3-1-2022

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Thrombosis Update 6 (2022) 100100

Contents lists available at ScienceDirect

Thrombosis Update

journal homepage: www.sciencedirect.com/journal/thrombosis-update

Predictors of anticoagulation adherence in patients with acute pulmonary embolism

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ARTICLE INFO

Keywords:
Pulmonary embolism
Adherence
Anticoagulation

ABSTRACT

Background: Anticoagulation (AC) adherence after acute pulmonary embolism (PE) is vital to prevent mortality and future recurrence of venous thromboembolism (VTE). We aimed to analyze factors affecting AC adherence after acute PE.

Methods: Consecutive adult patients with CT angiography or V/Q scan confirmed acute PE were included in a single-center retrospective study from April 2016 to May 2020. Adherence data, including AC refill dates, were collected from pharmacies, and adherence measures including Continuous Measure of Medication Acquisition (CMA), Proportion of Days Covered (PDC), and Optimal Medication Adherence (OMA) were calculated per standardized formulas. Univariable and multivariable linear and logistic regression was used to analyze different variables affecting AC adherence.

Results: A total of 118 out of 144 patients had sufficient follow-up data to measure adherence and were included in the final analysis. Mean age was 60 ± 15 years, with 64 (54.2%) women; 70 (59.3%) White, 26 (22%) African American, 13 (11%) Hispanic; 58 (49.2%) patients had private insurance, 48 (40.7%) Medicare, 11 (9.3%) Medicaid. Type of AC comprised of 57 (48.3%) apixaban, 17 (14.4%) rivaroxaban, 8 (6.8%) warfarin, 6 (5.1%) enoxaparin, and 30 (25.4%) patients with changing AC. In univariable regression, African American and Medicaid-insured patients had significantly lower adherence, while advancing age, apixaban usage, and 30-day follow-up clinic visit showed a higher adherence. However, in multivariable regression, African American race (PDC -0.135, p = 0.006, CI (−0.231, −0.040) | OMA Adjusted OR 0.166, p = 0.030, CI (0.033, 0.837)) and other non-White, non-Hispanic races (PDC -0.314, p = 0.009, CI (−0.548, −0.080)) were associated with lower AC adherence.

Conclusion: In our study, African American and other minority race patients showed lower AC adherence after hospital admission for acute PE. Further studies are needed to address underlying contributors and improve adherence in this population.

1. Introduction

Approximately 900,000 people in the U.S. are affected by pulmonary embolism (PE) annually, with 150,000 to 250,000 PE-related hospitalizations [1]. Up to 100,000 will die annually from PE-related complications [1]. Ten to thirty percent of people will die within one month of diagnosis and one-third will have a recurrence within 10 years [2]. Complications associated with PE include hypotension, hypoxemia, cardiac dysrhythmias, and sudden cardiac death, depending on the severity of PE [3]. In addition to the physiologic complications, PE also leads to decreased quality of life correlating with PE severity [4].

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https://doi.org/10.1016/j.tru.2022.100100
Received 24 September 2021; Received in revised form 24 November 2021; Accepted 14 January 2022
Available online 19 January 2022

Abbreviations

AC	Anticoagulation
CMA	Continuous Measure of Medication Acquisition
OMA	Optimal Medication Adherence
PDC	Proportion of Days Covered
PE	Pulmonary Embolism
PERT	Pulmonary Embolism Response Team
VTE	Venous Thromboembolism

Anticoagulation medications are the cornerstone of PE management [5]. The standard duration of AC is three to six months, but extended AC is recommended for unprovoked PE or those patients with high risk of recurrence [6]. Uninterrupted anticoagulation is critically important as gaps in therapy can lead to increased complications and even death. Prior cohort studies have shown a significant increase in mortality and risk of recurrent venous thromboembolism (VTE) when AC is not strictly adhered to [7]. Non-adherence has also been associated with increased healthcare expenditure both in the inpatient and outpatient settings [8].

There is a potential role for implementation of a Pulmonary Embolism Response Team (PERT) in increasing medication adherence. Over 38% of patients diagnosed with VTE are lost to follow-up [9]. Establishing a pathway for the targeted transition of care for PE and attendance at a post-PE clinic may help improve adherence. Other studies have also shown increased DOAC use post PERT implementation and with patient education [10].

