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RESEARCH ARTICLE

NOACS OR WARFARIN AFTER THROMBOLYSIS FOR THE TREATMENT OF ACUTE INTERMEDIATE-HIGH RISKPULMONARY EMBOLISM: NO-WAR STUDY

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ABSTRACT

Aims: Thrombolysis and anticoagulation were the main treatment methods for acute pulmonary embolism. Anticoagulation therapy is recommended in the guidelines for patients with intermediate-low and low-risk PE, and emergency thrombolysis is recommended for high-risk or massive PE, in order to stabilize hemodynamics and reduce early mortality. Warfarin has been the anticoagulant of choice for pulmonary embolismHowever, there remains controversy about the treatment of acute intermediate-high-risk PE.Novel oral anticoagulants (NOACs) are increasingly used as an alternative. The study was aimed at assessing efficacy and safety of new oral anticoagulants (NOACs) after thrombolysis versus warfarin treatment on echocardiographic parameters and clinical outcome during hospitalization and in six mounth after admission, in patients with acute intermediate-high-Risk Pulmonary Embolism. Although the use of thrombolysis has been investigated in these patients, anticoagulation remains the standard treatment approach. Rivaroxaban and apixaban have shown similar efficacy and, in some cases, reduced major bleeding compared with standard approaches for acute treatment. The direct oral anticoagulants do not require regular coagulation monitoring. **Methods:** Consecutive patients (study court: age 42-85 years), with a episode acute pulmonary embolism,with onset of symptoms since no more than 6 hours, normal blood pressure (>95 mmHg), right ventricle dysfunction (RVD) at echocardiography and positive lung spiral CT were in double blind fashion randomized: a group received 100 mg of alteplase (10-mg bolus, followed by a 90-mg i.v. infusion over a period of 2 hours) and warfarin after 48-72 h in according with INR target , and a group received 100 mg of alteplase (10-mg bolus, followed by a 90-mg i.v. infusion over a period of 2 hours) and NOACs (rivaroxaban or apixaban on randomization 1:1) after 48-72 h. In addition to alteplase , both groups received unfractionated heparin treatment for 48 h. Echocardiogram was performed at entry and 48 or 72, discharge and 6 months after randomization. **Results:** 44 patients were included in the study, 22 assigned to warfarin and 22 to NAOCs. The 2 groups were well matched with regard to features and clinical presentation. NAOCs group showed an safety and a reduction in clinical events during hospitalization and follow up was also observed. **Conclusions:** Our data suggest that NOACs after thrombolysis a favorable trend in clinical outcome and could merit consideration in patients with acute intermediate-high-Risk Pulmonary Embolism. The new anticoagulation have been shown to reduce the risk of recurrent venous thromboembolism when given for 6 months. This use after thrombolysis, at this time, is off-label and should could be considered and included in the new guidelines.

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INTRODUCTION

Intermediate-risk, submassive PE is characterized by right ventricular dysfunction (RVD) and/or myocardial necrosis, as indicated by elevated biomarkers, in the absence of persistent hypotension or shock. The use of prognostic measures, such as the PESI model, may help clinicians with decisions on the overall management of these patients.

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Thrombolysis and anticoagulation were the main treatment methods for acute pulmonary embolism. Anticoagulation therapy is recommended in the guidelines for patients with intermediate-low and low-risk PE, and emergency thrombolysis is recommended for high-risk or massive PE, in order to stabilize hemodynamics and reduce early mortality. Warfarin has been the anticoagulant of choice for pulmonary embolismHowever, there remains controversy about the treatment of acute intermediate-high-risk PE.Novel oral anticoagulants (NOACs) are increasingly used as an alternative.Although the 30-day mortality rate of acute PE has been declining, approximately 10% of patients with acute PE

