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Dosing Accuracy of Direct Oral Anticoagulants in an Academic Medical Center

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Abbreviated title: Inpatient DOAC dosing

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ABSTRACT

Background /Objective: Direct-acting oral anticoagulants (DOACs) are increasingly used to prevent or treat thromboembolism. Our goal was to compare how well initial DOAC prescribing for adult inpatients adhered to FDA-approved dosing recommendations.

Design: Retrospective analysis

Setting: Single academic medical center from July 1, 2014-June 30, 2015

Patients: 508 adult inpatients

Measurements: DOAC prescriptions were evaluated to determine whether they met FDA-recommended dosing/administration according to patient age, weight, sex, race, kidney function, diagnoses, and concomitant medications

Results: DOACs were prescribed in 635 admissions (247 apixaban, 97 dabigatran, 291 rivaroxaban). The indication was atrial fibrillation/flutter (AF) in 465 (8% with bioprostheses/valve repair), chronic deep venous thrombosis (DVT) in 67, acute DVT in 32, acute pulmonary emboli (PE) in 19, chronic PE in 23, prevention of DVT after hip/knee surgery in 19, and non-FDA-approved indications in 10. Sixteen percent of orders for venous thromboembolic disease were for patients with active malignancy. Dosages not concordant with recommendations were prescribed for apixaban in 18%, rivaroxaban in 14% and dabigatran in 7 % ($p=0.04$). Lower than recommended dosing was more common than higher ($p<0.05$). Half of deviations were continuations of outpatient dosing. AF and post knee/hip surgery dosing deviations were more common than for venous thromboembolic diseases ($p<0.001$) but not related to prescriber specialty.

Conclusions: Variations from DOAC prescribing recommendations that could affect clinical efficacy were identified. Education and point of care decision support tools to improve dosing are needed as are outcome data of patients receiving DOACs at lower than recommended doses or off-label indications.

Keywords: direct-acting oral anticoagulant, drug prescribing, dosing errors,

INTRODUCTION

Direct-acting oral anticoagulants (DOACs) have been introduced into clinical use for stroke prevention in patients with non-valvular atrial fibrillation (NVAF), prevention of venous thrombosis after hip or knee surgery, and treatment of deep vein thrombosis (DVT) or pulmonary emboli. (1-7) Advantages of DOACs over warfarin are often stated as fixed dosing, minor drug and food interactions, wider therapeutic index, and no need for laboratory test monitoring. (1, 8) Yet, recommended DOAC dosages vary by renal function and therapeutic indications. Dosing recommendations for prevention of stroke in patients with NVAF are based on estimated creatinine clearance (dabigatran, rivaroxaban, edoxaban), age (apixaban), weight (apixaban, edoxaban), and serum creatinine (apixaban, edoxaban), and presence of cirrhosis (by Child-Pugh class (9) (10), apixaban, edoxaban) (4-6, 11, 12) Dosing recommendations based on co-administration of strong CYP450 and P-glycoprotein inhibitors or inducers vary by DOAC. In addition, dabigatran cannot be crushed and must be stored in original packaging and rivaroxaban should be taken with food when the dose is over 10 mg.

We hypothesized that the complexity of DOAC dosing may not be recognized by prescribers. Our goal was to investigate prescribing of DOACs in adults admitted to a large academic medical center by comparing the initial prescribed dose to FDA-approved prescribing information.

METHODS:

Data Collection:

Electronic medical record (EMR) identification of adult inpatients prescribed DOACs (apixaban, dabigatran, edoxaban, or rivaroxaban) from July 1, 2014 through June 30, 2015 at the Univeristy of California, San Francisco Medical Center, a large academic hospital. Collection of demographic and medical information related to therapeutic indication, contra-indications, or dose adjustments (by International Statistical Classification of Diseases and Related Health Problem (ICD) 9 and 10, venous thromboses, phlebitis or thrombophlebitis, pulmonary or venous emboli, atrial arrhythmias, surgical procedures, cirrhosis and/or ascites or liver disease, coagulopathies, artificial heart valve or implanted device), medications including preceding parenteral anticoagulants, and laboratory data (serum creatinine, estimated glomerular filtration rate (eGFR) (by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)(13), International Normalized Ratio or activated partial thromboplastin time and bilirubin (if available) before the first DOAC order. Creatinine clearance was calculated by Cockcroft and Gault (14) with total body weight per drug label recommendation. Child Pugh class was calculated if cirrhosis was diagnosed. (10) DOAC dose, frequency, dosing directions and prescriber medical specialty were determined.

