Evaluation of the Appropriateness of Direct Oral Anticoagulant Selection and Monitoring in the Outpatient Setting

Journal of Pharmacy Technology
2017, Vol. 33(3) 108–113
© The Author(s) 2017
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/8755122517698976
journals.sagepub.com/home/pmt

Kristin N. Rieser, PharmD¹, Eric I. Rosenberg, MD²,
and Katherine Vogel Anderson, PharmD^{1,2}

Abstract

Background: Direct oral anticoagulants (DOACs) share many indications with warfarin but require less frequent follow-up and monitoring. There is limited data available on the prescribing of DOACs and appropriate laboratory monitoring in a real-world clinical setting. **Objective:** To determine if patients receiving care at 2 University of Florida (UF) Health Internal Medicine clinics are prescribed DOACs according to Food and Drug Administration (FDA)–approved labeling. Secondary objectives were to determine the percentage of patients receiving appropriate baseline laboratory tests prior to DOAC initiation and the frequency of laboratory monitoring. **Methods:** This retrospective chart review evaluated patients enrolled at 2 UF Health Internal Medicine practices within the UF Health system who were prescribed a DOAC between April 2014 and April 2015. Adherence to FDA-approved dosing recommendations and baseline laboratory tests were compared to previously published data. This study was approved by the UF Institutional Review Board. **Results:** A total of 194 patients met inclusion criteria. Ninety-six patients (49.5%) were on a DOAC prior to data collection; 98 patients (50.5%) started a DOAC during data collection. Of the 194 patients, 155 (79.9%) were prescribed DOACs per FDA-approved labeling ($P = .0005$); 79 (40.8%) obtained a complete blood count, serum creatinine, and liver function tests prior to DOAC initiation. **Conclusions:** Prescribing practices were significantly better than published data; however, 1 in 5 patients were not prescribed a DOAC according to FDA-approved labeling. Less than half of the patients started on a DOAC obtained the recommended labs prior to medication initiation.

Keywords

anticoagulants, anticoagulation, ambulatory care, prescribing patterns, drug monitoring

Background

Between 2010 and 2015, 4 direct oral anticoagulants (DOACs) became available for the treatment of venous thromboembolism and stroke prevention in patients with non-valvular atrial fibrillation (dabigatran, rivaroxaban, apixaban, and edoxaban). Three DOACs are also indicated for deep vein thrombosis prophylaxis following orthopedic surgery (dabigatran, rivaroxaban, apixaban). Because the DOACs have fewer lifestyle restrictions and require less frequent monitoring than warfarin, it is not surprising these agents are favored by many providers and patients. Since 2011, there have been more than 13 million prescriptions written for rivaroxaban in the United States.¹ In fact, claims data for patients with atrial fibrillation showed that by mid-2013 DOACs accounted for 62% of new anticoagulation prescriptions.² It is expected that DOACs will gain even more popularity as the most recent edition of the American College of Chest Physicians Antithrombotic Guidelines endorse DOACs over warfarin for the treatment of venous

thromboembolism in non-cancer patients.³ In addition, reversal agents are becoming available for these previously “non-reversible” anticoagulants. Dabigatran is the only DOAC with an available reversal agent; however, a reversal agent for the factor Xa inhibitors is currently under Food and Drug Administration (FDA) review.⁴

There are many factors to address when prescribing the appropriate dose of a DOAC, with some of the most important being: indication, renal function, and concomitant medications. Dabigatran and all 3 factor Xa inhibitors are permeability glycoprotein (p-gp) substrates, and every DOAC except dabigatran is also a substrate for CYP3A4. There is a lack of evidence to guide practitioners in

¹The University of Florida College of Pharmacy, Gainesville, FL, USA

²The University of Florida College of Medicine, Gainesville, FL, USA

Corresponding Author:

Kristin N. Rieser, University of Florida College of Pharmacy, HPNP Building, 1225 Center Drive, Gainesville, FL 32608, USA.
Email: krieser@umc.edu

determining if DOAC dose adjustments are needed when co-administered with strong p-gp or CYP inhibitors. The European Heart Rhythm Association (EHRA) provides suggestions for dose adjustments in patients with atrial fibrillation.⁵ However, many of these recommendations are based on pharmacokinetic studies and have not been prospectively studied.

