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

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

**Background**—In patients with acute pulmonary embolism, 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 pulmonary embolism and echocardiographic RV to left ventricular dimension (RV/LV) ratio ≥1.0 were randomized to receive unfractionated heparin and an USAT regimen of 10 to 20 mg recombinant tissue plasminogen activator over 15 hours (n=30; USAT group) or unfractionated heparin 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 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 ratios were 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 1 death (in the heparin group), no major bleeding, 4 minor bleeding episodes (3 in the USAT group and 1 in the heparin group; P=0.61), and no recurrent venous thromboembolism.

**Conclusions**—In patients with pulmonary embolism 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.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01166997.

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**Key Words:** pulmonary embolism

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

**Editorial see p 420**

**Clinical Perspective on p 486**

Systemic thrombolysis improves hemodynamic parameters and reverses RV dilatation and dysfunction but is associated with rates of major bleeding complications in up to 20% and intracranial hemorrhage in up to 3%. Systemic thrombolysis is standard treatment for high-risk PE; however, it is withheld in more than two thirds of such patients. 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 RV dysfunction and reducing adverse clinical events without causing an increase in the complication rate compared with 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 with high-frequency (2.2 MHz), low-power (0.5 W per element) ultrasound. Ultrasound itself cannot dissolve thrombus; however, it causes reversible disaggregation and separation of un–cross-linked fibrin fibers, increasing thrombus permeability for thrombolytic drugs.16–18 In addition, thrombus penetration by 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 recombinant tissue plasminogen activator (rtPA) 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 4 without stratification.

Inclusion criteria were acute symptomatic PE confirmed by contrast-enhanced computed tomography (CT) with embolus located in at least 1 main or proximal lower lobe pulmonary artery and RV to left ventricular dimension (RV/LV) ratio ≥1 obtained from the echocardiographic apical 4-chamber view. Exclusion criteria were age <18 or >80 years; index PE symptom duration >14 days; insufficient echocardiographic image quality in the apical 4-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 international normalized ratio ≥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, obstetric delivery, cardiopulmonary resuscitation, or other invasive procedure <10 days; allergy, hypersensitivity, or thrombocytopenia from heparin or rtPA; severe contrast allergy to iodinated contrast; known right-to-left cardiac shunt (eg, from a large patent foramen ovale or atrial septal defect); large (>10 mm) right atrial or RV thrombus; hemodynamic decompensation, defined as the need for cardiopulmonary resuscitation, or systolic blood pressure <90 mm Hg for at least 15 minutes, or drop of systolic blood pressure by at least 40 mm Hg for at least 15 minutes 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 mm Hg or diastolic >105 mm Hg); pregnancy, lactation, or parturition <30 days; participation in any other investigational drug or device study; life expectancy <90 days; and 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 a 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 before enrollment. ULTIMA is registered at http://www.clinicaltrials.gov (NCT01166997).

Figure 1. Study flow chart. Overall, 6 patients (5 in the ultrasound-assisted catheter-directed thrombolysis [USAT] group and 1 in the heparin group) were not evaluable for the primary outcome analysis because of inadequate echocardiographic images. Two patients in the heparin group had no follow-up (FU) visit because of death in 1 patient and hospitalization for major depression in another patient. CT indicates computed tomography; PE, pulmonary embolism; and RV/LV, right ventricular to left ventricular.

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)
Contrast-Enhanced Chest CT
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, 0–40 points; maximum, 20 points per lung). Nonobstructive 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 nonobstructive embolus without thrombus in a proximal feeder artery received 1 score point. Score points were multiplied by 2 in case of obstructive embolus.

Anticoagulation Therapy
UFH was administered immediately after randomization as an intravenous bolus of 80 IU/kg, followed by an infusion of 18 IU/kg per hour (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. For patients who had received LMWH or fondaparinux at a weight-adjusted therapeutic dose, the start of the UFH infusion was delayed until 8 to 12 hours after the last LMWH injection and until 20 to 24 hours after the last fondaparinux injection. The UFH infusion was adjusted to achieve and maintain activated partial thromboplastin time corresponding to therapeutic heparin levels (equivalent to 0.3–0.7 IU/mL by factor Xa inhibition). The minimum duration of the UFH infusion was 24 hours for all patients. Postprocedure anticoagulation therapy was left to the discretion of the investigators. Initiation of vitamin K antagonist or a switch from UFH to LMWH or fondaparinux was suggested in case of embolus located in both main or proximal lower lobe pulmonary arteries.

