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Is it Time to Reappraise for Black-Box Warning on AngioJet Rheolytic Thrombectomy in Patients with Pulmonary Embolism: A Systematic Review and Meta-analysis

ABSTRACT

Background: AngioJet rheolytic thrombectomy (ART) system has been widely used as a catheter-directed treatment (CDT) method in acute pulmonary embolism (PE), however, there has been a controversy regarding the safety of its use. In this systematic review and meta-analysis, we evaluated the efficacy and safety outcomes of ART in patients with PE.

Methods: Our meta-analysis have been based on search in the MEDLINE, EMBASE, and Cochrane Library for studies published up to August 2022. The primary outcomes were overall pooled rates of major bleeding (MB) and minor bleeding (mB), worsening renal function (WRF), bradycardia/conduction disturbance (BCD), and PE-related and all-cause mortality in patients who underwent ART.

Results: Among the 233 studies documented at initial search, 24 studies were eligible for meta-analysis, and a total of 427 PE patients who underwent ART were evaluated. Overall pooled rates of MB and mB were 9.6% (95% CI 5.9%-15.2%) and 9.2% (95% CI 6.1%-13.6%), transient BCD and WRF were 18.2% (95% CI 12.4%-26%) and 15% (95% CI 10%-21.8%), and PE-related death and all-cause death were 12.7% (95% CI 9.1%-17.3%) and 15% (95% CI 11%-20%), respectively. However, significant heterogeneity and some evidence of funnel plot asymmetry and publication bias were noted for MB, BCD and WRF, but not for PE-related death and all-cause death.

Conclusion: Overall pooled rates of bleeding events, BCD and WRF episodes, PE-related death and all-cause death may be considered as encouraging results for efficacy and safety issues of ART utilization in specific scenarios of acute PE, and a reappraisal for black-box warning on ART seems to be necessary.

Keywords: Angiojet rheolytic thrombectomy, catheter-directed thrombolysis, pulmonary embolism

META-ANALYSIS

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INTRODUCTION

Acute pulmonary embolism (PE) has been documented as one of the most frequent lethal cardiovascular diseases, and acute-onset hemodynamic instability in this setting usually implicates nearly 30%-50% obstruction in the pulmonary arterial (PA) territory.[1,2] Right ventricle (RV) pressure overload and strain manifested by RV diameter to left ventricle diameter ratio (RV/LVr), either assessed by echocardiography (Echo) or computed tomography (CT), have been documented to predict clinical worsening even in the low-risk status.[1,2] The European Society of Cardiology/European Respiratory Society (ESC/ERS) 2014 and 2019 PE Guidelines have recommended an updated acute phase treatment strategies based on definition of high-, intermediate high-, intermediate low-, and low-risk groups (HR, IHR, ILR, and LR).[1,2] The patients at HR status have been considered to require urgent primary pharmacological (or alternatively, surgical or interventional) reperfusion therapies.[1,2] Moreover, for patients who develop hemodynamic instability, rescue thrombolytic treatment has also been recommended, and catheter-directed treatments (CDT) as alternatives to rescue thrombolytic treatment should be considered.[2] However, systemic thrombolytic treatment has been documented to increase the risk of major bleeding events, including intracranial hemorrhage.[1,2]

Along the 6-decade adventure of several CDT systems, only 5 devices, Greenfield simple suction embolectomy catheter, EKOSONIC endovascular thrombolysis system (Boston Scientific), FlowTriever system (Inari Medical), Penumbra Indigo Aspiration System (Penumbra Inc., CA, USA), and BASHIR Endovascular Catheter (Thrombolex Inc.) have been approved by Food and Drug Administration.[3-7] Experience for CDT systems in submassive or massive PE has mainly been based on off-label utilization in anecdotal case reports, small retrospective series comprising highly selected patient groups, non-randomized studies or registries and meta-analyses of heterogeneous datasets.[8-17] AngioJet rheolytic thrombectomy (ART) (Boston Scientific) system has been widely used as a CDT method which generates high pressure and circumferential saline jet expulsions at the catheter tip creating a local low-pressure zone to entrain, fragmentation and aspiration of thrombi.[17-43] Moreover, on-the-wire design of ART allows aspiration thrombectomy procedures along all subsegmentary pulmonary artery branches selected.[17-43] However, the mortality rate in unstable settings remains high, and a controversy regarding the safety concerns of the ART procedure still exists.[8,9,17-43]

In this systematic review and meta-analysis, we aimed to evaluate the efficacy and safety outcomes of ART treatments in acute patients with PE at HR or IHR status, or in other terms, massive or submassive PE.

METHODS

Our systematic review and meta-analysis have been based on searches in the MEDLINE, EMBASE, and the Cochrane Library for studies published up to August 2022, conducted in the English language and in humans.

HIGHLIGHTS

- AngioJet rheolytic thrombectomy (ART) system has been widely used as a CDT method in patients with acute pulmonary embolism (PE) at high risk (HR) or intermediate-high risk (IHR). However, in unstable conditions, mortality rate remains high, and a debate persists regarding the safety concerns associated with the ART procedure.
- This systematic review and meta-analysis evaluate the effectiveness and safety outcomes of ART treatments in patients with acute PE at HR or IHR status, or in other terms, massive or submassive PE.
- Overall pooled rates of major and minor bleeding events, transient bradycardia and worsening renal function episodes, PE-related death and all-cause death may be considered to provide encouraging results for ART utilization in specific circumstances of acute PE. Consequently, a reconsideration of the black-box warning on ART appears to be warranted.

Search Strategy and Selection Criteria

Major conference proceedings of cardiology, pulmonology, and vascular radiology were searched manually. In addition, we performed a manual search by checking all the references of studies. A computerized search using the terms "mechanical thrombectomy OR rheolytic thrombectomy OR AngioJet OR catheter directed thrombolysis" AND "pulmonary embolism" was conducted. All searches were conducted by 3 authors (B.K., I.H.T., and A.K.), and 2 authors (I.H.T. and A.K.) independently assessed study eligibility and extracted data. Disagreements were resolved by consensus. The ART studies reporting the prevalence of all-cause mortality, PE-related mortality, major bleeding (MB), minor bleeding (mB), worsening renal function (WRF), and/or bradycardia/conduction disturbance (BCT) were considered to be eligible for meta-analysis.

Study Outcomes

The primary outcomes of our meta-analysis were the prevalence of MB and mB, WRF, BCD, all-cause mortality, and PE-related mortality in patients who underwent ART procedure with an indication of acute PE. Moreover, pre- and post-procedural obstruction scores, RV/LVr, pulmonary artery systolic and mean pressures (PASP and PAMP) estimated by Doppler echo, and invasively measured by right heart catheterization were evaluated in cases of available data.

Statistical Analysis

The meta-analysis was conducted using R Statistical Software (v3.5.6), using the packages "meta" and "metafor" for meta-analysis. A random-effects model (DerSimonian and Laird method) was applied to estimate the pooled prevalence across the studies. The Clopper—Pearson method was used to calculate 95% CIs of single proportions (continuity correction of 0.5 in studies with zero cell frequencies). Estimates were normalized using the Logit transformation for single proportions and raw mean for single means. An inverse variance method was used for weighting each study in the meta-analysis. For the difference of subgroup analysis, we employed post hoc analysis. Potential demographic, clinical, and drugs as modifiers were further explored by meta-regression. Meta-regression coefficients and corresponding *P*-values are reported. For summary estimates, $P < .05$ (2-tailed) was considered statistically significant. Heterogeneity between studies was assessed using tau^2 and the I^2 index. As a guide, I^2 <25% indicated low, 25%-50% moderate, and >50% high heterogeneity. Publication bias was evaluated by the Egger test and funnel plot.

