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Meta-analysis

A Meta-analysis of Standard Versus Ultrasound-Assisted Catheter-Directed Thrombolysis in the Management of Acute Pulmonary Embolism

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ABSTRACT

Background: Standard catheter-directed thrombolysis (SCDT) harnesses the therapeutic benefit of systemic thrombolytics while minimizing bleeding complications in patients presenting with pulmonary embolism (PE). Ultrasound-assisted catheter-directed thrombolysis (USAT) theoretically improves upon SCDT by disrupting fibrin and increasing the surface area exposed to thrombolytic agent. However, it is unclear if this translates into improved outcomes.

Methods: A systematic search of prior publications comparing SCDT and USAT in patients with intermediate or high-risk PE was conducted. Primary outcomes of interest were bleeding events, ICU and hospital length of stay. Secondary outcomes included changes in pulmonary artery systolic pressure (PASP), mean pulmonary artery pressure (mPAP), and right ventricle to left ventricle diameter (RV/LV) ratio. Studies that lacked comparison groups were excluded. Bias assessments were performed using the Cochrane tools for randomized and nonrandomized studies. Data was collated utilizing the Cochrane Review Manager software, and all analyses assumed random effects.

Results: Our search yielded 7 observational studies and 1 randomized control trial. The studies included a total of 543 patients who underwent either SCDT (n = 273) or USAT (n = 270) for intermediate or high-risk PE. The synthesized analysis showed no significant differences in bleeding between the groups. There were no differences in ICU or hospital lengths of stay, changes in PASP, or mPAP. Reductions in RV/LV ratio were greater with SCDT (mean difference, −0.16; 95% CI, −0.27 to −0.06; $P = .003$).

Conclusions: In comparison to SCDT, USAT did not result in improved clinical or hemodynamic outcomes in patients presenting with PE. Results were limited by heterogeneity among the included studies.

Introduction

Acute pulmonary embolism (PE) affects more than 200,000 people in the United States each year and leads to significant morbidity and mortality.[1] Acute right ventricular failure with a resultant decrease in the cardiac index is the primary cause of death in these patients. Rapid resolution of PE with systemic thrombolytic therapy is frequently used in hemodynamically unstable patients presenting with high-risk PE.[2] Systemic thrombolytics also prevent hemodynamic decompensation in patients with intermediate-risk PE but at the expense of increasing the risk of major hemorrhage and stroke in this population.[3]

Standard catheter-directed thrombolysis (SCDT) has emerged as a targeted treatment modality that infuses thrombolytic agents directly into the thrombus through a multiside-hole catheter. This approach harnesses the therapeutic benefit of thrombolytics while minimizing the required dose and mitigating bleeding complications. Ultrasound-assisted catheter-directed thrombolysis (USAT) theoretically improves SCDT by utilizing a high-frequency ultrasound transducer to disrupt fibrin interactions and increase the surface area of the thrombus exposed to the lytic agent.[4,5] Clinical trials have demonstrated that USAT has lower rates of bleeding complications and significantly improves the right ventricle–to–left ventricle diameter (RV/LV) ratio and pulmonary artery (PA) pressures compared to systemic anticoagulation alone in patients with intermediate-risk PE.[6]

Although multiple studies have demonstrated the safety and efficacy of USAT, it remains unclear whether this more costly treatment approach provides additional clinical benefit compared with SCDT. Several retrospective analyses have demonstrated similar outcomes between the 2

Abbreviations: ICU, intensive care unit; MD, mean difference; PA, pulmonary artery; PASP, pulmonary artery systolic pressure; PE, pulmonary embolism; RV/LV, right ventricle–to–left ventricle diameter; SCDT, standard catheter-directed thrombolysis; USAT, ultrasound-assisted catheter-directed thrombolysis.

Keywords: catheters; meta-analysis; pulmonary embolism; thrombolysis; ultrasound.

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modalities.[7-13] However, many of these studies focus on hemodynamic parameters and are not statistically powered to detect superiority in clinically relevant end points such as bleeding complication rates and lengths of stay. This review synthesizes the current literature into a higher-powered analysis that primarily seeks to determine whether USAT results in improved rates of bleeding complications and decreased lengths of stay than SCDT in patients presenting with high-risk and intermediate-risk PE. Our study also compares changes in PA pressures and RV/LV ratio to determine whether there are any significant differences in hemodynamic outcomes for SCDT and USAT in this population.

Methods

Search strategy and study selection

This meta-analysis was conducted in compliance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. A PRISMA checklist is included in the supplemental material (Supplemental Figures S1 and S2). A detailed protocol and search strategy were prospectively registered at PROSPERO, an international database of prospectively registered systematic reviews and meta-analyses (ID# CRD42021277367). Four authors (E.S.B., M.T.P.M., P.V.D., and A.D.) performed a comprehensive search of PubMed, Embase, Scopus, and Google Scholar (each author performed a search in 1 of the 4 databases) to identify articles comparing SCDT and USAT. Queries were limited to articles published from inception to August 29, 2021, and utilized the following key phrases: "pulmonary embolism," "catheter thrombolysis," "catheter-directed thrombolysis," "catheter-directed therapy," "EKOS," "ultrasound-assisted thrombolysis," "ultrasonic therapy," "ultrasound-potentiated fibrinolysis," "ultrasound-accelerated thrombolysis," and "standard versus ultrasound-assisted thrombolysis."

Once duplicate articles were removed, the remaining articles were divided among the same 4 authors to be screened for inclusion. The following eligibility criteria were used to select studies to be included in the analysis: (1) included adult patients with acute high-risk (with hemodynamic instability) or intermediate-risk (with evidence of elevated cardiac biomarkers or right ventricle dysfunction) pulmonary embolism, (2) compared SCDT and USAT using the Endovascular system EKOS EkoSonic (EKOS Corp), and (3) reported at least 1 of the clinical or hemodynamic outcomes of interest. Articles were excluded if they met the following criteria: (1) violated ethical policy, (2) included patients aged <18 years, (3) review articles or meta-analyses, (4) case reports and case series with less than 10 patients, (5) conference abstracts, and (6) articles not written in the English language. Citations identified through the initial database search were then divided among the authors to screen for eligibility for inclusion. Articles that obviously included irrelevant material or met the exclusion criteria based on information presented in the titles and abstracts were excluded. The remaining full-text articles were first assessed by each of the 4 authors (E.S.B., M.T.P.M., P.V.D., and A.D.) independently and then discussed as a group to reach a final consensus on the articles to be included. Final decisions regarding which articles to include were guided by the quality of the study design and methods.

