Supplementary Online Content

Shore S. Ho PM, Lambert-Kerzner A, et al. Site-Level Variation and Associated Strategies for Improving Adherence to Dabigatran. *JAMA*. doi: 10.1001/jama.2015.2761

This supplementary material has been provided by the authors to give readers additional information about their work.

eMETHODS

Study design, site selection

At present, there is no uniformity in assessing or enforcing adherence to Target Specific Oral Anticoagulants (TSOAC) within the VHA. However, the Veterans Health Administration (VHA) Pharmacy Benefits Management Services (PBM) provides clinical guidance on TSOAC use. National VHA criteria for TSOAC use are in place and aim to select patients for safe and appropriate use of these drugs based on currently available evidence.[1] The criteria for use contain inclusion and exclusion criteria as well as issues for consideration and are designed to meet the needs of the majority of patients, though exceptions are evaluated at the local level according to usual Pharmacy and Therapeutics processes. In the absence of evidence informing on the optimal management of patients on TSOACs, VHA PBM also developed guidance for oversight and monitoring that includes recommendations for providing specialized patient education, conducting baseline and follow-up laboratory testing, and assessing for medication adherence and side-effects during follow-up.[2] The monitoring guidance is flexible to allow for local adaptation and is not strictly enforced.

Accordingly, we performed a mixed methods study qualitatively examining site practices followed by quantitative estimation of site-level adherence and the association between site practices and adherence. We included VHA sites with $\geq$ 20 patients filling a dabigatran prescription of at least 30 days at a VHA pharmacy between October-1-2010 and September-30-2012 with at least 30 days of follow-up (Figure 1).

Purposive and snowball sampling techniques were utilized at eligible sites to obtain data for the qualitative portion of this study. Purposive sampling is a form of non-probability sampling where participants meeting a certain criteria are approached by the interviewer and snowball sampling is achieved by asking a participant to suggest other appropriate participants.[3-5] Outpatient and anticoagulation clinic supervisors were initially contacted by e-mail to explain goals and procedures of this study and request participation. Clinic supervisors provided contact information for persons in the hospital deemed to be most appropriate for the inquiry, who were then interviewed. Based on responses gathered from our qualitative inquiries, site-level strategies aimed at improving TSOAC adherence were identified and subsequently analyzed quantitatively to examine if they were statistically associated with improved adherence. The Colorado Multiple Institutional Review Board approved this study, and waiver of informed patient consent was granted.

Interview process and data collection

We used semi-structured telephone interviews composed of open-ended questions with specific probes asking about all procedures involved in managing dabigatran. Similar methods have been previously used in other studies to gain insights into site-level practices for observed variation in care provided.[6,7] Interview questions were developed after obtaining input from a multidisciplinary group of cardiologists, pharmacists, internists, public health professionals and mixed methodologists. This process also involved pretesting the interview guide among pharmacists involved at the local VHA

site to formally obtain input and further refine it. Supplemental Table 1 details the interview guide used.

To ensure consistency, all interviews were performed by a single, trained interviewer (SS) and audiotaped after obtaining participant consent. Furthermore, to maximize the likelihood of soliciting candid and unbiased feedback, participants were not asked for identifying information or notified about their site's performance with respect to patient adherence to dabigatran. All taped interviews were transcribed by a professional transcriptionist and subsequently analyzed.

Qualitative analysis plan

We used an iterative, inductive and deductive toolkit of analytical strategies drawing primarily on content analysis methodology.[8] Analysis began with in-depth reading of interviews followed by initial inductive coding. We began with identifying codes as they emerged and added codes deductively based on interview questions and a prior knowledge of the process.[9]

