in more than 30% of cases, whereas the mortality rate is more than 70% in patients presenting with cardiac arrest [2]. In the ICOPER study, 58.3% of patients presenting with haemodinamic instability died within three months compared to 15.1% of patients without [1]. Deaths directly due to PE occur for around 10% in the first hour, for 32.2% in the first 24 hours, for 67.7% in the first week and for 90.3% in the first month [2, 3]. In 2008, European Society of Cardiology identified three classes with different early mortality risk, based on haemodynamic profile associated or not with echocardiographic and/or biomarkers of right heart dysfunction or myocardial damage (Figure **1**) [4]. Recommendations for pharmacological treatment and monitoring of acute PE differs according to the early mortality risk (Figure **2**) [4].

Historically, the pharmacological treatment of PE consists in three phases [5-7]. In the acute phase beginning once diagnosis is performed, anticoagulant parenteral drugs, such as systemic intravenous thrombnolysis in haemodynamic unstable PE or intravenous unfractioned heparin (UFH) or subcutaneous LMWH or fondaparinux in haemodynamic stable PE represent the choice treatment. Oral anticoagulants vitamin K antagonists (VKAs) are overlapped to parenteral anticoagulnts for at least five days and until the therapeutic range of the International Normalized Ratio (INR) is reached; at this point parenteral anticoagulants are discontinued. VKAs should be prolonged for at least 3-6 months (long-term phase). Finally, after this time, VKAs should be continued or discontinued on the basis of risk factors which have provoked PE (phase of extended treatment) [5,6].

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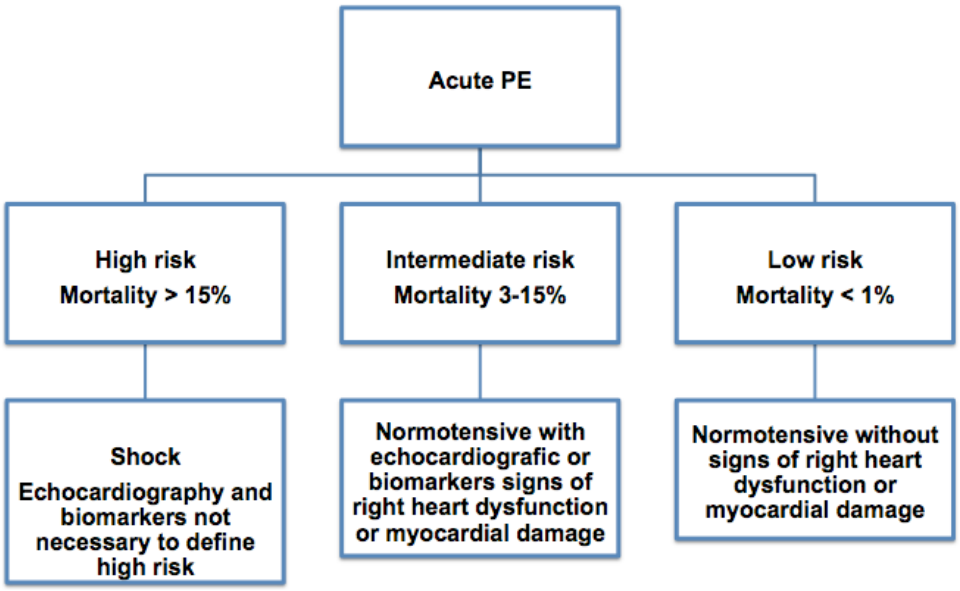

Figure 1: Early mortality risk according to ESC criteria.