The Heart Rhythm Society of America and American College of Chest Physicians have published guidance for choosing a DOAC according to baseline laboratory tests.^{3,6} However, there is no recommendation about follow-up. The EHRA recommends obtaining a complete blood count (CBC), comprehensive metabolic panel (CMP), and liver function tests (LFTs) prior to initiating a DOAC. Thereafter, a metabolic panel, CBC, and LFTs should be checked yearly for patients with adequate kidney function (creatinine clearance [CrCl] > 60 mL/min), every 3 to 6 months for patients older than 75 and/or with a creatinine clearance less than 60 mL/min, and at every care transition that could alter co-administered medications.⁵ These recommendations are based on the frequency of monitoring in the landmark DOAC trials. For example, in ROCKET AF, investigators assessed renal function, liver function, and bleeding at baseline and at weeks 26, 52, and 104.⁷

Appropriate prescribing of DOACs is a topic of interest given their increasing popularity. Most recently, the Veterans Health Administration (VA) published data evaluating the use of DOACs in over 32,000 patients, between 2011 and 2014. In this study, it was found that 4.58% of DOAC prescriptions across 130 sites were potentially inappropriate and that rates varied widely between sites (0% to 12.6%).⁸ Smaller studies outside of the Veteran's Health Administration have found that rates of inappropriate DOAC prescribing can be as high as 39%.^{9,10}

Currently, 2 internal medicine practices within the University of Florida (UF) Health system provide pharmacist-managed anticoagulation services for patients who are prescribed warfarin; patients taking DOACs are not enrolled in the anticoagulation service. It is not known how many UF Health Internal Medicine patients are prescribed a DOAC, nor how these patients are monitored after DOAC initiation. Therefore, the purpose of this retrospective review was to determine if patients receiving care at UF Health Internal Medicine are prescribed DOACs according to FDA-approved labeling. Baseline laboratory data for patients initiating a DOAC and the frequency of laboratory follow-up thereafter was also assessed.

Methods

Using the health system electronic medical record, Epic, a retrospective chart review was conducted by a single pharmacist on patients enrolled at 2 UF Health Internal Medicine clinics (UF Health Internal Medicine at the Medical Plaza

and at Tower Hill), who were prescribed a DOAC between April 1, 2014, and April 30, 2015. Patients who were established with a UF Health Internal Medicine primary care provider, and who were therefore eligible for enrollment in the pharmacist-managed anticoagulation services at each site, were included. Patients who were not established with a primary care provider at either UF Health clinic were excluded from data collection. Approval for this review was obtained from the University of Florida Institutional Review Board.

Data collected included patient demographics at DOAC initiation; indication for anticoagulation therapy; comorbidities; DOAC dose and frequency; previous anticoagulation therapy; co-administered medications; laboratory test results between April 1, 2014, and April 30, 2015; and bleeding or thrombotic events between April 1, 2014, and April 30, 2015. All medications that were active on a patient's profile while also on a DOAC were considered co-administered medications.

The primary objective of this review was to assess the appropriateness of DOAC prescribing, as determined by FDA-approved labeling (Table 1). Inappropriate prescribing of a DOAC was categorized as incorrect dose, incorrect duration of therapy, or unapproved indication. The secondary objectives were to evaluate if appropriate baseline laboratory tests were ordered and the frequency of laboratory monitoring for patients on a DOAC for the entire study period (12 months). Using the EHRA recommendations for laboratory monitoring, patients older than 75 years of age with a creatinine clearance greater than 60 mL/min would qualify for laboratory monitoring every 6 months; patients with a creatinine clearance less than 60 mL/min, regardless of age, would qualify for more frequent (ie, every 3 months) monitoring; and patients younger than 75, with adequate renal function (CrCl > 60 mL/min), would qualify for yearly laboratory monitoring.⁵

Using a χ^2 analysis, our findings were compared to the following data from a single retrospective study of 395 patients published in 2015, which found that 61% of patients were on appropriate therapy based on current FDA-approved labeling, 63% of patients obtained a baseline serum creatinine as part of a metabolic panel prior to DOAC initiation, 54% of patients obtained a baseline complete blood count prior to DOAC initiation, and 26% of patients obtained baseline liver function tests prior to DOAC initiation.⁹ An association between appropriate prescribing of a DOAC and frequency of adverse events was also explored.

