Meta-Analysis of Catheter Directed Ultrasound-Assisted Thrombolysis in Pulmonary Embolism

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Ultrasound-assisted catheter directed thrombolysis (USAT) has been shown to improve hemodynamic function and reduce bleeding complications in patients with acute massive or submassive pulmonary embolism. We performed a meta-analysis to better evaluate the efficacy and safety of USAT. We conducted an extensive literature search in PUBMED, MEDLINE, and EMBASE databases from January 1, 2008 to December 31, 2018. Efficacy outcomes of interest were pulmonary artery systolic pressure, mean pulmonary pressure, ratio of right ventricular to left ventricular diameter, cardiac index, tricuspid annular plane systolic excursion, Miller Index Score, and Qanadli Score. Safety outcomes were in-hospital mortality, long-term mortality, major and minor bleeding complications, and recurrent pulmonary embolism. Meta-analysis was performed using Cochrane Collaboration Review Manager (version 5.1). Effect size was estimated using random effects model, with 95% confidence intervals (CIs). Twenty-eight studies (n = 2,135) met inclusion criteria. Compared with pretreatment parameters, post-USAT was associated with a reduction in the mean Miller Index Score and Qanadli Score by 10.55 (95% CI −12.98 to −8.12) and 15.64 (95% CI −19.08 to −12.20), respectively. Cardiac index and tricuspid annular plane systolic excursion improved by 0.68 L/m^2 (95% CI 0.49 to 0.87) and 3.68 mm (95% CI 2.43 to 4.93), respectively. Pulmonary artery systolic pressure and mean pulmonary pressure after therapy were reduced by a mean difference of 16.69 mm Hg (95% CI −19.73 to −13.65) and 12.13 mm Hg (95% CI −14.67 to −9.59) respectively. The right ventricular to left ventricular diameter dimension ratio decreased by 0.35 (95% CI −0.40 to −0.30) after therapy. In-hospital mortality in patients who underwent USAT was 2.9%, and total long-term mortality was 4.1%. Major and minor bleeding complications were seen in in 5.4% and 6.0% of patients, respectively. Recurrent events occurred in 0.2% of patients after USAT. In conclusion, USAT is a safe and effective procedure associated with significant hemodynamic and clinical improvement in patients with massive and submassive pulmonary embolism. **(Am J Cardiol 2019;124:1470−1477)**

Pulmonary embolism (PE) is the third most common cardiovascular disorder in the US and causes an estimated 150,000 to 200,000 deaths annually.[1] Among patients diagnosed with acute PE, those with either right ventricular (RV) dysfunction or myocardial necrosis but without hemodynamic collapse are classified as submassive PE, whereas those with circulatory collapse are categorized as massive PE. Overall, RV dysfunction associated with massive or submassive PE results in mortality as high as 5% to 17%.[2] Therapies such as systemic fibrinolysis and embolectomy have the potential to lower mortality in patients with massive or submassive PE. However, systemic fibrinolysis is associated with major bleeding rates as high as 20% with intracranial hemorrhage in up to 3%.[3] Ultrasound-Guided Catheter Directed Thrombolysis (USAT) is an alternative intervention for patients with massive or submassive PE and has the advantage of delivering a smaller, more concentrated dose of thrombolytic therapy, whereas its ultrasound component allows greater penetration into the thrombus. In this manner, USAT augments the effect of the thrombolytic therapy whereas decreasing the bleeding risk.[4] Because the existing case-control trials and cohort studies evaluating the clinical outcomes of USAT include a relatively small number of patients, we performed a meta-analysis of the pooled data on clinical outcomes from all available case-control or cohort studies.

Methods

A systematic literature search was conducted using PUBMED, MEDLINE, and EMBASE databases from January 1, 2008 to December 31, 2018, using the key words "pulmonary embolism," "ultrasound" and "catheter directed." We also manually reviewed the reference lists of

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retrieved original studies, review articles, and conferences' abstracts using the data bases listed above.

We considered studies eligible for the meta-analysis if they fulfilled the following criteria: (1) original case-control, randomized control trials, or cohort studies that study USAT in patients with massive and/or submassive PE (2) studies that include basic population characteristics, safety, and efficacy outcomes. Studies were excluded from the meta-analysis for the following reasons: (1) nonhuman studies, (2) case reports or case series, (3) reviews, (4) meta-analysis, (5) studies published in non-English language.

