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ORIGINAL ARTICLE

Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial

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Summary. *Background:* Acute pulmonary embolism (PE) can worsen quality of life due to persistent dyspnea or exercise intolerance. *Objective:* Test if tenecteplase increases the probability of a favorable composite patient-oriented outcome after submassive PE. *Methods:* Normotensive patients with PE and right ventricular (RV) strain (by echocardiography or biomarkers) were enrolled from eight hospitals. All patients received low-molecular-weight heparin followed by random assignment to either a single weight-based bolus of tenecteplase or placebo, administered in a double-blinded fashion. The primary composite outcome included: (i) death, circulatory shock, intubation or major bleeding within 5 days or (ii) recurrent PE, poor functional capacity (RV dysfunction with either dyspnea at rest or exercise intolerance) or an SF36® Physical Component Summary (PCS) score < 30 at 90-day follow-up. *Results:* Eighty-three patients were randomized; 40 to tenecteplase and 43 to placebo. The trial was terminated prematurely. Within 5 days, adverse outcomes occurred in three placebo-treated patients (death in one and intubation in two) and one tenecteplase-treated patient (fatal intracranial hemorrhage). At 90 days, adverse outcomes occurred in 13 unique placebo-treated patients and five unique tenecteplase-treated patients Thus, 16 (37%) placebo-treated and six (15%) tenecteplase-treated patients had at least one adverse outcome (exact two-sided $P = 0.017$). *Conclusions:* Treatment of patients with submassive pulmonary embolism with tenecteplase was associated with increased probability of a favorable composite outcome.

Keywords: pulmonary embolism; quality of life; randomized controlled trial; thrombolytic therapy; ventricular function, right.

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Introduction

The adjunctive use of fibrinolysis to treat acute submassive pulmonary embolism (PE) remains controversial. In patients without contraindications, published clinical guidelines consistently recommend fibrinolysis for massive PE, defined as PE that causes systolic arterial hypotension [1–3]. However, the same guidelines conflict in their recommendations for fibrinolysis for submassive PE, defined as PE that does not cause systolic arterial hypotension, but does cause right ventricular strain. Some of the conflict arises from a dearth of randomized clinical trials that precludes ability to assess a number needed to treat for survival in this subgroup [4,5]. Mortality as a primary

outcome hampers clinical trials of submassive PE because the short-term mortality rate directly attributable to PE is below 2% [6,7]. This implies the need for an impractically large sample size, compelling the need for a composite endpoint, which is more likely to have larger differences between treatment groups [8,9].

In addition to risk of death, patients with submassive PE may suffer persistent right ventricular dysfunction that can impair their quality of life by causing dyspnea and exercise intolerance [10–16]. If associated with deep vein thrombosis, their quality of life can be further degraded by the post-thrombotic syndrome [17,18]. We therefore designed a primary composite outcome from the perspective of the patient: to survive the PE without need for life supporting interventions in hospital and on follow-up, and at 90 days to have good functional capacity (defined as normal right ventricular function on echocardiography, a New York Heart Association functional class better than 3, and adequate exercise tolerance on 6-min walk test) and perception of wellness on the physical component portion of the SF-36 no worse than two standard deviations below normal [9].

In the present investigation, all patients received standard therapy with low-molecular-weight heparin followed by random assignment to either a weight-based, single bolus of placebo or tenecteplase. We hypothesized that a larger proportion of patients who received tenecteplase would have a favorable composite outcome.

Methods

Study design and regulatory controls

This was a multicenter, double-blinded, intention to treat, placebo-controlled, randomized controlled efficacy trial. The rationale and methodology are described in more detail in a separate publication [9]. The trial was registered on clinicaltrials.gov (NCT00680628) in 2008 and conducted under IND100274 from the US Food and Drug Administration (FDA). The clinical trial was named by the investigators as Tenecteplase or Placebo: Cardiopulmonary Outcomes at Three months (TOPCOAT). The protocol was approved by the Institutional Review Boards at each participating site. All patients signed written informed consent in the physical presence of a site investigator. The study was monitored for safety by an independent Data Safety and Monitoring Committee.

Study setting and population

Prospective enrollment occurred at eight academic medical centers in the US where the authors practice. The inclusion criteria were: (i) age > 17 years; (ii) PE diagnosed on computed tomographic pulmonary angiography performed within 24 h; and (iii) normal arterial systolic blood pressure with evidence of right ventricular strain, manifested by (a) hypokinesis on echocardiography, (b) elevated troponin I or T using local thresholds (values exceeding the 99 percentile with coefficient of variability < 10%) or (c) brain natriuretic peptide (BNP) measurement > 90 pg mL^{-1} or NT proBNP > 900 pg mL^{-1} (not more than 6 h prior to CT angiography and not more than 30 h before enrollment). The initial echocardiography had to be ordered as part of standard care. Severity criteria initially included a pulse oximetry reading < 95% within the previous 2 hours in all locations except Aurora, CO, and Salt Lake City, UT, but this criterion was dropped after 15 patients were enrolled [19].