die within 3 months after the diagnosis, usually as a result of unstable hemodynamics. Based on clinical severity, echocardiography, computed tomography pulmonary angiography , and biomarkers, the 2014 European Society of Cardiology (ESC) guidelines divided PE into 3 groups: high risk, intermediate risk, and low risk. The intermediate-risk group was divided into intermediate-high-risk and intermediate-low-risk group. The intermediate-high-risk group usually has right ventricular (RV) dysfunction and elevated circulating levels of biomarkers of myocardial injury.The MAPPET-3 trial, conducted in 2002, was one of the earliest studies to evaluate the use of thrombolytic agents in patients with submassive PE. This study compared heparin plus alteplase 100 mg with heparin plus placebo, both administered over a period of two hours. The incidence of the primary endpoint was significantly higher in the heparin-plus-placebo group than in the heparin-plus-alteplase group (P = 0.006), and the probability of 30-day event-free survival was higher in the heparin-plus-alteplase group (P = 0.005). The randomized, double-blind PEITHO trial compared tenecteplase plus heparin with placebo plus heparin in 1,005 patients with intermediate-risk PE. All of the patients had RVD.

Thus, thrombolytic therapy was shown to prevent hemodynamic decompensation, but at an increased risk of major hemorrhage and stroke.In meta-analysis, Xu and colleagues analyzed data from seven studies involving a total of 1,631 patients with intermediate-risk PE treated with thrombolytics or anticoagulants. The two treatment groups were not significantly different with regard to 30-day, all-cause mortality (P = 0.08). The patients treated with thrombolytic agents, however, had significantly lower rates of clinical deterioration (P < 0.01) and recurrent PE (P = 0.01). There was no difference in the rates of major bleeding events between the two groups (P = 0.25). Thrombolytic therapy can reduce all-cause mortality in patients with intermediate-high-risk PE, but the rate of hemorrhage is high, especially in elderly patients. Systemic thrombolysis has not been routinely recommended as a primary treatment for patients with intermediate-high-risk PE. Thrombolytic therapy in patients with intermediate-high-risk PE can reduce the short-term mortality rate. The incidence of chronic thromboembolic pulmonary hypertension was increased in the later stage of anticoagulant therapy. Warfarin is a vitamin K antagonist, which exerts its anticoagulant effect by inhibiting the clotting factors II, VII, IX and X. Regrettably, it is, however, prone to numerous drug and food interactions, which necessitates regular blood testing to maintain the international normalisation ratio (INR) within the therapeutic range. Significant patient time and medical resources are required and the effective vigilance of medical practitioners in the bespoke tailoring of warfarin dose to the individual is far from straight forward.

Novel oral anticoagulants (NOACs) have a more specific mode of action directly targeting just one clotting factor. The factor Xa inhibitors and direct thrombin (factor IIa) inhibitors produce a more predictable and less labile anticoagulant effect, which is less susceptible to drug and food interactions and do not require regular monitoring. Factor Xa inhibitors and direct thrombin (factor IIa) inhibitors, novel oral anticoagulants (NOACs) are effective in NOACs could progress to being the first-line therapy for The NOACs are a safe and effective alternative to warfarin. The NOACs are at least as good as warfarinfor the prevention of ischaemic stroke and systemicembolic events and confers the additional advantage ofhalving the number of haemorrhagic strokes whichdrives an overall reduction in mortality. There is also areduction in major bleeding events associated with theNOACs when compared to warfarin. Cessation of longtermNOAC use and switch to warfarin may be associatedwith an increase in the composite of ischaemicstroke and systemic embolic events as well as majorbleeding in the 30 days after cessation. In patients with PE and RVD, in hospital mortality ranges from 5 to 17% (1,5-8). RVD maintains its prognostic value in hemodynamically stable patients with PE. Indeed, in these patients RVD is associated with an in-hospital mortality of about 5%, significantly higher than in patients without RVD (6,7). Our endpoints were: 1) feasibility and safety, 2) effects on hemorrhageevents, venous thromboembolism (venous doppler, echocardiography and lung spiral CT and clinical outcome during hospitalization and in the first 180 days after admission.