Three authors (JL, DP, and MY) screened all articles independently. All discrepancies were reviewed and resolved by a fourth author. After identifying the articles that met inclusion criteria, we extracted data from the studies using a shared data extraction form that included the first author, year of the publication, total number of participants, number of participants who underwent USAT, basic population characteristics (mean age and gender ratio), type and dose of thrombolytic therapy, duration of thrombolytic therapy, follow-up technique (e.g., echocardiography and angiography), duration of follow-up, hospital stay, and intensive care unit stay. Data on efficacy outcomes included Miller Index Score, Qanadli Score, pulmonary artery systolic pressure (PASP), mean pulmonary artery pressure (PAP), right ventricle to left ventricle dimension (RV/LV) ratio, cardiac index, and tricuspid annular plane systolic excursion (TAPSE). We also collected data on safety outcomes including in-hospital mortality, total long-term mortality, major bleeding complications, minor bleeding complications, and recurrent PE. Major bleeding was defined as fatal bleed, symptomatic bleeding in a critical area or organ, such as intraspinal, intraocular, intracranial, retroperitoneal, intraarticular, pericardial, intramuscular or compartment syndrome, or bleeding causing a decrease in hemoglobin level of $\geq$2 g/dL requiring transfusion of 2 or more units of whole blood or red cells. Minor bleeding was bleeding that did not fit the definition of major bleeding. Some studies used Society of Interventional Radiology criteria to define the bleeding outcome which is essentially similar to the above defined criteria.

Meta-analysis was performed using Cochrane Collaboration Review Manager (version 5.1). Effect size was estimated using random effects model, and mean differences with 95% confidence intervals (CIs) were calculated.

Results

The literature search generated 502 results. Articles that did not report USAT use for submassive and massive PE were excluded after title review. We identified 79 articles for abstract and full-text review. Fifty-one studies were excluded after full text review because they did not meet the inclusion criteria of the meta-analysis. Finally, 28 studies were included for quality appraisal and the meta-analysis (Figure 1).[5–32]

A total of 2,135 patients were included in the 28 included studies. Within the total population, 1,430 patients received treatment with USAT. The basic characteristics of the study and population characteristics are listed in Table 1. All included studies used the EKOS EkoSonic device and tissue plasminogen activator for thrombolysis.

The use of USAT was associated with significant improvement in the hemodynamic parameters of interest (Table 2) compared with pretreatment. The Miller Score index was used to estimate thrombus load as well as to assess obstruction and perfusion index. The mean reduction in Miller score after USAT was 10.55 (95% CI −12.98 to −8.12; Figure 2.1). In addition, the Qanadli score was used to quantify pulmonary vascular obstruction. After USAT, the mean reduction in the Qanadli score was 15.64 (95% CI −19.08 to −12.20; Figure 2.2). Both PASP and mPAP post-USAT were reduced by mean differences of 16.69 mm Hg (95% CI −19.73 to −13.65) and 12.13 mm Hg (95% CI −14.67 to −9.59) respectively (Figures 2.3 and 2.4). The RV/LV ratio, predictive of the RV size, decreased by 0.35 (95% CI −0.40 to −0.30) after therapy (Figure 2.5). Cardiac index improved by 0.68 L/m^2 (95% CI 0.49 to 0.87) after therapy (Figure 2.6) as well as tricuspid annular plane systolic excursion by 3.68 mm (95% CI 2.43 to 4.93; Figure 2.7).

These patients were followed for a duration of 30 days to 3 years. Hospital length of stay ranged from 3 days to 21 days on average, whereas intensive unit length of stay varied from 1 to 5 days on average. Adverse outcomes were relatively low in patients who received USAT (Table 3). Forty-two patients who received USAT died during their hospital stay (2.9% of all patients receiving USAT). The total long-term mortality of patients receiving USAT at the time of follow-up was 4.1% (n = 58). Recurrent PE was reported in 3 patients (0.21% of the total USAT population). Major bleeding complications occurred in 5.4% of patients (n = 77), whereas minor bleeding complications were observed in 6.0% (n = 86) of patients.

Discussion

Our study is the largest meta-analysis on the efficacy and safety of using USAT for treatment of massive or submassive PE. Our results suggest that USAT is generally safe and provides rapid and effective improvement in various hemodynamic parameters.

Despite being the gold standard for the treatment for acute massive and submassive PE, standard anticoagulation does not dissolve the established clot. Furthermore, systemic thrombolysis is associated with increased risk of bleeding, including a 2% to 3% increase in intracranial hemorrhage.[3] In fact, in a randomized trial comparing standard anticoagulation and systemic thrombolysis for patients with PE, thrombolysis was associated with a 47% decrease in mortality but also a 2.7 times greater odds of major bleeding and 4.6 times greater odds of intracranial hemorrhage.[33] USAT has evolved to be the most effective technique in terms of balancing the need to rapidly reduce clot burden, while minimizing the risk of major bleeding complications. Overall, USAT allows for direct delivery of a lower total dose of thrombolytic to the clot,[4] thus providing greater efficacy than standard anticoagulation while reducing the risk of bleeding compared with systemic thrombolytic therapy.

