OBSERVATIONAL STUDY PROTOCOL PEDIS

Title of the study:	Prevalence of pulmonary embolism (PE) among patients referred to Emergency Departments for dyspnea on exertion
Code of the study:	PEDIS
Version of Protocol:	Final Version 1.2
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List of abbreviation and acronyms

CI	Confiedence interval
CT scan	computed tomography scan
EC	Ethics Commitee
e-CRF	Electronic Case Report Form
IRB	Istitutional Review Board
PE	Pulmonary Embolism
PIOPED	Prospective Investigation of Pulmonary Embolism Diagnosis

Background Information and Rationale

Pulmonary embolism (PE) is an insidious disease, frequently not recognized or mistaken for other pathologies, and is accompanied by a high mortality rate if not properly identified and treated (1). The onset modalities that often lead to erroneous diagnostic conclusions include angina-type chest pain, right or congestive heart failure, the exacerbation of chronic obstructive pulmonary disease, pneumonic pulmonary thickening, pleuritic pleural effusion and syncope (2). Recently it has been shown that the application of an adequate diagnostic algorithm can allow the recognition of PE in over 17% of patients hospitalized for a syncopal episode (3). In the PIOPED II study, 16% of patients with documented PE had come to the observation for exertional dyspnea, that is, a shortness of breath for physical activities that usually do not determine it (4). The most common cause is congestive heart failure. Other conditions that can cause it are chronic obstructive pulmonary disease, lung disease (e.g. pneumonia), aortic stenosis, severe anemia, hyperthyroidism, lung cancer, liver and kidney disease and psychopathological disorders. Although PE has been identified among the conditions that can cause exertional dyspnea (4), it is rarely suspected and its prevalence in subjects who reach the Emergency Departments for this condition is unknown.

The international guidelines for the diagnostic approach to patients with suspected EP recommend the use of a clinical probability score in combination with the result of a laboratory test, the D-Dimer (2). The most commonly used stratification model is the one described by Wells and associates, which scores a number of partly anamnestic and partly clinical parameters, and allows to identify as having a high pre-test clinical probability those subjects who score at least 4 (5). Based on the results of several clinical studies, patients with both a low clinical probability and negative D-Dimer can be regarded as not having PE (2). Accordingly, these patients do not require further diagnostic tests. In order to reduce the risk of false positivity D-Dimer tests (test of high sensitivity to thromboembolism, but of poor specificity), an algorithm that takes into account the patient's age has been successfully tested in subsequent studies of wide international impact. More specifically, it has been shown that with the adoption of sensitive D-dimer tests (cutoff 500 ng/ml) it is safe to withhold pulmonary CT angiography from patients older than 50 years whose laboratory test does not exceed a value that is achieved my multiplying their age by 10 (6).

General Aims and Study Objectives

This observational, cross-sectional, multicenter Italian study aims at investigating the prevalence of PE in a consecutive series of patients who refer to the Emergency Departments (either spontaneously or sent by their attending physicians) for the recent (less than one months) development of exertional dyspnea.

Objectives

To assess the prevalence of PE (and its 95% CI) in the overall population as well as in relevant subgroups (patients who will be imaged, patients without potential explanations for dyspnea).

Investigational Plan

Study design

The PEDIS study is an observational study, national multicenter and no Profit.

Setting
Emergency departments

Timeline
Data planned for the study beginning (first patient enrollment): 1 July 2018
Data planned for the last patient enrollment: 1 September 2019 or the achievement of the target of 600 patients.

Study population
All consecutive patients who refer to the Emergency Departments of the participating centers will be eligible for the study provided they are older than 18 and younger than 75 years, and have developed one or more episodes of exertional dyspnea since less than one month.

Inclusion Criteria
Subjects meeting the following criteria

- Age older than 18 and younger than 75
- Recent (less than one month) development of exertional dyspnea

Exclusion Criteria
Subjects meeting the following criteria:

- Anticoagulation required for other indications
- Contraindication to CT angiography (allergy to the contrast dye, severe renal failure [creatinine clearance < 30 ml/min])
- Involvement in simultaneous clinical trials
- Unable to provide their written informed consent

Study Procedures
Enrolment Procedures
All eligible patients will be interviewed and examined by trained study physicians. The presence of already known potential explanations for the dyspnea (see before) will be assessed. In addition, symptoms of the lower extremities will be elicited, as well as the presence of risk factors for venous thromboembolism (VTE), including recent surgery, trauma or infectious disease, ongoing hormonal treatment, prolonged immobilization, active cancer and history of VTE. The severity of dyspnea will be classified according to the modified scale of the Medical Research Council.
The presence or absence of pulmonary embolism will be assessed with the use of a validated algorithm based on pre-test clinical probability and D-dimer result. The D-dimer level will be assessed with the quantitative assay routinely used in each participating center, and the cut-off will be adjusted to patients age in a standardized fashion. The pre-test clinical probability will be assessed by the simplified Wells score that classifies it as being “likely” or “unlikely”. In patients in whom the pre-test clinical probability is low (“unlikely”) and the D-dimer result is negative, no further testing will

be done, and PE will be considered excluded. In patients with high clinical probability, positive D-dimer result, or both, computed tomography (CT) pulmonary angiography will be performed. Criterion for the presence of PE will be an intraluminal filling defect on CT angiography. In patients with PE, the thrombotic burden will be assessed by a central adjudication committee through the identification of the most proximal location of the embolus on CT angiography.