Data extraction and outcome measurements

Selected studies were divided among a group of 4 authors (E.S.B., M.T.P.M., P.V.D., and A.D.) who extracted information on baseline study characteristics, procedural characteristics (thrombolytic dose, infusion time, and catheters used), and outcome measurements. The extracted data from each study were combined into a spreadsheet and subsequently verified the remaining 3 authors in the group. One selected study[13] was published by the authors in this group who had access to additional data from the study's patient cohort. We incorporated some of these additional data on baseline patient characteristics and invasive PA pressure measurements into our analyses.

The primary outcomes of interest were major and minor bleeding events (defined by the Global Utilization of Streptokinase and tissue plasminogen activator for Occluded Arteries criteria), intensive care unit (ICU) length of stay, and hospital length of stay. Emphasis was placed on clinical outcomes as these are crucial to informing management decisions, and the current literature does not include studies powered to detect differences in clinical end points. The secondary outcomes included a change in the pulmonary artery systolic pressure (PASP), a change in the invasive mean PA pressure, and a change in the RV/LV ratio (measured with computed tomography or echocardiographic images). The secondary outcomes were selected because they are important surrogate markers for outcomes in patients with acute PE and have been reported frequently in the literature. A study was included in a given analysis if it reported adequate data on the outcome of interest and provided a clear explanation of the methods used for data collection.

Data synthesis and statistical analysis

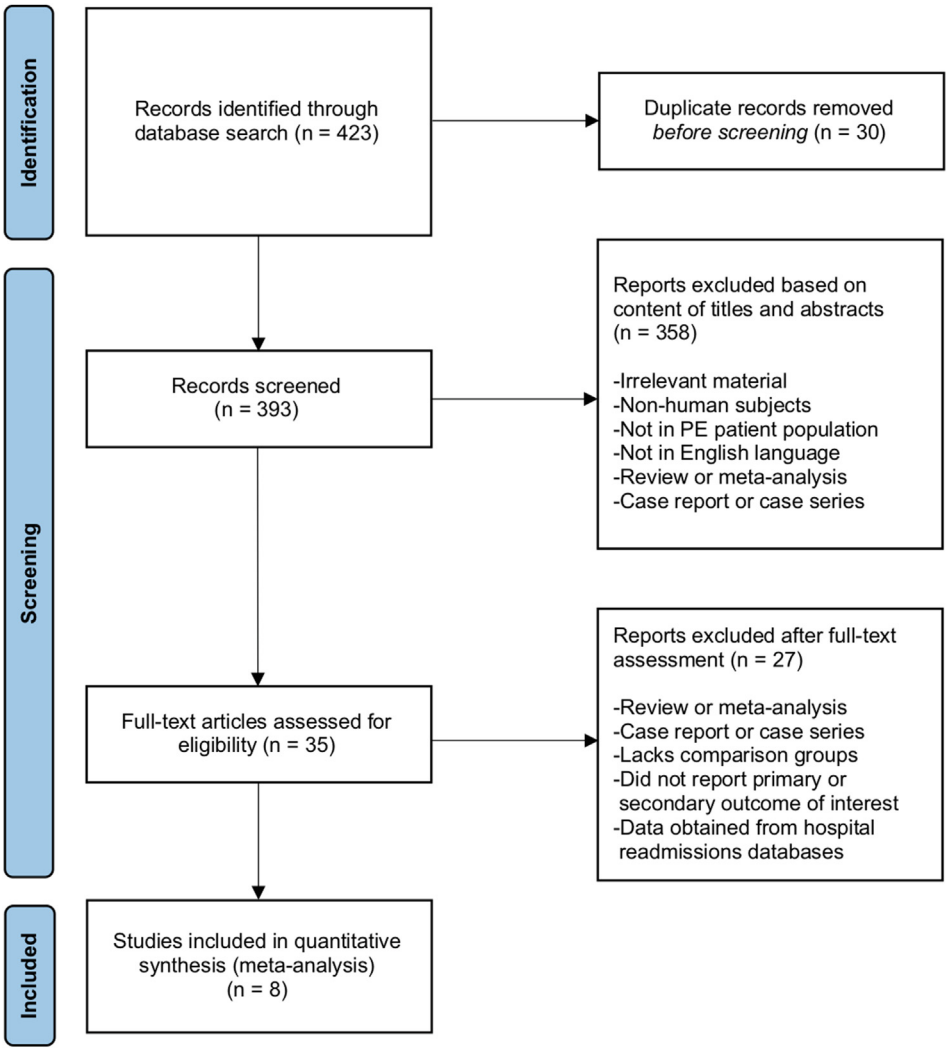
Verified data were input into the Cochrane Review Manager (RevMan) version 5.3 software (The Cochrane Collaboration) for data synthesis. Odds ratios (ORs) and mean differences (MDs) between the 2 cohorts, USAT and SCDT, were estimated using the Der-Simonian Laird random-effects model, which accounted for differences between the included studies' designs and methods. A corresponding 95% CI was set, and 2-sided P values of $<.05$ were considered statistically significant. Forest plots to display results were generated using the RevMan software.

The risk of bias for each of the included studies was discussed by a group of 3 authors (E.S.B., M.T.P.M., and A.D). The results of this discussion were formally characterized using the Cochrane ROBINS-I (Risk of Bias in Nonrandomized Studies of Interventions) tool for nonrandomized studies and the Cochrane RoB2 (risk of bias in randomized trials) tool for the randomized controlled trial included. Funnel plots were constructed using the RevMan software for each level of analysis for the graphic assessment of publication bias. Heterogeneity was assessed using the Higgins and Thompson I^2 statistics, with I^2 values of 25%, 25% to 75%, and 75%, corresponding to low, moderate, and high levels of heterogeneity, respectively. Sensitivity analyses were performed excluding all outcomes from the single randomized controlled trial to determine whether the results were consistent among the nonrandomized studies.

