Meta-Analysis of Prevalence and Short-Term Prognosis of Hemodynamically Unstable Patients With Symptomatic Acute Pulmonary Embolism

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There remains limited information about the prevalence and outcomes of hemodynamic unstable patients with acute pulmonary embolism (PE). We performed a systematic review and meta-analysis of prospective registries that enrolled patients with acute PE to assess the prevalence and prognostic significance of hemodynamic instability for the primary outcome of short-term all-cause mortality, and the secondary outcome of short-term PE-related mortality. We also assessed the association between use of thrombolytic therapy versus no use and short-term outcomes in the subgroup of unstable patients. We used a random-effects model to pool study results; and I^2 testing to assess for heterogeneity. The authors' search retrieved 4 studies that enrolled 1,574 patients with unstable PE (1,574/40,363; 3.9%; 95% confidence interval [CI], 3.7% to 4.1%). Hemodynamic instability had a significant association with short-term all-cause mortality (odds ratio [OR], 5.9; 95% CI, 2.7 to 13.0; $I^2 = 94\%$), and with PE-related death (OR, 8.2; 95% CI, 3.4 to 19.7). In unstable patients, thrombolytic therapy was associated with reduced odds of short-term all-cause mortality (OR, 0.69; 95% CI, 0.49 to 0.95), and PE-related death (OR, 0.66; 95% CI, 0.45 to 0.97). In conclusion, hemodynamic instability significantly increased the risk of death shortly after PE diagnosis. Use of thrombolytic therapy was associated with significantly reduced short-term mortality. **(Am J Cardiol 2019;123:684−689)**

Pulmonary embolism (PE) is a leading cause of death in the Western world.[1,2] Small studies have described the prevalence, natural history, and prognostic significance of hemodynamic instability in PE.[3−6] According to these studies, hemodynamically unstable PE can be detected in approximately 3% to 12% of patients with acute symptomatic PE, and short-term mortality rates vary from 15% in patients with isolated hypotension to 30% in patients with shock, and up to 65% in patients with cardiac arrest at presentation.[3−6] Though guidelines recommend the use of thrombolytic therapy for unstable patients with PE that do not have major contraindications owing to bleeding risk,[7−9] only 1 small randomized controlled trial has demonstrated the efficacy of thrombolytic therapy in patients with "life-threatening" PE.[10] We conducted a systematic review and meta-analysis of PE registries to clarify the prevalence and prognostic significance of hemodynamic instability in patients with acute PE. Further, we assessed the association between use of thrombolytic therapy and short-term outcomes.

Methods

The authors used methods recommended in "Meta-Analysis of Observational Studies in Epidemiology: A Proposal for Reporting" guidelines.[11] We searched MEDLINE with PubMed interface and EMBASE for prospective registry studies of patients with acute symptomatic PE from 1980 to January 2018, with no language limits. The search strategy combined the following terms: (Registry* [TIAB] OR "Registries" [Mesh]) AND ((pulmonary [TIAB] AND (embol* [TIAB] OR thromboembolis* [TIAB])) OR "Pulmonary embolism" [Mesh]). Full studies of all potentially appropriate abstracts were reviewed. Hand searching

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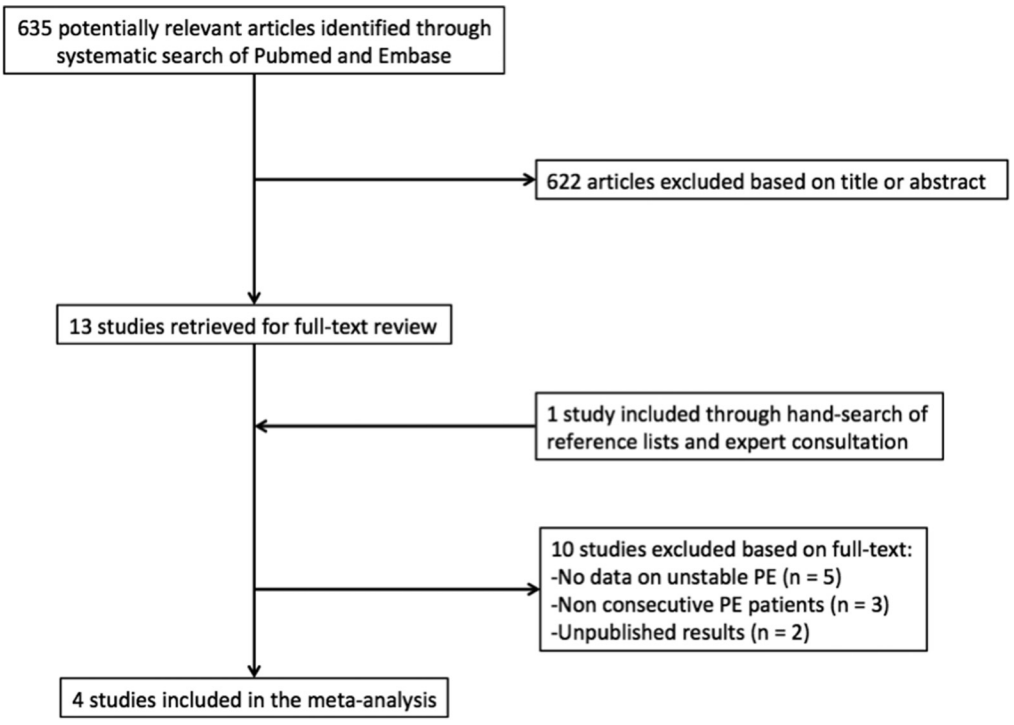

