

Original Research

Delayed versus non-delayed anticoagulation after systemic alteplase for high-risk and intermediate-risk pulmonary embolism – a retrospective observational study

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Background

The timing of therapeutic anticoagulation after systemic thrombolysis for high-risk and intermediate-risk pulmonary embolism has not been thoroughly studied regarding bleeding risk and other outcomes.

Objectives

This study aims to compare clinically relevant outcomes between two common approaches of anticoagulation after systemic alteplase for high-risk and intermediate-risk pulmonary embolism.

Methods

A retrospective, multicenter, cohort study was conducted for 77 patients with high-risk and intermediate-risk pulmonary embolism from 2013 to 2023. Delayed anticoagulation (DAC) was defined as therapeutic, parenteral anticoagulation ordered for administration after systemic alteplase when the partial thromboplastin time (PTT) was below two times the upper limit of normal or after a clinician-directed time delay. Non-delayed anticoagulation (NDAC) was defined as therapeutic, parenteral anticoagulation ordered for administration after systemic alteplase regardless of PTT value or time delay. The primary outcome was a composite of major bleeding or clinically relevant non-major (CRNM) bleeding. Secondary outcomes included minor bleeding, blood transfusion requirements, intracranial hemorrhage, readmission within 30 days, recurrent thrombotic events, intensive care unit length of stay, and survival to hospital discharge.

Results

DAC and NDAC were associated with similar occurrences of major or CRNM bleeding after adjusting for the number of baseline bleeding and clotting risk factors (adjusted odds ratio [aOR], 0.61; 95% confidence interval [CI], 0.13 – 1.85). No statistically significant differences in secondary outcomes were observed except for a lower odds of survival to hospital discharge with DAC (OR, 0.07; 95% CI, 0.00 – 0.47).

Conclusion

DAC and NDAC after systemic thrombolysis may be associated with similar bleeding risks.

1. INTRODUCTION

1.1. BACKGROUND

Pulmonary embolism (PE) is a significant cause of morbidity and mortality.¹ PEs are generally divided into three categories based on hemodynamic stability and high-risk features: high risk, intermediate risk, and low risk.²

The management of PEs is recently detailed by the European Society of Cardiology (ESC) guidelines.³ For high-risk PE, systemic thrombolysis followed by anticoagulation is recommended to dissolve and prevent an embolus when the benefits outweigh the risks of bleeding.^{4,5} Although various dosing strategies exist for high-risk and intermediate-risk PE, with the dosing for high-risk PE extrapolated mostly from the literature for intermediate-risk PE,⁶⁻¹² literature is scarce regarding the optimal timing of anticoagulation.

Anticoagulation may be administered immediately following thrombolysis, once the partial thromboplastin time (PTT) is below two times the upper limit of normal, several hours after systemic alteplase (tissue plasminogen activator, tPA) administration, or once the serum fibrinogen is greater than 100 mg/dL (although not as widely described).¹³⁻¹⁵ Ultimately, the timing of anticoagulation poses the question of balancing the risks of clot propagation and bleeding.

1.2. IMPORTANCE

Only one study evaluated outcomes in patients receiving delayed versus early parenteral anticoagulation.¹⁶ However, this retrospective study addressed only one criterion for anticoagulant timing – an arbitrary one-hour time delay – which does not fully reflect clinical practice. Additionally, this study lacks a comprehensive description of patients, especially regarding bleeding risk and stratification based on high-risk and intermediate-risk PE.

1.3. GOALS OF THIS INVESTIGATION

This study aims to compare clinically relevant outcomes between two common approaches of initiating anticoagulation after systemic thrombolysis with tPA for high-risk and intermediate-risk PEs in these critically ill patients.

2. METHODS

2.1. STUDY DESIGN

This study, approved by the Novant Health Institutional Review Board, was a retrospective, observational cohort study. Considering the most common approaches of anticoagulant administration after systemic thrombolysis, delayed anticoagulation (DAC) was defined as therapeutic, parenteral anticoagulation ordered to be administered after systemic tPA when the PTT was below two times the upper limit of normal, defined as a PTT value less than 70 seconds using an institutional laboratory reference range of 22 to 35 seconds, or if anticoagulation was ordered to be administered after a clinician-directed time delay, as indicated in the medical record. Non-delayed anticoagulation (NDAC) was defined as therapeutic, parenteral anticoagulation ordered to be administered after systemic tPA regardless of PTT value or time delay, as indicated in the medical record. Notably, there were no institutional order sets or pathways across the years of inclusion for obtaining serial PTT or fibrinogen levels following tPA administration, prescribing catheter-directed tPA versus systemic tPA, or standardizing the anticoagulant or dose of tPA.