RESULTS

Among the 233 studies documented at initial search, 24 studies were eligible for meta-analysis, and a total of 427 PE patients (age 58.3 ± 8.8 years, female 45.3%) who underwent ART were found. The PE was bilateral in 48.97% of these reports, and concomitant deep vein thrombosis was also documented in 70.2% of PE events. Baseline clinical characteristics of patients in these studies are summarized in Table 1. According to different definitions, the reported rates of high-risk (HR), overall intermediate risk (IR), and intermediate high-risk (IHR) status were 51.52%, 48.47%, and

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Table 1. Clinical and Hemodynamic Characteristics of ART Trials

Author	n	Age, years	Male %	DVT %	HR %	IHR PE %	IR PE %	Massive PE %	Submassive PE %
Koning[1997]	2	73	2	0	0	2	2	2	0
Voigtlander[1999]	5	56.8	4		5	0	0	5	0
Zeni[2003]	17	51.7	9	12	17	0	0	17	0
Siablis[2005]	6	59.2	4		6	0	0	6	0
Chauhan[2007]	14	63	7		10	4	4	10	4
Margheri[2008]	25	66.4	16	21	8	12	17	8	17
Spies[2008]	13	51	7		13	0	0	13	0
Kuo[2009]	3	49.6	1		3	0	0	3	0
Vecchio[2008]	30	67.9	16	25	9	21	21	13	17
Chechi[2009]	51	66.7	25	44	14	8	37	34	17
Arzamendi[2010]	10	43.7	3	6	10	0	0	10	0
Hubbard[2011]	11	60.2	9		3	8	8	9	2
Ferrigno[2011]	16	54.4	7		5	11	11	5	11
Wong[2012]	2	64.5	1	1	2	0	0	2	0
Nassiri[2012]	15	59	8	10	1	14	14	14	1
Bonvini[2013]	10	73	5		10	0	0	10	0
Latacz[2016]	2	43	1	0	0	2	2	2	0
Das[2017]	13	56.2	10	10	3	10	10	5	8
Latacz[2018]	7	52.7	3	2	2	5	5	2	5
Villalba[2019]	32	65.8	17	23	23	9	9	23	9
Li[2020]	44	58.3	21	32	21	23	23	11	33
Pelliccia[2020]	33	43	20	11	33	0	0	33	0
Gong[2021]	10			10	10	0	0	10	0
Akbal[2022]	56	62	32	38	12	44	44	12	44

ART, angiojet rheolytic thrombectomy; PE, pulmonary embolism; DVT, deep vein thrombosis; HR, high risk; IHR, intermediate-high risk, IR, intermediate risk.

40.51%, and % of massive and sub-massive PE were 60.65% and 39.35%, respectively.

The procedural characteristics and changes in RV/LVr and obstruction scores compared with baseline are given in Supplementary Table 1 (P < .0001 for all). Overall ART duration was reported in 3 series, with median and interquartile values were 329.5 (230.3-416) seconds. Adjunctive fibrinolytic was documented to be utilized in 44.96% of ART procedures.

The changes in PASP and PAMP compared with baseline are presented in Supplementary Table 2 (P < .0001 for all).

Overall pooled echocardiographic, CT angiographic, and hemodynamic measurements before and after ART are given in Table 2.

Prevalence values reported in these 24 studies were pooled with random effect meta-analysis to evaluate primary endpoints.

Major Bleeding and Minor Bleeding Events

The overall pooled proportion of MB in 24 studies was 9.6% (95% CI 5.9%-15.2%), but heterogeneity was significant (tau^2 = 0.65, I^2 = 46.7%, P-value for heterogeneity .007) (Figure 1). Both the funnel plot and Egger's test provided some evidence of funnel plot asymmetry and publication bias (Egger's test P < .001) (Supplementary Figure 1A). Multiple meta-regression analysis revealed that MB risk was significantly associated with aging (P = .023), but not with gender (P = .699) or adjuvant t-PA (P = .212) (Supplementary Figure 2A). Meta-regression analysis showed that these 3 variables could explain the 74.9% (R^2) of the total heterogeneity of the model. The overall pooled proportion of minor

Table 2. Overall Pooled Echocardiographic, CT Angiographic, and Hemodynamic Measures Before and After ART

	Study (n)	RE, pooled mean, 95% CI	I^2, %
Obstruction score (baseline)	10	20.9 (19.2-22.5)	88.5
Obstruction score (final)	11	11.4 (9.7-13.1)	87.4
RV/LV ratio (baseline)	4	1.30 (1.14-1.46)	89.3
RV/LV ratio (final)	2	1.10 (0.75-1.45)	98.2
PASP-Echo (baseline)	5	53.8 (44.6-62.9)	94.2
PASP-Echo (final)	3	37.7 (29.8-45.6)	83.2
PASP-RHC (baseline)	4	51.1 (39.2-62.9)	91.2
PASP-RHC (final)	4	37.2 (30.5-43.9)	84.3
PAMP-RHC (baseline)	4	37.5 (28.9-46.1)	93.7
PAMP-RHC (final)	4	29.1 (25.6-32.6)	75.2

Echo, echocardiogram; LV, left ventricle; PASP, pulmonary artery systolic pressure; PAMP, pulmonary artery mean pressure; RHC, right heart catheterization; RV, right ventricle; RHC, right heart catheterization.

Major bleeding

Study	Events	Total	Weight (common)	Weight (random)	IV, Fixed + Random, 95% CI
Akbal	4	56	10.7%	8.0%	0.071 [0.020; 0.173]
Li	2	44	5.5%	6.2%	0.045 [0.006; 0.155]
Latacz	0	7	1.4%	2.6%	0.000 [0.000; 0.410]
Pelliccia	0	33	1.4%	2.7%	0.000 [0.000; 0.106]
Hubbard	0	11	1.4%	2.7%	0.000 [0.000; 0.285]
Villalba	1	32	2.8%	4.4%	0.031 [0.001; 0.162]
Margheri	10	25	17.4%	9.0%	0.400 [0.211; 0.613]
Wong	0	2	1.2%	2.4%	0.000 [0.000; 0.842]
Chechi	4	51	10.7%	8.0%	0.078 [0.022; 0.189]
Das	0	13	1.4%	2.7%	0.000 [0.000; 0.247]
Siablis	0	6	1.3%	2.6%	0.000 [0.000; 0.459]
Nassiri	0	15	1.4%	2.7%	0.000 [0.000; 0.218]
Latacz	0	2	1.2%	2.4%	0.000 [0.000; 0.842]
Ferrigno	2	16	5.1%	6.0%	0.125 [0.016; 0.383]
Chauhan	2	14	5.0%	5.9%	0.143 [0.018; 0.428]
Bonvini	0	10	1.4%	2.7%	0.000 [0.000; 0.308]
Koning	0	2	1.2%	2.4%	0.000 [0.000; 0.842]
Voigtlander	0	5	1.3%	2.6%	0.000 [0.000; 0.522]
Zeni	1	17	2.7%	4.3%	0.059 [0.001; 0.287]
Spies	0	13	1.4%	2.7%	0.000 [0.000; 0.247]
Arzamendi	0	10	1.4%	2.7%	0.000 [0.000; 0.308]
Kuo	0	3	1.3%	2.5%	0.000 [0.000; 0.708]
Gong	0	10	1.4%	2.7%	0.000 [0.000; 0.308]
Vecchio	11	30	20.1%	9.2%	0.367 [0.199; 0.561]
Total (common effect, 95% CI)		**427**	**100.0%**	--	**0.142 [0.106; 0.187]**
Total (random effect, 95% CI)			--	**100.0%**	**0.096 [0.059; 0.152]**