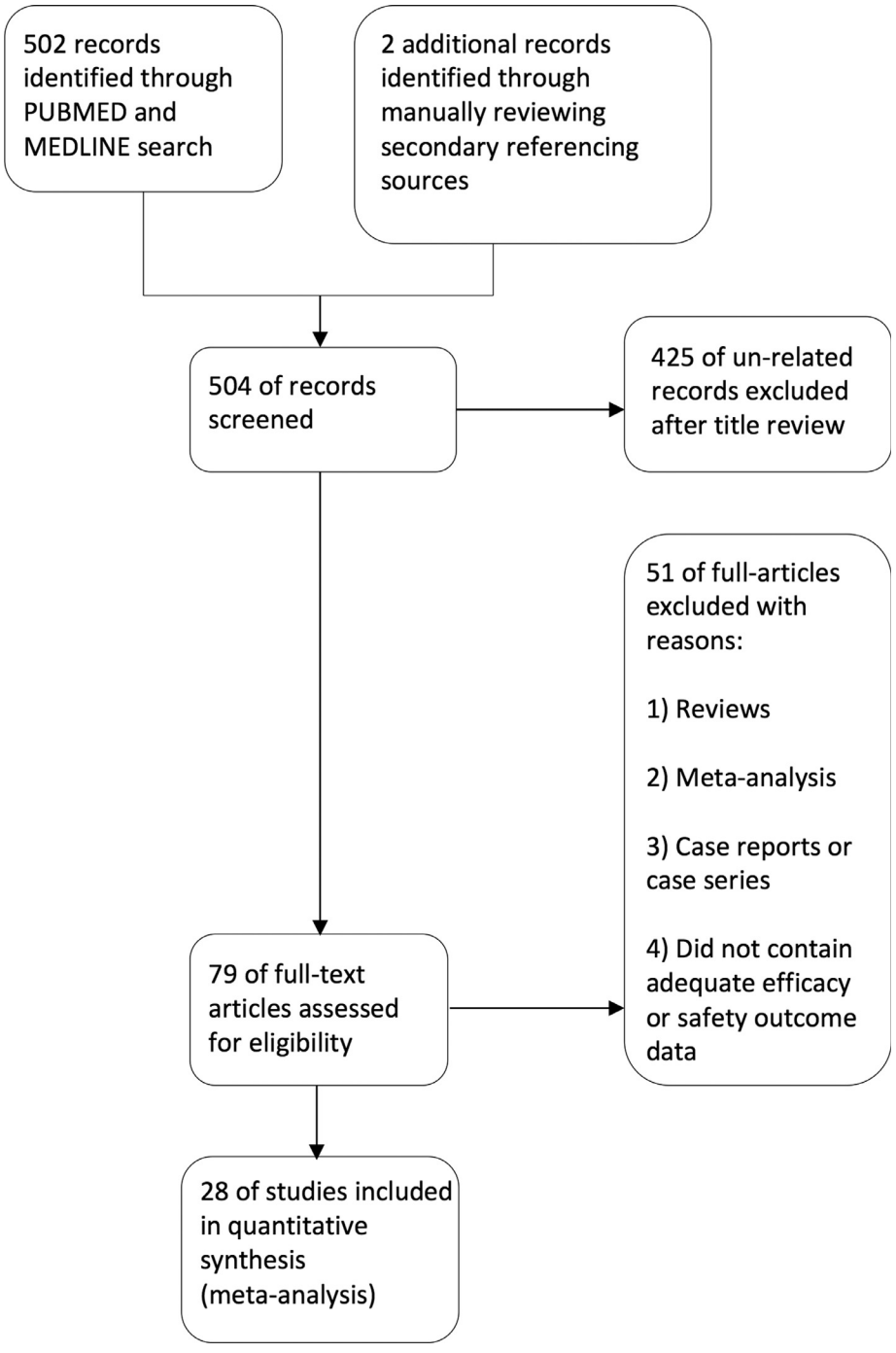

Figure 1. Study flow diagram.

Our meta-analysis study showed significant improvement in hemodynamic parameters including PASP, mPAP, RV/LV ratio, Miller Index Score, Qanadli Score, TAPSE, and cardiac index in patients with acute massive and submassive pulmonary treated with USAT. Our study confirmed the findings of 3 previous meta-analyses by Hayek et al, Mostafa et al, and Kaymaz et al that demonstrated similar improvement in hemodynamic measures after treatment with USAT.[34–36] For efficacy outcomes, Hayek et al observed a significant reduction in the mean pulmonary pressure by 8 mm Hg (95% CI 5.4 to 10.7; p <0.0001), a decrease in the RV/LV ratio by 0.35 (95% CI 0.27 to 0.45) and 10.2 points decrease in Miller score (95% CI 7.2 to 13.2) after therapy with USAT in patients with high-risk PE. Our study demonstrated a larger reduction in mPAP of 12.13 mm Hg (95% CI −14.67 to −9.59) and a similar decrease in RV/LV ratio of 0.35 (95% CI −0.40 to −0.30) and in Miller Score of 10.55 (95% CI −12.98 to −8.12) after therapy.

