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Warfarin Time in Therapeutic INR Range and Direct Oral Anticoagulant Adherence for Venous Thromboembolism Across the Spectrum of Weight and Body Mass Index: Findings from Veterans Health Administration

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Abstract

The evidence of direct oral anticoagulants (DOACs) usage for venous thromboembolism (VTE) in patients at extremes of body weight or mass index is limited. In such situations, warfarin may be more frequently used. We investigated warfarin time in the therapeutic international normalized ratio range (TTR) and DOAC adherence based on the calculated proportion of days covered (PDC) by pill coverage from a DOAC prescription in patients with VTE across all body sizes. Using data from the Veterans Health Administration (VA), we identified first-time patients with VTE between 2013 and 2018 treated with warfarin or DOACs. We analyzed 28,245 patients with warfarin TTR (N = 10,167) or DOAC PDC(N = 18,078). For warfarin-treated patients after index VTE, mean TTR was lower over shorter treatment durations (TTR 30 vs TTR 180 [mean ± SD]: 43.8% ± 33.5% vs 58.8% ± 23.5%). Mean TTR over 180 days after VTE was lowest for patients <60 kg (TTR 180 [mean ± SD]: <60kg: 49.3% ± 24.2% vs ≥60 to <100 kg: 57.8% ± 23.4%; $P < .0001$). For DOAC-treated patients over 180 days after index VTE, mean PDC was lowest for patients <60 kg (PDC 180 [mean ± SD]: < 60kg: 76.9% ± 33.2% vs ≥ 60 to <100 kg: 83.6% ± 27.7%; $P < .0001$).

Most DOAC-treated patients attained sufficient adherence across the body size spectrum while warfarin-treated patients <60kg were at risk for low TTR.

Keywords

BMI, high body weight, warfarin, direct oral anticoagulant, TTR, PDC, venous thromboembolism

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Introduction

Pharmacokinetic studies of direct oral anticoagulants have raised concerns that direct oral anticoagulants (DOAC) peak and trough concentrations in patients at extremes of body weight, as compared to average body weight, may be outside the therapeutic range with unclear effects on drug effectiveness and safety.[1–3] Accordingly, consensus statements have, until 2021, recommended against the routine use of DOACs for venous thromboembolism (VTE) in patients >120 kg or >40 kg/m2,[4–6] with low patient weight included in the dose

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adjustment algorithm for some DOACs. However, the prescribed dose of warfarin, the primary alternative anticoagulant to DOAC, is associated with body mass index (BMI).[7,8] Accordingly, it is plausible that time in therapeutic international normalized ratio (INR) range (TTR), may be lower for patients at extremes of body weight, particularly early in the treatment course. With TTR associated with improved VTE outcomes,[9,10] risk of suboptimal TTR in patients with higher and lower weight would be an important factor to include in patients' and clinicians' shared decision-making process when deciding between DOAC or warfarin for VTE.

Notably, the INR and TTR are ubiquitously measured and calculated as part of routine clinical care for patients on warfarin to guide dosing, with TTR widely adopted as a process and quality measure by multiple stakeholders. Considering there is no directly analogous measure to TTR for DOAC-treated patients, we opted to utilize the proportion of days covered (PDC) by DOAC to investigate the quality of DOAC therapy, an established measure for medication adherence.[11,12]

Therefore, considering the uncertainty on optimal anticoagulation strategy across the body size spectrum, we sought to determine (1) warfarin-treated VTE patients' TTR by weight and BMI in the Veterans Health Administration (VA) healthcare system, which utilizes pharmacist-led anticoagulation clinics to manage warfarin INR monitoring and DOAC dosing[13] and (2) DOAC-treated VTE patients' PDC covered by DOAC[1,12] by weight and BMI respectively.

Methods

We performed a retrospective cohort study using data from the United States VA healthcare system from October 1, 2013 to September 30, 2018. We linked datasets, for all VA users, from (1) the VA National Patient Care Database,[14] (2) the VA Decision Support System national pharmacy extract,[15] (3) the VA Fee Basis Inpatient and Outpatient datasets, (4) the VA Laboratory Decision Support System extract,[16] (5) Medicare inpatient and outpatient institutional claims data (part A, part B, and carrier files),[17] (6) the VA Vital Status File,[16,18] which provided validated combined mortality data from VA, Medicare, and Social Security Administration sources, and (7) the VA Vital Sign File,[19] which contains patient weight and height measurements obtained during routine care. The methods for data linkage and cohort creation have been previously described in detail.[20–22]

We identified patients with newly-diagnosed VTE, who were treated with anticoagulation, using primary or secondary International Statistical Classification of Diseases and Related Health Problems, Ninth (ICD-9) or Tenth (ICD-10) Revisions, diagnosis codes associated with an inpatient or outpatient VA encounter. Methods used to identify the top-level VTE cohort have been described previously.[19–21] We excluded patients (1) with VTE in 4 years prior to index VTE diagnosis; (2) with a concomitant indication for anticoagulation (ie, atrial fibrillation and/or mechanical heart valve) in 2 years prior to 30 days after index VTE diagnosis; (3) without a prescription for DOAC (apixaban, dabigatran, edoxaban, or rivaroxaban) or warfarin in 30 days after index VTE diagnosis (including index date); (4) with 2 or more oral anticoagulants (OACs) prescribed on the index prescription date after index VTE diagnosis; (5) with no weight measurements in 90 days prior to 90 days after index VTE diagnosis; (6) with no height measurements in 4 years prior to 4 years after index VTE diagnosis; (7) a weight measurement inconsistent with adjacent weight measurements; (8) <18 years of age at the time of index VTE diagnosis or with missing sex information; and (9) without TTR or PDC available in the 180, 90, 60, or 30 days after index VTE treatment.