Standardized Procedure of USAT
In the USAT group, the time between the baseline echocardiogram and initiation of the catheter procedure had to be <4 hours. All patients were treated with the use of 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 3 components: an Intelligent Drug Delivery Catheter (IDDC); a removable MicroSonic Device 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 ECG monitoring. Venous access was obtained at the common femoral vein with the use of a 6F introducer sheath for patients who were scheduled for unilateral EkoSonic device placement or a 10F double-lumen introducer sheath for those who were scheduled for bilateral EkoSonic device insertion. Invasive pressure recordings and a blood sample for mixed venous oxygen saturation measurement 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 MicroSonic Device was inserted into the IDDC.

A continuous infusion of rtPA at 1 mg/h and saline coolant at 35 mL/h 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 rtPA was reduced to 0.5 mg/h per catheter for 10 hours. The maximum tPA 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 rtPA infusion and ultrasound delivery were discontinued. Thereafter, the EkoSonic devices were removed in the intermediate or intensive care unit. After removal of the MicroSonic Device, 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 was manually compressed until local hemostasis was achieved.

Echocardiography
Before the recruitment phase, core laboratory instructions for obtaining digitized echocardiographic images from standardized transthoracic cardiac views with ECG tracings were provided during an investigator meeting. Pulsed and continuous-wave Doppler studies were captured by still frames and 2-dimensional or color Doppler images from cine loops of at least 3 cardiac cycles from standardized cardiac views. Because a RV/LV ratio >1 was an inclusion criterion, and the difference in RV/LV ratio from baseline to 24 hours was the primary end point, particular attention was paid to obtain at least 3 adequate cine loops from the apical 4-chamber view for the measurement of RV/LV ratio. DICOMformatted 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 4-chamber view included the subannular end-diastolic RV/LV ratio (Figure 2) and tricuspid annular plane systolic excursion. From the parasternal short-axis and apical 4-chamber views, RV systolic dysfunction (none, mild, moderate, severe) was graded, and the pressure gradient between the RV and the right atrium was 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. The Data Safety Monitoring Board terminated patient enrollment after at least 25 patients in each group were known to be evaluable for the primary end point (Figure 1).

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

![Figure 2. Instructions for study sites and core laboratory for measurement of subannular right ventricular to left ventricular (RV/LV) ratio from the echocardiographic apical 4-chamber view: (1) Obtain an end-diastolic image defined as last available image before onset of tricuspid valve closure. (2) Obtain center line through interventricular septum (gray vertical line). (3) Obtain tricuspid annular line (gray 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 subannular line with the use of endocardial borders (red arrows). (6) Calculate RV/LV ratio.](http://circ.ahajournals.org/)

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Outcome Measures
The primary end point 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 after 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 U of red blood cells or involvement of a critical site (intracranial, intraspinal, intracardiac, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome). Clinically overt bleeding not fulfilling the criteria of 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 end points were adjudicated by the Data Safety Monitoring Board 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 a mean of 0.31 (SD 0.20), and therapy with UFH alone resulted in a nonsignificant reduction in RV/LV ratio by a mean of 0.10 (SD 0.30). We assumed that USAT would have a similar effect on reducing RV/LV ratio at 24 hours compared with tenecteplase and used the means and SDs 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 with a power of 80% at a 2-sided P value of 0.05 by t test.

Continuous data are presented as mean±SD or, in case of a skewed distribution, as median values with ranges. Comparison of binary data between the groups was performed with the Fisher exact test. Within-group comparisons of continuous data were performed with the 2-sided paired t test. Within-group ordinal data were compared with the 2-sided Wilcoxon signed-rank test. Between-group continuous data were compared with the 2-sided unpaired t test or Wilcoxon rank sum test. Between-group ordinal data were compared with the exact Mantel-Haenszel χ² 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 with the use of 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
Before enrollment, 11 patients (37%) 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 (29045±7712 versus 32873±5917 U; 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 patients (87%) received a bilateral USAT procedure (only 1 lung treated), with a mean total rtPA 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 the 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 End Point 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, the 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 versus 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, which was lower in the USAT group than in 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 RV to right atrial pressure gradient (surrogate for systolic pulmonary artery pressure) was significantly greater in the USAT group than in the control group (9.8±9.9 versus 0.3±10.9 mmHg; P=0.03; Table 2). From baseline to 90 days, there was a significant difference in RV 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 1 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 LMWH. Overall, there were no major bleeding complications and 4 minor bleeding episodes: 3 patients (10%) in the USAT group (2 with transient hemoptysis without medical intervention, 1 with access-site groin hematoma managed with manual compression) and 1 patient (3%) in the heparin group with muscular hematoma at the injection site of LMWH during the index hospitalization and transient anal bleeding after endoscopic removal of a 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 RV dilatation at 24 hours, without an increase in bleeding complications.

