Assessment of Patient Adherence to Direct Oral Anticoagulant vs Warfarin Therapy

Salma I. Patel, MD, MPH; Chad Cherington, MD; Robyn Scherber, MD;
Kathryn Barr, CNP; Ryan McLemore, PhD; Donald E. Morisky, ScD;
Stephen Cha, MS; Farouk Mookadam, MD; and Fadi Shamoun, MD

From the Department of
Sleep Medicine at Mayo Clinic in
Rochester, Minnesota (Dr Patel);
the Division of Hematology
and Medical Oncology
(Dr Cherington), the Division
of Cardiovascular Diseases
(Ms Barr and Drs Mookadam
and Shamoun), and the
Division of Biomedical
Statistics and Informatics
(Dr McLemore and Mr Cha)
at Mayo Clinic in Scottsdale,
Arizona; the Department of
Hematology and Oncology at
Oregon Health and Sciences
University in Portland
(Dr Scherber); and the
Department of Community
Health Sciences at the
University of California, Los
Angeles Fielding School of
Public Health (Dr Morisky).

Address correspondence to
Fadi Shamoun, MD,
Division of Cardiovascular
Diseases, Mayo Clinic,
13400 E Shea Blvd,
Scottsdale, AZ 85259-5452.

E-mail:
shamoun.fadi@mayo.edu

Context: Direct oral anticoagulants (DOACs) may be as effective as, and at times safer than, warfarin. Because DOACs do not require regular serum level monitoring, patients' interaction with the health care system may be reduced. To the authors' knowledge, although studies have evaluated warfarin adherence, few studies have evaluated the real-world adherence to DOACs.

Objective: To evaluate whether a difference exists between medication adherence of patients taking DOACs vs patients taking warfarin.

Methods: The electronic medical records of the Anticoagulation Clinic database at Mayo Clinic in Scottsdale, Arizona, were reviewed. Inclusion criteria were adults taking DOACs and a matching cohort taking warfarin between January 1, 2011, and December 30, 2013. The Morisky Medication Adherence Scale-8 item, a validated medication adherence tool, was used to evaluate adherence in both cohorts, and the qualitative covariates were analyzed using ordinal logistic regression.

Results: Of 324 surveys that were sent, 110 patients (34.0%) responded. Most patients took DOACs for atrial fibrillation, and few took DOACs for venous thromboembolism. Overall, 60 of 66 patients (90.9%) in the DOAC group and 42 of 44 patients (95.5%) in the warfarin group reported medium or high adherence. Difference in adherence scores between the 2 groups was not statistically significant (P=.8).

Conclusion: Similar adherence was noted between DOACs and warfarin regardless of the frequency of serum level monitoring.

J Am Osteopath Assoc. 2017;117(1):7-15
doi:10.7556/jaoa.2017.002

Keywords: apixaban, dabigatran, direct oral anticoagulants, medication adherence, rivaroxaban, warfarin

Direct oral anticoagulants (DOACs), such as apixaban, dabigatran, rivaroxaban, and edoxaban, offer alternatives to warfarin that do not require routine serum level monitoring. Several clinical trials have shown that DOACs are as effective as, and at times safer than, warfarin.[1-12] These medications may not always replace warfarin as first-line therapy because warfarin has an antidote and a method of routine serologic monitoring through the international normalized ratio (INR). However, DOACs have fixed doses that do not change along with vitamin K dietary intake, although sometimes renal function must be monitored. Dabigatran is the only DOAC with an antidote, idaricuzumab, that is approved by the US Food and Drug Administration.[13,14] Antidotes for the other DOACs are currently in clinical trials.[15] Monitoring of serum levels for dabigatran via the hemoclot thrombin inhibitor and ecarin clotting time assays are not widely available.[16]

The INR monitoring required with warfarin therapy enables an interaction between patients and the health care system that may promote warfarin adherence. The International Normalized Ratio Adherence and Genetics study[17,18] looked at factors affecting nonadherence to warfarin among 111 patients and found that the lack of adherence ranged between 20% and 30% during 1 year. Of all patients, 40% were adherent 80% of the time or less, and 15% were adherent 50% of the time or less.[17,18] In general, medication adherence is higher in clinical trials than in everyday use, and still, trials average an adherence rate of 43% to 78%.[19,20] Although studies have evaluated warfarin adherence, to our knowledge, few studies[21,22] have evaluated the real-world adherence to DOACs.