Accuracy of search results was confirmed by record review of the first 200 patients. Manual review was performed for encounters without coded ICD-9/10 approved DOAC indications (30%) and to determine the admission specific indication when multiple diagnostic indications were coded. ICD-9 venous thrombosis codes were reviewed to differentiate acute from chronic events.

The study protocol was approved by the UCSF Committee on Human Research (Institutional Review Board).

Data Analysis

The main outcome was concordance or discordance of the first DOAC prescribing order with FDA-approved prescribing information at the time. Initial classification was by two independent reviewers (pharmacist and physician or two pharmacists) followed by adjudication and individual record review by two independent reviewers of all initial prescribing orders classified as discordant. A third reviewer adjudicated any disagreement. Records and notes were reviewed to identify stated or potential reasons for dosing variation and pre-admission prescriptions. Data are presented as mean ± standard deviation, and raw numbers and percentages. Differences in patient characteristics by DOAC or therapeutic indication were determined by ANOVA with Bonferroni correction for post hoc comparisons. Dosing information was categorized as the same, lower, higher, or avoid (drug-drug or drug-disease interaction) per FDA-approved prescribing information and we used Chi-squared tests to determine whether variation in dosing occurred by individual DOAC, therapeutic indications or prescriber specialty. Relationships between dosing variation and age or renal function was tested by ANOVA with Bonferroni correction for post hoc comparisons.

RESULTS

There were 635 admissions with apixaban, dabigatran, or rivaroxaban prescribed for 508 patients. (Table 1). Edoxaban was not on the formulary and not prescribed during the time period. The therapeutic indication was prevention of embolic stroke in patients with atrial fibrillation/flutter in 465 or 73% (with valvular disease and/or tissue valve in 35), chronic DVT in 67 or 11% (with active malignancy in 14), acute DVT in 32 (with malignancy in 2), acute PE

in 19 (with malignancy in 4), chronic PE in 23 (with malignancy in 3), for prevention of DVT after hip or knee surgery in 19. DOACs were prescribed for unapproved indications in 10 that were excluded from further analysis (mural thrombus in 3, low ejection fraction in 2, bedrest immobilization in 2, aortic aneurysm in 1, thrombocytosis in 1, extensive superficial venous thrombosis in 1). (Table 2)

Patients with atrial fibrillation were older with lower creatinine clearance than patients with other diagnoses with a mean (± SD) age of 72.1 ± 12.7 y compared to 53.1 ± 10.9 for patients with chronic PE, 55.5 ± 14 for acute PE, 56.4 ± 15.9 for chronic DVT, 57.9 ± 18.4 for acute DVT, and 61.4 ±11.6 for DVT prevention after knee/hip surgery ($p<.0001$ for all comparisons) and estimated creatinine clearance (ml/min) of 76.8 ±43.5 compared to 92.4 ±44.4 for prevention of DVT after knee/hip surgery, 111 ±53 for chronic DVT, 118 ±55 for acute DVT patients, 126 ± 60 for chronic PE, and 127 ±54 for patients with acute PE ($p<.0001$, all comparisons). Differences between patient groups by therapeutic indication were not detected for weight, BMI, or serum creatinine.

The most frequent prescribing deviation from recommendations was omission of directions to administer rivaroxaban with food in 248 of 268 (93%) of prescriptions that were not for prevention of DVT after hip/knee surgery when the 10 mg dose is appropriately administered without food. Doses were the same as recommended for 82% of apixaban, 84% of rivaroxaban , and 93% of initial dabigatran orders ($p<0.05$ for differences; Table 3). Dosages not concordant with FDA recommendations were prescribed in 44 of 243 (18.1%) apixaban orders, 41 of 286 (14.3%) rivaroxaban orders and 7 of 89 (7.2 %) of initial dabigatran orders. Lower than recommended doses were more common than higher than recommended doses (Table 3, Figure 1) and were prescribed in 15.2% vs. 2.1% of apixaban, 9.4% vs. 3.5 % of rivaroxaban and 4.2%

vs. 1.0% of dabigatran initial orders ($p<0.05$). Failure to avoid use due to drug-drug or drug-disease interactions was uncommon (1-2 %). There were more deviations from recommended doses for patients with atrial fibrillation/flutter or DVT prevention after hip/knee surgery than treatment of acute or chronic PE or acute DVT (Table 3). No significant difference between prescribed and recommended doses by the specialty of the prescriber was detected.