To clean weight and height data, removing values likely to be erroneous, we excluded (1) weight measurements < 34.1 kg (75 lbs) or > 318.2 kg (700 lbs) and (2) height measurements < 1.2 m (48 in) and > 2.1 m (84 in). These exclusion thresholds were based on established methodology and army enlistment criteria for height.[23] After excluding weight outliers, we selected patients' weight measurement closest to index VTE diagnosis in the 90 days prior to VTE (inclusive of day of diagnosis) or, if none available, the weight measurement closest to index VTE diagnosis in the 90 days after VTE. To assess for intra-patient weight outliers, we determined if the ratio of patients' assigned weight to adjacent weight measurements were ≥ 1.50 or < 0.67. For patients with weight ratios greater or less than the stated threshold, we (1) excluded the outlier measurement if ≥ 4 total weight measurements were available in the 90 days prior to 90 days after index VTE or (2) excluded the patient if ≤ 3 total weight measurements were available in the 90 days prior to 90 days after index VTE. This method excluded outliers attributable to unit conversion errors and has been previously used to clean VA vital sign data.[23] We selected patient's height using similar methodology from measurements obtained in the 4 years prior to 4 years after index VTE diagnosis and calculated BMI (kg/m^2).

We stratified patients into the following weight categories: (1) < 60, (2) ≥ 60 to <100, (3) ≥ 100 to <120, (4) ≥ 120 to <140, and (5) ≥ 140 kg. Separately, we stratified patients into the following BMI categories: (1) < 25, (2) ≥ 25 to <30, (3) ≥ 30 to <35, (4) ≥ 35 to <40, (5) ≥ 40 to <50, and (6) ≥ 50 kg/m^2. These categories were consistent with prior literature.[24,25] Baseline characteristics were described using previously described methods,[19–21] by weight and BMI categories and by OAC class (ie, warfarin and DOAC) for each analyzed treatment duration.

We categorized patients as DOAC or warfarin-treated based on their initial OAC prescription in the 30 days after index VTE diagnosis (including index date), regardless of whether low-molecular weight heparin, unfractionated heparin, or fondaparinux were prescribed. Index VTE treatment date was defined as the date of first oral anticoagulation prescription, whether that was DOAC or warfarin. Notably, VTE diagnosis and treatment dates may differ if a contraindication to immediate anticoagulation was present or if heparin products were utilized prior to oral anticoagulation. We calculated warfarin-treated and DOAC-treated patients' TTR and PDC, respectively, over 180, 90, 60, and 30 days after index

VTE treatment. We reported TTR and PDC as continuous and dichotomized variables, with 0.6 and 0.8 as thresholds for TTR and PDC, respectively. These thresholds were selected based on established cut points for adequacy of TTR for atrial fibrillation and medication adherence, respectively.[26–29] We calculated TTR using the Rosendaal method, which assigns an INR value to each day between successive-measured INR values using linear interpolation.[30] The proportion of time in which the interpolated and measured INR values were between 2.0 and 3.0 equates to the TTR using a validated approach. Days spent in hospital were ineligible for TTR calculation, with a requirement that ≥50% of days were eligible in the TTR denominator. PDC was defined as the total number of nonhospitalized days DOAC was supplied, based on prescription fill dates, pill counts, and prescribed administration frequency, divided by the observation period (eg, 180, 90, 60, 30 days).[11,31] Censoring events included OAC discontinuation, OAC switch (ie, warfarin to DOAC, DOAC to warfarin, or DOAC to DOAC), death, hospitalization for bleed or recurrent VTE, or end of study time period. We defined OAC discontinuation as no OAC re-prescription within 14 days of the date on-hand OAC would be estimated to run out, which was determined based on prescription date, prescribed pill count, and ideal adherence to prescribed administration frequency. As treatment duration was not controlled, cohort size differed across analyzed treatment durations (30 to 180 days).

Statistical Methods

We assessed TTR in the warfarin group and PDC in the DOAC group (continuous and dichotomized), separately, by patient weight category over 180-day, 90-day, 60-day, and 30-day observed treatment durations. Differences between weight categories were assessed with the χ^2 and analysis of variance (ANOVA) test for categorical and continuous variables, respectively. We used multivariable generalized linear mixed models to determine the association of weight categories (predictor variable) to TTR and PDC (outcome variables), as continuous and dichotomized variables. For the models with dichotomized outcomes, the assumed distribution was binary and link function was logit. The models reference weight category was ≥60 to <100 kg (ie, average body size) and included the following covariates: age, sex, race, antiplatelet prescription, HAS-BLED score, Charlson comorbidity index, and all baseline comorbidities (anemia, coronary artery disease, chronic kidney disease, diabetes, heart failure, hypertension, peripheral artery disease, prior myocardial infarction, prior stroke or transient ischemic attack). For the HAS-BLED score, one point each was assigned for the presence of hypertension, abnormal renal function, stroke, previous bleeding or concurrent antiplatelet therapy, age >65 years, drug use, or alcohol use. All analyses were also performed by BMI category, with ≥25 to <30 kg/m^2 used as the reference category in models.

All analyses were performed with SAS version 9.2 (SAS Institute, Inc., Cary, NC) and STATA version 11.0 (College Station, TX). All tests of significance were two-tailed, with a P value of <0.05 indicating significance. The primary investigator had full access to all study data and takes responsibility for its integrity and the data analysis. This study was approved by local institutional review board (Stanford University: FWA00000935, Stanford Health Care: FWA00000934) and the VA Research and Development Committee (Palo Alto, CA). These data were obtained with permission from the VA Corporate Data Warehouse and stored and analyzed on the VA Informatics and Computing Infrastructure (VINCI). Data are not available to share due to data use agreements and restrictions on use of Veterans' data, but access to the master files may be requested from VINCI by eligible investigators.