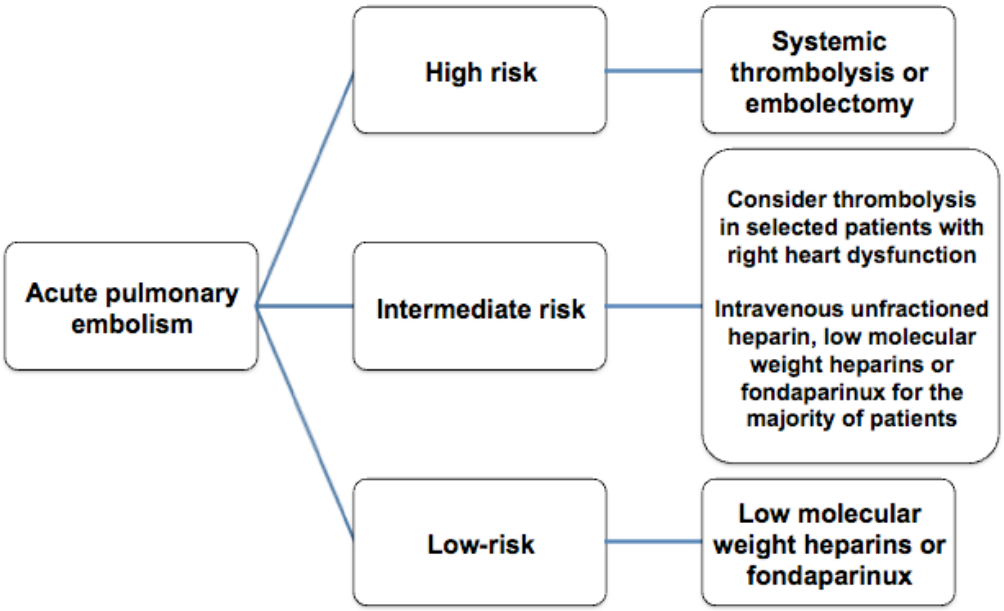

Figure 2: PE treatment based on early mortality risk.

UFH, LMWHs, fondaparinux and VKAs are indirect anticoagulants [8,9]. UFH, LMWHs and fondaparinux require the presence of antithrombin (AT) for their anticoagulant activity [8]. Binding with AT in a selected site of their molecular structure composed by a pentasaccharidic unit, UFH and LMWHs inhibit the activated Factor II (thrombin) and factor X (FXa) in a different proportion (thrombin/FXa ratio 4:1 for UFH, 1:1 for LMWHs) [8]. Fondaparinux, a synthetic penthasaccaride, is a molecule containing only the pentasaccharidic structure of heparins and inhibits solely FXa by binding with AT [8]. VKAs inhibit the gamma-carboxylation of vitamin K dependent coagulation factors (II, VII, IX, X, protein C and S) leading to their inactivity [9].

Despite the good efficacy and safety profiles for their clinical use contributing to reduce mortality and morbidity of thromboembolic diseases, parenteral and old oral anticoagulants have limitations leading to their underuse in clinical practice, especially for VKAs. Briefly, VKAs have an unpredictable pharmacologic profile in different patients, based on genetic factors and multiple food and drug interactions [9]. Therefore VKAs require close laboratory monitoring of International Normalized Ratio (INR) with patients' discomfort

and frequent dose adjustments. Therefore they have a narrow therapeutic window, the risk of thrombo-embolism recurrence being increased at lower levels of anticoagulation (INR <2.0) and bleeding risk being higher when INR is over 3.0 [9]. VKAs have a long half-life and a slower onset and offset of action requiring a bridging (overlapping) therapy with parenteral anticoagulants such as intravenous or subcutaneous UFH or LMWHs or fondaparinux. After their withdrawal, they are eliminated from plasma in three-five days [9]. Due to these limitations the time in therapeutics range (TTR) is often sub-optimal in the real practice, being less than 60% [10]. VKAs present many contrain-dications to their use, contraindications which are prevalent in more than 20% of potential patients [11].

Both when intravenously and subcutaneously administered, UFH shows a wide variability of its anticoagulant effect due to lack of linearity in its dose/effect response. Therefore its anticoagulant effect needs of laboratory monitoring by using the activated partial thromboplastin time (aPTT) and its dose must be frequently adjusted. Its half-life is dose-dependent and its elimination is not influenced by renal function. Osteoporosis, allergy, and thrombocytopenia drug-induced are not negligible side effects [9].