Results

An electronic report was generated from Epic, which included 275 patients who received a prescription for a DOAC, written by an Internal Medicine provider, between April 1, 2014, and April 30, 2015. Of these patients, 194 met

Table 1. Dosing Recommendations Based on FDA-Approved Labeling.

Medication	Indication	FDA Approval Date	Dose	Dose Adjustments
Apixaban ¹¹	Treatment of DVT/PE	August 2014	10 mg twice daily × 7 days followed by 5 mg twice daily	N/A
	Reduction in the risk of recurrence of DVT/PE		2.5 mg twice daily after 6 months of treatment	N/A
	Reduction in risk of stroke in NVAf	December 2012	5 mg twice daily	2.5 mg twice daily ^a
	DVT prophylaxis following knee replacement surgery	March 2014	2.5 mg twice daily for 12 days	N/A
	DVT prophylaxis following hip replacement surgery		2.5 mg twice daily for 35 days	N/A
Edoxaban ¹²	Treatment of DVT/PE ^b	January 2015	60 mg once daily	30 mg once daily in CrCl 15-50 mL/min ^c
	Reduction in risk of stroke in NVAf		60 mg once daily	30 mg once daily in CrCl 15-50 mL/min ^d
Dabigatran ¹³	Treatment of DVT/PE ^b	April 2014	150 mg twice daily	N/A
	Reduction in the risk of recurrence of DVT/PE		150 mg twice daily	N/A
	Reduction in risk of stroke in NVAf	October 2010	150 mg twice daily	75 mg twice daily in CrCl 15-30 mL/min ^e
	DVT prophylaxis following hip replacement surgery	November 2015	110 mg orally first day followed by 220 mg once daily	N/A
Rivaroxaban ¹⁴	Treatment of DVT/PE	November 2012	15 mg twice daily × 21 days followed by 20 mg once daily	N/A
	Reduction in the risk of recurrence of DVT/PE		20 mg once daily	N/A
	Reduction in risk of stroke in NVAf	November 2011	20 mg once daily	15 mg once daily in CrCl 15-50 mL/min
	DVT prophylaxis following knee replacement surgery	July 2011	10 mg daily for 12 days	N/A
	DVT prophylaxis following hip replacement surgery		10 mg daily for 35 days	N/A

Abbreviations: FDA, US Food and Drug Administration; DVT, deep vein thrombosis; PE, pulmonary embolism; CrCl, creatinine clearance; NVAf, nonvalvular atrial fibrillation.

^aApixaban 2.5 mg twice daily if any 2 of the following are met: age ≥80, body weight ≤60 kg, creatinine, serum ≥1.5 mg/dL.

^bInitiated after 5 to 10 days of parenteral anticoagulation.

^cEdoxaban 30 mg once daily for patients with CrCl 15-50 mL/min, body weight ≤60 kg, or co-administration of PGP inhibitor.

^dNot recommended in CrCl >95 mL/min.

^eDabigatran 75 mg twice daily for patients with CrCl of 30-50 mL/min and concomitant use of dronedarone or ketoconazole.

inclusion criteria; 96 (49.5%) patients were on a DOAC prior to April 1, 2014, and 98 (50.5%) patients initiated therapy during the study period. Because Internal Medicine providers are required to attend in the hospital multiple times throughout the year, provider names are often associated with discharge prescriptions written for patients who are not established at either practice. As such, these patients, who were included in the report, were excluded from analysis.

Atrial fibrillation was the most common indication for a DOAC, accounting for 146 (76.3%) of the patients (Table 2). Apixaban (83, 42.8%) was the most frequently prescribed DOAC, followed by rivaroxaban (75, 38.6%) and dabigatran (36, 18.6%). There were no patients who were prescribed edoxaban.