Figure 1. Flow chart of the study selection process. Abbreviations: PE, pulmonary embolism.

of cited bibliographies and investigator files complemented the literature search.

The study *primarily* aimed to clarify the prevalence of hemodynamic instability in patients with acute symptomatic PE, and to assess for an association between hemodynamic instability and short-term (ie, through 90 days after the diagnosis of PE) all-cause mortality in patients with acute symptomatic PE. We a priori chose to use short-term all-cause mortality as the primary outcome because of its clinical importance and the fact that it is less prone to misclassification compared with other outcomes. The study *secondarily* aimed to assess for an association between hemodynamic instability and short-term PE-related death. The study also assessed the association between use of thrombolytic therapy versus no use and short-term outcomes in the subgroup of unstable PE patients.

One reviewer (DJ) performed the database search and initial screening of titles and abstracts. Two investigators (AQ and DJ) independently carried out full text screening of all eligible studies. We included a study if: (1) it was prospective; (2) participants were consecutive patients with acute symptomatic PE objectively diagnosed with standard imaging techniques; (3) it provided information on unstable PE patients; and (4) it reported mortality outcomes. Randomized trials were excluded.

For each study, investigators abstracted the data regarding study design (number of included patients; single-center or multicenter), patient characteristics (age, gender, and percentage of patients with high-risk PE), treatment strategies (number of patients who received thrombolysis), and outcomes. Two investigators (AQ and DJ) used the Quality in Prognosis Studies tool to independently assess the quality of the eligible studies.[12]

For primary analyses, we pooled the data using Mantel-Haenszel random-effects models with odds ratio (OR) as the effect measure with the related 95% confidence interval (CI). Statistical heterogeneity between groups was measured using the Cochran's Q statistic and the Higgins I^2 statistic.[13] Statistically significant heterogeneity was considered to be present at $p < 0.10$ and $I^2 > 50\%$. The Begg rank correlation method assessed for publication bias. We ran supplemental preplanned sensitivity analyses with inverse variance fixed-effects models with OR as the effect measure to ascertain the robustness of results. All analyses were carried out using Review Manager 5.2 (The Cochrane Collaboration, Oxford, United Kingdom) and MetaDisc version 1.4.[14]

Results

Of the 635 studies screened, 13 appeared potentially eligible and underwent an in depth review.[3–6,15–23] We did not include 5 registries because data on unstable PE were confirmed to be unavailable,[15–19] or 3 registries that did not enroll consecutive patients with acute PE.[3,20,21] Two additional registries have not published their results yet.[22,23] Hand searching found 1 additional study[24]; therefore a total of 4 registries with 40,363 patients with acute PE met the eligibility criteria and were included in the analysis[4–6,24] (Figure 1). We identify these studies by their acronyms as follows: International Cooperative Pulmonary Embolism Registry (ICOPER),[6] Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry (EMPEROR),[5] Italian Pulmonary Embolism Registry (IPER),[4] and Registro Informatizado de la Enfermedad Tromboembólica (RIETE).[24]

Table 1
Characteristics of the studies of patients with acute pulmonary embolism

Registry	Year	Study design	Unstable PE (%)	Women (%)	Age, Mean (SD) of unstable PE	Follow-up (months)	Mortality, % of unstable PE
ICOPER[6]	2006	Multicenter	4.5%	55%	–	3	–
EMPEROR[5]	2012	Multicenter	3.1%	53%	63.3	In-hospital	14%
IPER[4]	2012	Multicenter	12%	57%	74 (14)	In-hospital	32%
RIETE[24]	2018	Multicenter	3.5%	53%	68.1 (17.1)	1	14%

Abbreviations: **P**E = Pulmonary embolism; SD = standard deviation.

