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A meta-analysis of efficacy and safety of catheter-directed interventions in submassive pulmonary embolism

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Abstract. – OBJECTIVE: Catheter-directed interventions, such as catheter-directed thrombolysis (CDT), are becoming a popular therapeutic option for patients with hemodynamically stable pulmonary embolism (PE) and right ventricle (RV) dysfunction (submassive PE). We wished to quantitatively assess therapeutic efficacy and safety of catheter-directed interventions in submassive PE.

MATERIALS AND METHODS: PubMed, Embase, Cochrane and Scopus were searched for studies on catheter-directed interventions and submassive PE. Studies reporting data on therapeutic efficacy (RV to left ventricle [RV/LV] ratio, systolic pulmonary artery pressure) and safety outcomes (in-hospital and 30-day mortality rates, major and minor bleeding rates) were retained and assessed.

RESULTS: The final reference sample included 13 publications (11 papers and 2 conference abstracts), collectively enrolling 422 patients with submassive PE. The majority (8/13) studies were retrospective studies. One study was a randomized controlled study. Nine of 13 studies utilized CDT with or without ultrasound-assisted thrombolysis. The post-therapy pooled mean change of RV/LV ratio was -0.3 (95% confidence interval [CI]: -0.42, -0.18), and the pooled mean decrease of pulmonary artery pressure was -19.41 (95% CI: -27.65, -11.17) mm Hg. Safety outcome analysis demonstrated low pooled rates of adverse events (in-hospital mortality: 0.00 [95% CI: 0.00, 0.01]; 30-day mortality: 0.00 [95% CI: 0.00, 0.03]; major bleeding: 0.00 [95% CI: 0.00, 0.02]; minor bleeding: 0.05 [95% CI: 0.01, 0.12]).

CONCLUSIONS: This meta-analysis demonstrates evidence of therapeutic efficacy and low rates of adverse events of catheter-directed interventions in submassive PE.

Key Words:
Pulmonary embolism, Intermittent risk, Submassive, Catheters, Thrombolytic therapy, Thrombectomy, Efficacy, Safety, Adverse effects, Meta-analysis.

Introduction

Pulmonary embolism (PE) is common and can lead to substantial health problems, including fatal outcome. The blockage of pulmonary artery occurs because of occlusion by thrombus or other extravasal objects (tumor, fat emboli, or air). This is associated with changes in systemic hemodynamic which range from extensive to mild. The drop in systemic systolic pressure below 90 mm Hg for longer than 15 min is defined as "massive" or "hemodynamically unstable" PE[1,2]. It is considered an indication for acute administration of systemic thrombolytic therapies[2,3]. In contrast, thrombolysis use is controversial in patients with PE and stable hemodynamics. The latter type of PE is called "submassive". Since patients with submassive PE are considered as being at intermediate risk, submassive PE is also often called "intermediate". The current convention is that patients with this form of PE require only anticoagulant therapy. It is believed that the benefit of thrombolysis use does not outweigh the adverse effects associated with thrombolysis, such as extensive bleeding.

Thrombolysis may be indicated in a subset of patients with submassive PE aggravated by the right ventricular (RV) dysfunction and/or signs of cardiac injury (for example, increased blood troponin levels). RV dysfunction is defined by the end diastolic ratio of right ventricle to left ventricle. At the ratio above 0.9, RV dysfunction is considered pronounced or severe[2], and it is associated with worse patient prognosis.

As mentioned afore, thrombolysis may bring about potentially fatal adverse effects. Not surprisingly, efforts are being undertaken to identify better suitable patients in whom the benefits of thrombolysis administration will outweigh the

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associated risks. An alternative approach is to minimize systemic adverse effects of thrombolytic therapy.

The latter approach also includes the use of catheter-directed thrombolysis (CDT). CDT has gained popularity during the past few years. It allows for administration of a low-dose thrombolytic agent in proximity to thrombus, thereby minimizing the risk of adverse effects of thrombolysis. This technique can be complemented with the ultrasound (ultrasound-assisted catheter-directed thrombolysis, CDT-USAT). In this modification, thrombolytic effects of the drug are thought to be potentiated by ultrasound oscillations. Moreover, catheter-directed intervention may remove the thrombus by fragmentation or aspiration, which does not require supplementary thrombolytic therapies[3].

Clinical experience with catheter-directed interventions is being amassed, and attempts have been undertaken to assess their safety. In the last two years, several qualitative and quantitative assessments of the literature have been published, all of them focusing on some aspect of thrombolysis. Recently, recommendations were summarized[4] for the treatment of submassive pulmonary embolism. In patients with RV dysfunction, the suggestion is to restrict thrombolysis to patients < 75 years old with low risk of bleeding[4]. Another review on this subject[5] stratified patients with submassive PE into “intermediate-low” and “intermediate-high” risk subgroups, based on cardiac biomarkers, presence of RV dysfunction and PE severity. These recommendations aim to better identify patients in whom thrombolytic therapy would pose fewer risks. There have also been quantitative analysis of literature (mostly, of randomized controlled studies) for assessment of risks that are associated with thrombolytic therapy in patients with submassive PE. In total, four meta-analysis have been published on this subject. Cao et al[6] conducted a meta-analysis of randomized controlled studies in submassive PE subjected to systematic thrombolysis or anticoagulant therapy, with the focus on mortality, PE recurrence and bleeding risks. These authors assumed mortality and PE recurrence as indicators of the therapeutic benefit of thrombolytic therapy, whereas bleeding (major or minor) was considered as a safety parameter. As thrombolytic therapy did not show significantly lower rates of mortality or PE recurrence, the authors concluded that thrombolytic therapy was not more beneficial than anticoagulants alone[6]. Out of two safety outcomes, only the rate of minor bleeding was significantly increased[6]. Another meta-analysis by Nakamura et al[7] confirmed that addition of systemic thrombolytic to the treatment of submassive PE does not decrease the risk of mortality or PE recurrence. Still, as found by Nakamura et al[7], thrombolytic therapy appears to decrease the likelihood of clinical deterioration requiring treatment escalation. Two most recent meta-analysis looked at catheter-directed therapies. Mostafa et al[8] analyzed controlled and uncontrolled studies in massive and submassive PE for evidence that CDT-USAT decreases the risk for all-cause mortality or bleeding. This meta-analysis concludes that the therapy appears to be both effective and safe, with the mortality rate more than two times lower than the one reported for systemic thrombolysis[8]. Finally, Tafur et al[9] compared mortality and bleeding between controlled and uncontrolled studies using CDT with *vs.* without CDT-USAT. Again, both studies on massive and submassive PE were pooled in the aggregate evaluation. No additional benefit of CDT with USAT over CDT alone was found[9].