According to our findings, USAT achieved similar efficacy outcomes to systemic thrombolytic therapy in the treatment for acute massive and submassive PE. The

Table 1
Basic characteristics of included studies

Author	Year	Total N	Male	Age (yrs)	Massive PE	Sub-M PE	tPA dose*	tPA duration* (h)
Kaymaz et al	2018	141	59	61.8 ± 16.2	17	124	36.1 ± 15.3 mg	24.5 ± 8.1
Edla et al	2018	41	22	60.55 ± 12.3	-	-	24 ± 1.1 mg	12
Doheny et al	2018	46	25	56.8 ± 19.4	0	46	18.4 ± 4.7 mg	17.4 ± 5.2
Mohan et al	2018	30	16	50 (17−82)	-	-	0.5−2 mg/h	20.1 ± 6.9
Schissler et al	2018	104	46	53.9 ± 16.9	-	-	0.5−1 mg/h	-
Hennemeyer et al	2018	79	37	59 ± 15.93	9	27	0.5 mg/h	15−22
Avgerinos et al	2017	317	152	58.8 ± 15.8	90	123	23.2 ± 10.7 mg	17.0 ± 9.1
Graif et al	2017	24	11	53.3 ± 18	3	21	0.59 ± 0.23 mg/h	23.9 ± 8.8
Lee et al	2017	91	46	55.4 ± 15.3	3	88	1 mg/h	18.3 ± 5
Ozcinar et al	2017	38	-	64.5 (24−89)	-	-	21.6 ± 4.9 mg	15
Fuller et al	2017	27	11	54 ± 15.5	0	27	1 mg/h	12
Liang et al	2016	63	7	60.6 ± 12.8	2	34	27.5 ± 12.9 mg	12−24
Kaymaz et al	2016	75	36	60.8 ± 16.1	15	60	35.4 ± 16.7 mg	24
Piazza et al	2015	150	73	59 ± 16.1	31	119	23.7 ± 2.9 mg	24
McCabe et al	2015	53	119	57.6 ± 16.2	0	53	24.6 ± 9 mg	15.9 ± 3.0
Nykamp et al	2015	45	-	58.5 ± 6.2	-	-	30.5 (14−66) mg	14.2
Bagla et al	2015	45	25	56.5 ± 13.6	0	45	24 mg	12−24
Bloomer et al	2015	137	69	59 (24−91)	17	120	17 (2−48) mg	24
George et al	2015	221	131	52 ± 16	-	-	24 mg	12−24
Kuo et al	2015	101	53	60.3 ± 14.9	28	73	30.3 ± 9.1 mg	23.2 ± 8.1
Dumantepe et al	2014	22	13	53.7 ± 10.5	14	19	23 (16−35) mg	20.5 (14−25)
Kucher et al	2014	59	28	64 ± 15	0	59	10.5 ± 0.6 mg	15
Kennedy et al	2013	60	35	61 ± 16	12	48	35.1 ± 11.1 mg	19.6 ± 6
Quintana et al	2013	10	6	58 (23−80)	8	2	18 (7−38) mg	20.8
Engelberger et al	2013	52	33	65 ± 14	14	38	20.1 ± 3.7 mg	15.4 ±1.2
Engelhardt et al	2011	24	11	60 ± 16	5	19	33.5 ± 15.5 mg	19.7 ± 8.1
Lin et al	2009	25	5	59 ± 17	11	0	17.2 ± 2.4 mg	17.4 ± 5.2
Chamsuddin et al	2008	10	5	54.2 (31−85)	10	0	0.9 ± 0.2 mg/h	24.8 ± 8.4

N = Total number of patients; yrs = years old; PE = pulmonary embolism; Sub-M = submassive; tPA = tissue plasminogen activator; mg = milligrams; h = hours.
* Mean values reported.

Tenecteplase Italian Pulmonary Embolism trial showed that in patients with intermediate risk PE, weight adjusted intravenous tenecteplase reduced the RV/LV ratio from 1.36 at baseline to 1.04 over 24 hours (mean absolute reduction 0.32).[2] Our study demonstrated a similar reduction in RV/LV ratio post-USAT (−0.35). In the Moderate Pulmonary Embolism Treated with Thrombolysis trial, patients with moderate PE treated with low-dose systemic thrombolysis were found to have a reduction in PASP from 50 ± 6 mm Hg on admission to 34 ± 7 mm Hg 48 hours after therapy (net reduction of 16 mm Hg). Our meta-analysis showed a similar reduction in mean PASP of 16.69 mm Hg (95% CI −19.73 to −13.65) in patients treated with USAT.[37] Overall, these data suggest that treatment of acute massive and submassive PE with USAT is effective in improving hemodynamic parameters and reducing signs of RV strain.