DOAC use was categorized as appropriate for 155 out of 194 (79.9%) of patients. Among the patients who were categorized as receiving inappropriate DOAC therapy, 31 (77.5%) were on the wrong dose, 6 (15.0%) were on a DOAC for a non-FDA-approved indication, and 3 (7.5%) continued therapy longer than recommended (Table 3).

Of the 98 patients who initiated a DOAC during the study period, 40 (40.8%) had all 3 recommended laboratory tests assessed (metabolic panel, liver function, and complete blood count) in the 30 days prior to DOAC initiation. As part of a metabolic panel, serum creatinine was obtained for 61 patients (62.2%), liver function was obtained for 45 patients (45.9%), and a complete blood count was obtained for 54 patients (55.1%; Table 3). Seventy-four patients

Table 2. Baseline Characteristics.

Characteristic	Frequency, n (%)
Gender	N = 194
Male	100 (51.5)
Female	94 (48.5)
Age (years), mean (SD)	67.22 (13.38)
DOAC initiation prior to study period	96 (49.5)
DOAC initiation during study period	98 (50.5)
Primary indication for anticoagulation	
Atrial fibrillation	148 (76.3)
Venous thromboembolism	43 (22.2)
Orthopedic procedure	2 (1.0)
Stroke ^a	1 (0.5)
DOAC prescriptions	
Apixaban	83 (42.8)
Dabigatran	36 (18.6)
Edoxaban	0 (0.0)
Rivaroxaban	75 (38.6)
Past medical history	
Hypertension	143 (73.7)
Diabetes mellitus	52 (26.8)
Coronary artery disease	55 (28.3)
Heart failure	35 (18.0)
Gastroesophageal reflux disease/peptic ulcer disease	22 (11.3)
Stroke/transient ischemic attack	31 (15.9)
Venous thromboembolism	50 (25.7)
Bleeding event	26 (13.4)
Hypercoagulable state	6 (3.0)
Bioprosthetic heart valve	5 (2.5)
Renal function by CrCL	
>50 mL/min	150 (77.3)
30-49 mL/min	42 (21.6)
15-29 mL/min	2 (1.0)
CHADS ₂ score, mean (SD)	2.15 (2.5)
CHA ₂ DS ₂ -VASc score, mean (SD)	3.80 (3.5)
Co-administered medications that increase bleeding risk	
On at least 1 medication	135 (65.9)
Antiplatelet agent	108 (55.6)
NSAID	18 (9.2)
SSRI/SNRI	45 (23.1)
Omega 3 fatty acid	38 (19.5)
Systemic corticosteroid	4 (2.0)
P-gp inhibitor	47 (24.2)

Abbreviations: DOAC, direct oral anticoagulant; CrCL, creatinine clearance; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; p-gp, permeability glycoprotein.

^aOne person was prescribed a DOAC for stroke, not specified as being cardioembolic/related to atrial fibrillation or atrial flutter.

(75.5%) had a metabolic panel reassessed after DOAC initiation, with the average time to first laboratory follow-up of 3.6 months. Using the EHRA recommendations, 107 patients (55.2%) qualified for yearly labs, 18 (9.3%) qualified for labs every 6 months, and 69 (35.5%) for labs every 3 months. In patients who were on a DOAC for the duration of the study period, a metabolic panel was assessed an average of 2.9 times per year (ie, more frequently than recommended) for patients who qualified for yearly laboratory follow-up, 1.8 times per year (less frequently) for patients who qualified for monitoring every 6 months, and 3.8 times per year (less frequently) for patients who qualified for monitoring every 3 months.

Fifteen adverse events were identified, 2 of which were thrombotic and 11 of which were related to bleeding. There was no difference in the frequency of adverse events between the patients categorized as being on appropriate versus inappropriate DOAC therapy (66.7% vs 33.3%, $P = .18$). The majority of patients (65.9%) were on at least one medication that increased the risk of bleeding (Table 2). It should be noted that 108 (55.6%) patients were also prescribed an antiplatelet. While only 55 patients had a documented history of coronary artery disease, it is possible that patients were taking aspirin if they had diabetes or a history of stroke/transient ischemic attack.