Heterogeneity: $Tau^2 = 0.6511$; $Chi^2 = 43.13$, df = 23 ($P < 0.01$); $I^2 = 47\%$

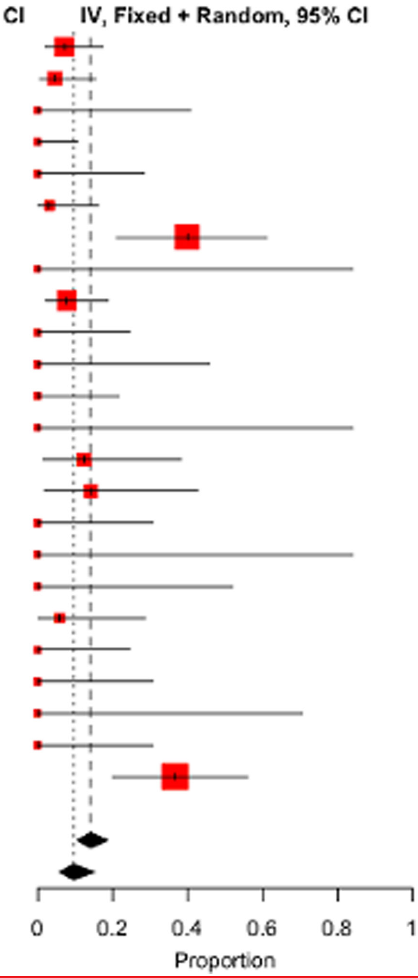


Figure 1. Overall pooled rate of major bleeding events in ART trials.

bleeding events was 9.2% (95% CI 6.1%-13.6.1%) ($tau^2 = 0.11$, $I^2 = 9\%$, *P*-value for heterogeneity .330) (Supplementary Figure 3).

Bradycardia/Conduction Disturbance

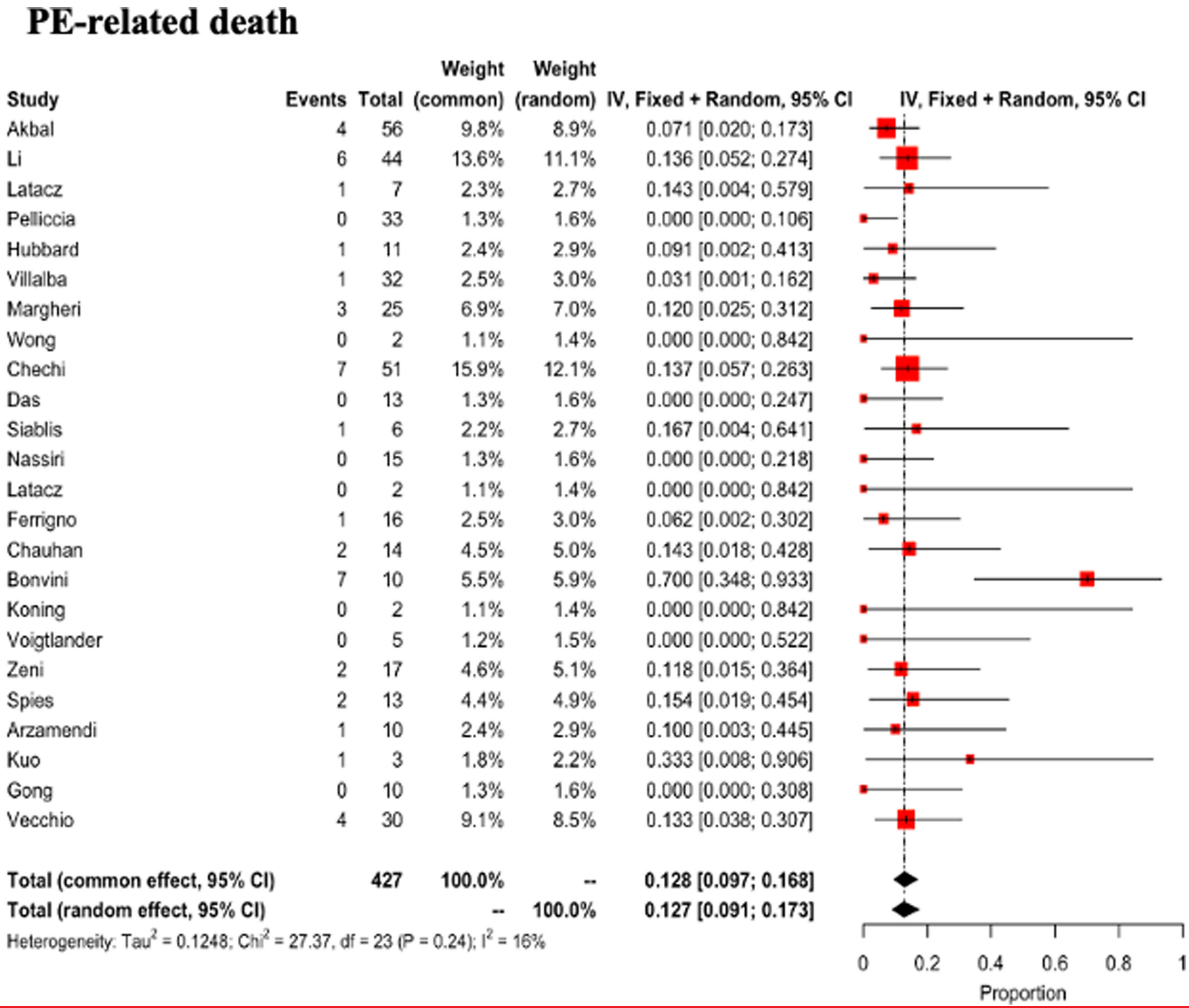
The pooled proportion of BCD in 24 studies was 18.2% (95% CI 12.4%-26%), and heterogeneity was significant ($tau^2 = 0.52$, $I^2 = 52.2\%$, *P*-value for heterogeneity .002) (Supplementary Figure 4). Both the funnel plot and Egger's test provided some evidence of funnel plot asymmetry and publication bias (Egger's test *P*-value .004) (Supplementary Figure 1B). In multiple meta-regressions analysis, no variables were found to be related to BCD.

Worsening Renal Function

The pooled proportion of WRF in 24 studies was 15% (95% CI 10%-21.8%), and heterogeneity was significant ($tau^2 = 0.39$, $I^2 = 43.6\%$, *P*-value for heterogeneity .013) (Supplementary Figure 5). Both the funnel plot and Egger's test provided some evidence of funnel plot asymmetry and publication bias (Egger's test $P < .001$) (Supplementary Figure 1C). Multiple meta-regression analysis revealed that WRF risk was significantly associated with male gender ($P = .0002$), but not with age ($P = .371$) or HR status at presentation ($P = .526$) (Supplementary Figure 2C). Meta-regression analysis showed that these 3 variables could explain the 100% (R^2) of the total heterogeneity of model.