A reason for deviations from FDA dosing recommendations was not stated in the EMR for most cases. Exceptions were fluctuating renal function cited in eight instances.

For apixaban, patients prescribed lower than recommended doses were older than those prescribed recommended doses (78.1 ± 12.2 vs. 71 ± 13.6 y; $p=0.003$) and the majority (76%) of those prescribed lower than recommended doses were over the age of 75 years. Lower than recommended apixaban doses were continuations of prior outpatient doses in slightly over half (20 of 37) while a quarter were co-prescribed antiplatelet drugs (aspirin in 10, clopidogrel in 1 and prasugrel in 1). For rivaroxaban, older age was associated with both lower ($p =0.003$) and higher ($p<0.001$) than recommended dosing. Variations from prescribing recommendations were continuations of outpatient rivaroxaban doses in about two-thirds (26 of 41; 63.4 %) with 13 receiving antiplatelet drugs. For dabigatran, 6 of 7 orders not in agreement with recommendations were continuations of outpatient dosing.

The specific equation used to estimate renal function also had the potential to lead to dosing errors. Among the 41 rivaroxaban patients categorized as receiving doses discordant with recommendations, 8 would have had an inappropriate DOAC dose if eGFR were used instead of eCrCL as recommended. No relationships were detected for other patient variables/measures and dosing deviations from recommendations.

DISCUSSION

We examined initial hospital orders for DOACs in adults admitted to a single academic medical center during 2014-2015. Dabigatran, apixaban and rivaroxaban were prescribed for prevention of stroke in patients with atrial fibrillation/flutter (AF) in three quarters of the encounters similar to national patterns. (15) Prescribing departures from FDA-approved recommendations ranged from failure to prescribe rivaroxaban with food to failure to recognize drug-drug interactions in 1-2 %. Unexpectedly, lower than recommended dosing was more common than higher than recommended dosing of the three DOACs.

Rivaroxaban bioavailability is dose dependent with the presence of food required to enhance absorption for doses over 10 mg that are used for prevention of stroke in patients with non-valvular AF or treatment of DVT or PE. (16) (5) Peak rivaroxaban concentrations are 75% higher and the total area under the concentration vs. time curve after dosing is 40% higher when rivaroxaban is administered with high fat high calorie meals compared to the fasting state. (16) If rivaroxaban is not administered with food, drug concentrations and pharmacologic effects may be less than in clinical trials that specified co-administration with food. (17-19). A small survey of outpatients receiving rivaroxaban found that 23% reported taking it without food. (20) With electronic pharmacy systems in almost all hospitals and electronic prescriber order entry in most, automated addition of directions for rivaroxaban administration with food for doses over 10 mg to labels or dispensing instructions could easily correct this deviation from recommended practice.

Lower than recommended doses were prescribed in 9.4% of orders for rivaroxaban and 15.2% of orders for apixaban, with dose-deviations often appearing to be a continuation of outpatient doses. Patients 75 years or older were more likely to receive lower than recommended dosing of

apixaban. Reductions in apixaban doses from 5 mg twice daily to 2.5 mg twice daily are recommended in patients with non-valvular AF with two of the following criteria: age ≥ 80 y, weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL or co-administration of a strong PgP inhibitor to a patient without 2 of the 3 dose reduction criteria. Our study was not designed to determine reasons for under-dosing, but we speculate that clinicians may have considered patients aged 75-79 y to be similar to those 80 years of age or older, or, older and not as healthy as those enrolled in randomized trials. (21-23) (24, 25) The median age of our patients with AF receiving apixaban was 75y (interquartile range of 16) vs 70y (interquartile range 63-76) in the pivotal trial comparing warfarin to apixaban. (21) Renal function was also lower with 37% having eCrCL below 50 mL/min compared to 17% in ARISTOTLE. (21). Twenty-six percent of our apixaban-treated AF patients qualified for the lower 2.5 mg twice daily compared to only 5 % of ARISTOTLE participants (21) further suggesting differences between patients in our sample compared to randomized trial participants.