Data extracted from the electronic medical record via chart review included patient demographics, comorbidities, clotting risk factors (Table 1),¹⁷ baseline vitals and laboratory values, and information regarding tPA and anticoagulant administration. Absolute and relative contraindications to tPA were also collected to determine the number of bleeding risk factors (Table 2).¹⁸ Via chart review, patients

Table 1. Clotting Risk Factors

Clotting Risk Factors
• Active cancer or history of prior cancer • On estrogen therapy at home • History of thrombophilia • History of prior DVT or PE • Concurrent DVT • Obesity (BMI > 30 kg/m²) • Age > 40 years • Pregnant or postpartum • History of prolonged immobilization • Multiple trauma on admission

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; PE, pulmonary embolism.

were also categorized as experiencing high-risk or intermediate-risk PE based on the ESC criteria.³

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed as feasible.¹⁹

2.2. SETTING

A four-state health network of more than 15 medical centers across the southeastern United States

2.3. SELECTION OF PARTICIPANTS

Eligible patients included those ≥ 18 years admitted from an emergency department from 2013 to 2023; received tPA 100 mg or received 50 mg initially or as a re-dose for high-risk or intermediate-risk PE; and were administered therapeutic, parenteral anticoagulation following tPA. Patients were excluded if they were transferred from an outside hospital, administered catheter-directed tPA, administered tenecteplase due to administration and pharmacokinetic differences with tPA, or did not complete the tPA infusion due to a reaction.

2.4. OUTCOMES

The primary outcome was a composite of major bleeding or clinically relevant non-major (CRNM) bleeding. Based on standardized definitions, major bleeding was defined as fatal bleeding; symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; bleeding causing a fall in hemoglobin levels of 2 g/dL or more; and/or bleeding leading to a transfusion of two units or more of whole blood or packed red blood cells. CRNM bleeding was characterized by any sign or symptom of hemorrhage that did not fit the criteria for major bleeding, but met at least one of the following criteria: requiring medical intervention by a healthcare professional, leading to hospitalization or increased level of care, or prompting a face-to-face evaluation.^{20,21}

Clinically relevant secondary outcomes included minor bleeding, blood transfusion requirements, intracranial hemorrhage, readmission within 30 days, recurrent deep vein

Table 2. Absolute and Relative Contraindications for IV tPA Utilized to Identify Bleeding Risk Factors

Absolute Contraindications	• Active internal bleeding or known bleeding diatheses (excluding menses) • History of ischemic stroke within the last 3 months • Any history of ICH • Symptoms suggestive of SAH, ICH, known ICH or neoplasm, AV malformation, or aneurysm at any time before or during tPA • Recent intracranial or intraspinal surgery within the last 3 months
Relative Contraindications	• Age > 75 years • Use of DOAC or heparin product prior to tPA • Pregnant at time of admission • Non-compressible vascular puncture at time of tPA • Traumatic or prolonged CPR (> 10 minutes) at time of tPA • History of internal bleeding within the last 2 – 4 weeks • History of chronic, severe, and poorly controlled hypertension • Severe, uncontrolled hypertension (SBP > 180 mmHg or DBP > 110 mmHg) • History of dementia • History of ischemic stroke > 3 months • History of major surgery within the last 3 weeks

Abbreviations: AV, arteriovenous; CPR, cardiopulmonary resuscitation; DBP, diastolic blood pressure; DOAC, direct oral anticoagulant; ICH, intracranial hemorrhage; IV, intravenous; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure; tPA, alteplase.

thrombosis (DVT) or PE, intensive care unit length of stay, and survival to hospital discharge. Based on a standardized definition, minor bleeding was defined as any bleeding not classified as either major or CRNM bleeding.^{20,21}

2.5. DATA ANALYSES

The χ^2 test was used for the primary outcome. Fisher's exact test was used for all other nominal outcomes: minor bleeding, blood transfusion requirements, intracranial hemorrhage, readmission within 30 days, recurrent DVT and PE, and survival to hospital discharge. The Mann-Whitney U test was used for the outcome of intensive care unit length of stay. Statistical significance was set at a two-tailed p -value < 0.05.

Logistic regression was performed for the primary outcome and the outcome of survival to hospital discharge, when comparing DAC versus NDAC. While avoiding overfitting, additional variables for the multivariable analysis of the primary outcome included the number of bleeding risk factors and the number of clotting risk factors, based on biological plausibility regarding bleeding events. Multivariable analysis was not conducted for survival to hospital discharge due to overfitting. Furthermore, exploratory analyses, via logistic regression analyses of survival to hospital discharge when comparing DAC versus NDAC, were performed for the high-risk and intermediate-risk PE subgroups.

Bootstrapped odds ratios (OR) and 95% confidence intervals (CI) are reported for the aforementioned logistic regression analyses, obtained by utilizing a direct model building strategy, 5000 samples, the percentile method for the 95% CI, and 2,000,000 as the seed for the Mersenne Twister. Goodness of fit was assessed via the Hosmer-Lemeshow test. Statistical analyses were performed using Social Science Statistics (2018, Jeremy Stangroom) and IBM SPSS Statistics (Version 29.0.0.0, Armonk, NY).