Pulmonary Embolism Related Death and All-cause Death

The pooled proportion of PE-related death and all-cause death in 24 studies was 12.7% (95% CI 9.1%-17.3%) and 15% (95% CI 11%-20%, respectively (Figures 2 and 3). Heterogeneity was not significant for PE-related death ($tau^2 = 0.12$, $I^2 = 16\%$, *P*-value for heterogeneity .241) and all-cause death ($tau^2 = 0.14$, $I^2 = 20\%$, *P*-value for heterogeneity .190) (Figures 2 and 3). Both the funnel plot and Egger's test provided no evidence of funnel plot asymmetry and publication bias (Egger's test *P* value .317 for PE-related death and .339 for all-cause death) (Supplementary Figures 1D and 1E). In multiple meta-regression analysis, aging was significantly associated with both PE-related death ($P = .007$) and all-cause death ($P = .017$), but male gender was related to decreased risks for PE-related death ($P = .011$) and all-cause death ($P = .014$)


PE-related death

Study	Events	Total	Weight (common)	Weight (random)	IV, Fixed + Random, 95% CI
Akbal	4	56	9.8%	8.9%	0.071 [0.020; 0.173]
Li	6	44	13.6%	11.1%	0.136 [0.052; 0.274]
Latacz	1	7	2.3%	2.7%	0.143 [0.004; 0.579]
Pelliccia	0	33	1.3%	1.6%	0.000 [0.000; 0.106]
Hubbard	1	11	2.4%	2.9%	0.091 [0.002; 0.413]
Villalba	1	32	2.5%	3.0%	0.031 [0.001; 0.162]
Margheri	3	25	6.9%	7.0%	0.120 [0.025; 0.312]
Wong	0	2	1.1%	1.4%	0.000 [0.000; 0.842]
Chechi	7	51	15.9%	12.1%	0.137 [0.057; 0.263]
Das	0	13	1.3%	1.6%	0.000 [0.000; 0.247]
Siablis	1	6	2.2%	2.7%	0.167 [0.004; 0.641]
Nassiri	0	15	1.3%	1.6%	0.000 [0.000; 0.218]
Latacz	0	2	1.1%	1.4%	0.000 [0.000; 0.842]
Ferrigno	1	16	2.5%	3.0%	0.062 [0.002; 0.302]
Chauhan	2	14	4.5%	5.0%	0.143 [0.018; 0.428]
Bonvini	7	10	5.5%	5.9%	0.700 [0.348; 0.933]
Koning	0	2	1.1%	1.4%	0.000 [0.000; 0.842]
Voigtlander	0	5	1.2%	1.5%	0.000 [0.000; 0.522]
Zeni	2	17	4.6%	5.1%	0.118 [0.015; 0.364]
Spies	2	13	4.4%	4.9%	0.154 [0.019; 0.454]
Arzamendi	1	10	2.4%	2.9%	0.100 [0.003; 0.445]
Kuo	1	3	1.8%	2.2%	0.333 [0.008; 0.906]
Gong	0	10	1.3%	1.6%	0.000 [0.000; 0.308]
Vecchio	4	30	9.1%	8.5%	0.133 [0.038; 0.307]
Total (common effect, 95% CI)		**427**	**100.0%**	--	**0.128 [0.097; 0.168]**
Total (random effect, 95% CI)			--	**100.0%**	**0.127 [0.091; 0.173]**

Heterogeneity: $Tau^2 = 0.1248$; $Chi^2 = 27.37$, df = 23 ($P = 0.24$); $I^2 = 16\%$

Figure 2. Overall pooled rate of PE-related death in ART trials.

(Supplementary Figures 2D and 2E). However, HR status was not related with PE-related death ($P = .422$) and all-cause death ($P = .852$). Meta-regression analysis showed that these 3 variables could explain 100% (R^2) of the total heterogeneity of the model.

DISCUSSION

This systematic review and meta-analysis, pooling data from 427 patients, provide a current landscape for the utilization of ART in patients with acute PE at HR or IHR status, or in other terms, massive or submassive PE. Adjunctive fibrinolytic was documented in 45% of ART procedures. However, heterogeneity was significant for MB, BCD, and WRF, but not for PE-related death and all-cause death. Moreover, both the funnel plot and Egger's test provided some evidence of funnel plot asymmetry and publication bias for major bleeding, BCD, and WRF, whereas no evidence of funnel plot asymmetry and publication bias was found for PE-related and all-cause death. Major bleeding was associated with aging, and WRF risk was related to the male gender. Aging was significantly associated with increased risks, and male gender was related with decreased risks, for PE-related and all-cause death. However, HR status was not related with PE-related or all-cause death.

The vast majority of the historical data regarding the efficacy and safety concerns of CDT in submassive or massive PE have been derived from case series, registries, and pooled analyses, which might suffer from publication bias.[8,9,10-43] Furthermore, the superiority of one CDT system over others remains to be clarified. A recently published clinical consensus statement of the ESC Working Group on Pulmonary Circulation and Right Ventricular Function and European Association of Percutaneous Cardiovascular Intervention for Percutaneous Treatment Options for Acute Pulmonary

All-cause death

Study	Events	Total	Weight (common)	Weight (random)	IV, Fixed + Random, 95% CI
Akbal	5	56	10.5%	9.1%	0.089 [0.030; 0.196]
Li	6	44	12.0%	9.8%	0.136 [0.052; 0.274]
Latacz	2	7	3.3%	3.9%	0.286 [0.037; 0.710]
Pelliccia	0	33	1.1%	1.5%	0.000 [0.000; 0.106]
Hubbard	1	11	2.1%	2.7%	0.091 [0.002; 0.413]
Villalba	1	32	2.2%	2.8%	0.031 [0.001; 0.162]
Margheri	4	25	7.8%	7.5%	0.160 [0.045; 0.361]
Wong	0	2	1.0%	1.3%	0.000 [0.000; 0.842]
Chechi	8	51	15.6%	11.4%	0.157 [0.070; 0.286]
Das	0	13	1.1%	1.5%	0.000 [0.000; 0.247]
Siablis	1	6	1.9%	2.5%	0.167 [0.004; 0.641]
Nassiri	0	15	1.1%	1.5%	0.000 [0.000; 0.218]
Latacz	0	2	1.0%	1.3%	0.000 [0.000; 0.842]
Ferrigno	1	16	2.2%	2.7%	0.062 [0.002; 0.302]
Chauhan	3	14	5.4%	5.8%	0.214 [0.047; 0.508]
Bonvini	7	10	4.9%	5.3%	0.700 [0.348; 0.933]
Koning	0	2	1.0%	1.3%	0.000 [0.000; 0.842]
Voigtlander	1	5	1.8%	2.4%	0.200 [0.005; 0.716]
Zeni	2	17	4.1%	4.7%	0.118 [0.015; 0.364]
Spies	2	13	3.9%	4.5%	0.154 [0.019; 0.454]
Arzamendi	2	10	3.7%	4.3%	0.200 [0.025; 0.556]
Kuo	1	3	1.5%	2.0%	0.333 [0.008; 0.906]
Gong	0	10	1.1%	1.5%	0.000 [0.000; 0.308]
Vecchio	5	30	9.6%	8.6%	0.167 [0.056; 0.347]
Total (common effect, 95% CI)		**427**	**100.0%**	--	**0.151 [0.117; 0.193]**
Total (random effect, 95% CI)			--	**100.0%**	**0.150 [0.110; 0.201]**