LMWHs are subcutaneously administered in fixed doses. After administration, these are rapidly absorbed in a linear dose-dependent manner. Plasma peak con-centration is quick and dose-dependent. Bio-availability is around 90%. Their anticoagulant activity is more predictable compared to UFH and do not require laboratory monitoring. Half-life is brief and dose-dependent. Clearance of LMWHs is almost completely influenced by renal function. Osteoporosis, allergy and thrombocytopenia drug induced even less frequently could happen for LMWHs such as for patients treated with UFH [9].

Fondaparinux has a fast onset of action and a predictable and dose-dependent anticoagulant activity and a linear pharmacokinetics, therefore it does not require laboratory monitoring. It has a wide bio-availability, a longer half-life compared with LMWHs, around 17 hours, permitting the once daily adminis-tration. Clearance of fondaparinux is completely due to kidneys, therefore this drug is absolutely contraindicated in severe renal failure. Osteoporosis and thrombocytopenia drug-induced are really rare [9].

THE NEW ORAL ANTICOAGULANTS

The limitations of VKAs and parenteral anticoa-gulants have lead the pharmaceutical industry to search for new molecules that could overcome these limitations by allowing the clinician to have the availability of more manageable but equally effective and safe drugs and favoring, if possible, the patients compliance by reducing their discomfort [12]. Therefore, in the last years, the pharmacological res-earch has produced new oral anticoagulant molecules acting on specific and single targets of the coagulation cascade. Those who have reached the marketing are fundamentally divided into two groups: the direct thrombin (factor IIa) inhibitors and the direct inhibitors of activated factor X (FXa). After the phase I and II studies, new oral anticoagulants (NOACs) have been tested in clinical randomized controlled phase III trials designed to evaluate their efficacy and safety.

Due to brief half-life, the NOACs quickly reach the plasma peak concentration and therefore have a quick onset of action. The NOACs do not require an induction phase in order to determine their anticoagulant effect and therefore they don't need of a phase of overlapping with parenteral anticoagulant drugs. The NOACS have a linear pharmacodynamics with predictable dose/ response relationship and anticoagulant effect. Therefore they can be administered at fixed dose and don't require dose adjustment. For the same reason the NOACs don't require routine laboratory monitoring [12]. Once the NOACs are discontinued their elimination from plasma is relatively fast, especially in patients with normal renal function. The NOACs do not interact with food and have little interaction with other drugs [12]. All these pros seem promise advantages for the clinical use of NOACs over VKAs.

The NOACs have a linear pharmacodynamics with a predictable dose/response profile [12]. The plasma concentration and the antithrombotic effect of the NOACs are dose-dependent. At the prophylactic or therapeutic doses, the NOACs modestly prove changes on the common coagulation testing and the effect on coagulation parameters is more evident at the peak of plasma concentration and at steady state. For these reasons the NOACs have been tested in clinical trials of phase III without routine laboratory monitoring, which is not recommended in clinical practice [13, 14]. The available data on the effect of NOAC on coagulation parameters derived mainly from the pre-clinical, dose-finding studies [14]. At prophylactic doses and therapeutic doses, dabigatran does not interact substantially on prothrombin time (PT). The activated partial thromboplastin time (aPTT) is prolonged by dabigatran in a curve-linear manner. For lower concentrations, dabigatran prolongs the aPTT in a

linear fashion, while at higher concentrations, reached in case of overdose, the increase in aPTT loses this linearity and tends to plateau. Dabigatran instead prolongs the thrombin time (TT) and the Ecarin Clotting Time (ECT) in a linear, dose and plasma concentration-dependent. The inhibitors of factor Xa determine a prolongation of PT and a less evident prolongation of aPTT in a concentration-dependent manner, while they proves a linear concentration-dependent increasing of the anti-Xa activity [13-16].