The goal of reperfusion therapy is to facilitate RV 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 after 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 after USAT compares well with the difference of 0.31±0.20 after an intravenous bolus of weight-adjusted tenecteplase in the TIPES trial. In a randomized, controlled trial comparing a 2-hour intravenous infusion of rtPA (total dose of 100 mg) versus a double bolus of 10 U reteplase separated by 30 minutes, a significant reduction in pulmonary artery pressure and an increase in cardiac index within 24 hours were found in both groups. In ULTIMA, invasive hemodynamic measurements in the USAT group confirmed a 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

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**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>USAT Group (n=30)</th>
<th>Heparin Group (n=29)</th>
<th>$P$ Value</th>
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</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Age, mean±SD, y</td>
<td>64±15</td>
<td>62±13</td>
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<tr>
<td>Body mass index, mean±SD</td>
<td>31±7</td>
<td>29±7</td>
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<tr>
<td>Women, n (%)</td>
<td>19 (63)</td>
<td>12 (41)</td>
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<td><strong>Comorbidities and risk factors</strong></td>
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<td></td>
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<tr>
<td>Systemic hypertension, n (%)</td>
<td>20 (67)</td>
<td>15 (52)</td>
<td>0.29</td>
</tr>
<tr>
<td>Tobacco use, n (%)</td>
<td>4 (13)</td>
<td>7 (24)</td>
<td>0.33</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
<td>6 (20)</td>
<td>4 (14)</td>
<td>0.73</td>
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<td>Renal insufficiency (creatinine clearance &lt;50 mL/min), n (%)</td>
<td>4 (13)</td>
<td>5 (17)</td>
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<td>Cancer, n (%)</td>
<td>5 (17)</td>
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<td>Congestive heart failure, n (%)</td>
<td>2 (7)</td>
<td>1 (3)</td>
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<tr>
<td>Coronary artery disease, n (%)</td>
<td>2 (7)</td>
<td>1 (3)</td>
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<td>Prior stroke, n (%)</td>
<td>0 (0)</td>
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<tr>
<td>Prior deep vein thrombosis, n (%)</td>
<td>4 (13)</td>
<td>9 (31)</td>
<td>0.13</td>
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<tr>
<td>Prior PE, n (%)</td>
<td>4 (13)</td>
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<tr>
<td><strong>PE severity</strong></td>
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<td></td>
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<tr>
<td>Tachycardia &gt;100 bpm, n (%)</td>
<td>8 (27)</td>
<td>7 (24)</td>
<td>1.00</td>
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<td>Systolic arterial pressure, mean±SD, mmHg</td>
<td>137±19</td>
<td>131±18</td>
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<td>Diastolic arterial pressure, mean±SD, mmHg</td>
<td>80±13</td>
<td>77±13</td>
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<td>Heart rate, mean±SD, bpm</td>
<td>88±13</td>
<td>86±12</td>
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<td>Respiratory rate, mean±SD, per minute</td>
<td>20±6</td>
<td>20±8</td>
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<td>Oxygen saturation during oxygen supplement, mean±SD, %</td>
<td>96±3</td>
<td>96±3</td>
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<td>Troponin test positive, n (%)</td>
<td>16/20 (80)</td>
<td>17/22 (77)</td>
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<td>RV/LV ratio by CT, mean±SD</td>
<td>1.4±0.3</td>
<td>1.3±0.2</td>
<td>0.56</td>
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<td>Pulmonary occlusion score by CT, median (minimum–maximum)</td>
<td>27 (9–36)</td>
<td>24 (13–38)</td>
<td>0.24</td>
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<tr>
<td>Bilateral main pulmonary artery embolism, n (%)</td>
<td>12 (40)</td>
<td>5 (17)</td>
<td>0.08</td>
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<tr>
<td>Bilateral lower-lobe pulmonary artery embolism, n (%)</td>
<td>22 (73)</td>
<td>25 (86)</td>
<td>0.33</td>
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<tr>
<td>Unilateral main pulmonary artery embolism, n (%)</td>
<td>8 (27)</td>
<td>10 (34)</td>
<td>0.58</td>
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<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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CT indicates computed tomography; PE, pulmonary embolism; RV/LV, right ventricular to left ventricular; and USAT, ultrasound-assisted catheter-directed thrombolysis.
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 compared with anticoagulation with heparin alone reduced the composite primary end point of death and hemodynamic collapse within 7 days of randomization (2.6% versus 5.6%; \( P =0.015 \)), at the cost of an increased risk of major bleeding (11.5% versus 2.4%; \( P<0.001 \)).22 In ULTIMA, only 1 death occurred in the control group, and the study was too small to draw firm conclusions.