Heterogeneity: $Tau^2 = 0.1433$; $Chi^2 = 28.71$, $df = 23$ ($P = 0.19$); $I^2 = 20\%$

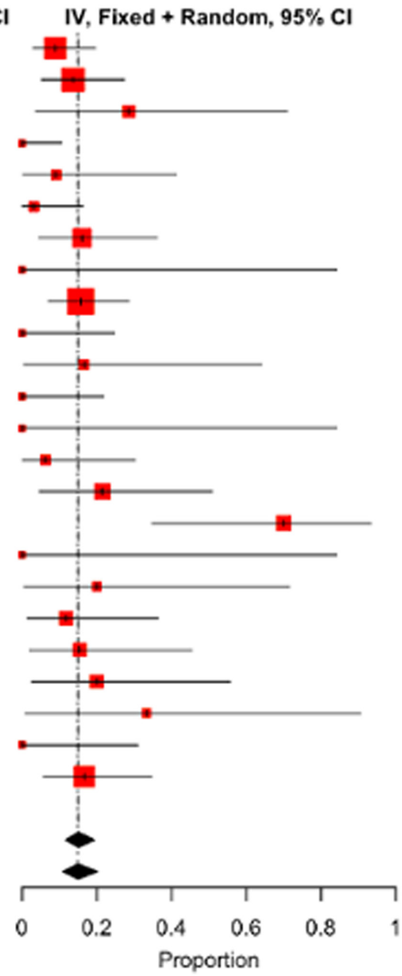


Figure 3. Overall pooled rate of all-cause death in ART trials.

Embolism aims to describe and standardize currently available management strategies with CDT, patient selection, timing, and techniques in this setting.[12]

Although ART has been utilized as a CDT system in patients with massive or submassive PE for a long-term period, a controversy related to some safety concerns of this system originated from an early meta-analysis on 68 PE patients treated with ART.[8] The authors concluded that 76% of all major complications were attributable to ART, and suggested that this device should not be used as the initial mechanical treatment in future CDT protocols for patients with acute massive PE.[8] Thereafter, Food and Drug Administration has issued a black-box warning on the commercially available ART device for Food and Drug Administration its use in patients with acute PE.

Transient BCDs have been the most frequently reported complications of ART and were considered to be due to hemolysis followed by adenosine release triggered by activation bursts of the system.[17-43] However, short bursts (less than 10 pulses at a time) with 20-30 seconds apart between bursts seem to allow clearance of adenosine or other lysis products, and recovery of sinus rhythm.[38,42,43] A potential for local thermal injury related with ART was investigated in human saphenous vein segments mounted in an ex vivo perfusion system, and continuous ART for 4 minutes and pulsed ART for 8 cycles of 30 seconds followed by 10 seconds of deactivation were reported to increase temperature with mean maximum temperatures up to 44.11°C and 43.81°C, respectively.[38] Moreover, ART resulted in significant intima/media thinning with immunohistology staining for heat shock protein 90 expression in treated segments.[38] These results raise questions about the potential risk of local thermal injury with longer durations of ART bursts.[38]

The occurrence of severe hyperkalemia and hemoglobinuria as a result of hemolysis are other important issues.[42,44,45] Hyperkalemia may exacerbate the electrical instability, and hemoglobinuria may cause WRF in these patients already at risk because of hemodynamic instability and contrast utilization for diagnostic CT and selective PA injections during the ART procedure.[8-45]

Recently published single-center studies comprising patients with acute PE at HR or IHR status, or in other terms, massive or submassive PE, reported promising results for ART utilization in certain circumstances.[39-42] The reported technical success rate was 100% in all these series.[39-42] Uniformly, ART resulted in significant improvement in clinical, echocardiographic, CT, hemodynamic, and angiographic measures including RV pressure overload and strain, RV/LVr, perfusion, and/or obstruction indexes, and IHR versus HR was associated with more marked improvements in shock index, vital and angiographic parameters, and a shorter length of intensive care.[39-42] In-hospital mortality ranged from 3.1% to 13.6% in these series and was significantly associated with HR status or shock.[39-42] WRF was associated with older age or HR, but forced diuresis with controlled saline hydration seemed to prevent the majority of WRF episodes.[41,44] Our meta-analysis demonstrated the current status of ART utilization for patients with acute PE at HR or IHR status. Overall pooled rates of MB and mB events, and transient BCD and WRF episodes were found to be lower than previously reported. The pooled rates of PE-related death and all-cause death, without any evidence of funnel plot asymmetry and publication bias, seem to be consistent with severity of background clinical and/or hemodynamic status in these patients needing ART. Older age was related with increased risk for MB, and PE-related and all-cause death. Male gender was related with increased risk of WRF but decreased risks for PE-related and all-cause death risk. However, HR status before ART could not be translated to having increased PE-related or all-cause death rates.

Study Limitations

The absence of prospective and randomized data, significant heterogeneity, and some evidence of funnel plot asymmetry and publication bias for pooled rates of MB, BCD, and WRF have remained as important limitations of this meta-analysis. Nevertheless, neither PE-related death, nor all-cause death analysis seemed to suffer from these limitations, and this may be considered to increase the reliability of these outcome measures in the evaluation of the ART. Although HR status prior to ART was reported to increase in-hospital or early mortality in some single-center series, this relation was not confirmed by multiple meta-regression analysis.

CONCLUSION

Besides the clinically relevant improvements in obstructive burden and RV pressure strain with ART utilization, overall pooled rates of bleeding, BCD, and WRF episodes, as well as PE-related death and all-cause death, may be considered as promising results for safety issues of this technique in specific scenarios of acute PE. Therefore, a reconsideration of the black-box labeling on ART appears to be necessary.

Impact on Daily Practice

Overall pooled rates of bleeding events, transient bradycardia, and worsening renal function episodes, as well as PE-related death and all-cause death, may be considered to provide encouraging results for ART utilization in specific circumstances of acute PE. A reappraisal of the black-box warning on ART seems to be necessary.

