Randomized Controlled Trial of Ultrasound-Assisted Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism

Running title: Kucher et al.; Ultrasound thrombolysis for pulmonary embolism

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Abstract

Background—In patients with acute pulmonary embolism (PE), systemic thrombolysis improves right ventricular (RV) dilatation, is associated with major bleeding, and is withheld in many patients at risk. This multicenter randomized controlled trial investigated whether ultrasound-assisted catheter-directed thrombolysis (USAT) is superior to anticoagulation alone in the reversal of RV dilatation in intermediate-risk patients.

Methods and Results—Fifty-nine patients (63±14 years) with acute main or lower lobe PE and echocardiographic right-to-left ventricular dimension (RV/LV) ratio ≥1.0 were randomized to receive unfractionated heparin (UFH) and an USAT regimen of 10-20 mg rt-PA over 15 hours (N = 30, USAT group), or UFH alone (N = 29, heparin group). Primary outcome was the difference in the RV/LV ratio from baseline to 24 hours. Safety outcomes included death, major and minor bleeding, and recurrent venous thromboembolism (VTE) at 90 days. In the USAT group, the mean RV/LV ratio was reduced from 1.28±0.19 at baseline to 0.99±0.17 at 24 hours (p<0.001); in the heparin group, mean RV/LV ratio was 1.20±0.14 and 1.17±0.20, respectively (p=0.31). The mean decrease in RV/LV ratio from baseline to 24 hours was 0.30±0.20 versus 0.03±0.16 (p<0.001), respectively. At 90 days, there was one death (in the heparin group), no major bleeding, 4 minor bleedings (3 in the USAT group and 1 in the heparin group; p=0.61), and no recurrent VTE.

Conclusions—In PE patients at intermediate risk, a standardized USAT regimen was superior to anticoagulation with heparin alone in reversing RV dilatation at 24 hours, without an increase in bleeding complications.


Key words: pulmonary embolism
Introduction

Acute pulmonary embolism is a potentially life-threatening disease, spanning a wide spectrum of clinical outcomes.\(^1\) Hemodynamically stable patients with preserved right ventricular size and function are classified as low-risk patients and have excellent short-term prognosis once therapeutic levels of anticoagulation therapy are established.\(^2\) In contrast, hemodynamically unstable patients are at high-risk of death from worsening right ventricular failure and cardiogenic shock with a hospital mortality rate greater than 15\%.\(^3,4\) Approximately one quarter of hemodynamically stable patients with PE are at intermediate risk with mortality rates ranging from 3-15\% if imaging or biomarker evidence of right ventricular dilatation or dysfunction is present.\(^5,6\)

Systemic thrombolysis improves hemodynamic parameters,\(^7\) reverses right ventricular dilatation and dysfunction,\(^8,9\) but is associated with rates of major bleeding complications in up to 20\% and intracranial hemorrhage in up to 3\%.\(^10,11\) Systemic thrombolysis is standard treatment for high-risk PE,\(^2,11\) however it is withheld in more than two thirds of such patients.\(^4,12\) The use of systemic thrombolysis for patients at intermediate risk remains controversial. Current consensus guidelines recommend against the routine use of systemic thrombolysis in these patients.\(^11,13\)

An ideal PE reperfusion strategy should be effective in reversing right ventricular dysfunction and reducing adverse clinical events without causing an increase in the complication rate as compared to treatment with anticoagulation alone. Catheter interventions with or without locally administered thrombolysis have been performed with high clinical success rates,\(^14,15\) but clinical evidence from randomized trials is lacking for any of the various techniques. Ultrasound-assisted catheter-directed thrombolysis (USAT) combines conventional catheter-directed
thrombolysis (CDT) with high-frequency (2.2 MHz), low-power (0.5 Watt per element) ultrasound. Ultrasound itself cannot dissolve thrombus, however, it causes reversible disaggregation and separation of uncrosslinked fibrin fibers, increasing thrombus permeability for thrombolytic drugs. In addition, thrombus penetration of thrombolytic drugs is enhanced by acoustic streaming from ultrasound pressure waves. The ULTrasound Accelerated ThrombolysIs of PulMonAry Embolism (ULTIMA) trial investigated whether a standardized fixed-dose USAT regimen is superior to anticoagulation alone in the reversal of RV dilatation in intermediate-risk PE patients.

Methods

Patients and study design

From November 2010 to January 2013, 59 patients with intermediate-risk PE from 8 tertiary care hospitals in Germany and Switzerland were randomized in an open-label fashion to receive unfractionated heparin (UFH) and an USAT regimen of 10 mg rt-PA over 15 hours per treated lung via the EkoSonic® Endovascular System (N = 30, USAT group), or UFH alone (N = 29, heparin group). Randomization was performed in blocks of four without stratification.