Discussion

We found that DOAC prescribing practices at UF Health Internal Medicine are significantly better than published data from smaller, single-system sites. However, we also found that 1 in 5 patients is inappropriately prescribed a DOAC, which is worse than data published by the VA. It is important to note that the VA publishes Criteria for Use to guide practitioners when initiating therapy with a DOAC. In addition, many VA medical centers require clinical pharmacist approval prior to DOAC initiation. Theoretically, both of these practices may lead to more appropriate DOAC prescribing. Although UF Health Internal Medicine is much different than a VA practice setting, an important similarity is the presence of a clinical pharmacist.

The most common error identified was inappropriate DOAC dose. Despite the frequent serum creatinine laboratory tests that were obtained, DOAC dose adjustments were not made based on these results. This might be because renal function was being assessed frequently for reasons other than anticoagulation monitoring, and the patient's DOAC regimen was not being reviewed when new laboratory results were available. In addition, laboratory tests could have been ordered by other physicians, rather than the patient's primary provider, in which case the primary care provider may not have been made aware that new results were available. Although assessment of renal function, liver

Table 3. Appropriate DOAC Prescribing and Baseline Laboratory Tests at DOAC Initiation.

Outcome	Our Study (n = 98)	Simon et al ⁹ (n = 395)
Inappropriate DOAC use according to FDA-approved labeling (P = .0005)	39 (20.1)	154 (39.0)
Inappropriate dose	31 (77.5)	
Inappropriate duration of therapy	3 (7.5)	
Inappropriate indication	6 (15.0)	
Obtained recommended baseline laboratory tests ^a	40 (40.8)	
Metabolic panel (P = .912)	61 (62.2)	247 (63.0)
CBC (P = .876)	54 (55.1)	212 (54.0)
LFTs (P = .003)	45 (45.9)	101 (26.0)

Abbreviations: DOAC, direct oral anticoagulant; FDA, US Food and Drug Administration; CBC, complete blood count; LFT, liver function test.

^aRecommended laboratory tests include metabolic panel, CBC, and LFT.

function, and a complete blood count is recommended prior to initiating a DOAC,⁵ we found that only 40% of patients received all 3 laboratory tests 30 days prior to DOAC initiation. We are unable to conclude if discrepancies in dosing and inconsistency in the ordering of baseline labs was due to a lack of understanding of how to use DOACs, because of the lack of oversight by the prescribing physicians, or missing data. For example, if the DOAC was initiated by an outside provider or cardiologist, we would not have had access to this data.

It is difficult to determine the need for dose adjustments when DOACs are co-administered with interacting medications, given that there is limited prospective data. Only in the edoxaban trials were dose adjustments prospectively studied when patients were prescribed p-gp inhibitors.^{15,16} The dabigatran package insert recommends decreasing the dose to 75 mg twice daily for atrial fibrillation patients with a creatinine clearance between 30 and 50 mL/min who are taking dronedarone or ketoconazole.¹³ In our review, 3 patients met the criteria for the reduced dose of dabigatran based on their renal function and concomitant medications. However, all 3 of these patients remained on dabigatran 150 mg twice daily. In addition, the dose of DOACs for the treatment of acute venous thromboembolism differs from the dosing to prevent venous thromboembolism after orthopedic surgery. We found 2 patients who continued a DOAC longer than recommended after orthopedic surgery because the prescription was improperly renewed by the primary care provider.

It is established that 63% of atrial fibrillation patients also have a valvular abnormality of any kind.¹⁷ Currently, DOACs are only FDA approved for use in patients with non-valvular atrial fibrillation. Nonvalvular atrial fibrillation was interpreted differently in the designs of the different DOAC trials, and due to this variation, it can be difficult to determine which patients are candidates for a DOAC. The American Heart Association defines valvular atrial fibrillation as that which occurs in patients with rheumatic

mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.¹⁸ The Aristotle and Engage AF TIMI 48 trials did not exclude patients with bioprosthetic valves; however, these studies were not powered to assess DOAC efficacy in this specific patient population.^{15,19} In our study, we identified 5 patients who were prescribed a DOAC and had a bioprosthetic valve in the aortic or mitral position.

