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# Ultrasound Accelerated Thrombolysis in patients with acute pulmonary embolism: A systematic review and proportion meta-analysis

Ashraf Mostafa [1], Alexandros Briasoulis *,[1], Mohamed Shokr, Artemis A. Briasouli, Sidakpal Panaich, Cindy Grines

*Division of Cardiology, Detroit Medical Center, Wayne State University, Detroit, MI, USA*

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*Dear Editor-in-chief,*

Acute pulmonary embolism (PE) is a common and major cause of hemodynamic collapse and sudden death [1]. The mainstay therapy of acute PE remains to be systemic anticoagulation, adjunctive systemic thrombolysis is considered in patients with acute massive or submassive PE.[1] Massive PE patients are hemodynamically unstable, who carry high risk of in-hospital mortality greater than 15% [2], whereas those with submassive PE are usually hemodynamically stable patients with significant right ventricular (RV) dysfunction, elevated cardiac biomarkers, with mortality rates ranging from 3–15% [2,3]. Massive or submassive PE often results in severe hypoxia, RV failure with subsequent hemodynamic collapse. Recent studies suggested that systemic thrombolytic therapy is associated with a lower all-cause mortality (2.2% vs 3.9%) compared to anticoagulation alone, at the expense of an increased risk of major bleeding (9.2% vs 3.4%) [4]. Catheter-based revascularization therapy has emerged as potential alternative to systemic thrombolysis in patients with massive and submassive PE with high clinical success rates >85% and relatively low rates of major procedural complications <5% [5]. Many small sized studies have indicated that ultrasound-assisted catheter-directed thrombolysis (UAT) is effective in reversing the hemodynamic consequences of high and intermediate risk PEs in comparison with anticoagulation alone [6–14]. The aggregate effect of those studies has not been systematically reviewed. The present systematic review and proportion meta-analysis was designed to systematically evaluate prospective and retrospective cohort studies and assess the effects of UAT on all-cause mortality and bleeding rates in patients with massive or submassive PE.

We systematically searched the electronic databases, MEDLINE, PUBMED, EMBASE and the Cochrane Library for Central Register of Clinical Trials, using the MESH terms, "ultrasound-assisted thrombolysis", "Ultrasound-Accelerated Thrombolysis", "pulmonary embolism". We limited our search to studies in human subjects and English language in peer-reviewed journals published until September 2015. Additionally, a manual search of all relevant references from the screened articles and reviews of ultrasound-assisted thrombolysis and pulmonary embolism was performed for additional clinical studies.

We included prospective studies and retrospective cohorts published as original articles in peer-reviewed scientific journals in English. The primary outcome measure was the development of all-cause mortality, major and minor bleeds. The definitions of major bleeding used in individual studies are presented in Table 1. The Newcastle-Ottawa tool was used for the quality assessment of cohort studies. Two authors (A.B. and A.M.) independently assessed the risk of bias and quality of studies in each eligible trial.

We used software (StatsDirect version 2.7.9) to pool estimates of all-cause mortality, major and minor bleeding rates, using both fixed and random effects models for combining proportions. In the absence of heterogeneity, pooled estimates of odd risks (ORs) with their 95% confidence intervals (CIs) were calculated using the Mantel–Haenszel method. A DerSimonian–Laird random-effects model for ORs estimation of all outcomes was used in the presence of heterogeneity. The Freeman–Tukey variant of the arcsine square root transformation was used to account for the fact that proportions with extreme values (e.g., close to 0 or 1) have lower variances. Statistically significant heterogeneity was defined as an $X^2$ P-value less than 0.05 or an $I^2$ statistic greater than 75%. Reported values are two-tailed, and hypothesis-testing results were considered statistically significant at $P < 0.05$. The small study effect, including publication bias, was tested using funnel plot, the Egger's and Begg–Mazumdar test.

We identified 11 studies of ultrasound-assisted thrombolysis in patients with pulmonary embolism. The baseline characteristics of the included studies are summarized on Table 1. All of them were reported

* Corresponding author at: Wayne State University/Detroit Medical Center, Department of Cardiology, Detroit, IL 48226, USA.
*E-mail address:* alexbriasoulis@gmail.com (A. Briasoulis).
[1] Equally contributed.

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**Table 1**
Interventions and characteristics of individual studies.

| Study | Year | Design | Sample size | Mean age (years) | M/F | Massive PE (%) | Submassive PE (%) | Follow-up (days) | Total rt-PA dose (mg) median | Definition of major bleeding | Pre/post-treatment RV/LV ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Chamsudiin et al. | 2008 | Retrospective | 10 | 54.2 | 5/5 | 100 | 0 | 120 | 21.8 | Society of Interventional Radiology criteria | N/A |
| Lin et al. | 2009 | Retrospective | 11 | 59 | 5/6 | 18 | 82 | 30 | 17.2 | Fatal or requiring transfusion of PRBCU or cessation of the thrombolytic or involvement of critical site | N/A |
| Engelhardt et al. | 2011 | Retrospective | 24 | 61.7 | 11/13 | 21 | 79 | 7 | 33.5 | Fatal or requiring transfusion of PRBCU or cessation of the thrombolytic or involvement of critical site | 1.33/1 |
| Quintana et al. | 2013 | Retrospective | 10 | 58 | 6/4 | 20 | 80 | 14 | 18 | Unclear definition | N/A |
| Kennedy et al. | 2013 | Retrospective | 60 | 61 | 35/25 | 20 | 80 | 90 | 35.1 | Society of Interventional Radiology criteria | N/A |
| Engelberger et al. | 2013 | Retrospective | 52 | 65 | 33/19 | 27 | 73 | 90 | 21 | Fatal or ≥2 g/dl fall in hb or transfusion of ≥2 PRBCU or involvement of critical site | 1.42/1.06 |
| ULTIMA | 2013 | Prospective randomized control | 30 | 64 | 11/19 | 0 | 100 | 90 | 20.8 | Fatal or ≥2 g/dl fall in hb or transfusion of ≥2 PRBCU or involvement of critical site | 1.28/0.99 |
| Dumantepe et al. | 2014 | Retrospective | 22 | 53.7 | 13/9 | 26 | 74 | 180 | 21 | Minor bleeding defined as access related bleeding | 1.29/0.92 |
| SEATTLE II | 2014 | Prospective | 150 | 59 | 73/77 | 20.7 | 79.3 | 30 | 23.7 | GUSTO criteria | 1.55/1.13 |
| McCobe et al | 2015 | Retrospective | 53 | 57.6 | 27/24 | 0 | 100 | 30 | 24.6 | Nonspecific | 1.12/0.98 |
| PERFECT | 2015 | Prospective | 101 | 60.3 | 53/48 | 28 | 73 | 30 | 30.27 | Society of Interventional Radiology criteria | N/A |