Inclusion criteria were acute symptomatic PE confirmed by contrast-enhanced computed tomography (CT) with embolus located in at least one main or proximal lower lobe pulmonary artery and a right-to-left ventricular dimension (RV/LV) ratio ≥ 1 obtained from the echocardiographic apical four-chamber view. Exclusion criteria were age < 18 or > 80 years; index PE symptom duration > 14 days; insufficient echocardiographic image quality in the apical four-chamber view that prohibited the measurement of the RV/LV ratio; known significant bleeding risk; administration of thrombolytic agents within the previous 4 days; active bleeding;
known bleeding diathesis; known coagulation disorder; platelet count < 100 000/mm³; previous use of vitamin K antagonists with INR > 2.5 on admission; history of any intracranial or intraspinal surgery or trauma or intracranial/intraspinal bleeding; intracranial neoplasm, arteriovenous malformation, or aneurysm; gastrointestinal bleeding < 3 months; internal eye surgery or hemorrhagic retinopathy < 3 months; major surgery, cataract surgery, trauma, obstetrical delivery, cardiopulmonary resuscitation, or other invasive procedure < 10 days; allergy, hypersensitivity, or thrombocytopenia from heparin, rt-PA; severe contrast allergy to iodinated contrast; known right-to-left cardiac shunt, for example from a large patent foramen ovale or atrial septal defect; large (>10 mm) right atrial or right ventricular thrombus; hemodynamic decompensation defined as the need for cardiopulmonary resuscitation, or systolic blood pressure < 90 mm Hg for at least 15 min, or drop of systolic blood pressure by at least 40 mm Hg for at least 15 min with signs of end organ hypoperfusion (cold extremities or low urinary output < 30 mL/h or mental confusion), or need for catecholamine administration to maintain adequate organ perfusion and a systolic blood pressure of > 90 mm Hg; severe hypertension on repeated readings (systolic > 180 mmHg or diastolic > 105 mmHg); pregnancy, lactation or parturition < 30 days; participation in any other investigational drug or device study; life expectancy < 90 days; inability to comply with study assessments.

During the enrollment period, investigators registered screening failure patients with objectively confirmed PE. Overall, the screening failure rate was 84%, with anatomically small PE and an RV/LV ratio < 1 as the main reasons (Figure 1).

The study was approved by the ethics committees of the participating institutions, and all patients provided written informed consent prior to enrollment. ULTIMA is registered at ClinicalTrials.gov (NCT01166997).
Contrast-enhanced chest computed tomography

Digitized copies of the baseline chest CT scans were transferred to the CT core laboratory which confirmed the presence of PE in all enrolled patients. In addition, the core laboratory calculated the pulmonary occlusion score using the Qanadli index (range 0 to 40 points, maximum 20 points per lung). Non-obstructive embolus located in a lobar or main pulmonary artery received score points equal to the number of arising segmental branches (maximum 10 points per lung). A segmental artery containing non-obstructive embolus without thrombus in a proximal feeder artery received one score point. Score points were multiplied by two in case of obstructive embolus.

Anticoagulation therapy

Unfractionated heparin (UFH) was administered immediately after randomization as an intravenous bolus of 80 IU/Kg, followed by an infusion of 18 IU/kg/h (with a maximum initial infusion rate of 1800 IU/h). For patients already receiving UFH, low molecular weight heparin (LMWH) or fondaparinux before randomization, the initial UFH bolus was omitted. Patients who had received LMWH or fondaparinux at a weight-adjusted therapeutic dose, the start of the UFH infusion was delayed until 8-12 hours after the last LMWH injection and until 20-24 hours after the last fondaparinux injection. The UFH infusion was adjusted in order to achieve and maintain aPTT corresponding with therapeutic heparin levels (equivalent to 0.3 to 0.7 IU/mL by factor Xa inhibition). The minimum duration of the UFH infusion was 24 hours for all patients. Post-procedure anticoagulation therapy was left to the discretion of the investigators. Initiation of vitamin K antagonist or switch from UFH to LMWH or fondaparinux was allowed 36 hours after randomization. The minimum suggested duration of anticoagulation therapy was 3 months.

Standardized procedure of ultrasound-assisted catheter-directed thrombolysis (USAT)
In the USAT group, the time between the baseline echocardiogram and initiation of the catheter procedure had to be less than 4 hours. All patients were treated using EkoSonic MACH4e Endovascular Systems (EKOS Corporation; Bothell, WA). Bilateral device placement was suggested in case of embolus located in both main or proximal lower lobe pulmonary arteries.

