SSC Subcommittee Project/Collaborative Project

NAME OF PROJECT

Risk Stratification for Death in Patients with Acute Pulmonary Embolism
Subcommittee: Predictive and diagnostic variables in thrombosis

Person responsible (Chair / Principal Investigator): Cecilia Becattini

Description Abstract

Pulmonary embolism is characterized by a large variety of clinical presentations which are associated with different risks for short-term death. International Scientific Societies (European Society of Cardiology, American Heart Association, American College of Chest Physician) recommend stratification for the risk of short-term death to drive acute clinical care in patients with acute pulmonary embolism (PE). However, there is no consensus about the optimal strategy for risk stratification beyond the categorization as hemodynamically stable or unstable patients. The European Society of Cardiology (ESC) proposed a comprehensive strategy for risk stratification that includes both clinical and instrumental criteria. Based on this strategy, patients are divided by the ESC into three categories at low (1.2%), intermediate (3.4 to 10%) or high (15-30%) risk for death. To qualify for the intermediate-risk group, hemodynamically stable patients should have a not-low risk for death according to PESI or simplified PESI scores. This intermediate-risk group includes about 60% of patients with acute PE who can be highly heterogeneous concerning clinical features and the severity of PE. The ESC guidelines suggest to further classify the intermediate category into intermediate-low and intermediate-high risk of death according to the presence/absence of right ventricle dysfunction assessed by echocardiography or CTPA and/or by the presence/absence of increase in troponin levels (Table 1). North American guidelines also adopted a categorization of patients with acute pulmonary embolism: the American Heart Association/American College of Cardiology in three categories of massive, submassive and low-risk, the CHEST guidelines in two categories based on presence or absence of hypotension.

The aim of risk stratification is to tailor the acute treatment of patients with acute pulmonary embolism on the estimated risk for death. More specifically, the aim is the prompt identification of patients that could benefit from pulmonary reperfusion as well as of patients that could be safely managed by short hospital stay or even home treatment. According to the ESC guidelines, intermediate-high risk patients are also candidates to initial monitoring and rescue reperfusion in case of clinical deterioration. However, an international cohort study showed that the sub-stratification of intermediate-risk patients (intermediate-high and intermediate-low) according to the ESC guidelines is probably not efficient in discriminating two categories of patients at different risk of death and requires improvement.
The main long-term objective of this study is to reach a standardization of risk stratification for short-term death in patients with acute pulmonary embolism.

To reach this objective the project is divided into three phases with specific aims and designs:

- **Aim 1**: to assess the current use of risk stratification procedures vs clinical gestalt in the management of patients with acute pulmonary embolism;

- **Aim 2**: to critically review and potentially compare the accuracy of different tools for
  a. the identification of patients at low risk for short term death;
  b. the identification of patients at high risk for short term death;
  c. risk stratification of patients with acute pulmonary embolism who are not at low or at high risk for short term death (intermediate risk);

- **Aim 3**: to use the evidence from Aim 2 (a, b and c) to produce a document for standardization of risk stratification in patients with acute pulmonary embolism;

- **Aim 4**: to validate in a prospective project the standardized tool for risk stratification in patients with acute pulmonary embolism vs clinical gestalt.

**Design and methodology (Data expected to collect, sample size and statistical analysis):**

The methodology of the study is peculiar for the four different aims of the study.

In particular:

- **Aim 1**: survey to be electronically sent to ISTH, European Society of Cardiology, American College of Cardiology, American Society of Hematology, European Respiratory Society, European Society of Emergency Medicine, American Academy of Emergency Medicine, American College Emergency Medicine members as an initiative of the World Thrombosis Day;

- **Aim 2 (a, b, c)**: three separate systematic reviews of the literature (and meta-analyses if feasible) will be performed on
  a. The accuracy of different tools for the identification of patients at low risk for short term death;
b. different definitions for the identification of patients at high risk for short term death;

c. accuracy of different tools for risk stratification of patients with acute pulmonary embolism who are not at low or at high risk for short term death (intermediate risk);