3. RESULTS

3.1. PATIENT CHARACTERISTICS

Among 98 patients with PE administered systemic tPA, 21 patients met exclusion criteria, leaving 77 patients included. No patients were readmitted for the same diagnosis or administered anticoagulation using the fibrinogen-directed approach. Baseline characteristics between the DAC and NDAC groups were similar except for race, presence of renal disease, heart rate, and temperature. The median age in both groups was mostly elderly (DAC = 69 years versus NDAC = 68 years) (Table 3). High-risk PE occurred in 57 patients (DAC = 75% versus NDAC = 74%). Notably, six patients experienced cardiac arrest due to high-risk PE (DAC = 17% versus NDAC = 4%), and a large number of patients experienced concurrent DVTs (DAC = 42% versus NDAC = 60%). Additionally, there were four deaths from PE-related cardiac arrests across both groups, which all occurred in the DAC group. There were also two deaths from cardiac arrest upon initial presentation to the emergency department, which all occurred in the DAC group.

Most patients were administered 100 mg tPA (DAC = 71% versus NDAC = 77%) with minimal redosing (DAC = 4% versus NDAC = 4%). Additionally, most patients were administered unfractionated heparin (UFH) (DAC = 96% versus NDAC = 92%) using the high-dose protocol (DAC = 91% versus NDAC = 92%), although a small number of patients were administered enoxaparin (DAC = 0% versus NDAC = 8%) or argatroban (DAC = 4% versus NDAC = 0%). A majority of the mean percentage of anti-Xa or PTT values were therapeutic during the UFH infusions (DAC = 53% versus NDAC = 42%). However, although both groups experienced similar subtherapeutic anti-Xa or PTT values during the UFH infusions (DAC = 22% versus NDAC = 23%), the NDAC group experienced more supratherapeutic anti-Xa or PTT values compared to the DAC group (DAC = 25% versus NDAC = 35%).

Table 3. Patient Characteristics

Characteristic	DAC (n = 24)	NDAC (n = 53)
Baseline Demographics		
High-risk PE, n (%)	18 (75)	39 (74)
Age (years, median [IQR])	69 (60 – 74)	68 (59 – 74)
Sex, n (%)		
Male	8 (33)	27 (51)
Female	16 (67)	26 (49)
Race, n (%)		
White	10 (42)	36 (68)
Black	12 (50)	17 (32)
Hispanic/Latino	2 (8)	0 (0)
BMI (kg/m ² , mean ± SD)	40 ± 13	36 ± 9
Weight (kg, mean ± SD)	117 ± 43	106 ± 26
Cardiac arrest due to high-risk PE, n (%) ^a	4 (17)	2 (4)
Hypertension, n (%)	17 (71)	31 (58)
Diabetes mellitus, n (%)	8 (33)	17 (32)
Any cardiovascular disease, n (%)	4 (17)	7 (13)
Hyperlipidemia, n (%)	10 (42)	22 (42)
History of stroke, n (%)	1 (4)	0 (0)
Liver impairment, n (%)	0 (0)	1 (2)
Pulmonary disease, n (%)	5 (21)	7 (13)
Renal disease, n (%)	5 (21)	2 (4)
Smoker, n (%)	3 (13)	11 (21)
Baseline Bleeding Risk Factors		
Active internal bleeding or known bleeding diatheses (excluding menses), n (%)	13 (54)	32 (60)
History of ischemic stroke within the last 3 months, n (%)	0 (0)	0 (0)
Any history of ICH, n (%)	0 (0)	0 (0)
Symptoms suggestive of SAH, ICH, known ICH or neoplasm, AV malformation, or aneurysm at any time before or during tPA, n (%)	0 (0)	0 (0)
Recent intracranial or intraspinal surgery within the last 3 months, n (%)	0 (0)	0 (0)
Age > 75 years, n (%)	6 (25)	12 (23)
Use of DOAC or heparin product prior to tPA, n (%)	12 (50)	30 (57)
Pregnant at time of admission, n (%)	0 (0)	0 (0)
Non-compressible vascular puncture at time of tPA, n (%)	8 (33)	8 (15)
Traumatic or prolonged CPR (> 10 minutes) at time of tPA, n (%)	2 (8)	1 (2)
History of internal bleeding within the last 2 – 4 weeks, n (%)	0 (0)	0 (0)
History of chronic, severe, and poorly controlled hypertension, n (%)	0 (0)	1 (2)
Severe, uncontrolled hypertension (SBP > 180 mmHg or DBP > 110 mmHg), n (%)	1 (4)	3 (6)
History of dementia, n (%)	1 (4)	1 (2)
History of ischemic stroke > 3 months, n (%)	0 (0)	0 (0)
History of major surgery within the last 3 weeks, n (%)	0 (0)	2 (4)
Baseline Clotting Risk Factors		
Active cancer, n (%)	5 (21)	6 (11)
History of prior cancer, n (%)	2 (8)	8 (15)
On estrogen therapy at home, n (%)	1 (4)	1 (2)
History of thrombophilia, n (%)	23 (96)	45 (85)