The DOAC trials estimate that warfarin nonadherence ranges from 22% to 58%.[17,18,23-28] This finding is concerning because 34% to 43% of patients taking warfarin have levels outside the therapeutic range.[29,30] Several observational studies have linked a number of risk factors to warfarin nonadherence, including younger age, male sex, lower stroke risk, poor cognitive function, poverty, and poor health literacy.[24,31-34] Physicians can be culpable as well by not following guidelines[35] or by giving alternating doses, which further decreases adherence.[36] In general, patients have a poor knowledge base about taking warfarin.[37]

Several researchers have voiced concern over adherence to DOACs.[38-40] Many of the DOAC clinical trials did not report adherence rates; when reported, the adherence rates were higher than with warfarin.[21,22,41] One retrospective study of 3 centers in Sweden compared the adherence to dabigatran with adherence to warfarin and found that adherence to dabigatran was not notably different from warfarin in regard to safety and efficacy.[42] Another study of adherence based on medication fill dates and the days of supply on pharmacy claims with median follow-up of 1.1 years noted that adherence was slightly higher with DOACs (47.5%) than with warfarin (40.2%).[43]

In the present study, we aimed to retrospectively evaluate adherence using primarily a validated adherence score, the Morisky Medication Adherence Scale-8 item (MMAS-8), among US patients who took DOACs and compare their results with a similar cohort that took warfarin. We hypothesized that more frequent health care visits and acute DOAC monitoring via the INR would increase medication adherence.

Methods

We reviewed electronic medical records in the Anticoagulation Clinic database at Mayo Clinic in Scottsdale, Arizona, to identify all patients who took a DOAC between January 1, 2011, and December 30, 2013. Patients aged 17 years or younger and patients who were pregnant were excluded. An equivalent number of patients who took warfarin were also included for comparison. The project was reviewed and approved by the institutional review board at Mayo Clinic.

A 20-question survey that included the MMAS-8 was mailed to all consecutive patients who took a DOAC or warfarin within this period. Patients were asked to answer multiple-choice questions about what type and duration of anticoagulant medication they were taking, why they were taking this medication, what method they used to remember to take medication, missed dosage, risks and complications, and demographic characteristics. The validated MMAS-8 score was used to evaluate adherence to the medication. Patients are considered to have low adherence with scores less than 6, medium adherence with scores of 6 to 7, and high adherence with a score of 8.[44-46]

