



# A REVIEW ARTICLE ON VARIOUS STRATEGIES FOR PATIENT EDUCATION ABOUT ANTICOAGULANT THERAPY WITH WARFARIN

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## ABSTRACT:

Patient education is an important component in quality management of the anticoagulated patient. Because it is time consuming for clinicians. Education of the anticoagulated patient is often neglected. I searched the medical literatures in order to identify the best patient education strategies.

**Key words:** Anticoagulants, patient education, anticoagulated patient.

## INTRODUCTION:

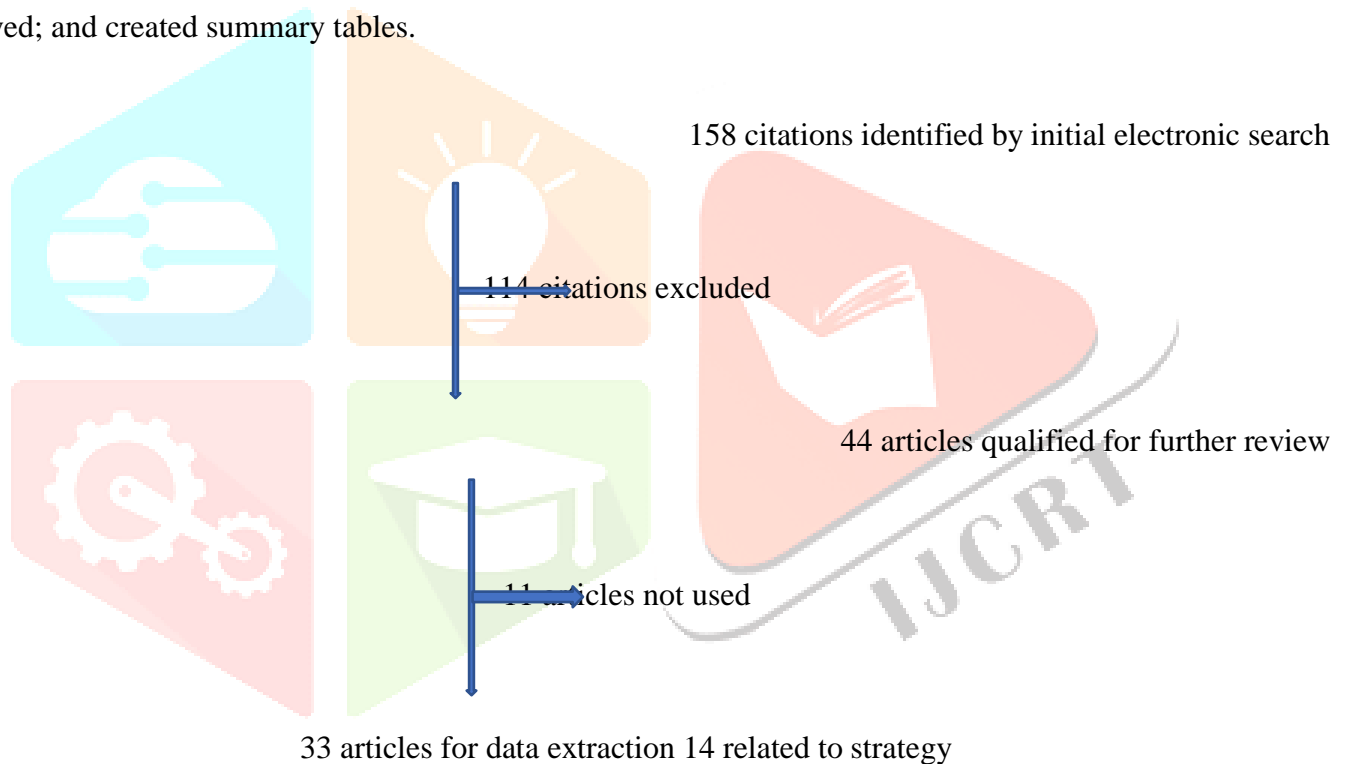
1. Anticoagulants are widely used to prevent and treat thromboembolic events, but are also high-risk medication.
2. They are associated with increased risk of bleeding and are one of the top drugs causing emergency hospitalization.
3. Taking anticoagulants incorrectly (i.e non-adherence) can increase risk of bleeding or thromboembolic events. Drug interaction, and in case of warfarin, dietary interactions also increase the risk of anticoagulants-related adverse events.
4. Furthermore, Warfarin is a narrow therapeutic index medication and requires regular blood test optimal anticoagulant effect.
5. Thus, it is imperative that patients receive extensive high-quality patient education while taking anticoagulation therapy.

