Original Article

New Indications for Dabigatran: A Suggestion from a Drug Use Evaluation Study

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Received: March 2017.
Accepted: July 2017.

ABSTRACT

Objective: Dabigatran etexilate is a novel oral anticoagulant with several advantages over warfarin such as no need for routine monitoring and fewer drug interactions. This drug was added to our hospital's formulary in 2012. The objective of this study was to assess the rational drug use of dabigatran at a large teaching hospital. **Methods:** A prospective cross-sectional study was performed from November to June 2015 at Alzahra teaching hospital, Isfahan, Iran. All patients who received at least one dose of dabigatran were eligible for inclusion. Data were collected on patient demographics, indication, dosing regimen, adverse events, concurrent anticoagulant therapy, and laboratory data (including renal function). **Findings:** A total of sixty patients were included in our study. The majority of patients (n = 40, 66.7%) was prescribed dabigatran for deep vein thrombosis prophylaxis. Only one patient received dabigatran with appropriate indication, dose, and duration. Thirty-six (60%) of our patients had thrombocytopenia at the time of dabigatran initiation. We also detected that ten patients (16.7%) received this drug for heparin-induced thrombocytopenia (HIT). In 32 patients, platelet levels increased after dabigatran initiation. Only seven patients received the appropriate dose of dabigatran (regarding both indication and renal function). **Conclusion:** Unlabeled use and incorrect dosing of dabigatran in this study emphasize the need to develop a hospital protocol for dabigatran use within our facility. We suggest proper education of clinicians about novel drugs, pharmacist interventions, and further studies about the safety and efficacy of dabigatran for the new indication (such as HIT).

Keywords: *Clinical audit, Dabigatran etexilate, drug utilization review*

Introduction

Oral anticoagulants are broadly utilized for long-term prevention and treatment of venous thromboembolism (VTE). Vitamin K antagonists (VKAs) such as warfarin had an essential role in oral anticoagulation treatment for a long time. Frequent blood tests, drug–drug interaction, and drug–food interactions made patient adherence to VKA challenging. Non-Vitamin k anticoagulants (NOACs), which include dabigatran, rivaroxaban, apixaban, and edoxaban designed to overcome the limitation of warfarin.[1] NOACs are at least as effective as warfarin and can be given in fixed dose without routine coagulation monitoring. In addition, as a class, NOACs are connected with significantly less intracranial bleeding than warfarin.[2,3]

In 2010, dabigatran etexilate (Pradaxa®), an oral direct thrombin inhibitor, received US Food and Drug Administration (FDA) approval for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF). Results from the randomized evaluation of long-term anticoagulation therapy trial demonstrated the superiority of dabigatran 150 mg by mouth twice daily, in the reduction of stroke

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How to cite this article: Ashrafi F, Rezaie N, Mousavi S. New indications for dabigatran: A suggestion from a drug use evaluation study. J Res Pharm Pract 2017;6:211-6.

Access this article online

Quick Response Code:

Website: www.jrpp.net

DOI: 10.4103/jrpp.JRPP_17_54

and systemic embolism in patients with NVAF.[4] The incidence of major bleeding was similar between the agents; however, dabigatran demonstrated a lower risk for intracranial bleeding, but with an increased risk for major gastrointestinal (GI) bleeding, compared with warfarin.[4]

Two clinical trials, RE-COVER and RE-COVER II, designed to compare dabigatran with warfarin for the treatment of acute deep vein thrombosis (DVT) and pulmonary embolism (PE). A pooled analysis of the results from 5107 patients in both studies showed that dabigatran maintained noninferiority with respect to the primary outcome (death due to VTE) (hazard ratio [HR]: 1.09, 95% confidence interval [CI]: 0.76–1.57) and no increase in major bleeding.[5,6] Hence, in April 2014, dabigatran received new FDA indications for the treatment of DVT and PE and for the risk reduction of recurrent DVT and PE in previously treated patients. In the RE-SONATE trial, dabigatran was found to be superior to placebo (HR: 0.08, 95% CI: 0.02–0.25) for prevention of recurrent VTE; however, compared to placebo, dabigatran increased the risk of major bleeding.[7]

