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Apixaban or Rivaroxaban Versus Warfarin for Treatment of Submassive Pulmonary Embolism After Catheter-Directed Thrombolysis

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Abstract

Background: Little data exist on the use of direct oral anticoagulant (DOAC) factor Xa inhibitors for submassive pulmonary embolism (PE) after catheter-directed thrombolysis (CDT). The objective of this evaluation was to determine whether the transition from parenteral anticoagulation to DOACs for submassive PE after CDT would decrease hospital length of stay (LOS) compared to warfarin. **Methods:** A retrospective review of patients diagnosed with submassive PE who underwent CDT was conducted from January 1, 2012, to February 28, 2017. Hospital LOS and major and minor bleeding events were recorded during hospitalization and at 90 days. **Results:** Sixty-two patients met the inclusion criteria, 36 in warfarin group and 26 in the DOAC group. Overall, patients receiving rivaroxaban or apixaban had a shorter median hospital LOS compared to warfarin (4.0 vs 6.1 days, $P = .002$). In the multivariate regression analysis, administration of DOAC was an independent predictor of decreased hospital LOS, β: −2.1, 95% confidence interval (−3.5 to −0.7). **Conclusion:** Among patients with submassive PE, initiation of a DOAC shortly after CDT may result in a decreased hospital LOS compared to parenterally bridged warfarin.

Keywords
anticoagulants, pulmonary embolism, catheter-directed thrombolysis, factor Xa inhibitors

Introduction

Submassive or intermediate-risk pulmonary embolism (PE), defined as PE without systemic hypotension and with either right ventricular (RV) dysfunction or myocardial necrosis, accounts for 40% to 50% of patients presenting with acute PE.[1,2] These patients can have a mortality rate almost double than those who present with normal RV function.[3] Various treatment modalities exist for the immediate management of submassive PE. Catheter-directed thrombolysis (CDT) involves intravascular administration of a thrombolytic agent via a multiple side-hole catheter directly at the thrombus site.[1] Ultrasound-assisted catheter-directed thrombolysis (USAT) combines conventional CDT with high-frequency, low-energy ultrasound technology to increase permeability of thrombolytics into the clot.[4]

Following CDT, patients are traditionally managed with systemic unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) bridged to warfarin. The American

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College of Chest Physicians recommend that parenteral anticoagulation continue for a minimum of 5 days and until the international normalized ratio is 2.0 or above for at least 24 hours (grade 1B).[5]

Recent evidence has demonstrated that direct oral anticoagulants (DOACs), specifically factor Xa inhibitor agents, are favorable treatment options for PE, and DOACs are now recommended over warfarin for patients with noncancer-related venous thromboembolism (VTE).[6] Apixaban and rivaroxaban are direct factor Xa inhibitors shown in phase III trials to be noninferior to conventional therapy with less major bleeding. However, these trials did not include patients with submassive PE and excluded those who received any form of thrombolysis, including CDT.[7,8]

Little data exist on the use of apixaban or rivaroxaban for submassive PE after CDT.[9] Given the predictable pharmacokinetics and rapid therapeutic effect, there is no "bridging period" with these agents. Also, no additional laboratory monitoring is required, making them a convenient treatment option. Therefore, we sought to determine whether the transition from UFH or LMWH to DOACs for submassive PE after CDT would decrease hospital length of stay (LOS) compared to warfarin.

Materials and Methods

This retrospective review of intensive care unit (ICU) patients was approved by both The University of Pittsburgh Medical Center (UPMC) Quality Improvement (QI) Committee and The University of Pittsburgh's Institutional Review Board (PRO16080502). The UPMC QI Committee agreed with this evaluations' distinction as QI prior to the collection of any patient-related data. The UPMC Presbyterian Hospital is a large academic tertiary medical center.