## METHODOLOGY:

### STUDY SELECTION:

We searched the MEDLINE and google scholar databases using the words “Warfarin” or “anticoagulation”, and “patient education”. we initial identified 158 citations, A total of 114 citations were excluded because patients were of pediatric age (4), the article was not related to patient education (25), did not contain original data or inadequate program description (52), was focused solely on patient self-testing(2), was a duplicate citation(3), the article was judged otherwise irrelevant ( 12), or no abstract was available (16).

After exclusion, a total of 44 articles selected for further review. Upon further review, an additional 11 articles were excluded because of inadequate description, finally leaving a total of 33 articles for data extraction. I extracted data on clinical setting, study design, group size, content source, time and personnel involved; and created summary tables.



## RESULTS:

14 articles had a description of the research methods or program that was adequate and consistent with objectives of identifying the duration, timing program and personnel requirements of the educational program. five programs used a nurse or pharmacist, four used a physician, and two studies used personnel (lay educators 1, videotapes 1). The duration of the educational intervention ranges from 1 -10 sessions. Patient group size most often averaged 3-5 patients but ranged from as low as 1 patient to as much as 11

patients. While the majority of the educational effects occurred in inpatient setting, most seemed relevant to contemporary outpatient setting.

Although 13 articles offered information about education content, I summarized the categories suggested by these studies and listed the potential topics for each category.

### Patient education strategies related to warfarin and anticoagulation

Citation	Location	Study Design	Stated Goal	Group Size	Personnel involved	Strategy/Duration/Frequency
Menendez-Jandula et al <sup>13</sup>	2005 Barcelona, Spain	RCT	To prove the value of self-management on INR control and clinical outcomes	5–8 patients and option of having family member present	Specially trained nurse	2 sessions of 2 hours on consecutive days Based on German model
Koertke et al <sup>14</sup>	2005 Westphalia, Germany	Program description	To describe the principles of a training course to learn INR self-management	Not more than 5 patients	Not stated	Welcome period Two phase (hospital, 6 months later) Average duration 3–4 hours (1.5 for theoretical and 1.5 for device handling)
Voller et al <sup>15</sup>	2004 Westphalia, Germany	Program description	To evaluate the effects of a training program on patient knowledge	2–5 patients	Not stated	Two half day sessions 2–7 days apart. Patient logbook
Khan et al <sup>16</sup>	2004 Newcastle, U.K.	RCT	To prove the value of education and self-monitoring on INR control and quality of life	2–3 patients	Led by physician	1 two hour educational session
Gadisseur et al <sup>17</sup>	2003 Leiden, Netherlands	RCT	To examine effects of self-management on quality of life	4–5 patients	Specialized teams of physicians and nurses	3 weekly sessions of 90–120 minutes
Singla et al <sup>18</sup>	2003 Philadelphia, U.S.	Cohort Survey	To examine effects of group education on knowledge	11 persons	Pharmacist or nurse	1 one hour session