With everything taken into account, dabigatran provides an effective alternative therapy to warfarin. Dabigatran etexilate is a quickly absorbed prodrug with low bioavailability that is rapidly hydrolyzed into its active form (dabigatran) in blood. Its anticoagulant effect is a result of direct thrombin inhibition of thrombin, which prevents the formation of fibrin.[8] In respect to warfarin, there are few factors that influence the pharmacokinetics and pharmacodynamic of dabigatran. Approximately, 80% of dabigatran excreted renally and required dose reduction for patients with reduced creatinine clearance (CrCl). Both forms of dabigatran (prodrug and active form) lack cytochrome p450 interactions. However, the prodrug dabigatran etexilate is a p-glycoprotein substrate.[9] A little direction has been given on how to address these interactions in practice.

The lack of a reversal agent and the lack of availability of laboratory testing to determine the degree of anticoagulation activity of dabigatran are some of the challenges connected with this drug. Dabigatran has a curvilinear relationship with activated partial thromboplastin time (aPTT), which is not sensitive enough to qualify the degree of anticoagulation. Dabigatran can also falsely elevate prothrombin time (PT) and international normalized ratio (INR), which reduces the clinical utility of these results.[10] Ecarin clotting time and diluted thrombin time provide a more direct measure of anticoagulation, but most laboratories are not adequately equipped to perform these tests.[11,12] Lack of laboratory parameters makes it difficult to manage dabigatran dosage in case of drug interactions or in especial population (e.g., the elderly, obese patients, or those with renal dysfunction). Furthermore, choosing dabigatran as an anticoagulant for acute VTE treatment necessitates a treatment course with a parenteral anticoagulation. Table 1 summarizes dabigatran dosing recommendation.[13]

Dabigatran was added to the Iranian University health system formulary on March 2012. Unfortunately, there is not guidance or order set to initiate therapy with dabigatran. The purpose of this study was to evaluate the use of dabigatran at a large teaching hospital. The primary objective of this medication use evaluation (MUE) was to determine the appropriateness of dabigatran use while also reviewing potential outcomes for safety and effectiveness within a tertiary care hospital.

Table 1: Dabigatran dosing recommendation based on US FDA labeling

Indication	Renal function	Dosage
Reduction in risk of stroke and systemic embolism in nonvalvular AF	CrCl >30 ml/min	150 mg, BID
	CrCl 15-30 ml/min	75 mg, BID
	CrCl <15 ml/min or on dialysis	No recommendation
	CrCl 30-50 mL/min with concomitant use of P-gp inhibitors	Reduce dose to 75 mg BID if given with P-gp inhibitors dronedarone or systemic ketoconazole
	CrCl <30 mL/min with concomitant use of P-gp inhibitors	Avoid coadministration
Treatment of DVT and PE	CrCl >30 ml/min	150 mg, BID
Reduction in the risk of recurrence of DVT and PE	CrCl ≤30 ml/min or on dialysis	No recommendation
	CrCl <50 mL/min with concomitant use of P-gp inhibitors	Avoid coadministration
Prophylaxis of DVT and PE following hip replacement surgery	CrCl >30 ml/min	110 mg on D1, then 220 mg OD
	CrCl ≤30 ml/min or on dialysis	No recommendation

CrCl=Creatinine clearance, BID=Twice daily, OD=Once daily, AF=Atrial fibrillation, DVT=Deep vein thrombosis, PE=Pulmonary embolism, P-gp=P-glycoprotein, US FDA=United States food and drug administration

Methods

This was a prospective cross-sectional study which conducted in an 850-bed university hospital with inpatient and outpatient care services, affiliated to Isfahan University of Medical Sciences, in Isfahan, Iran. All patients who received dabigatran (even 1 dose) from November 2015 to June 2015 were identified and selected through the pharmacy computer system. The charts of each patient were reviewed, and data were retrieved. All included patients followed up till discharge or death.