Protocol of the study (Figure 1) and follow up

The study population was screened from all patients admitted to emergency department within 6 hours from onset of sudden acute dyspnoea. The study was designed as a prospective, randomized, double-blind, trial. Randomization was decided at entry before echocardiogram and lung spiral lung CT, by an external team of physicians (at least two) who were blinded about study protocol. The patients believed with high probability of embolism pulmonary (Blood Pressure > 95 mmHg, dyspnoea, chest pain, tachypnoea, oxygen saturation <90% in room air, hypoxemia PO2<75 mmHg, PCO2< 40 mmHg and history suggestive for thrombosis risk and/or predisposing factors for venous thrombo-embolism, and ECG alterations) were included into the study and received an intravenous bolus of 5000 U of unfractionated heparin just before randomization. After heparin administration the patients were randomized in two groups and before undergoing further diagnostic workup. In all the patients were performed, troponin I,NT-pro-BNP, d-dimer, echocardiogram examination, and spiral computed tomography (CT).When final diagnosis of PE was obtained they received the assigned treatment: 100 mg of alteplase (Actilyse as a 10-mg bolus, followed by a 90-mg intravenous infusion over a period of 2 hours). In addition to alteplase both groups continued to receive unfractionated heparin treatment (1000 U/h and/or according aPTT).

After 48 or 72 h a group recieved warfarin togheter enoxaparin, until the INR was within the therapeutic range for 2 consecutive days, when only warfarin was maintained also after discharge and during follow up of 6 mounth. Other group recieved single drug therapy on randomization (1:1) rivaroxaban (15 mg twice a day for 3 weeks and then 20 mg once daily) or apixaban (10 mg twice a day for 7 days and then 5 mg twice a day) without enoxaparin until at discharge and 6 mounth. After baseline clinical and laboratory parameters patients were evaluated with a complete physical examination, a careful check symptoms, blood pressure (BP), heart rate (HR) every 6 h for the first 24 h then every 12 h until clinical stabilization and every daily subsequently up to discharge. Follow up: After discharge, the patients were followed as outpatients at 1st monthand 6 months (total follow up 6 months) to evaluate a recurrence of PE; and at every follow up clinical, ECG, echocardiographic and laboratory assessments were performed. In addition, spiral CT and Doppler of the inferior limbs were repeated 6 months after. Two blinded

physicians evaluated the clinical status and if recurrence of PE was present and side effects were also recorded.

MATERIALS AND METHODS

Patient selection and eligibility criteria

A single-center, prospective, randomized, active control comparisontrial was conducted in the Department of Cardiology, Ingrassia Hospital Palermo (Italy). The diagnosis of acute intermediate-high-risk PE was based onthe 2014 ESC guidelines.Prognostic stratification is of utmost importance for clinical management of acute pulmonary em-bolism (PE). Clinical presentation, echocardiography and biomarkers represented the key points.The non high risk PE was divided in intermediate rand low risk PE based on echocardio-graphic and biomarkers signs of right heart dysfunction (RHD) and myocardial damage. This approach was not an academic speculation but permitted to define the early mortality risk (>15% in high risk, 3-15% in intermediate risk, <1% in low risk) and bring the most appropriate treatment. Practical clinical scores, such as the Pulmonary Embolism Severity Index, PESI, in its original or simplified version, demonstrated to have high prognostic power to identify high (early mortality risk over 10%) and low risk (early mortality risk ≤ 1%) patients. All patients were subjected to punteggio PESI, for the stratification of the risk of pulmonary embolism after diagnosis. All patients were diagnosed bycomputed tomography pulmonary angiography and symptomatic onset less than 3 days prior toadmission, echocardiogram demonstrating RV dysfunctionor pulmonary hypertension,B-type natriuretic peptide, d-dimer and cardiac troponin I greater than the upper limitof normal.

Exclusion criteria and study design

Exclusion criteriawere as follows: high-risk PE,presence of contraindications to thrombolytic therapyandother serious organ disease.From March 2015 to January 2018, 91 hospitalized patients were screened. Excluded from the study were 33 patients with intermediate-low-risk PE and low-risk PE, 10 patients with serious organ disease (major surgery, digestive tract hemorrhage, renal insufficiency), and 5 patients who declined to participate in this trial. A total of 44 patients with intermediate high- risk PE were available for the study and signed informed consent. no patient lost in follow-up.