Results

The analysis cohort included 28,245 patients with warfarin TTR (N = 10,167) or DOAC PDC (N = 18,078) available over 180 days after index VTE diagnosis. Over the 90, 60, and 30 days after VTE, TTR, or PDC were available for 38,114; 41,404; and 41,785 patients, respectively (Figure 1). Across all TTR/PDC time intervals, warfarin-treated patients, as compared to DOAC-treated, weighed more (TTR/PDC 180: 99.3 ± 23.4 kg vs 95.8 ± 21.4 kg, $P < .0001$), were less likely to have chronic kidney disease (TTR/PDC 180 20.1% vs 25.8%, $P < .0001$), and were more likely to be male (TTR/PDC 180: 95.2% vs 93.9%, $P < .0001$) and have prevalent cardiovascular disease (Supplemental Table 1). For the TTR/PDC 180-day cohort, across increasing weight categories, warfarin-treated patients were younger (<60 vs ≥ 140 kg: 69.4 ± 13.2 vs 59.9 ± 9.4, $P < .0001$) and were more likely to be male (<60 vs ≥ 140 kg: 82.1% vs 98.3%, $P < .0001$), diabetic (<60 vs ≥ 140 kg: 14.4% vs 52.3%, $P < .0001$), hypertensive (<60 vs ≥ 140 kg: 54.2% vs 70.4%, $P < .0001$), and to have chronic kidney disease (<60 vs ≥ 140 kg: 20.4% vs 25.0%, $P = .0001$) (Table 1). Similar trends in baseline characteristics were observed for DOAC-treated patients (Table 2) and for warfarin-treated and DOAC-treated patients when stratified by BMI, except female sex was more likely across increasing BMI categories (warfarin-treated patients: < 25 vs ≥ 50 kg/m^2: 4.2% vs 7.0%, $P < .0001$; Supplemental Table 2).

For warfarin-treated patients, TTR after VTE, both mean and ≥0.6, were numerically lower over shorter observed treatment durations (TTR 30 vs TTR 180 [mean ± SD]: 43.8% ± 33.5% vs 58.8% ± 23.5%; TTR 30 vs TTR 180 [≥ 0.6]: 33.5% vs 49.2%). Mean TTR and TTR ≥0.6 over the 180 days after VTE were lowest for patients <60 kg (TTR mean ± SD: < 60kg: 49.3% ± 24.2%; ≥ 60 to <100 kg: 57.8% ± 23.4%; ≥ 100 to <120 kg: 60.5% ± 23.5%; ≥ 120 to <140 kg: 61.2% ± 23.2%; ≥ 140 kg: 59.5% ±24.0%; $P < .0001$) (TTR ≥0.6: < 60kg: 33.8%; ≥ 60 to <100 kg: 47.3%; ≥ 100 to <120 kg: 51.8%; ≥ 120 to <140 kg: 53.7%; ≥ 140 kg: 51.3%; $P < .0001$) (Table 3 and Figure 2). When compared by BMI, mean TTR, and TTR ≥0.6 over the 180 days after VTE were lowest for patients <25 kg/m^2 (TTR mean ± SD: < 25 kg/m^2: 53.4% ± 23.5%; ≥ 25 to <30 kg/m^2: 59.1% ± 23.4%; ≥ 30 to <35 kg/m^2: 59.9% ± 23.4%; ≥ 35 to <40 kg/m^2: 60.7% ± 23.1%; ≥ 40 to <50 kg/m^2: 60.8% ± 23.1%; ≥ 50 kg/m^2: 58.7% ± 25.2%; P