Table 2. Echocardiographic Core Laboratory Data

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>24 h</th>
<th>90 days</th>
<th>Difference: Baseline vs 24 h</th>
<th>Difference: Baseline vs 90 d</th>
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</thead>
<tbody>
<tr>
<td>RV/LV ratio, mean±SD</td>
<td>USAT Heparin</td>
<td>USAT Heparin</td>
<td>USAT Heparin</td>
<td>USAT Heparin</td>
<td>USAT Heparin</td>
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<tr>
<td>1.28±0.19</td>
<td>1.20±0.14</td>
<td>0.99±0.17</td>
<td>1.17±0.20</td>
<td>0.92±0.15</td>
<td>0.96±0.16</td>
</tr>
<tr>
<td>n</td>
<td>26</td>
<td>29</td>
<td>28</td>
<td>26</td>
<td>27</td>
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<tr>
<td>Between-group comparison</td>
<td>( P=0.07 )</td>
<td>( P=0.001 )</td>
<td>( P=0.36 ) &amp;</td>
<td>( P&lt;0.001 )</td>
<td>( P=0.07 )</td>
</tr>
<tr>
<td>Within-group comparison</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>RV systolic dysfunction, n</td>
<td>None/mild/moderate/severe</td>
<td>0/45/11/13</td>
<td>5/10/10/2</td>
<td>1/9/7/11</td>
<td>19/5/0/0</td>
</tr>
<tr>
<td>Between-group comparison</td>
<td>( P=0.37 )</td>
<td>( P=0.01 )</td>
<td>( P=0.003 ) &amp;</td>
<td>( P&lt;0.001 )</td>
<td>( P=0.01 )</td>
</tr>
<tr>
<td>Within-group comparison</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>TAPSE, mean±SD, mm</td>
<td>15.7±3.8</td>
<td>19.9±5.8</td>
<td>18.6±4.3</td>
<td>19.4±5.0</td>
<td>21.4±4.6</td>
</tr>
<tr>
<td>n</td>
<td>20</td>
<td>20</td>
<td>23</td>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td>Between-group comparison</td>
<td>( P=0.01 )</td>
<td>( P=0.56 )</td>
<td>( P=0.21 ) &amp;</td>
<td>( P=0.02 )</td>
<td>( P=0.16 )</td>
</tr>
<tr>
<td>Within-group comparison</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>RV/RA pressure gradient, mean±SD, mmHg</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>
</tr>
<tr>
<td>n</td>
<td>17</td>
<td>22</td>
<td>14</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>Between-group comparison</td>
<td>( P=0.91 )</td>
<td>( P=0.18 )</td>
<td>( P=0.62 ) &amp;</td>
<td>( P=0.03 )</td>
<td>( P=0.91 )</td>
</tr>
<tr>
<td>Within-group comparison</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Minimum IVC diameter, mean±SD, mm</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>
</tr>
<tr>
<td>n</td>
<td>10</td>
<td>10</td>
<td>8</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Between-group comparison</td>
<td>( P=0.65 )</td>
<td>( P=0.02 )</td>
<td>( P=0.80 ) &amp;</td>
<td>( P=0.02 )</td>
<td>( P=0.69 )</td>
</tr>
<tr>
<td>Within-group comparison</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

IVC indicates inferior vena cava; NA, not applicable; RV/LV, right ventricular to left ventricular; RV/RA, right ventricular to right atrial; TAPSE, tricuspid annular systolic excursion; and USAT, ultrasound-assisted catheter-directed thrombolysis.