Table 2
Quality assessment of studies included in the systematic review

Study	*Study participation*	*Study attrition*	*Prognostic factor measurement*	*Outcome measurement*	*Study confounding*	*Statistical analysis and reporting*
Kucher[6]	Moderate bias	Low bias	Low bias	Moderate bias	Low bias	Low bias
Lin[5]	Low bias	Low bias	Low bias	Moderate bias	Moderate bias	Moderate bias
Casazza[4]	Moderate bias	Low bias	Moderate bias	Moderate bias	Low bias	Low bias
Jimenez[24]	Low bias	Low bias	Low bias	Moderate bias	Low bias	Low bias

Demographic features of study populations (age and gender) were similar across the studies, and all the included patients had an objective diagnosis of PE. Time to study end point was different in the registries (Table 1). ICOPER, EMPEROR, and RIETE defined unstable PE as the presence of arterial hypotension (systolic blood pressure <90 mm Hg) at the time of diagnosis of PE,[5,6,24] whereas IPER included arterial hypotension, cardiogenic shock, or cardiac arrest in its definition.[4]

Regarding study quality assessment criteria (Table 2), the risk of selection bias was low in 2 studies,[5,24] and moderate in 2 studies.[4,6] The risk of attrition bias (ie, likelihood that relation between unstable PE and outcome are different for completing and noncompleting participants) was low in all the studies. Three studies adequately described methods for the assessment of hemodynamic instability.[5,6,24] The 4 studies[4–6,24] used all-cause mortality as the primary outcome, and EMPEROR, IPER, and RIETE used PE-specific mortality as the secondary outcome. In none of the studies an independent blinded committee adjudicated the etiology of death. IPER, ICOPER, and RIETE accounted for important potential confounders to assess for an association between hemodynamic instability and short-term mortality[4,6,24]; only RIETE accounted for potential confounders to assess for an association between thrombolytic therapy and mortality.[24] The use of appropriate statistical analyses in 3 studies[4,6,24] limited the potential for the incorporation of and presentation of invalid results, whereas 1 study did not perform any predictive statistics.[5]

In the 4 cohorts that enrolled 40,363 consecutive patients with acute PE, 1,574 (3.9%; 95% CI, 3.7% to 4.1%) had unstable PE and 38,789 (96.1%; 95% CI, 95.9% to 96.3%) did not. Overall, 296 of 1,574 patients with unstable PE died (19%; 95% CI, 17% to 21%) compared with 2,224 of 38,789 without instability (5.7%; 95% CI, 5.5% to 6.0%). Pooled results from the 4 cohorts showed that unstable PE was associated with 5.9-fold increased odds of short-term all-cause mortality (95% CI, 2.7 to 13.0; $I^2 = 94\%$) (Figure 2). There was no evidence of publication bias using the Begg rank correlation method. The 4 studies also reported on deaths resulting from PE. Overall, 1,239 events were observed: 198 in 1,574 patients with hemodynamic instability (13%; 95% CI, 11% to 14%) and 1,041 in 38,789 without hemodynamic instability (2.7%; 95% CI, 2.5 to 2.9). Unstable PE was associated with 8.2-fold increased odds of short-term PE-related mortality (95% CI, 3.4 to 19.7, $I^2 = 93\%$) (Figure 2).

Of the 1,574 patients with acute unstable PE, 362 (23%; 95% CI, 21% to 25%) received thrombolysis and 1,212 (77%; 95% CI, 75% to 79%) did not. Overall, 64 of 362 patients with unstable PE who received thrombolytic therapy died (18%; 95% CI, 14% to 22%) compared with 232 of 1,212 unstable patients who did not receive thrombolytic therapy (19%; 95% CI, 17% to 22%). In unstable patients, pooled results from the 4 cohorts showed that patients who received thrombolytic therapy had a significant lower all-cause mortality (OR, 0.69; 95% CI, 0.49 to 0.95; $I^2 = 0\%$) than those who did not receive it (Figure 3). In unstable patients with acute PE, those receiving thrombolytic therapy had a statistically significantly lower risk of PE-related death (OR, 0.66; 95% CI, 0.45 to 0.97; $I^2 = 0\%$) than those who did not receive it (Figure 3). Repeating all the analyses using inverse variance fixed-effects models with OR as the effect measure yielded similar results (On-line Figures 4 and 5).