Patients

Patients with a diagnosis code for submassive PE who received treatment with CDT or USAT were evaluated from January 1, 2012, to February 28, 2017. Patients were identified via *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* Code 415.1x or *ICD-10* Code I26.99, cross-referenced with the UPMC PE registry, and subsequently determined whether criteria for submassive PE were met. Submassive PE was defined as acute PE without systemic hypotension (systolic blood pressure $\geq$90 mm Hg) but with either RV dysfunction or myocardial necrosis. Right ventricular dysfunction was determined by the presence of RV dilation on echocardiography or computed tomography (CT) scan, brain natriuretic peptide (BNP) >90 pg/mL or electrocardiographic changes such as new complete or incomplete right bundle-branch block, anteroseptal ST-segment elevation or depression, or anteroseptal T-wave inversion. Myocardial necrosis was defined as troponin >0.1 ng/mL.[1]

Patients were excluded if they were younger than 18 years of age, died less than 24 hours after CDT start, did not receive any oral anticoagulant (OAC) during admission, or if they had a documented complication from the CDT procedure. Catheter-directed thrombolysis was performed with alteplase therapy using conventional catheter-directed lysis or with ultrasound assistance via the EKOS catheter (EKOS Ekosonic Endovascular System; EKOS Corporation, Bothell, Washington).[10] At our institution, a multidisciplinary PE team is available for consultation, guidance, and decision-making. If CDT is considered, vascular surgery or interventional cardiology subsequently performs the procedure, but the technique, catheter type, and alteplase dose is at the discretion of these services. The treating physician dictates the intensity and duration of heparin infusions.

Data Collection

All data were collected from the electronic health record. Demographics, troponin, and BNP were recorded upon hospital admission. Pulmonary artery systolic pressure (PASP) was estimated from the first echocardiogram prior to CDT. If the patient underwent a right heart catheterization prior to CDT, the mean pulmonary artery pressure (mPAP) was documented from this procedure. Serum creatinine was recorded at the time of transition to OAC. Variables used to calculate the Pulmonary Embolism Severity Index (PESI) score included age, sex, history of cancer, heart failure, chronic lung disease, heart rate, systolic blood pressure, respiratory rate, oxygen saturation (Sao_2), mental status, and temperature, also recorded upon PE diagnosis.[11] Type of parenteral anticoagulation was documented before and after CDT. The specific OAC selected as well as the date and time of first dose were recorded. Based on this information, patients were categorized into either the DOAC or the warfarin group. If a patient received more than 1 type of OAC, the OAC at the time of discharge determined the patient's group. Time to initiation of OAC was defined as time from hospital admission to the first OAC documentation. Rivaroxaban and apixaban are the preferred DOAC agents on the UPMC health-system medication formulary and thus were the only agents evaluated.

Outcomes

The primary outcome was hospital LOS, defined as the number of days from the patient's arrival at our institution until discharge. Secondary end points included ICU LOS and major or minor bleeding events during hospitalization. We also reviewed 90-day outcomes such as bleeding events, clotting events, and mortality. Major bleeding was defined as clinically overt and associated with a decrease in the hemoglobin level of 2.0 g/dL or more, if bleeding led to the transfusion of 2 or more units of red cells, or if bleeding was intracranial or retroperitoneal, occurred in another critical site (intraspinal, intraocular, pericardial, intra-articular, or intramuscular with compartment syndrome), or contributed to death. Minor bleeding was defined as bleeding that did not meet major bleed criteria but associated with intervention, discomfort, or impairment of activities of

Table 1. Baseline Characteristics.[a]

Variable	All Patients (N = 62)	Warfarin (n = 36)	DOAC (n = 26)
Age, years	59 (46-65)	61 (44-65)	57 (48-64)
Gender, female	33 (53)	25 (69)	8 (31)
Serum creatinine (at time of transition), mg/dL	0.8 (0.7-0.9)	0.8 (0.7-0.9)	0.9 (0.7-0.9)
Troponin, ng/mL	0.29 (0.13-0.5)	0.35 (0.18-0.51)	0.27 (0.08-0.35)
BNP, pg/mL	281 (157-479)	265 (117-492)	288 (141-445)
PASP,[b] mm Hg	52 (44-62)	52 (44-61), n = 32	55 (44-64), n = 20
mPAP,[c] mm Hg	35 (31-39)	34 (34-38), n = 11	37 (31-38), n = 13
Weight, kg	103 (93-118)	103 (91-113)	106 (97-125)
PESI score[d]	89 (67-106)	87 (66-106)	89 (76-104)
HR, beats per minute	113 (101-124)	110 (95-121)	116 (108-126)
SBP,[d] mm Hg	132 (119-148)	133 (119-143)	131 (121-151)
RR,[d] breaths per minute	20 (18-24)	20 (18-24)	22 (19-24)
SaO_2,[d] %	95 (92-97)	95 (92-97)	95 (93-97)