Despite these recent publications, important knowledge gaps remain. Firstly, these meta-analysis used mortality, alone or in composite scores, to gauge the curative effect. It can be argued that with low mortality rates associated with submassive PE, this clinical parameter may not be sensitive enough to assess the clinical benefit. Notably, no study directly analyzed the change in clinical indices, such as improvement of RV/LV ratio. Secondly, the last two meta-analysis[8,9] pooled clinical studies on massive and submassive PE. However, there is an important difference between these two PE types. Massive PE calls for aggressive therapeutic interventions, and there is a clear benefit for thrombolysis administration[5]. In contrast, administration of thrombolytic therapy in submassive PE continues to raise questions[10]. Thus, despite the latest meta-analysis, the uncertainty about thrombolysis in submassive PE remains. Thirdly, while the meta-analysis by Cao et al[6] and Nakamura et al[7] specifically focused on submassive PE, they analyzed systemic thrombolytic therapy and not CDT. Fourthly, these studies did not assess catheter-directed interventions without thrombolysis.

To address these knowledge gaps, we conducted a quantitative assessment of the evidence to date regarding catheter-directed interventions

(CDT, CDT-USAT, catheter-directed fragmentation or aspiration of the thrombus), with the focus on clinical indices of treatment efficacy and safety.

Materials and Methods

Databases and Search Strategy

The search of electronic databases for relevant clinical studies was done by two authors (BingHeng Lou and LiHua Wang) under the guidance of an expert research librarian. Four electronic databases (PubMed, Embase, Cochrane Library and Scopus) were searched for papers and conference abstracts published from January 1, 2015 through May 31, 2016. With the anticipated scarcity of clinical studies, we aimed to include all published papers, case series and/or conference abstracts if they presented data from ≥ 5 patients. The limit on the past decade was because CDT is a relatively recent development for treatment of submassive PE. Excluded were the studies that dealt with massive PE or studies that reported data unseparated for submassive and massive PE. We further excluded review articles, meta-analysis, and textbooks, as well as animal studies, case reports/series or conference abstracts with 1-4 patients. Finally, studies reporting surgical embolectomy and publications presenting clinical guidelines were also excluded.

PubMed was searched as follows. MeSH Term and keyword searches were combined using Boolean operators AND and OR. The initial search was on "pulmonary embolism" as MeSH term, with the filter set to 2005/01/01-2016/05/31 (search #1). Then, we searched for "submassive" OR "intermediate", both either as text words, or word in the title or abstract. The filter was the same as above (search #2). The next step (search #3) combined these searches (#1 and #2). Subsequently, we searched PubMed using "catheters" (MeSH term OR Text Word OR Title/Abstract, filter set to 2005/01/01-2016/05/31; search #4). The final step was to combine all these searches: #3 and #4. This revealed 57 publications.

Embase was searched similarly to PubMed (#1: pulmonary embolism.mp. or lung embolism/; limit 1 to yr = "2005-Current"; #2: [submassive or intermediate].mp.; limit #2 to yr = "2005-Current"; #3: #1 and #2; #4: catheter.mp or catheter/; limit 3 to yr = "2005-Current"; #5: #3 and #4). Thus, we identified 94 published papers and conference abstracts.

Cochrane search identified only 1 publication. The search strategy was as follows: #1: MeSH descriptor: [Pulmonary Embolism] explode all trees; #2: "submassive":ti,ab,kw OR "intermediate": ti, ab, kw; #3: #1 and #2; #4: MeSH descriptor: [Catheters] explode all trees; #5: "catheter":ti, ab, kw; #6: #4 OR #6; #7: #3 and #6.

The final database to search was Scopus. As this database has a different search engine, we decided to include all publications in PE and to manually exclude the publications on massive PE afterwards (#1: TITLE-ABS-KEY (pulmonary embolism) and PUBYEAR > 2004; #2: TITLE-ABS-KEY (pulmonary embolism) and PUBYEAR > 2004; #3: #1 and #2; $4: TITLE-ABS-KEY (catheter) and PUBYEAR > 2004; #5: #3 and #4). Thereby, we found 106 publications.

These searches yielded the total of 258 publications and conference abstracts (Figure 1). Then, we removed 80 duplicated references and 46 references after reviewing of publication titles (Figure 1). Thereby, the pool of selected references was shrunk to 132 publications. Most exclusion was caused because of the focus on a different disease. Also, we excluded review articles. Afterwards, we screened publications and conference abstracts using their synopsises (paper abstracts and conference abstracts itself). This led to the exclusion of further 81 references (Figure 1). At this step, the predominant reason for exclusion was that the publication was either a conference abstract with little or no relevance to our research question, or because it was review article or textbook. The 51 remaining references were analyzed for suitability based on the full text. Thirty-eight references (mostly conference abstracts with insufficient data) were excluded (Figure 1). Thereby, our final reference sample comprised 13 publications (11 papers and 2 conference abstracts; Figure 1). These references were included in the meta-analysis.

Data Extraction and Compiled Indices

Two investigators (BHL and LHW) independently compiled all outcome measures into a predesigned table. In some studies, information had to be inferred from the reported data. This work was done by two investigators independently, and a subsequent discussion was held to reconcile the differences.

The extracted indices comprised study design (prospective or retrospective, controlled or uncontrolled), number of patients with submassive

PE, RV/LV ratio, systolic pressure in the pulmonary artery (mm Hg), Miller index for obstruction of pulmonary artery, length of ICU and hospital stay (days). These were considered the indices of a therapeutic effect. The in-hospital mortality, 30-day mortality, major and minor bleeding events, intracranial bleeding, PE recurrence or other adverse events comprised the safety indices.

Statistical Analysis

Calculations were performed with the help of Stata 12.0 software (StataGroup, College Station, TX, USA).

For aggregate analysis of qualifying studies, we utilized either pooled estimates of mean changes, calculated in Stata using the "metan"-based command, or proportions. Where applicable, the standard deviation (SD) of the difference in means was calculated using the following formula:

$$SD_{difference\ in\ means} = \sqrt{SD^2_{before} + SD^2_{after}\ 2 \times r \times SD_{before} \times SD_{after}}$$

where SD_{before} and SD_{after} respectively represent SD before and after the intervention. The correlation coefficient r was conservatively selected as 0.5[11]. Proportions were calculated as a number of patients experiencing a particular event over the total number of patients in a study. Pooled proportions were calculated using "metaprop", the Stata command for binomial data[12]. Most of the qualifying studies were retrospective studies with no control group. We used the random effects model for meta-analysis. This model accounts for variance between and within the studies. The heterogeneity I^2 test was used to assess heterogeneity of the selected studies.

Results

General Characteristics of Selected Studies

Our final reference sample included 13 publications, and comprised 11 papers and 2 conference abstracts (Figure 1). These publications are characterized in Tables I-II. These Tables respectively represent therapeutic effect and safety indices.

The selected studies collectively enrolled 422 patients with submassive PE. Eight out of 13 studies were retrospective studies[13-20], one study had a mixed prospective and retrospective design (15 patients enrolled prospectively and 30 patients analyzed retrospectively)[21]. There were three prospective studies[22-24], including one randomized controlled study[23]. The randomized controlled study comprised two study arms, CDT-USAT (30 patients) and anticoagulant therapy (heparin only)[23]. Since retrospective studies comprised the majority of our reference sample, we expected to deal with high heterogeneity between studies.

The absolute majority of studies did not have a control group. Thus we relied on pooled estimates of mean changes or proportions, instead of risk ratios. For this reason, from the sole RCT in our analysis only the data from the CDT-USAT arm were included in the analysis.