A data collection standard form was developed, pretested, and modified before including following data: patient demographic details (ID number, gender, age, weight, etc.), admitting diagnosis, units of admission, dates of admission and discharge, prescribing data for the use of dabigatran (including indication, dose, dosing interval, route of administration, duration of therapy, and contraindication), detail of other anticoagulant therapy before or concomitant with dabigatran (including the agent, dose, duration of therapy, and transitioning between anticoagulants), laboratory data (including red blood cells, white blood cell, hemoglobin and platelet count, PT, aPTT, INR, and serum creatinine), reasons for discontinuation, documented bleeding or thromboembolism, and patient's outcome (dead or alive). Serum creatinine was used to assess renal function by calculation of CrCl utilizing the modification of diet in renal disease equation. Dosing was considered appropriate based on the dosing adjustments recommended by the manufacturer in Table 1.

The appropriateness of the initial regimen ordered was assessed based on the dabigatran indication, dose, frequency, and appropriate transition. We used manufacturer's recommendation and Lexicomp drug information to determine the appropriate or inappropriate use of dabigatran.

Data are summarized as relative frequencies for categorical variables and mean standard deviation for normally distributed continuous variables. Calculations were made with SPSS 20.0, Chicago, IL, USA.

Results

A total of sixty patients received dabigatran during the study period. The mean age was 59.9 ± 19.8 (range 17–96 years). About 21.6% of our patients aged >75 years old. Male subjects constituted 71.7% (n = 43) of patients. The most common admission diagnosis was as follows: different type of cancers (n = 12), DVT/PE (n = 11), mesenteric ischemia and bowel obstruction (n = 6), and cholecystitis (n = 5). Table 2 summarizes the baseline characteristics of patients.

Only one patient received dabigatran with appropriate indication, dose, and duration. In six cases (6%), the indication (five cases of DVT prophylaxis and one case of DVT treatment) and dose (150 mg/twice daily) were appropriate, but those patients received dabigatran for less than the recommended duration.

The indications for patient's dabigatran use are presented in Table 3. According to package labeling at the time of the study, use for appropriate indications occurred in 100% of dabigatran encounters (treatment of DVT and PE and prevention of recurrent DVT and PE in adults). Nearly 35% of patients had contraindication at the time of dabigatran initiation (nine patients with a significant risk factor for major bleeding and 12 patients who received concomitant treatment with any other anticoagulant agent, for example, unfractionated heparin (UFH), enoxaparin, or warfarin). Forty (66.7%) patients received this drug

Table 2: Baseline patient's characteristics

Characteristics	Number of patients (n=60)
Age (years)	59.9±19.8 (17-96)
<20	2 (3.3)
20-40	11 (18.3)
41-60	16 (26.7)
61-80	21 (35)
81-100	10 (16.7)
Sex (male/female)	43 (71.7)/17 (28.3)
On-admission diagnosis	
Cancer	12
DVT/PE	11
Mesenteric ischemia	6
Cholecystitis	5
CVA	3
COPD	3
Myocardial infarction	2
ESRD	2
Other	16
Length of hospital stay (days)	27.1±25.5 (5-160)
Laboratory data	
Platelet (at admission) (/mm^3)	142,021.3±91,231.8
INR	1.87±1 (1.13-7.6)
PT	15.7±3.7 (10.4-25.9)
PTT	40.2±11.7 (26.7-73.5)
Hemoglobin (g/dl)	10.3±1.6 (7.2-18.4)
Serum creatinine (mg/dl)	1.48±1.17 (0.5-6.2)

Data presented as mean±SD (range), or n (%), where applicable. SD=Standard deviation, COPD=Chronic obstruction pulmonary disease, CVA=Cerebrovascular accident, DVT=Deep vein thrombosis, PE=Pulmonary embolism, ESRD=End-stage renal disease, INR=International normalized ratio, PTT=Partial thromboplastin time, PT=Prothrombin time

for DVT prophylaxis. However, 36 (60%) patients had thrombocytopenia at the time of dabigatran initiation. Ten cases (16.7%) of heparin-induced thrombocytopenia (HIT) and 9 cases (15%) of disseminated intravascular coagulation (DIC) were the other presentation at the time of dabigatran start. In six cases of suspected HIT, platelet level increased after dabigatran initiation.

