VALIDATION OF A PATIENT DECISION AID FOR CHOOSING BETWEEN DABIGATRAN AND WARFARIN FOR ATRIAL FIBRILLATION

Christina Hong[1], Shara Kim[1], Greg Curnew[2,5], Sam Schulman[2,5], Eleanor Pullenayegum[3,4], Anne Holbrook[1,2,3,4]

[1]Division of Clinical Pharmacology & Therapeutics, McMaster University; [2]Department of Medicine, McMaster University; [3]Department of Clinical Epidemiology and Biostatistics, McMaster University; [4]Centre for Evaluation of Medicines, St Joseph's Healthcare Hamilton; [5]Thrombosis and Atherosclerosis Research Institute, Hamilton

Corresponding Author: *holbrook@mcmaster.ca*

ABSTRACT

Background
Decision aids have been helpful to support patients in decision-making including anticoagulation. With the introduction of new oral anticoagulants (NOACs), it will be important to assist patients and physicians in shared decision-making about NOACs and warfarin.

Objectives
To validate a patient decision aid (DA) for warfarin versus dabigatran, the first NOAC approved for atrial fibrillation (AF).

Methods
Participants without AF and not taking anticoagulants were recruited for the validation exercise. The decision aid described AF, stroke, and hemorrhagic events in terms of incidence, clinical presentation, and prognosis. Warfarin and dabigatran were then compared on multiple clinical and process outcomes as outlined in the pivotal clinical trial. Our primary outcome was confidence in making a treatment decision, using a decisional conflict scale. Secondary outcomes were change in knowledge scores and ratings of clarity, helpfulness and comprehensiveness.

Results
35 patients (mean age 62.7 [SD 9.68], 37.1% female) participated. After use of the decision aid, the mean total decisional conflict score was low at 18.9 (SD: 14.2). Mean knowledge score improved significantly from 4.60 (SD 1.48) to 6.42 (SD 0.80) out of a total score of 7. Only one participant (2.9%) found the decision aid difficult to understand. All 35 participants rated the DA as helpful for making a decision about anticoagulant treatment for AF. Two participants (5.7%) requested more information on adverse effects of the two drugs.

Conclusion
Our DA to allow patients to make an informed decision with their physician regarding dabigatran versus warfarin in AF, proved understandable, comprehensive and helpful.

Key Words: *Decision aid; atrial fibrillation; anticoagulation; warfarin; dabigatran; validation*

Atrial fibrillation (AF) is a common cardiac arrhythmia that affects approximately 350,000 people in Canada.[1] To reduce the risk of stroke, anticoagulants are recommended for most

of these patients.[2] Warfarin has been the sole oral anticoagulant for nearly 60 years and has proven efficacy in preventing strokes, systemic embolism, pulmonary embolism and deep vein thrombosis.[3] Currently more than five million warfarin prescriptions are dispensed annually in Canada.[4] Warfarin is one of the most cost-effective chronic therapies on the market with 68% reduction in stroke rates and a significant decrease in all-cause mortality in AF.[5] However, it is a narrow therapeutic index drug in that its main harm - bleeding, occurs at doses close to its effective dose.[3] This, along with drug and food interactions[6] and some pharmacogenetic variability in metabolism,[3,7] mandates laboratory monitoring of its anticoagulant effect.[8] Although a useful medication adherence and safety check for physicians, frequent monitoring of the prothrombin time can be an impediment for some patients. Dabigatran is the first novel oral anticoagulant (NOAC) approved for AF and, although it does not require laboratory monitoring, it has its own set of problems including contraindication in severe renal impairment, lack of antidote for bleeding, more adverse gastrointestinal symptoms leading to discontinuation, and twice daily dosing.[9,10] Furthermore, physicians need to consider the patient's individual risk of stroke and bleeding to decide whether either drug is recommended or safe.[2,11,12] Therefore, it is important for the patient to consider both the benefits and disadvantages of warfarin and dabigatran before deciding with their physician about their treatment.

Patient decision aids (PtDAs) are tools that can improve patient knowledge and facilitate an informed personal decision about health care options.[13] PtDAs should accurately and objectively provide the necessary information about treatment choices and outcomes, tailored as much as possible to the patient's individual risk profile. We have previously completed two PtDA studies on anticoagulants, both showing somewhat surprising results regarding patients' treatment choices once fully informed on benefits, harms and importance of outcomes.[14,15] Given the trade-offs between warfarin and dabigatran, a PtDA may lead to more informed decisions, and potentially result in better medication adherence and clinical outcomes. The objective of this study was to develop and validate a PtDA to assist patients to make an informed and confident choice between dabigatran and warfarin for stroke prophylaxis in AF.