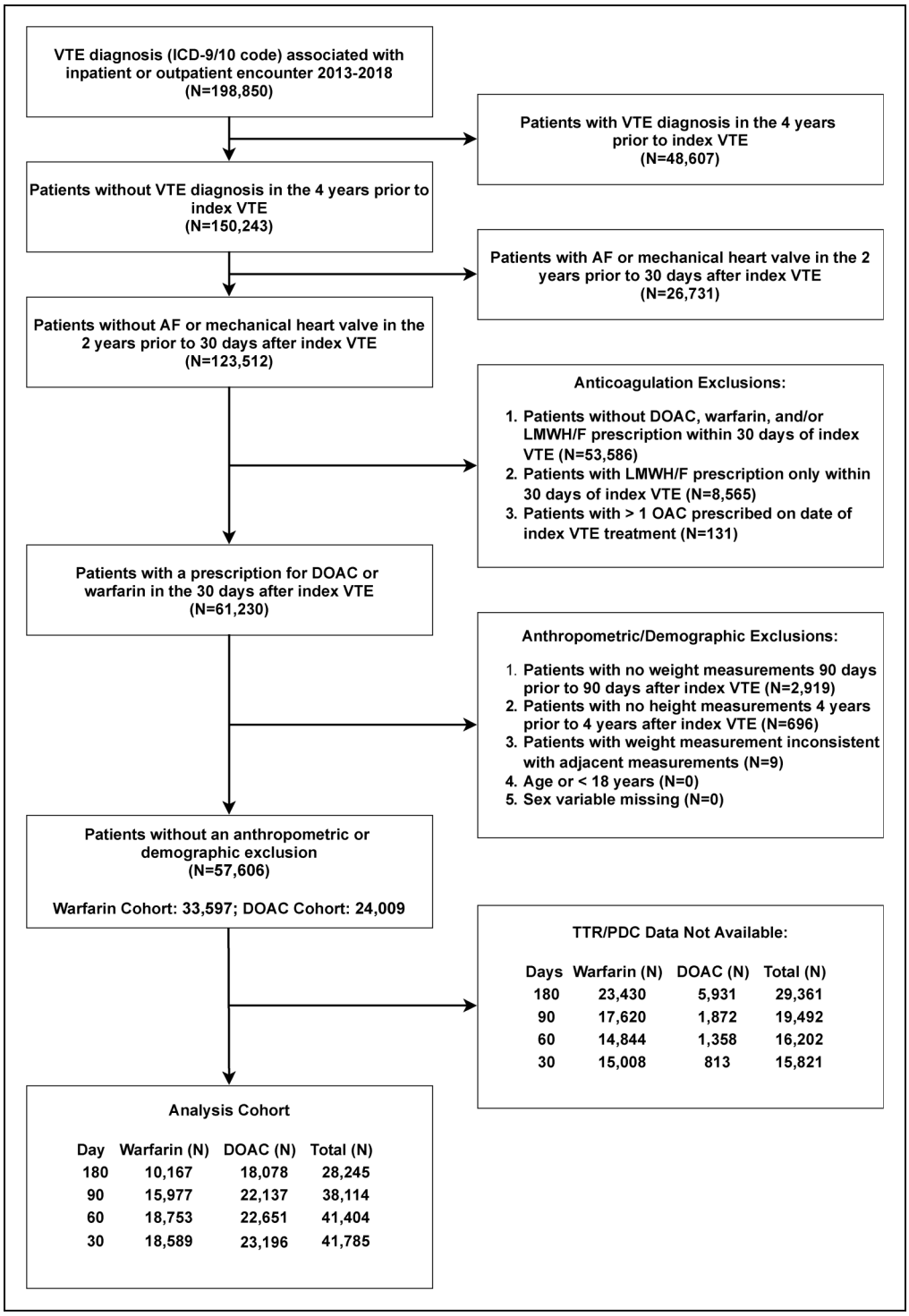

Figure 1. Cohort exclusion diagram. Inclusion and exclusion criteria used to select analysis cohort. Abbreviations: AF, atrial fibrillation; DOAC, direct oral anticoagulant; ICD-9, International Classification of Diseases, Ninth Revision; INR, international normalized ratio; LMWH/F, low molecular weight heparin or fondaparinux; OAC, oral anticoagulant; PDC, proportion of days covered; TTR, time in therapeutic INR range; VTE, venous thromboembolism.

< .0001) (TTR ≥0.6: < 25 kg/m^2: 40.5%; ≥ 25 to <30 kg/m^2: 49.3%; ≥ 30 to < 35 kg/m^2: 50.9%; ≥ 35 to <40 kg/m^2: 52.2%; ≥ 40 to <50 kg/m^2: 54.0%; ≥ 50 kg/m^2: 49.7%; P < .0001) (Supplemental Table 3 and Supplemental Figure 1).

After multivariate regression, weight <60 kg, as compared to ≥60 to <100 kg, was associated with lower odds of TTR (TTR continuous: odds ratio [OR] 0.73; 95% confidence interval [CI] 0.60-0.90; P = .0032; TTR ≥0.6: OR 0.59; 95% CI 0.43-0.80;

Table 1. Baseline Characteristics for Patients With 180-Day Warfarin TTR by Weight.

	Total (N = 10,167)	<60 kg (N = 201)	≥60 to <100 kg (N = 5541)	≥100 to <120 kg (N = 2707)	≥120 to <140 kg (N = 1137)	≥140 kg (N = 581)	*P* value*
Age, years	64.5 ± 11.9	69.4 ± 13.2	66.4 ± 12.4	62.8 ± 10.9	61.2 ± 0.5	59.9 ± 9.4	<.0001
Sex (female)	484 (4.8%)	36 (17.9%)	300 (5.4%)	99 (3.7%)	39 (3.4%)	10 (1.7%)	<.0001
Race							
White	7724 (76.0%)	148 (73.6%)	4135 (74.6%)	2084 (77.0%)	895 (78.7%)	462 (79.5%)	.0028
Black	2083 (20.5%)	48 (23.9%)	1192 (21.5%)	536 (19.8%)	203 (17.9%)	104 (17.9%)	
Asian	22 (0.2%)	1 (0.5%)	15 (0.3%)	2 (0.1%)	4 (0.4%)	0	
Hawaiian/Pacific Islander	62 (0.6%)	2 (1.0%)	33 (0.6%)	12 (0.4%)	13 (1.1%)	2 (0.3%)	
Native American	68 (0.7%)	0	39 (0.7%)	20 (0.7%)	4 (0.4%)	5 (0.9%)	
Multiracial	130 (1.3%)	2 (1.00%)	81 (1.5%)	31 (1.2%)	12 (1.1%)	4 (0.7%)	
Missing/ unknown	78 (0.8%)	0	46 (0.8%)	22 (0.8%)	6 (0.5%)	4 (0.7%)	
Comorbidities							
Comorbidity index							
Charlson	1.68 ± 1.61	2.04 ± 1.49	1.67 ± 1.61	1.62 ± 1.61	1.75 ± 1.61	1.77 ± 1.57	.0008
HAS-BLED score	2.03 ± 1.26	2.48 ± 1.30	2.11 ± 1.29	1.93 ± 1.24	1.92 ± 1.20	1.86 ± 1.08	<.0001
Anemia	962 (9.5%)	50 (24.9%)	605 (10.9%)	199 (7.4%)	73 (6.4%)	35 (6.0%)	<.0001
Heart failure	757 (7.5%)	17 (8.5%)	425 (7.7%)	169 (6.2%)	92 (8.1%)	54 (9.3%)	.0412
Hypertension	6037 (59.4%)	109 (54.2%)	3097 (55.9%)	1660 (61.3%)	762 (67.0%)	409 (70.4%)	<.0001
Prior MI	260 (2.6%)	6 (3.0%)	163 (2.9%)	57 (2.1%)	24 (2.1%)	10 (1.7%)	.0849
Diabetes	3451 (33.9%)	29 (14.4%)	1506 (27.2%)	1055 (39.0%)	557 (49.0%)	304 (52.3%)	<.0001
Chronic kidney disease	2042 (20.1%)	41(20.4%)	1039 (18.8%)	550 (20.3%)	268 (23.6%)	144 (25.0%)	.0001
Prior stroke/TIA	612 (6.0%)	19 (9.5%)	400 (7.2%)	115 (4.3%)	56 (4.9%)	22 (3.8%)	<.0001
Coronary artery disease	1759 (17.3%)	28 (13.9%)	1002 (18.1%)	458 (16.9%)	200 (17.6%)	71 (12.2%)	.0052
Peripheral artery disease	797 (7.8%)	26 (12.9%)	533 (9.6%)	144 (5.3%)	67 (5.9%)	27 (4.7%)	<.0001

Values are mean ± SD or n (%).
*Differences between weight categories assessed with the $\chi 2$ test and ANOVA test for categorical and continuous variables, respectively.
Abbreviations: INR, international normalized ratio; MI, myocardial infarction; TIA, transient ischemic attack; TTR, time in therapeutic INR range.