The first round of surveys was mailed in July 2014, and the second round was mailed in August 2014. Patients who did not respond via mail were contcted via telephone between September 2014 and January 2015. Survey mailings and telephone interviews were conducted by the Survey Research Center at Mayo Clinic. Patients were also excluded if they declined to participate, could not be reached, were medically unable to complete the survey, did not complete the Health Insurance Portability and Accountability Act of 1996 consent
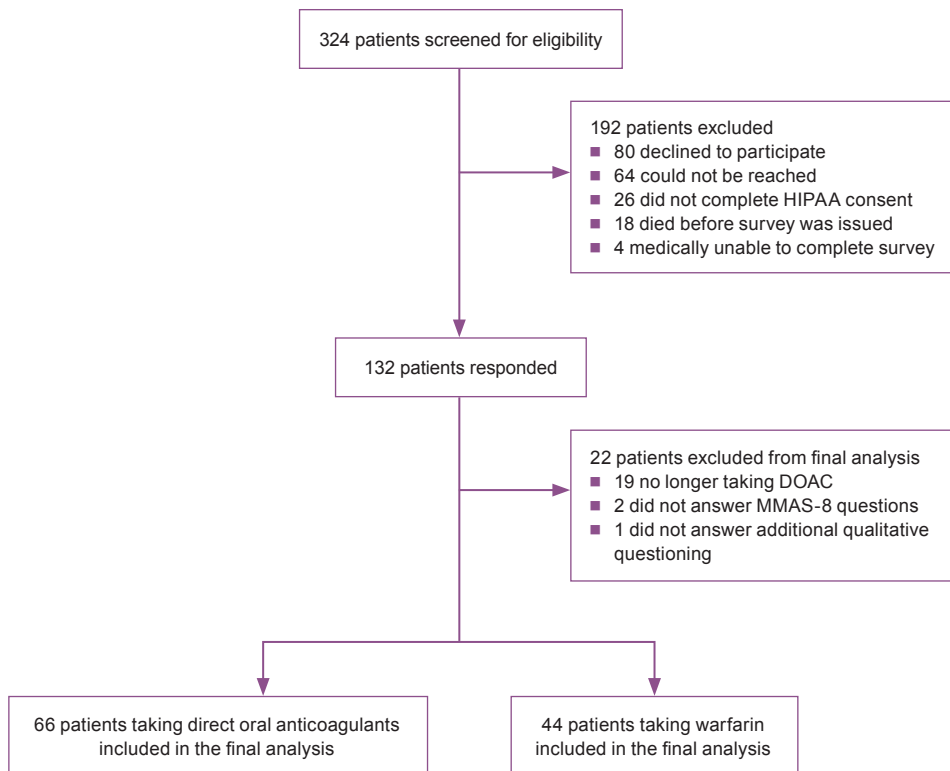
Figure.
Diagram illustrating flow of patients through study. *Abbreviations:* DOAC, direct oral anticoagulant; HIPAA, Health Insurance Portability and Accountability Act of 1996; MMAS-8, Morisky Medication Adherence Scale-8 item.

form, or died before the survey was issued. Further exclusion criteria included patients who no longer took a DOAC and those who did not answer any MMAS-8 questions and additional qualitative reasoning.

Data were summarized by frequency and analyzed with the Fisher exact test, unpaired t test, or Pearson χ^2 test, as appropriate. Multivariate regression was performed to determine whether type of anticoagulant and cost, depression, anxiety, complexity in tracking medications, delay in prescription refills, or intentional stopping of medication had affected adherence. These data were synthesized to help determine medication adherence, education, and complications of DOAC use. A P value of

less than .05 was considered statistically significant. All statistical analyses were performed in SAS software (version 9.4; SAS Institute, Inc).

Results

A total of 324 patients were identified who were taking DOACs (*Figure*). Of the 324 patients, 192 (59.3%) were excluded. Of the 132 patients who responded, 19 (14.4%) were no longer taking DOAC, 2 (1.5%) did not answer any MMAS-8 questions, and 1 (0.7%) did not answer the additional qualitative questioning, leaving 110 patients for further data analysis. Of the 110 study

patients, 66 (60%) were taking a DOAC and 44 (40%) were taking warfarin. Most patients had been taking an anticoagulant for more than 3 months, with 63 of 66 in the DOAC group (95.5%) and 43 of 44 in the warfarin group (97.7%). Patients who took a DOAC had a mean (SD) age of 70.1 (8.6) years, and 47 (71.2%) were men. Patients who took warfarin had a mean (SD) age of 68.3 (10.3) years, and 26 (59.1%) were men. No difference in adherence was found regarding age (P=.33), sex (P=.21), or prescribed oral anticoagulant medication (P=.65) (*Table 1*).