Definition of the conclusion of the study

Stoplines:

- after enrolling 300 patients, if the lower limit of the 95% CI of the prevalence of PE is $\geq$ 20%; otherwise:
- after enrolling 600 patients

Outcome of the study

Primary endpoint

- Prevalence of PE in the overall population

Secondary endpoints:

Prevalence of PE in the following subgroups:

- patients with high pre-test clinical probability and/or positive D-dimer
- patients without potential explanations for the dyspnea
- each of the 5 severity groups of the modified scale of the Medical Research Council

Statistical consideration

Bias

To avoid patient's selection bias, the investigators are asked to consecutively include the observed patients or, if it is not possible, to declare the criterion adopted for enrolment (e.g. one day a week, one week a month, etc.).

Sample size

Based on pilot data, we assume a prevalence of PE in patients with dyspnea on exertion between 10 and 15%. In order to obtain a two-sided 95% confidence interval (CI) of 2.5% for the prevalence of PE, we estimate that a sample size of 550 patients is required. All centers will be asked to contribute patients until the achievement of the overall sample size.

Statistical analysis plan

The prevalence of PE and the associated 95% CI will be calculated for the entire group of patients and for relevant subgroups. For comparison of baseline characteristics between patients with and without PE, the chi-square test will be used for categorical parameters, while the Student's t-test will be used for continuous parameters. Odds ratios and their 95% CIs will be calculated using logistic regression. The 95% CIs and P values will be calculated according to the normal approximation of the binomial distribution. No adjustments will be made for multiple testing.
An interim analysis will be perfoermed after the inclusion of 300 patients. If the lower limit of the 95% CI around the prevalence of PE is $\geq$ 20%, the study will be interrupted.

Study administration

Data collection and management

Patient's personal data will be collected (in anonymous form), date of birth, gender, weight, height, liver and hepatic enzymes, past clinical history, thrombotic/haemorrhagic risk factors, lifestyle habits, type of treatment

The monitor of the study will check data quality and completeness by remote monitoring.

Data will be anonymously entered by the investigator in the eCRF, by assigning a patient identification code.

The adopted database is REDCap stored in the server owned by Fondazione Arianna Anticoagulazione, which is responsible for maintaining, and backing up the database..

Each access to the eCRF will be managed by personal user name and a password.

The security system requires that the password be changed at the first access; it requires a length of at least 8 characters and provides for a periodic 3-month expiry.

It is obviously possible to disable the login, if it is deemed necessary by the system administrator.

Investigators can have full access only to their patient's data.

Every night the data backup is automatically performed.

Ethics

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with the protocol and ICH-GCP.

This is an observational study and all drug prescriptions and clinical investigations are independent from the study.

The protocol and any amendments and the informed consent form (or information/non-opposition letter, as allowed by local regulations) will have to obtain Institutional Review Board or Ethics committee (IRB/EC) approval prior to initiation of the study.

Informed Consent Form

Participation in this study is entirely voluntary. Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP and local regulations. A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) a legal representative may sign for the subject. A copy of the signed consent form will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records. Once a patient has been enrolled in the study, he/she may withdraw his/her consent to participate in the study at any time without prejudice. Patients will not be entered in the database if the informed consent has not been obtained.

Procedures implemented to guarantee data confidentiality

The investigators collected patient's personal data in anonymous form by assigning a patient identification code.

The adopted database is RedCap. Data anonymously entered in the eCRF will be recorded and stored in the server owned by Fondazione Arianna Anticoagulazione. Each access to the eCRF will be managed by personal user name and a password.
The security system requires that the password be changed at the first access; it requires a length of at least 8 characters and provides for a periodic 3-month expiry.
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Investigators can have full access only to their patient's data. Every night the data backup is automatically performed.

Administrative Issues

Support of the study

Participation in the PEDIS study is entirely voluntary and no form of remuneration or refund is given to the investigators.
The PEDIS study is supported by own funds of the Promoter, for the preparation, working and maintenance of all the necessary activities, i.e. informatic and monitoring activities, statistical analysis of results, production of reports and publication of scientific papers.

Publication

Role of Promoter and Investigators
The Promoter and the investigators may suggest specific analysis, regarding all or some data of the central database. The authorship of the article must provide who proposed the analysis, who performed the data analysis, who took part in writing the article.

Data handling and record keeping

All data and results and all intellectual property rights to the data and results derived from the study will be the property of the Promoter Fondazione Arianna Anticoagulazione according to D.M. 17 Dicembre 2004. This study is a No Profit Study (D.M. 17 Dicembre 2004, Art. 1, comma 2, lettera c).

Final report and publication

Within 12 months from the completion of the trial and in accordance with ICH-GCP, the promoter provides the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required. All data and results and all intellectual property rights to the data and results derived from the study will be the property of Fondazione Arianna Anticoagulazione, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators. All publication or communication (oral or written) will respect the international requirements: "Uniforms requirements for Manuscripts Submitted to Biomedical Journals".

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