The summary of administered interventions is listed in Table I. Three works[14,19,24] utilized CDT as intervention, six studies[13,15,17,20,21,23] administered CDT-USAT, and two studies[15,18] administered two variants of CDT (either CDT-USAT or CDT, or CDT in combination with thrombolysis or mechanical thrombectomy). The remaining study[20] used a catheter-directed mechanical intervention. Researches involving thrombolysis most commonly utilized drug administration via bilateral catheter (Table I). The most commonly used drug was recombinant tissue plasminogen activator (Table I). The drug was usually utilized at ~1 mg/hour, sometimes as a bolus administration. The total dose mostly ranged from ~20-24 mg (Table I), and two investigations[14,17] utilized higher doses of thrombolytic drug.

Proportions of patients with elevated troponin levels, the sign of myocardial injury were reported by 5 studies[15,19-21,23].

We next extracted information on pre-defined indices of therapeutic efficacy (RV/LV ratio, systolic pressure in the pulmonary artery, Miller index for obstruction of pulmonary artery, and length of ICU and hospital stay). The most commonly used indices were RV/LV ratio and systolic pressure in the pulmonary artery. Thus, six studies[13-15,20,21,23] assessed RV/LC ratio as indicator of intermediate risk of PE, eleven studies[13-15,20,21,23] used different measures of systolic pressure in pulmonary artery. By contrast, other parameters showing clinical efficacy (Miller index, and length of ICU and hospital stay) were used less frequently (respectively, by 2, 3 and 5 studies). Therefore, in the aggregate analysis were used changes RV/LV ratio and pulmonary artery pressure as indices of therapeutic efficacy.

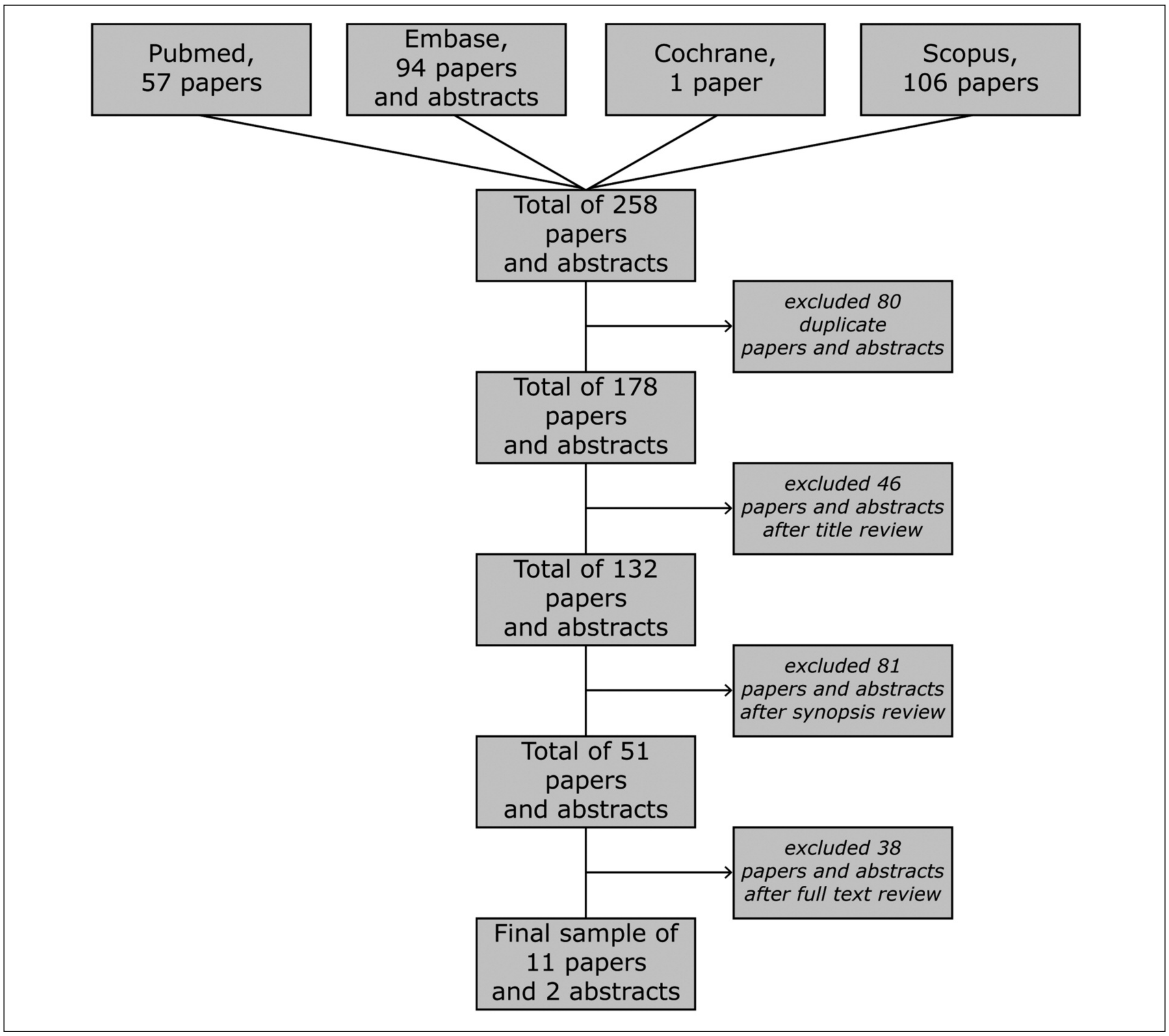

Figure 1. Reference sample identified by PubMed, Embase, Cochrane and Scopus searches. The search strategy is presented according to PRISMA guidelines.

As for safety outcomes, we extracted the following indices from the selected studies: in-hospital mortality, 30-day mortality, major or minor bleeding episodes, intracranial bleeding events, PE recurrence or other reported adverse events. These were utilized as rates (that is, proportions of patients experiencing a particular adverse event about the total number of patients with submassive PE). The in-hospital and 30-day mortality rates, and major and minor bleeding rates were reported by most studies. These outcomes were pooled in the aggregate analysis. In contrast, outcomes such as PE recurrence rate, which were reported only by a small number of studies and predominantly as "absent", were described qualitatively in the subsequent text.

Therapeutic Efficacy

As discussed in the introduction, we decided to analyze the therapeutic efficacy of catheter-based interventions in submassive PE based on cardiovascular parameters. The above characterization of selected papers demonstrated that RV/LV ratio and systolic pressure in pulmonary artery were the most frequently used indices of therapeutic efficacy. Thus we utilized these two indices in our aggregate analysis.

Six studies[13-16,21,23] reported initial RV/LV ratio. The pooled mean of reported ratio was 1.30 (95% confidence interval 1.12, 1.49), which fits well the definition of submassive PE with RV dysfunction (> 0.9). Patients with such RV dysfunction are considered at intermediate risk. One

Table I. Summary of analysed publications: indices of therapeutic effect.