Results

Search results

Initial database searches yielded 393 citations after duplicates were removed. After screening titles and abstracts for the exclusion criteria, 358 articles were removed. After the remaining 35 full-text citations were reviewed by each author independently, an additional 26 articles were excluded. The studies removed at this level of screening commonly did not include the appropriate comparison groups, did not include adequate numbers of patients, or did not report any of the primary or secondary outcomes of interest. The study by Beyer et al[14] met all eligibility criteria, but concerns were raised as the study had



Central Illustration.
Flow diagram of systematic search. Process for the systematic literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement.

obtained data from a Nationwide Readmissions Database. The group reached a consensus to exclude this article from our analyses because these methods deviated significantly from those of the other observational studies included. The remaining 8 articles were included in the final analysis. A flow chart summarizing this process is shown in the Central Illustration.

Study characteristics

The 8 studies included in this meta-analysis comprise 7 observational studies (5 single centers and 2 multicenter) and 1 randomized controlled trial by Avgerinos et al,[15] the Standard vs. Ultrasound-Assisted Catheter Thrombolysis for Submassive Pulmo- nary Embolism (SUNSET sPE) trial. Together, the studies include data from 543 patients, with 273 patients in the SCDT treatment cohort and 270 in the USAT treatment cohort. Of the patients who received SCDT, 23.1% had high-risk PE and 76.9% had intermediate-risk PE. Of the patients who received USAT, 8.9% had high-risk PE, and 91.1% had intermediate-risk PE. The mean age of patients included in the study was 58.7 ± 14.1 years, and 50.8% were men. A summary of the included studies is shown in Table 1.[7-13,15] The baseline patient characteristics and comorbid medical conditions reported for each study population are summarized in Table 2.[7-13,15]

There was substantial variability in the procedural characteristics between the individual studies. Lin et al[8] and Graif et al[10] reported both lower thrombolytic doses and lower infusion times for USAT. Allen et al[13] also reported lower infusion times for USAT. Conversely, Rao et al[11] reported significantly lower thrombolytic doses for SCDT, and Rothschild et al[12] reported significantly lower infusion times for SCDT. The synthesis of these data showed no significant differences in reported thrombolytic doses (MD, −0.68; 95% CI, −3.85 to 2.48; $P = .67$) or infusion times (MD, 1.36; 95% CI, −0.65 to 3.37; $P = .19$) between the combined groups (Figure 1). Heterogeneity was high for both the thrombolytic dose ($I^2 = 80\%$) and infusion time ($I^2 = 79\%$).

Among the observational studies included in the analyses, 3 were determined to have serious overall risks of bias. Lin et al[8] reported significant differences in procedure protocols throughout the study period. These differences may have had a significant effect on the

Table 1. Summary of studies included in the meta-analysis.

Reference, year	Group	No. of patients	Massive	Submassive	Age, y	Male sex	Thrombolytic dose, mg	Infusion time, h
Lin et al,[8] 2009	SCDT	14/25 (56)	14/25 (56.0)	0/25 (0.0)	62.0 ± 16.0	7/14 (50.0)	25.4 ± 5.3	26.7 ± 8.6
	USAT	11/25 (44)	11/25 (44.0)	0/25 (0.0)	59.0 ± 17.0	5/11 (45.5)	17.2 ± 2.4	17.4 ± 5.2
Kuo et al,[7] 2015	SCDT	63/92 (69)	28/92 (27.7)	35/92 (38.0)	60.3 ± 14.9	53/92 (52.5)	25.6 ± 11.7	20.8 ± 11.5
	USAT	29/92 (31)	0/92 (0.0)	29/92 (31.5)			30.3 ± 9.1	23.2 ± 8.1
Liang et al,[9] 2016	SCDT	27/63 (42.9)	6/63 (9.5)	21/63 (33.3)	57.1 ± 17.5	10/27 (37.0)	23.2 ± 13.7	23.7 ± 13.9
	USAT	36/63 (57.1)	2/63 (3.2)	34/63 (54.0)	60.6 ± 12.8	17/36 (47.2)	27.5 ± 12.9	15.4 ± 5.3
Graif et al,[10] 2017	SCDT	36/60 (60.0)	5/60 (8.3)	31/60 (51.7)	59.1 ± 11.4	20/36 (55.6)	33.6 ± 13.9	30.4 ± 12.6
	USAT	24/60 (40.0)	3/60 (5.0)	21/60 (35.0)	53.3 ± 18.0	11/24 (45.8)	27.1 ± 11.3	23.9 ± 8.8
Rao et al,[11] 2019	SCDT	33/70 (47.1)	6/70 (8.6)	25/70 (35.7)	57.4 ± 12.7	15/33 (45.5)	24.7 ± 12.2	13.3 ± 3.9
	USAT	37/70 (52.9)	5/70 (7.1)	34/70 (48.6)	65.2 ± 12.8	22/37 (59.5)	25.1 ± 6.3	13.3 ± 3.2
Rothschild et al,[12] 2019	SCDT	36/98 (36.7)	4/98 (4.1)	32/98 (32.7)	60.4 ± 15.7	17/36 (47.2)	28.7 ± 14.0	22.9 ± 14.5
	USAT	62/98 (63.3)	3/98 (3.1)	59/98 (60.2)	57.7 ± 15.4	30/62 (48.4)	34.4 ± 17.3	31.5 ± 17.3
Allen et al,[13] 2021	SCDT	23/54 (42.6)	0/54 (0.0)	23/54 (42.6)	60.0 ± 2.3	11/23 (47.8)	23.0 ± 0.8	12.0 ± 0.4
	USAT	31/54 (57.4)	0/54 (0.0)	31/54 (57.4)	59.0 ± 2.5	15/31 (48.4)	20.0 ± 0.8	11.0 ± 0.5
Avgerinos et al,[15] 2021	SCDT	41/81 (50.6)	0/81 (0.0)	41/81 (50.6)	55.0 ± 14.0	20/41 (48.8)	18.0 ± 7.0	14.0 ± 5.0
	USAT	40/81 (49.4)	0/81 (0.0)	40/81 (49.4)	52.0 ± 13.0	23/40 (57.5)	19.0 ± 7.0	14.0 ± 6.0
Combined	SCDT	273/543 (50.3)	63/273 (23.1)	210/273 (76.9)	58.7 ± 13.6	100/273 (47.6)	25.3 ± 10.8	20.5 ± 10.1
	USAT	270/543 (49.7)	24/270 (8.9)	246/270 (91.1)	58.1 ± 13.9	123/270 (51.0)	25.1 ± 9.8	19.7 ± 8.2