METHODS

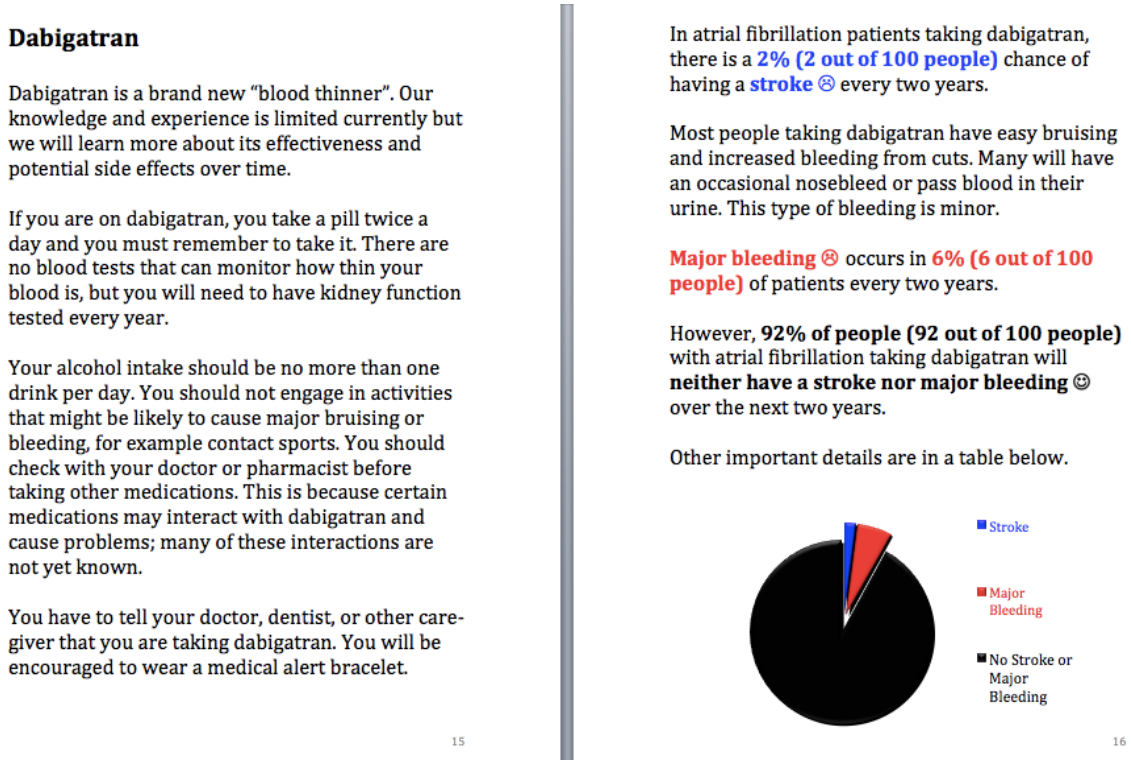
The study was approved by Hamilton Health Sciences/McMaster Faculty of Health Sciences Research Ethics Board.

Development of Decision Aid

We modified our previous PtDA[14] developed and validated for warfarin with average benefit:harm data and two comparators presenting individualized benefit:harm profiles, to compare warfarin and dabigatran (PtDA-WD) according to the latest recommendations of the Patient Decision Aids Research Group[16] and the International Patient Decision Aid Standards Collaboration.[17] The data presented in the PtDA-WD reference the results of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, the only high quality comparative evidence on benefits and harms available at the time.[9] This trial compared two fixed doses of dabigatran, 110 mg and 150 mg twice daily, with warfarin in patients with AF who are at increased risk of stroke.[9] Only the 150 mg-dose was found to be superior for the primary outcome of reducing the risk of stroke and systemic embolism, so this dose was compared with warfarin in our decision aid. The PtDA-WD provides general information on AF, stroke and bleeding. It then explains the benefits, harms, lifestyle implications and costs of each drug (warfarin and dabigatran) using words, numbers with timeframe, diagrams and tables. A sample page is shown in Figure 1. Since dabigatran is a new drug, comparative information was limited to pivotal clinical trials such as the RE-LY trial,[9] product monographs,[18,19] regulatory information from the FDA[20] and Canadian Common Drug Review[21] and key post-marketing data from the Institute for Safe Medication Practices.[22] All text was reviewed to achieve a Grade 10 reading level as measured by the Simplified Measure of

Gobbledygook (SMOG) readability test.[23] Pre-testing with a convenience sample of 17 people resulted in minor changes to improve clarity and content.