There was no documentation in the electronic medical record indicating that patients were contacted for follow-up regarding DOAC therapy. Although it has been shown that institutions with structured follow-up and education for patients on DOACs have improved adherence,²⁰ we were unable to assess adherence in this study due to lack of access to refill records. In terms of adverse events, the majority occurred in patients who were prescribed the correct DOAC dose. Overall, the rate of adverse events was low, but it is likely that this is an underestimate due to poor documentation in the electronic medical record.

Although our study was retrospective in nature, it does highlight 3 areas for improvement going forward. First, since DOAC dose adjustments were not made according to laboratory results, it would be reasonable to enroll these patients in the established pharmacist-managed anticoagulation service. In doing so, when labs are drawn, the pharmacist can review results and adjust DOAC doses accordingly. Second, the pharmacist can also reconcile concomitant medications to ensure that the DOAC is prescribed for the correct duration according to the indication. Finally, since we have no way to check adherence, and it is established that adherence to a DOAC is required for efficacy, the pharmacist can confirm that the patient has access to medication.

Conclusions

This study provides insight regarding DOAC prescribing practices in a real-world, outpatient, internal medicine clinic setting. We found that, as compared to previously

published data in similar clinical settings, DOACs are more often prescribed appropriately. However, there remains opportunity for improvement when it comes to DOAC dose adjustment and follow-up.

Authors' Note

Results of this article were presented at the 2016 Florida Residency Conference in Tampa, Florida, May 2016.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Janssen Pharmaceuticals, Inc. Xarelto prescribing information. <https://www.xarelto-us.com/blood-thinner>. Accessed March 8, 2017.
2. Desai NR, Krumme AA, Schneeweiss S, et al. Patterns of initiation of oral anticoagulants in patients with atrial fibrillation- quality and cost implications. *Am J Med*. 2014;127:1075-1082.e1.
3. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease. *Chest*. 2016;149:315-352. doi:10.1016/j.chest.2015.11.026.
4. Portola Pharmaceuticals. Portola Pharmaceuticals receives complete response letter from FDA for biologics license application for AndexXa™ (andexanet alfa) [Press release]. Retrieved from <https://www.portola.com/clinical-development/andexanet-alfa-fxa-inhibitor-antidote/>. Accessed March 8, 2017.
5. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace*. 2015;17:1467-1507.
6. Heart Rhythm Society. NOAC selection and prescribing considerations. http://resources.hrsonline.org/afib-algorithm/afib-algorithm_1.html. Accessed May 10, 2016.
7. ROCKET AF Study Investigators. Rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation: rationale and design of the ROCKET AF study. *Am Heart J*. 2010;159:340-347.e1.
8. Rose AJ, Reisman JI, Allen AL, Miller DR. Potentially inappropriate prescribing of direct-acting oral anticoagulants in the Veterans Health Administration. *Am J Pharm Benefits*. 2016;8(4):e75-80.
9. Simon J, Hawes E, Deyo Z, Bryant Shilliday B. Evaluation of prescribing and patient use of target specific oral anticoagulants in outpatient setting. *J Clin Pharm Ther*. 2015;40(5):525-530.
10. Tellor KB, Patel S, Armbruster AL, Daly MW. Evaluation of the appropriateness of dosing, indication and safety of rivaroxaban in a community hospital. *J Clin Pharm Ther*. 2015;40:447-451.
11. Eliquis (apixaban) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2014.
12. Savaysa (edoxaban) [package insert]. Parsippany, NJ: Daiichi Sankyo, Inc; 2015.
13. Pradaxa (dabigatran) [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2013.
14. Xarelto (rivaroxaban) [package insert]. Gurabo, PR: Janssen Ortho, LLC; 2014.
15. Giugliano RP, Ruff CT, Braunwald E, et al; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093-2104.
16. The Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369:1406-1415.
17. Lip GY, Laroche C, Dan GA, et al. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EurObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace*. 2014;16:308-319.
18. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:e199-e267.
19. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981-992.
20. Shore S, Carey EP, Turakhia MP, et al. Adherence to dabigatran therapy and longitudinal patient outcomes: insights from the Veterans Health Administration. *Am Heart J*. 2014;167:810-817.