Furthermore, our meta-analysis confirmed that USAT is a relatively safe procedure with low mortality and major bleeding. We found that 2.9% of all patients receiving USAT died during their hospital stay. The overall long-term mortality at the time of follow-up of these patients was 4.1%. Recurrent PE was reported in 3 patients (0.21% of the total USAT population). Major and minor bleeding complications occurred in 5.4% and 6.0% of patients after

Table 2
Summary of hemodynamic parameters and efficacy outcomes before and after thrombolysis

Parameters	$n^{(\#)}$	$N^{(\#\#)}$	Mean difference (95% CI) random effects model	P(Q)*	$I^{2(\S)}$	$\tau^{2(\|\|)}$
Mean PASP (mm Hg)	16	947	−16.69 (−19.73 to −13.65)	<0.00001	80.0%	29.51
Mean PAP (mm Hg)	13	602	−12.13 (−14.67 to −9.59)	<0.00001	84.0%	18.43
RV/LV Ratio	16	886	−0.35 (−0.40 to −0.30)	<0.00001	80.0%	0.01
Cardiac Index (L/min/m^2)	3	109	0.68 (0.49 to 0.87)	0.61	0.00%	0.00
TAPSE (mm)	2	200	3.68 (2.43 to 4.93)	0.14	54.0%	0.45
Miller Index Score	7	332	−10.55 (−12.98 to −8.12)	<0.00001	91.0%	10.90
Qanadli Score	3	230	−15.64 (−19.08 to −12.20)	0.18	46.0%	3.65

PASP = pulmonary artery systolic pressure; PAP = pulmonary pressure; RV = right ventricular; LV = left ventricular; TAPSE = tricuspid annular plane systolic excursion; $N^{(\#)}$ = number of studies reporting the outcome; $N^{(\#\#)}$ = number of patients included in the analysis; $^{(\S)}I^2$ = index for degree of heterogeneity; $\tau^{2\,(\|)}$ = tau-squared measure of heterogeneity; P(Q)* = P-wave for Cochran's Q-score for heterogeneity.

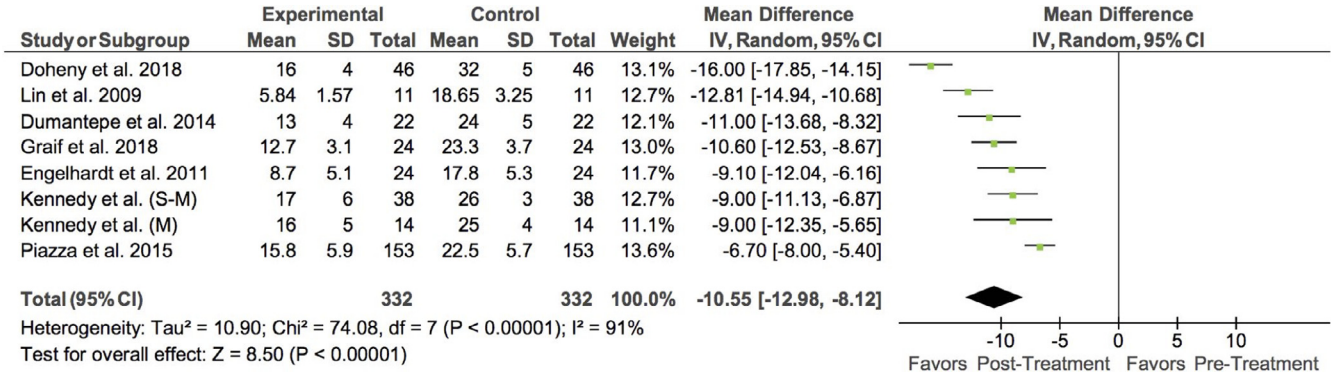

Figure 2.1. Forrest plot of Miller Score.

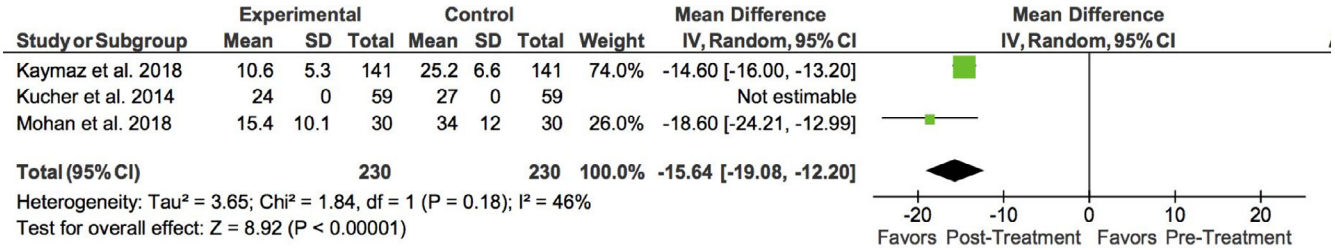

Figure 2.2. Forrest plot of Qanadli Score.