Between the DOAC group and the warfarin group, no difference was found in techniques patients used to remind themselves to take their medication. In both groups, most patients used a pill sorting box or remembered to take medication without a reminder (*Table 1*). Overall, 58 of 66 patients (87.9%) in the DOAC group and 42 of 44 patients (95.5%) in the warfarin group showed good health literacy when asked if they knew what to do if they missed a dose. Most patients said they were aware of the risks of missing a dose and cited the most frequent reasons for missed medications as "sometimes forgetting" (25 [22.7%]) and "feeling hassled" (13 [11.8%]). In contrast, 91 patients (82.7%) reported never or rarely having difficulty remembering to take their medication; 15 (13.6%), difficulty once in a while; and 3 (2.7%), sometimes having difficulty. One patient reported usually having difficulty remembering his or her medications. Of 110 patients, 15 (13.6%) reported living alone, 108 (98.2%) reported a high school education or higher, and 92 (83.6%) reported a combined annual income of more than $35,000.

Atrial fibrillation was the most common reason for taking an anticoagulant (82 [74.5%]). Notably more patients were taking a DOAC (56 of 66 [84.8%]) than warfarin (26 of 44 [59.0%]) for atrial fibrillation (P=.003). Overall, 8 of 66 patients (12.1%) were taking a DOAC for deep vein thrombosis compared with 10 of 44 (22.7%) who were taking warfarin (P=.19). In addition, 4 of 66 patients (6.0%) were taking a DOAC for pulmonary embolism compared with 10 of 44 (22.7%) who were taking warfarin.

Thirty-five of 66 patients (53%) in the DOAC group and 14 of 44 patients (32%) in the warfarin group were taking an additional anticoagulant. The most common additional medication was aspirin, followed by clopidogrel, ticagrelor, and dipyridamole (*Table 1*). The survey asked about bleeding complications but not whether dual or triple anticoagulants were taken during these events.

Medication Adherence

The DOAC group showed high adherence, which could be explained by patients' perception of the importance of anticoagulants compared with other medications, such as those for hypertension or diabetes. The difference between the DOAC and warfarin groups' adherence ratings was not statistically significant (P=.67) (*Table 2*). No statistical significance was found in adherence scores among the different DOACs (P=.22) (*Table 3*).

Discussion

Osteopathic physicians are trained to consider the whole patient when approaching health care. Medication adherence can play a large role in health outcomes and thus should be considered during patient education. Most patients in the present study who took DOACs had adherence scores similar to patients taking warfarin. No statistically significant difference was found between the 2 groups in adherence scores with an effect size or mean of 0.54. No statistically significant difference in adherence was found regarding age, sex, prescribed oral anticoagulant medication, method of reminder, addition of anticoagulant, bleeding complications, and DOAC education (ie, knowledge of missed dose). Most of the patients in the present study had a high school education or higher, knew what to do when they missed their medications, and had a mean combined income level of $35,000, all of which have been shown to positively affect adherence levels.[47]

Notably more patients took DOACs for atrial fibrillation and more patients took warfarin for pulmonary embolism than for other conditions. Possible explanations include physicians' familiarity with the DOACs and their

Table 1.
Characteristics of Patients Taking Direct Oral Anticoagulants (DOACs) or Warfarin (N=110)[a]