FIG.1 Sample page from Pt-DA-WD



Participants

We included adults aged 18 years and older, who were able to read and understand English and demonstrated adequate cognition. This required a score of more than 21 of a total of 28 on the Short Blessed Test, a validated orientation-memory-concentration (OMCT) test for cognitive impairment.[24] Patients who had known atrial fibrillation or who were already anticoagulated were excluded, so that interference with recommended therapy based on a research tool, would be avoided. In addition, the PtDA-WD is targeted towards newly diagnosed AF patients, who would not have experience with the diagnosis or with anticoagulant therapy. Our experience has been that patients with cardiovascular risk factors or co-morbidities are readily able to participate in this type of simulation. Recruitment was structured such that at least half of the sample would be 65 years or older, to be representative of the population recommended for anticoagulation. Participants were recruited from a combined internal medicine and cardiology clinic in Hamilton, Ontario. The attending physician briefly described the project to potential participants and introduced them to the interviewers. The interviewers then explained the study in detail. Interested patients provided written informed consent and then proceeded directly to the study. Once the participants

provided written informed consent, a stopwatch was used to record total interview time and the time to complete the PtDA-WD.

Interview Process

Participants who passed the Short Blessed Test for memory proceeded through the interview. Demographics, number of currently prescribed medications and current medical conditions were collected. The participant was then asked to answer the seven-question AF knowledge questionnaire. This tested prior knowledge about AF, warfarin and dabigatran. Next, the participant proceeded to the PtDA-WD itself. The script was read to each participant by the interviewer to ensure that reading literacy did not interfere with the study. Having read the PtDA-WD, Time 1 was recorded. At the end of PtDA-WD, the participant was asked to decide which treatment - dabigatran or warfarin, they would choose if they had AF. Comprehension of the content in the PtDA-WD was then assessed by having participants repeat the AF knowledge questions. In addition, participants formally rated their degree of confidence and comfort with their decision, using a modified Decisional Conflict Scale (DCS).[13,14,15] This scale also addresses factors that contribute to uncertainty. Three questions relevant to support in the DCS were removed because they were not applicable to the study.

Participants were then asked to indicate any external influences that may have affected their treatment decision. Choices included knowing someone with AF, fear of stroke, fear of serious bleeding, fear of heart attack, inconvenience of regular blood tests, inconvenience of taking pills twice per day, preference for newer drug, cost of the drugs, and reluctance to take a drug whose name sounds like rat poison. The final section examined the helpfulness and quality of the PtDA-WD, and gathered general feedback or comments. After completion of the interview, time 2 was recorded.

Statistical Analyses

Sample size was set at approximately 30 people, based on previous PtDA studies and using the principle of saturation – sample size is sufficient once no new comments to improve the DA are forthcoming.

Our primary outcome was the decisional conflict scale.[25] For this scale, a score below 25 is indicative of low decisional conflict and is associated with implementing decisions, while a score higher than 37 is associated with decision uncertainty and a delay in making a decision.[25] The total score is based on four sub-scores on uncertainty, feeling informed, having clear values and effective decisions. Secondary outcomes included patient ratings on clarity, comprehension, and helpfulness.

Results were summarized descriptively. Predictive Analytics SoftWare (PASW) Statistics 18 was used for correlation analyses. Student paired T test was used to compare the pre and post knowledge scores. One-way ANOVA was used to test for correlation between education level and the improvement of knowledge, which is measured by the change in knowledge scores.

RESULTS

Participant Characteristics

Of the 50 individuals who were approached, 46 were willing to participate in the study. Six of the participants did not pass the Short Blessed memory test and five were excluded because they had AF or were currently taking warfarin. The baseline demographics are outlined in Table 1. For the 35 participants, mean age was 62.7 [SD] 9.68, range from 40 to 85 years, and with 15 above the age of 65. Thirteen (37.1%) were female and 17 (48.6%) had a college degree or higher. The mean OMCT error score was 1.89. All but one had suffered a previous vascular event or had at least one vascular risk factor. Thirty-two (91.4%) of the participants were taking at least one prescription medication, 17 (48.6%) were taking five or more prescription medications and 26 (74.3%) were taking aspirin.