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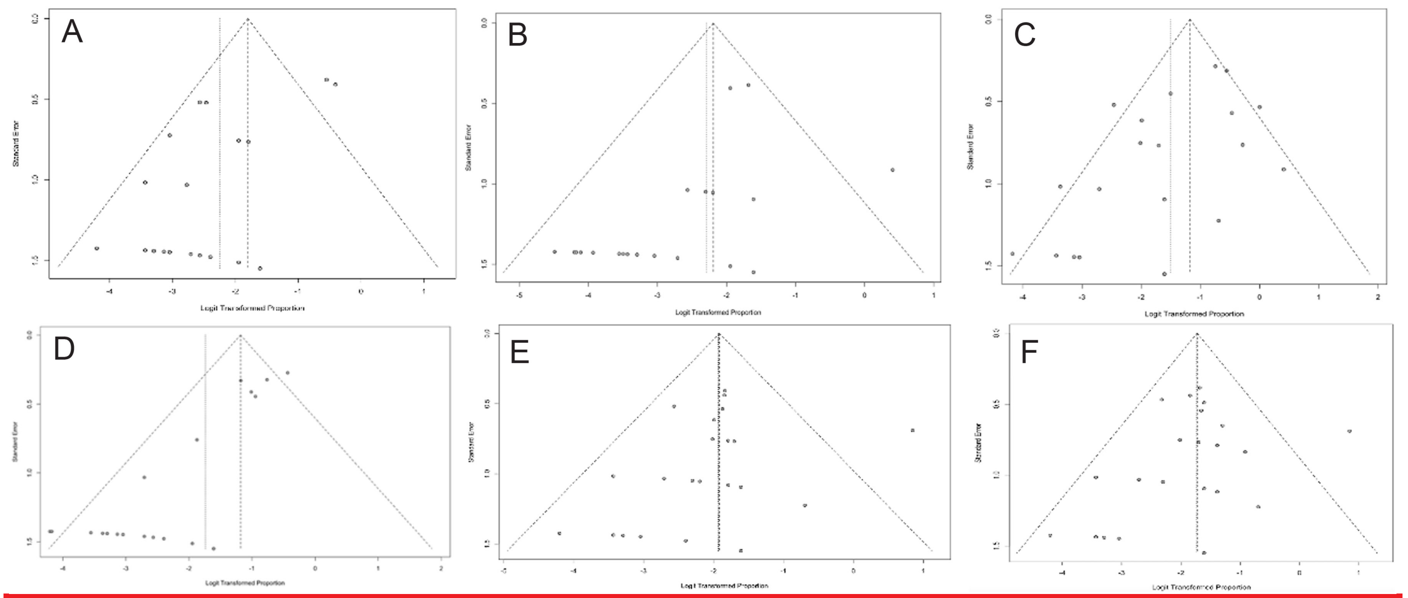
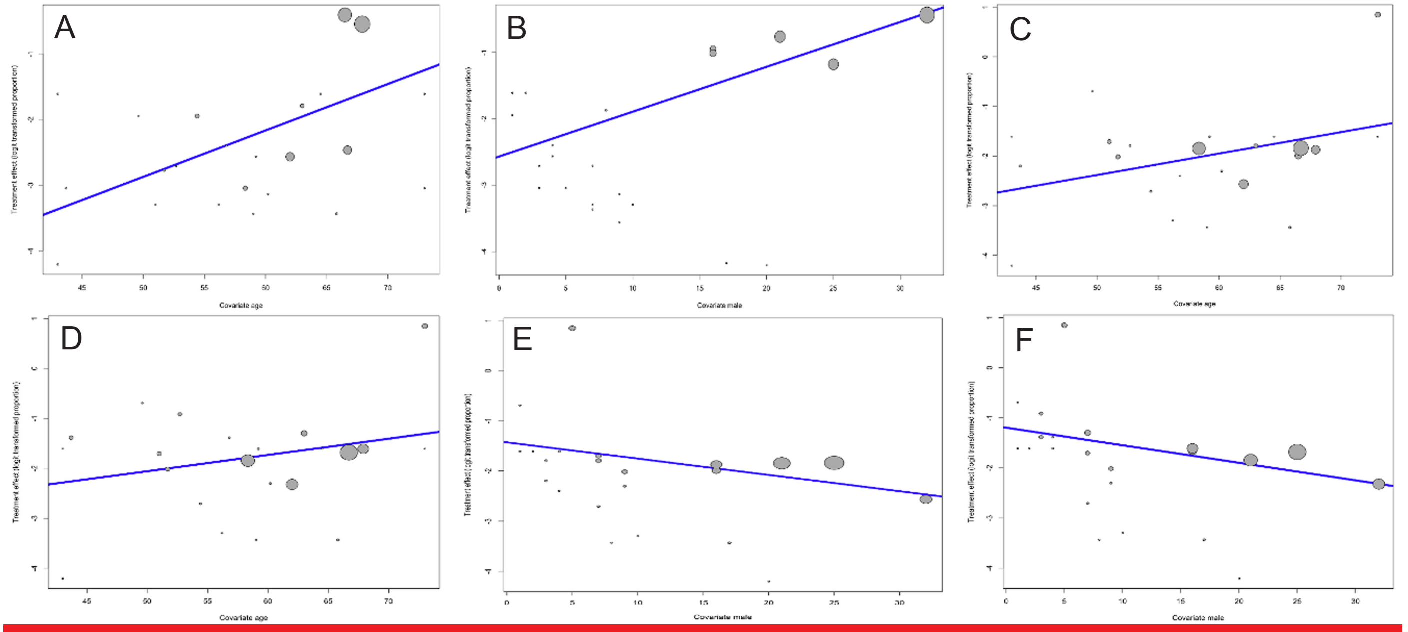


Supplementary Figure 1. (A) Funnel plot for major bleeding data in ART trials. B) Funnel plot for minor bleeding data in ART trials. C) Funnel plot for bradycardia-conduction disturbances data in ART trials. D) Funnel plot for worsening renal function data in ART trials. E) Funnel plot for PE-related deaths in ART trials. F) Funnel plot for all-cause deaths in ART trials.

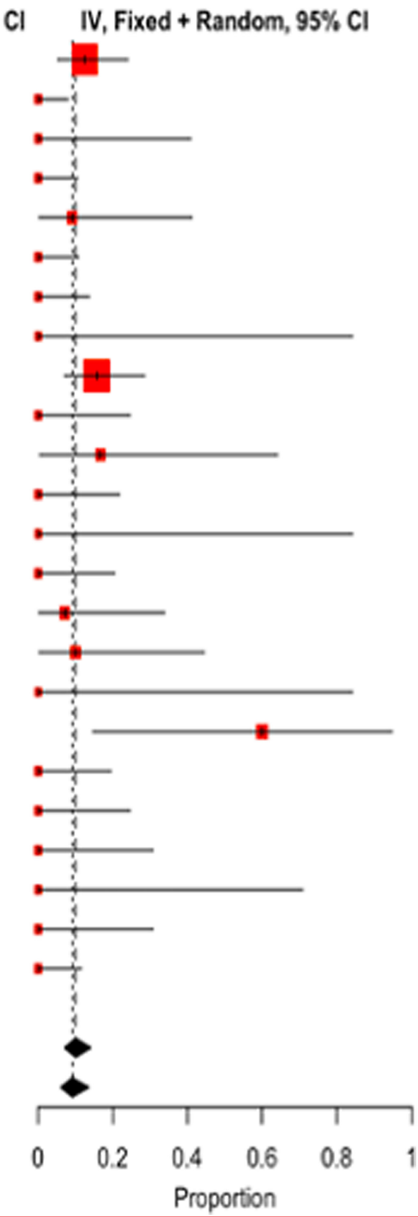


Supplementary Figure 2. (A) Increasing risk of major bleeding with aging in ART trials. B) Increased risk of worsening renal function in male gender in ART trials. C) Increased risk of PE-related mortality with aging in ART trials. D) Increased risk of all-cause mortality with aging in ART trials. E) Decreased risk of PE-related mortality after ART in male gender. F) Decreased risk of all-cause mortality after ART in male gender.

