

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

**4,800**

Open access books available

**122,000**

International authors and editors

**135M**

Downloads

Our authors are among the

**154**

Countries delivered to

**TOP 1%**

most cited scientists

**12.2%**

Contributors from top 500 universities



**WEB OF SCIENCE™**

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.

For more information visit [www.intechopen.com](http://www.intechopen.com)



---

# Non-Vitamin K Antagonist Oral Anticoagulants, Clinical Use, Real-World Data, and Reversal of Anticoagulant Effect

---

Özcan Başaran, Volkan Doğan, Ibrahim Altun and Murat Biteker

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/64464>

---

## Abstract

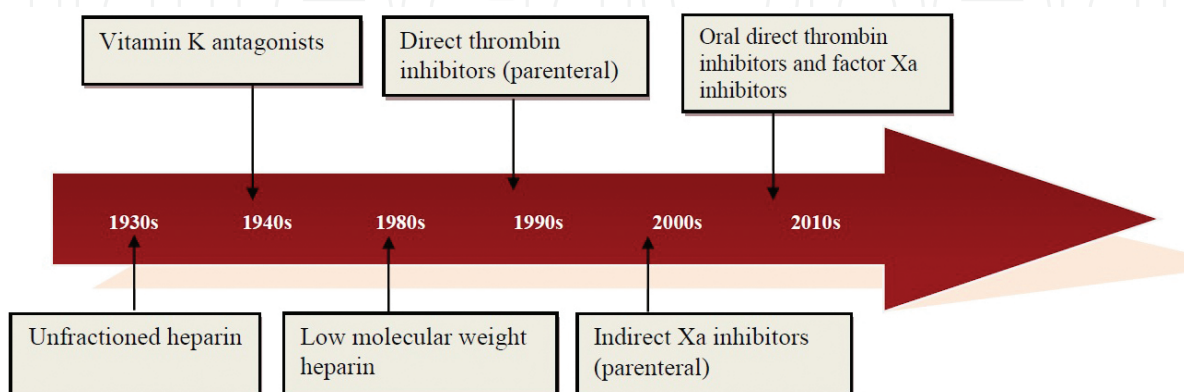
Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice and is associated with a higher risk of thromboembolic events. CHA<sub>2</sub>DS<sub>2</sub>-VASc score enables identification of those patients with AF who will most benefit from anticoagulation therapy and low-risk patients with AF who do not need any antithrombotic therapy. Antithrombotic drugs especially oral anticoagulants (OACs) are the mainstay of therapy to prevent stroke in patients with AF. Although vitamin K antagonists (VKAs) were the only available drugs for decades, numerous non-vitamin K antagonist oral anticoagulants (NOACs) have been developed and marketed for stroke prevention in recent years. The risk of stroke was reported to decline up to 68 % with OAC therapy, associated with good anticoagulation control with VKAs, assessed by time in therapeutic range (TTR). In low TTR values, VKAs were found to be associated with severe complications, and a minimum TTR of 58 % should be achieved to expect a net benefit from being on OAC therapy. Narrow therapeutic index, drug-drug interactions, and the need for close monitoring are the main disadvantages of VKAs, and management of patients have dramatically improved after the introduction of NOACs. NOACs have a more predictable anticoagulant effect which allows a fixed-dose regimen. The efficacy and safety of NOACs have been shown not only in large randomized controlled clinical trials but also in observational studies. The main advantages of NOACs such as “fixed-dose regimen” and “no need for regular anticoagulant therapy monitoring” may also be the Achilles heel of the use of these agents. Fixed-dose regimen may not be appropriate for elderly, for patients with chronic kidney disease, and for patients using interacting drugs. Adherence to NOAC therapy is another concern as it may be as low as 50 % in the chronic use of cardiovascular drugs, especially if the drug has no apparent effect to the patient. Thus, appropriate use of

OACs among non-valvular AF (NVAF) patients is essential for stroke prophylaxis. We intended to review the use of OAC therapy among (NVAF) patients.