Data are presented as either the number of patients within a group followed by the percentage of the treatment cohort in parentheses or as the mean ± SD. Data on age and patient sex were not available for the different treatment groups in the study by Kuo et al.[7] This study was excluded from the calculation of the combined mean age and percentage of male patients. The number of patients included in each study ranged from 25 to 101, with most studies including over 50 patients. Approximately half of the participants were treated with SCDT, and the other half were treated with USAT. Most patients included in the analysis presented with intermediate-risk pulmonary embolism with the evidence of elevated cardiac biomarkers or right ventricle dysfunction but no hemodynamic instability.
SCDT, standard catheter-directed thrombolysis; USAT, ultrasound-assisted catheter-directed thrombolysis.

results because more patients in the SCDT cohort received treatment early in the study period before protocol changes were implemented. Additionally, the interventions for each comparison group were performed by different groups of physicians (interventional radiology for SCDT and vascular surgery for USAT). Because of these deviations from the intended interventions, this study was determined to be at a serious risk of bias. Similarly, Liang et al[9] reported changes in procedure protocols throughout the study period and were designated as being at serious risk of bias. The study by Graif et al[10] was also found to pose serious risks for bias because it reported more frequent follow-up visits for patients in the SCDT group, which likely led to the administration of higher doses of thrombolytics and may have affected the study's findings. The remainder of the included studies showed moderate risks of bias related to differences in baseline characteristics because of the retrospective nature of the studies. The study by Kuo et al[7] was also at an increased risk of bias because of the inclusion of multiple subgroup analyses. The results of the risk of bias assessments categorized by confounding domains are summarized in Supplemental Figure S3. The assessment of the randomized controlled trial raised some concerns for increased risk of bias largely because of the lack of blinding of groups collecting outcomes measurements. Funnel plots were generated and visually assessed for symmetry to evaluate the risk of bias for the studies included in each analysis and are included in Supplemental Figure S4.

Table 2. Baseline patient characteristics.

Reference, year	Group	Prior VTE	Malignancy	CHF	HTN	Smoking[a]	CAD	Diabetes	Obesity[b]/BMI	Troponin[c]
Lin et al,[8] 2009	SCDT (14)	n/a	2 (14.3)	n/a	n/a	2 (14.3)	n/a	n/a	1 (7.1)	n/a
	USAT (11)	n/a	1 (9.1)	n/a	n/a	4 (36.4)	n/a	n/a	2 (18.2)	n/a
Kuo et al,[7] 2015	SCDT (63)	n/a	12 (11.9)	n/a	21 (20.8)	n/a	5 (5.0)	14 (13.9)	50 (49.5)	n/a
	USAT (29)									
Liang et al,[9] 2016	SCDT (27)	12 (44.4)	3 (11.1)	1 (3.7)	n/a	n/a	4 (14.8)	n/a	n/a	21 (77.8)
	USAT (36)	9 (25.0)	7 (19.4)	2 (5.6)	n/a	n/a	4 (11.1)	n/a	n/a	29 (80.6)
Graif et al,[10] 2017	SCDT (36)	n/a	3 (8.3)	n/a	25 (69.4)	4 (11.1)	n/a	11 (30.6)	25 (69.4)	21 (58.3)
	USAT (24)	n/a	4 (16.7)	n/a	11 (45.8)	1 (4.2)	n/a	4 (16.7)	15 (62.5)	17 (70.8)
Rao et al,[11] 2019	SCDT (33)	n/a	n/a	n/a	n/a	9 (27.3)	n/a	6 (18.2)	33 ± 6	12 (36.4)
	USAT (37)	n/a	n/a	n/a	n/a	11 (29.7)	n/a	8 (21.6)	38 ± 15	9 (24.3)
Rothschild et al,[12] 2019	SCDT (36)	6 (16.7)	1 (2.8)	n/a	25 (69.4)	2 (5.6)	n/a	11 (30.6)	22 (61.1)	0.92 ± 1.75
	USAT (62)	9 (14.5)	2 (3.2)	n/a	36 (58.1)	5 (8.1)	n/a	11 (17.7)	46 (74.2)	0.34 ± 0.39
Allen et al,[13] 2021	SCDT (23)	5 (21.7)	4 (17.4)	2 (8.7)	7 (30.4)	3 (13.0)	0 (0.0)	5 (21.7)	40 ± 11	0.61 ± 0.69
	USAT (31)	10 (32.3)	4 (12.9)	3 (9.7)	9 (29.0)	4 (12.9)	3 (5.6)	6 (19.4)	36.1 ± 11	0.87 ± 1.3
Avgerinos et al,[15] 2021	SCDT (41)	13 (31.7)	2 (4.9)	1 (2.4)	19 (46.3)	11 (26.8)	5 (12.2)	n/a	37 ± 9	0.73 ± 1.75
	USAT (40)	8 (20.0)	2 (5.0)	1 (2.5)	15 (37.5)	7 (17.5)	4 (10.0)	n/a	37 ± 8	0.24 ± 0.39

A summary of baseline characteristics and pertinent comorbid medical problems for the participants included in each study is shown. Data are presented as either the number of patients within a group followed by the percentage of the treatment cohort in parentheses or the mean ± SD. The information reported in each study was highly variable. None of the individual studies reported differences in the reported baseline characteristics between treatment groups.
BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; HTN, hypertension; n/a, not applicable; VTE, venous thromboembolism.
[a] Includes patients who were current or former smokers at the time of the study. [b] Includes patients with class I, II, or III obesity at the time of the study. [c] Represented as troponin elevation based on the normal values defined by the study institution or as mean troponin value.