The study had 24 exclusion criteria listed in a previous publication [9]. In summary, exclusions included systolic hypotension (< 90 mmHg), inability to walk, contraindications to fibrinolysis, and end-stage conditions.

Treatment protocol

After informed consent, all patients were treated with full-dose low-molecular-weight heparin (LMWH), 1 mg kg^{-1} enoxaparin, or weight-based dalteparin, 200 units kg^{-1}, administered subcutaneously prior to injection of study drug or placebo. If the patient was receiving unfractionated heparin, this was discontinued and LMWH was started. A venous blood specimen was obtained for baseline studies. Study group assignment occurred by a predetermined, blocked permuted 1 : 1 randomization sequence that was prepared by the study statistician and linked to a unique study ID number used by a research pharmacist to prepare placebo or tenecteplase in 0.9% saline in an opaque syringe. Patients received tiered dose tenecteplase in accordance with the TNKase® insert (Genentech Inc., San Francisco, CA, USA). A site investigator injected the syringe contents as soon as practicable. A study-specific order form was placed on the chart to continue low-molecular-weight heparin for the remainder of their hospital stay. Depending upon the site, the clinical care team could unblind the randomization assignment by either opening the envelope or calling the research pharmacy. The envelope had clear language indicating that unblinding was to occur only if absolutely necessary to make emergent treatment decisions. Decisions about long-term anticoagulant therapy were at the discretion of the clinical care team.

Measurements and outcomes

Five-day adverse outcomes were PE related or treatment related. Adverse outcomes from PE were death, circulatory shock (hypotension requiring vasopressor infusion), or need for intubation. Adverse outcomes from treatment were death from hemorrhage, any intracranial or intraspinal hemorrhage, active bleeding with > 2 g dL^{-1} drop in hemoglobin within 24 h requiring transfusion, and any bleeding that required surgery, endoscopic or intravascular treatment. All patients had a complete blood count

and fibrinogen concentration measured at enrollment and on days 1 and 2. On each day, a study coordinator personally visited each patient to record any bleeding episodes, including minor bleeding, using a standardized case report form.

After discharge, all patients without active cancer were treated with warfarin sodium with a target international normalized ratio (INR) for the prothrombin time between 2 and 3. Patients with active cancer were treated with low-molecular-weight heparin injections. We assessed quality of anticoagulation by the time in therapeutic range (TTR), defined as the percentage of INR measurements that were found to be between 2 and 3 in the timeframe of 1 week after discharge and 90-day follow-up.

At 90 days, all survivors returned for measurements to assess for adverse outcomes in the form of venous thromboembolism recurrence, poor functional capacity or poor physical health-related quality of life. All patients had study-funded transthoracic echocardiography, conducted with a specific protocol to assess for right ventricular size, pressure and systolic function. Echocardiograms were interpreted by a board-certified cardiologist who was blinded to treatment and outcome. We assessed for the following adverse outcomes within 90 days:

1 Venous thromboembolism recurrence required image-proven evidence of a new pulmonary arterial filling defect observed on repeat CT pulmonary angiography, or a new deep venous thrombosis observed on compression ultrasound.
2 Poor functional capacity outcome required two components. (i) Right ventricular hypokinesis or dilation (right ventricle > left ventricle in apical four chamber view), or an estimated right ventricular systolic pressure > 45 mmHg, assessed on transthoracic echocardiography. (ii) Exercise intolerance or dyspnea at rest. Exercise intolerance was defined as inability to walk 330 m using the 6-min walk test, performed in accordance with American Thoracic Society guidelines. Severe dyspnea was defined by a New York Heart Association functional class of 3 or 4, assessed by the questionnaire of Kubo *et al*. [20,21]
3 Poor physical health-related quality of life outcome required a normalized Physical Component Summary score from the Standard Form 36 (SF 36™) below 30 (i.e. < 2 standard deviations below the normative score of 50) [10,22]. Impact of post-thrombotic syndrome was assessed with the VEINES QOL survey (we planned for a score < 40 to be considered a poor physical health-related outcome) [23].

Secondary outcomes measured within 5 days included dependence upon intensive care services, rate of unblinding, rate of hospital discharge, hemoglobin and fibrinogen concentrations, total number of days of minor bleeding, and frequency of all-cause Good Clinical Practice-defined adverse events. Secondary outcomes measured at 90 days included the proportion with a New York Heart Association functional class ≥ 3, and the mean 6-min walk distance, change in pulse oximetry with walking, the mental health component score from the SF-36, the VEINES-QOL score, and the patients' self-assessment of their overall health status on a 1–10 scale, with 1 indicating the worst possible and 10 the best possible health.

