Concept Form

Proposed Study Title	
Study Title:	CONTEMPORARY CLINICAL MANAGEMENT OF ACUTE PULMONARY EMBOLISM
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Principal Investigator Contact Information	
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Study Information	
Indication	Pulmonary embolism
Phase:	Observational study
Number of Subjects:	5000

Background and Rationale

Acute pulmonary embolism is a common and potentially life-threatening disease. The incidence is estimated to be 0.5 to 1.5% person-years. The estimated short-term mortality in patients with pulmonary embolism ranges from about 1% to more than 30% during the hospital stay. Recent guidelines recommend to tailor clinical management based on the estimated risk for short-term death. The early management of these patients concerns diagnosis (according to hemodynamic status and pre-test clinical probability assessment), hospitalization (intensive care unit vs. medical wards vs. short hospital stay) and acute treatment (thrombolysis vs. anticoagulant treatment).

Early reperfusion by thrombolytic therapy or mechanical approach and admission to Intensive Care Units is recommended for hemodynamically unstable patients (high risk). Those patients who are hemodynamically stable and have no signs of right ventricle dysfunction or injury (as assessed by echocardiography, CT angiography or troponin levels>), or who have low risk of death according to clinical scores are candidates to short-term hospital stay or even home treatment (low risk). Patients who are hemodynamically stable but have evidence of right ventricle dysfunction or injury should be admitted and carefully followed-up for their potential risk of hemodynamic deterioration during the first 7 days (intermediate risk).

Initial anticoagulation with heparin (mainly low-molecular weight) followed by vitamin K antagonists (VKAs) has been the standard treatment for the majority of the patients with venous thromboembolism for several decades. Long term treatment with low-molecular weight heparin is usually preferred in patients with cancer-associated venous thromboembolism.

Non-vitamin K antagonist oral anticoagulants (NOACs) with the potential for administration in fixed doses with no need for monitoring have been evaluated in phase III clinical trials in the treatment of venous thromboembolism. A meta-analysis of studies in patients presenting with acute PE randomized to receive treatment with NOACs or conventional treatment (11,539 patients) showed a 2.4% and a 2.6% recurrence rate of venous thromboembolism in patients randomized to NOACs or conventional anticoagulants, respectively (OR 0.89, 95% CI 0.7-1.12; I-squared 0%). However, data on pulmonary embolism severity according to clinical scores, right ventricle dysfunction or injury were not reported in these large studies. Thus, it remains to be addressed whether NOACs can be an appropriate treatment for the overall severity spectrum of patients with acute pulmonary embolism.

Moreover, the real-life adherence to current guidelines on the management of patients with acute pulmonary embolism concerning diagnosis, risk stratification and treatment (including physicians preferences on anticoagulation therapies) is undefined. Final, risk factors for bad outcome in patients with low- / intermediate-risk need to be better evaluated.

Objectives

The aim of the study is to assess contemporary clinical course and clinical management strategies (primary end-point) in patients with acute pulmonary embolism in every-day clinical practice in Cardiology and Internal Medicine Departments with specific attention to

- Diagnostic strategies
- Use of risk stratification procedures
- Treatment strategies in the acute in-hospital phase across the full spectrum of severity of patients with acute pulmonary embolism.
- Adherence to current guidelines on the management of acute pulmonary embolism released by the European Society of Cardiology (regarding diagnosis, risk stratification, hospitalization and treatment)

These items will be evaluated in the overall study population and compared between patients admitted in Cardiology or Internal Medicine Departments.

- Risk factors for in-hospital and 30-day death, with particular reference to patients with intermediate / low-risk PE (co-primary end-point)

- Combined end-point death+clinical deterioration within 30 days from the index episode, and relevant risk factors (secondary end-point)

Hypothesis

The hypothesis that is going to be tested in this study is that clinicians have acknowledged recent advances on the clinical management of patients with acute pulmonary embolism and that this led to a good adherence to current guidelines by the European Society of Cardiology both in Cardiology and in Internal Medicine Departments.

Study Design/Clinical Plan

This is a prospective, observational, multicenter study.

Patients - Inclusion Criteria

Consecutive patients with acute, symptomatic, objectively confirmed pulmonary embolism will be eligible for inclusion in the study.

Criteria for objective diagnosis of acute pulmonary embolism are

- Positive CT angiography
- High probability perfusion lung scan
- Intermediate probability perfusion lung scan associated with objective diagnosis of deep vein thrombosis in patients with symptoms of acute pulmonary embolism
- Right ventricle dysfunction in patients with cardiogenic shock.

Inclusion criteria

- Age ≥ 18 years
- Informed consent

Patients - Exclusion Criteria

- None

Visit schedule and follow-up period

For the purposes of the study, patients will be evaluated at discharge and 30 days after the index pulmonary

embolism

Treatment

Due to the observational nature of the study, treatments will be decided by the attending physician and according to common clinical practice

Safety Assessment

Safety outcomes

The primary safety outcome of the study will be the composite of

- Major bleeding according to ISTH definition, occurring during the follow-up period up to 30 days from diagnosis of index pulmonary embolism.

Data on clinically relevant non-major bleedings will be also collected.

Statistical Plans

In order to

- achieve information on the clinical course of high, intermediate and low-risk patients with acute pulmonary embolism,
- observe a number of cases with intermediate / low-risk PE died at 30 days from diagnosis and adequate to evaluate around 10 variables able to possibly predict poor patients' outcome by means of logistic regression analysis

expecting an incidence of death of 3% and 0.5% for patients with intermediate or low-risk, respectively, it is estimated that 2100 patients with intermediate pulmonary embolism and 2500 with low-risk pulmonary embolism should be included in the study. In the same time frame, it is estimated that around 400 patients with high-risk pulmonary embolism will be observed. The expected mortality in these patients is 10-15%. According to these estimates, we would be able to have about 100 deaths in study patients and this will empower assessment of independent predictors of death. Besides already known predictors (hypotension, right ventricle dysfunction – imaging and BNP – and increased troponin), the role of comorbidities and clinical features as well as adherence to current guidelines on pulmonary embolism (risk stratification adequate, appropriateness of acute treatment) as determinants of prognosis will be assessed. The same features will be tested as predictors of death or clinical deterioration.

The impact of clinical characteristics on death and on death or clinical deterioration will be evaluated by means of univariate and multivariate logistic and multinomial logistic regression models, respectively. Variables with a p-value<0.10 at the univariate analysis will be considered for the multivariate model and covariates will be selected for the final model by means of a stepward selection procedure. A time-to-event analysis will be also

performed.

Timelines and Study Plans	
Number of Sites:	200
Study Start Date (submission to Ethics Committees):	July 2017
Study End Date (final report):	September 2019
Number of Subjects:	5000
First Patient In Date:	July 2017
Last Patient Out Date:	September 2019
Enrollment Period in Months:	24

Publication Plan	
Where are you planning to submit for publication? Please specify possible target journals	Circulation, European Heart Journal, JAMA Intern Med ….
Are you planning to present your data at a scientific meeting? Please specify	European Society of Cardiology, European Society of Internal Medicine, National Congresses of Internal Medicine and Cardiology
Please list your target date for submission of the manuscript	December 2019-March 2020