History of prior DVT or PE, <i>n</i> (%)	7 (29)	15 (28)
Concurrent DVT, <i>n</i> (%)	10 (42)	32 (60)
History of prolonged immobilization, <i>n</i> (%)	3 (13)	11 (21)
Multiple trauma on admission, <i>n</i> (%)	0 (0)	0 (0)
Obesity (BMI > 30 kg/m ²), <i>n</i> (%)	20 (83)	38 (72)
Pregnant or postpartum, <i>n</i> (%)	1 (4)	0 (0)
Age > 40 years, <i>n</i> (%)	22 (92)	49 (92)
Unprovoked PE, <i>n</i> (%)	9 (38)	24 (45)
Medication Administration		
tPA dose, <i>n</i> (%)		
100 mg	17 (71)	41 (77)
50 mg	7 (29)	12 (23)
tPA re-dosed, <i>n</i> (%)	1 (4)	2 (4)
tPA infusion duration (minutes, mean ± SD)	105 ± 31	117 ± 32
Anticoagulation, <i>n</i> (%)		
UFH ^b	23 (96)	49 (92)
Enoxaparin	0 (0)	4 (8)
Argatroban	1 (4)	0 (0)
Number of patients administered UFH using the high-dose UFH infusion protocol, <i>n</i> (%) ^c	21 (91)	45 (92)
Percentage of subtherapeutic anti-Xa or PTT values during UFH infusion (%; mean ± SD) ^d	22 ± 20	23 ± 24
Percentage of therapeutic anti-Xa or PTT values during UFH infusion (%; mean ± SD) ^d	53 ± 23	42 ± 23
Percentage of supratherapeutic anti-Xa or PTT values during UFH infusion (%; mean ± SD) ^d	25 ± 21	35 ± 26
Time from tPA administration to the final PTT value obtained before anticoagulant administration (minutes, mean ± SD) ^e	301 ± 619	10 ± 34
Time from tPA to anticoagulant administration (minutes, mean ± SD)	575 ± 597	176 ± 100
Baseline Vitals		
Heart rate (bpm, mean ± SD)	104 ± 21	114 ± 16
SBP (mmHg, mean ± SD)	116 ± 26	117 ± 29
DBP (mmHg, mean ± SD)	70 ± 16	75 ± 17
Mean arterial pressure (mmHg, mean ± SD)	86 ± 18	89 ± 20
Temperature (°F, mean ± SD)	97.8 ± 0.8	98.2 ± 0.9
Oxygen saturation (%; mean ± SD)	93 ± 7	93 ± 8
Laboratory Values		
Baseline hemoglobin (g/dL, mean ± SD)	13.0 ± 2.3	13.7 ± 2.1
Baseline hematocrit (%; mean ± SD)	40.4 ± 6.4	42.8 ± 9.1
Baseline platelet count (10 ³ cells/mL, mean ± SD)	197 ± 77	206 ± 64
Baseline INR (ratio, mean ± SD) ^f	1.4 ± 0.5	1.3 ± 0.6
Baseline PTT (seconds, mean ± SD) ^g	44 ± 36	39 ± 28
Number of PTT values obtained before anticoagulant administration (mean ± SD) ^h	1.6 ± 1.2	0.9 ± 0.4
Final PTT value obtained after tPA administration and before anticoagulant administration (seconds, mean ± SD) ⁱ	46 ± 13	62 ± 30
Peak pre-tPA fibrinogen (mg/dL, mean ± SD) ^j	421 ± 0	393 ± 123
Lowest post-tPA fibrinogen (mg/dL, mean ± SD) ^j	119 ± 97	67 ± 21

Abbreviations: AV, arteriovenous; BMI, body mass index; CPR, cardiopulmonary resuscitation; DAC, delayed anticoagulation; DBP, diastolic blood pressure; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ICH, intracranial hemorrhage; INR, international normalized ratio; IQR, interquartile range; NDAC, non-delayed anticoagulation; PE, pulmonary embolism; PTT, partial thromboplastin time; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure; SD, standard deviation; tPA, alteplase; UFH, unfractionated heparin.

^aThere were four deaths from PE-related cardiac arrests across both groups, which all occurred in the DAC group. Additionally, there were two deaths from cardiac arrest upon initial presentation to the emergency department, which all occurred in the DAC group.

^bThere were four patients in the DAC group (17%) and three patients in the NDAC group (6%) administered an initial UFH bolus prior to initiation of the UFH infusion.