- Aim 3: a consensus paper will be produced and released on the standardization of risk stratification in patients with acute pulmonary embolism with the proposal of a model/tool/definition which combines the evidence from Aim 2;

- Aim 4: randomized study (center randomization) to assess the clinical outcome of patients with acute pulmonary embolism managed by the use of a standardized tool vs clinical gestalt for risk stratification;

Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):

Aim 1: a call to action will be sent by email to

a. ISTH headquarters,

b. Coordinators of ESC working groups,

c. AHA/ACC section,

d. ASH Scientific Committees

e. European Respiratory Society - Assembly on Pulmonary Vascular Diseases

f. European Society of Emergency Medicine

g. American Academy of Emergency Medicine

h. American College of Emergency Physicians

inviting to participate on a survey on the use of risk stratification models for the risk of death to manage patients with acute pulmonary embolism in everyday clinical practice. The survey is to be considered a World Thrombosis Day initiative.

A questionnaire will be emailed to the members of the participating international Societies in Q4 2019 and the results will be analyzed in Q1 2020. As the clinical spectrum of patients with acute pulmonary embolism is highly heterogeneous, in this phase of the project the aim is to
SSC Subcommittee Project/Collaborative Project

assess the perceived need for and the actual use of formal risk assessment models to manage patients with acute pulmonary embolism. The rationale of involving several international Societies in the project is aimed at obtaining the most complete figure of the current clinical management of patients with acute pulmonary embolism.

The questionnaire will be focused on the use of risk stratification tools (clinical models, echocardiography, CT assessment of right ventricle, biomarkers).

The optimal results would be to obtain at least 1500 completed questionnaire by receiving response from at least 10% of recipients.

A paper will be prepared reporting on the results of the survey. The paper will be submitted within Q2-Q3 2020.

**Aim 2**: three separate groups of project members will be identified to manage 3 systematic reviews (and, potentially, meta-analyses) on risk stratification in patients with acute pulmonary embolism. The three critical reviews will focus on:

- **d.** accuracy of different tools for the identification of patients at low risk for short term death;
- **e.** different definitions for the identification of patients at high risk for short term death;
- **f.** accuracy of different tools for risk stratification of patients with acute pulmonary embolism who are not at low or at high risk for short term death (intermediate risk);

The three workgroups will start working in Q4 2019, with a common methodology. Literature search and study selection will be completed within the end of Q4. Data extraction and analysis will be conducted within Q1 2020. The results will be shared and commented during a joint web session at the end of Q1-starting of Q2 2020. Additional searches/analyses would be run within Q2. Three manuscripts will be prepared for publication, resuming the results of the three critical reviews (and, potentially, meta-analyses). Manuscript will be submitted within Q3 2020.

**Aim 3**: an ISTH consensus paper on the standardization of risk stratification in patients with acute pulmonary embolism will be prepared by the Committee members with the proposal of a model/tool/definition which combines the evidence from Aim 2a, 2b and 2c.

As this project will be based on the results of aim 1 and 2, it will be started on Q3-Q4 2020.

**Aim 4**: pragmatic (randomized) study (center randomization) to assess the clinical outcome of patients with acute pulmonary embolism managed by the use of a standardized tool vs clinical
gestalt for risk stratification. Results of Aim 1 will be of help in identifying study centers worldwide.

This will be a pragmatic (randomized) international study. The expected 30-day mortality in the general population of patients with acute PE is in the range of 5 to 7%. The use of risk driven clinical management should at least reduce mortality by 30%. By estimating a proportion of death at 30 days of 7% in the clinical gestalt arm and a 4% in the standardized tool arm, we will need 906 patients per group to show a statistically significant difference with a power of 90% and alfa level of 0.05. By expecting a 10% proportion of not-evaluable patients the sample size in increased to 996 patients per group.

(As randomization may influence the standard clinical practice the study is designed as a pragmatic trial in which study centers will be divided into two groups according to the results of the survey in Aim 1. Centers where risk stratification is not used will represent the clinical gestalt arm. Centers used to manage PE patients according to risk stratification tools will represent the standardized tool arm. In order to improve feasibility and reduce the duration of the project we aim to include 100 study centers worldwide. A specific insurance may not be necessary as the nature of the study is anyway observational.)