After initial coding was completed, analysts compared and combined codes. The analytic team (SS, ALK, PMH) reviewed documents to clarify code interpretation and came to consensus when disagreements occurred thus defining the initial codebook. Emergent codes were added to the codebook throughout this analysis. We then applied resulting shared set of codes to remaining transcripts and jointly identified emergent themes through inter-subjective agreement. This allowed researchers to confirm, refute or expand findings. An inter-coder agreement based on coding passages the same way with similar codes was assessed with an agreement of 80%. Preliminary results were reviewed

by members of the multidisciplinary research team comprised of members with clinical, methodological and public health backgrounds to assess their representativeness, thoroughness and comprehensiveness. The analytic team met weekly to discuss interviews, codes, memos, themes and emerging conclusions. An audit trail was created that documented all analytic procedures and decisions. Finally, we triangulated results from qualitative findings with quantitative data.[6]

Triangulation is a method to check and establish validity of the study by analyzing the research question from multiple perspectives.[4-6] We performed investigator triangulation that refers to corroboration of how qualitative data is interpreted by evaluation of the same data by multiple investigators. In our study, inter-investigator agreement during analysis of data obtained from our qualitative inquiry was over 80%. In addition we performed methodological triangulation by assessing if our qualitative data collection resulted in a quantitatively significant result.

Quantitative Data source

Detailed data on patient demographics, vital status, date, time and location of service, diagnoses and procedures of all inpatient and outpatient visits within VHA or at non-VHA facilities that were paid by the VHA as well as pharmacy data on dabigatran utilization including prescription fill and cancel dates, amount dispensed expressed as days supplied were obtained from VHA Corporate Data Warehouse (CDW); a previously described national data repository that has been used in other studies as well.[10-12] Since VHA has a closed pharmacy system with a fixed, non-tiered copayment, patients have

strong financial incentives to fill prescriptions within the system, particularly for newer therapies that have higher copayments in private sector.

Variables

Outcome variable – Adherence measured as proportion of days covered (PDC)

Primary outcome was patient adherence to dabigatran, measured as proportion of days covered (PDC). Consistent with prior literature, PDC was defined as total number of non-hospitalized days in which dabigatran was supplied divided by observation time (supplemental figure 1). Number of outpatient days supplied for dabigatran was determined from prescription fill dates and number of pills dispensed. The observation interval began from day of first prescription fill. If outpatient dabigatran supply was interrupted secondary to hospitalization for any cause, duration of inpatient stay was excluded from both the numerator and denominator but resumed after discharge. Data was also gathered on non-VHA hospitalizations paid for by the VHA. We also accounted for any provider prescription cancellation orders by excluding all days after the cancel date from our PDC calculation. Pre-determined end-points for calculation of PDC included death, transition to warfarin or end of study period. Consistent with prior literature and on-treatment analysis of the RE-LY trial, patients with PDC $\geq$80% were classified as adherent.[13-15]

We used refill data in our assessment of adherence as laboratory tests for dabigatran levels are not available and other surveillance measures such as electronic monitors recording bottle opening are not readily feasible.[15,16] Moreover, refill compliance has been shown to be an accurate marker of patient adherence in closed pharmacy systems

such as the VHA when measured at multiple points in time, correlating with other adherence measures such as drug blood levels. Therefore our estimates of refill adherence are more specific than prior measures. Additionally, any errors in estimation of duration of therapy would provide more conservative adherence estimates and would apply to all sites universally.

Covariates

Demographic covariates included age, sex and race. Race was obtained by self-report and included since previous studies have shown racial variation in medication adherence.[17] Clinical covariates included hypertension, diabetes mellitus, congestive heart failure, myocardial infarction, stroke, chronic kidney disease, chronic liver disease, peripheral arterial disease, bleeding requiring hospitalization in the year prior to dabigatran initiation, depression, alcohol and drug abuse. Treatment covariates included warfarin use in 100 days preceding dabigatran initiation and concomitant clopidogrel use. Site-level covariates included location (northeast, south, midwest or west), number of patients on dabigatran, academic status (defined by affiliation with an internal medicine residency program), median household income within the site's county (obtained from U.S. Census Bureau, 2012)[18], and proportion of urban patients within the site.