Concerns regarding bleeding or falls in older patients, may also have contributed to lower than recommended doses. Recent analyses of patients at risk for falls confirmed that increased risk of falling was associated with more bone fractures, bleeding and all-cause death but not stroke or systemic emboli, and with less severe bleeding with the DOAC edoxaban compared to warfarin. (26). While a rationale for personalized or lower than recommended dosing of apixaban may exist in very old patients and those at risk of falls and bleeding, more data are needed to determine outcomes of lower than recommended doses of DOACs before such an approach can be endorsed. Monitoring of anticoagulant effect in patients who receive lower doses than investigated in clinical trials could provide important information. Assays to measure DOAC

effects exist and are likely to be more available due to the use of reversal agents in the setting of bleeding with DOACs. (27)

We had anticipated higher than recommended dosing for rivaroxaban as recommendations are based on creatinine clearance while laboratories routinely report estimated glomerular filtration rate (eGFR) that can provide higher estimates of renal clearance and estimated DOAC doses in older and smaller individuals. (28). Higher than recommended dosing was found in only 3.5% of our sample. In half, eGFR estimates were higher than creatinine clearance estimates. An international post-marketing registry of rivaroxaban use for prevention of stroke in patients with NVAF that included outpatients reported 36% of patients with creatinine clearances below 50 ml/min received a higher dose than recommended and 15% received lower than expected dosing based on creatinine clearance. (29) A more recent outpatient registry report of patients with NVAF that received apixaban, dabigatran, or rivaroxaban found that overall 9.4% received lower than recommended dose and 3.4% were overdosed with a similar 34% of those receiving rivaroxaban with a CrCL of 15-50 ml/min receiving higher than recommended dosing. (30)The lower rate of higher than recommended doses that we observed may have been related to the routine measurement of serum creatinine and attention to dosing adjustments for renal function in the inpatient setting compared to the outpatient setting. Additionally, renal function data may not be available to outpatient pharmacies limiting potential input on dosing recommendations. One cardiac society recommends that renal function be monitored annually in patients with normal creatinine clearance and at intervals in months that is equal to the creatinine clearance divided by 10 for patients with renal dysfunction receiving DOACs. (11). A hospital encounter provides an opportunity to assess or reassess renal status to optimize DOAC dosing.

Dabigatran was the first DOAC introduced into use in the United States with the same dose recommended for prevention of stroke in patients with atrial fibrillation or venous thromboembolic disease with reductions for creatinine clearance below 30 ml/min or creatinine clearance between 30-50 mL/min and concomitant use of potent P-gp inhibitors dronedarone or systemic ketoconazole. The relative simplicity of dosing may have been responsible for the lowest rate of prescribing outside of recommendations observed in this study, but the low dabigatran use limits analyses on contributing factors.

Failure to avoid drug use in combination with strong Pgp inducers or inhibitors was infrequent yet should be preventable. Current prescribing recommendations refer to "strong" Pgp inhibitors and list different specific agents that interact with each DOAC without a standardized definition or classification. Standardized classifications or reference sources would be helpful.

Our primary goal was to compare initial prescribed dosing of DOACs to FDA-approved prescribing directions. However, therapeutic indication data warrant discussion. In our sample, 7.5% of patients with AF had bioprosthetic valves or recent mitral valve repair or replacement. Using the definition of "non-valvular" AF found in the 2014 AHA/ACC/HRS AF guidelines (1) of "absence of rheumatic mitral valve disease, a prosthethic heart valve, or mitral valve repair, these patients would not appear to be candidates for DOACs. However, arguments have been put forth that a bioprosthetic heart valve or native valve after valve repair do not have risk profiles for thromboembolism that differ from other forms of "non-valvular" AF and would be equally responsive to DOAC therapy. (31) Data are sparse, but retrospective subanalyses of limited numbers of patients with valvular disease (including bioprostheses and mitral repair patients but excluding mechanical valves) enrolled in the pivotal DOAC studies support this