P = .0009). Weight in categories ≥100 kg were associated wither higher odds of TTR ≥0.6, as compared to ≥60 to <100 kg (Table 5). When TTR 180 was stratified by BMI, findings were similar with the exception that BMI in categories ≥30 m/kg^2 were not associated with TTR, as compared to ≥25 to <30 m/kg^2 (Supplemental Table 5).

For DOAC-treated patients, PDC after VTE, both mean and ≥0.8, were numerically higher over shorter treatment durations (PDC 30 vs PDC 180 [mean ± SD]: 92.8% ±20.7% vs 84.1% ± 27.2%; PDC 30 vs PDC 180 [≥ 0.8]: 89.5% vs 77.7%). Mean PDC and PDC ≥0.8 over the 180 days after VTE were lowest for patients <60 kg (PDC mean ± SD: < 60kg: 76.9% ± 33.2%; ≥ 60 to <100 kg: 83.6% ± 27.7%; ≥ 100 to <120 kg: 85.1% ± 26.4%; ≥ 120 to <140 kg: 86.3% ± 24.8%; ≥ 140 kg: 85.8% ± 24.6%; *P* < .0001) (PDC ≥0.8: < 60 kg: 69.3%; ≥ 60 to <100 kg: 76.9%; ≥ 100 to <120 kg: 79.0%; ≥ 120 to <140 kg: 80.4%; ≥ 140 kg: 81.2%; *P* < .0001) (Table 4 and Figure 2). After multivariate regression, weight <60 kg, as compared to ≥60 to <100 kg, was associated with lower PDC and odds of PDC ≥0.8 (PDC continuous: OR 0.76; 95% CI 0.64-0.91; *P* = .0028; PDC ≥0.8: OR 0.68; 95% CI 0.56-0.84; *P* = .0003). Weight in categories ≥100 kg were associated with higher PDC and odds of PDC ≥0.8, as compared to ≥60 to <100 kg (Table 5). When PDC 180 was stratified by BMI, findings were similar with the exception that BMI ≥30 to <35 m/kg^2 was not associated with TTR, as compared to ≥25 to <30 m/kg^2 (Supplemental Tables 4 and 5; Supplemental Figure 1).

Discussion

Across the VA healthcare system, which utilizes pharmacist-led anticoagulation clinics to manage warfarin INR monitoring and DOAC prescription, we found that warfarin-treated patients <60 kg were at risk for low TTR. Additionally, we found that TTR was suboptimal, regardless of patient weight, particularly early in the treatment course. For DOAC-treated patients, a large proportion of patients exceeded the PDC threshold associated with medication adherence, regardless of weight. For patients at extremes of body weight, these findings provide useful information when deciding between warfarin or DOAC for VTE.

Across the VTE literature, TTR is estimated to be 54% over the first month of treatment with warfarin,[10] substantially higher than calculated in our study. This discrepancy may be

Table 2. Baseline Characteristics for Patients With 180-Day DOAC PDC by Weight.

	Total (N = 18,078)	<60 kg (N = 491)	≥60 to <100 kg (N = 10,799)	≥100 to <120 kg (N = 4569)	≥120 to <140 kg (N = 1628)	≥140 kg (N = 591)	*P* value*
Age, years	65.3 ± 13.4	68.3 ± 14.9	67.0 ± 13.6	63.2 ± 12.4	60.8 ± 12.0	59.1 ± 11.0	<.0001
Sex (female)	1104 (6.1%)	92 (18.7%)	735 (6.8%)	202 (4.4%)	62 (3.8%)	13 (2.2%)	<.0001
Race							.0005
White	13,687 (75.7%)	336 (68.4%)	8164 (75.6%)	3493 (76.5%)	1242 (76.3%)	452 (76.5%)	
Black	3807 (21.1%)	140 (28.5%)	2251 (20.8%)	945 (20.7%)	347 (21.3%)	124 (21.0%)	
Asian	37 (0.2%)	3 (0.6%)	29 (0.3%)	2 (<0.1%)	3 (0.2%)	0	
Hawaiian/Pacific Islander	112 (0.6%)	5 (1.0%)	77 (0.7%)	21 (0.5%)	5 (0.3%)	4 (0.7%)	
Native American	106 (0.6%)	2 (0.4%)	73 (0.7%)	24 (0.5%)	5 (0.3%)	2 (0.3%)	
Multiracial	154 (0.9%)	4 (0.8%)	101 (0.9%)	33 (0.7%)	9 (0.6%)	7 (1.2%)	
Missing/unknown	175 (1.0%)	1 (0.2%)	104 (1.0%)	51 (1.1%)	17 (1.0%)	2 (0.3%)	
Comorbidities							
Comorbidity index							
Charlson	1.45 ± 1.51	1.82 ± 1.6	1.42 ± 1.51	1.44 ± 1.52	1.55 ± 1.54	1.55 ± 1.52	<.0001
HAS-BLED score	2.08 ± 1.26	2.33 ± 1.39	2.13 ± 1.28	2.01 ± 1.22	1.96 ± 1.19	1.80 ± 1.11	<.0001
Anemia	1283 (7.1%)	68 (13.9%)	838 (7.8%)	264 (5.8%)	94 (5.8%)	19 (3.2%)	<.0001
Heart failure	1065 (5.9%)	37 (7.5%)	595(5.5%)	254 (5.6%)	121 (7.4%)	58 (9.8%)	<.0001
Hypertension	9825 (54.4%)	207 (42.2%)	5601 (51.9%)	2615 (57.2%)	1033 (63.5%)	369 (62.4%)	<.0001
Prior MI	288 (1.6%)	8 (1.6%)	181 (1.7%)	66 (1.4%)	28 (1.7%)	5 (0.85%)	.4944
Diabetes	5014 (27.7%)	66 (13.4%)	2505 (23.2%)	1523 (33.3%)	659 (40.5%)	261 (44.2%)	<.0001
Chronic kidney disease	4656 (25.8%)	79 (16.1%)	2437 (22.6%)	1371 (30.0%)	563 (34.6%)	206 (34.7%)	<.0001
Prior stroke/TIA	712 (3.9%)	31 (6.3%)	478 (4.4%)	154 (3.4%)	39 (2.4%)	10 (1.7%)	<.0001
Coronary artery disease	2612 (14.5%)	77 (15.7%)	1584 (14.7%)	638 (14.0%)	242 (14.9%)	71 (12.0%)	.2917
Peripheral artery disease	836 (4.6%)	36 (7.3%)	539 (5.0%)	184 (4.0%)	54 (3.3%)	23 (3.9%)	.0002