Summary of the composite criterion standard for an adverse outcome

(i) Any PE-related or treatment-related serious adverse outcomes within 5 days of enrollment. (ii) Image-confirmed recurrent PE or deep venous thrombosis within 3 months. (iii) Poor functional capacity at 3 months. (iv) A normalized Physical Component Summary score < 30 from the SF-36. (v) A VEINES QOL score < 40 in patients with known deep venous thrombosis. Patients with an adverse outcome within 5 days were invited to follow-up at 90 days, but each patient was only counted once in the summation of patients with an adverse outcome.

Data analysis and sample size

Means of continuous data were compared with an unpaired *t*-test or a paired *t*-test. Proportions were compared with 95% confidence intervals and *P* values from the Exact test. Frequencies were tested with Fisher's exact test. The sample size was estimated at 82 per group with complete data to show a 20% increase in the proportion of patients who reach the composite endpoint of a good outcome, with $\alpha = 0.05$ at a power of 80%. For analysis of the component scale, SF-36 values are presented as raw data and the Mental Component Summary and Physical Component Summary scores are normalized to a mean of 50 with a standard deviation of 10. SF-36 component scores were compared with a two-sided *P* value for the Z distribution with $\alpha = 0.01$ to account for multiple comparisons [24]. The study was monitored for stopping criteria of harm or benefit using the Lan and DeMets alpha-spending approach [25].

Results

We recruited patients from August 2008 until October 2012. The database was completed and locked on 15 December 2013, at which time unblinding occurred. Figure 1 shows the Consort diagram for the study. Six hundred and forty-three patients with inclusion criteria were screened and informed consent was obtained in 87 (13.5%). No patient withdrew after informed consent. Randomization allocated 40 patients to tenecteplase and 43 to placebo. Table 1 shows the clinical characteristics of the study population, including the demographic data, frequency of co-morbid conditions and data that indicate