First author, journal year	Study description	Number of patients with submassive PE	CDT details	Thrombolysis details	RV/LV ratio before *vs.* after	Systolic pressure in pulmonary artery, mm Hg, before *vs.* after
Dilektasli et al, Med Sci Monit 2016	Retrospective	9	CDT	Total of 24 (10) mg tPA*	N/A	Decrease by 20 (9-30)[†]
Bagla et al, J Vasc Interv Radiol 2015	Prospective/ retrospective	45 (15 prospective/ 30 retrospective) uncontrolled study	CDT-USAT	Unilateral catheter (3 patients): total of 24 mg tPA; bilateral catheter (42 patients): total of 12 mg tPA per each catheter	1.59 (0.54) *vs.* 0.98 (0.2)*	49.8 (13.76) *vs.* 31.1 (9.9)*
Dumantepe et al, J Card Surg 2015	Prospective uncontrolled study	25	Percutaneous mechanical thrombectomy	Not applicable	0.98 (0.13) *vs.* 0.83 (0.06)*	46.77 (7.7) *vs.* 22 (3.6)*
Engelberger et al, Eur Heart J 2015	Retrospective study	38	CDT-USAT	Unilateral catheter (6 patients), bilateral catheter (32 patients); total of 20.1 (3.7) mg tPA, administered with or without initial bolus*	1.4 (0.2) *vs.* 1.06 (0.26)*	60 (15) *vs.* 42 (13)*
Kuo et al, Chest 2015	Prospective uncontrolled study	73	CDT including thrombolysis for 72 patients, CTD with mechanical thrombectomy	0.5-1 mg/hour tPA or 100,000 International Units/hour . urokinase Total dose N/A[#]	N/A	N/A[#]
McGabe et al, Am J Cardiol 2015	Retrospective study	53	CDT-USAT	Total of ~20 mg tPA	1.12 (0.3) *vs.* 0.98 (0.2)*	51.4 (15.5) *vs.* 40.7 (10.8)*
Al-Hakim et al, J Thorac Imaging 2014	Retrospective study	18	CDT-USAT (12 patients), CDT (6 patients)	Total of 20 mg tPA (CDT-USAT) or total of 23.7 mg tPA (CDT)	N/A	-5.6 (-1.9, -9.6)[‡]
Dumantepe et al, J Card Surg 2014	Retrospective study	14	CDT-USAT	N/A[#]	N/[#]	N/A[#]
Gaba et al, Am J Roentgenol 2014	Retrospective study	19	CDT	Total of 57 (31) mg tPA*	1.5 (0.3)* *vs.* N/A[#]	30 (10) *vs.* 20 (8)*
Kucher et al, Circulation 2014	Randomized controlled study (CDT-USAT *vs.* heparin only)	30 (CDT-USAT group)	CDT-USAT	Unilateral catheter (4 patients): total of 10.5 (0.6) mg tPA; bilateral catheter (26 patients): total of 20.8 (3.0) mg tPA*	1.28 (0.19)* *vs.* 0.99 (0.17)[#]	N/A[¶]
Ruzsa et al, J Am Coll Cardiol 2014	Prospective uncontrolled study	26	CDT	N/A	N/A	60.78 (18.67) *vs.* 19.7 (12.36)*
Kennedy et al, J Vasc Interv Radiol 2013	Retrospective study	48	CDT-USAT	N/A[#]	N/A	47.0 (15) *vs.* 37.13 (13)*
Engelhardt et al, Thromb Res 2011	Retrospective study	24	CDT-USAT	Total of 33.5 (15.5) mg tPA, administered with initial bolus*	N/A[#]	N/A[#]

Footnote: N/A: not available; tPA: tissue plasminogen activator. Data are presented as means or means (SD) [marked with "*"] or median (range) [marked with "&"]. [†]Median (interquartile range). [#]Findings not presented separately for submassive and massive PE. [¶]Finding presented as indirect, surrogate measure. [‡]Mean (95% conference interval).

Table II. Summary of analysed publications: safety indices.

First author, journal year	Number of patients with submassive PE	In-hospital mortality	30-day mortality	Number of major bleeding episodes	Number of minor bleeding episodes	Number of intracranial bleeding episodes	PE recurrence
Dilektasli et al, Med Sci Monit 2016	9	1	1	1	3	N/A	1
Bagla et al, J Vasc Interv Radiol 2015	45	0	0	2	4	0	0
Dumantepe et al, J Card Surg 2015	25	0	N/A	0	2	N/A	N/A
Engelberger et al, Eur Heart J 2015	38	N/A	N/A	N/A	N/A	N/A	N/A
Kuo et al, Chest 2015	73	2	0	0	N/A	0	N/A
McGabe et al, Am J Cardiol 2015	53	0	N/A	N/A	N/A *	0	0
Al-Hakim et al, J Thorac Imaging 2014	18	N/A	N/A	1	0	N/A	N/A
Dumantepe et al, J Card Surg 2014	14	0	N/A	N/A	N/A	N/A	N/A
Gaba et al, Am J Roentgenol 2014	19	1	1	0	0	1	0
Kucher et al, Circulation 2014	30	0	0	0	3	0	0
Ruzsa et al, J Am Coll Cardiol 2014	26	N/A	1	N/A	N/A	N/A	N/A
Kennedy et al, J Vasc Interv Radiol 2013	48	0	0	1	N/A	N/A	N/A
Engelhardt et al, Thromb Res 2011	24	0	N/A	N/A	N/A	N/A	N/A

Footnote: N/A: not available (either not reported, or reported without separation for submassive and massive PE). *Bleeding episodes reported, by not classified into major or minor bleed.

study[14] enrolled patients with both submassive and massive PE, and reported a combined post-intervention RV/LV ratio (that is, not discriminating between submassive and massive PE). Therefore, calculation of the change of RV/LV ratio was done based on data from five studies[13,15,16,21,23]. This calculation revealed the pooled mean (95% confidence interval) change of -0.3 (-0.42, -0.18). The comparison of this change with the pooled mean of initial RV/LV ratio indicated marked improvement or even normalization (that is, decrease below < 0.9) of this parameter in the majority of patients.

Notably, the degree of between-study heterogeneity as presented by I^2 was high (95.1%; Figure 2). We decided, however, to retain this analysis as it illustrates direction and approximate magnitudes of RV/LV ratio change. The literature currently lacks aggregate analysis of cardiovascular indices of therapeutic efficacy of catheter-directed interventions in submassive PE. Our decision was further supported by expert recommendations[25] that analysis should not be excluded based solely on I^2. The experts anticipate heterogeneity to arise from clinical studies and encourage further data analysis to identify the causes for heterogeneity[25,26]. We will further address this issue in the Discussion.