Values are mean ± SD or n (%).

*Differences between weight categories assessed with the χ^2 test and ANOVA test for categorical and continuous variables, respectively.

Abbreviations: ANOVA, analysis of variance; DOAC, direct oral anticoagulant; INR, international normalized ratio; MI, myocardial infarction; PDC, proportion of days covered; TIA, transient ischemic attack; TTR, time in therapeutic INR range.

Table 3. Warfarin TTR for Venous Thromboembolism by Weight.

	Total	<60 kg	≥60 to <100 kg	≥100 to <120 kg	≥120 to <140 kg	≥140 kg	*P* value*
TTR 180 day							
N	10,167	201	5541	2707	1137	581	
TTR (mean ± SD)	58.8% ± 23.5%	49.3% ± 24.2%	57.8% ± 23.4%	60.5% ± 23.5%	61.2% ± 23.2%	59.5% ± 24.0%	<.0001
TTR ≥ 0.6	5001 (49.2%)	68 (33.8%)	2621 (47.3%)	1403 (51.8%)	611 (53.7%)	298 (51.3%)	<.0001
TTR 90 day							
N	15,977	367	8818	4187	1736	869	
TTR (mean ± SD)	54.5% ± 27.3%	45.6% ± 26.7%	53.3% ± 27.2%	56.4% ± 27.3%	56.5% ± 27.5%	56.5% ± 27.5%	<.0001
TTR ≥ 0.6	6894 (43.2%)	114 (31.1%)	3674 (41.7%)	1908 (45.6%)	804 (46.3%)	394 (45.3%)	<.0001
TTR 60 day							
N	18,753	483	10,492	4814	1984	980	
TTR (mean ± SD)	50.7% ± 30.9%	41.7% ± 30.2%	49.8% ± 30.6%	52.6% ± 31.0%	52.3% ± 31.1%	52.4% ± 31.7%	<.0001
TTR ≥ 0.6	7506 (40.0%)	138 (28.6%)	4094 (39.0%)	2027 (42.1%)	832 (41.9%)	415 (42.4%)	<.0001
TTR 30 day							
N	18,589	531	10,507	4693	1921	937	
TTR (mean ± SD)	43.8% ± 33.5%	36.8% ± 33.6%	43.6% ± 33.1%	44.4% ± 33.1%	44.9% ± 34.2%	45.0% ± 34.4%	<.0001
TTR ≥ 0.6	6228 (33.5%)	141 (26.6%)	3486 (33.2%)	1591 (33.9%)	677 (35.2%)	333 (35.5%)	.0022

*Difference between weight categories assessed with the χ^2 and ANOVA test for categorical and continuous variables, respectively.

Abbreviations: ANOVA, analysis of variance; INR, International normalized ratio; SD, standard deviation; TTR, time in therapeutic range; N, number.

attributable to more intensive INR monitoring in research protocols and raises concern for early suboptimal VTE outcomes for real-world warfarin-treated patients. Importantly, the VA utilizes pharmacist-led anticoagulation clinics for INR monitoring, which have been associated with higher TTR than other healthcare systems.[32] Paradoxically, PDC over the first month of treatment with DOAC was high. However, this may overestimate medication adherence as few patients are expected to need a DOAC refill by 30 days. Notably, DOAC adherence, as measured by PDC, has also been shown to be high when