Abbreviations: BNP, brain natriuretic peptide; HR, heart rate; mPAP, mean pulmonary artery pressure; PASP, pulmonary artery systolic pressure; PESI, Pulmonary Index Severity Index; RR, respiratory rate; Sa_{O_2}, saturation of oxygen in arterial blood; SBP, systolic blood pressure.
[a]Data reported as median (interquartile range) or n (%).
[b]Recorded from echocardiogram.
[c]Recorded from right heart catheterization.
[d]Recorded on pulmonary embolism diagnosis.

daily life.[7,8] Clotting events were defined as new or recurrent deep venous thrombosis, PE, or another vascular event such as acute coronary syndrome or ischemic stroke. Ninety-day outcomes were determined by review of outpatient and readmission progress notes after discharge.

Statistics

SPSS (version 24; IBM Corp, Armonk, New York) software was used for data analysis. Continuous variables are reported as median $\pm$ interquartile (IQ) range, and differences between groups were calculated using the Mann-Whitney U test. Dichotomous variables were compared using Fisher exact test. Linear regression was used to evaluate factors associated with hospital LOS and to account for potential confounding variables. Each collected variable was screened as a predictive risk factor in univariate analyses. Due to a high number of patients with missing data points, 2 variables (PASP and mPAP) were not included in the univariate analyses. Variables with a P value $\leq$.10 in the univariate screening process were included into a multivariate model. Time to discharge curves were generated using the Cox multivariate proportional hazards model that included the significant cofactors in the multivariate linear regression analysis. Throughout the evaluation, P values of <.05 were considered statistically significant.

Results

Sixty-two patients met the inclusion criteria, 36 in warfarin group and 26 in DOAC group. Of the patients in the DOAC group, 19 were prescribed rivaroxaban and 7 received apixaban. Baseline characteristics stratified by OAC are depicted in Table 1. The groups were well matched overall, with the exception of a greater number of female patients in the warfarin group. All patients met criteria for RV dysfunction with a median BNP of 265 ng/mL in warfarin group and 288 ng/mL in the DOAC group. Patients also had signs of myocardial necrosis with median troponin of 0.35 ng/mL in warfarin group and 0.27 ng/mL in DOAC group. The median PESI score on admission in all patients was 89, indicating intermediate risk of 30-day mortality (3.2%-7.1%).[11] The PESI scores were similar between the 2 groups (warfarin = 87, DOAC = 89, P = .58).

Table 2. Type of Parenteral Anticoagulation Before and After Catheter-Directed Lysis.[a]

Parenteral Anticoagulant	Warfarin (n = 36)	DOAC (n = 26)
Pre-CDT anticoagulation		
Heparin	33 (92)	25 (96)
Heparin and enoxaparin	3 (8)	0 (0)
Argatroban	0 (0)	1 (4)
Post-CDT anticoagulation		
Heparin	23 (64)	21 (81)
Heparin and enoxaparin	13 (36)	4 (15)
Argatroban		1 (4)
Time to OAC, days	2.9 (2.1-3.7)	2.3 (1.9-3.3)

Abbreviations: CDT, catheter directed thrombolysis; DOAC, direct oral anticoagulant; OAC, oral anticoagulation.
[a]Data reported as median (interquartile range) or n (%).

The use of parenteral anticoagulation was similar between the groups (Table 2). The majority of patients received exclusively heparin prior to CDT (92% in warfarin group, 96% in DOAC group). After the procedure, 64% and 81% of patients were prescribed solely UFH in the warfarin and DOAC groups, respectively. There was no difference in the time to initiation of OAC in the warfarin versus DOAC groups (2.9 vs 2.3 days, P = .16). Three patients were originally prescribed warfarin but subsequently transitioned to rivaroxaban within 3 days of starting OAC.