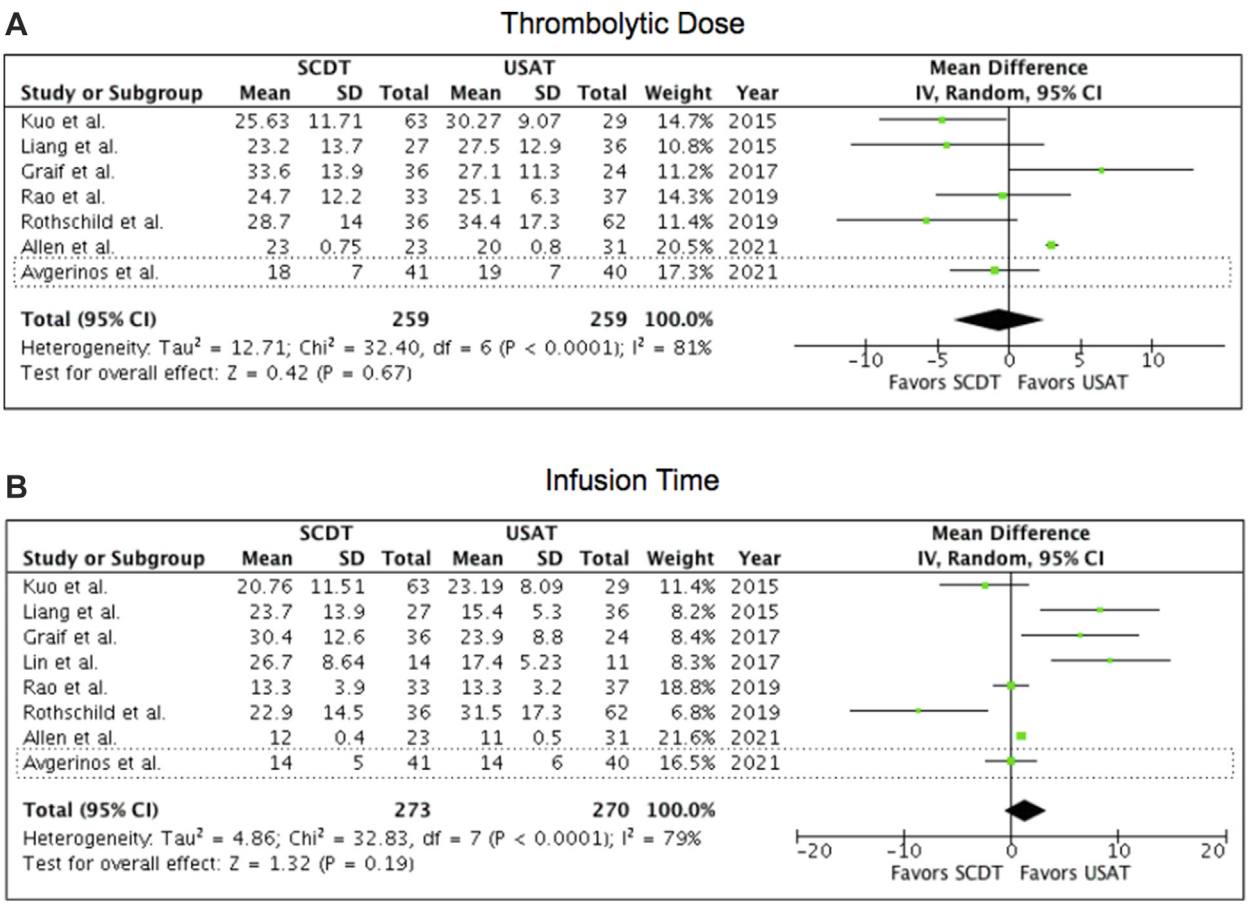


Figure 1.

Thrombolytic dose and infusion time. Forest plots demonstrate (**A**) thrombolytic dose and (**B**) infusion time for standard catheter-directed thrombolysis (SCDT) and ultrasound-assisted catheter-directed thrombolysis (USAT). The green square indicates the mean difference for each study calculated by subtracting the average thrombolytic dose (in milligrams) or average infusion time (in hours) in the USAT group from that of the SCDT group. Horizontal lines indicate the 95% CI. Data obtained from the randomized control trial are shown within the dotted line box. The combined MD and 95% CI for each analysis are represented by a black diamond. There was marked variability between the procedure details of each study, but the combined groups had no significant differences in mean thrombolytic dose or infusion time for SCDT and USAT.

Outcomes

Major and minor bleeding complications were the most commonly reported outcomes among the selected studies. One observational study by Lin et al[8] reported significantly lower rates of major bleeding in patients treated with USAT. The study by Avgerinos et al[15] and 4 of the observational studies reported similar rates of bleeding outcomes between the groups, but the overall rates of these complications were low.[9,11,12] Taken individually, these studies lack statistical power to detect differences between the 2 cohorts. However, the results of our combined analyses show that there were no significant differences in the rates of Global Utilization of Streptokinase and tissue plasminogen activator for Occluded Arteries major bleeding events (OR, 0.66; 95% CI, 0.18-2.45; $P = .53$) or minor bleeding events (OR, 0.67; 95% CI, 0.22-2.00; $P = .47$) between patients treated with USAT and SCDT (Figure 2). Heterogeneity was low for both major ($I^2 = 0\%$) and minor ($I^2 = 0\%$) bleeding.

In 1 single-center observational study, Liang et al[9] reported significantly longer lengths of hospital stay for patients in the SCDT group. By contrast, Avgerinos et al[15] showed significantly longer lengths of stay for patients in the USAT group. Neither study found differences in ICU length of stay. Rothschild et al[12] showed no differences in an overall hospital or ICU length of stay. Our synthesis showed that there were no differences in the mean ICU length of stay (MD, 0.03; 95% CI, −1.64 to −1.71; $P = .97$; Figure 3) or mean hospital length of stay (MD, 0.14; 95% CI, −3.89 to 4.17; $P = .95$; Figure 3). However, the heterogeneity was high for both the ICU length of stay ($I^2 = 52\%$) and hospital length of stay ($I^2 = 86\%$).

Data from Allen et al[13] showed significantly greater reductions in invasive mean PA pressures among patients treated with SCDT. Rao et al[11] and Rothschild et al[12] did not find any differences in invasive PA pressure measurements between the 2 groups. Our synthesis showed that reductions in PASP (MD, 0.32; 95% CI, −4.63 to 5.28; $P = .90$) and mean PA pressure (MD, −2.21; 95% CI, −5.19 to 0.76; $P = .14$) were similar between the 2 groups (Figure 4). Heterogeneity was moderate for both PASP reduction ($I^2 = 38\%$) and mean PA pressure reduction ($I^2 = 22\%$). Avgerinos et al[15] reported significantly greater reductions in the RV/LV ratio among patients in the SCDT group. However, the authors note that the study was not powered to detect differences in this outcome. Two observational studies[12,13] found no significant differences in the RV/LV ratio between the groups. In our combined analysis, reductions in the RV/LV ratio were greater among patients treated with SCDT than with USAT (MD, −0.16; 95% CI, −0.27 to −0.06; $P = .003$; Figure 4). Heterogeneity was low for RV/LV ratio reduction ($I^2 = 0\%$).