Minor bleeding

Study	Events	Total	Weight (common)	Weight (random)	IV, Fixed + Random, 95% CI
Akbal	7	56	23.9%	18.9%	0.125 [0.052; 0.241]
Li	0	44	1.9%	2.4%	0.000 [0.000; 0.080]
Latacz	0	7	1.8%	2.3%	0.000 [0.000; 0.410]
Pelliccia	0	33	1.9%	2.4%	0.000 [0.000; 0.106]
Hubbard	1	11	3.5%	4.2%	0.091 [0.002; 0.413]
Villalba	0	32	1.9%	2.4%	0.000 [0.000; 0.109]
Margheri	0	25	1.9%	2.4%	0.000 [0.000; 0.137]
Wong	0	2	1.6%	2.0%	0.000 [0.000; 0.842]
Chechi	8	51	26.3%	20.0%	0.157 [0.070; 0.286]
Das	0	13	1.9%	2.4%	0.000 [0.000; 0.247]
Siablis	1	6	3.3%	3.9%	0.167 [0.004; 0.641]
Nassiri	0	15	1.9%	2.4%	0.000 [0.000; 0.218]
Latacz	0	2	1.6%	2.0%	0.000 [0.000; 0.842]
Ferrigno	0	16	1.9%	2.4%	0.000 [0.000; 0.206]
Chauhan	1	14	3.6%	4.3%	0.071 [0.002; 0.339]
Bonvini	1	10	3.5%	4.2%	0.100 [0.003; 0.445]
Koning	0	2	1.6%	2.0%	0.000 [0.000; 0.842]
Voigtlander	3	5	4.7%	5.4%	0.600 [0.147; 0.947]
Zeni	0	17	1.9%	2.4%	0.000 [0.000; 0.195]
Spies	0	13	1.9%	2.4%	0.000 [0.000; 0.247]
Arzamendi	0	10	1.9%	2.3%	0.000 [0.000; 0.308]
Kuo	0	3	1.7%	2.1%	0.000 [0.000; 0.708]
Gong	0	10	1.9%	2.3%	0.000 [0.000; 0.308]
Vecchio	0	30	1.9%	2.4%	0.000 [0.000; 0.116]
Total (common effect, 95% CI)		**427**	**100.0%**	**--**	**0.101 [0.071; 0.141]**
Total (random effect, 95% CI)			**--**	**100.0%**	**0.092 [0.061; 0.136]**

Heterogeneity: $Tau^2 = 0.1088$; $Chi^2 = 25.40$, $df = 23$ ($P = 0.33$); $I^2 = 9\%$

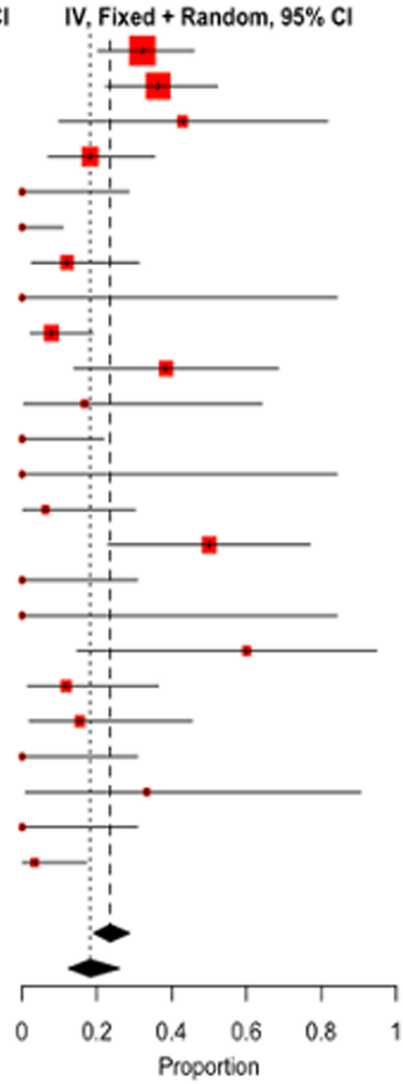


Supplementary Figure 3. Overall pooled rate of minor bleeding in ART trials.

Bradycardia-conduction disturbances

Study	Events	Total	Weight (common)	Weight (random)	IV, Fixed + Random, 95% CI
Akbal	18	56	22.6%	8.9%	0.321 [0.203; 0.460]
Li	16	44	18.8%	8.7%	0.364 [0.224; 0.522]
Latacz	3	7	3.2%	4.9%	0.429 [0.099; 0.816]
Pelliccia	6	33	9.1%	7.4%	0.182 [0.070; 0.355]
Hubbard	0	11	0.9%	2.1%	0.000 [0.000; 0.285]
Villalba	0	32	0.9%	2.1%	0.000 [0.000; 0.109]
Margheri	3	25	4.9%	6.0%	0.120 [0.025; 0.312]
Wong	0	2	0.8%	1.8%	0.000 [0.000; 0.842]
Chechi	4	51	6.8%	6.8%	0.078 [0.022; 0.189]
Das	5	13	5.7%	6.4%	0.385 [0.139; 0.684]
Siablis	1	6	1.5%	3.1%	0.167 [0.004; 0.641]
Nassiri	0	15	0.9%	2.1%	0.000 [0.000; 0.218]
Latacz	0	2	0.8%	1.8%	0.000 [0.000; 0.842]
Ferrigno	1	16	1.7%	3.4%	0.062 [0.002; 0.302]
Chauhan	7	14	6.5%	6.7%	0.500 [0.230; 0.770]
Bonvini	0	10	0.9%	2.1%	0.000 [0.000; 0.308]
Koning	0	2	0.8%	1.8%	0.000 [0.000; 0.842]
Voigtlander	3	5	2.2%	4.0%	0.600 [0.147; 0.947]
Zeni	2	17	3.3%	4.9%	0.118 [0.015; 0.364]
Spies	2	13	3.1%	4.8%	0.154 [0.019; 0.454]
Arzamendi	0	10	0.9%	2.1%	0.000 [0.000; 0.308]
Kuo	1	3	1.2%	2.7%	0.333 [0.008; 0.906]
Gong	0	10	0.9%	2.1%	0.000 [0.000; 0.308]
Vecchio	1	30	1.8%	3.5%	0.033 [0.001; 0.172]
Total (common effect, 95% CI)		**427**	**100.0%**	**--**	**0.236 [0.191; 0.287]**
Total (random effect, 95% CI)			**--**	**100.0%**	**0.182 [0.124; 0.260]**

Heterogeneity: $Tau^2 = 0.5232$; $Chi^2 = 48.08$, $df = 23$ ($P < 0.01$); $I^2 = 52\%$

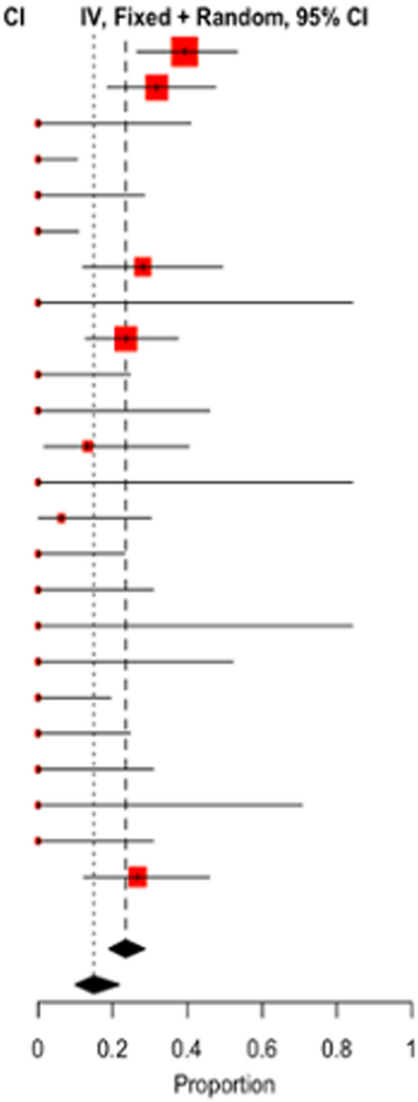


Supplementary Figure 4. Overall pooled rate of bradycardia-conduction disturbances in ART trials.