References:

1. Target Specific Oral Anticoagulants (TSOACs) Criteria for Use for Use for Stroke Prevention in Nonvalvular Atrial Fibrillation. Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives, Veterans Health Administration, Department of Veterans Affairs. January 2014; http://www.pbm.va.gov/PBM/clinicalguidance/criteriaforuse/Anticoagulants_Target_Specific_Oral_TSOACs_CFU_and_Algorithm_for_Nonvalvular_Atrial_Fibrillation_Rev_Dec_2014.pdf. Accessed January 11, 2015.
2. Guidance for the Oversight and Monitoring of Dabigatran. Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives, Veterans Health Administration, Department of Veterans Affairs. 2011; http://vaww.national.cmop.va.gov/PBM/Clinical Guidance/Clinical Recommendations/Dabigatran Monitoring and Oversight Guidance.doc. Accessed December, 2014.
3. Barbour RS. Checklists for improving rigour in qualitative research: a case of the tail wagging the dog? *Bmj.* May 5 2001;322(7294):1115-1117.
4. Giacomini MK, Cook DJ. Users' guides to the medical literature: XXIII. Qualitative research in health care A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA : the journal of the American Medical Association.* Jul 19 2000;284(3):357-362.
5. Patton MQ. *Qualitative evaluation and Research Methods.* London, England: Sage Publications; 1990.
6. Curry LA, Nembhard IM, Bradley EH. Qualitative and mixed methods provide unique contributions to outcomes research. *Circulation.* Mar 17 2009;119(10):1442-1452.
7. Bradley EH, Holmboe ES, Mattera JA, Roumanis SA, Radford MJ, Krumholz HM. A qualitative study of increasing beta-blocker use after myocardial infarction: Why do some hospitals succeed? *JAMA : the journal of the American Medical Association.* May 23-30 2001;285(20):2604-2611.
8. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse education today.* Feb 2004;24(2):105-112.
9. An overview of content analysis. Practical Assessment, Research and Evaluation [website]. Available: http://PAREonline.net/getvn.asp?v=7&n=17. Accessed January 20, 2014.
10. Fihn SD, Francis J, Clancy C, et al. Insights from advanced analytics at the Veterans Health Administration. *Health affairs.* Jul 2014;33(7):1203-1211.
11. http://www.hsrd.research.va.gov/for_researchers/vinci/cdw.cfm. Accessed November 12, 2014.
12. Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA : the journal of the American Medical Association.* Nov 6 2013;310(17):1829-1836.

13. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation.* Jun 16 2009;119(23):3028-3035.
14. Advisory Committee Briefing Document. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM226009.pdf. Accessed November 12, 2014.
15. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *Journal of clinical epidemiology.* Jan 1997;50(1):105-116.
16. Gulseth MP, Wittkowsky AK, Fanikos J, Spinler SA, Dager WE, Nutescu EA. Dabigatran etexilate in clinical practice: confronting challenges to improve safety and effectiveness. *Pharmacotherapy.* Dec 2011;31(12):1232-1249.
17. Charles H, Good CB, Hanusa BH, Chang CC, Whittle J. Racial differences in adherence to cardiac medications. *Journal of the National Medical Association.* Jan 2003;95(1):17-27.
18. U.S. Census Bureau. (2012). Small area income and poverty estimates: State and county estimates for 2012. December 18, 2014. Available at: https://www.census.gov/did/www/saipe/data/statecounty/data/2012.html.

eTable 1. omponents of the ualitati e tool- it

1. Has adherence to dabigatran among patients been of concern to you and why or why not?
2. Can you describe what happens after a clinician orders dabigatran for a patient Specific probes if not answered : - Parameters assessed prior to dabigatran initiation? Does it include adherence to other medications and how is this determined? - Is initial education provided before dispensing the medication for the first time?
3. Are there practices in place to provide dedicated follow-up to patients on dabigatran and can you describe them in detail?
Specific probes if not answered: - Who is involved in following-up these patients? - Frequency and duration of follow-up - How are patients contacted? - Since when have these patients been followed-up? - Are all patients on dabigatran followed-up? - What is assessed during these visits? Is education re-inforced? - What happens if patients are identified as non-adherent? - Are practices centralized or do community based outpatient clinics have different policies?
4. Are there any protocols in place to address questions patients on dabigatran might have regarding the medication and could you describe them?