On average, time taken to complete the decision aid and make a decision choice was 19.8 minutes with 9.9 additional minutes to complete the evaluation questionnaires.

TABLE 1 Baseline Characteristics

Characteristic	**Participants (n = 35)**
Age	**Years (SD)**
Mean Age	62.7 (9.68)
Gender	**n (%)**
Female	13 (37.1)
Education Level	**n (%)**
Elementary school only	5 (14.3)
Secondary school only	13 (37.1)
College or university only	11 (31.4)
Post-graduate education	6 (17.1)
Number of Prescription Medicines	**n (%)**
0 Prescription Medicines	3 (8.6)
1-4 Prescription Medicines	15 (42.9)
5-7 Prescription Medicines	7 (20.0)
>7 Prescription Medicines	10 (28.6)
Medical History	**n (%)**
Cardiovascular Disease (Previous transient ischemic attack, stroke, angina, or myocardial infarction)	7 (20.0)
No Cardiovascular Disease but diabetes, hypertension, or hypercholesterolemia	27 (77.1)
Bleeding Disorder	1 (2.9)

Atrial Fibrillation Knowledge

The mean participant knowledge score pre-decision aid was 4.60 (SD=1.48) out of the possible total of seven correct answers. After the DA presentation, the mean participant knowledge score was 6.43 (SD=0.80). The difference in mean knowledge scores was statistically significant ($p = 0.01$). Education level was tested for correlation with improvement in knowledge, which is defined by the difference between pre-and post-decision aid knowledge test scores. There was no statistically significant association between knowledge scores and education level ($p = 0.12$).

Treatment Decision

After considering the decision aid, twenty-nine (82.9%) of the participants chose warfarin as their treatment as a hypothetical AF patient, with six (17.1%) choosing dabigatran. The most common factors reported as influencing treatment decisions were fear of having a stroke (88.6%), fear of having a heart attack (82.9%), preference to taking one pill per day instead of two (74.3%), fear of having a major bleeding complication (71.4%), concerns about the cost of the new drug (51.4%) and perceived safety issues (37.1%). Details are outlined in Table 2.

TABLE 2 Outcomes

Cognition Screen Test	**Mean Score (SD)**
(OMCT)	1.89 (1.97)
Factors Influencing Decision	**No (%) Participants Listing Factor**
Fear of stroke	31 (88.6)
Fear of heart attack	29 (82.9)
Number of pills per day	26 (74.3)
Fear of major bleed	25 (71.4)
Cost of drug	18 (51.4)
Other Influential factors:	15 (42.9)
Dabigatran- too new/unknown safety	7
Warfarin- more familiar/has monitoring and antidote	6
Other	5
Decisional Conflict Scores	**Mean Scores (SD)**
Informed subscale	14.6 (11.4)
Values Clarity subscale	19.5 (15.2)
Uncertainty subscale	25.0 (22.4)
Effective Decision subscale	18.8 (17.9)
Total score	18.9 (14.2)
Ratings of Quality of Information Presented	**Mean Scores (SD)** **Poor=1, Fair=2, Good=3, Excellent=4**
Atrial Fibrillation	3.49 (0.60)
Risk of Stroke	3.40 (0.55)
Risk of Bleeding	3.46 (0.55)
Benefits of Warfarin	3.31 (0.57)
Risks of Warfarin	3.26 (0.65)
Benefits of Dabigatran	3.29 (0.61)
Risks of Dabigatran	3.26 (0.77)
Summary Table	3.51 (0.50)

Decisional Conflict

Mean decisional conflict total score and subscale scores are summarized in Table 2. The scores were generally low ranging from 14.6 to 25 out of a possible total of 100. The mean total decisional conflict was 18.9 (SD=14.2). All subscale scores related to being informed, having clear values, the level of uncertainty and making an effective decision were consistent with this total score.

Acceptability

Feedback on the PtDA-WD was positive with the components on AF, stroke, bleeding, warfarin, dabigatran and the summary table rated Good or Excellent in terms of clarity and content (Table 2). The majority of participants, twenty-nine (82.9%), thought the length of the PtDA-WD was appropriate, while six (17.1%) found it too long. Thirty-two (91.4%) felt the amount of information in the presentation was sufficient. Four (11.4%) thought that additional information on adverse effects, drug interactions, kidney function tests and AF could be provided in the presentation. Twenty-eight (80.0%) said that the presentation was balanced, but four (11.4%) said the PtDA-WD favoured warfarin while three (8.7%) said it favoured dabigatran. Twenty-four (68.6%) found the PtDA-WD easy to understand, while ten (28.6%) thought the level of difficulty in understanding was medium and one (2.9%) found it difficult.