Table 3. In-Hospital and 90-day Outcomes.[a]

Outcome	All Patients (n = 62)	Warfarin (n = 36)	DOAC (n = 26)	*P* Value
In-Hospital Outcomes				
ICU LOS, days	2.7 (2.2-3.9)	2.7 (2.0-4.0)	2.7 (2.5-3.6)	.68
Hospital LOS, days	5.6 (3.9-8.0)	6.1 (5.0-9.5)	4.0 (3.8-5.8)	.002
Major bleed	0	0	0	-
Minor bleed	3 (5)	3 (8)	0	.26
90-Day Outcomes				
Nonmajor bleed, n	0	0	0	
Major bleed, n	0	0	0	
Clotting event, n	1	1 (recurrent PE)	0	
Alive at 90 days, n	61	36	25[b]	

Abbreviations: DOAC, direct oral anticoagulant; ICU, intensive care unit; LOS, length of stay; PE, pulmonary embolism.
[a]Data reported as median (interquartile range) or n (%).
[b]Unable to determine for 1 patient.

Table 4. Predictors of Hospital Length of Stay.[a]

Predictor of Hospital Length of Stay	β Value (95% Confidence Interval)	*P* Value
DOAC administration	−2.1 (−3.5 to −0.7)	.004
BNP	0.002 (0 to 0.003)	.03
Minor bleed	8.2 (4.6 to 11.8)	<.001

Abbreviations: BNP, brain natriuretic peptide; DOAC, direct oral anticoagulant.
[a]A *P* Value of <.1 was considered to be significant in the univariate analysis and those variables were used in the multivariate linear regression analysis.

Overall, patients receiving rivaroxaban or apixaban had a shorter median hospital LOS compared to warfarin (4.0 vs 6.1 days, $P = .002$). Intensive care unit LOS was the same in both the groups (2.7 vs 2.7 days, $P = .68$; Table 3). There were no major bleeds in either cohort, and 3 patients had a minor bleed, all in the warfarin group. At 90 days, 61 patients were alive, and there were no additional bleeding events in either group. One patient in the warfarin group experienced a clotting event, in the form of a recurrent PE. In the multivariate regression analysis, the administration of DOAC was an independent predictor of decreased hospital LOS, β: −2.1, 95% confidence interval (CI; (−3.5 to −0.7; Table 4). The Cox proportional hazards model demonstrated that the use of DOAC after CDT was associated with a decrease in time to discharge, $P = .001$ (Figure 1).

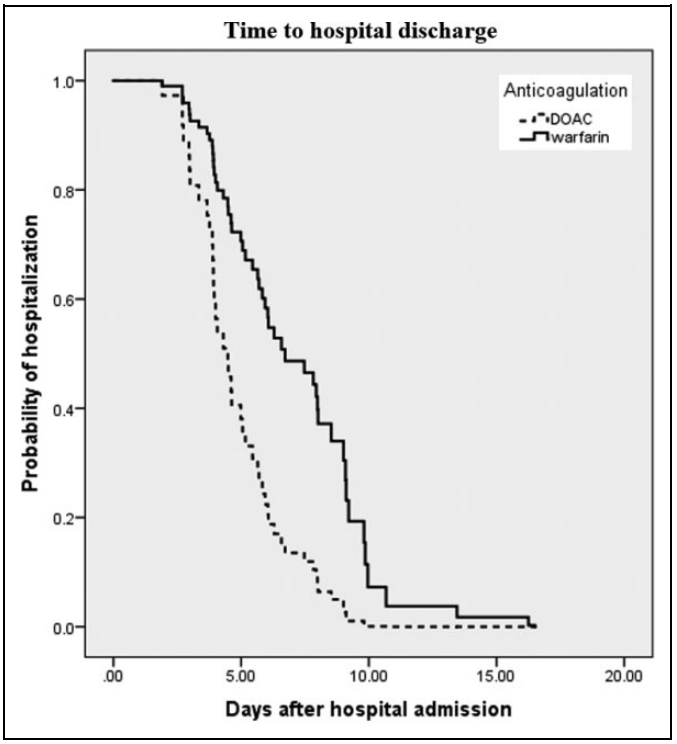

Figure 1. Probability of hospitalization according to treatment group. In a Cox multivariate proportional hazards model controlling for baseline BNP and bleeding, the use of DOAC after CDT was associated with a significant decrease in hospital length of stay compared to warfarin ($P = .001$). BNP indicates brain natriuretic peptide; CDT, catheter-directed thrombolysis; DOAC, direct oral anticoagulant.