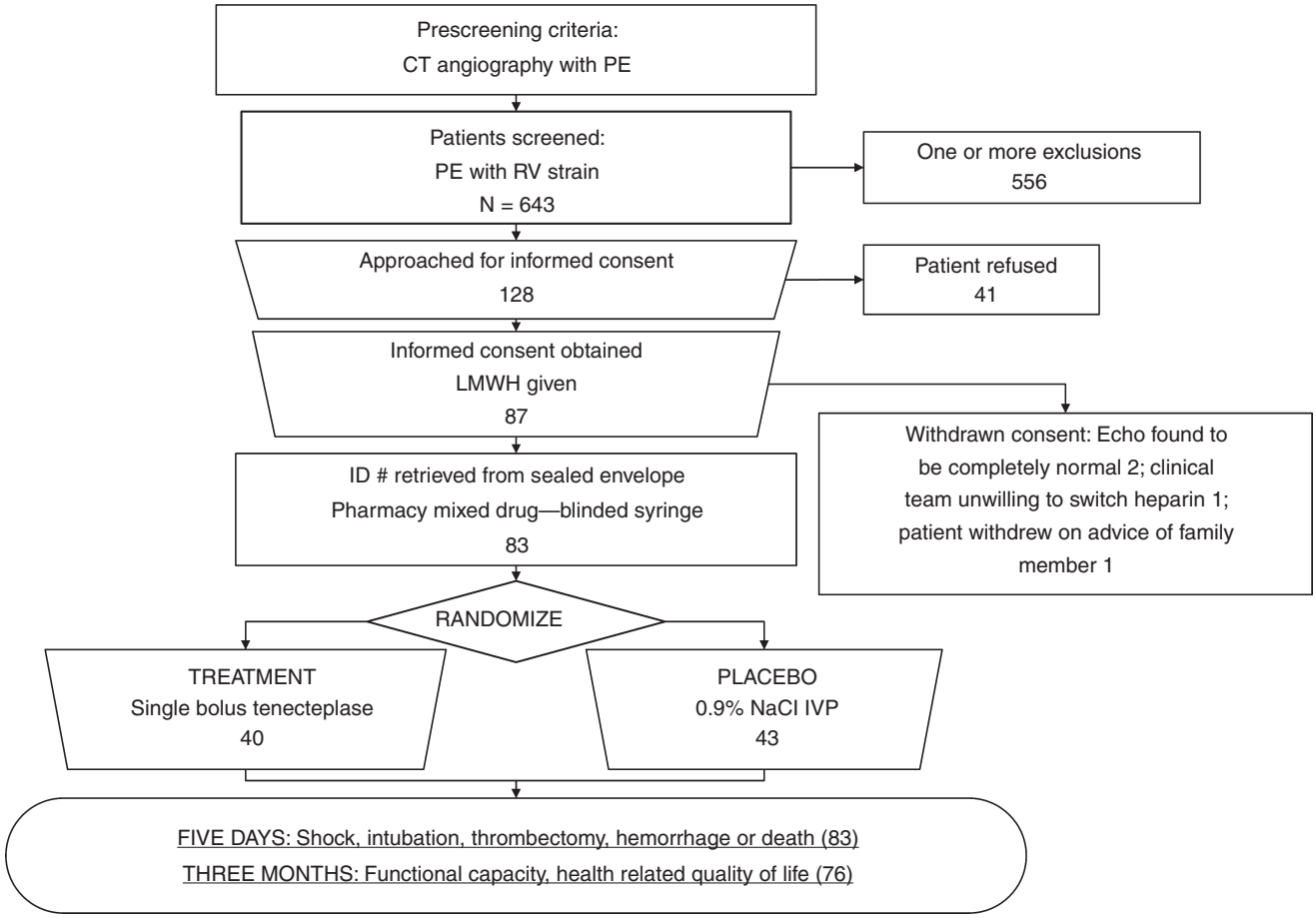

Fig. 1. Flow diagram of study enrollment and outcomes. Exclusions (in order of frequency observed): (i) contraindications to fibrinolysis or frailty precluding the 6-min walk test (228, 41%), (ii) investigator unavailable (144, 26%); (iii) clinical care team decided to give fibrinolytics (139, 25%), (iv) creatinine clearance < 30 mL min^{-1} (22, 4%), (v) other situation precluding follow-up (22, 4%).

the severity of the PE, stratified by treatment group. None of the variables were significantly different between groups, although the data suggest a trend ($P < 0.20$) with gender, Hispanic ethnicity, malignancy and COPD. Table 1 shows the percentage of the sample who had abnormal echocardiography, and the percentage with abnormal biomarkers BNP and troponin I. The frequency with which these screening tests for severity were performed was: echocardiography in 54 (65%), BNP in 69 (83%) and troponin in 83 (100%). Table 2 shows the breakdown of concomitant limb venous thrombosis stratified by treatment group. There were no significant differences in the frequency or location of deep venous thrombosis between the two groups. Regarding quality of anticoagulation during the 3 months after discharge, patients randomized to tenecteplase had a mean TTR of 48% (SD 24%) and a median TTR of 50% (1st–3rd quartiles, 33–67%). Patients randomized to placebo had a mean TTR of 49% (SD 20%) and a median TTR of 50% (1st–3rd quartiles, 33–60%).

Table 3 and Fig. 2 show the main results of the study. Three patients treated with placebo had an adverse outcome within 5 days, including one who died from cardiac arrest that was directly attributed to PE, and two who required endotracheal intubation, vasopressor support and catheter thrombectomy. One patient treated with tenecteplase died from intracranial hemorrhage that occurred 5 h after drug administration, representing the only patient with a major bleed that occurred during the 5-day period of surveillance. No patient died in the period between hospital discharge and 90 days. We obtained complete follow-up data on 39/43 survivors from the placebo group (90%) and 37/39 (94%) of the tenecteplase group.

At follow-up, 13 (30%; 95% CI, 17–46) patients treated with placebo developed a study-defined adverse outcome, compared with five (12.5%; 95% CI, 4–27) patients treated with tenecteplase. None of these 18 patients had a prior serious adverse outcome. Thus, including the patients with adverse outcomes that occurred within 5 days, 16/43 patients (37%; 95% CI, 23–53) treated with placebo and 6/40 patients (15%; 95% CI, 6–30) treated with tenecteplase had an adverse outcome (95% confidence interval for the difference of 22%, 3.2–40;