Table 3: Indications for the use of dabigatran

Variables	Patients (*n*=60)
Nonvalvular AF	-
Treatment of PE	11 (18.3)
Treatment of DVT	8 (13.3)
Prophylaxis of DVT	40 (66.7)
Prophylaxis of PE	1 (1.7)
Clinical condition at the time of dabigatran initiation	
Thrombocytopenia	36 (60)
HIT	10 (16.7)
DIC	9 (15)
Laboratory data	
Platelet (/mm^3)	
At initiation	86,046.6±91,284 (15,000-509,000)
During treatment	134,844.5±118,328 (9000-599,500)
Mean of INR during treatment	1.6±0.72 (1-6)
Mean of PT during treatment	15.4±5.4 (9-45)
Mean of PTT during treatment (seconds)	41.1±19.1 (28-107)
Mean of serum creatinine during treatment (mg/dl)	1.46±1.7 (0.5-12.4)
CrCl (ml/min)	
>30	54 (90)
15-30	5 (8.3)
<15	1 (1.7)
Dabigatran dose (mg)	
75	3 (5)
110	49 (81.7)
150	8 (13.3)
Dabigatran interval	
Daily	14 (8.3)
BID	46 (76.7)

Data presented as mean±SD (range), or *n* (%), where applicable. SD=Standard deviation, DVT=Deep vein thrombosis, INR=International normalized ratio, PE=Pulmonary embolism, PT=Prothrombin time, PTT=Partial thromboplastin time, BID=Twice daily, CrCl=Creatinine clearance, DIC=Disseminated intravascular coagulation, HIT=Heparin-induced thrombocytopenia, AF=Atrial fibrillation

Table 4 summarizes the concurrent anticoagulant therapy with dabigatran. In 46 patients, UFH was administered before dabigatran initiation. Four patients received warfarin concomitantly with dabigatran. For patients with therapy discontinued before discharge, reasons included transitioning to other anticoagulants, worsening renal function, death, thromboembolic and bleeding complications, and completion of anticoagulant therapy.

In 32 patients, platelet levels increased after dabigatran initiation. In the remaining, the platelet levels stay unchanged. Three cases of minor bleeding (nose and mouth) and one case of the GI disturbance were reported after dabigatran use.

Seven patients received the appropriate dabigatran dose regarding indication. Dose adjustment was not performed in six patients. Six patients received dabigatran despite CrCl <30 ml/min. In total, 80% of our patients received 110 mg of dabigatran. The drug-taking intervals have been suitable in 76.7% of patients.

The mean duration of treatment with dabigatran was 9.6 ± 7.5 days (range 1–39 days) until discharge from hospital. Thirty patients (50%) received dabigatran in duration from 1 week to 1 month. Surgeons (different specialty) (n = 23) were the most prescriber of dabigatran. Thirty-nine (65%) of our patients died during the study period.

Discussion

Drug use evaluation is a necessary process in hospital setting, especially for any new medication which was added to the formulary system. Many hospitals have well-established guideline, protocol, and monitoring systems for patients receiving warfarin. The goal is to ensure the safe use of warfarin and to reduce harm from this drug. About the new medication (in this case novel anticoagulants) is crucial to evaluate the appropriate use of these agents along with potential safety and effectiveness outcomes.

Overall, dabigatran therapy was not prescribed and dose appropriately in the majority of our patients. All of our patients received this drug for FDA approved indications, but only five patients (8.3%) had not any underlying coagulation disorders; the rest of the patients at least had thrombocytopenia (n = 36). It means that, in nearly all patients, dabigatran was prescribed when