*Differences between neighboring categories of right ventricular systolic dysfunction were scored as 1.
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 rtPA bolus is effective and safe in unstable PE patients at high risk of death from RV failure.

The long-term benefit of early hemodynamic improvement after 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 RV 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. ULTIMA was not designed to show long-term superiority of USAT versus anticoagulation alone with regard to improvement in RV enlargement. Although there was a late “catch-up” in patients with heparin alone, we found a trend for improvement in RV enlargement and significantly improved RV systolic function at 90 days in favor of USAT. Adequately sized studies are warranted to investigate whether USAT improves RV 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 RV function in patients with acute PE are debatable. In ULTIMA, we standardized the measurement of RV/LV ratio obtained from the apical 4-chamber view and provided well-defined instructions to investigators and core laboratory before 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 noninferiority for bleeding complications in comparison to anticoagulation alone, it is reassuring that no major bleeding complication was observed after 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 iliofemoral deep vein thrombosis seeks 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 activated partial thromboplastin time levels) and of vitamin K antagonists (according to international normalized ratio 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 2 days after initiation of treatment. Finally, data sets for additional RV echocardiographic analyses were incomplete for several patients because of 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 RV dysfunction at 24 hours.

### Acknowledgments

The following members also participated in the ULTIMA study: Mira Bartz-Batliner, University Hospital Bern; Karl Halbritter, Ralph Schneider, University Hospital Carl Gustav Carus of Technical University Dresden; Stefan Hochreuther, Ralph Oechringhaus, Hospital Lippe-Detmold, Germany; core laboratory (echocardiography): Felix Tanner, University Hospital Zurich, Switzerland; core laboratory (CT): Allen Taylor, Washington Hospital Center, Washington, DC; Data Safety Monitoring Board: Kirk Beach, University of Washington, Seattle; Keith Comess, Bellingham, WA; Kwame Amankwah, Syracuse University, Syracuse, NY; Biostatistics: Andrea Skelly, Tacoma, WA; P.Y. Liu, Seattle, WA; Data Safety Monitoring Board nonvoting member: Jocelyn Kersten, EKOS Corporation, Bothell, WA; Clinical Event Reviewer: Stavros Konstantinides, Center for Thrombosis and Hemostasis, University of Mainz, Mainz, Germany; Study Coordination: KRAUTH Medical KG (GmbH & Co.), Hamburg, Germany; Clinical and Regulatory Affairs: Hans-Joachim Lau, Hamburg, Germany; Monitoring Clinical and Regulatory Affairs: Beate Dannenberger, Hamburg, Germany; Data Management: Nextrials, Inc, San Ramon, CA.

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DISCLOSURES

Dr. Kucher reports being a consultant for EKOS Corp and having received honoraria from Sanofi-Aventis, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, and Bayer. The other authors report no conflicts.

REFERENCES


CLINICAL PERSPECTIVE

Acute pulmonary embolism remains a potentially life-threatening disease. The most important predictors of early death are systemic arterial hypotension and imaging or biomarker evidence of right ventricular dysfunction at the time of diagnosis. For patients at increased risk of death, prompt revascularization by systemic fibrinolysis improves right ventricular dysfunction and may improve survival and recurrent embolism; however, it is associated with a high rate of major bleeding complications. In routine clinical practice, many patients at increased risk are managed with anticoagulation therapy alone without attempting revascularization. The Ultrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) trial investigated whether a fixed-dose, catheter-directed, ultrasound-assisted thrombolysis regimen (10 mg recombinant tissue plasminogen activator per treated lung over 15 hours; n=30) is superior to management with anticoagulation alone (n=29) in the reversal of right ventricular dilatation in intermediate-risk patients. Patients were eligible if they had embolism of at least 1 main or lower lobe pulmonary artery and echocardiographic right ventricular to left ventricular ratio ≥1.0. There was significant reversal of right ventricular dilatation at 24 hours in the catheter group, whereas no improvement in right ventricular enlargement was found in the heparin alone group. There were no major bleeding complications in either study group. Future studies will determine the clinical efficacy and safety of ultrasound-assisted thrombolysis for treating patients at increased risk of death.
Randomized, Controlled Trial of Ultrasound-Assisted Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism

Nils Kucher, Peter Boekstegers, Oliver J. 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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