Our initial analysis included data from multiple observational studies and 1 randomized control trial. We performed a series of sensitivity

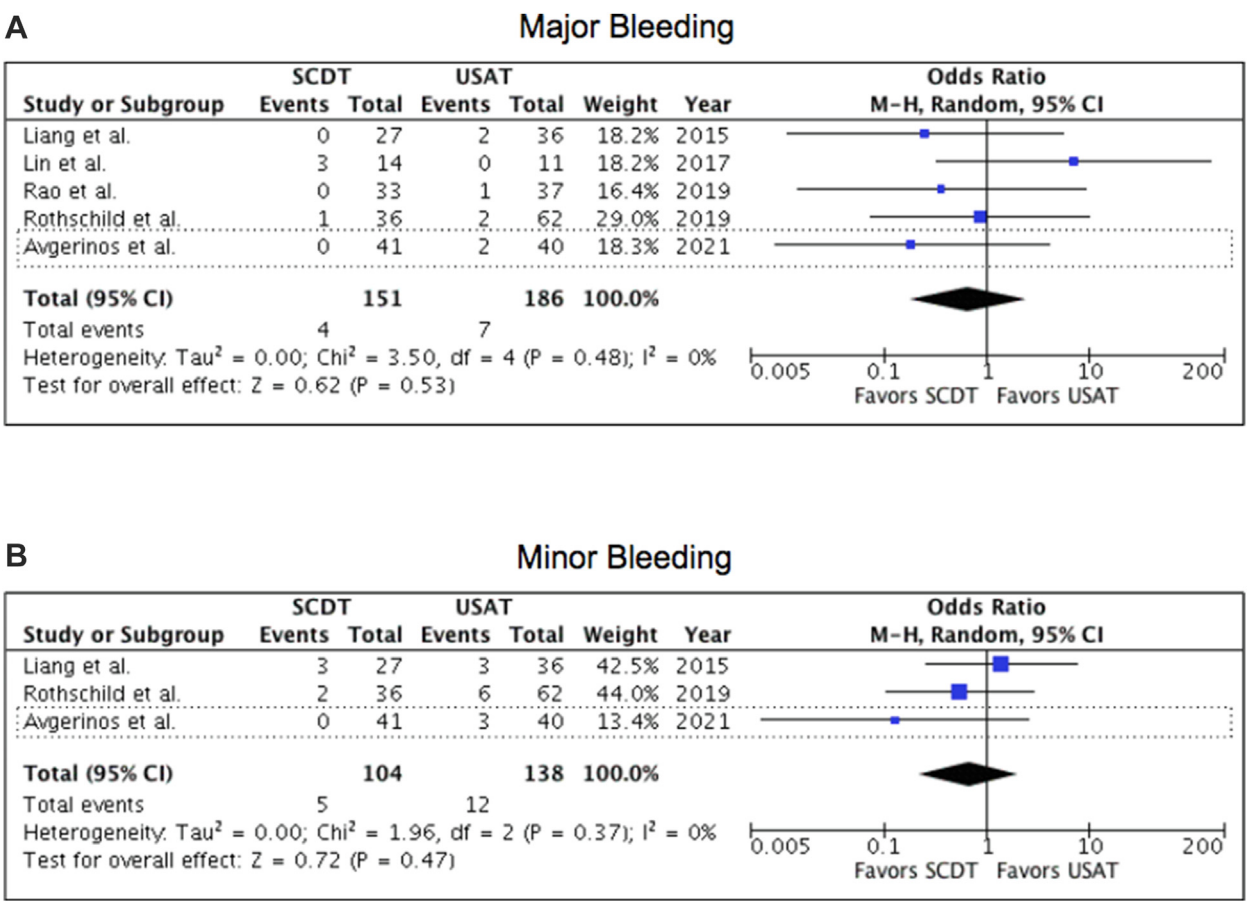


Figure 2.
Bleeding events. Forest plots comparing rates of (**A**) major and (**B**) minor bleeding events. The green square indicates the odds ratio for each study calculated by dividing the incidence of bleeding events in the standard catheter-directed thrombolysis (SCDT) group divided by the incidence of bleeding events in the ultrasound-assisted catheter-directed thrombolysis (USAT) group. Horizontal lines indicate the 95% CI. Data obtained from the randomized control trial are shown within the dotted line box. The combined odds ratio and 95% CI for each analysis are represented by a black diamond. There were no differences in rates of major or minor bleeding events among the studies that reported these outcomes.

analyses to determine whether the results were affected by the exclusion of the randomized trial. The results were unchanged for major bleeding (OR, 0.88; 95% CI, 0.21-3.74; $P = .86$), minor bleeding (MD, 0.86; 95% CI, 0.26-2.81; $P = .81$), ICU length of stay (MD, 0.64; 95% CI, −1.55 to 2.83; $P = .57$), and hospital length of stay (MD, 1.83; 95% CI, −4.24 to 7.90; $P = .55$) (Supplemental Figure S5). However, after removing data from the randomized trial, synthesis of the remaining 2 observational studies that reported change in the RV/LV ratio showed no significant differences between SCDT and USAT (MD, −0.12; 95% CI, −0.26 to 0.02; $P = .09$; Supplemental Figure S5). Heterogeneity remained low for bleeding outcomes and changes in RV/LV ratio but was even greater for ICU and hospital length of stay ($I^2 = 64\%$ and $I^2 = 90\%$).