The EkoSonic Endovascular System consists of three components: an Intelligent Drug Delivery Catheter (IDDC); a removable MicroSonic Device (MSD) containing multiple small ultrasound transducers distributed over the treatment zone; and the EkoSonic control unit. The insertion of the catheter system was performed at the cardiac catheterization laboratory with continuous haemodynamic and electrocardiographic monitoring. Venous access was obtained at the common femoral vein using a 6 French introducer sheath for patients who were scheduled for unilateral EkoSonic device placement or a 10 French double-lumen introducer sheath for those who were scheduled for bilateral EkoSonic device insertion. Invasive pressure tracings and a blood sample for the mixed venous oxygen saturation were obtained from the main pulmonary artery. Systemic arterial oxygen saturation was recorded either from a peripheral arterial blood sample or transcutaneous oxygen saturation measurement. Thereafter, a 0.035 inch guidewire and a standard diagnostic angiographic catheter were used to cross the embolic occlusion. The main and lower lobe pulmonary arteries were considered for catheter insertion only. With the guidewire tip in a safe position within a large lower lobe segmental branch, the angiographic catheter was exchanged for the IDDC. Finally, the guidewire was removed and the MSD was inserted into the IDDC.

A continuous infusion of rt-PA at 1 mg/hour and saline coolant at 35 ml/hour per catheter and intravascular ultrasound delivery were then initiated. After catheter placement, patients were transferred for continuous monitoring to the intermediate or intensive care unit. After 5 hours of
treatment, the infusion rate of rt-PA was reduced to 0.5 mg/hour per catheter for 10 hours. The maximum t-PA dose was 20 ± 1 mg for patients with bilateral device placement and 10 ± 0.5 mg for patients with unilateral device placement.

At 15 ± 1 hours, the rt-PA infusion and ultrasound delivery was discontinued. Thereafter, the EkoSonic devices were removed in the intermediate or intensive care unit. After removal of the MSD, invasive pressure tracings were recorded from the IDDC. Once a typical pressure tracing of the main pulmonary artery trunk was obtained, a blood sample for the follow-up mixed venous oxygen saturation was taken. Follow-up systemic arterial oxygen saturation was taken as described above. Finally, the IDDC and the introducer sheath were removed and the puncture site manually compressed until local haemostasis was achieved.

**Echocardiography**

Prior to the recruitment phase, core laboratory instructions for obtaining digitized echocardiographic images from standardized transthoracic cardiac views with electrocardiographic tracing were provided during an investigator meeting. Pulsed and continuous-waved Doppler studies were captured by still frames and 2D or color Doppler images by cine loops of at least 3 cardiac cycles from standardized cardiac views. Because RV/LV ratio > 1 was an inclusion criteria and the difference in RV/LV ratio from baseline to 24 hours the primary endpoint, particular attention was paid to obtain at least 3 adequate cine loops from the apical four-chamber view for the measurement of RV/LV ratio. Dicom-formatted echocardiographic images from the examinations at baseline, 24 ± 2 hours, and 90 days were transferred to the core laboratory for data acquisition. Echocardiographic measurements from the apical four-chamber view included the subannular end-diastolic RV/LV ratio (Figure 2) and tricuspid annular plane systolic excursion (TAPSE); from the parasternal short-axis and apical
four-chamber views, RV systolic dysfunction (none, mild, moderate, severe) was graded and the pressure gradient between the right ventricle and the right atrium obtained; the minimum diameter of the intrahepatic inferior vena cava was obtained from a subcostal view. The core laboratory was blinded to group assignment and reported the number of evaluable patients for the primary outcome measure to the Data Safety Monitoring Board (DSMB). The DSMB terminated patient enrollment after at least 25 patients in each group were known to be evaluable for the primary endpoint (Figure 1).

Data on baseline RV/LV ratio measured by the investigator were not available to the core laboratory but were compared to the data obtained by the core laboratory to assess interobserver agreement.

Outcome measures

The primary endpoint of ULTIMA was the difference in the RV/LV ratio from baseline to 24 hours, evaluated by the blinded core laboratory.

Patients were scheduled for a 90-day follow-up clinical visit and repeated echocardiography. Safety outcomes included death, hemodynamic decompensation as defined in the exclusion criteria, major and minor bleeding, recurrent venous thromboembolism (VTE), and serious adverse events up to 90 days post randomization. Major bleeding was defined as overt bleeding associated with a fall in the hemoglobin level of at least 2.0 g/dl or with transfusion of ≥ 2 units of red blood cells, or involvement of a critical site (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome).

Clinically overt bleeding not fulfilling the criteria of a major bleeding was classified as a minor bleeding complication. There was routine surveillance for recurrent VTE during 90-day follow-up. Recurrent VTE was diagnosed if suspected symptoms or signs of deep vein thrombosis or acute PE...
were objectively confirmed by an imaging test (new filling defect by pulmonary angiography or contrast-enhanced chest CT, new high-probability perfusion defect revealed by lung scan, or positive compression ultrasound study for deep vein thrombosis). There was no routine surveillance for asymptomatic recurrent VTE. Patient chart documents and case report forms were verified by independent data monitors. All clinical adverse events and secondary endpoints were adjudicated by the DSMB and the Clinical Event Reviewer.