therapy, respectively. The mortality rate is similar but the risk of major bleeding is significantly lower in patients treated with USAT, compared with those reported from previous large controlled studies on systemic thrombolysis, such as the Pulmonary Embolism Thrombolysis trial (PEITHO).[38] The PEITHO trial compared tenecteplase plus heparin with placebo plus heparin in normotensive patients with intermediate-risked PE, and reported a 2.4% 30-day mortality in the tenecteplase group and a high major bleeding risk of 11.5% in the tenecteplase group. Additionally, in the Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis trial by Kuo et al, 100 consecutive patients with massive and submassive PE were administered standard catheter-directed thrombolysis (CDT) in 64% of the patients and USAT in the remaining 36% of patients, and reported zero major or intracranial bleeding events.[24]

The significantly lower bleeding risk in patients receiving USAT is likely attributed to the shortened duration of treatment and smaller total dose of thrombolytic therapy used. Most studies included in our meta-analysis used a total dose of 24 mg of thrombolytic over 12 or 24 hours for patients

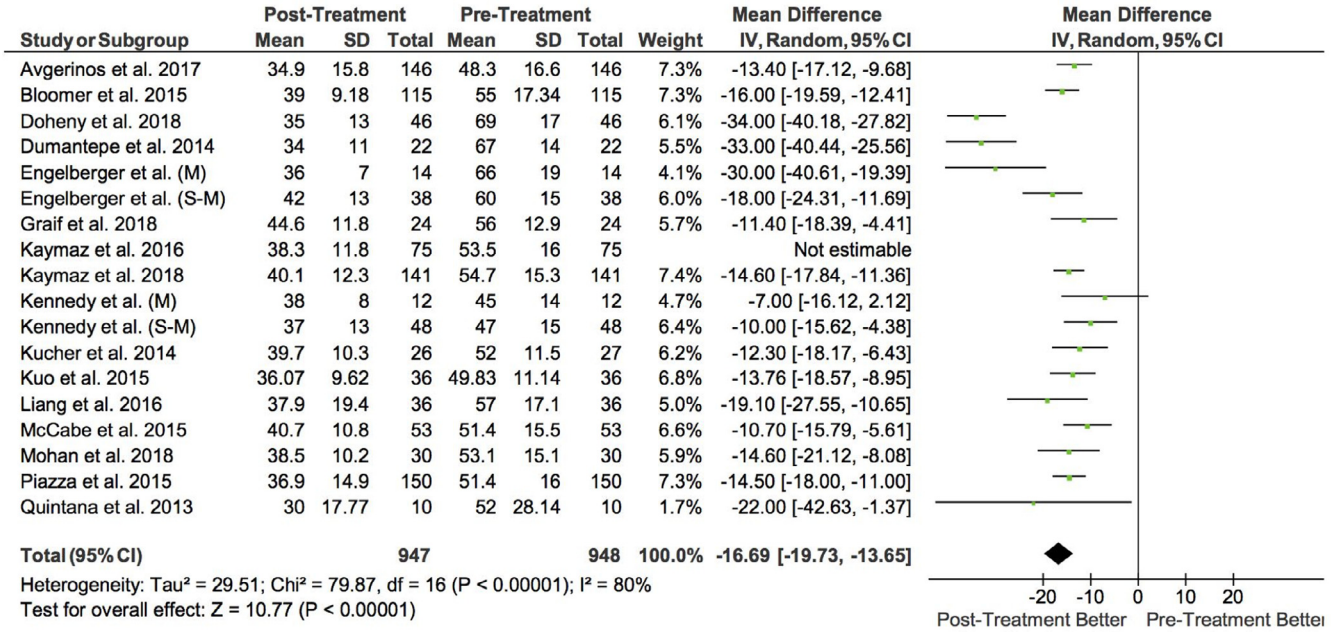

Figure 2.3. Forrest plot of pulmonary artery systolic pressure.