### Studies testing patient knowledge regarding anticoagulation

Citation	Setting/Study population	Questions – Number and Type	Administration
Hu et al <sup>30</sup>	2006 Large urban teaching hospital 100 mechanical valve patients	20, True-False	Scripted telephone survey Trained medical student
Zeolla et al <sup>12</sup>	2006 OAK test U.S., Recruited from 4 pharmacies and 2 clinics 122 volunteers	20, Multiple choice, Validity and reliability testing	Self administered Excluded illiterate patients 7th grade reading level
Roche-Nagle, Chambers <sup>31</sup>	2006 Dublin teaching hospital anticoagulation clinic 150 consecutive patients	8, Specific answers	Standardized interview
Davis et al <sup>11</sup>	2005 Two NYC anticoagulation clinics 52 patients	18, Multiple choice	Self administered Single visit Excluded low literacy patients
Briggs et al <sup>32</sup>	2005 AKA test Two Chicago inner city, pharmacist-managed anticoagulation clinics 60 patients	28, Multiple choice, Validity and reliability testing	Self administered Excluded illiterate patients 7th grade reading level
Voller et al <sup>15</sup>	2004 Three German 3 teaching centers 76 patients	13, Multiple choice	Questions not available
Nadar et al <sup>33</sup>	2003 3 U.K. teaching hospital anticoagulation clinics 180 patients who attended the clinic > 5 times	9, Short answer	Language concordance, personal interview

**Topics for education of the anticoagulated patient**

category	Educational topic
Basics of anticoagulation	Description of the coagulation system Normal blood clotting compare with clotting of an anticoagulated patient warfarin-mechanism
Risk-benefit	Risk of bleeding versus-descriptive versus numerical complications of thromboembolic
adherence	Colour and strength of tablets what to do if dose missed
Accessing healthcare professionals	When to call the doctor When to seek emergency care Anticoagulation services
Diet	Basic of vitamin K Specific foods

**TAKING ANTICOAGULATION MEDICATION SAFELY**

Before giving warfarin prescription, doctor and nurse be aware of following:

- All the medications, herbal supplements, and vitamins are currently taking should keep an updated list with the patient at all times.
- Any allergies or bad reaction that the patient had with food or medications in the past.
- The patient health and illness history, especially if patient had any problems with bleeding in the past.

**BEFORE STARTING WARFARIN MEDICATION:**

- The patient should ask the doctor the following questions:
- How will this medication help me?
- What side effects should I expect and what should I do about them?
- How and when do I take this medication?
- How long I should use this medication?

Inform the doctor if pregnant or if planning for pregnancy.

## WHY THE PATIENTS NEED TO HAVE BLOOD TESTS DONE:

The amount of warfarin to each person is different. In order to find the best dose of warfarin for the patient, a blood test called INR (international normalized ratio) will be done. The INR measures how long it takes for blood to clot.

The goal of warfarin therapy is to keep the INR within a certain target range, as determined by the doctor. If the INR is too high, then the patient is at higher risk for bleeding problems. If it is too low, then the patient may be at risk for developing blood clots.

change warfarin When the patient first start taking warfarin, expect to have the blood checks as dosage.

Once INR is in the prescribed target range then dose of warfarin will become more regular and the blood testing will be done less often.

## WHILE THE PATIENTS ARE TAKING THIS MEDICATION

Be sure to keep track of:

- INR blood test results
- The dose of medication taken each day
- The date of next INR blood test
- Any problems or side effects that patient experience
- Any other instructions or other information from the doctor or nurse

## HOW TO TAKE ANTICOAGULATION MEDICATION

Take the anticoagulation at the same time every day, as directed by the doctor or nurse. This is important because it makes the medication work more effectively. If the dose is miss or skip, contact the doctor or clinic. **DO NOT** take a double dose.

Based on the INR, you may have to change the dose of warfarin frequently, especially when taking of medication starts. The required dose of warfarin varies greatly among patients. Patients needing a higher dose of warfarin are not at greater risk of side effects than those requiring lower doses.