^cOnly patients who were administered UFH were included (*n* = 72). The remaining patients in the DAC and NDAC groups were administered the low-dose UFH infusion protocol,

specifically two patients in the DAC group and four patients in the NDAC group. The institutional UFH high-dose protocol (therapeutic reference range for anti-Xa = 0.4 – 0.7 units/mL, PTT = 60 – 90 seconds) is commonly used for patients with PE, DVT, mechanical valve (with active thrombosis), or other active thrombosis. The institutional UFH low-dose protocol (therapeutic reference range for anti-Xa = 0.3 – 0.5 units/mL, PTT = 60 – 80 seconds) is commonly used for patients with acute coronary syndrome, atrial fibrillation, or other indications with higher bleeding risk.

^dOnly patients who were administered a UFH infusion and had an anti-Xa or PTT value measured during the infusion were included ($n = 71$). Of the 71 patients, one patient (1%) was administered the UFH infusion using the PTT protocol. The anti-Xa protocol is the institutional preferred method of UFH monitoring due to the limited interference associated with anti-Xa values. However, PTT monitoring may be used with conditions that interfere with the accuracy of measuring and interpreting anti-Xa levels, including recent direct oral anticoagulant use. The institutional UFH high-dose protocol utilizes a therapeutic reference range of 0.4 – 0.7 units/mL for anti-Xa levels and 60 – 90 seconds for PTT levels. The institutional UFH low-dose protocol utilizes a therapeutic reference range of 0.3 – 0.5 units/mL for anti-Xa levels and 60 – 80 seconds for PTT levels.

^ePatients were assigned a value of “0 minutes” if no PTT values were obtained, if the PTT values were only obtained before tPA and anticoagulant administration, or if the PTT values were obtained only after anticoagulant administration.

^fBaseline INR mean was obtained from the initial INR value present, regardless of timing. Not all patients had INR values present. There were 22 patients in the DAC group (92%) with INR values present, with INR values obtained after tPA administration in two of these patients. There were 45 patients in the NDAC group (85%) with INR values present, with INR values obtained after tPA administration in three of these patients.

^gBaseline PTT mean was obtained from the initial PTT value present, regardless of timing. Not all patients had PTT values present. There were 21 patients in the DAC group (88%) with PTT values present; initial PTT values were obtained after tPA administration in four of these patients, and of these four patients, those initial PTT values were obtained after anticoagulant administration in zero patients. There were 49 patients in the NDAC group (92%) with PTT values present; initial PTT values were obtained after tPA administration in nine of these patients, and of these nine patients, those initial PTT values were obtained after anticoagulant administration in four patients.

^hPatients were assigned a value of “0” if no PTT values were obtained, or if the PTT values were obtained only after anticoagulant administration.

ⁱOnly patients who had PTT values obtained both after tPA administration and before anticoagulant administration were included. There were 14 patients in the DAC group (58%) and five patients in the NDAC group (9%) who met these criteria.

^jThere was one patient in the DAC group (4%) and two patients in the NDAC group (4%) with a pre-tPA fibrinogen value. There were three patients in the DAC group (13%) and three patients in the NDAC group (6%) with a post-tPA fibrinogen value. The institutional reference range for fibrinogen was 228 – 518 mg/dL.

Overall regarding medication administration, patients in the DAC group experienced a larger mean number of PTT values obtained before anticoagulant initiation (DAC = 1.6 versus NDAC = 0.9), longer mean time from tPA administration to the final PTT value obtained before anticoagulant administration (DAC = 301 minutes versus NDAC = 10 minutes), and longer mean time of anticoagulation initiation after tPA administration (DAC = 575 minutes versus NDAC = 176 minutes).

3.2. OUTCOMES

There was no statistically significant difference between DAC and NDAC for the primary outcome (DAC = 21% versus NDAC = 30%, $p = 0.393$) (Table 4). Considering the 21 composite bleeding events, logistic regression analysis was not statistically significant (OR, 0.61; 95% CI, 0.13 – 1.78), even when adjusting for the number of bleeding and clotting risk factors (adjusted OR [aOR], 0.61; 95% CI, 0.13 – 1.85).

There were no statistically significant differences regarding the secondary outcomes except survival to hospital discharge, favoring NDAC (DAC = 79% versus NDAC = 98%, $p = 0.010$). Considering the 71 patients who survived to hospital discharge, logistic regression analysis was statistically significant (OR, 0.07; 95% CI, 0.00 – 0.47).

Exploratory analyses of the high-risk PE subgroup found a statistically significant association in survival to hospital discharge, favoring NDAC (OR, 0.07; 95% CI, 0.00 – 0.47). Five patients in the DAC group and one patient in the NDAC group did not survive to discharge, with four deaths in the DAC group and the singular death in the NDAC group attributed to the high-risk PE. The remaining death in the DAC group was attributed to post-cardiac arrest brain death. Additionally, for the intermediate-risk PE subgroup, there was a 100% rate of survival to hospital discharge.