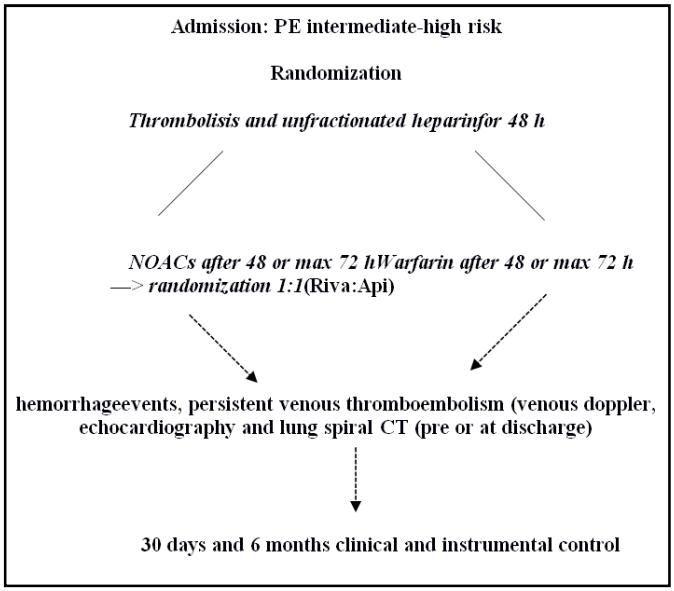
Statistical Analysis

Results are expressed as mean SD. Data were analyzed using the 2-tailed test to identify differences between groups. Nominal data was analyzed by the chi-square test; P <0.05 was assumed as statistically significant.We calculated event distributions with the Kaplan-Meier method and compared them by log-rank analysis.

Clinical outcome and results

The incidence of mortality was the same in the NOAC group compared to the Warfarin group during hospitalization.In addition, the Warfarin group showed, during follow-up, further clinical events and in particular 5 cases of persistent venous thromboembolism at 6 months.

Flow chart of the study



An interesting fact was that in the NOACs group in spite of an increase in minor bleeding, a reduction in days of hospitalization. During hospitalization and at 6 months, major and minor bleeding (hematoma, epistaxis and haematuria) the difference between two groups was not significant. There were 6 cases of major bleeding during hospitalization that required transfusions. All patients who bleed had a supra-therapeutic prolongation of aPTT (> 100 sec) probably related to heparin overdose. At the time of bleeding, both patients had started anticoagulation. These 6 patients after transfusion were treated again with oral anticoagulation a few days later without problems. There were 4 deaths due to recurrence of pulmonary embolism (two cases) and other causes (one gastrointestinal hemorrhagic, one per stroke). In the follow-up 5 cases of minor bleeding occurred due to overdose of warfarin (epistaxis or haematuria). It was sufficient to reduce the warfarin dose and the bleeding disappeared.

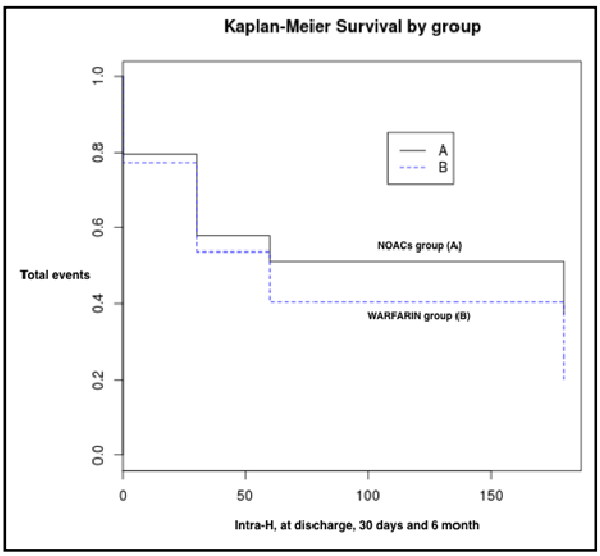


Fig. 1. Kaplan Curvelog rank test)

Chi square statistic: 2.772688 (degrees of freedom : 1 This is the number of groups, minus 1, p-value: 0.095885).Low p-value, below a pre-set critical value such as 0.05, indicates rejection of the omnibus null hypothesis, that there is no difference in survival rates of the groups.