## IMPORTANT PRECAUTIONS WHILE TAKING ANTICOAGULATION MEDICATION

- Stay safe while taking medication
- Be careful when using objects (such as sharp objects) that can cause injury or bleeding
- Call the doctor or go to the hospital immediately if patient have any cuts or injuries that will not stop bleeding even after applying constant pressure

Call the doctor or the clinic when;

- While start of taking new medication or stop taking
- Any major diet changes or before starting any kind of weight loss plan
- If patient have any questions about the medications or blood testing
- Go for blood tests as instructed

## **SIDE EFFECTS**

The most common side effects are slight visible bleeding. sometimes may notice;

- A small amount of bleeding from gums while brushing the teeth
- Occasional nosebleeds, especially in winter when the air is dry
- Easy brushing
- Bleeding after a minor cut that stops within a few minutes
- Menstrual bleeding that is a little heavier than normal

## **HOW TO PREVENT SIDE EFFECTS**

- Use a soft toothbrush
- If sensitive to dry air, use a humidifier in the winter
- Avoid contact sports or activities in which injuries are common
- Eat a regular and nutritious diet and discuss any planned diet changes with the doctor or nurse

## **IF THE PATIENT HAS MINOR CUT OR BRUISE**

Treat the injury with basic first aid. If significant bleeding continues for longer than 10 minutes despite applying pressure, call the doctor or go to a hospital emergency room.

## **CONDITIONS THAT REQUIRE IMMEDIATE MEDICAL ATTENTION**

- Large amounts of noticeable bleeding
- Red, dark, coffee, or cola coloured urine
- Bowel movements that are red or look like tar
- Bleeding for the gums or nose that does not stop quickly, within 10 minutes
- Vomit that is coffee coloured or bright red
- Anything red in colour that the patient coughup
- A cut that will not stop bleeding within 10 minutes
- A serious fall or hit on head
- Any unexplained dizziness or weakness

## GOING TO THE DENTIST

Before going to doctor inform about intake of warfarin. the doctor may ask about most recent INR results or may request about blood test reports before the appointment.

Usually the dental treatment can go ahead as normal without any anticoagulants dose being stopped or the dose being adjusted.

## DIET PLAN

Vitamin K affects the way that blood clots form. It is found in ,any foods and it can affect the INR results.it is important to eat a healthy and balanced diet. All of these foods are healthy, but eating them in large amounts may lower the INR results. There is no right or wrong amount of vitamin K that one should take. It is more important to take in the same amount each day. That way, the INR results will stay consistent.

## FOODS RICH IN VITAMIN K

- Green leafy vegetables (kale, spinach, green leaf or romaine lettuce)
- Parsley
- Asparagus
- Broccoli
- Coleslaw
- Brussels sprouts.

## THE FOODS SHOULD TAKE, BUT IN SMALL QUANTITY

- Flaxseeds
- Garlic
- Cranberry juice
- Mango
- Ginger
- Green tea
- Avocado
- Soy (soy milk, tofu)
- Avoid natto (fermented soy), grapefruit, Seville oranges, tangelos and their juices

## ABOUT ALCOHOL

Alcohol can affect the anticoagulant dose. Keep the alcohol intake at two drinks or less per day. Avoid binge drinking. It will affect the INR and can result in other serious problems.

## NEW ORAL ANTICOAGULATION MEDICATIONS

Recently three new oral anticoagulant medication available in Canada. These are DABIGATRAN (also called Pradaxa) RIVAROXABAN (also called Xarelto) APIXABAN (also called Eliquis)

- These new medications CANNOT be taken by patients with severe heart valve problems, artificial heart valves, or severe kidney disease
- Blood test should be done to check the kidney functions
- These new medications **do not need INR blood work** monitoring or dose changes



## Conclusion:

Patient education is entering a new era where the accountability in educational outcomes, interest in literacy, and the process of patient education is influenced by cost. step necessary in improving anticoagulation outcomes is prioritizing educational content and using validate instruments.