Change in systolic pulmonary artery pressure was reported by all sampled studies. Three works[17,22,27] presented the data before and after the intervention unseparated for submassive and massive PE, which precluded their inclusion in the aggregate analysis. One paper[23] used decrease of the pressure gradient from RV to right atrial pressure as a surrogate measure for systolic pulmonary artery pressure. This also prevented its inclusion in the analysis. Two of the remaining 9 studies reported statistical parameters other than mean and SD, either as mean decrease (95% confidence interval)[18] or as median and interquartile range[19]. Based on statistical parameters of the

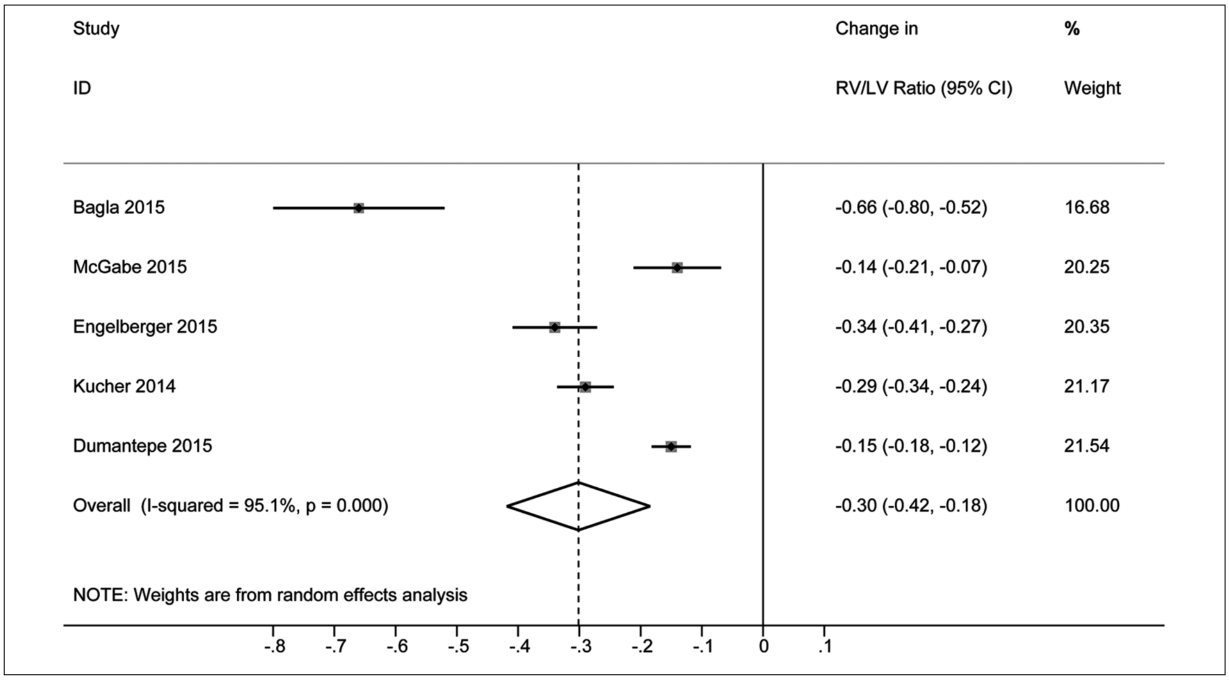

Figure 2. Forest plot of pooled difference in means and 95% confidence intervals: change in RV/LV ratio.

former study, we calculated the mean and SD of difference, and included this report in the aggregate analysis. Since such calculation was not feasible based on the data by the latter study, it was not included in the analysis. Therefore, we used 8 investigations[13-16,20,21,24] for aggregate analysis of change in systolic pulmonary artery pressure (Figure 3).

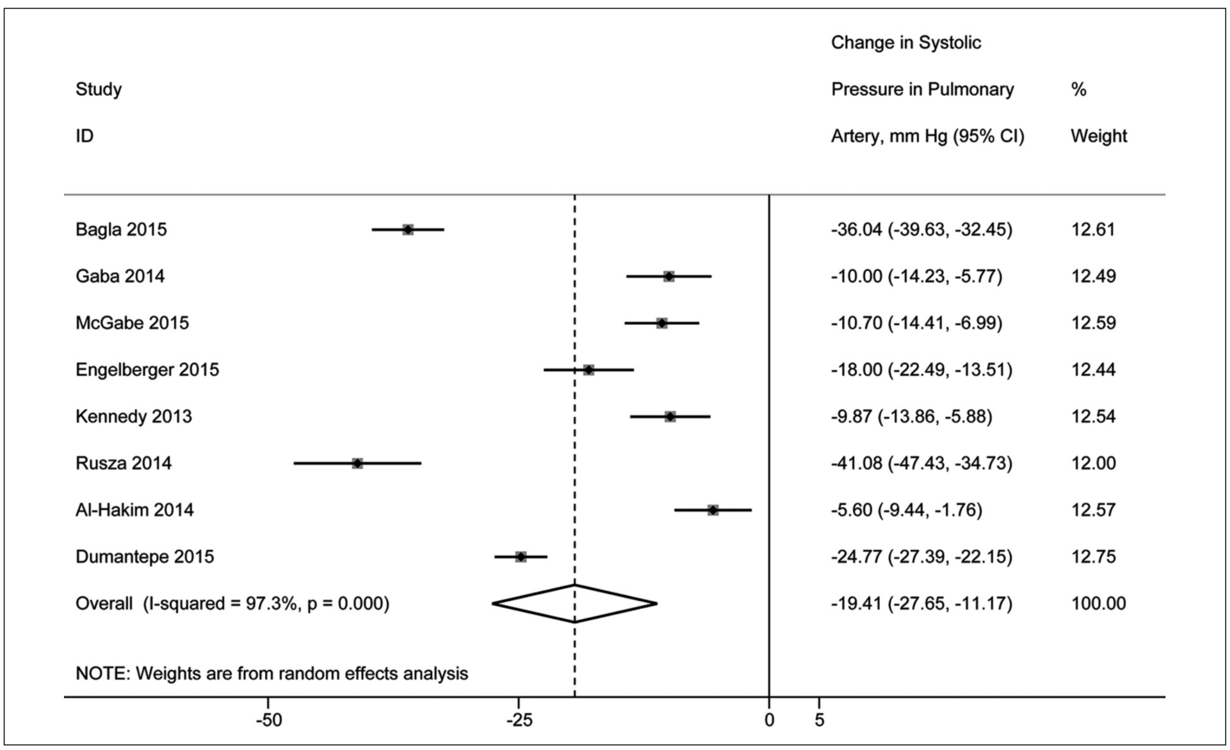

Figure 3. Forest plot of pooled difference in means and 95% confidence intervals: change in systolic pulmonary artery pressure.

These 8 investigations demonstrated the pooled mean decrease of -19.41 (95% confidence interval: -27.65, -11.17) mm Hg (Figure 3). As with RV/LV ratio, the heterogeneity was high (I^2 of 97.3) in the aggregate analysis of systolic pressure in the pulmonary artery (Figure 3). Similar to the data on RV/LV ratio, we decided to retain the analysis of systolic pulmonary artery pressure due to its high pathophysiological and clinical relevance to submassive PE.