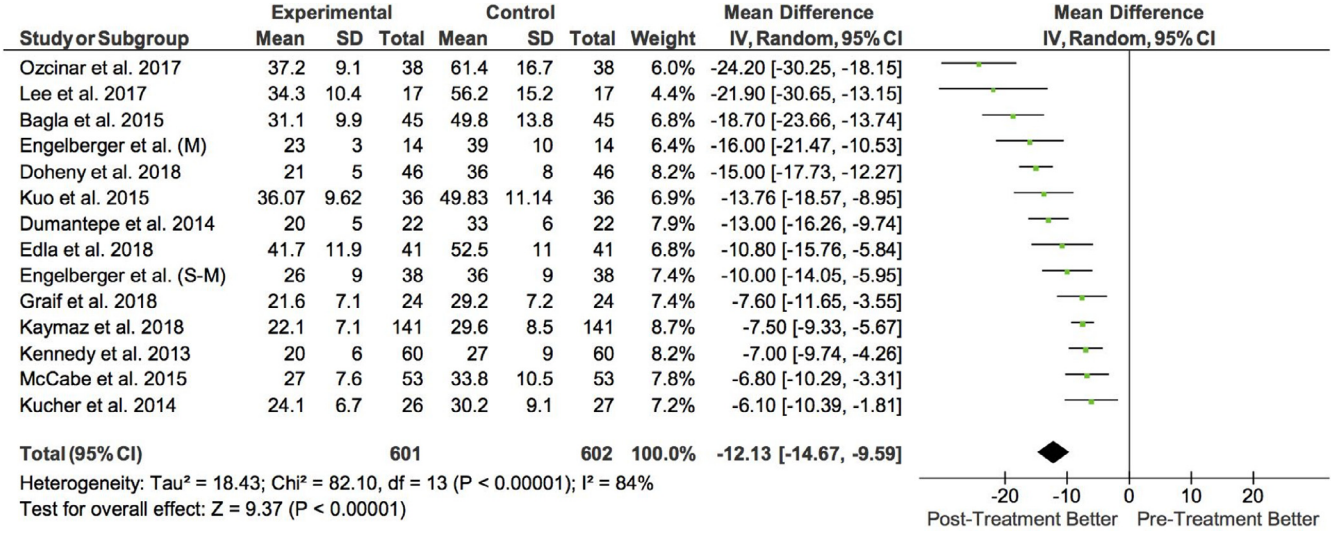

Figure 2.4. Forrest plot of mean pulmonary artery pressure.

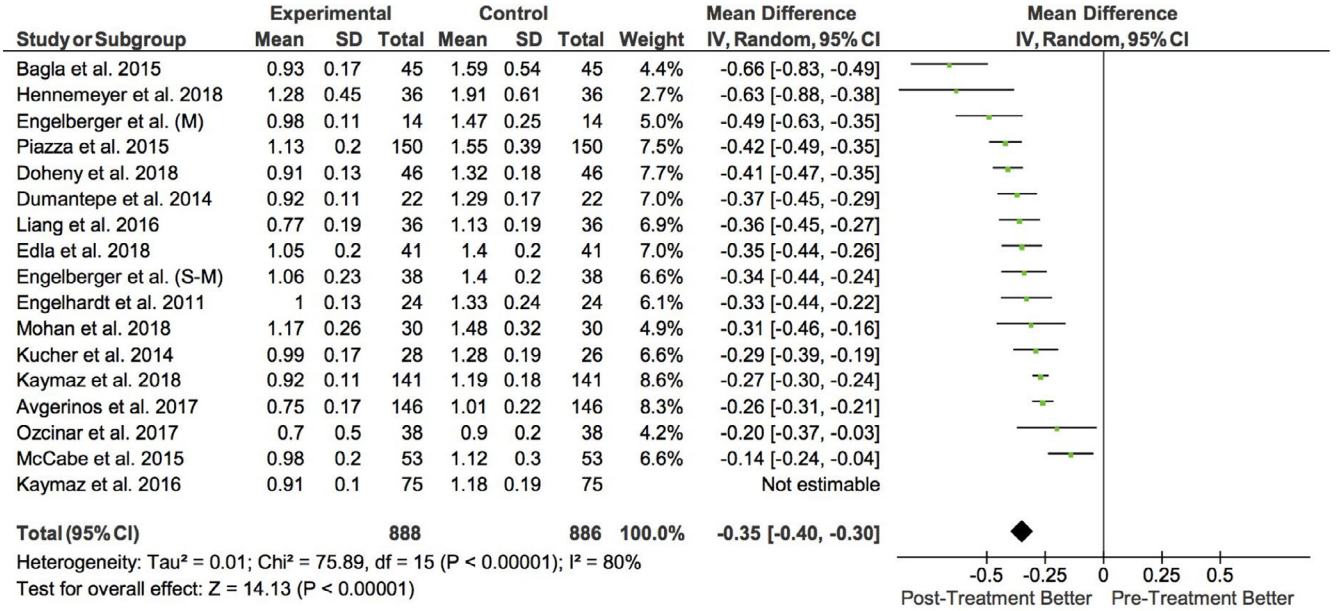

Figure 2.5. Forrest plot of right ventricular to left ventricular diameter ratio.

with bilateral and unilateral PE. A study by Raabe et al showed that the average time to complete lysis using USAT delivered via EKOS system was 24.7 hours as compared with 53.4 hours with conventional CDT reported by the National Venous Thrombosis registry.[39] In the PEITHO trial, patients who were assigned to undergo fibrinolysis received a single weight-based intravenous bolus given over a period of 5 to 10 seconds of fibrinolytic agent tenecteplase, with the dose ranging from 30 mg to 50 mg depending on body weight.[38]