Statistical analysis

Sample size assumptions were based on the Tenecteplase Italian Pulmonary Embolism Study (TIPES) in which therapy with weight-adjusted intravenous tenecteplase significantly reduced the RV/LV ratio at 24 hours by mean 0.31 (standard deviation: 0.20) and therapy with UFH alone resulted in a non-significant reduction in RV/LV ratio by mean 0.10 (standard deviation: 0.30).9 We assumed that USAT would have a similar effect on reducing RV/LV ratio at 24 hours as compared with tenecteplase and used the mean and standard deviations of the difference in RV/LV ratio from the tenecteplase and heparin groups for sample size calculation. The estimated sample size was 24 per group using a power of 80% at a two-sided p value of 0.05 by t-test.

Continuous data are presented as means ± standard deviations (SD) or in case of a skewed distribution as median values with ranges. Comparison of binary data between the groups was performed using the Fisher’s exact test. Within-group comparison of continuous data was performed using the two-sided paired t-test. Within-group ordinal data were compared using the two-sided Wilcoxon signed-rank test. Between-group continuous data were compared using the two-sided unpaired t-test or Wilcoxon rank sum test. Between-group ordinal data were compared using the exact Mantel-Haenszel chi-square test. Interobserver agreement for the echocardiographic baseline RV/LV ratio between the investigator and core laboratory
measurements was assessed by Bland-Altman analysis. All statistical analyses were performed using SAS software version 9.2.

Results

Clinical characteristics

Among the 59 patients, mean age was 63 ± 14 years and 53% were women. The most frequent comorbidities were systemic hypertension (59%), diabetes mellitus (17%), renal insufficiency (15%), and cancer (12%), with no difference between the study groups (Table 1). Baseline vital parameters including systemic arterial pressure, heart and respiratory rates, and oxygen saturation were similar between the groups, as well as core laboratory chest CT findings of the pulmonary occlusion score and RV/LV ratio.

Treatment details

Prior to enrollment, 11 (37%) patients in the USAT group and 9 (31%) in the heparin group had received antithrombotic treatment with weight adjusted doses of LMWH or fondaparinux (p = 0.78). The mean total UFH dose from randomization to 24 hours was lower in the USAT group than in the heparin group (29,045 ± 7,712 versus 32,873 ± 5,917 units; p = 0.04). In the USAT group, placement of the EKOS catheters was technically successful in all patients with a median procedure time of 42 (range 15-102) minutes. Twenty-six (87%) patients received a bilateral USAT procedure (one device per lung) with a mean total r-tPA dose of 20.8 ± 3.0 mg. Four (13%) patients received an unilateral USAT procedure (only one lung treated) with a mean total r-tPA dose of 10.5 ± 0.6 mg. The mean hospital stay was 8.9 ± 3.4 days in the USAT group and 8.6 ± 3.9 days in the heparin group (p = 0.80).

Interobserver agreement in baseline RV/LV ratio
In 54 (98%) of 55 analyzed patients, there was agreement between investigators and core laboratory for identifying patients with a baseline RV/LV ratio ≥ 1. The mean (± SD) difference in the baseline echocardiographic RV/LV ratio between investigator and core laboratory measurements was 0.02 ± 0.15 (Figure 3).

**Primary endpoint analysis**

In the USAT group, the mean RV/LV ratio was reduced from 1.28 ± 0.19 at baseline to 0.99 ± 0.17 at 24 hours (p <0.001). In the heparin group, mean RV/LV ratio was 1.20 ± 0.14 at baseline and 1.17 ± 0.20 at 24 hours (p = 0.31). The mean difference in RV/LV ratio from baseline to 24 hours was 0.30 ± 0.20 vs. 0.03 ± 0.16 (p < 0.001), respectively.

**Additional echocardiographic assessment**

There was no difference in any of the baseline echocardiographic right heart parameters between the groups except for tricuspid annular plane systolic excursion (TAPSE) which was lower in the USAT group than the heparin group (Table 2). From baseline to 24 hours, the between-group changes of all assessed echocardiographic right heart parameters were significant in favor of the USAT group. For example, early reduction in right ventricular-to-right atrial pressure gradient (surrogate for systolic pulmonary artery pressure) was significantly greater in the USAT group as compared with the control group (9.8 ± 9.9 mm Hg vs. 0.3 ± 10.9; p = 0.03) (Table 2). From baseline to 90 days, there was a significant difference in right ventricular systolic dysfunction and a trend in the difference in RV/LV ratio in favor of the USAT group.