## Reference:

1. Prevent Harm from High-Alert Medications. Institute for Healthcare Improvement; Cambridge, MA, USA: 2012. [(accessed on 29 March 2018)]. Available online: <http://www.ismp.org/Tools/highalertmedications.pdf>.
2. Piazza G., Nguyen T.N., Cios D., Labreche M., Hohlfelder B., Fanikos J., Fiumara K., Goldhaber S.Z. Anticoagulation-associated adverse drug events. *Am. J. Med.* 2011;124:1136–1142. doi: 10.1016/j.amjmed.2011.06.009.
3. The Joint Commission National Patient Safety Goals 2018. [(accessed on 19 April 2018)]; Available online: [https://www.jointcommission.org/assets/1/6/NPSG\\_Chapter\\_HAP\\_Jan2018.pdf](https://www.jointcommission.org/assets/1/6/NPSG_Chapter_HAP_Jan2018.pdf).
4. Garcia D.A., Witt D.M., Hylek E., Wittkowsky A.K., Nutescu E.A., Jacobson A., Moll S., Merli G.J., Crowther M., Earl L., et al. Delivery of optimized anticoagulant therapy: Consensus statement from the Anticoagulation Forum. *Ann. Pharmacother.* 2008;42:979–988. doi: 10.1345/aph.1L098.
5. Saokaew S., Permsuwan U., Chaiyakunapruk N., Nathisuwan S., Sukonthasarn A. Effectiveness of pharmacist-participated warfarin therapy management: A systematic review and metaanalysis. *J. Thromb. Haemost.* 2010;8:2418–2427. doi: 10.1111/j.1538-7836.2010.04051.x
6. Bishop M.A., Streiff M.B., Ensor C.R., Tedford R.J., Russell S.D., Ross P.A. Pharmacist- managed international normalized ratio patient self-testing is associated with increased time in therapeutic range in patients with left ventricular assist devices at an academic medical center. *ASAIO J.* 2014;60:193–198. doi: 10.1097/MAT.0000000000000047.
7. Bungard T.J., Gardner L., Archer S.L., Hamilton P., Ritchie B., Tymchak W., Tsuyuki R.T. Evaluation of a pharmacist-managed anticoagulation clinic: Improving patient care. *Open Med.* 2009;3:e16–e21.
8. Challen L., Agbahiwe S., Cantieri T., Olivetti J.G., Mbah T., Mendoza-Becerra Y., Munoz C., Nguyen M., Partee K., Lal L., et al. Impact of Point-of-Care Implementation in Pharmacist-Run Anticoagulation Clinics within a Community-Owned Health System: A Two-Year Retrospective Analysis. *Hosp. Pharm.* 2015;50:783–788. doi: 10.1310/hpj5009-783.
9. Chilipko A.A., Norwood D.K. Evaluating warfarin management by pharmacists in a community teaching hospital. *Consult. Pharm.* 2014;29:95–103.
10. Garton L., Crosby J.F. A retrospective assessment comparing pharmacist-managed anticoagulation clinic with physician management using international normalized ratio stability. *J. Thromb. Thrombolysis.* 2011;32:426–430. doi: 10.1007/s11239-011-0612-7.
11. Holden J., Holden K. Comparative effectiveness of general practitioner versus pharmacist dosing of patients requiring anticoagulation in the community. *J. Clin. Pharm. Ther.* 2000;25:49–54. doi: 10.1046/j.1365-2710.2000.00262.x.