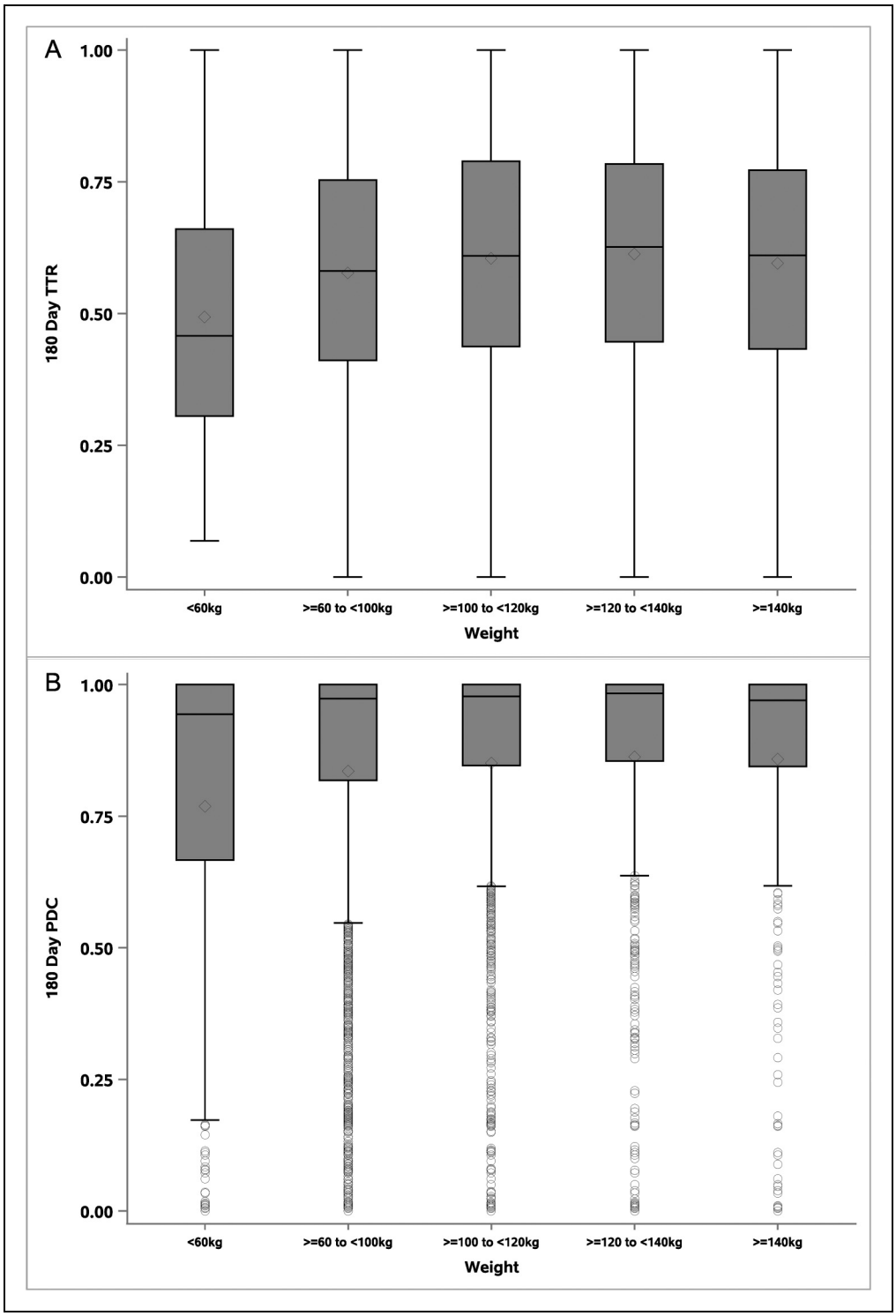

Figure 2. Warfarin TTR and DOAC PDC for venous thromboembolism by weight. Boxplots for warfarin TTR (panel A) and DOAC PDC (panel B) for venous thromboembolism by patients' weight category. Horizontal box lines (from top to bottom) represent third quartile, median, and first quartile with diamond representing mean. Whiskers represent the largest and smallest observed value that falls within 1.5*(interquartile range) from the third quartile for the upper whisker and the first quartile for the lower whisker, respectively. Open circles represent values more extreme than whiskers. If data points did not reach the computed ranges, whiskers represent the upper and lower data point values. Abbreviations: DOAC, direct oral anticoagulant; INR, international normalized ratio; PDC, proportion of days covered; TTR, time in therapeutic INR range; VTE, venous thromboembolism.

Table 4. DOAC Proportion of Days Covered for Venous Thromboembolism by Weight.

	Total	<60 kg	≥60 to <100 kg	≥100 to <120 kg	≥120 to <140 kg	≥140 kg	*P* value*
PDC 180 day							
N	18,078	491	10,799	4569	1628	591	
PDC (mean ± SD)	84.1% ± 27.2%	76.9% ± 33.2%	83.6% ± 27.7%	85.1% ± 26.4%	86.3% ± 24.8%	85.8% ± 24.6%	<.0001
PDC ≥ 0.8	14,042 (77.7%)	340 (69.3%)	8304 (76.9%)	3609 (79.0%)	1309 (80.4%)	480 (81.2%)	<.0001
PDC 90 day							
N	22,137	641	13,296	5539	1945	716	
PDC (mean ± SD)	86.3% ± 25.3%	81.1% ± 29.2%	85.9% ± 25.6%	87.0% ± 24.8%	87.6% ± 23.7%	88.1% ± 22.4%	<.0001
PDC ≥ 0.8	17,449 (78.8%)	454 (70.8%)	10,407 (78.3%)	4441 (80.2%)	1569 (80.7%)	578 (80.7%)	<.0001
PDC 60 day							
N	22,651	669	13,616	5663	1978	725	
PDC (mean ± SD)	86.9% ± 24.4%	82.3% ± 27.6%	86.6% ± 24.7%	87.4% ± 24.1%	88.0% ± 22.8%	88.5% ± 21.7%	<.0001
PDC ≥ 0.8	17,765 (78.4%)	472 (70.6%)	10,602 (77.9%)	4537 (80.1%)	1574 (79.6%)	580 (80.0%)	<.0001
PDC 30 day							
N	23,196	693	13,964	5796	2000	743	
PDC (mean ± SD)	92.8% ± 20.7%	90.0% ± 24.9%	92.6% ± 21.0%	92.9% ± 20.7%	94.1% ± 18.3%	94.6% ± 16.3%	<.0001
PDC ≥ 0.8	20,753 (89.5%)	598 (86.3%)	12,459 (89.3%)	5194 (89.6%)	1826 (91.3%)	676 (91.0%)	.0016

*Difference between weight categories assessed with the χ^2 and ANOVA test for categorical and continuous variables, respectively.
Abbreviations: ANOVA, analysis of variance; DOAC, direct oral anticoagulant; PDC, proportion of days covered; SD, standard deviation; N, number.

Table 5. Association of Weight With 180-Day Warfarin TTR or DOAC PDC (Reference: ≥ 60 to <100 kg).