Decision Aid Preference

Twenty (57.1%) found the pictograms helpful in addition to the pie charts. In terms of preferred method of presentation, twenty (57.1%) preferred a face-to-face presentation whereas ten (28.5%) preferred a booklet. All thirty-five (100%) of the participants rated the PtDA-WD as being helpful in making the treatment decision. Ten (28.6%) provided additional feedback that commonly included how the PtDA-WD was exceptionally helpful, enjoyable or well administered.

DISCUSSION

To our knowledge, this is the first study to develop and assess the impact of presenting patients with information on both the benefits and harms of warfarin treatment in comparison to any of the new oral anticoagulants for AF. Therefore, we believe that the development and validation of this decision aid is novel and addresses an important clinical need. Several key findings were suggested by this study. First, since the knowledge test scores improved to a high level, the PtDA-WD does seem to transmit necessary information. Second, the low mean decisional conflict score of 18.9 is a reassurance that the decision aid would allow patients to confidently make a treatment choice. The alignment of sub-scales to suggest patients felt informed, were clear about what they value, and were likely to implement their choice and be satisfied with it, provide a form of internal validity. Finally, the general consensus that the information was complete, high quality, balanced and helpful provides face validity.

Several PtDAs have been developed which compare warfarin, aspirin or no treatment for AF.[14,26,27,28] Recently, a clinical decision aid was also developed to assist physicians in determining an optimal antithrombotic regime, including dabigatran.[29] However, our DA is directed towards patients, compares dabigatran and warfarin, and provides information about AF, stroke, bleeding and anticoagulant options. This information bridges a knowledge gap and allows patients to be able to actively participate in the decision-making.

An important limitation of our study is that the sample consists of patients who do not have AF and are hypothetically considering the treatment options. The results may not accurately portray the values and opinions of patients who are making a real decision about their treatment, but the main point of our study was to develop an effective DA tool. Our sample size, although meeting our goals for validation of the DA, was small, recruited from one urban centre and slightly younger than the average population with AF.[30] Finally, we were unable to organize intra-rater reliability assessment, which would have been a useful addition to our validity testing.

We believe that our PtDA-WD, with minor adjustments in adverse effect information, colour and worksheet, is ready to be evaluated in a large sample of patients with AF. Ideally, this would take place within a randomized trial where the control group did not receive the decision aid, with outcomes addressing treatment choice, decision conflict and resource utilization.

Although the information provided may be especially helpful to primary care practitioners who may be less informed on anticoagulant issues than specialists, the short patient visit times are a

challenge to feasibility. We are aware of hospital clinics organized specifically to assist patients and their primary providers to decide between a NOAC and warfarin. This setting might be ideal for an evaluation study. Future development also needs to expand the PtDA-DW to include all three of the current NOACs (dabigatran, rivaroxaban and apixaban).

CONCLUSION

We have validated a decision aid that will allow patients to participate with their physician in deciding between dabigatran and warfarin for AF.

Acknowledgements
The authors thank Sue Troyan for assistance in designing the study, the coding of the data for analysis and the interview training.