Despite the increased risk of complications when treatment strategies for PE are not followed as prescribed, medication non-adherence is an ongoing challenge. There is a scarcity of data assessing factors contributing to medication non-adherence, leaving the physician and care team poorly equipped to address this issue. Our study aims to identify factors that may predict poor anticoagulation adherence to better understand the barriers these patients face and prevent adverse PE-related events.

2. Methods

This was a single-center retrospective study performed at a tertiary care urban teaching hospital from April 2016 to May 2020. The institutional review board approved the study.

2.1. Study population

Consecutive adult (>18 years) patients hospitalized with a primary or secondary acute PE diagnosis as confirmed by CT angiography or V/Q scan were included in the initial screen. Exclusion criteria included patients for whom anticoagulation was contraindicated, patients with clinically suspected PE without any imaging confirmation, patients with a low-risk PE who were discharged directly from the emergency department without PERT activation or hospitalization, and patients who died during the index hospitalization. Of 144 consecutive patients initially enrolled in the study, 26 (22%) were subsequently excluded (Fig. 1).

2.2. Data collection

Data collection included the type of anticoagulation prescribed on discharge, anticoagulation refill dates from the patient's pharmacy, insurance type, completion of 30-day follow-up clinic visit, whether the patient received an in-hospital education package regarding the diagnosis and treatment of PE, as well as demographic data (age, gender, and race). Data was collected through retrospective chart review using electronic medical record and stored using REDCap (Research Electronic Data Capture: Vanderbilt University, TN) web-based database. The refill dates were obtained by calling patient pharmacies. Patients hospitalized long enough to be seen by a member of the PERT team were also given an educational package containing images and a summary of PE symptomatology, diagnosis, and treatment in patient-friendly language, as well as links for further reading, before discharge (Appendix 1).

2.3. Outcome parameters

The primary outcome of interest was anticoagulation adherence. This was measured objectively in three different ways: (i) Continuous Measure of Medication Acquisition (CMA), (ii) Proportion of Days Covered (PDC), and (iii) Optimal Medication Adherence (OMA). The CMA is an extension of the Medication Possession Ratio (MPR), one of the most common methods of assessing pharmaceutical adherence [11]. The MPR is calculated as the sum of days of a particular medication filled in a given refill period divided by the number of days in that period. When this ratio is assessed over several refill intervals, it is referred to as

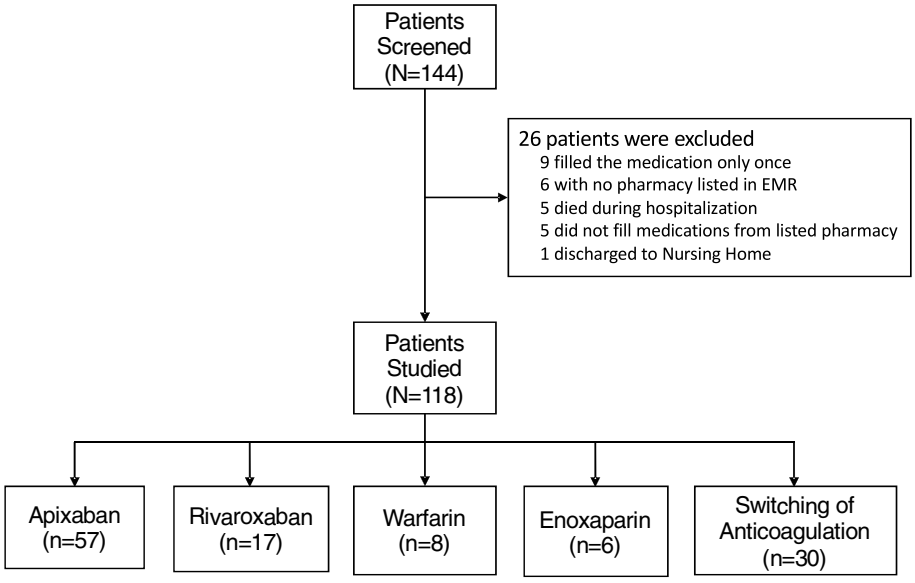

Fig. 1. Flowchart of patient selection and anticoagulation on discharge.

the CMA, as shown in Equation 1 [11].