Table **1** summarizes the pharmacokinetic and pharmacodynamic characteristics of NOACs.

Table 1: Pharmacological Characteristics of NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Selective, competitive, direct inhibition of activated factor II (thrombin)	Selective, competitive, direct inhibition of activated factor X	Selective, competitive, direct inhibition of activated factor X	Selective, competitive, direct inhibition of activated factor X
Pro-drug	yes (dabigatran etexilate)	no	no	no
Molecular weight (Daltons)	628 pro-drug (etexilate) 471 active drug	436	460	548
Half-life	7-9 h after first dose 12-14 h after multiple doses	9 h in young and adults 12 h elderly over 75 years	12 h	8-10 h
Time to reach plasma peak concentration (Tmax)	0.5-2 h	2-4 h	3 h	1-2 h
Bio-availability	6.5%	> 80%	> 50%	>45%
Excrection	Kidney 80%	Kidney 66%, of which 33% unmodified Biliary-faecal system 35%	Kidney 25% Biliary-faecal system 75%	Kidney 35% Biliary-faecal system 65%
Plasma proteins binding	35%	90%	85%	55%
Volume distribution	60-70 L	0.6-1.5 L/Kg	0.3 L/Kg	Not reported
Cytochrome P450 interaction	no	no	no	no
Substrate of cytocrome P3A4	no	yes	yes	yes
Substrate of P-Glycoprotein	yes	yes	yes	yes
Drugs interaction	Inhibitors and inductors of P-glyco-protein	Inhibitors and inductors of cytochrome CYP3A4 and P-glyco-protein	Inhibitors and inductors of cytochrome CYP3A4 and P-glyco-protein	Inhibitors and inductors of cytochrome CYP3A4 and P-glyco-protein
Food interaction	No (contemporary administration with food delays plasma peak concentration of two hours)	no	no	no
Standard dose and rate of administration in PE treatment	150 mg Twice/daily	15 mg twice/daily for three weeks followed by 20 mg once/daily	10 mg twice/daily foro ne week follone by 5 mg twice/daily	60 mg once /daily
Safety in pregnancy	Not demonstrated	Not demonstrated	Not demonstrated	Not demonstrated
Dyalizability	yes	no	no	no
Specific antidote	no	no	no	no
Possible reverse measures	Non activated or activated PCCs raFVII Dyalisis	Non activated PCCs	Non activated PCCs	Non activated PCCs

Legend: PCC=prothrombin complex concentrate; FFP=fresh frozen plasma; raFVII=recombinant activated factor VII.

EFFICACY AND SAFETY OF NOACS IN THE ACUTE AND LONG-TERM PHASES OF PE TREATMENT

NOACs have been tested in the acute and long-term phases of stable PE treatment. NOACs have been compared with the standard of care, represented by parenteral anticoagulants plus warfarin when started from the acute phase (EINSTEIN-PE study for rivaroxaban, AMPLIFY study for apixaban) or warfarin alone when started from the long-term phase (RE-COVER I and II studies for dabigatran, HOKUSAI study for edoxaban) [17-21]. Table **2** summarizes the general characteristics of the studies.

NOACs Versus Parenteral Treatment Plus Warfarin in the Acute Phase of Treatment

i) Rivaroxaban

In the EINSTEN-PE study around 5000 patients with PE (25% of them with concurrent symptomatic deep vein thrombosis) were randomized to receive rivaroxaban 15 mg x 2 twice daily for three weeks followed by 20 mg once daily or enoxaparin for at least five days overlapped to warfarin with INR target 2.5. The two treatment regimens were compared at 3, 6 and 12 months in terms of efficacy represented by symptomatic VTE recurrence and safety represented by major and clinically relevant non major bleedings. This study found that rivaroxaban was efficacy as standard treatment and superior compared to it on safety, significantly reducing major bleedings [1,1% *vs*. 2.2%, (HR 0.49, 95% CI, 0.31-0.79, p = 0.003] [17]. This trial is the only one referred to patients with PE solely.