Table 1. At entry

	NOACs group	WARFARIN group	P value
Patients	22	22	NS
Age	59 +\- 14,4	53,7 +\- 14,4	0,22
Pulmonary Embolism Severity Index (PESI) Risk class IV	14\22	14\22	NS
Pulmonary Embolism Severity Index (PESI) Risk class III	8\22	8\22	NS
Deep vein thrombosis	12\22	12\22	NS
Oral contraceptive pills	2\22	2\22	NS
Surgery (orthopedic,abdominal and gynaecological) within the last 6 weeks	6\22	6\22	NS
Previous Cardiovascular	5\22	5\22	NS
Previous Pulmonary	7\22	7\22	NS
HR (beats\min)	102,68 +\-5,16	102,77+\-5,0	0.95
SBP (mmHg)	115,45 +\-10,65	107,5 +\-12,40	0,027
RV\LV	0,955 +\-0,09	0,955 +\-0,10	1
d-dimer	22\22	22\22	NS
TnT positive	20\22	20\22	NS
NT-pro-BNP	22\22	22\22	NS

Table 2. At discharge

	NOACs group	WARFARIN group	P value
Patients	22	22	NS
Age	59 +\- 14,4	53,7 +\- 14,4	0,22
HR (beats\min)	66,13+\- 4,44	65,81+\- 4,61	0.81
SBP (mmHg)	115,45 +\-10,65	107,5 +\-12,40	0,027
RV\LV	0,955 +\-0,09	0,955 +\-0,10	1
Pulmonary Hypertension	35,09+\-\2,60	36,04+\-\2,63	0,23
Major Hemorrahage non fatal	3 (13,6%)	3 (13,6%)	NS
Bleedings minor	10 (45,4%)	9 (40,9%)	0,0001
Venous Thromboembolism persistent	5 (22%)	8(36%)	0,0001
Hospital stay (<15 gg)	14\22	11\22	0,0001
Total events	18	20	

Table 3. At 30 days

	NOACs group	WARFARIN group	P value
Patients	22	22	NS
Age	59 +\- 14,4	53,7 +\- 14,4	0,22
HR (beats\min)	66,04+\- 4,42	65,72+\- 4,47	0.81
SBP (mmHg)	115,68 +\-10,36	113,18+\-10,6	0,4
RV\LV	0,905 +\-0,08	0,955 +\-0,10	0,07
Pulmonary Hypertension	24,72+\-2,23	24,63 +\-2,28	0,89
Major Hemorrahage	0	0	NS
Bleedings minor	2 (9%)	3 (13%)	0,0001
Venous Thromboembolism persistent	3 (13%)	7 (31,8%)	0,0001
total events	5	10	

Table 4. At 6 month

	NOACs group	WARFARIN group	P value
Patients	20	20	NS
Age	56,4 +\-12,4	50,75 +\- 11,44	0,14
HR (beats\min)	66,35 +\-4,1	66,05 +\-4,49	0,82
SBP (mmHg)	116 +\- 9,94	107,75 +\-12,1	0,02
RV\LV	0,703 +\-0,043	0,726 +\-0,059	0,16
Pulmonary Hypertension	22+\-3,2	23,15 +\-3,1	0,25
Bleedings minor	1 (5%)	1 (5%)	NS
Venous Thromboembolism persistent	2 (10%)	5 (22,7 %)	0,0001
Major Hemorrahage	1	1	NS
Recurrent PE fatal	1	1	NS
Death (recurrent PE fatal, gastrointestinal and ictus hemorrhagic)	2	2	NS
total events	6	11	

The alternate hypothesis that one or more of the groups has a different different survival rate.