Safety Indices

Four outcomes (in-hospital mortality and 30-day mortality rates, and major and minor bleeding rates) were combined in respective aggregate analysis. All four outcomes demonstrated low rates of adverse events reported by selected studies. Thus, the estimated pooled rate of in-hospital mortality was zero (95% confidence interval: 0.00, 0.01) (Figure 4), with low between-studies heterogeneity (I^2 = 0). Similar observa-

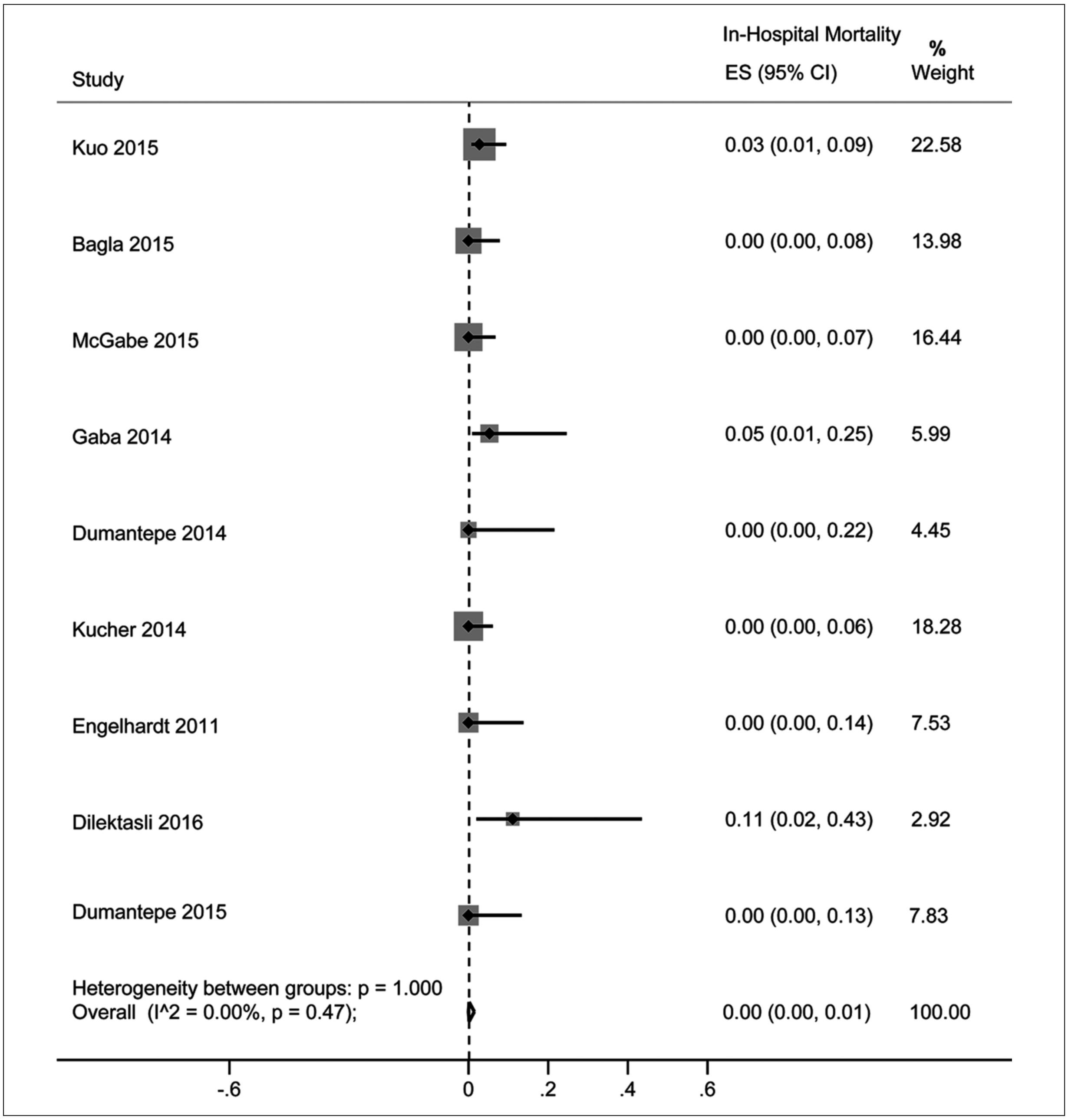

Figure 4. Forest plot of pooled proportions (95% confidence intervals): in-hospital mortality rate.

tions were made upon analysis of the 30-day mortality rate (pooled mean: 0.00; 95% confidence interval: 0.00, 0.03), albeit with a moderate heterogeneity ($I^2 = 39.50\%$) (Figure 5). Furthermore, the rates of major and minor bleeding episodes were also low in the selected reference sample (respectively, Figures 6-7), with the degree of heterogeneity comparable to that of the 30-day mortality rate. Other adverse events occurred at a comparably low rate. For example, only one study[14] reported 1 episode of intracranial bleeding for the total of 19 included patients, and another study reported 1 episode of PE recurrence (per 14 patients)[19].

Discussion

As addressed in the Introduction, the present meta-analysis aimed at addressing the current lack of quantitative assessments of catheter-directed interventions (CDT, CDT-USAT, catheter-directed fragmentation or aspiration of the thrombus) in submassive PE, with a specific focus on clinical-relevant therapeutic efficacy and safety outcomes. By PubMed, Embase, Cochrane and Scopus searches, we identified a sample of 13 clinical studies reported in 11 papers and 2 conference abstracts[13-24,27]. We extracted data on RV/LV and systolic pressure in pulmonary artery