Discussion

Catheter-directed thrombolysis has emerged as a common treatment modality in patients with acute PE, which harnesses the therapeutic benefit of systemic thrombolysis while mitigating the associated bleeding risks. USAT theoretically improves SCDT by utilizing high-frequency ultrasound to disrupt fibrin interactions and increase the surface area exposed to the thrombolytic agent.[4] The first randomized control trial to test a catheter-based intervention for the management of patients presenting with acute PE was the Ultrasound-Accelerated Thrombolysis of PE (ULTIMA) trial, published in 2014. This study demonstrated that USAT (n = 30) administering 10 mg of tissue plasminogen activator per lung over 15 hours was superior to systemic anticoagulation alone (n = 29) in reducing the RV/LV ratio at 24 hours postintervention in patients presenting with intermediate-risk PE (n = 59). Importantly, the ULTIMA trial found that there was no increased risk of bleeding complications among patients treated with USAT.[14]

The efficacy of USAT was redemonstrated in a larger (n = 150) single-arm trial published in 2015 (Submassive and Massive Pulmonary Embolism Treatment With Ultrasound Accelerated Thrombolysis Therapy [SEATTLE II] study). This study included patients with both high-risk and intermediate-risk PE who underwent USAT using a dose of 24-mg tissue plasminogen activator (either as 1 mg/h for 24 hours through a single catheter for unilateral PE or 1mg/h for 12 hours through 2 drug-delivery devices for bilateral PE). The study found that USAT resulted in significantly greater reductions in PASP, RV/LV diameter ratio, and thrombus burden with minimal major bleeding events and no incidence of intracranial hemorrhage.[6]

Although the ULTIMA and SEATTLE II trials established favorable outcomes in patients treated with USAT, these studies did not include SCDT control groups to determine the specific impact of ultrasound assistance on outcomes. Over the past several years, there have been multiple observational studies that aim to compare the outcomes of

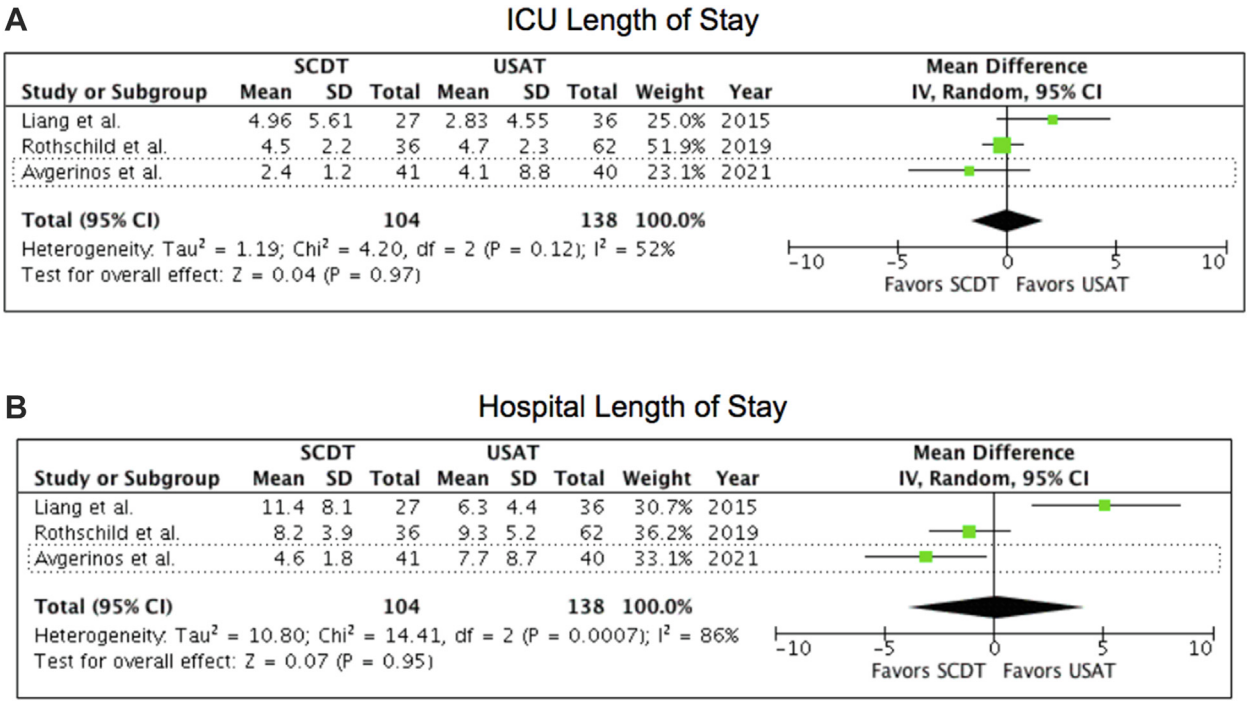


Figure 3.
ICU and hospital length of stay. Forest plots comparing differences in length of (**A**) intensive care unit (ICU) stay and (**B**) overall hospital stay. The green square indicates the mean difference for each study calculated by subtracting the average length of stay (in days) in the ultrasound-assisted catheter-directed thrombolysis (USAT) group from that of the standard catheter-directed thrombolysis (SCDT) group. Horizontal lines indicate the 95% CI. Data obtained from the randomized control trial are shown within the dotted line box. The combined mean difference and 95% CI for each analysis are represented by a black diamond. There were no differences in ICU or overall hospital length of stay between the groups.

SCDT and USAT. In general, most of these studies failed to find significant differences in clinical and hemodynamic end points. Many of these studies were limited by small sample sizes and lacked statistical power.

To our knowledge, the SUNSET sPE trial published in 2021 is the first randomized controlled trial that directly compared outcomes of SCDT with those of USAT. This study included 81 patients with intermediate-risk PE, 41 treated with SCDT, and 40 with USAT. The study demonstrated that there was no significant difference in the primary end point of pulmonary artery thrombus clearance. The authors also reported differences in additional outcomes, including changes in the RV/LV ratio and hospital length of stay favoring SCDT. However, the sample size was also a major limitation, and the trial was not designed to assess these end points.[15]

The EkoSonic EKOS Endovascular System is the only ultrasound catheter approved by the Food and Drug Administration for the treatment of acute PE. The estimated cost is roughly ten-fold that of the standard multihole catheters used for SCDT.[4] This cost is not obviously outweighed by decreased infusion times or lengths of ICU or hospital stay with USAT. The stark difference in cost between these 2 treatment approaches demands evidence for superior clinical outcomes in USAT to justify the considerable increase in expense.

The current meta-analysis seeks to address the disparate findings within the current literature comparing SCDT with USAT in patients with acute PE. The comparison of major and minor bleeding risks showed no significant differences between the groups. Although no differences in ICU or hospital lengths of stay were found, these results should be interpreted with caution because of the significant variation in results across studies. Analysis of hemodynamic parameters, including reductions in invasive systolic and mean PA pressures showed no additional benefit with USAT compared with SCDT alone. Although our initial analyses suggested that SCDT results in greater reductions in the RV/LV ratio, these findings were driven by the single randomized trial and were not reproduced in sensitivity analyses excluding this study. Regardless of whether the randomized trial data are included, our analyses consistently show that reductions in the RV/LV ratio are not greater for the USAT group.