A decreased duration of thrombolytic therapy also leads to early hemodynamic improvement, likely contributing to the low mortality rate in patients treated with USAT. The

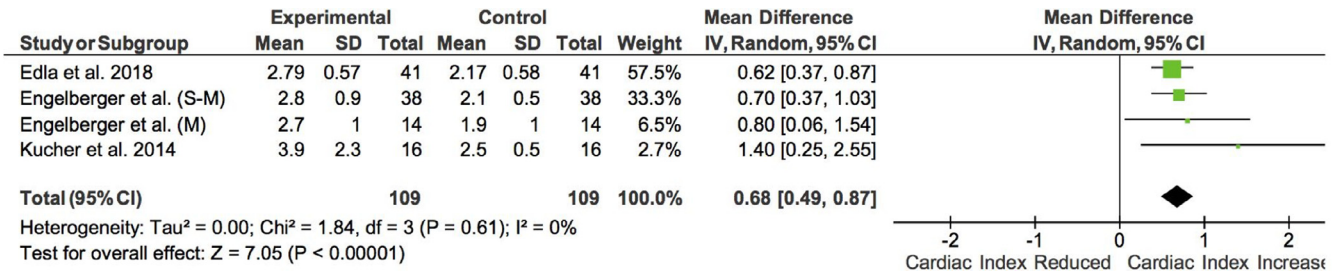

Figure 2.6. Forrest plot of cardiac index.

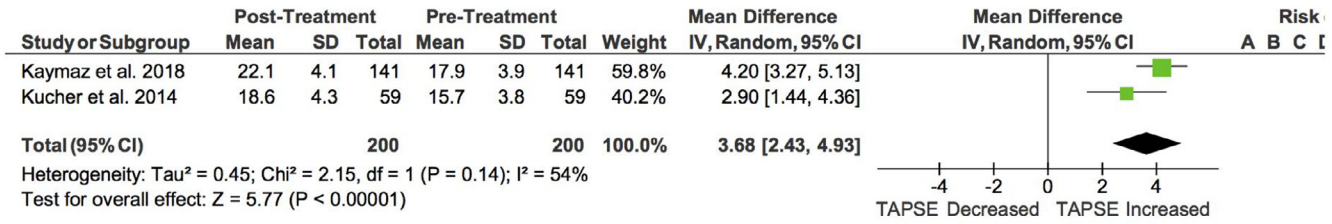

Figure 2.7. Forrest plot of tricuspid annular plane systolic excursion.

Table 3
Summary of safety outcomes in patients treated with USAT (n = 1,430)

Outcomes	Number of patients affected (%)
In-hospital mortality	42 (2.9%)
Long-term mortality	58 (4.1%)
Major bleeding	77 (5.4%)
Minor bleeding	86 (6.0%)
Recurrent PE	3 (0.21%)

USAT = ultrasound assisted catheter directed thrombolysis; N = total number of patients; % = percentage of patients affected.

long-term benefit of early hemodynamic improvement in patients with massive and submassive PE has been well established. It has been shown that there is persistent improvement in the echocardiographic parameters over a long period of time after hemodynamic improvement is achieved.[40] This response is seen more favorably in patients who underwent thrombolysis. Therefore, theoretically early improvement in hemodynamic measures will potentially reduce the incidence of chronic pulmonary hypertension.

Of note, USAT also has several advantages over mechanical techniques such as embolectomy. The mechanical techniques pose a risk of vessel wall injury, valvular damage, and pulmonary embolization as the result of vessel wall contact and clot fragmentation. USAT avoids these potential complications by increasing permeability of the clot by nonmechanical means. Although rare, some of the potential complications of USAT include perforation of cardiovascular structures, cardiac tamponade, pulmonary hemorrhage, and distal thrombus embolization. A limitation to our meta-analysis is that the studies included were mostly retrospective and nonrandomized studies. We used patients as self-controls for treatment effect of USAT, without a direct comparison to systemic fibrinolysis. In addition, as inherent to meta-analyses of nonrandomized data, our conclusions are subject to publication and selection bias. However, since there are a limited number of published studies and most are nonrandomized, we believe that aggregate data meta-analysis in such situations can provide a better effect size estimate with a larger pooled sample size.

In conclusion, USAT therapy has favorable outcomes on hemodynamic parameters and lower bleeding complications in patients with massive or submassive PE. In the future, randomized, controlled clinical trials with comparable standard anticoagulation, systemic fibrinolysis, and CDT would be critical in expanding our knowledge of how ultrasound-facilitated, catheter-directed, low-dose fibrinolysis should be used in patients with acute PE.

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