Table 1 Patient demographic data, comorbid conditions and severity criteria

Clinical finding	Placebo		Tenecteplase		*P*
	N = 43		*N* = 40		
Male gender	29	67%	20	50%	0.09
Caucasian race	26	60%	28	70%	0.37
Black race	17	40%	11	28%	0.26
Other race	1	2%	1	3%	0.99
Hispanic ethnicity	5	12%	1	3%	0.11
Surgery within the previous 6 weeks	4	9%	1	3%	0.21
Trauma within the previous 6 weeks	2	5%	3	8%	0.42
Coronary artery disease without myocardial infarction	1	2%	1	3%	0.99
Prior myocardial infarction	2	5%	0	0%	0.24
Systolic heart failure	2	5%	1	3%	0.99
Prior history of PE or DVT	9	21%	6	15%	0.41
Active malignancy*	4	9%	9	23%	0.08
Malignancy under chemotherapy treatment	0	0%	5	12.5%	0.01
Chronic obstructive pulmonary disease	3	7%	0	0%	0.12
History of asthma	6	14%	4	10%	0.52
Any connective tissue disease	4	9%	4	10%	0.99
Diabetes mellitus	6	14%	4	10%	0.52
Prior stroke	1	2%	0	0%	0.99
Human immunodeficiency virus	0	0%	1	3%	0.99
Body mass index > 40 kg m^{-2}	6	14%	6	15%	0.99
Age > 75 years	4	9%	4	10%	0.99
Pulse oximetry < 94%	30	70%	27	68%	0.99
Pulse rate > 110 beats min^{-1}	12	28%	9	23%	0.47
Systolic blood pressure < 100 mmHg	11	26%	10	25%	0.99
Troponin elevated†	21	49%	20	50%	0.99
Brain natriuretic peptide elevated‡	26	60%	20	50%	0.28
Right ventricular dysfunction on echocardiography§	21	49%	18	45%	0.66
Age (years, mean and SD)	54 (14)		57 (14)		0.38
Body mass index (kg m^{-2})	34 (9)		33 (9)		0.46
Pulmonary arterial systolic pressure (mmHg)	55 (11)		58 (11)		0.36

PE, pulmonary embolism; DVT, deep venous thrombosis. *Patient report of ongoing care by an oncologist. †Above the 99th percentile for normal with imprecision coefficient of variability < 10%, 83 patients had troponin performed; ‡> 90 pg mL−1 for brain natriuretic peptide or > 900 pg mL−1 for pro-brain natriuretic peptide, 69 patients had either test performed; §right ventricular hypokinesis on echocardiography, 54 had echocardiography.

Table 2 Frequency and location of concomitant deep venous thrombosis

Most proximal location of thrombosis	Placebo		Tenecteplase	
Any deep venous thrombosis	21	49%	19	48%
Femoral vein	12	28%	8	20%
Popliteal vein	8	19%	11	28%
Calf vein	6	14%	4	10%
Saphenous vein	0	0%	1	3%
Axillary vein	2	5%	0	0%

two-sided $P = 0.017$; Fisher's exact $P = 0.027$). No patient had a VEINES QOL score < 40, but four patients in the placebo group had a score worse than two standard deviations below the mean compared with no patients in the tenecteplase-treated group.

Secondary outcomes measured in-hospital included level of care, hospital dependency, laboratory values and bleeding events. Regarding hospital dependency, the proportion of patients who remained in the intensive care unit on day 2 was significantly higher with placebo (20.5%) compared with tenecteplase (5%, $P = 0.03$, Fisher's exact). Figure 3 shows that a significantly higher proportion of patients treated with placebo remained in the hospital, starting on day 3 after enrollment. On days 1 and 2, the mean fibrinogen concentration was 417 ± 146 and 451 ± 189 mg dL^{-1}, respectively, in placebo-treated and 370 ± 162 and 391 ± 185 mg dL^{-1} respectively in tenecteplase-treated patients ($P = 0.2$, unpaired *t*-test, day 1 comparisons). Hemoglobin values were not different on day 2: 12.7 ± 1.8 g dL^{-1} for placebo vs. 12.3 ± 1.8 g dL^{-1} for tenecteplase ($P = 0.4$). Members of the clinical care team opened the sealed envelope to reveal the randomization assignment in three patients treated with placebo and two treated with tenecteplase. All but one of these patients had a serious adverse outcome that prompted unblinding. The one patient without a serious adverse event was a placebo-treated patient. The total number of hospital days on which patients experienced any clinically observable bleeding in the first 5 days after enrollment was 11 days in the placebo group and 19 days in the tenecteplase group. Of note, one patient treated with tenecteplase who had undergone hysterectomy 31 days prior developed vaginal bleeding that produced transient hypotension, requiring fluid resuscitation, but the bleeding event did not meet the predefined criteria as a treatment-related adverse outcome. During the entire hospitalization, the total number of Good Clinical Practice-reportable adverse events of any type that were not part of the main composite outcome were similar between groups, with 23 (53%) in the placebo-treated group and 24 (55%) in the tenecteplase-treated group. All adverse events that did not meet the study's predefined criteria for an adverse outcome, including the bleeding events, are presented for each patient according to treatment group in supplemental Table 1.

Table 4 and Fig. 4 show preplanned secondary outcomes at the 90-day follow-up. Of note, we found no clinically important difference between groups in the mean 6-minute walk distance or any of the scales used in the Mental Component Summary score from the SF-36. The only significant difference was a higher patient self-assessment of overall health using a 1-10 scale in the tenecteplase group.