ii) Apixaban

In the AMPLIFY study 2691 patients treated with apixaban at dose of 10 mg twice daily for one week followed by 5 mg x 2 twice daily were compared with 2704 patients treated with parenteral treatment overlapped with warfarin with INR target 2.5 [18]. This trial showed any difference between the two regimens of care in terms of efficacy, whilst found that apixaban significantly reduced major bleedings (relative risk reduction, RRR, 69%), clinically relevant non major bleedings (RRR 52%) and total bleedings (RRR 56%) [18].

NOACs Versus Warfarin in the Long-Term Phase

iii) Dabigatran

In RE-COVER I trial dabigatran 150 mg twice/daily starter after a parenteral regimen of standard treatment of at least five days was compared with warfarin at dose aimed to mantain INR in therapeutic range (2.0-3.0) [19]. This trial demonstrated that dabigatran is not inferior to warfarin in terms of efficacy. Furthermore the RE-COVER I demonstrated that dabigatran is not inferior to warfarin in terms of safety when considering major bleedings and superior to warfarin when considering major and clinically relevant non major bleedings together analyzed [19]. The twin trial RE-COVER II confirmed main findings of RE-COVER I trial, but, even if communicated, these results are yet unpublished [20].

iv) Edoxaban

The HOKUSAI trial is a double blind multicenter trial in which edoxaban at dose of 60 mg once/daily (30 mg once/daily in patients with creatine clearance 30-50 ml/min or body weight under 60 Kg) started after a phase of parenteral antithrombotic treatment was compared to warfarin (INR target 2.0-3.0) in patients with venous thromboembolism. Around 3300 of 8300 patients presented PE [21]. Edoxaban was found to be not inferior to warfarin in terms of efficacy, whereas the NOAC was superior to warfarin in terms of major and

Table 2: Summary of General Characteristics of Patients Enclosed in Phase III RCTs in Acute and Long Term Phases of PE Treatment

	EINSTEIN-PE	AMPLIFY	RE-COVER	HOKUSAI
Mean age (years)	57.5	57	55	57
Age > 75 years	15.4%	14.2%	nr	16.5%
Males/Females	53%47%	59%/41%	58%/42%	52.3%/47.7%
Creatinine Clearance > 50 ml/min	91.7%	94%	nr Mean 105±40 ml/min	93%
Creatinine Clearance 30-50 ml/min	8.3%	6%	nr	7%
Unprovoked venous thromboembolism	64.5%	89.8%	nr	63%
Warfarin time in therapeutic range	62.7%	61%	60%	63.5%

Table 3: Main Findings of Phase III RCTs on NOACs for Acute or Sub-Acute Treatment of PE

RCT	Patients with acute PE randomized (number)	NOAC	Comparator	Efficacy	Safety	
				Symptomatic recurrent VTE RR (95% CI) or symptomatic recurrent VTE and VTE related mortality RR (95% CI)	Major and clinically relevant non major bleedings RR (95% CI)	Major bleedings RR (95% CI)
Acute phase						
EINSTEIN-PE	4832	Rivaroxaban	Enoxaparin-warfarin	1.12 (0.75–1.68)	0.90 (0.76–1.07)	0.49 (0.31–0.79)*
AMPLIFY	1836	Apixaban	Enoxaparin-warfarin	0.84 (0.60–1.18)	0.44 (0.36–0.55)*	0.31 (0.17-0.55)*
Sub-acute phase						
RE-COVER I	786	Dabigatran	warfarin	1.10 (0.65–1.84)	0.63 (0.47–0.84)*	0.82 (0.45–1.48)
RE-COVER II	2589 (total PE + DVT)	Dabigatran	warfarin	1.09 (0.65-1.81)	nr	0.69 (0.36-1.33)
HOKUSAI	3319	Edoxaban	warfarin	0.73 (0.50–1.06)	0.81 (0.71–0.94)*	0.84 (0.59–1.21)