4. DISCUSSION

This study found no statistically significant association between NDAC and DAC for any outcome except survival to hospital discharge, suggesting possibly similar safety be-

tween NDAC and DAC and less bleeding risk with NDAC as presumed. Of note, as a secondary outcome, the statistically significant difference in survival to hospital discharge between NDAC and DAC is an exploratory observation and requires further studies to confirm this finding.

The extensive clot burden, especially with the high number of concurrent DVTs, may have balanced bleeding risks. Additionally at the individual level, the complex interactions of tPA and anticoagulation on hemostatic and fibrinolytic processes may be varied.²² Within the total sample, PE-related cardiac arrests and deaths from cardiac arrest upon initial presentation to the emergency department all occurred in the DAC group, which may suggest an extensive clot burden was unresolved fully in the DAC group and therefore may have influenced the results, especially survival to hospital discharge.

In the inherently sicker high-risk PE subgroup, the possible reduced odds of survival to hospital discharge may also be associated with reduced PE resolution from delaying anticoagulation,^{3,5} as four patients in the DAC group died from the high-risk PE versus one patient in the NDAC group. The shock state induced by high-risk PE and the ischemia-perfusion injury with cardiac arrest, along with any targeted temperature management post-arrest,^{23,24} may have also affected survival via altered drug disposition and metabolism.

Additionally, patients administered UFH, who mostly utilized the high-dose anti-Xa protocol and minimally an initial bolus, experienced therapeutic levels ~50% of the time. Although higher than previous studies utilizing activated partial thromboplastin time (aPTT) levels due to increased interference with aPTT, this can lead to discordance from anti-Xa values in 46% to 60% of instances and may result in thromboembolic or bleeding events.^{25–28} Furthermore, the differences in therapeutic attainment with UFH could have affected the outcomes; for example, the NDAC group experienced more supratherapeutic anti-Xa or PTT values compared to the DAC group. Although expected to produce more bleeding events for the NDAC group, this may have been balanced by other factors such as baseline clotting risk factors. Also, the DAC group experienced a

Table 4. Primary and Secondary Outcomes

Outcomes	DAC (n = 24)	NDAC (n = 53)	p-value
Primary Outcome			
Major bleeding or CRNM bleeding, n (%) ^a	5 (21)	16 (30)	0.393
Major bleeding, n (%)	1 (4)	6 (11)	0.424
CRNM bleeding, n (%)	4 (17)	12 (23)	0.763
Secondary Outcomes			
Minor bleeding, n (%)	3 (13)	2 (4)	0.172
Required blood transfusion, n (%)	3 (13)	9 (17)	0.744
ICH, n (%)	0 (0)	0 (0)	1.000
Readmitted within 30 days, n (%)	0 (0)	3 (6)	0.548
Recurrent DVT, n (%)	0 (0)	0 (0)	1.000
Recurrent PE, n (%)	2 (8)	0 (0)	0.094
Intensive care unit length of stay (days, mean $\pm$ SD)	4 $\pm$ 4	3 $\pm$ 3	0.150
Survival to hospital discharge, n (%)	19 (79)	52 (98)	0.010

Abbreviations: CRNM, clinically relevant non-major; DAC, delayed anticoagulation; DVT, deep vein thrombosis; ICH, intracranial hemorrhage; NDAC, non-delayed anticoagulation; PE, pulmonary embolism; SD, standard deviation.

^aWithin the NDAC group, there were two patients who experienced both major and CRNM bleeding.

greater percentage of therapeutic anti-Xa or PTT values, which may have balanced the delay in anticoagulation and therefore influenced survival via clot resolution and propagation.

The apparent baseline differences between groups could have also affected the outcomes. The differences in race may have been random. The differences in renal disease may have affected the renal clearance of enoxaparin, although unlikely to be clinically significant with the minimal administration. Additionally, patients with clinically unstable heart rates and temperatures may have been biased in administration of NDAC over DAC.

Overall, the generally elderly sample and the heterogeneity within the sample, including variations in tPA dosing, UFH dosing, overall anticoagulant administration, and time to anticoagulant administration (with large standard deviations) from prescriber ordering to pharmacist verification and nursing administration, may further limit the statistical evaluation and generalizability. In relation to this time to anticoagulant administration, DAC patients experienced more PTT measurements before anticoagulant initiation and longer delays to anticoagulation, and the procedural and logistical differences involved in these tasks, such as obtaining PTT measurements and waiting for the results, could have influenced bleeding events, as the greater time for tPA clearance may have decreased the interaction of anticoagulation initiation on fibrinolytic pathways.²⁹ Furthermore, possible chest wall trauma for the six patients experiencing cardiac arrest may have influenced bleeding events.