Expected timeline:

Project stage/set up The project is currently in development. An international Steering has been identified for the general project: Cecilia Becattini (Italy), Maria Cristina Vedovati (Italy, Stefano Barco (Germany), Sanjeev Chunilal (Australia) Marc Carrier (Canada). Investigators for the individual subprojects will be involved worldwide in order to promote collaboration, knowledge exchange and representativeness of the main project. Fundraising will start as soon as the project will be finally accepted. A final protocol will be prepared within Q3-Q4 2019 for aims 1-2. The results of these projects will be hopefully submitted to ISTH 2020 meeting. The finalization of aim 3 requires the completion of Aims 1 and 2 and is expected for Q2-Q3 2020. The finalization of a protocol for aim 4 is set in Q2-Q3 2020 to take advantage of the results of the aims 1-3. As this is a clinical study including 100 centers worldwide it is expected that a full study period of 2 years and 6 months will be required for completion.

Launch: the project will be launched at ISTH 2019 and the projects will start as soon as the ISTH approval.

Duration: the overall duration of aim 1-3 is 16 months. About 3 years are required for aim 4 (1 for set-up and 2 for recruitment).

Finalization/analysis: A final protocol will be prepared within Q3-Q4 2019 for aims 1-2. The results of these projects will be hopefully submitted to ISTH 2020 meeting.
SSC Subcommittee Project/Collaborative Project

The finalization of aim 3 requires the completion of Aims 1 and 2 and is expected for Q2-Q3 2020.
The finalization of a protocol for aim 4 is set in Q2-Q3 2020 to take advantage of the results of
the aims 1-3. As this is a clinical study including 100 centers worldwide it is expected that a full
study period of 2 years and 6 months will be required for completion. A

Reporting: the status of the project will be updated at every ISTH meeting. The results of the
individual phases of the project will be submitted for publication and the abstracts submitted to
ISTH meetings.

Expected outcomes (ie. publications):

Publication type (SSC Communication, Guidance document or original article):

Aim 1: the results of this subproject will be presented during an international meeting and
published as a stand-alone manuscript;

Aim 2: the intent is to have 3 independent communications and manuscripts, each originating
from an individual aim (2a, 2b and 2c). However, it is not clear at this stage if each of the aim
would result in a stand-alone paper. The final decision will derive from the results of the
individual subprojects.

Aim 3: an SSC document on standardization of risk stratification in patients with acute
pulmonary embolism;

Aim 4: this part of the project allows a double publication: the study design paper and the full-
result paper as stand-alone manuscripts.

Description of project set/up and management, needed infrastructure and resources (summary):

The members of the Steering Committee for this SSC project will participate in 2 formal
meetings by web in Q3-earlyQ4 2019 in order to finalize the project. In the mean-while the
members will communicate by email in order to finalize the structure of the project.

Aim 1: this part of the project will be seen as part the international activities of the World
Thrombosis Day. October 13 could be seen as a deadline to collect collaboration from
international societies and having set a survey that will be circulated in Q4 2019; in this phase
the steering committee members will work by email and could need secretarial assistance and
informatic assistance to realize a web-page to circulate the survey within the end of Q4 or early
Q1 2020;

Aim 2: the activities of this part of the project will be started in parallel with the activity of Aim
1; the crucial part will be the identification of 3 groups of dedicated young investigators each
SSC Subcommittee Project/Collaborative Project

caired by one or two members of the Steering Committee of the SSC project. Support may be required for literature search in these projects unless it is provided by the members of the Steering Committee of the SSC project themselves.

Aim 3: the Steering Committee members of the SSC project will communicate by email or web meetings for this specific part of the project; no specific support is identified at this stage.

Aim 4: this part of the project seems not to be feasible without support for electronic CRF, secretarial coordination and project management activity.

Possible references:


The project group:
Cecilia Beccatine (Italy, project leader), Maria Cristina Vedovati (Italy), Stefano Barco (Germany), Marc Carrier (Canada), Sunjeev Chunilal (Australia), Erik Klok (The Netherlands), and Marc Righini (Switzerland).