	Unadjusted*		Multivariate regression*,†	
Warfarin-treated patients‡	OR (95% CI)	*P* value	OR (95% CI)	*P* value
TTR (continuous)				
≥140 kg	1.06 (0.98-1.14)	0.18	1.10 (0.96-1.25)	0.16
≥120 to <140 kg	1.12 (1.05-1.18)	0.0002	1.15 (1.05-1.27)	.0046
≥100 to <120 kg	1.10 (1.05-1.15)	<0.0001	1.11 (1.04-1.20)	.0026
<60 kg	0.72 (0.63-0.82)	<0.0001	0.73 (0.60-0.90)	.0032
TTR ≥ 0.6				
≥140 kg	1.16 (0.98-1.38)	0.09	1.28 (1.07-1.53)	.0081
≥120 to <140 kg	1.30 (1.14-1.48)	<0.0001	1.41 (1.23-1.61)	<.0001
≥100 to <120 kg	1.20 (1.09-1.32)	0.0001	1.26 (1.14-1.39)	<.0001
<60 kg	0.57 (0.42-0.77)	0.0002	0.59 (0.43-0.80)	.0009
DOAC treated patients‡				
PDC (continuous)				
≥140 kg	1.23 (1.03-1.46)	0.0217	1.27 (1.06-1.53)	.0114
≥120 to <140 kg	1.18 (1.06-1.32)	0.0037	1.21 (1.07-1.37)	.0020
≥100 to <120 kg	1.10 (1.03-1.19)	0.0067	1.12 (1.04-1.21)	.0040
<60 kg	0.73 (0.61-0.86)	<0.0001	0.76 (0.64-0.91)	.0028
PDC ≥ 0.8				
≥140 kg	1.30 (1.05-1.61)	0.0168	1.43 (1.15-1.78)	.0013
≥120 to <140 kg	1.23 (1.08-1.41)	0.0017	1.33 (1.16-1.52)	<.0001
≥100 to <120 kg	1.12 (1.03-1.22)	0.0101	1.17 (1.07-1.28)	.0005
<60 kg	0.69 (0.56-0.84)	0.0003	0.68 (0.56-0.84)	.0003

*Generalized linear mixed model.
†Multivariate model includes age, sex, race, antiplatelet prescription, HAS-BLED score, Charlson comorbidity index, and all baseline comorbidities (anemia, coronary artery disease, chronic kidney disease, diabetes, heart failure, hypertension, peripheral artery disease, prior myocardial infarction, prior stroke or transient ischemic attack).
‡Reference: ≥ 60 to <100 kg.
Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; INR, International normalized ratio; OR, odds ratio; PDC, proportion of days covered; TTR, time in therapeutic INR range.

DOACs are prescribed to prevent atrial fibrillation associated strokes.[33]

Warfarin-treated patients <60 kg were at risk for low TTR, compared to those of average weight, across all analyzed treatment durations. Our study did not assess whether these patients were candidates for DOAC and it is possible that warfarin was their only OAC treatment option. However, for patients <60 kg with VTE who are candidates for warfarin or DOAC, these findings are

relevant to patients and clinicians engaging in shared decision making on treatment selection. Interestingly, DOAC-treated patients <60 kg also had lower PDC compared to patients with average weight, suggesting that medication adherence may be more challenging for both warfarin and DOAC patients <60 kg. Importantly, the proportion of DOAC-treated patients <60 kg with PDC ≥ 0.8, an accepted threshold for medication adherence, was 77% at 180 days.

For warfarin-treated and DOAC-treated VTE patients in weight categories ≥100 kg, TTR and PDC over 180 days of treatment were higher than for those of average weight. A trend toward higher TTR in obese individuals, as compared to average BMI individuals, has been previously reported across all anticoagulation indications.[34] Further investigation is needed to understand why these patients may have better INR control while on warfarin therapy and DOAC adherence. Notably, an "obesity paradox" has been described for atrial fibrillation patients, with obese patients having a lower risk of stroke and systemic embolism.[35] If higher TTR and PDC demonstrated in our study for obese VTE patients generalized to the AF population, this paradox may be partially mediated through improved quality of anticoagulation. Importantly, in our study, DOAC-treated patients in higher weight categories frequently achieved PDC ≥ 0.8 over 180 days of treatment (~80%), while warfarin-treated patients in higher weight categories achieved TTR ≥ 0.6 approximately 50% of the time.

Our study has important limitations, which include clinically meaningful differences in patients' baseline variables across weight and BMI categories and by OAC treatment (DOAC vs warfarin). Although these variables were controlled for in multivariate analyses, residual confounding (eg, provoked, unprovoked, and/or cancer associated VTE) cannot be ruled out and these findings should be treated as hypothesis generating. Although the overall cohort was large, there were fewer patients at the extremes of the weight and BMI distributions included. Finally, these results may not generalize outside the VA healthcare system, which utilizes pharmacist-led anticoagulation clinics which have been associated with high rates of on-label DOAC dosing and time in therapeutic range for warfarin-treated patients and has a predominantly male population.

Conclusion

In conclusion, we found that warfarin-treated patients <60 kg were at risk for low TTR and that TTR was suboptimal, regardless of patient weight, particularly early in the treatment course. For DOAC-treated patients, a large proportion of patients exceeded the PDC threshold associated with medication adherence, regardless of weight. These findings may suggest superior anticoagulation quality for DOAC-treated patients, in particular for those at extremes of body weight, and should be considered when deciding between warfarin or DOAC for VTE.

Declaration of Conflicting Interests

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Supplemental Material

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Abbreviation List

CI	confidence interval
DOAC	direct oral anticoagulant
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision

INR	international normalized ratio
IQR	interquartile range
OAC	oral anticoagulation
OR	odds ratio
PDC	proportion of days covered
TTR	time in therapeutic INR range
VKA	vitamin K antagonist
VTE	venous thromboembolism