Equation 1.

$$CMA = \frac{Number\ of\ days\ of\ medication\ supplied\ within\ refill\ periods}{Number\ of\ days\ in\ refill\ periods}$$

The major drawback to this method is that when a medication is refilled before the end of an initial refill period, the periods overlap, and the total number of days the prescription is filled becomes greater than the total number of days in the initial refill period, resulting in a CMA >1, or adherence >100%.

The PDC is defined as the ratio of the number of days of drug on-hand to the total number of days in the respective time period, as shown in Equation 2 [11].

Equation 2.

$$PDC = \frac{Number\ of\ days\ with\ medication\ on\ hand}{Number\ of\ days\ in\ period}$$

In recent years the PDC has gained popularity as a more accurate gauge of medication adherence. Unlike the CMA, there is no potential overlap of days covered, and the maximum value for the PDC is 1, indicating 100% adherence [11]. However, accurately gauging whether a patient is covered during a given interval can at times be challenging and lead to a more technically difficult computation to perform compared to the MPR or CMA [12]. The OMA is a binary variable. Patients with CMA or PDC >0.8 were classified as having OMA, and those below that threshold did not have OMA. As the OMA relies in part on the CMA, the OMA can also be misleadingly optimistic when a medication is filled early in a given refill period.

2.4. Statistical analysis

Categorical variables are presented as numbers (%) and continuous variables were listed as mean ± standard deviation (SD). Continuous variables were tested for normality using standard methods. Assumptions of regression analysis were evaluated and met for the given data. Univariable and multivariable linear and logistic models were used to determine significant associations between different measures of adherence (CMA, PDC, and OMA) with age, gender, race, type of anticoagulant, type of insurance, and patients with 30-day follow-up, using STATA15 (StataCorp LLC, TX). Variables with proven significance in the univariable model were included in the multivariable model. Additional variables were chosen as medication adherence is often influenced by appropriate patient understanding, insurance coverage, and anticoagulation dosing regimens [13].

3. Results

Of the 144 patients initially enrolled in the study, 118 (82%) filled their medication more than once and therefore had sufficient data to calculate the CMA, PDC, and OMA. Table 1 shows the demographics of the included 118 patients. The mean age was 60 ± 15 years, with 64 (54.2%) women and 54 (45.8%) men. Of all patients included in the study, there were 70 (59.3%) White, 26 (22%) African American, 13 (11%) Hispanic, 3 (2.5%) other minority races, and 6 (5%) unknown ethnicities. Fifty-eight (49.2%) patients had private insurance, 48 (40.7%) Medicare, 11 (9.3%) Medicaid, and 1 (0.8%) self-pay. Patients were prescribed one of the several forms of AC based on patient-provider preference, age, insurance, and underlying co-morbidities: 57 (48.3%) patients took apixaban, 17 (14.4%) rivaroxaban, 8 (6.8%) warfarin, and 6 (5.1%) enoxaparin. The remaining 30 (25.4%) patients switched from one form of AC to another during the study due to cost, availability, drug failure, or patient-provider preference.

Of the 118 patients analyzed, 58 (49.2%) had a PDC of 1, and 56 (47.4%) had a CMA of at least 1, indicating 100% adherence. The PDC had a range of 0.081–1 and a mean of 0.88 ± 0.20 (SD). The CMA had a range of 0.081–12.85 and mean of 1.08 ± 1.27. Ninety-four (79.7%) patients achieved more than 80% adherence or OMA.

Table 1
Baseline demographics.

Age — yrs (mean ± SD)	60 ± 15
Gender — no. (%)	
Male	54 (45.8%)
Female	64 (54.2%)
Race	
White	70 (59.3%)
African American	26 (22.0%)
Hispanic	13 (11.0%)
Other (minority)	3 (2.5%)
Missing	6 (5.0%)
Anticoagulant Type — no. (%)	
Warfarin	8 (6.8%)
Apixaban	57 (48.3%)
Rivaroxaban	17 (14.4%)
Enoxaparin	6 (5.1%)
vChanging/Mixed	30 (25.4%)
30-Day Follow-Up Visit — no. (%)	
Yes	110 (93.2%)
No	8 (6.8%)
Insurance Type — no. (%)	
Private	58 (49.2%)
Medicare	48 (40.7%)
Medicaid	11 (9.3%)
Self-pay	1 (0.8%)
In-Hospital Education — no. (%)	
Yes	84 (71.2%)
No	34 (28.8%)