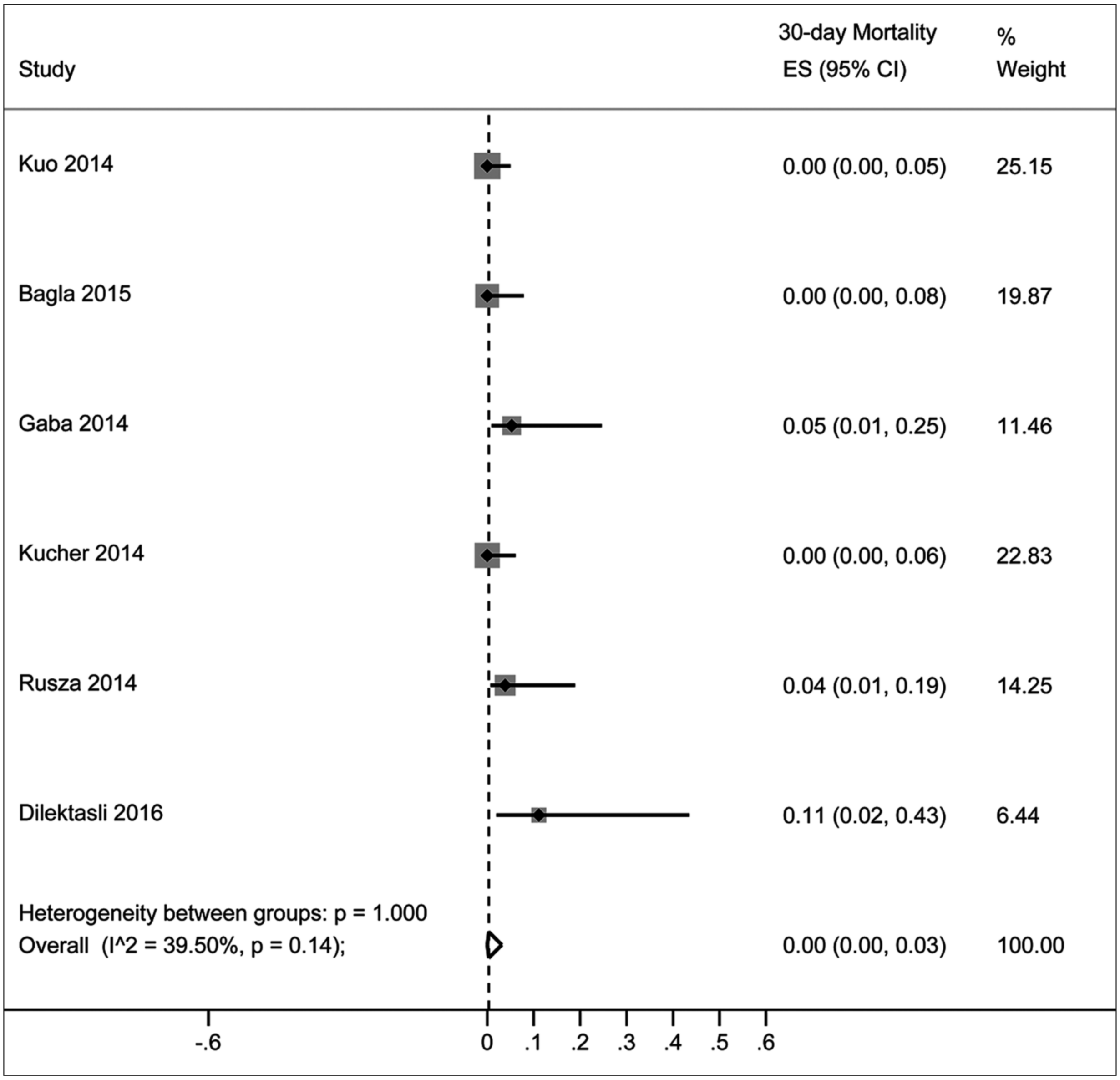

Figure 5. Forest plot of pooled proportions (95% confidence intervals): 30-day mortality rate.

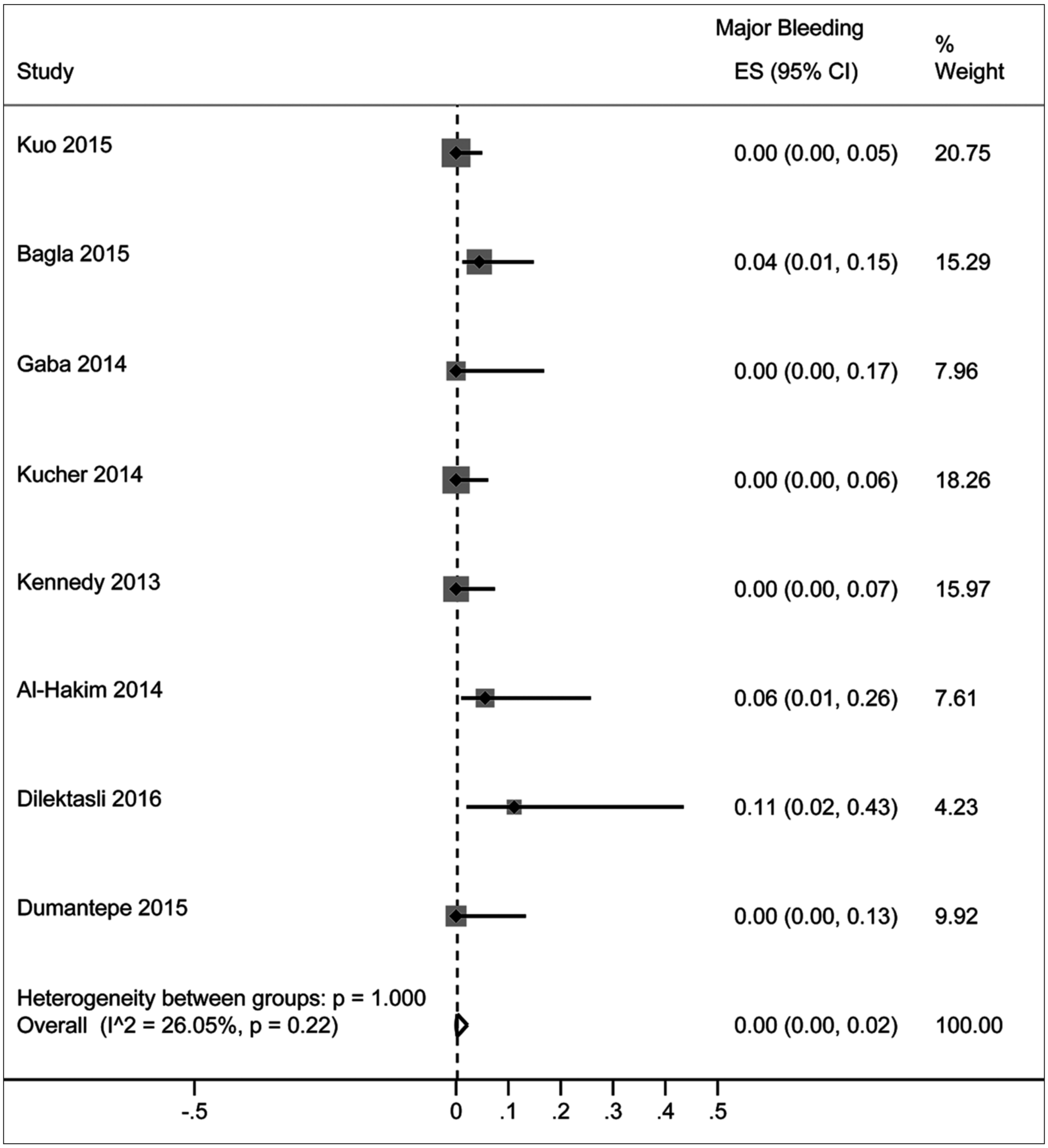

Figure 6. Forest plot of pooled proportions (95% confidence intervals): major bleeding rate.

as therapeutic efficacy outcomes, whereas the rates of in-hospital mortality, 30-day mortality, and major and minor bleeding episodes served as safety outcomes.

As mentioned above, an important difference exists between recently published meta-analysis and ours[6-9]. We extracted the data only from submassive PE that was treated by catheter-directed interventions. Furthermore, we utilized clinically relevant outcomes (RV/LV ratio and systolic pulmonary artery pressure) to evaluate therapeutic efficacy. This is in contrast to previous meta-analysis, which utilized mortality rates as a therapeutic efficacy outcome. The approach employed by previous meta-analysis requires a comparison to a control group, and this precludes from pool-