PE; pulmonary embolism, rt-PA; recombinant tissue plasminogen activator, RV; Right Ventricle, LV; Left Ventricle, GUSTO; Global Use of Strategies to Open Occluded Arteries, hb; hemoglobin, PRBCU; Packed red-blood-cell-units.

between 2008 and 2015.These studies enrolled 523 patients that received UAT for treatment of PE with an average follow up duration of 53 days. The mean age of patients was 60 years. With exception of one study [6] that included only patients with massive PE, the remaining studies included ~20% patients with massive and 80% patients with submassive PE. On the basis of quality assessment, nine studies were deemed to be at low risk of bias [6–9,11,12,14–16] and two studies at high risk of bias [10,13]. The primary outcome measure of our study was the development of all-cause mortality, severe and non-severe bleeding as defined in the outcome section. The pooled clinical all-cause mortality was 4.1% (95% CI: 2.3%, 6.3%) without significant heterogeneity between studies (Q = 9.4, P = 0.3 for heterogeneity; I2 14.4%) (Fig 1). The pooled clinical major bleeding rate was 2.3% (95% CI: 1%, 4%) without significant heterogeneity between studies (Q = 11.5, P = 0.12 for heterogeneity; I2 30.2%) (Fig. 2). The pooled clinical minor bleeding rate was 10.9% (95% CI: 6.3%, 16.5%) with significant heterogeneity between studies (Q = 16.6, P = 0.035 for heterogeneity; I2 51.8%). No evidence of publication bias was with the Egger test (P = 0.17) and funnel plot analysis. In comparison to results of the systemic thrombolysis trials ICOPER [15], PEITHO [18] and MAPPET [16], our meta-analysis on UAT showed a lower death rate compared to systemic thrombolysis in ICOPER study (P < 0.001), and similar death rate to PEITHO and MAPPET trials (P = 0.2, and P = 0.8, respectively). UAT was associated with a lower rate of major bleeding as compared to

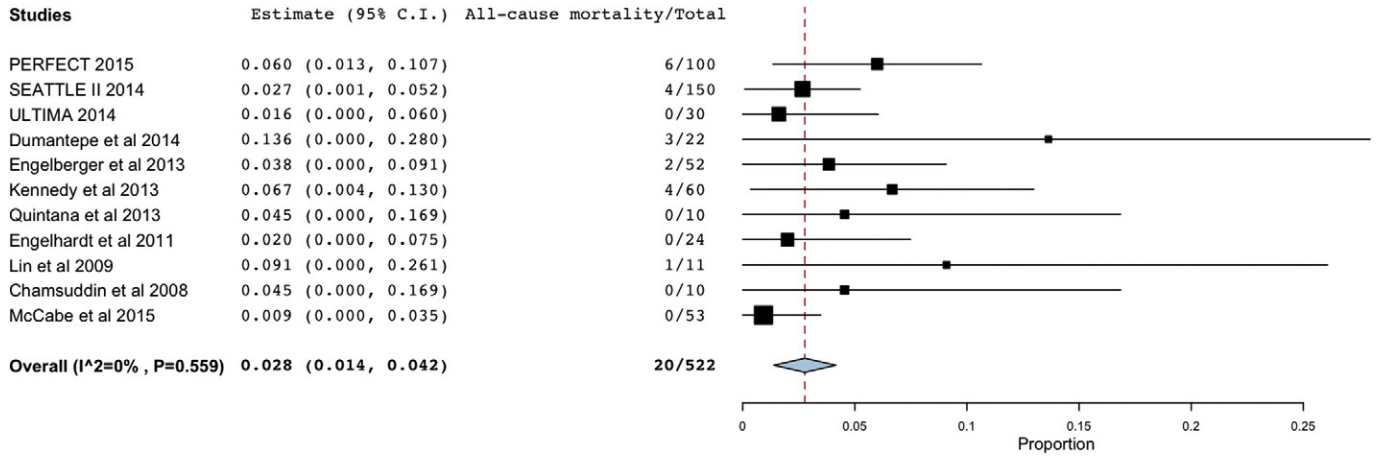


**Fig. 1.** Fixed-effect meta-analysis for all-cause mortality. The figure presents mortality rates from individual studies, and 95% confidence interval (CI) for each trial, overall estimate of pooled proportion with 95% CI.