In univariable analysis, increasing age (PDC coeff. = 0.003, p = 0.018, CI (0.001, 0.005) | OMA Unadjusted OR = 1.034, p = 0.027, CI (1.004, 1.064)), treatment with apixaban (PDC coeff. = 0.160, p = 0.033, CI (0.013, 0.307) | OMA Unadjusted OR = 5.000, p = 0.058, CI (0.948, 26.378)), and attending 30-day follow-up in clinic (PDC coeff. = 0.183, p = 0.012, CI (0.041, 0.324)) were statistically significant for higher adherence. Conversely, African American race (PDC coeff. = −0.174, p < 0.001, CI (−0.258, −0.091) | OMA Unadjusted OR = 0.130, p = 0.002, CI (0.036, 0.465)), other minority race (PDC coeff. = −0.290, p = 0.014, CI (−0.519, −0.061)), and Medicaid-insured patients (PDC coeff. = −0.270, p < 0.001, CI (−0.391, −0.148) | OMA Unadjusted OR = 0.080, p = 0.001, CI (0.019, 0.345)) had significantly lower adherence. However, when adjusted for confounding variables in multivariable regression, African American race (PDC coeff. = −135%, p = 0.006, CI (−0.231, −0.040) | OMA Adjusted OR = 0.166, p = 0.030, CI (0.033, 0.837)) and other non-White, non-Hispanic races (PDC coeff. = −0.314, p = 0.009, CI (−0.548, −0.080)) independently had lower anticoagulation adherence when compared to their White counterparts as measured by PDC (Tables 2 and 3, Fig. 2). Appendix 3 shows AC adherence measured using CMA.

4. Discussion

Anticoagulation for a minimum of three months is the standard therapy for patients with reversible, provoked first incidence of acute PE who otherwise do not have contraindications for anticoagulation. Non-adherence with anticoagulation can increase rates of complications from VTE, including mortality and recurrence [7]. Prior studies in atrial fibrillation — another clinical entity which requires regular use of AC to prevent systemic thromboembolism — identified factors that predict anticoagulation non-adherence, including minority race, unmarried status, physical inactivity, alcohol use, self-reported poor physical or mental health, or sleep quality, inadequate health literacy, low-dose aspirin use, diabetes, forgetfulness, and medication concerns [14,15]. Conversely, age 65–84, presence of hypertension, behavioral factors such as routine and external intervention, and medication knowledge have been associated with higher levels of adherence [14,15]. Our study evaluated several factors that may impact anticoagulation adherence,

Table 2
Predictors of Anticoagulation Compliance measured as Proportion of Days Covered (PDC).

	Univariable Regression		Multivariable Regression	
	Coefficient (95% CI)	*p* value	Coefficient (95% CI)	*p* value
Age	0.003 (0.001, 0.005)	0.018	0.002 (−0.002, 0.006)	0.337
Female	−0.003 (−0.076, 0.071)	0.942	–	–
Race				
White	Reference		Reference	
African American	−0.174 (−0.258, −0.091)	<0.001	−0.135 (−0.231, −0.040)	0.006
Hispanic	−0.005 (−0.111, 0.100)	0.924	0.001 (−0.116, 0.118)	0.987
Others	−0.290 (−0.519, −0.061)	0.014	−0.314 (−0.548, −0.080)	0.009
Anticoagulant				
Warfarin	Reference		Reference	
Apixaban	0.160 (0.013, 0.307)	0.033	0.018 (−0.139, 0.176)	0.820
Rivaroxaban	0.140 (−0.027, 0.307)	0.099	−0.032 (−0.203, 0.138)	0.706
Enoxaparin	0.096 (−0.114, 0.306)	0.368	−0.114 (−0.335, 0.107)	0.306
Changing/Mixed	0.062 (−0.093, 0.217)	0.427	−0.056 (−0.222, 0.110)	0.502
30-Day Follow-Up Visit	0.183 (0.041, 0.324)	0.012	−0.061 (−0.253, 0.131)	0.530
Insurance				
Private	Reference		Reference	
Medicare	−0.038 (−0.111, 0.034)	0.296	−0.058 (−0.151, 0.036)	0.221
Medicaid	−0.270 (−0.391, −0.148)	<0.001	−0.049 (−0.224, 0.126)	0.580
Self-pay	0.076 (−0.298, 0.449)	0.689	0.097 (−0.238, 0.433)	0.564
In-Hospital Education	0.049 (−0.032, 0.129)	0.233	–	–

Table 3
Predictors of Anticoagulation Compliance measured as Optimal Medication Adherence (OMA).