Specific probes if not answered:

- Who does the patient contact (anticoagulation clinic/ outpatient pharmact/ designated RN/ clinician) and how do they contact them?

5. In your experience, what aspects of follow-up care have worked well in ensuring patients are adherent to dabigatran and why?

6. What in your opinion would help improve patient adherence to dabigatran further and why?

7. In your opinion should patients on dabigatran be provided dedicated follow-up and why? If yes, how long should it continue for?

8. Should the anticoagulation clinic be involved in managing these patients?

eTable 2. Indications and contra-indications for use of dabigatran

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Indication for Dabigatran
• Diagnosis of non-valvular atrial fibrillation (AF) with AF documented by electrocardiogram • Presence of one additional risk factor for stroke (CHADS2 or CHA2DS2VASc) score ≥1 • Creatinine Clearance ≥30mL/min • No anemia or thrombocytopenia
Contra-indications for dabigatran use
• History of valvular heart disease (prosthetic heart valve or hemodynamically relevant valve disease) • Stroke in previous 2 weeks or severely disabling stroke in 6 months • Co-existing alternative anticoagulation indication (thrombo-embolic disease) • Active infection endocarditis • Active liver disease • Concomitant use of P-glycoprotein inducers • Creatinine clearance <30 mL/min • Creatinine clearance 30-50 mL/min with use of dronedarone or systemic ketoconazole • Hypersensitivity to dabigatran • Active pathological bleeding • Pregnancy

eTable 3. aseline characteristics of stud population and stud sites stratified b site performance