**Invasive hemodynamic measurements in the USAT group**

In comparison to baseline, there was a significant reduction in pulmonary artery and right atrial pressure and an increase in cardiac index at completion of USAT (Table 3).

**Clinical outcomes**
At 90 days, there were no episodes of hemodynamic decompensation or recurrent VTE among the 59 patients. There were no deaths in the USAT group and one death from pancreatic cancer in the heparin group 20 days after randomization (p = 1.00). At the 90-day visit, all patients were on anticoagulation therapy with vitamin K antagonists or low molecular weight heparin. Overall, there were no major bleeding complications and 4 minor bleedings: 3 (10%) patients in the USAT group (two with transient hemoptysis without medical intervention, one with access-site groin hematoma managed with manual compression) and 1 (3%) patient in the heparin group with muscular hematoma at the injection site of low-molecular weight heparin during the index hospitalization and transient anal bleeding following endoscopic removal of colon polyp 80 days after enrollment)(p = 0.61). There were no serious adverse events related to the study treatments.

**Discussion**

In PE patients at intermediate risk of death, a standardized USAT regimen was superior to anticoagulation with heparin alone in reversing right ventricular dilatation at 24 hours, without an increase in bleeding complications.

The goal of reperfusion therapy is to facilitate right ventricular recovery, to increase systemic perfusion, to improve symptoms and survival, and to prevent chronic thromboembolic pulmonary hypertension. In ULTIMA, we found early improvement in all assessed echocardiographic parameters following a standardized USAT regimen whereas most echocardiographic parameters did not improve at 24 hours in the control group of patients treated with heparin alone. The difference in RV/LV ratio from baseline to 24 hours of 0.30 ± 0.20 following USAT compares well with the difference of 0.31 ± 0.20 after an intravenous bolus of weight-adjusted tenecteplase in the TIPES study. In a randomized-controlled trial comparing a
2-hour intravenous infusion of rt-PA (total dose of 100 mg) versus a double bolus of 10 units reteplase separated by 30 minutes, a significant reduction in pulmonary artery pressure and an increase in cardiac index within 24 hours was found in both groups. In ULTIMA, invasive hemodynamic measurements in the USAT group confirmed significant reduction in pulmonary artery pressure and an increase in cardiac index after completion of USAT. It is reasonable to suggest that fixed low-dose USAT is similarly effective in improving echocardiographic and hemodynamic parameters of right heart function within 24 hours in comparison to systemic full-dose thrombolysis. In the Pulmonary Embolism International Thrombolysis (PEITHO) trial of 1006 patients at intermediate risk, intravenous weight-adjusted tenecteplase as compared with anticoagulation with heparin alone reduced the composite primary endpoint of death and hemodynamic collapse within 7 days of randomization (2.6% vs 5.6%, p = 0.015), at the cost of an increased risk of major bleeding (11.5% vs 2.4%, p < 0.001). In ULTIMA, only one death occurred in the control group, and the study was too small to draw firm conclusions about the clinical efficacy and safety of USAT in comparison to anticoagulation alone. Of note, the ULTIMA patients were hemodynamically stable, and it remains unclear whether USAT with intrapulmonary r-tPA bolus is effective and safe in unstable PE patients at high risk of death from right ventricular failure.

The long-term benefit of early hemodynamic improvement following reperfusion treatment for acute PE is less well established. In a randomized controlled trial of systemic thrombolysis versus anticoagulation alone, there was persistent improvement in echocardiographic parameters of right ventricular function through 6-month follow-up in favor of the patients who underwent thrombolysis. In another randomized controlled trial of systemic urokinase versus heparin alone, pulmonary artery pressure and pulmonary vascular resistance at
rest and during exercise at 7-year follow-up were lower in the thrombolysis group.\textsuperscript{24} ULTIMA was not designed to show long-term superiority of USAT versus anticoagulation alone with regard to improvement in right ventricular enlargement. Although there was a late “catch-up” in patients with heparin alone, we found a trend for improvement in right ventricular enlargement and significantly improved right ventricular systolic function at 90 days in favor of USAT. Adequately sized studies are warranted to investigate whether USAT improves right ventricular enlargement and dysfunction in the long term. Although evidence from randomized trials is lacking, it is reasonable to suggest that a reperfusion strategy with early improvement in hemodynamic parameters may potentially reduce the incidence of chronic pulmonary hypertension, the main long-term complication of acute PE.

The standardization and reproducibility of echocardiographic parameters for assessing right ventricular function in patients with acute PE is debatable. In ULTIMA, we standardized the measurement of RV/LV ratio obtained from the apical four-chamber view and provided well-defined instructions to investigators and core laboratory prior to the enrollment period (Figure 2). The interobserver agreement between investigators and core laboratory for measuring RV/LV ratio was reasonable, confirming that this parameter may also be useful for future PE studies.