Study limitations

The results of this meta-analysis were limited and should be interpreted with several considerations. First, most studies included were observational and had moderate-to-severe overall risks of bias. In addition, the assessment of heterogeneity for thrombolytic doses and infusion times suggests that there was significant variation in the treatment delivery between the studies, which may have affected the results. Furthermore, the SCDT cohort had a greater proportion of patients categorized as having high-risk PE. Because of the limited availability of data on baseline patient characteristics, we were unable to account for baseline differences between the 2 treatment cohorts in our synthesized analyses.

Conclusion

This meta-analysis addresses the important question of whether USAT results in superior outcomes in the treatment of acute PE compared with SCDT alone. We found no additional benefit in the rates of bleeding complications, although this may be because of the significant variability in the thrombolytic dose and procedure protocols between study centers. Additionally, there was no difference in the mean ICU length of stay or a trend toward shorter hospital stay with SCDT; however, there was a significant heterogeneity in these secondary outcomes. We found no differences in reductions in invasive PA pressures or reductions in RV/LV ratios with USAT. Our results suggest that SCDT may be a more cost-effective treatment approach that produces similar outcomes to USAT. Additional research using consistent treatment protocols is necessary to further investigate differences in outcomes and costs for these 2 treatment modalities.

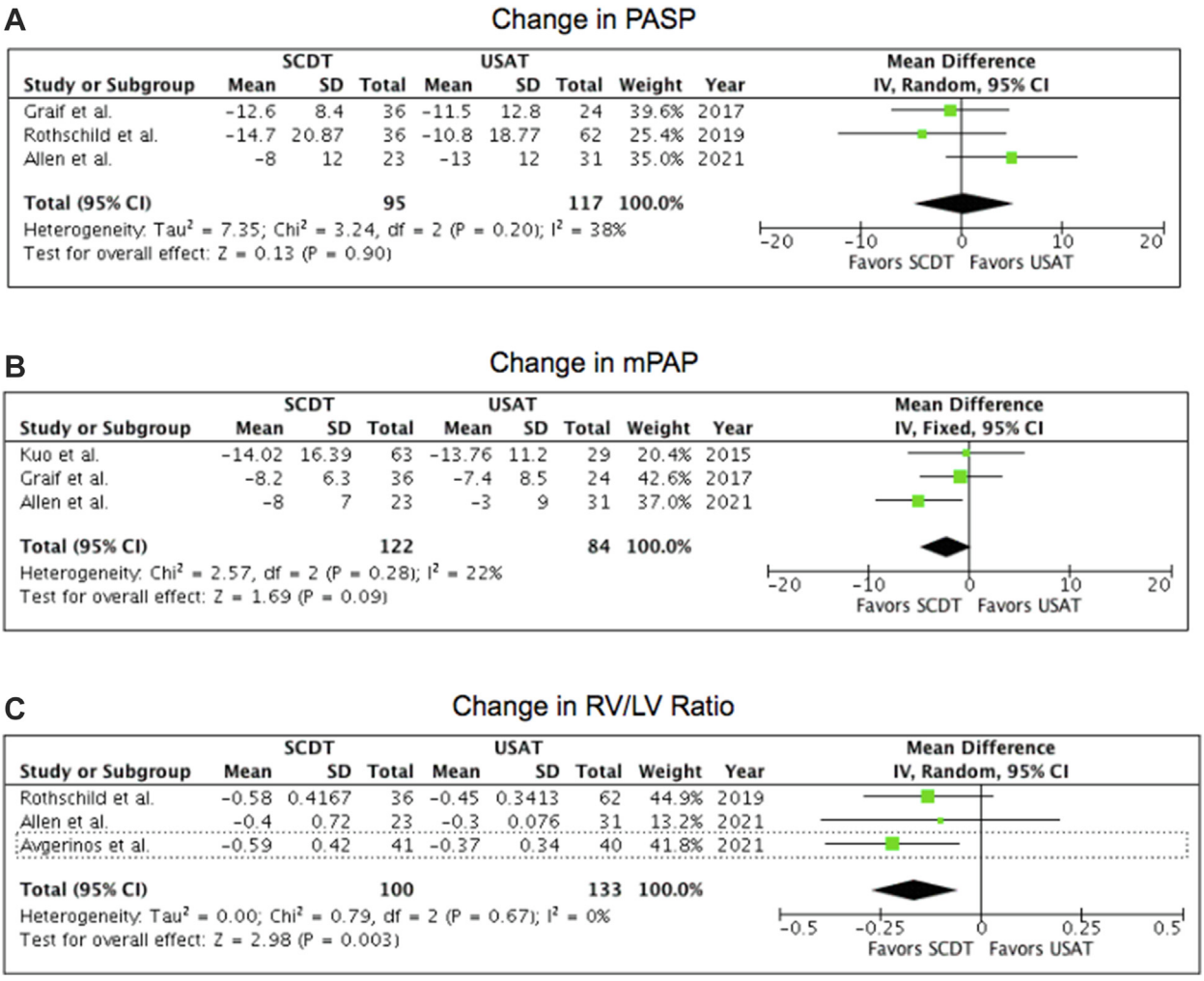


Figure 4.

Hemodynamic parameters. Forest plots comparing changes in hemodynamic outcomes with standard catheter-directed thrombolysis (SCDT) and ultrasound-assisted catheter-directed thrombolysis (USAT). The change in pre and postprocedure parameters was first calculated by subtracting the preprocedure from the postprocedure mean. The mean difference (green squares) was then calculated for each study by subtracting the change in the USAT group from the change in the SCDT group. The 95% CIs are represented by horizontal lines. Data obtained from the randomized control trial are shown within the dotted line box. The combined MD and 95% CI for each analysis are represented by a black diamond. There were no differences in the reduction in (**A**) pulmonary artery systolic pressure (PASP) or (**B**) mean pulmonary artery pressure (mPAP) achieved with either intervention. SCDT resulted in greater reductions in (**C**) right ventricle–to–left ventricle diameter (RV/LV) ratio than USAT.

Data availability

Additional data for changes in RV/LV ratio measurements for the study by Allen et al[13] can be obtained from the corresponding author. The remainder of the data included in this report is available publicly.

Declaration of competing interest

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Ethics statement and patient consent

This research adheres to the relevant ethical guidelines.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2022.100514.

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