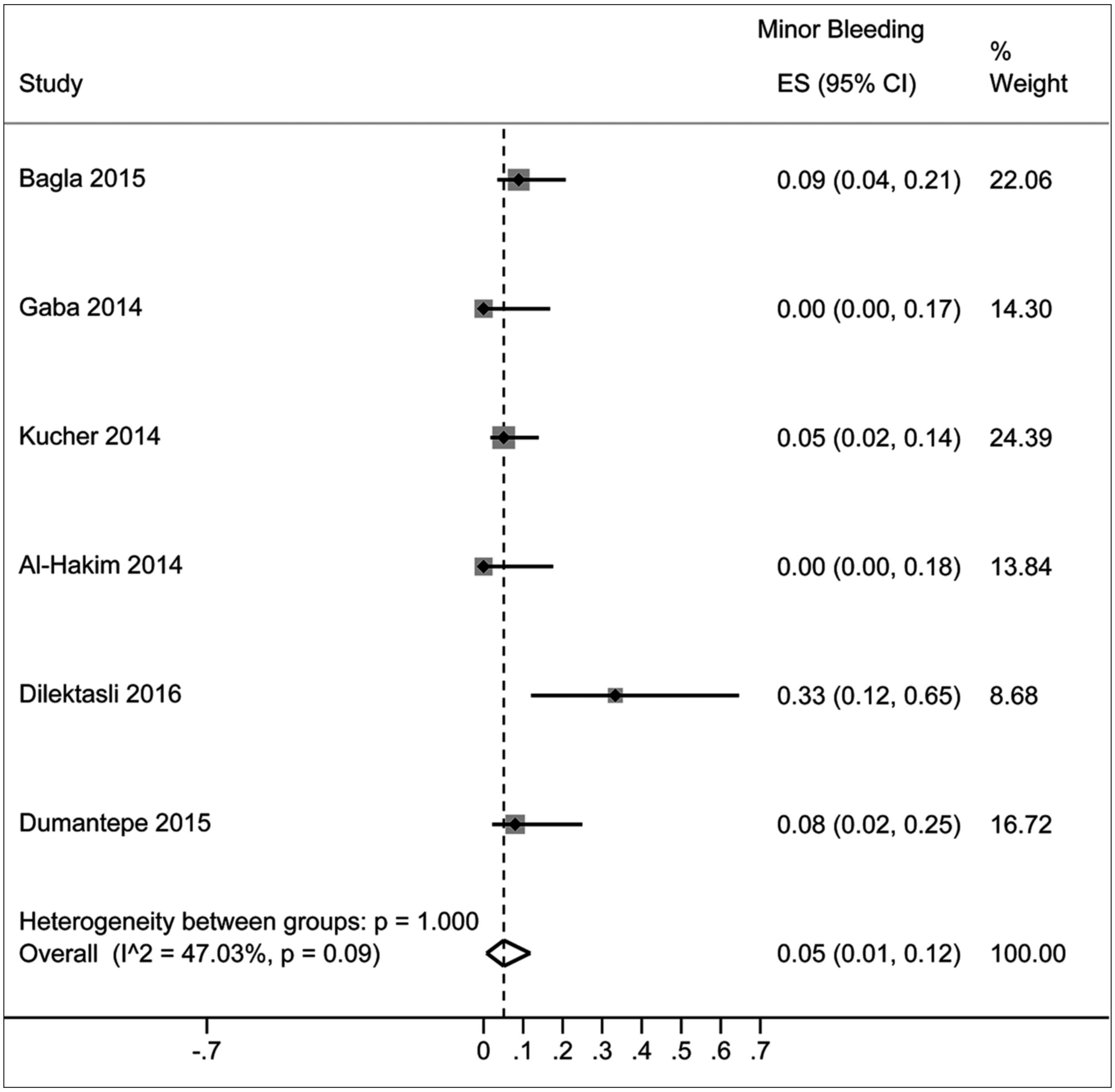

Figure 7. Forest plot of pooled proportions (95% confidence intervals): minor bleeding rate.

ing uncontrolled studies into the aggregate analysis. As catheter-directed interventions, including CDT with or without USAT, are a relatively recent addition to the therapeutic armamentarium for submassive PE, we did not anticipate to find many controlled clinical studies. In fact, our reference sample included only one randomized controlled study[23]. This study provided the data from the intervention group, whereas control group data were not utilized in our meta-analysis. Thereby, we could utilize pooled estimates of mean changes for aggregate analysis of therapeutic efficacy outcomes and rates for safety outcomes. The latter were expressed as proportions of patients with a particular adverse event over the total number of patients in a study.

Some sampled studies analyzed the efficacy and safety of catheter-directed interventions in a mixed cohort of patients with submassive and massive PE. From those studies, we extracted only the data which were clearly identifiable as representing submassive PE. Importantly, all investigations reported changes in systolic pressure in the pulmonary artery, and the majority of sampled studies (8/13) presented the data as mm Hg, enabling the aggregate analysis. The decrease in pulmonary artery pressure was sizeable (pooled mean estimate of -19.41 mm Hg; 95 confidence interval: -27.65, -11.17) and clinically relevant. The high degree of heterogeneity in this analysis could be because of patient heterogeneity in the aggregate sample. This patient heterogeneity was also in RV/LV ratio, which is closely related to pulmonary artery pressure. Thus, initial RV/LV ratio reported in several papers ranged from the mean value of 0.98[20] to ≥ 1.4 in several papers[14,15,21]. In the same vein, the degree of decreases in pulmonary artery pressure and RV/LV ratio was also quite heterogeneous.

High degree of heterogeneity of RV/LV ratio and pulmonary artery pressure could also have arisen from different techniques used to diagnose RV dysfunction and increase of the pulmonary artery pressure in these patients. Thus, some studies assessed RV/LV ratio only by computer tomography based methods[20], whereas others had this parameter diagnosed by computer tomography based methods in some patients and by echocardiography in other patients[15]. Similarly, pulmonary artery pressure was measured directly in some studies[15] and indirectly, by transthoracic echocardiography, in other studies[19].

Another potential source of heterogeneity is the intervention itself. The majority of patients in the pooled sample (264/422 patients) received CDT-USAT, but there were also patients treated with CDT alone (132/422 patients) or by catheter-directed mechanical thrombus fragmentation (26/422 patients). This could also have contributed to high degree between-studies heterogeneity in our pooled reference sample.

Nonetheless, decreases in both pulmonary artery pressure and RV/LV ratio were sizeable and consistent with one another. This is plausible, given that pulmonary artery pressure is defined by the size of the pulmonary embolism[28] and is expected to normalize after removal of the mechanical obstruction. As for RV dysfunction, this clinical outcome is associated with pulmonary artery pressure in both PE and other diseases with increased pulmonary artery pressure[29]. Therefore, RV dysfunction should be rectified following normalization of systolic pressure in pulmonary artery, as was the case in our reference sample. Simultaneous decrease of both RV/LV ratio and pulmonary artery pressure further illustrates the clinical efficacy of catheter-directed interventions in submassive PE.

Notably, not all patients with submassive PE showed increases in troponin levels despite RV strain and implied injury. Thus, the randomized controlled study in our reference sample reported elevated troponin levels in only 77-80% of the patients[23]. The proportion of troponin-positive patients in other studies was even more variable, ranging from as low as ~60%[21] to as high as 91%[15]. We conclude that a sizeable proportion of patients with RV dysfunction may not be easily identifiable by elevated markers of myocardial injury. Therefore, a diagnosis of patients with RV dysfunction may require employment of additional tests, potentially those reported previously[30].

The limitation of this meta-analysis was a high degree of heterogeneity of the outcomes indicating therapeutic efficacy. Furthermore, we did not sample "grey" literature that could have contained useful information. Also, we did not address the questions to experts in the field.

Conclusions

In this meta-analysis of recent articles on catheter-directed interventions to alleviate submassive PE, we observed evidence of therapeutic efficacy and low rates of adverse effects. The most frequently utilized intervention was CDT combined with USAT. At the moment, this evidence mostly stems from uncontrolled and retrospective studies. Thus, prospective controlled studies are needed to confirm further our conclusions.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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