Legend=*significant difference; nr=not reported; PE=pulmonary embolism; DVT=deep vein thrombosis; RCT=randomized clinical trial; NOAC=new oral anticoagulant.

clinically relevant non major bleedings together considered or total bleedings [21]. Of much interest, edoxaban was significantly much more effective compared to warfarin in reducing the VTE recurrences in the subgroup of patients with right heart dysfunction based on brain natriuretic peptide measurement (hazard ratio, 0.52; 95% CI, 0.28 to 0.98) and computer tomography pulmonary angiography (hazard ratio 0.42; 95% CI, 0.15 to 1.20) maintaining safety [21].

The main findings of phase III RCTs on NOACs in the acute and sub-acute treatment of PE are summarized in Table **3**.

THE ACUTE-SUBACUTE PHASES OF PE TREATMENT: WHAT DOES IT CHANGES?

The abovementioned trials demonstrated that NOACs are affective at least as the standard treatment (Figure **3**). Furthermore these trials showed that NOACs are safer compared to the standard treatment, despite only in EINSTEIN-PE and AMPLIFY the difference is statistically significant, with a RRR of 51% and 65% respectively (Figure **4**). It's of utmost importance to remark that major safety is detectable already in the initial phase of treatment, in other words in the acute and sub-acute phase of treatment and it prolongs for all the follow-up of the abovementioned studies.

Due to their pharmacological characteristics, such as short half-life, immediate and predictable anticoagulant effect, overlapping phase with parenteral therapy and routinely laboratory monitoring not necessary, NOACs place as a new and real alternative to the PE standard of care, promising a single drug approach from acute to long-term or extended treatment phases or a rapid switch from parenteral drugs without overlapping phase, once acute phase is ended (Figure **5**).

Finally NOACs may represent a real revolution for the practical management of acute heamodynamically stable PE, especially in low risk patients. According to guidelines, this subgroup of patients should be at home treated or quickly discharged from hospitals. However physicians are often reluctant to treat PE out of hospitals. Main reason for it may be represented from the needing to follow these patients in hospital until INR target is reached and this is possible in around 5-7 days. It's quite intuitive that NOACs may lead to quick hospital discharges for the abovementioned properties, reducing costs and patients discomfort.

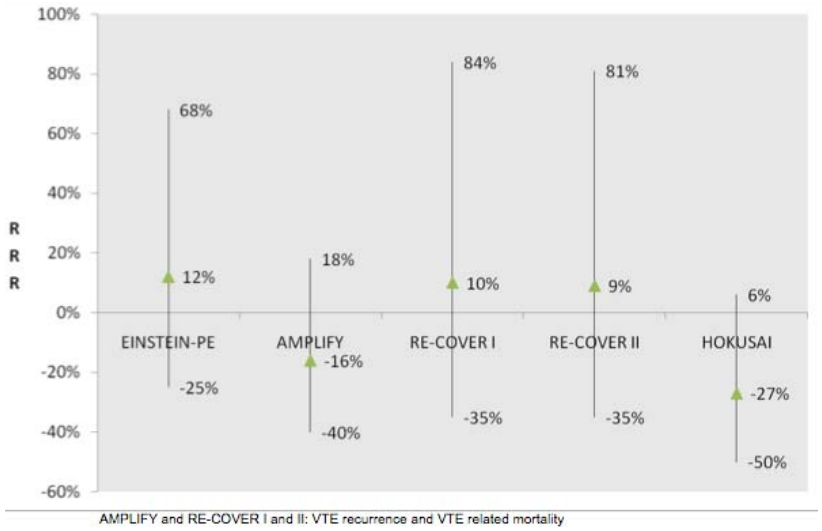

Figure 3: Relative risk reduction (RRR, 95% CI) of VTE recurrence with NOACs on warfarin in phase III RCTs.