Discussion

In this meta-analysis of 4 large PE registries that included 40,363 patients with acute symptomatic PE, patients with hemodynamic instability had a 5.9-fold increased risk of short-term death compared with patients without instability. Unstable patients that received thrombolytic therapy had a lower risk of all-cause and PE-related mortality than unstable patients who did not receive thrombolytic therapy.

In patients with acute symptomatic PE, studies have reported prevalences of hemodynamic instability that range from 3.1% to 12%.[4,5] The prevalence of hemodynamic instability in this meta-analysis (3.9%) confirms that

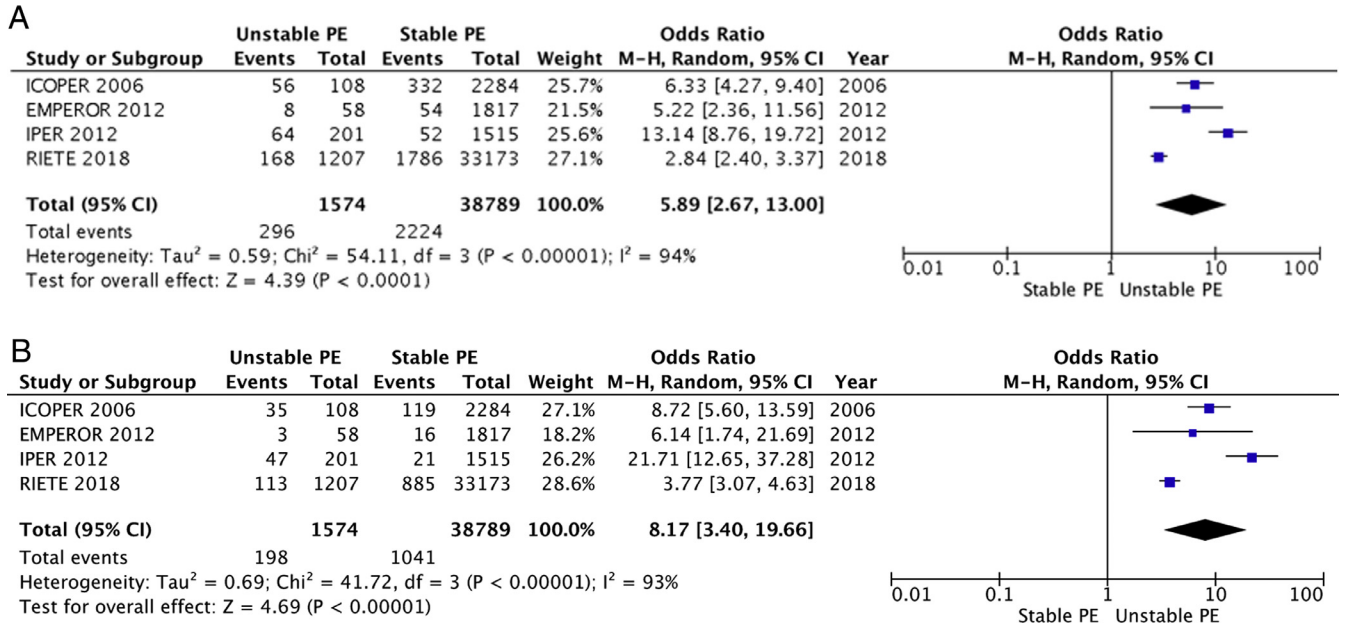

Figure 2. Odds ratio of short-term mortality based on the presence or absence of hemodynamic instability in patients with acute pulmonary embolism: random-effects meta-analysis. (*A*) All-cause mortality. (*B*) PE-related death. Abbreviations: CI = confidence interval; M-H = Mantel-Hanszel; PE = pulmonary embolism.