DISCUSSION

At present, medical behavior, dictated by the philosophy of "not doing any harm," has led many doctors not to use life-saving drugs such as thrombolytics in patients with moderate to high-risk PE. One of the ways to identify and choose acceptable risks is to ask yourself questions on the best or worst thing that happen if I do this. So a careful approach can lead to better evaluation of the benefit in patient management with high-risk pulmonary embolism. Once you make the diagnosis of PE, one must follow a precise algorithm which consists of three steps: What is the patient's clinical status?, is there a RV dysfunction?, and is thrombolysis indicated ?. To obtain these data, echocardiographic examination is very important. In fact, an increased RV–left ventricle diameter ratio, hypokinesia of the free RV wall, increased velocity of the jet of tricuspid regurgitation, and

decreased tricuspid annulus plane systolic excursion indicating RV dysfunction have been reported in ≥25% of patients with PE in prognostic stratification and used to risk stratify patients. Meta-analyses have shown that RV dysfunction detected by echocardiography and increased hs-Tn high sensitivity-troponin (TNI) and BNP levels is associated with an elevated risk of short-term mortality in patients without hemodynamic instability.Patients with intermediate-high PE, with RV dysfunction or injury to the myocardium, may have an elevated risk of early death or major complications, even while measured hemodynamics are stable.Thrombolytic therapy can dissolve intravascular thrombosis rapidly, relieve pulmonary arterial pressure, and improve the dysfunction of right heart. compared with the simple anticoagulation therapy, thrombolysis combined with anticoagulant therapy can significantly improve the RV diameter and pulmonary artery pressure. The innovative and revolutionary attitude, not only by guidelines but also by all doctors involved in emergency, regards the stratification of the patient's first medical contact, which becomes "patient-centered" and "PE-centered," then not the "burden" thrombotic but the criticality of the clinical picture. The clinical classification of the severity of an episode of acute PE is based on the estimated PE-related early mortality risk defined by in-hospital or 30-day mortality. Contemporary classification of acute pulmonary embolism (PE) severity is based on the risk of early death, which is influenced by demographic factors, comorbidity, and the functional status of the right ventricle (RV) under acute pressure overload. For normotensive patients who present with imaging findings that indicate RV dysfunction and biochemical evidence of myocardial injury, anticoagulation remains the primary treatment option. This recommendation is supported by the Pulmonary Embolism Thrombolysis (PEITHO) trial, which showed that patients fulfilling these latter criteria were unlikely to derive a net clinical benefit from routine use of systemic thrombolysis in view of the high risk for major bleeding.

Furthermore, during the hospital stay and 6-month follow-up, the incidence of adverse events was significantly lower than those in simple coagulation therapy. However, the excess bleeding after thrombolysis was higher than from anticoagulation alone.The latest guidelines suggest that we should attempt to curethe patients with acute intermediate-high-risk PE by anticoagulant therapy, but if hemodynamics become unstable, then thrombolytic therapy should be considered as a rescue treatment method. Research demonstrates that both therapeutic pathways can improve patients' clinical symptoms, but thrombolysis is able to remarkably decrease the mortality of patients with high risk and intermediate-high-risk PE.Meyer and colleagues recently reviewed the main advances or recommendations in the care of patients with PE, including recent data on the use of thrombolytic treatment. In the authors' opinion, thrombolytic therapy should be given in cases of hemodynamic worsening in patients with "high-intermediate risk" PE. The incidence of bleeding complications in patients with PE treated with thrombolytic agents is approximately 20%, but the incidence of fatal bleeding, usually intracranial, is <1%. Oral anticoagulants should be initiated as soon as possible and preferably on the same day as the parenteral anticoagulant. Vitamin K antagonists have been the "gold standard" in oral anticoagulation for more than 50 years, and warfarin and acenocoumarol remain the predominant anticoagulants prescribed for PE.

Pulmonary embolism can be life threatening and difficult to diagnose as signs and symptoms are not specific. European guidelines recommend stratification of pulmonary embolism by risk of early mortality. Anticoagulation is indicated in patients with a positive multidetector computed tomography or high-probability lung scan. An important part of the management of patients with pulmonary embolism has traditionally been anticoagulant treatment with parenteral heparins and oral vitamin K antagonists. Although effective, this dual-drug approach is associated with limitations. Direct oral anticoagulants that may overcome some of these problems have been tested in phase III clinical trials for the treatment of venous thromboembolism. Of these, rivaroxaban and apixaban have demonstrated non-inferiority to standard therapy when given as single-drug approaches for venous thromboembolism treatment, and provided significant reductions in major bleeding rates. There may be a benefit to extended anticoagulation with direct oral anticoagulants for the prevention of recurrent venous thromboembolism. The main innovation deriving from the introduction of NAO in the therapy of TEP is related to the rapidity of action that allows the possibility of transition from the traditional overlapping therapy represented by an initial phase of parenteral therapy with heparins, followed by a period of embryo with AVK before the AVK alone to a switching therapy with the NAOs in which the initial phase of parenteral therapy follows, without overlapping, the direct passage to the anticoagulant therapy or to a single drug therapy in which the therapy starts from the beginning with an NAO.