REFERENCES

1. Heart and Stroke Foundation of Canada. Atrial fibrillation-be pulse aware. (August 2011). http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.5052135/k.2C86/Heart_disease__Atrial_fibrillation.htm (Feb 19, 2012).
2. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest 2012 Feb;141(2 Suppl): e531S-75S.
3. Hirsh J, Dalen J, Anderson DR, et al. Oral anticoagulants mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 2001 Jan;119(1 Suppl):8S-21S.
4. Campeau L. Top Rx Drugs of 2010. (2011) http://www.canadianhealthcarenetwork.ca/pharmacists/news/drug-news/top-rx-drugs-of-2010-9850 (May 24, 2011).
5. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation: American college of chest physicians evidence-base clinical practice guidelines (8th Edition). Chest 2008 Jun;133(6 Suppl):546S-592S.
6. Holbrook A, Labiris R, Goldsmith CH, Ota K, Harb S, Sebaldt RJ. Influence of decision aids on patient preferences for anticoagulant therapy: a Randomized trial. CMAJ 2007 May 22;176(11):1583-1587.
7. Rieder MJ, Reiner AP, Gage BF, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med 2005 Jun 2;352(22):2285-2293.
8. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest 2012 Feb;141(2 Suppl):e152S-84S.
9. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009 Sep 17;361(12):1139-1151.
10. Zeidan A, Faltas B, Streiff M. Dabigatran etexilate: what do hospitalists need to know? J Hosp Med 2012 Mar;7(3):262-269.
11. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro heart survey on atrial fibrillation. Chest 2010 Feb;137(2):263-272.
12. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010 Nov;138(5):1093-1100.
13. Stacey D, Bennett CL, Barry MJ, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2011 Oct 5;(10) (10):CD001431.
14. Holbrook AM, Nikitovic M, Troyan S, Pullyenagum E, Crowther M. Will individualized benefit-harm risk information affect patients' decisions regarding warfarin? Can J Clin Pharmacol 2010 March 26;17(1):e123.
15. Holbrook A, Labiris R, Goldsmith C, Ota K, Harb S, Sebaldt R. Influence of decision aids on patient preferences for anticoagulant therapy: a randomized trial. CMAJ 2007 May;176:1583-1587.

16. Ottawa Hospital Research Institute. Patient Decision Aid. http://decisionaid.ohri.ca/index.html (Nov 22, 2012).
17. Elwyn G, O'Connor A, Stacey D, et al. Developing a quality criteria framework for patient decision aids: Online international Delphi consensus process. BMJ 2006 Aug 26;333(7565):417.
18. Bristol-Myers Squibb Canada. Coumadin [pdf on Internet]. (July 12, 2012). http://www.bmscanada.ca/static/products/en/pm_pdf/COUMADIN_EN_PM.pdf (Oct 28, 2012).
19. Boehringer Ingelheim Canada Ltd. Pradax [pdf Internet]. (January 27, 2012). http://www.boehringer-ingelheim.ca/_content/dam/internet/opu/ca_EN/documents/humanhealth/product_monograph/Pradax-pm.pdf (Oct 28, 2012).
20. U.S. Food and Drug Administration. FDA drug safety communication: safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate) [Internet]. (July 12, 2012) http://www.fda.gov/Drugs/DrugSafety/ucm282724.htm (October 28, 2012).
21. Canadian Agency for Drugs and Technologies in Health. CEDAC final recommendation: Dabigatran etexilate [pdf on Internet]. (June 22, 2011) http://www.cadth.ca/media/cdr/complete/cdr_complete_Pradax_June-27-11.pdf. (Oct 28, 2012).
22. Institute for Safe Medication Practices. Anticoagulants the leading reported drug risk in 2011 [pdf on Internet]. (May 31, 2012) http://www.ismp.org/quarterwatch/pdfs/2011Q4.pdf (Oct 28, 2012).
23. McLaughlin G. SMOG: Simple measure of gobbledygook(2008). http://www.harrymclaughlin. com/SMOG.htm (October 28, 2012)
24. Katzman R, Brown T, Fuld P, Peck A, Schechter R, Schimmel H. Validation of a short Orientation-Memory-Concentration Test of cognitive impairment. Am J Psychiatry 1983 Jun;140(6):734-739.
25. O'Connor AM. Validation of a decisional conflict scale. Med Decis Making 1995 Jan-Mar;15(1):25-30.
26. Fraenkel L, Street RL Jr, Fried TR. Development of a tool to improve the quality of decision making in atrial fibrillation. BMC Med Inform Decis Mak 2011 Oct 6;11:59.
27. Thomson RG, Eccles MP, Steen IN, et al. A patient decision aid to support shared decision-making on anti-thrombotic treatment of patients with atrial fibrillation: Randomised controlled trial. Qual Saf Health Care 2007 Jun;16(3):216-223.
28. Man-Son-Hing M, Laupacis A, O'Connor AM, et al. A patient decision aid regarding antithrombotic therapy for stroke prevention in atrial fibrillation: a randomized controlled trial. JAMA 1999 Aug 25;282(8):737-743.
29. LaHaye SA, Gibbens SL, Ball DG, Day AG, Olesen JB, Skanes AC. A clinical decision aid for the selection of antithrombotic therapy for the prevention of stroke due to atrial fibrillation. Eur Heart J 2012 Sep;33(17):2163-2171.
30. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med 1995 Mar 13;155(5):469-473.