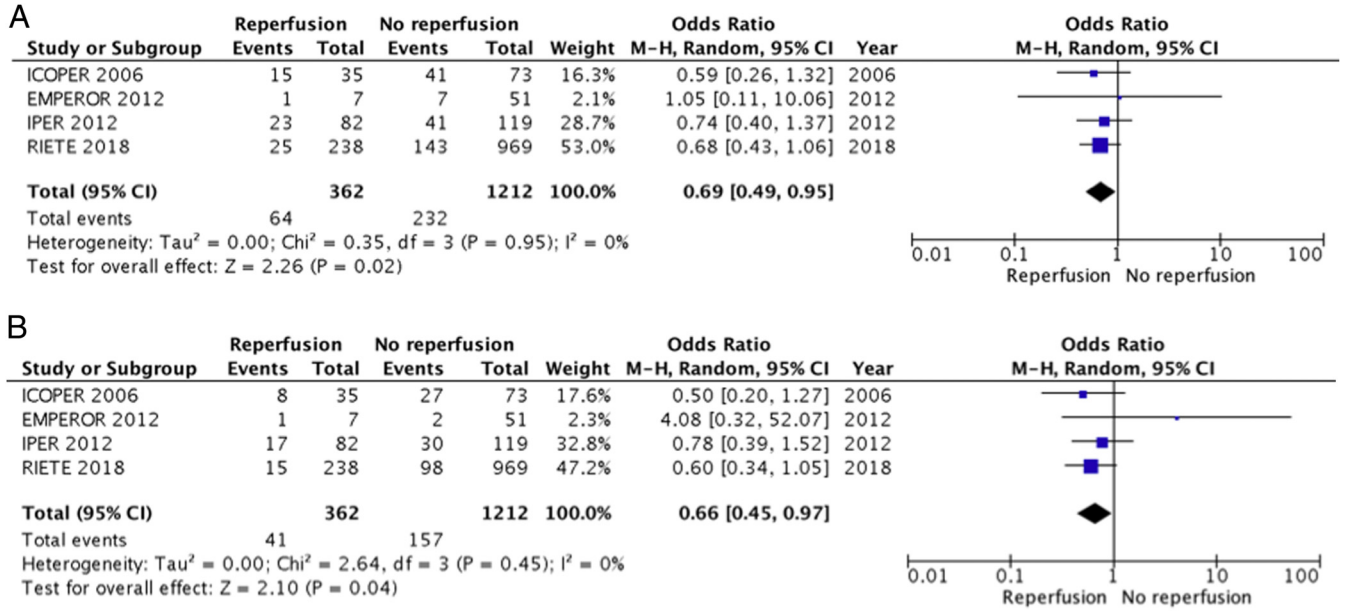

Figure 3. Odds of mortality in patients with unstable pulmonary embolism treated with thrombolytic therapy versus anticoagulation: random-effects meta-analysis. (*A*) All-cause mortality. (*B*) PE-related death. Abbreviation: M-H = Mantel-Hanszel.

hypotension is an uncommon finding in patients with PE. With the development of computed tomography pulmonary angiography technique,[25] has likely decreased the incidence of unstable PE due to screening bias for smaller emboli.

This meta-analysis shows that hemodynamic instability is associated with short-term death in patients with acute symptomatic PE, and confirms that hemodynamic status remains the most important short-term prognostic factor for such patients.[8] Though clinicians typically give thrombolysis in an attempt to decrease the risk of death from PE, the indications for its use require further study.[26] This study also showed that patients with unstable acute PE who received thrombolytic therapy had almost a one-third lower risk of all-cause and PE-related mortality than those who did not receive it. In contrast, in a large, state-wide sample of patients hospitalized for acute PE, Ibrahim et al found that thrombolytic therapy did not have a significant effect on the survival of 803 patients with PE-associated systolic hypotension.[27] However, only a minority (6.9%) of unstable patients in that study received thrombolysis, versus

23% in this study, and the lack of association between thrombolysis and mortality may have occurred due to a lack of statistical power.

This meta-analysis has limitations. Although the large total sample size, the proportion of patients with hemodynamic instability, and the death rate all allowed for reasonable estimates of risk, this study was not aimed at proving the efficacy of thrombolytic therapy in such patients. This was also hampered by lack of detailed information in most of the included studies for potential mediators and confounders. Future studies, including an individual patient-level pooled analysis, may prove helpful to assess this issue. However, the varied settings and patient characteristics in and within the registries improved the generalizability of the study results. Further, limitations of each of the included studies may have introduced significant biases into this meta-analysis's estimates of the prognostic value of hemodynamic instability. However, we are not aware of fatal flaws in either of the 4 included studies. Finally, our main analysis showed a significant variation in study outcomes between studies, which may be reflective of differences in patient selection, duration of follow-up, outcome ascertainment, or a combination of these.

In conclusion, this systematic review showed that the majority of patients who present with acute symptomatic PE do not have hemodynamic instability. Though unstable acute PE patients have markedly worse outcomes compared with stable PE patients, only one-fifth of such patients received advanced therapies. For patients who have acute PE associated with hemodynamic instability, thrombolytic therapy is associated with a one-third lower risk of all-cause and PE-related mortality in comparison to anticoagulation.

Conflict of interest statement

The authors declared no conflicts of interest.

Casazza[4] and Jimenez[25] authored studies assessed by this meta-analysis.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.11.009.

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