Variable	DOAC (n=66)	Warfarin (n=44)	P Value[b]
Age, y, mean (SD)	70.1 (8.64)	68.3 (10.29)	.33[c]
Sex, Men	47 (71)	26 (58)	.21
Taking This Medication for >3 mo	63 (97)	43 (98)	.65
Reason for Taking Medication			
Atrial fibrillation	56 (85)	26 (59)	.003
Deep vein thrombosis	8 (12)	10 (23)	.19
Pulmonary embolism	4 (6)	10 (23)	.017
Prevention of blood clot from hip or knee surgery	0	0	
Other	13 (20)	18 (41)	.019
Time Took Medication, %			.25[d]
>90	61 (94)	44 (100)	
70-89	3 (5)	0	
50-69	1 (2)	0	
Method Used to Remember to Take Medication			
Alarm or timer	5 (8)	4 (9)	>.99
Written reminder	0	1 (2)	.40
Pill sorting box	41 (62)	24 (55)	.44
I just remember to take	30 (45)	21 (48)	.85
Someone keeps track for me	4 (6)	3 (7)	>.99
Decided to stop taking	4 (7)	1 (2)	.20
"Do you know what to do if you miss a dose?"			.39[d]
No	3 (5)	1 (2)	
Yes	58 (88)	42 (95)	
Don't know	5 (8)	1 (2)	
Aware of Risk of Missing a Dose	65 (98)	42 (95)	.56
Complications	8 (12)	9 (21)	.29
Deep vein thrombosis	0	1 (2)	.40
Stroke	0	0	
Gastrointestinal bleeding	1 (2)	2 (5)	.56
Coughing up any blood	0	0	
Other	7 (11)	9 (20)	.17
"Do you also take any of the following medications?"			
Aspirin	18 (28)	11 (26)	.83
Clopidogrel	4 (7)	1 (2)	.65
Ticagrelor	4 (7)	0	.15
Dipyridamole	4 (7)	0	.15
Other	5 (9)	2 (5)	.70

[a] Data are given as No. (%) unless otherwise indicated.
[b] P values were calculated using the Fisher exact test unless otherwise indicated.
[c] P value was calculated using the unpaired t test.
[d] P values were calculated using the Pearson χ² test.

Table 2.
Adherence Rating and MMAS-8 Scores
of Patients Taking a DOAC vs Warfarin (N=110)

Variable	DOAC (n=66)	Warfarin (n=44)	P Value
Adherence Rating, No. (%)			.67
Low adherence	6 (9)	2 (5)	
Medium adherence	21 (32)	15 (34)	
High adherence	39 (59)	27 (61)	
MMAS-8 Score, mean (SD)	7.38 (0.90)	7.43 (0.80)	.80

Abbreviations: DOAC, direct oral anticoaguant; MMAS-8, Morisky Medication Adherence Scale-8 item.

indication or comfort level prescribing them to manage atrial fibrillation vs pulmonary embolism. Patients treated for atrial fibrillation are often assigned to long-term anticoagulation therapy, and patients treated for deep vein thrombosis or pulmonary embolism may be taking an anticoagulant on a temporary or a long-term–to-lifelong basis. Lifelong anticoagulation therapy may also have an effect on adherence because the number of patients adhering to medication use has been shown to decrease over time. Osterberg and Blaschke[19] reported reduced adherence after 3 months of anticoagulation.

The present study reported a moderate adherence rate of 32% and 34% in the DOAC and warfarin groups, respectively, and a high adherence rate of 59% and 61%. To the authors' knowledge, no universal standards have been defined for medication adherence, and previous studies have individualized definitions of adherence. Some studies[25,26] have reported rates of 34% to 43% of INR levels outside the normal range. Davis et al[47] used the 4-item MMAS to survey 52 patients at a large inner city hospital and found that more than half of the respondents reported an income less than $10,000. Half of the respondents had adequate adherence, but of these respondents, 73% had poor anticoagulation control, which was arbitrarily defined as less than 70% of INR levels in the therapeutic range. The respondents also had low

health literacy and a lower income, and 65% of patients had been taking warfarin for more than a year; these factors reportedly lead to poor adherence.[19,24] Avila et al[23] also used the 4-item MMAS in Brazil to measure warfarin adherence and found that 39% of patients had high adherence, 58% had medium adherence, and 3% had low adherence. More than 90% of surveyed patients had high and medium adherence, with time taking anticoagulation therapy and medication cost as factors in INR stability.[23] Studies of warfarin using a medication bottle cap that can record occurrence and time of bottle opening and pharmacy refill tracking found nonadherence to be 20% to 21%.[17,27] For DOACs, many trials did not analyze adherence. Two trials of dabigatran reported 94% to 98% adherence,[48,49] and another trial for rivaroxaban reported 94% adherence.[50]