Recent evidence has shown that direct oral anticoagulants, particularly factor Xa inhibitors, are favorable treatment options for PE are now recommended on warfarin for patients with non-cancer related venous thromboembolism (VTE). Apixaban and rivaroxaban are the direct factor Xa inhibitors shown in the phase III studies not less than conventional therapy with less important bleeding. However, these studies did not include patients with submissives PE and excluding those who have received any form of thrombolysis. Predictable pharmacokinetics obtained and rapid therapeutic effect, there is no "bridge" period "with these agents, and no additional laboratory monitoring is necessary, making them a convenient option treatment. Therefore, we tried to determine the efficacy and safety (and also the hospital stay) compared to warfarin.
This article clinical may be interesting to bridge the gap on the treatment of new anticoagulants after 48 h after thrombolysis.
The primary safety outcome is major bleeding. Secondary outcomes include all-cause mortality, the overall duration of hospital stay (index event and repeated hospitalizations) and the temporal pattern of recovery of right ventricular function over the 6-month follow-up period. By applying and evaluating a contemporary risk-tailored treatment strategy for acute PE, this study probably will implement the recommendations of current guidelines and contribute to their further evolution. Thrombolytic treatment did not affect long-term mortality rates, and it did not appear to reduce residual dyspnea or RV dysfunction in these patients. In contrast, reductions in 'major bleed' for initial/long-term treatment were significantly better with rivaroxaban . Results from the current study indicate that the NOACs offer clinical benefit over conventional therapy (warfarin) while highlighting relative differences in their bleeding profile. The result of this study was satisfactory and shows how treatment with new anticoagulants (apixaban or rivaroxaba) after MPE thrombolysis could be considered.

Under analysis of the nao group

Follow-up : 6 months

	APIXABAN 5mg x 2	RIVAROXABAN 20 mg	P value
Patients	11	11	NS
Age	60,18+\-13,65	57+\-17,71	0,881
PESI IV	7	7	NS
Major hemorrahage	0	1	0.3293
Bleedings minor	0	1	0.3293
Venous thromboembolism persistent	1	1	NS
Reccurent PE fatal	1	0	0.3293
Death	1	1	NS

Limitations of the study

These are very preliminary data involving a selected small number of patients, which need further larger studies with broader inclusion criteria. The study is also limited by selecting a subset of patients. Probably, a longer observation could give more complete results. The present study presents data of 44 patients only from 1 centers. The 180-day follow-up provides information only on a medium-term prognosis. The long-term prognosis has yet to be evaluated by other studies.

Conclusions

PE management is challenging in many ways starting with, at times, deceptive clinical presentations.Thus, a decompensating patient may seem compensated but present with a life-threatening RV dysfunction. The same high-risk patient with PE may be treated completely differently depending on concomitant factors such as age, context and local resources. Future challenges to reduce the risk of bleeding and improve clinical results include improved risk stratification of bleeding, tailored heparin dosing and enhanced thrombolysis monitoring of treatment and insertion of new oral anticoagulants instead of warfarin.

Our data suggest that in patients with acute intermediate-high Pulmonary Embolism, NOACs after thrombolysis is associated with a rapid reduction in RVD and this reduction shows a favorable trend in clinical outcomes, but these effects still need to be defined for a long time. term. There were no differences on the endopoint of the bleeding compared to the warfarin group. Overall, the study shows the feasibility of NOACs after thrombolysis treatment in patients with acute intermediate-high Pulmonary Embolism and does not raise safety concerns. Moreover, this study suggests that thrombolysis can be used in patients with acute sub-massive pulmonary embolism.

Before intro

The breathlessness persisted. I felt emotions that words could not express but that continued to live in the gaze that reflected, in fact, the silent timbre of restlessness.

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