The results of this study are similar to Schwab-Daugherty et al., comparing 95 patients receiving delayed, parenteral anticoagulation (at least one hour after systemic tPA) to 75 patients receiving early anticoagulation (within one hour of tPA or continuous anticoagulation during tPA) for PE.¹⁶ There was a similarly low and statistically non-significant number of patients experiencing major bleeds.

Additionally, despite no statistically significant difference with in-hospital mortality, both studies identified a numerically lower mortality with earlier anticoagulation.

Overall, limitations of this study included its retrospective nature which may limit the internal validity, especially with the heterogeneity and confounders. In terms of confounders within this retrospective study, unaccounted additional variables, such as the use of home antiplatelet medications and the uremia associated with renal insufficiency,³⁰ may have further influenced bleeding events. Secondly, although no power calculation was performed, the study may have been underpowered given the small sample size, which may influence the statistically significant results, reduce statistical power, and limit generalizability of the results. However, these results may still provide an impetus for future research, and further research may be useful in accounting for these additional variables.

One strength was its multicenter design, improving generalizability. The external validity is further improved by the sample size compared to previous PE literature; in this study, 77 patients were included, which is more than those in previous literature, especially regarding high-risk PE.⁶⁻¹¹ Furthermore, logistic regression analyses were internally validated using statistical bootstrapping to account for the small sample size.

5. CONCLUSION

In patients with high-risk or intermediate-risk PE who do not receive catheter-directed tPA, DAC and NDAC after systemic tPA may be associated with similar occurrences of bleeding. Therefore, both DAC and NDAC may be reasonable pharmacologic strategies, as NDAC may not be associated with as extensive of a bleeding risk for these patients as presumed. However, these results should be interpreted with caution given the small sample size, heterogeneity,

and confounding variables within this retrospective study. Altogether, this study highlights the variability in the management of high-risk and intermediate-risk PE and encourages further studies to standardize and optimize care.

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None

CONFLICTS OF INTEREST

None

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REFERENCES

1. Gottlieb M, Moyer E, Bernard K. Epidemiology of pulmonary embolism diagnosis and management among United States emergency departments over an eight-year period. *Am J Emerg Med.* 2024;85:158-162. doi:[10.1016/j.ajem.2024.09.016](https://doi.org/10.1016/j.ajem.2024.09.016)
2. Zuo Z, Yue J, Dong BR, Wu T, Liu GJ, Hao Q. Thrombolytic therapy for pulmonary embolism. *Cochrane Database Syst Rev.* 2021;4(4):CD004437. doi:[10.1002/14651858.CD004437.pub6](https://doi.org/10.1002/14651858.CD004437.pub6)
3. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Heart J.* 2020;41:543-603. doi:[10.1093/eurheartj/ehz405](https://doi.org/10.1093/eurheartj/ehz405)
4. Kucher N, Goldhaber SZ. Management of massive pulmonary embolism. *Circulation.* 2005;112(2):e28-e32. doi:[10.1161/circulationaha.105.551374](https://doi.org/10.1161/circulationaha.105.551374)
5. Mohamad T, Kanaan E, Ogieuhi IJ, et al. Thrombolysis vs anticoagulation: unveiling the trade-offs in massive pulmonary embolism. *Cureus.* 2024;16(1):e52675. doi:[10.7759/cureus.52675](https://doi.org/10.7759/cureus.52675)
6. Becattini C, Agnelli G, Salvi A, et al. Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. *Thromb Res.* 2010;125(3):e82-86. doi:[10.1016/j.thromres.2009.09.017](https://doi.org/10.1016/j.thromres.2009.09.017)
7. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med.* 2014;370(15):1402-1411. doi:[10.1056/nejmoa1302097](https://doi.org/10.1056/nejmoa1302097)
8. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W, Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med.* 2002;347(15):1143-1150. doi:[10.1056/nejmoa021274](https://doi.org/10.1056/nejmoa021274)
9. Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. *J Thromb Haemost.* 2014;12(4):459-468. doi:[10.1111/jth.12521](https://doi.org/10.1111/jth.12521)
10. Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M, "MOPETT" Investigators. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). *Am J Cardiol.* 2013;111(2):273-277. doi:[10.1016/j.amjcard.2012.09.027](https://doi.org/10.1016/j.amjcard.2012.09.027)
11. Sharifi M, Berger J, Beeston P, et al. Pulseless electrical activity in pulmonary embolism treated with thrombolysis (from the "PEAPETT" study). *Am J Emerg Med.* 2016;34(10):1963-1967. doi:[10.1016/j.ajem.2016.06.094](https://doi.org/10.1016/j.ajem.2016.06.094)
12. Martin C, Sobolewski K, Bridgeman P, Boutsikaris D. Systemic thrombolysis for pulmonary embolism: a review. *P T.* 2016;41(12):770-775.
13. Ucar EY. Update on thrombolytic therapy in acute pulmonary thromboembolism. *Eurasian J Med.* 2019;51(2):186-190. doi:[10.5152/eurasianjmed.2019.19291](https://doi.org/10.5152/eurasianjmed.2019.19291)
14. British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. *Thorax.* 2003;58(6):470-483. doi:[10.1136/thorax.58.6.470](https://doi.org/10.1136/thorax.58.6.470)
15. Ceresetto JM, Marques MA. Systemic fibrinolytic therapy in pulmonary thromboembolism. *J Vasc Bras.* 2017;16(2):119-127. doi:[10.1590/1677-5449.007316](https://doi.org/10.1590/1677-5449.007316)
16. Schwab-Daugherty EM, Peng MR, Caraccio EE, Stevens SM, Woller SC. Timing of parenteral anticoagulation after thrombolysis for the treatment of pulmonary embolism. *Thromb Res.* 2020;195:58-61. doi:[10.1016/j.thromres.2020.07.001](https://doi.org/10.1016/j.thromres.2020.07.001)
17. Lutsey PL, Zakai NA. Epidemiology and prevention of venous thromboembolism. *Nat Rev Cardiol.* 2023;20(4):248-262. doi:[10.1038/s41569-022-00787-6](https://doi.org/10.1038/s41569-022-00787-6)
18. Fugate JE, Rabinstein AA. Absolute and relative contraindications to IV rt-PA for acute ischemic stroke. *Neurohospitalist.* 2015;5(3):110-121. doi:[10.1177/1941874415578532](https://doi.org/10.1177/1941874415578532)
19. von Elm E, Altman DG, Egger M, et al. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ.* 2007;335(7624):806-808. doi:[10.1136/bmj.39335.541782.AD](https://doi.org/10.1136/bmj.39335.541782.AD)

20. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S, Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *J Thromb Haemost*. 2015;13(11):2119-2126. doi:[10.1111/jth.13140](https://doi.org/10.1111/jth.13140)
21. Wells GA, Elliott J, Kelly S, et al. Bleeding classification system definitions. In: Wells GA, Elliott J, Kelly S, et al., eds. *Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention: Clinical and Economic Impact of Standard Versus Extended Duration*. Canadian Agency for Drugs and Technologies in Health; 2019:173-174.
22. Chapin JC, Hajjar KA. Fibrinolysis and the control of blood coagulation. *Blood Rev*. 2015;29(1):17-24. doi:[10.1016/j.blre.2014.09.003](https://doi.org/10.1016/j.blre.2014.09.003)
23. Lazzarin T, Tonon CR, Martins D, et al. Post-cardiac arrest: mechanisms, management, and future perspectives. *J Clin Med*. 2022;12(1):259. doi:[10.3390/jcm12010259](https://doi.org/10.3390/jcm12010259)
24. Anderson KB, Poloyac SM, Kochanek PM, Empey PE. Effect of hypothermia and targeted temperature management on drug disposition and response following cardiac arrest: a comprehensive review of preclinical and clinical investigations. *Ther Hypothermia Temp Manag*. 2016;6(4):169-179. doi:[10.1089/ther.2016.0003](https://doi.org/10.1089/ther.2016.0003)
25. Khor YH, Smith R, McDonald CF. Suboptimal management of unfractionated heparin compared with low-molecular-weight heparin in the management of pulmonary embolism. *Intern Med J*. 2014;44(4):339-344. doi:[10.1111/imj.12376](https://doi.org/10.1111/imj.12376)
26. Prucnal CK, Jansson PS, Deadmon E, Rosovsky RP, Zheng H, Kabrhel C. Analysis of partial thromboplastin times in patients with pulmonary embolism during the first 48 hours of anticoagulation with unfractionated heparin. *Acad Emerg Med*. 2020;27(2):117-127. doi:[10.1111/acem.13872](https://doi.org/10.1111/acem.13872)
27. Whitman-Purves E, Coons JC, Miller T, et al. Performance of anti-factor Xa versus activated partial thromboplastin time for heparin monitoring using multiple nomograms. *Clin Appl Thromb Hemost*. 2018;24(2):310-316. doi:[10.1177/1076029617741363](https://doi.org/10.1177/1076029617741363)
28. May JE, Siniard RC, Taylor LJ, Marques MB, Gangaraju R. From activated partial thromboplastin time to antifactor Xa and back again: the evolution of monitoring unfractionated heparin. *Am J Clin Pathol*. 2022;157(3):321-327. doi:[10.1093/ajcp/aqab135](https://doi.org/10.1093/ajcp/aqab135)
29. Romoli M, Vandelli L, Bigliardi G, et al. Fibrinogen depletion coagulopathy predicts major bleeding after thrombolysis for ischemic stroke: a multicenter study. *Stroke*. 2022;53(12):3671-3678. doi:[10.1161/STROKEAHA.122.039652](https://doi.org/10.1161/STROKEAHA.122.039652)
30. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):e44S-e88S. doi:[10.1378/chest.11-2292](https://doi.org/10.1378/chest.11-2292)