Discussion

In a real-world cohort of patients with submassive PE receiving CDT or USAT, we observed a shorter hospital LOS in patients transitioned to rivaroxaban or apixaban compared to warfarin. We report the first analysis of LOS and 90-day outcomes looking at DOAC versus parenteral anticoagulation and warfarin after CDT or USAT for patients with submassive PE. In a case series of 5 patients who underwent USAT for intermediate- to high-risk PE and were transitioned to rivaroxaban, no recurrent thrombotic events or bleeding episodes were noted.[9] Other than this case series, there is a paucity of data on the use of the DOAC agents for this specific indication.

Despite the lack of clinical trial data on apixaban and rivaroxaban following CDT, both have been evaluated in phase III trials for the initial and long-term treatment of hemodynamically stable patients with PE. However, patients requiring any form of thrombolytic therapy were excluded, and data on RV dysfunction and myocardial injury are not available for most patients who were included. Both studies assessed the severity of PE based on anatomical extent of vascular involvement.[7,8] Additionally, only a small percent of patients (12.9%) in the rivaroxaban group were initially admitted to the ICU, suggesting the risk of deterioration to severe PE was relatively low in this trial.[7] Therefore, it is unknown whether the results of these trials can be applied to patients with submassive PE and/or those who received CDT.

Currently, edoxaban is the only DOAC studied in a trial that included patients with submassive PE. In the Hokusai-VTE trial, about one-third of patients had evidence of RV dysfunction on CT scan and increased N-terminal pro-brain natriuretic

peptide (NT-proBNP) levels. The rate of recurrent VTE in the subgroup with NT-proBNP $\geq$500 pg/mL was 3.3% in the edoxaban group and 6.2% in the warfarin group (hazard ratio 0.52, 95% CI 0.28-0.98). In patients with RV dysfunction on CT, a nonsignificant reduction in recurrent VTE was observed with edoxaban when compared to warfarin (hazard ratio 0.42, 95% CI 0.15-1.20).[7] In addition to edoxaban, dabigatran is currently being investigated in the Pulmonary Embolism Thrombolysis (PEITHO)-2 trial, a prospective, multicenter, phase IV trial focusing on the safety, efficacy, and cost-effectiveness in patients with acute intermediate-risk PE (NCT02596555).

There have been several studies evaluating the impact of DOACs on hospital LOS and the subsequent cost savings incurred from prescribing these agents.[12-27] Among those specifically looking at PE, the only DOAC that has been evaluated is rivaroxaban. In a post hoc analysis of the EINSTEIN-PE trial, rivaroxaban was associated with a 1.7-day mean reduction in hospital LOS versus LMWH/warfarin ($P = .0002$). This translated to a US$3419 cost-savings in rivaroxaban-treated patients.[16]

Other retrospective or observational studies have demonstrated a 1.4 to 4 day shorter hospital LOS with rivaroxaban compared to parenterally bridged warfarin. Reduction in costs ranged from US$2245 to US$4000 per patient.[19,21,22,24,25,27,28] While none of these studies specifically evaluated patients with submassive PE or CDT, they still provide evidence that DOACs decrease hospital LOS compared to warfarin in patients with PE. Although we did not evaluate cost savings, it is reasonable to suggest the results would be similar to these previous studies, given the 2-day LOS reduction seen in our DOAC cohort.

This is a real-world evaluation of patients with submassive PE receiving CDT or USAT, a cohort of patients who were not represented in the randomized clinical trials of DOACs versus warfarin. We were able to evaluate patients 90 days after discharge, which allowed obtainment of long-term safety and efficacy assessments. However, this study is not without limitations, including the retrospective nature and the nonrandomized, single-center design. Additionally, we did not evaluate matched cohorts, so confounding variables may have been missed. However, our multivariate regression analysis demonstrated that choice of OAC was an independent predictor of hospital LOS. Ninety-day outcomes were derived from physician progress notes within our health system's network, so there may be events from other health records that were not available for review. Finally, since the patients in our cohort received only apixaban or rivaroxaban, the results cannot be applied to other DOACs such as edoxaban and dabigatran.

Conclusion

Among patients with submassive PE, initiation of apixaban or rivaroxaban shortly after CDT resulted in a decreased hospital LOS and favorable 90-day outcomes compared to parenterally bridged warfarin. Further studies assessing the efficacy and safety of DOACs in patients with RV dysfunction and/or injury are needed to confirm these results.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Rivera-Lebron has financial relationships with Actlion, Bayer and Gilead which are unrelated to this submitted work.

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