12. Young S., Bishop L., Twells L., Dillon C., Hawboldt J., O'Shea P. Comparison of pharmacist managed anticoagulation with usual medical care in a family medicine clinic. *BMC Fam. Pract.* 2011;12:88. doi: 10.1186/1471-2296-12-88.
13. Ingram S.J., Kirkdale C.L., Williams S., Hartley E., Wintle S., Sefton V., Thornley T. Moving anticoagulation initiation and monitoring services into the community: Evaluation of the Brighton and hove community pharmacy service. *BMC Health Serv. Res.* 2018;18:91. doi: 10.1186/s12913-018-2901-8.
14. Harrison J., Shaw J.P., Harrison J.E. Anticoagulation management by community pharmacists in New Zealand: An evaluation of a collaborative model in primary care. *Int. J. Pharm. Pract.* 2015;23:173–181. doi: 10.1111/ijpp.12148.
15. Locke C., Ravnan S.L., Patel R., Uchizono J.A. Reduction in warfarin adverse events requiring patient hospitalization after implementation of a pharmacist-managed anticoagulation service. *Pharmacotherapy.* 2005;25:685–689. doi: 10.1592/phco.25.5.685.63582.
16. Rudd K.M., Dier J.G. Comparison of two different models of anticoagulation management services with usual medical care. *Pharmacotherapy.* 2010;30:330–338. doi: 10.1592/phco.30.4.330.
17. Holbrook A., Schulman S., Witt D.M., Vandvik P.O., Fish J., Kovacs M.J., Svensson P.J., Veenstra D.L., Crowther M., Guyatt G.H. 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;141(Suppl. 2):e152S–e184S. doi: 10.1378/chest.11-2295.
18. Wittkowsky A.K. Impact of target-specific oral anticoagulants on transitions of care and outpatient care models. *J. Thromb. Thrombolysis.* 2013;35:304–311. doi: 10.1007/s11239-013-0879-y.
19. Zdyb E.G., Courtney D.M., Malik S., Schmidt M.J., Lyden A.E. Impact of Discharge Anticoagulation Education by Emergency Department Pharmacists at a Tertiary Academic Medical Center. *J. Emerg. Med.* 2017;53:896–903. doi: 10.1016/j.jemermed.2017.06.008.
20. Dharmarajan T.S., Gupta A., Baig M.A., Norkus E.P. Warfarin: Implementing its safe use in hospitalized patients from nursing homes and community through a performance improvement initiative. *J. Am. Med. Dir. Assoc.* 2011;12:518–523. doi: 10.1016/j.jamda.2010.04.007.
21. Wang Y., Kong M.C., Lee L.H., Ng H.J., Ko Y. Knowledge, satisfaction, and concerns regarding warfarin therapy and their association with warfarin adherence and anticoagulation control. *Thromb. Res.* 2014;133:550–554. doi: 10.1016/j.thromres.2014.01.002.
22. Manzoor B.S., Lee T.A., Sharp L.K., Walton S.M., Galanter W.L., Nutescu E.A. Real- World Adherence and Persistence with Direct Oral Anticoagulants in Adults with Atrial Fibrillation. *Pharmacotherapy.* 2017;37:1221–1230. doi: 10.1002/phar.1989.
23. Heidbuchel H., Verhamme P., Alings M., Antz M., Hacke W., Oldgren J., Sinnaeve P., Camm A.J., Kirchhof P. European Heart Rhythm Association. European Heart Rhythm Association practical guide on the use of new oral anticoagulants in patients with non- valvular atrial fibrillation. *Europace.* 2013;15:625–651. doi: 10.1093/europace/eut083.
24. Burnett A.E., Mahan C.E., Vazquez S.R., Oertel L.B., Garcia D.A., Ansell J. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J. Thromb. Thrombolysis.*

2016;41:206–232. doi: 10.1007/s11239-015-1310-7.