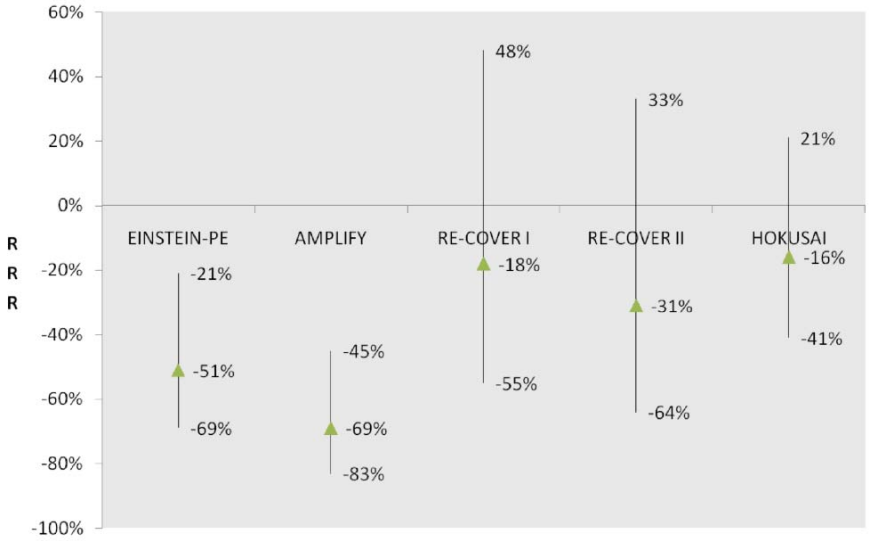

Figure 4: Relative risk reduction (95% CI) of major bleedings with NOACs on warfarin in phase III RCTs.

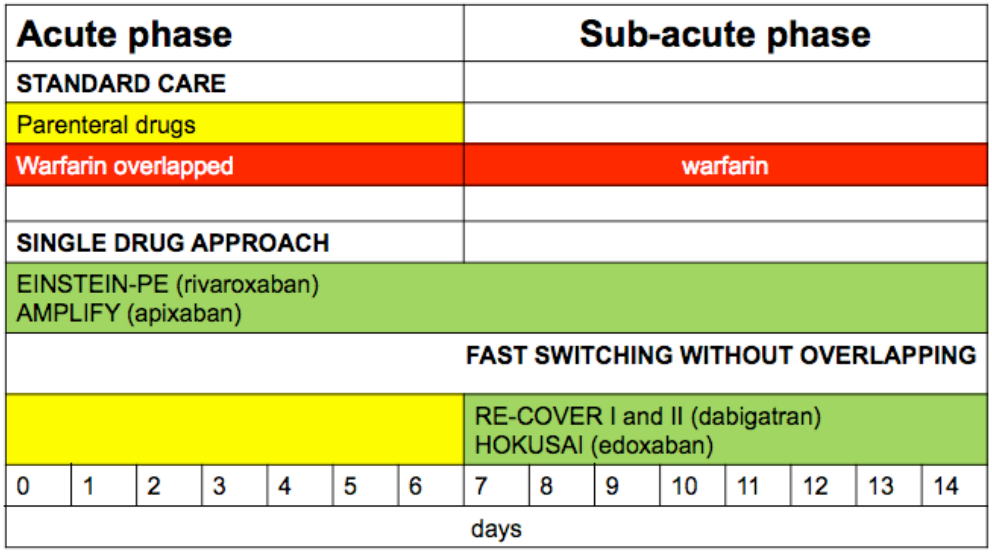

Figure 5: New approachs with NOACs in acute/sub-acute PE.

CONCLUSION

NOACs have demonstrated to be effective and safe in the acute and sub-acute phases of PE treatment, promising a new era for PE management.

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