Although ULTIMA was not designed to show non-inferiority for bleeding complications in comparison with anticoagulation alone, it is very reassuring that no major bleeding complication was observed following a standardized USAT regimen. A clinical study (NCT01513759) designed to confirm the safety of fixed low-dose USAT for patients with acute intermediate and high-risk PE is ongoing.

The study has several limitations. First, the contribution of ultrasound to the thrombolysis effect remains unclear because of the lack of a thrombolysis control group without ultrasound.
An ongoing randomized controlled trial in patients with ilio-femoral deep vein thrombosis aims to quantify the incremental thrombolytic effect of adding ultrasound to fixed low-dose local thrombolysis (NCT01482273). Second, we cannot rule out selection bias because it is possible that not all eligible patients presenting to the participating institutions were screened and considered for enrollment. Among the screened patients, most eligible patients were enrolled (see reasons for screening failure in Figure 1). Third, quality of anticoagulation therapy with dose adjustments of UFH (according to aPTT levels) and of vitamin K antagonists (according to INR values) was left to the investigators, and it was not monitored in ULTIMA. Of note, there were no recurrent symptomatic VTE events and no major bleeding episodes at 90 days in the treatment groups. Fourth, assessment of residual embolic burden by repeated contrast-enhanced CT was not performed. In a recent study, a similar USAT regimen significantly reduced the CT-angiographic pulmonary clot burden as assessed by the modified Miller score approximately two days after initiation of treatment.20 Finally, data sets for additional right ventricular echocardiographic analyses were incomplete for several patients due to poor quality of the echocardiographic images.

In summary, ULTIMA is the first randomized trial to test a standardized catheter intervention procedure in patients with acute PE and confirmed that a fixed-dose USAT regimen was superior to anticoagulation with heparin alone in improving right ventricular dysfunction at 24 hours.

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Conflict of Interest Disclosures: Dr. Kucher reports being consultant for EKOS Corp and having received honoraria from Sanofi-Aventis, Boehringer Ingelheim, Pfizer, Bristol Myers Squib, and Bayer. The other authors report no conflict interest.

References:


5. Fremont B, Pacouret G, Jacobi D, Puglisi R, Charbonnier B, de Labriolle A. Prognostic value
of echocardiographic right/left ventricular end-diastolic diameter ratio in patients with acute pulmonary embolism: Results from a monocenter registry of 1,416 patients. Chest. 2008;133:358-362.


Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>USAT group (N = 30)</th>
<th>Heparin group (N = 29)</th>
<th>p</th>
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<tr>
<td>Age (years), mean ± SD</td>
<td>64 ± 15</td>
<td>62 ± 13</td>
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<td>Body mass index, mean ± SD</td>
<td>31 ± 7</td>
<td>29 ± 7</td>
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<td>Women, N (%)</td>
<td>19 (63%)</td>
<td>12 (41%)</td>
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<tr>
<td><strong>Comorbidities and risk factors</strong></td>
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<td>Systemic hypertension, N (%)</td>
<td>20 (67%)</td>
<td>15 (52%)</td>
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<tr>
<td>Tobacco use, N (%)</td>
<td>4 (13%)</td>
<td>7 (24%)</td>
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<tr>
<td>Diabetes mellitus, N (%)</td>
<td>6 (20%)</td>
<td>4 (14%)</td>
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<td>Renal insufficiency (creatinine clearance &lt; 50 ml per minute), N (%)</td>
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<td>Coronary artery disease, N (%)</td>
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<td>Prior stroke, N (%)</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
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<td>Prior deep vein thrombosis</td>
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<td>9 (31%)</td>
<td>0.13</td>
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<tr>
<td>Prior pulmonary embolism</td>
<td>4 (13%)</td>
<td>2 (7%)</td>
<td>0.67</td>
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<td><strong>PE severity</strong></td>
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<tr>
<td>Tachycardia &gt; 100 beats per minute, N (%)</td>
<td>8 (27%)</td>
<td>7 (24%)</td>
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<td>Systolic arterial pressure (mm Hg), mean ± SD</td>
<td>137 ± 19</td>
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<td>Oxygen saturation during oxygen supplement (%), mean ± SD</td>
<td>96 ± 3</td>
<td>96 ± 3</td>
<td>0.92</td>
</tr>
<tr>
<td>Troponin test positive, N (%)</td>
<td>16/20 (80%)</td>
<td>17/22 (77%)</td>
<td>1.00</td>
</tr>
<tr>
<td>RV/LV ratio by computed tomography, mean ± SD</td>
<td>1.4 ± 0.3</td>
<td>1.3 ± 0.2</td>
<td>0.56</td>
</tr>
<tr>
<td>Pulmonary occlusion score by computed tomography, median (min-max)</td>
<td>27 (9-36)</td>
<td>24 (13-38)</td>
<td>0.24</td>
</tr>
<tr>
<td>Bilateral main pulmonary artery embolism, N (%)</td>
<td>12 (40%)</td>
<td>5 (17%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Bilateral lower lobe pulmonary artery embolism, N (%)</td>
<td>22 (73%)</td>
<td>25 (86%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Unilateral main pulmonary artery embolism, N (%)</td>
<td>8 (27%)</td>
<td>10 (34%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Unilateral lower lobe pulmonary artery embolism, N (%)</td>
<td>6 (20%)</td>
<td>2 (7%)</td>
<td>0.25</td>
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</tbody>
</table>
Table 2. Echocardiographic core laboratory data