25. Simon J., Hawes E., Deyo Z., Bryant Shilliday B. Evaluation of prescribing and patient use of target-specific oral anticoagulants in the outpatient setting. *J. Clin. Pharm. Ther.* 2015 doi: 10.1111/jcpt.12296.
26. Howard M., Lipshutz A., Roess B., Hawes E., Deyo Z., Burkhart J., Moll S., Shilliday B. Identification of Risk Factors for Inappropriate and Suboptimal Initiation of Direct Oral Anticoagulants. *J. Thromb. Thrombolysis.* 2017;43:149–156. doi: 10.1007/s11239-016-1435-3.
27. Eliquis Bristol-Myers Squibb Company; Princeton, NJ, USA: 2012.
28. Pradaxa [package insert] Boehringer Ingelheim Pharmaceuticals Inc.; Ridgefield, CT, USA: 2010  
Xarelto , Janssen Pharmaceuticals, Inc.; Titusville, NJ, USA: 2011.
29. Savaysa [package insert] Daiichi Sankyo, Inc.; Basking Ridge, NJ, USA: 2017.
30. Chan L.L., Crumpler W.L., Jacobson A.K. Implementation of pharmacist-managed anticoagulation in patients receiving newer anticoagulants. *Am. J. Health Syst. Pharm.* 2013;70:1285–1286, 1288. doi: 10.2146/ajhp120468.
31. Lane D.A., Aguinaga L., Blomström-Lundqvist C., Boriani G., Dan G.A., Hills M.T., Hylek E.M., LaHaye S.A., Lip G.Y., Lobban T., et al. Cardiac tachyarrhythmias and patient values and preferences for their management: The European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE) *Europace.* 2015;17:1747–1769. doi: 10.1093/europace/euv233.
32. James J. Patient engagement. *Health Affairs* 2013. [(accessed on 28 January 2018)]; Available online: [http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief\\_id=86](http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief_id=86).
33. Hibbard J.H., Greene J., Overton V. Patients with lower activation associated with higher costs; delivery systems should know their patients’ “Scores” *Health Aff.* 2013;32:216– 222. doi: 10.1377/hlthaff.2012.1064.
34. Institute of Medicine. Committee on Identifying and Preventing Medication Errors. *Preventing Medication Errors*.
35. The National Academies Press; Washington, DC, USA: 2006.
36. American Society of Health-System Pharmacy ASHP Guidelines on Pharmacist- Conducted Patient Education and Counseling. [(accessed on 29 March 2018)]; Available online: <https://www.ashp.org/DocLibrary/BestPractices/OrgGdlPtEduc.aspx>.
37. American Society of Hospital Pharmacists ASHP statement on pharmaceutical care. [(accessed on 29 March 2018)]; *Am. J. Hosp. Pharm.* 1993 50:1720–1723. Available online: <http://www.ashp.org/doclibrary/bestpractices/orgstpharmacare.aspx>.
38. Johnson A., Sandford J., Tyndall J. Written and verbal information versus verbal information only for patients being discharged from acute hospital settings to home. *Cochrane Database Syst. Rev.* 2003 doi: 10.1002/14651858.CD003716. Institute for Safe Medication Practices (ISMP) [(accessed on 28 January 2018)];2003 Available online: <https://www.ismp.org/Survey/surveyresults/NursingSurvey.asp>.
39. Health Literacy in Pharmacy. Agency for Healthcare Research and Quality; Rockville, MD, USA:

[(accessed on 29 March 2018)]. Available online: <http://www.ahrq.gov/professionals/education/curriculum-tools/pharmlitqi/ppt-slides.html>.

40. Davis T.C., Wolf M.S., Bass P.F., III, Thompson J.A., Tilson H.H., Neuberger M., Parker R.M. Literacy and misunderstanding prescription drug labels. *Ann. Intern. Med.* 2006; 145:887–894. doi: 10.7326/0003-4819-145-12-200612190-00144.
41. Hernández Madrid A., Potpara T.S., Dages N., Chen J., Larsen T.B., Estner H., Todd D., Bongioni M.G., Sciaraffiam E., Proclerm A., et al. Differences in attitude, education, and knowledge about oral anticoagulation therapy among patients with atrial fibrillation in Europe: Result of a self-assessment patient survey conducted by the European Heart Rhythm Association. *Europace.* 2016;18:463–467. doi: 10.1093/europace/euv448.
42. Anticoagulation Toolkit: Reducing Adverse Drug Events & Potential Adverse Drug Events with Unfractionated Heparin, Low Molecular Weight Heparins and Warfarin.
43. Moreland C.J., Kravitz R.L., Paterniti D.A., Li C.S., Lin T.C., White R.H. Anticoagulation education: Do patients understand potential medication-related emergencies? *Jt. Comm. J. Qual. Patient Saf.* 2013;39:22–31. doi: 10.1016/S1553-7250(13)39005-9.
44. Witt D.M., Clark N.P., Kaatz S., Schnurr T., Ansell J.E. Guidance for the practical management of warfarin therapy in the treatment of venous thromboembolism. *J. Thromb. Thrombolysis.* 2016;41:187–205. doi: 10.1007/s11239-015-1319-y