conclusion. (32) For the first months after biological valve replacement (including catheter-based valve replacement), recent European guidelines recommend vitamin K antagonists but also state that "NOACs probably deliver the same protection."(8) DOACs were also used for management of venous thromboembolic disease (both acute and chronic) in patients with active cancer. Our data predate the most recent American College of Chest Physician guidelines for treatment of VTE in patients with cancer stating Grade 2B recommendations for low molecular weight heparin (LMWH) over vitamin vitamin K antagonists and Grade 2C recommendations for LMWH over dabigatran, rivaroxaban, apixaban, or edoxaban. (33)

Our study has limitations; first, data were from a single U.S. academic medical center although similar rates of prescribing variation from recommendations has been reported for rivaroxaban and dabigatran for patients with non-valvular AF in other countries. (29, 34) Second, therapeutic indications may have been misclassified due to errors or incomplete EMR data or the case of multiple indications. Third, we analyzed the first DOAC order and not dispensing information or subsequent corrections; therefore, deviations from recommendations should not be interpreted as errors that reached patients. We evaluated dosing based on the measures at the time of hospital admission noting that in a significant fraction of deviations from recommended doses they represented a continuation of an outpatient dose when renal function or weight may have differed and it is unknown whether patients were counseled to take rivaroxaban with food in the outpatient setting. Fourth, the number of patients with acute DVT was small so firm conclusions cannot be drawn for this specific population. Finally, our estimates of off-label dosing may have been underestimates as data on cancer and cancer activity or cardiac valvular disease may not have been complete.

In conclusion, health care professionals are prescribing DOACs in ways that differ from recommendations that may reflect older ages and reduced renal function of clinical populations as compared to randomized clinical trial groups, but could also potentially alter clinical efficacy. Our findings support the need for evaluation of the appropriateness and dosing of DOACs at each encounter, for determining outcomes of patients treated with lower than recommended doses of DOACs, and outcomes of patients with bioprostheses or active malignancies receiving DOACs.

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Figure Legends

Figure 1. Comparison of initial DOAC Dosing to FDA-Recommended Dosing. Per Cent of initial orders categorized as lower, the same, higher, or to avoid use according to FDA recommendations are presented for apixaban, dabigatran, and rivaroxaban.

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Table 1. Patient Demographics

	Entire Group	Apixaban	Dabigatran	Rivaroxaban
Number of subjects	508	191	75	242
Sex (men, women)	286, 222	102, 89	51, 24	133, 109
Race (black/white/Asian/	34/316/67	13/111/36	2/49/10	19/156/21
Native American or Pacific	10/61/19	5/21/5	1/9/3	4/31/11
Island/Other/ Unknown)				
Hispanic/non-Hispanic/unknown	45/445/18	17/168/6	6/68/1	22/209/11
Age (y)	68.6 ± 14.7	72.2 ±13.8*	70.2 ±12.0*	65.2 ±15.3*
range	19-98	19-98	33-94	20-97
Weight (kg)	82.9 ± 24.8	78.8 ± 25.2*	86.8 ±24.3	84.9± 24.4*
range	36.4-225.5	36.4-179.8	49.1-156.8	39.3-225.5
Height (cm)	170.5 ±11	169.5 ±10.3	173.2 ±10.0	170.4 ± 11.6
range	143.5-203.2	143.5-195.6	152.4-198.1	147.3-203.2
Body Mass Index (M^2)	28.4 ± 7.2	27.2 ± 6.8*	28.7± 7.3	29.2±7.2*
range	14.4-71.3	14.8-50.9	17.6-59.0	14.4-71.3
Creatinine (mg/dL)	1.1± 0.7	1.1 ± 1.0*	1.0 ± 0.4	1.0 ± 0.3*
range	0.3-10.9	0.4-10.9	0.4-2.4	0.3-2.3
eCrCl (ml/min)^	86.9 ± 48.8	77.2 ± 50.0*	88.7± 48.0	94.1 ± 47.3*
range	4-297	4-297	18-261	24-267

Data are mean ± standard deviation (SD). ^eCrCl= estimated creatinine clearance by Cockcoft and Gault method using total body weight. Significant differences were detected between DOAC groups for age (rivaxaban vs. apixaban or dabigatran, $p<.02$), weight (rivaroxaban vs. apixaban, $p<.02$), Body Mass Index (rivaroxaban vs. apixaban, $p<.02$) and creatinine or eCrCl (apixaban vs. Rivaroxaban) by ANOVA post hoc Bonferroni Dunn method. No significant differences between sex or race proportions for the DOAC groups were detected.