	Unadjusted OR (95% CI)	*p value*	Adjusted OR (95% CI)	*p* value
Age	1.034 (1.004, 1.064)	0.027	1.044 (0.977, 1.116)	0.201
Female	0.984 (0.400, 2.421)	0.972	–	–
Race				
White	Reference		Reference	
African American	0.130 (0.036, 0.465)	0.002	0.166 (.033, 0.837)	0.030
Hispanic	1.063 (0.112, 10.123)	0.957	1.231 (0.093, 16.370)	0.875
Others	0.106 (0.006, 1.975)	0.133	0.047 (0.002, 1.235)	0.067
Anticoagulant				
Warfarin	Reference		Reference	
Apixaban	5.000 (0.948, 26.378)	0.058	2.221 (0.115, 42.743)	0.597
Rivaroxaban	2.800 (0.419, 18.689)	0.288	1.026 (0.049, 21.578)	0.987
Enoxaparin	1.200 (0.130, 11.052)	0.872	0.109 (0.002, 4.842)	0.252
Changing/Mixed	1.200 (0.237, 6.065)	0.825	0.810 (0.046, 14.326)	0.886
30-Day Follow-Up Visit	2.514 (0.556, 11.363)	0.231	–	–
Insurance				
Private	Reference		Reference	
Medicare	0.532 (0.185, 1.526)	0.241	0.199 (0.029, 1.377)	0.102
Medicaid	0.080 (0.019, 0.345)	0.001	0.261 (0.015, 4.400)	0.351
Self-pay	[a]	[a]	[a]	[a]
In-Hospital Education	0.774 (0.278, 2.156)	0.624	–	–

[a] Insufficient data.

including age, gender, race, type of anticoagulant, 30-day clinic follow-up visit, type of insurance, and the presence of in-hospital education.

In univariable analysis, increasing age, use of apixaban, and attendance at a 30-day follow-up clinic visit were statistically significant for higher PDC, while African American race and Medicaid-insured patients had significantly lower PDC. In multivariable regression, African American race resulted in lower PDC and OMA when compared to White race. Patients of other minority races also had a significantly lower PDC. These findings are consistent with prior studies exploring the impact of race on medication adherence across different types of medications and diseases, such as hypertension, dyslipidemia, and diabetes mellitus [16–19]. Additionally, only those adhering to a self-pay insurance model in our study maintained higher CMA. However, after carefully reviewing the underlying dataset, only one patient of the 118 analyzed was categorized into a self-pay insurance model. That patient had a corresponding CMA of 7.5, largely skewing the data and perceived significance of this finding in relation to true adherence. If anything, this finding serves as a further reminder of the shortcomings of CMA as a consistently accurate means of assessing adherence.

The next step in understanding the relationship between race and medication adherence would be to identify factors not measured in our dataset, which may be associated with race and may be driving reduced anticoagulation adherence and thus providing opportunities for improvement. These factors might include socioeconomic status, health literacy, physical and financial access to healthcare, mental health, and social support, among others. Several studies, however, have found that even after adjusting for underlying factors such as income, insurance coverage, health literacy, depression, and social support, medication non-adherence persists in African American patients at a significantly higher rate than White patients.[20,21]These findings could be due to additional factors that are difficult to measure but potentially function as a barrier to adherence, including greater concern for harmful medication side effects, fear of dependency, reluctance to add medication to existing regimens, and mistrust and skepticism of the medical system [20–24].

One avenue for mitigating these concerns may be through in-hospital education, an intervention that was explored in our study. Eighty-four (71.2%) of the 118 patients were in the hospital long enough to be given a newly developed information packet with patient-friendly language and images describing types of blood clots, signs and symptoms of PE, causes of PE, severity of PE, tests for diagnosis, treatments (medications and procedures), safety information, and links for further reading. PERT physicians reviewed images of each patient's PE with them, in addition to discussing various treatment modalities as per the standard protocol. These patients were also given a questionnaire before and after receiving the information packet to evaluate whether their understanding of PE changed after reading it (Appendix 2). Analysis in this study showed no significant differences in AC adherence with patients who received the in-hospital education versus those who did not. However, other studies have shown that patient education may lead to a significant increase in patient adherence, at least in the short term [25, 26]. Difference in outcome could be attributed to the low power of our study (due to small sample size) or types of education material provided (packet versus questionnaire versus one-on-one counseling versus ongoing periodic reminders and check-ins). Future avenues of investigation may be able to explore whether various types of patient education have a differential impact on disease comprehension and whether patient education specifically targeting factors associated with poor adherence yields improvements in adherence among African American