Table 4: Concurrent anticoagulant therapy with dabigatran

Drug	Before dabigatran initiation	Concurrent with dabigatran	After dabigatran	Appropriate transition
Unfractionated heparin	45	5	4	46
Enoxaparin	13	3	3	8
Warfarin	7	4	1	5

patients encountered some kind of coagulopathies, which was not appropriate regarding the available protocols for dabigatran use. Recently, novel anticoagulants were proposed as alternative agents in the treatment of HIT.[14] Positive results have been reported for the use of NOACs in the treatment of HIT.[15] We had ten patients with suspected HIT, which dabigatran was prescribed for them. In six of these patients, platelet levels increased after dabigatran initiation. VTE was not reported in none of these patients. Unfortunately, we do not have first-line drugs for treatment of HIT in our center (such as bivalirudin, argatroban, fondaparinux, or danaparoid). It seems that regarding the mechanism of dabigatran as a nonheparin anticoagulant and direct thrombin inhibitor, our physicians choose this drug for treatment of HIT, despite no indication at this time; however, our study was an MUE, and robust studies are needed to provide evidence about the safety and efficacy of dabigatran for treatment of HIT. About the other conditions of dabigatran prescribing such as thrombocytopenia (due to different causes) and DIC, the use of this drug is considered inappropriate at this time, till further study released. Furthermore, there were some case reports about dabigatran-induced thrombocytopenia and DIC in some patients.[16,17]

Our results showed that our physicians are not familiar with appropriate dosing, dose adjustment, and transition between dabigatran and other anticoagulants. Only seven patients received the appropriate dose of dabigatran (regarding indication and kidney function). According to Canadian labeling, use of dabigatran is contraindicated in CrCl <30 ml/min; six patients received this drug despite contraindication. Developing a protocol and appropriate education for clinician about indication, dosing, adverse effects, and contraindication of dabigatran is crucial in our center.

A retrospective chart review by Armbruster *et al*.[18] evaluated 458 patients who received dabigatran. Among them, 76 (16.6%) of patients were using an inappropriate regimen of this drug. 42.3% of patients received at least one dose of concomitant parenteral anticoagulants. Dabigatran was prescribed as a second-line drug in our study. Most of the patients received other anticoagulants before dabigatran initiation. Hence, we can consider that transition between anticoagulants was appropriate. Nearly 14.4% (66) patients in the mentioned study received inappropriate doses of dabigatran. Most of the patients (n = 426, 93%) received dabigatran for the treatment of atrial fibrillation (AF). In our center, warfarin is the first-line agent for AF treatment. None of our patients received dabigatran for this indication, and probably none of them had coagulopathies.

In another retrospective chart review, Nisly *et al*.[19] evaluated 78 patients who received dabigatran. Almost 87% of patients received the correct dosing based on indication and renal function. Appropriate transitions occurred in 44% of cases. Documented bleeding was reported in 5% of patients. We reported three cases of minor bleeding which can be attributed to dabigatran use. In other cases of reported bleeding, we could not correlate the bleeding to dabigatran, because, as we mentioned, most of our patients had underlying coagulation disorders.

Other MUE studies[20,21] reported the same problem about the incorrect dose and also off-label or unlabeled indications of dabigatran. This highlights the need to standardize a hospital protocol for dabigatran use. Otherwise, misuse of dabigatran may heighten the risk of clinical sequel.

Forty-five percent of our patients received dabigatran for <1 week, which is not enough, especially in case of DVT/PE prophylaxis. The new boxed warning of FDA emphasizes that premature discontinuation of dabigatran may increase the risk of thrombotic events.[22] In most of our patients, dabigatran changed to warfarin at discharge. This transition shows that, after stabilization of patients (improvement in coagulation disorders), the physicians prescribed warfarin, which is cheaper than dabigatran (in our country), and despite necessity for frequent monitoring and follow-up, our physicians have good and long experience of it.

Our study limitations are as follows: we did not evaluate drug interaction of dabigatran in our study, and we had not proper documentation of dabigatran adverse effects.

Less than 6% appropriate use of dabigatran in our study indicates that inclusion of every novel drug in the hospital formulary needs a well-defined protocol for using of that drug. Appropriate education of clinicians about these novel drugs is a necessary step in formulary development. This MUE also shows that the new potential of dabigatran utilization in the treatment of HIT. Of course, robust studies are needed to prove the efficacy and safety of dabigatran for this new indication. Dabigatran is an expensive drug in our country, and as our resources are limited, it is mandatory to develop national guideline and protocols for rational use of this drug. We also suggest further studies to evaluate potential drug interaction and adverse effects of dabigatran.