Potential sources of bias

To examine for potential bias from possible imbalanced randomization, we performed a post-hoc analysis of the

Table 3 Breakdown of all adverse outcomes in each treatment group

	Within 5 days		At 90-day follow-up						
Treatment	Death	Shock/ intubation	Recurrent VTE* and poor functional capacity† and low perception of wellness‡	Poor functional capacity† and low perception of wellness‡	Recurrent VTE* and low perception of wellness‡	Poor functional capacity† only	Recurrent VTE only	Low perception of wellness‡ only	None§
Placebo ($N = 43$)	1	2	1	5	2	2	1	2	27 (63%)
Tenecteplase ($N = 40$)	1	0	0	1	0	3	1	0	34 (85%)

*VTE, recurrent venous thromboembolism (two with pulmonary embolism, one with deep venous thrombosis and one with both in the placebo arm and one with deep venous thrombosis in the tenecteplase arm). †Poor functional capacity (right ventricular dysfunction on echocardiography plus either a New York Heart Association functional score ≥ 3 [21] or < 330 m walked in 6 min [20]). ‡Low perception of wellness by the Physical Component Summary score < 30 from the SF36 survey [22]). §None indicates the number of patients with no predefined adverse endpoint at 90-day follow-up.

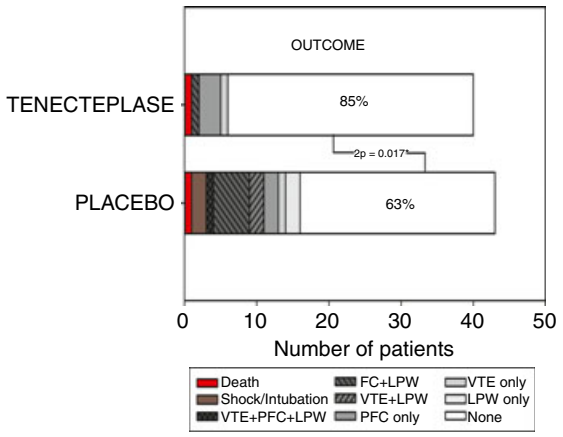

Fig. 2. Bar graph summarizing the main findings. The two-sided P value is from the exact test on independent proportions. *$P = 0.027$ by Fisher's exact. VTE, venous thromboembolism; PFC, poor functional capacity; LPW, low perception of wellness based upon physical component summary score < 30 from the SF-36.

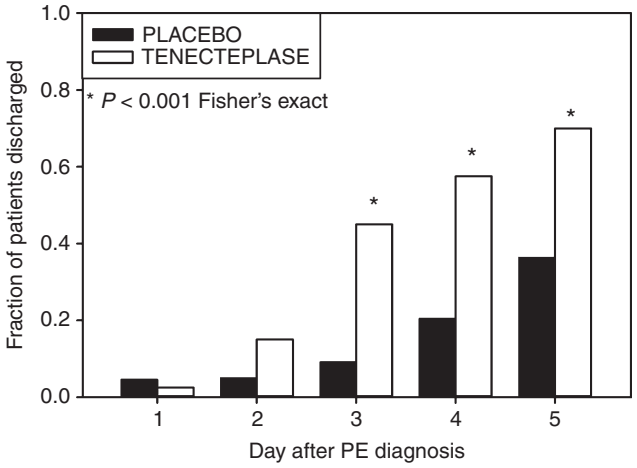

Fig. 3. Hospital discharge during the first 5 days after enrollment.

influence of variables with $P < 0.2$ in Table 1 (gender, Hispanic race, malignancy and COPD). We also created a new composite variable defined by absence of any prior cardiopulmonary, thromboembolic or malignancy history. We performed a conditional logistic regression, stratified by treatment, to determine if any of these variables were significantly predictive of outcome. This multivariate analysis does not suggest any of these six variables biased the outcome (all had $P > 0.1$). Regarding the two patients in the placebo group with low perception of wellness based on the SF-36 as their only adverse outcome, one patient had a prior history of COPD and the other had none of the co-morbid conditions listed in Table 1. If the SF-36 results were removed as a criterion for an adverse outcome, the significance level would decrease: 14/43 placebo patients vs. 6/40 patients (two-sided $P = 0.048$; Fisher's exact $P = 0.075$). If one more patient met an endpoint in the tenecteplase group, the P values would be 0.03 from the exact binomial and 0.053 by Fisher's exact.