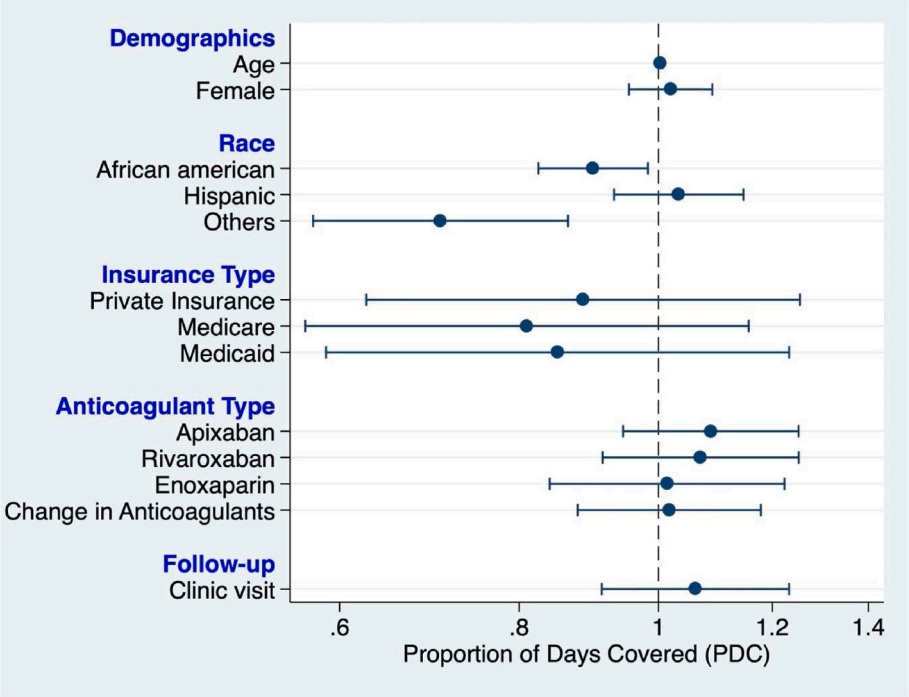

Fig. 2. Forest plot showing Predictors of Anticoagulation Adherence measured using Proportion of Days Covered (PDC) in a Multivariable Linear Regression Model (Logarithmic Scale).

patients.

The major strength of our study is that it includes a broad range of anticoagulant types, insurance types, and patient demographics, whereas prior studies have primarily focused on specific segments of patient populations.

4.1. Limitations

Several limitations must be acknowledged. Adherence measures used here were highly objective and relied mainly on medical charts and data collected from pharmacy records without subjective confirmation of adherence. A pharmacy refill does not necessarily imply that patients took all scheduled doses on time, known as medication compliance. Six (5.1%) patients had missing racial data. Other critiques include a small sample size of 144 patients within a single center study, with low power, which may limit applicability to the generalized population, difficulty in calculating PDC for warfarin due to frequent dosing changes based on INR, and variability in the quality of each individual calculated PDC (i.e., some patients had data for a few months whereas others had data over multiple years). There may also be unmeasured confounders, which could have influenced our findings.

Prior studies have demonstrated that African American patients have a higher mortality after PE compared to White patients [27]. Improving anticoagulant adherence in this specific patient population is crucial. Further studies are needed to address the factors leading to reduced adherence in African American and minority races.

5. Conclusions

In our study, a racial disparity exists in anticoagulation adherence after an acute PE. African American patients and other minority races had lower adherence compared to White patients. Further studies are needed to address underlying contributors and get the opportunities to improve adherence in this population.

Sources of funding

No specific funding was associated with this research.

Disclosures

The abstract was presented in the form of a poster at the annual scientific sessions of the American College of Cardiology 2021.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

Pulmonary Embolism Response Team members, Loyola University Medical Center.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tru.2022.100100.

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