Authors' Contribution

Farzaneh Ashrafi designed the study and revised the manuscript. Najmeh Rezaie collected and interpreted the data. Sarah Mousavi analyzed the data and drafted the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Green B, Mendes RA, Van der Valk R, Brennan PA. Novel anticoagulants - An update on the latest developments and management for clinicians treating patients on these drugs. J Oral Pathol Med 2016;45:551-6.
2. Mekaj YH, Mekaj AY, Duci SB, Miftari EI. New oral anticoagulants: Their advantages and disadvantages compared with Vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. Ther Clin Risk Manag 2015;11:967-77.
3. Sardar P, Chatterjee S, Lavie CJ, Giri JS, Ghosh J, Mukherjee D, *et al.* Risk of major bleeding in different indications for new oral anticoagulants: Insights from a meta-analysis of approved dosages from 50 randomized trials. Int J Cardiol 2015;179:279-87.
4. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, *et al.* Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: An analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation 2011;123:2363-72.
5. Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, *et al.* Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation 2014;129:764-72.
6. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, *et al.* Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361:2342-52.
7. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, *et al.* Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013;368:709-18.
8. Ganetsky M, Babu KM, Salhanick SD, Brown RS, Boyer EW. Dabigatran: Review of pharmacology and management of bleeding complications of this novel oral anticoagulant. J Med Toxicol 2011;7:281-7.
9. Cohen AT, Hamilton M, Bird A, Mitchell SA, Li S, Horblyuk R, *et al.* Comparison of the Non-VKA oral anticoagulants apixaban, dabigatran, and rivaroxaban in the extended treatment and prevention of venous thromboembolism: Systematic review and network meta-analysis. PLoS One 2016;11:e0160064.
10. Eby C. Novel anticoagulants and laboratory testing. Int J Lab Hematol 2013;35:262-8.
11. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, *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;17:1467-507.
12. Liew A, Eikelboom JW, O'Donnell M, Hart RG. Assessment of anticoagulation intensity and management of bleeding with old and new oral anticoagulants. Can J Cardiol 2013;29 7 Suppl:S34-44.
13. Boehringer Ingelheim Pharmaceuticals IBIPpiR, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2015. Available from: http://www.docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf. [Last accessed on 2016 Jan 10].
14. Ho PJ, Siordia JA. Dabigatran approaching the realm of heparin-induced thrombocytopenia. Blood Res 2016;51:77-87.
15. Skelley JW, Kyle JA, Roberts RA. Novel oral anticoagulants for heparin-induced thrombocytopenia. J Thromb Thrombolysis 2016;42:172-8.
16. Deidda A, Rapallo M, Sofia MD, Meloni L, Lampus SF, Pisanu C, *et al*. Thrombocytopenia possibly induced by dabigatran: A case report. J Pharmacovigil 2015;3:2015.
17. Verma A, Chhibber V, Emhoff T, Klinger D. Promise and challenges of anticoagulation with dabigatran. Clin Kidney J 2012;5:336-8.
18. Armbruster AL, Buehler KS, Min SH, Riley M, Daly MW. Evaluation of dabigatran for appropriateness of use and bleeding events in a community hospital setting. Am Health Drug Benefits 2014;7:376-84.
19. Nisly SA, Issacs AN, Doolin M, Morse C, Shiltz E. Medication utilization evaluation of dabigatran and rivaroxaban within a large, multicenter health system. J Health Syst Pharm Resid 2013;2:2-8.
20. Isaacs AN, Doolin M, Morse C, Shiltz E, Nisly SA. Medication utilization evaluation of dabigatran and rivaroxaban within a large, multi-center health system. Am J Health Syst Pharm 2016;73 5 Suppl 1:S35-41.
21. Hussain S, Gebran N, Hussain K, Soliman K. Drug use evaluation of dabigatran in a tertiary care hospital in United Arab Emirates. Eur J Hosp Pharm 2013;20:106-9.
22. Pradaxa [Dabigatran Etexilate Mesylate] Capsules; 2015. Available from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm250657.htm. [Last accessed on 2016 Dec 26].