<table>
<thead>
<tr>
<th></th>
<th>Baseline USAT</th>
<th>Baseline Heparin</th>
<th>24 hours USAT</th>
<th>24 hours Heparin</th>
<th>90 days USAT</th>
<th>90 days Heparin</th>
<th>Difference: Baseline - 24 hours USAT</th>
<th>Difference: Baseline - 24 hours Heparin</th>
<th>Difference: Baseline - 90 days USAT</th>
<th>Difference: Baseline - 90 days Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RV/LV ratio, mean±SD</strong></td>
<td></td>
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<tr>
<td>N</td>
<td>26</td>
<td>29</td>
<td>26</td>
<td>28</td>
<td>26</td>
<td>28</td>
<td>p&lt;0.001</td>
<td>p=0.07</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Between group comparison</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Within group comparison</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>p=0.001</td>
<td>p=0.31</td>
<td></td>
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<tr>
<td><strong>RV systolic dysfunction, N</strong></td>
<td></td>
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<tr>
<td>None/mild/moderate/severe</td>
<td>0/4/5/16</td>
<td>0/5/11/13</td>
<td>5/10/10/2</td>
<td>1/9/7/11</td>
<td>19/5/0/0</td>
<td>10/15/1/1</td>
<td>1.1±0.8*</td>
<td>0.3±0.4*</td>
<td>2.2±0.9*</td>
<td>1.5±0.9*</td>
</tr>
<tr>
<td>Between group comparison</td>
<td>p=0.37</td>
<td>p=0.01</td>
<td>p=0.003</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td></td>
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</tr>
<tr>
<td>Within group comparison</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>p&lt;0.001</td>
<td>p=0.02</td>
<td>p&lt;0.001</td>
<td>p=0.01</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>TAPSE (mm), mean±SD</strong></td>
<td></td>
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<tr>
<td>N</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>23</td>
<td>19</td>
<td>23</td>
<td>16±4.4</td>
<td>0.9±4.9</td>
<td>-6.1±4.6</td>
<td>-3.4±5.4</td>
</tr>
<tr>
<td>Between group comparison</td>
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<td></td>
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<tr>
<td>Within group comparison</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>p=0.014</td>
<td>p=0.43</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p=0.02</td>
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<tr>
<td><strong>RV/RA pressure gradient</strong></td>
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<tr>
<td>(mmHg), mean±SD</td>
<td>42.8±16.6</td>
<td>42.2±16.3</td>
<td>33.9±13.2</td>
<td>40.2±13.3</td>
<td>33.1±13.1</td>
<td>29.9±17.7</td>
<td>9.8±9.9</td>
<td>0.3±10.9</td>
<td>12.3±12.8</td>
<td>11.6±15.1</td>
</tr>
<tr>
<td>N</td>
<td>17</td>
<td>22</td>
<td>14</td>
<td>21</td>
<td>12</td>
<td>13</td>
<td>11±3.9</td>
<td>0.7±5.0</td>
<td>4.0±9.1</td>
<td>6.1±5.4</td>
</tr>
<tr>
<td>Between group comparison</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Within group comparison</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>p=0.01</td>
<td>p=0.91</td>
<td>p=0.01</td>
<td>p=0.01</td>
<td>p=0.03</td>
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</tr>
<tr>
<td><strong>Minimum IVC diameter</strong></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mm), mean±SD</td>
<td>15.5±6.2</td>
<td>14.4±4.3</td>
<td>10.8±3.4</td>
<td>17.4±6.8</td>
<td>9.4±3.6</td>
<td>9.9±5.2</td>
<td>7.2±3.9</td>
<td>0.7±5.0</td>
<td>4.0±9.1</td>
<td>6.1±5.4</td>
</tr>
<tr>
<td>N</td>
<td>10</td>
<td>10</td>
<td>8</td>
<td>10</td>
<td>8</td>
<td>13</td>
<td>6±7</td>
<td>7±7</td>
<td>4±7</td>
<td>7±7</td>
</tr>
<tr>
<td>Between group comparison</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within group comparison</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>p=0.01</td>
<td>p=0.72</td>
<td>p=0.44</td>
<td>p=0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Differences between neighboring categories of right ventricular systolic dysfunction were scored as 1.