Limitations

The survey in the present study had low rates of participation and recall bias. In the study by Davis et al,[47] patients completed surveys during office visits and had a higher participation rate than the current study's mailing and telephone survey approach. Possible explanations for the current study's low participation include patients' privacy concerns or confusion about the Health Insurance Portability and Accountability Act of 1996 consent form, time commitment, or forgetting to complete the survey in the requested time frame. Our anticoagulation clinic serves an older population (median age, 68-70 years), and some patients have 2 addresses in different climate zones. These factors may explain why 64 patients could not be reached by mail or telephone. In the current study, we measured medication adherence by survey because our population filled their prescriptions at many pharmacies in many locations; thus, the funding and time were limitations for medication refill monitoring.

Conclusion

We found no statistically significant difference between adherence to DOACs and warfarin. Although this study

Table 3.
Adherence Rating and MMAS-8 Scores
of Patients by Specific Anticoagulants (N=110)[a]

Variable	Direct Oral Anticoagulant			Warfarin (n=44)	P Value
	Apixaban (n=7)	Dabigatran (n=31)	Rivaroxaban (n=28)		
Adherence Rating, No. (%)					.22
Low adherence	2 (29)	2 (6)	2 (7)	2 (5)	
Medium adherence	2 (29)	7 (23)	12 (43)	15 (34)	
High adherence	3 (43)	22 (71)	14 (50)	27 (61)	
MMAS-8 Score, mean (SD)	7.07 (1.01)	7.54 (0.78)	7.29 (0.99)	7.43 (0.80)	.50

Abbreviation: MMAS-8, Morisky Medication Adherence Scale-8 item.

was not powered for significance, the small effect size adds weight to this result being generalizable. Overall, our patients' reported adherence rates were higher than those reported in a previous MMAS study[51] on warfarin adherence. We suspect that this difference in adherence rates may be accounted for by differences in health literacy and income levels, as well as duration taking anticoagulant medication.

Author Contributions

All authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; all authors drafted the article or revised it critically for important intellectual content; all authors gave final approval of the version of the article to be published; and all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgments

References

1. Agnelli G, Buller HR, Cohen A, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808. doi:10.1056/NEJMoa1302507

2. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med.* 2010;363(26): 2499-2510. doi:10.1056/NEJMoa1007903

3. Connolly SJ, Eikelboom J, Joyner C, et al; AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med.* 2011;364(9):806-817. doi:10.1056/NEJMoa1007432

4. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361(12):1139-1151. doi:10.1056/NEJMoa0905561

5. Eriksson BI, Borris LC, Friedman RJ, et al; RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med.* 2008;358(26):2765-2775. doi:10.1056/NEJMoa0800374

6. Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(11):981-992. doi:10.1056/NEJMoa1107039

7. Kakkar AK, Brenner B, Dahl OE, et al; RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet.* 2008;372(9632):31-39. doi:10.1016/S0140-6736(08)60880-6

8. Lassen MR, Ageno W, Borris LC, et al; RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med.* 2008;358(26):2776-2786. doi:10.1056/NEJMoa076016

9. Lassen MR, Gallus A, Raskob GE, et al; ADVANCE-3 Investigators. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med*. 2010;363(26):2487-2498. doi:10.1056/NEJMoa1006885

10. Lassen MR, Raskob GE, Gallus et al; ADVANCE-2 Investigators. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet*. 2010;375(9717):807-815. doi:10.1016/S0140-6736(09)62125-5

11. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med*. 2009;361(6):594-604. doi:10.1056/NEJMoa0810773

12. Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891. doi:10.1056/NEJMoa1009638

13. Pollack CV Jr, Reilly PA, Bernstein R, et al. Design and rationale for RE-VERSE AD: a phase 3 study of idarucizumab, a specific reversal agent for dabigatran. *Thromb Haemost*. 2015;114(1):198-205. doi:10.1160/TH15-03-0192

14. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373(6):511-520. doi:10.1056/NEJMoa1502000

15. Connors JM. Antidote for factor Xa anticoagulants. *N Engl J Med*. 2015;373(25):2471-2472. doi:10.1056/NEJMe1513258

16. Skeppholm M, Hjemdahl P, Antovic JP, et al. On the monitoring of dabigatran treatment in "real life" patients with atrial fibrillation. *Thromb Res*. 2014;134(4):783-789. doi:10.1016/j.thromres.2014.06.016

17. Kimmel SE, Chen Z, Price M, et al. The influence of patient adherence on anticoagulation control with warfarin: results from the International Normalized Ratio Adherence and Genetics (IN-RANGE) Study. *Arch Intern Med*. 2007;167(3):229-235.

18. Parker CS, Chen Z, Price M, et al. Adherence to warfarin assessed by electronic pill caps, clinician assessment, and patient reports: results from the IN-RANGE study. *J Gen Intern Med*. 2007;22(9):1254-1259.

19. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353(5):487-497.

20. Rosenman M, Simon T, Teal E, McGuire P, Jackson J, Tierney W. Atrial fibrillation and warfarin: time in therapeutic range-an electronic medical record system study of real-world practice [abstract]. *Circulation*. 2009;120(18 suppl 2):S521.

21. Yao X, Abraham NS, Alexander GC, et al. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. *J Am Heart Assoc*. 2016;5(2). doi:10.1161/JAHA.115.003074

22. Thorne K, Jayathissa S, Dee S, et al. Adherence and outcomes of patients prescribed dabigatran (Pradaxa) in routine clinical practice. *Intern Med J*. 2014;44(3):261-265. doi:10.1111/imj.12370

23. Avila CW, Aliti GB, Feijó MK, Rabelo ER. Pharmacological adherence to oral anticoagulant and factors that influence the international normalized ratio stability. *Rev Lat Am Enfermagem*. 2011;19(1):18-25.

24. Kneeland PP, Fang MC. Current issues in patient adherence and persistence: focus on anticoagulants for the treatment and prevention of thromboembolism. *Patient Prefer Adherence*. 2010;4:51-60.

25. Laporte S, Quenet S, Buchmüller-Cordier A, et al. Compliance and stability of INR of two oral anticoagulants with different half-lives: a randomised trial. *Thromb Haemost*. 2003;89(3):458-467.

26. Lavitola Pde L, Sampaio RO, Oliveira WA, et al. Warfarin or aspirin in embolism prevention in patients with mitral valvulopathy and atrial fibrillation. *Arq Bras Cardiol*. 2010;95(6):749-755.

27. Orensky IA, Holdford DA. Predictors of noncompliance with warfarin therapy in an outpatient anticoagulation clinic. *Pharmacotherapy*. 2005;25(12):1801-1808.

28. van der Meer FJ, Briët E, Vandenbroucke JP, Srámek DI, Versluijs MH, Rosendaal FR. The role of compliance as a cause of instability in oral anticoagulant therapy. *Br J Haematol*. 1997;98(4):893-900.

29. Skolarus LE, Morgenstern LB, Froehlich JB, Lisabeth LD, Brown DL. Guideline-discordant periprocedural interruptions in warfarin therapy. *Circ Cardiovasc Qual Outcomes*. 2011;4(2):206-210. doi:10.1161/CIRCOUTCOMES.110.959551

30. van Walraven C, Jennings A, Oake N, Fergusson D, Forster AJ. Effect of study setting on anticoagulation control: a systematic review and metaregression. *Chest*. 2006;129(5):1155-1166.

31. Arnsten JH, Gelfand JM, Singer DE. Determinants of compliance with anticoagulation: a case-control study. *Am J Med*. 1997;103(1):11-17.

32. Estrada CA, Martin-Hryniewicz M, Peek BT, Collins C, Byrd JC. Literacy and numeracy skills and anticoagulation control. *Am J Med Sci*. 2004;328(2):88-93.