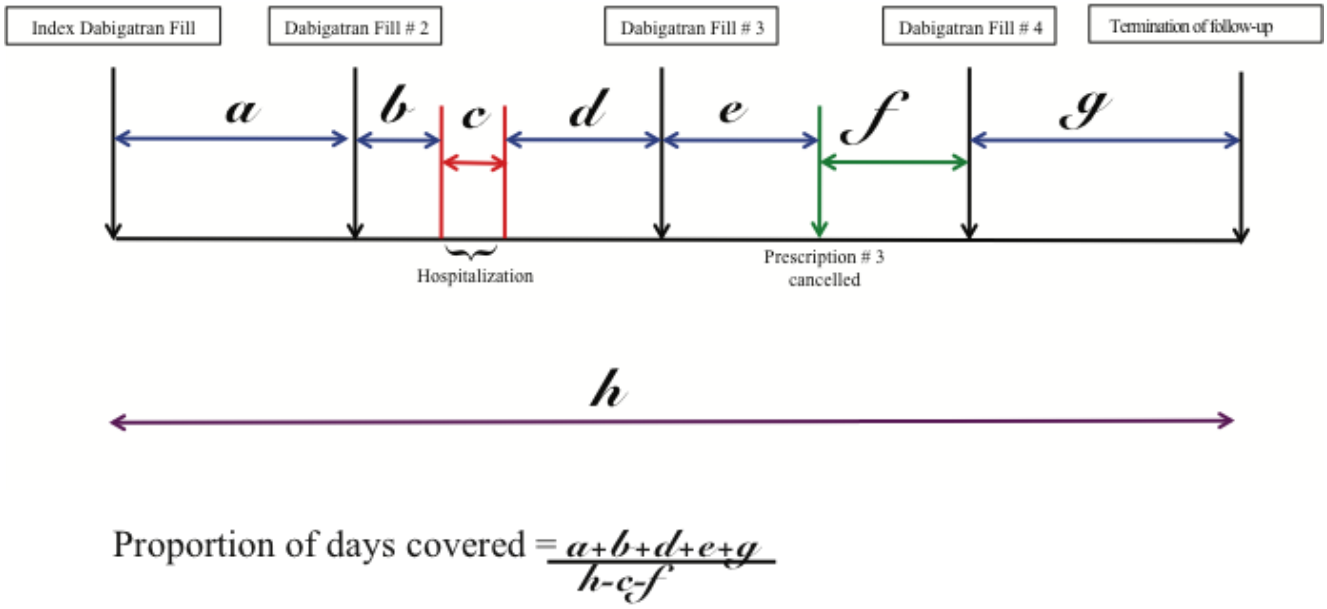
Characteristic	Participating sites (n=41 sites with 2,985 patients)	Non-participating sites (n=25 sites with 1,878 patients)	P value
Patient characteristics			
Age, years (mean ± SD)	70.8 ± 9.6	72.1 ± 9.9	<0.001
Male sex, n(%)	2,933 (98.3)	1,745 (98.1)	0.86
Race			0.54
White	2,471 (82.8)	1,419 (79.8)	
Other	300 (10.1)	184 (10.3)	
$CHADS_2$ score, median (IQR)	2 (2,3)	2 (2,3)	0.80
CHA_2DS_2VASc score, median (IQR)	3 (2,4)	3 (2,4)	0.39
Hypertension, n(%)	2,655 (88.9)	1,548 (87.1)	0.06
Diabetes Mellitus, n(%)	1,304 (43.7)	740 (41.6)	0.17
Congestive heart failure, n(%)	982 (32.9)	574 (32.3)	0.69
Prior myocardial infarction, n(%)	357 (12.0)	264 (14.8)	0.01
Prior stroke, n(%)	607 (20.3)	347 (19.5)	0.52
Chronic kidney disease, n(%)	363 (12.2)	232 (13.0)	0.40
Chronic liver disease, n(%)	117 (3.9)	45 (2.5)	0.01
Peripheral arterial disease, n(%)	552 (18.5)	296 (16.6)	0.12
Bleeding hospitalization, n(%)	251 (8.4)	143 (8.0)	0.70
Depression, n(%)	827 (27.7)	468 (26.3)	0.32
Alcohol abuse, n(%)	400 (13.4)	219 (12.3)	0.30
Drug abuse, n(%)	162 (5.4)	104 (5.8)	0.58

Previous warfarin use, n(%)	1,683 (56.4)	835 (47.0)	<0.001
Clopidogrel use, n(%)	150 (5.0)	109 (6.1)	0.12
	Site characteristics		
Patients per hospital, median (min, max)	53 (20, 269)	47 (21, 280)	0.92
Region, n(%)			0.34
Northeast	3 (7.3)	5 (20.0)	
South	18 (43.9)	10 (40.0)	
Midwest	12 (29.3)	4 (16.0)	
West	8 (19.5)	6 (24.0)	
Academic sites, n(%)	41 (100.0)	22 (88.0)	0.02
High performing sites*, n(%)	23 (56.1)	12 (48.0)	0.70

Legend: *Proportion of patients adherent to dabigatran $\geq$ median proportion adherent in this cohort (=74%) $CHADS_2$ score components include congestive heart failure (1 point), hypertension (1 point), age $\geq$75 years (1 point), diabetes mellitus (1 point), prior stroke (2 points); CHA2DS2VASc score components include congestive heart failure (1 point), hypertension (1 point), age $\geq$ 75 years (2 points), diabetes mellitus (1 point), prior stroke (2 points), vascular disease (1 point), age 65-74 years (1 point), female sex (1 point); IQR – interquartile range; max – maximum; min – minimum; SD – standard deviation.

eFigure. ictorial representation of roportion of a s co ered

calculation



Legend: Time periods labeled a, b, d, e and g represent time during which patient had dabigatran supply. Time period c represents duration of hospitalization and time period f represents duration following physician ordered prescription cancellation. Time period h represents total follow-up duration.