Table 2. Treatment Indications and Prescriber Specialties by Admission

	Total Sample	Apixaban	Dabigatran	Rivaroxaban
Initial DOAC orders (N (% row))	635	247 (38.9%)	97 (15.3%)	291 (45.8%)
Number with >one admission % column	96 15.1%	44 (45.8%) 17.8%	13 (13.5%) 13.4%	39 (40.6%) 13.4%
Therapeutic Indication				
Atrial Fibrillation/Flutter (valvular disease, n=35)	465 73.2%*	224 (48.2%) 90.7%	71 (15.3%) 73.2%	170 (36.6%) 58.4%
Acute Pulmonary Emboli (active malignancy, n=4)	19 3.0%	3 (15.8%) 1.2%	0 0	16 (84%) 5.6%
Acute Deep Venous Thrombosis (active malignancy, n=2)	32 5.0%	7 (21.8%) 2.8%	6 (18.8%) 6.3%	19 (59.4%) 6.5%
Chronic Deep Venous Thrombosis (active malignancy, n=14)	67 10.6%	7 (10.4%) 2.9%	17 (25.4%) 17.7%	42 (62.7%) 14.6%
Chronic Pulmonary Emboli (active malignancy, n=3)	23 3.6%	1 (4.3%) 0.4%	2 (8.7%) 2.1%	20 (87.0%) 7.3%
Prevention of Deep Venous Thrombosis (hip, knee replacement)	19 3.0%	1 (5.3%) 0.4%	0 0	18 (94.7%) 6.2%
*Unapproved Indication***	10 1.6%	4 1.6%	1 1.0%	6 2.1%
Prescriber Specialty				
Cardiology	202 31.7%	113 (55.9%) 45.7%	22 (10.9%) 22.7%	67(33.2%) 22.9%

Emergency Medicine	60 9.4%	34 (56.7%) 13.8%	2 (3.3%) 2.1%	24(40%) 8.2%
Hospital Medicine	131 20.6%	35 (26.7%) 14.2%	26 (19.8%) 26.8%	70 (53.4%) 24.1%
Other medical specialty	64 10.1%	19 (29.7%) 7.7%	16 (25.0%) 16.5%	29 (45.3%) 10.0%
Surgery	132 20.7%	41 (31.8%) 16.6%	28 (21.2%) 28.9%	63 (47.7%) 21.6%
Surgery Orthopedic	47 7.4%	6 (12.8%) 2.4%	3 (6.4%) 3.1%	38 (80.9%) 13.1%