Discussion

This study reports a clinical trial of fibrinolysis to treat acute submassive PE that employed a patient-oriented, composite outcome that included measurements that assess quality of life. This composite outcome was motivated by data from interviews and surveys of patients with submassive PE, administered hours, months and years after diagnosis [10,13,26]. Immediately after diagnosis, acutely symptomatic patients with submassive PE consistently indicate their desire to survive without the need for life supporting measures at any time, avoid PE

Table 4 Results of measurements at 90-day follow up

Measurement	Placebo $N = 39$		Tenecteplase $N = 37$		
	N or mean	% or SD	*N* or mean	% or SD	*P**
New York Heart Association functional class ≥ 3	8	20.5%	2	5.4%	0.051
New York Heart Association score	1.7	0.9	1.5	0.6	0.48
Right ventricular dilation or hypokinesis	13	33.3%	14	37.8%	0.64
Six-minute walk distance (m)	403	113	407	98	0.90
Six-minute walk distance < 330 m	11	28%	6	16%	0.19
Mean change in SaO_2% with walk test	−0.6%	2.2%	0.3%	2.2%	0.093
VEINES-QOL score	90	17	93	12	0.397
SF-36 Mental Component Summary	53	2	53	1	0.670
Self-assessment of overall health better than 3 months prior	29	74%	30	81%	0.43
Overall health assessment (1–10; 1 worst, 10 best)	2.4	1.6	3.3	2.0	0.036

N, number; SD, standard deviation; VEINES-QOL, post-thrombotic quality of life score; SF-36, Standard Form 36. *From exact binomial test or unpaired *t*-test.

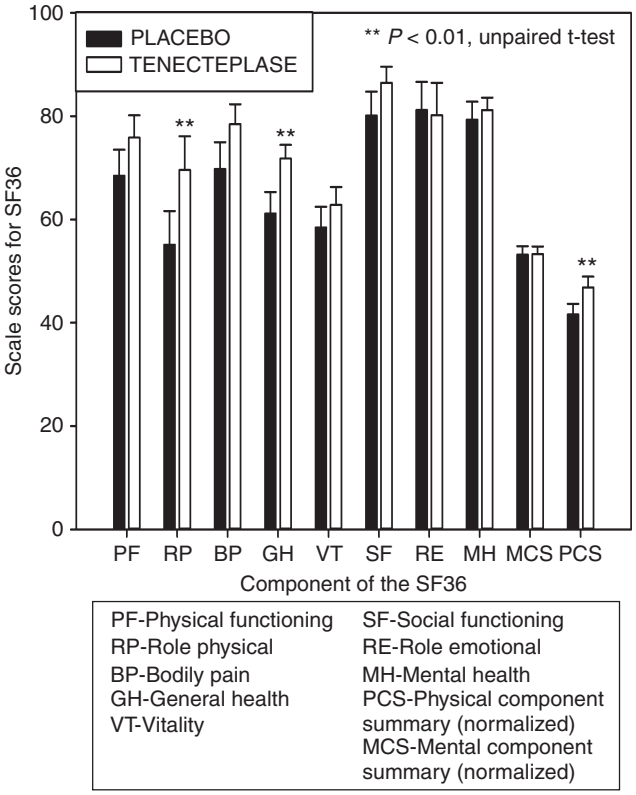

Fig. 4. Plot of SF-36 scores based upon treatment group. Normative scores are produced from a linear transformation of the raw scores to produce a mean of 50 and a standard deviation of 10. *P* values were adjusted for multiple comparisons.

recurrence, and to achieve resolution from dyspnea and exercise intolerance. Evidence supports their concerns. Stevinson *et al.* [26] found that 6 months after diagnosis, 13% of previously healthy patients from the US stated their overall health status was worse or not better than at the time they were diagnosed and acutely symptomatic with submassive PE. In a Dutch case-control study, Klok *et al.* [10] administered the SF-36 on average 3.6 years after PE diagnosis and found significant, global impairment in quality of life after PE. For TOPCOAT we therefore compiled an endpoint that included death, circulatory shock requiring vasopressor support, respiratory distress requiring intubation, and the 90-day endpoint of poor functional capacity or low self-perception of physical health.

Two other randomized trials have used tenecteplase to treat submassive PE [8,27]. The present study differs from these studies in the outcome, and the use of LMWH instead of unfractionated heparin as the anticoagulant. We believe that LMWH simplifies the treatment protocol and provides more reliable anticoagulation [28].

Patients with PE randomized to placebo were more likely to have an undesirable outcome than patients randomized to tenecteplase. The main drivers of this effect were the composite endpoint of impaired functional capacity and a low self-assessment of physical wellness from the SF-36 measured 3 months after PE diagnosis. It is of relevance that the SF-36 raw values from placebo patients in Fig. 4 agree with those from a study of Dutch patients assessed a median time of 25 months after PE [29]. Patients treated with tenecteplase spent less time in the intensive care unit and less overall time in the hospital and had no increase in adverse events or total days of any bleeding. The extensive exclusion criteria were designed to lower the risk of bleeding with fibrinolysis, but this sample included patients with higher risk criteria, including 13 with active malignancy, eight over age 75 years, and five with surgery within 6 weeks [30].