Worsening renal function

Study	Events	Total	Weight (common)	Weight (random)	IV, Fixed + Random, 95% CI
Akbal	22	56	24.9%	11.9%	0.393 [0.265; 0.532]
Li	14	44	17.8%	11.2%	0.318 [0.186; 0.476]
Latacz	0	7	0.9%	2.2%	0.000 [0.000; 0.410]
Pelliccia	0	33	0.9%	2.3%	0.000 [0.000; 0.106]
Hubbard	0	11	0.9%	2.2%	0.000 [0.000; 0.285]
Villalba	0	32	0.9%	2.3%	0.000 [0.000; 0.109]
Margheri	7	25	9.4%	9.4%	0.280 [0.121; 0.494]
Wong	0	2	0.8%	2.0%	0.000 [0.000; 0.842]
Chechi	12	51	17.1%	11.1%	0.235 [0.128; 0.375]
Das	0	13	0.9%	2.2%	0.000 [0.000; 0.247]
Siablis	0	6	0.9%	2.2%	0.000 [0.000; 0.459]
Nassiri	2	15	3.2%	5.7%	0.133 [0.017; 0.405]
Latacz	0	2	0.8%	2.0%	0.000 [0.000; 0.842]
Ferrigno	1	16	1.8%	3.8%	0.062 [0.002; 0.302]
Chauhan	0	14	0.9%	2.2%	0.000 [0.000; 0.232]
Bonvini	0	10	0.9%	2.2%	0.000 [0.000; 0.308]
Koning	0	2	0.8%	2.0%	0.000 [0.000; 0.842]
Voigtlander	0	5	0.9%	2.2%	0.000 [0.000; 0.522]
Zeni	0	17	0.9%	2.3%	0.000 [0.000; 0.195]
Spies	0	13	0.9%	2.2%	0.000 [0.000; 0.247]
Arzamendi	0	10	0.9%	2.2%	0.000 [0.000; 0.308]
Kuo	0	3	0.8%	2.1%	0.000 [0.000; 0.708]
Gong	0	10	0.9%	2.2%	0.000 [0.000; 0.308]
Vecchio	8	30	11.0%	9.9%	0.267 [0.123; 0.459]
Total (common effect, 95% CI)		**427**	**100.0%**	**--**	**0.235 [0.190; 0.286]**
Total (random effect, 95% CI)			**--**	**100.0%**	**0.150 [0.100; 0.218]**

Heterogeneity: $Tau^2 = 0.3894$; $Chi^2 = 40.79$, df = 23 ($P = 0.01$); $I^2 = 44\%$



Supplementary Figure 5. Overall pooled rate of worsening renal function in ART trials.

Supplementary Table 1. Procedural Characteristics and Changes in RV/LVr and Obstruction Scores Compared with Baseline

Author	Bilateral ART (%)	Unilateral ART (%)	Cath size, (Fr)	ART (sec)	Adjuvant t-PA (n)	Adjuvant t-PA (%)	RV/LV pre	RV/LV post	RV/LV Change (%)	Obst. Score pre	Obst. Score post	Obst. Score Change (%)
Koning[1997]	0	2	5		0	0						
Voigtlander[1999]	1	4	5		0	0				28.8	26	9.72
Zeni[2003]			6		10	58.8						
Siablis[2005]			6	528	4	66.7				18.83±2.9	6.83±2.8	63.72
Chauhan[2007]	10	4	6		5	35.7				17.9±2.9	11.8±2.5	34.07
Margheri[2008]			6		8	32						
Spies[2008]			6		4	30.8						
Kuo[2009]			6		2	66.6						
Vecchio[2008]			8		8	26.66				18.3±6.3	9.4±4.8	51.4
Chechi[2009]			6		11	21.6						
Arzamendi[2010]			8		2	20				22.4±2.8	9.8±2.7	56.25
Hubbard[2011]			7		8	72.7				23 (16-27)	13.5 (6-27)	41.3
Ferrigno[2011]			6		16	100				18.31±3.3	9.06±3.7	50.51
Wong[2012]	2	0	5		0	0						
Nassiri[2012]			6		10	67						
Bonvini[2013]	10	0	6		6	60				25±3.1	20±4.17	20
Latacz[2016]	2	0			0	0						
Das[2017]			6		0	0	1.43±0.23					
Latacz[2018]	1	6	6		0	0				22.71±5.69	12.28±8.68	45.91
Villalba[2019]			6		29	90.6	1.4 (1.1-2.5)			19.6±4.24	10.04±5.48	48.77
Li[2020]			6	15.6	40	90.9						43.46
Pelliccia[2020]			8		0	0	1.04±0.33	1.28±0.25	23.07	20.9±5.7	12.5±4.5	40.19
Gong[2021]			8	10		100						
Akbal[2022]	22	34	6	304	19	33.9	1.33±0.24	0.92±0.18	30.82	24.2±6.23	11.92±6.89	12.27

ART: Angiojet rheolytic thrombectomy, RV/LV: right ventricle diameter to left ventricle diameter ratio, Fr: French, t-PA: Tissue type plasminogen activator.

Supplementary Table 2. Changes in echocardiographic and hemodynamic measures of PASP and PAMP in ART trials

	Echocardiography			Right heart catheter				
Author	PASP pre (mm Hg)	PASP post (mm Hg)	PASP % change	PASP pre (mm Hg)	PASP post (mm Hg)	PAMP pre (mm Hg)	PAMP post (mm Hg)	PAMP % change
Koning[1997]				48	24			50
Voigtlander[1999]						34.7	26	25.07
Zeni[2003]								
Siablis[2005]								
Chauhan[2007]						32±7.2	28±6.4	12.5
Margheri[2008]								
Spies[2008]	48	47	2.08	47	45			4.25
Kuo[2009]				57.3±13.52	35.2±2.44			27.58
Vecchio[2008]				48.4±19.2	37.4±17.9			22.72
Chechi[2009]								
Arzamendi[2010]	60.7±19.9					34.6±13.11	26.9±8.2	22.25
Hubbard[2011]				38.6 (32-45)	28.7 (15-53)			25.64
Ferrigno[2011]						34.5±8	27.1±7	21.45
Wong[2012]								
Nassiri[2012]								
Bonvini[2013]				64±16.38	50±12.73			21.87
Latacz[2016]								
Das[2017]	37.1±7.2	28.75±11.9	22.5					
Latacz[2018]								
Villalba[2019]	53.5 (35-71)							
Li[2020]						48.41±11.76	33.48±8.99	30.84
Pelliccia[2020]	65±31	44±21	32.3					
Gong[2021]								
Akbal[2022]	56.7±14.3	40.2±13.4	29.1					

PASP and PAMP: pulmonary arterial systolic and mean pressures, respectively.