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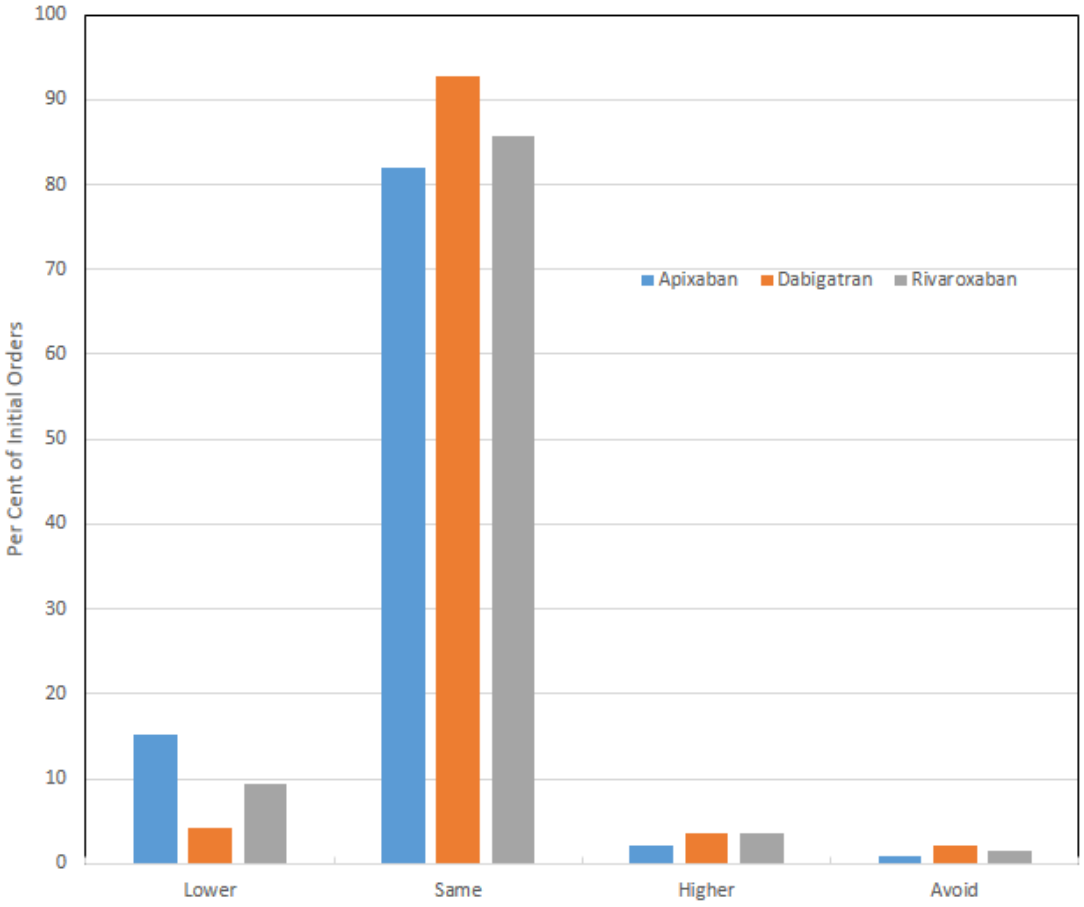
Per Cent by column ** mural thrombus in 3, low ejection fraction in 2, immobilization in 2, thrombocytosis in 1, aortic aneurysm in 1, superficial venous thrombosis in 1

Table 3. Observed Direct-acting Oral Anticoagulant (DOAC) Dosing in comparison to Prescribing Recommendations

DOAC*	Same as Recommended N (%)	Higher than Recommended N (%)	Lower than Recommended N (%)	Avoid Drug Use N (%)
Apixaban (n=243)	199 (81.9)	5 (2.1)	37 (15.2)	2 (0.8)
Dabigatran (n=96)	89 (92.7)	1 (1.0)	4 (4.2)	2 (2.1)
Rivaroxaban (n=286)	245 (85.7)	10 (3.5)	27 (9.4)	4 (1.4)
Therapeutic Indication**				
Atrial Fibrillation/Flutter (n=465)	384 (82.6)	14 (3.0)	63 (13.5)	4 (0.1)
Acute DVT (n=32)	29 (90.6)	0 (0)	2 (6.3)	1 (3.1)
Chronic DVT (n=67)	66 (98.5)	0 (0)	1 (1.5)	0 (0)
Acute PE (n=19)	18 (94.7)	0 (0)	1 (5.3)	0 (0)
Chronic PE (n=23)	20 (87.0)	0 (0)	1 (4.3)	2 (8.7)
DVT prevention (n=19) (hip, knee replacement)	16 (84.2)	2 (10.5)	0 (0)	1 (5.3)

*DOAC= Direct-acting oral anticoagulant, DVT =deep venous thrombosis, PE=pulmonary emboli. *p=.04 for dose same as recommended between DOACs; p=.06 for dose direction differences between DOACs. ** p=.001 for differences from recommended analyzed by therapeutic indication. Note: 10 patients receiving DOACs for unapproved indications were not included in analyses (see text).


100
90
80
70
60
50
40
30
20
10
0
Per Cent of Initial Orders
Apixaban
Dabigatran
Rivaroxaban
Lower
Same
Higher
Avoid