33. Platt AB, Localio AR, Brensinger CM, et al. Risk factors for nonadherence to warfarin: results from the IN-RANGE study. *Pharmacoepidemiol Drug Saf*. 2008;17(9):853-860. doi:10.1002/pds.1556

34. Seliverstov I. Practical management approaches to anticoagulation non-compliance, health literacy, and limited English proficiency in the outpatient clinic setting. *J Thromb Thrombolysis*. 2011;31(3):321-325. doi:10.1007/s11239-011-0560-2

35. Ganz DA, Glynn RJ, Mogun H, Knight EL, Bohn RL, Avorn J. Adherence to guidelines for oral anticoagulation after venous thrombosis and pulmonary embolism. *J Gen Intern Med*. 2000;15(11):776-781.

36. Hixson-Wallace JA, Dotson JB, Blakey SA. Effect of regimen complexity on patient satisfaction and compliance with warfarin therapy. *Clin Appl Thromb Hemost*. 2001;7(1):33-37.

37. Smith MB, Christensen N, Wang S, et al. Warfarin knowledge in patients with atrial fibrillation: implications for safety, efficacy,

and education strategies. *Cardiology*. 2010;116(1):61-69. doi:10.1159/000314936

38. Bellamy L, Rosencher N, Eriksson B. Adherence to a new oral anticoagulant treatment prescription: dabigatran etexilate. *Patient Prefer Adherence*. 2009;3:173-177.

39. Salmela B, Joutsi-Korhonen L, Armstrong E, Lassila R. Active online assessment of patients using new oral anticoagulants: bleeding risk, compliance, and coagulation analysis. *Semin Thromb Hemost*. 2012;38(1):23-30. doi:10.1055/s-0031-1300948

40. Testa S, Paoletti O, Zimmermann A, Bassi L, Zambelli S, Cancellieri E. The role of anticoagulation clinics in the era of new oral anticoagulants. *Thrombosis*. 2012;2012:835356. doi:10.1155/2012/835356

41. Rodriguez RA, Carrier M, Wells PS. Non-adherence to new oral anticoagulants: a reason for concern during long-term anticoagulation? *J Thromb Haemost*. 2013;11(2):390-394. doi:10.1111/jth.12086

42. Labaf A, Carlwe M, Svensson PJ. Efficacy and safety of novel oral anticoagulants in clinical practice: a report from three centers in Sweden. *Thromb J*. 2014;12(1):29. doi:10.1186/s12959-014-0029-6

43. Yao X, Abraham NS, Alexander GC, et al. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. *J Am Heart Assoc*. 2016;5(2):e003074. doi:10.1161/JAHA.115.003074

44. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens (Greenwich)*. 2008;10(5):348-354.

45. Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: response to authors. *J Clin Epidemiol*. 2011;64(3):255-257. doi:10.1016/j.jclinepi.2010.09.002

46. Krousel-Wood M, Islam T, Webber LS, Re RN, Morisky DE, Muntner P. New medication adherence scale versus pharmacy fill rates in seniors with hypertension. *Am J Manag Care*. 2009;15(1):59-66.

47. Davis NJ, Billett HH, Cohen HW, Arnsten JH. Impact of adherence, knowledge, and quality of life on anticoagulation control. *Ann Pharmacother*. 2005;39(4):632-636.

48. Schulman S, Kearon C, Kakkar AK, et al; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361(24):2342-2352. doi:10.1056/NEJMoa0906598

49. 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(6):810-817. doi:10.1016/j.ahj.2014.03.023

50. EINSTEIN-PE Investigators, Büller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366(14):1287-1297. doi:10.1056/NEJMoa1113572

51. Skeppholm M, Friberg L. Adherence to warfarin treatment among patients with atrial fibrillation. *Clin Res Cardiol*. 2014;103(12):998-1005. doi:10.1007/s00392-014-0742-y

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