These outcomes provide clinicians and patients with the first data that enable an evidence-based discussion that can include the short-term risks together with potential longer term health benefits of fibrinolysis for acute submassive PE. However, the data also suggest that clinicians should discuss an increased risk of bleeding, including the worst-case scenario of a disabling or fatal intracranial hemorrhage.

Table 5 Analysis for possible effect of imbalance in randomization

	Placebo (n = 40*)			Tenecteplase (n = 39*)			
	Outcome−	Outcome+	Subtotal (%)	Outcome−	Outcome+	Subtotal (%)	P
COPD	1	2	3 (8)	0	0	0 (0)	0.5304
Malignancy under treatment	0	0	0 (0)	3	2	5 (13)	0.4904
Male gender	19	8	27 (68)	15	4	19 (49)	0.4791
Hispanic ethnicity	4	1	5 (13)	1	0	1 (3)	0.3201
No prior cardiopulmonary disease, VTE or active cancer	14	4	18 (45)	16	4	20 (51)	0.1191

COPD, chronic obstructive pulmonary disease; VTE, venous thromboembolism. P values from conditional logistic regression. *Number of patients with complete follow-up, including one patient who died in each group.

This study has limitations. First, the study had to be terminated early, as a direct result of the principal investigator relocating to a new institution that led to insurmountable legal and administrative barriers required to reestablish the prime research site and transfer the consortia subcontracts. The challenges of initiating these agreements have been described [9]. The study was closed prior to unblinding. Secondary analyses of prematurely closed randomized trials have suggested that P values fluctuate randomly early during enrollment, and early termination may have caused unrecognized bias if it were coincident with a chance nadir in P value [31]. We carefully searched for the potential effect of imbalanced randomization in the post-hoc analysis in Table 5 and were unable to find any evidence of bias. We believed in advance that quality of life improvements would be associated with improved right ventricular function, but we found no difference in the frequency of right ventricular dilation or hypokinesis between groups at 90-day follow-up. It remains possible that we would have observed differences in right ventricular pressures if we had measured them during exercise [32,33].

We also acknowledge the absence of a perfect method to measure functional capacity or quality of life, and the SF-36 may not be measuring health status related to PE. We believe that patients generally regard an outcome that includes a dilated right heart associated with dyspnea at rest or marked exercise intolerance as undesirable. When this study was planned in 2008, no instrument had been specifically derived to assess quality of life after PE, and we used the SF-36 because of its long history as a standard tool to assess quality of life in clinical trials and outcome studies of many cardiopulmonary diseases, including pulmonary embolism [10,34]. This was a small study, carried out in a US population with a lower mean age than is observed in European studies of patients with PE [35]. Thus, our observed 2.5% rate of intracranial hemorrhage, which has 95% confidence intervals from zero to 12%, may be higher in other populations. Finally, the method of determining treatment effectiveness used a composite outcome that considered death statistically equivalent to a low score on a survey.

Conclusion

This small trial found that patients with submassive PE treated with a single bolus of tenecteplase had a modestly increased probability of a good functional outcome, but the sample size was too small to assess whether tenecteplase increases the risk of intracranial hemorrhage.

Addendum

J. A. Kline: study concept and design, acquisition of the data, analysis and interpretation of the data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical expertise, obtained funding, administrative, technical or material support, study supervision. J. A. Kline takes responsibility for the manuscript as a whole. J. Hernandez: acquisition of the data, administrative, technical or material support, study supervision. A. E. Jones, D. M. Courtney, C. Kabrhel, K. E. Nordenholz, D. B. Diercks, M. T. Rondina and J. R. Klinger: acquisition of the data, analysis and interpretation of the data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, technical or material support, study supervision. Data Safety Monitoring Chair: M. Rodger, Division of Hematology, University of Ottawa, Ottawa, Ontario, Canada. Study Monitor: M. M. Hogg, Murphy Clinical Consultants, Charlotte, NC, USA.

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Disclosure of Conflicts of Interest

J. A. Kline owns stock in CP Diagnostics LLC, is a consultant for Daiichi Sankyo Inc, Donawa Lifesciences Consulting and Stago Diagnostica, and has received funding from the Agency for Healthcare Reform, National Institutes for Health. This study was funded by an investigator-initiated grant from Genentech, Inc. A. E. Jones has received

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Adverse events that did not meet a study definition of a serious adverse outcome.

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