IVC = inferior vena cava; RV/RA = right ventricular to right atrial; RV/LV = right ventricular to left ventricular; TAPSE = tricuspid annular systolic excursion
Table 3. Invasive hemodynamic measurements in patients from the USAT group

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up*</th>
<th>Difference: Baseline - Follow-up</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary artery systolic pressure (mmHg)</td>
<td>52.0 ± 11.5</td>
<td>39.7 ± 10.3</td>
<td>12.3 ± 10.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>n = 27</td>
<td>n = 26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery diastolic pressure (mmHg)</td>
<td>19.6 ± 8.1</td>
<td>16.2 ± 5.4</td>
<td>3.2 ± 7.8</td>
<td>0.049</td>
</tr>
<tr>
<td></td>
<td>n = 27</td>
<td>n = 26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery mean pressure (mmHg)</td>
<td>30.2 ± 9.1</td>
<td>24.1 ± 6.7</td>
<td>5.7 ± 7.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>n = 27</td>
<td>n = 26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right atrial mean pressure (mmHg)</td>
<td>12.5 ± 6.0</td>
<td>8.8 ± 4.1</td>
<td>4.5 ± 7.3</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>n = 24</td>
<td>n = 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.5 ± 0.5</td>
<td>3.9 ± 2.3</td>
<td>-0.7 ± 0.6</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>n = 16</td>
<td>n = 15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Follow-up hemodynamic data were obtained at 18 ± 3 hours after initiation of therapy
Figure Legends:

Figure 1. Study flow chart. Overall, six patients (five in the USAT group and one in the heparin group) were not evaluable for the primary outcome analysis due to inadequate echocardiographic images. Two patients in the heparin group had no follow-up visit due to death in one patient and hospitalization for major depression in another patient.

Figure 2. Instructions for study sites and the core laboratory for the measurement of the subannular RV/LV ratio from the echocardiographic apical four-chamber view: 1. Obtain an end-diastolic image defined as last available image prior to the onset tricuspid valve closure, 2. Obtain center line through interventricular septum (grey vertical line). 3. Obtain tricuspid annular line (grey horizontal line) at septal insertion point of tricuspid valve (oblique arrow), perpendicular to interventricular septum line. 4. Obtain subannular line 1 cm above and parallel to annular line (vertical arrow). 5. Obtain RV and LV dimensions on the subannular line using endocardial borders (red arrows). 6. Calculate the RV/LV ratio.

Figure 3. Bland-Altman interobserver agreement plot of baseline RV/LV ratio measured from investigators and core laboratory. The x-axis depicts RV/LV ratio by core laboratory plus RV/LV ratio by investigator divided by two; the y-axis depicts RV/LV ratio from the core laboratory minus the RV/LV ratio by investigator. All measurements (except one) were within the limits of agreement, i.e., within two standard deviations of the RV/LV ratio mean difference.
PE patients diagnosed by Chest CT (N = 363)

Screening failure: N = 304 (84%)
- No main pulmonary artery embolism at CT (N = 125)
- RV/LV ratio < 1 at CT or echocardiography (N = 82)
- Active bleeding or increased risk of bleeding (N = 19)
- High-risk PE (N = 16)
- Major surgery or trauma within 10 days (N = 13)
- Asymptomatic or symptom duration > 14 days (N = 13)
- No patient consent (N = 12)
- Age > 80 years (N = 11)
- Life expectancy < 3 months (N = 6)
- Other reasons (N = 7)

Randomization (N = 59)

Data Safety Monitoring Board:
Randomization terminated if at least 25 patients per group with evaluable primary endpoint (RV/LV ratio) identified

Echocardiography Core Lab:
Blind assessment of echocardiograms

Received USAT + Heparin (N = 30)
- Primary endpoint evaluable (N = 25)
- FU visit at 3 months (N = 30)

Received Heparin alone (N = 29)
- Primary endpoint evaluable (N = 28)
- FU visit at 3 months (N = 27)

Figure 1
Figure 2
Figure 3
Randomized Controlled Trial of Ultrasound-Assisted Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism

Nils Kucher, Peter Boekstegers, Oliver Müller, Christian Kupatt, Jan Beyer-Westendorf, Thomas Heitzer, Ulrich Tebbe, Jan Horstkotte, Ralf Müller, Erwin Blessing, Martin Greif, Philipp Lange, Ralf-Thorsten Hoffmann, Sebastian Werth, Achim Barmeyer, Dirk Härtel, Henriette Grünwald, Klaus Empen and Iris Baumgartner

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