**Keywords:** Oral anticoagulants, Atrial fibrillation, Stroke prophylaxis

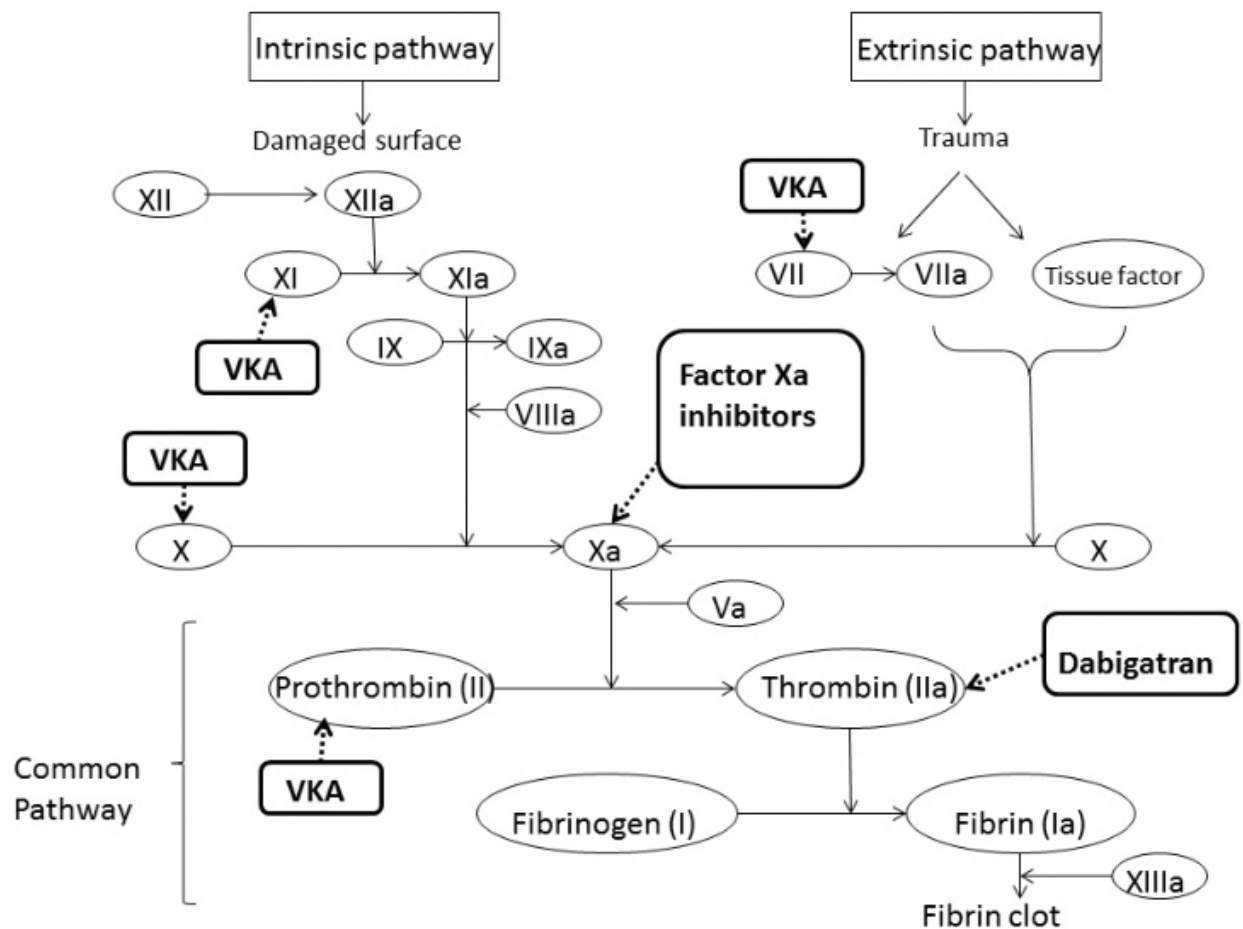
## 1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice and is associated with a higher risk of thromboembolic events [1]. The most devastating complication of AF is ischemic stroke. AF is the most frequent cause of cardioembolic stroke and nearly 20 % of all stroke events. Cardioembolic stroke has a greater morbidity and mortality comparing other stroke subtypes. Nevertheless, oral anticoagulant (OAC) drugs offer an effective stroke prevention strategy [2]. Recent guidelines recommend to start an OAC drug for patients who have AF and high risk of stroke assessed by stroke risk schemes [3]. The most recommended risk scheme is known by the acronym CHA<sub>2</sub>DS<sub>2</sub>VASc (congestive heart failure, hypertension, age  $\geq 75$ , diabetes, stroke history, vascular disease, ages 65–74, and sex), and patients with a score  $\geq 2$  should be anticoagulated. The discovery and development of anticoagulants are some of the most interesting in pharmaceutical history and started with the discovery of heparin in 1916 (**Figure 1**). Studies on anticoagulant drugs led to the commercialization of dicoumarol in 1941, and efforts to develop an effective rodenticide resulted in synthesis of warfarin (Wisconsin Alumni Research Foundation), which was approved for medical use in 1954. For decades, vitamin K antagonists (VKAs) were the only available oral anticoagulants. The risk of stroke was reported to decline up to 68 % with OAC therapy, associated with good anticoagulation control with VKAs, assessed by time in therapeutic range (TTR). In low TTR values VKAs were found to be associated with severe complications, and a minimum TTR of 58 % should be achieved to expect a net benefit from being on OAC therapy [4]. The use of VKAs can also be challenging due to narrow therapeutic index, drug-drug interactions, and the need for close monitoring. Over the last years, non-vitamin K antagonist oral anticoagulants (NOACs) have been developed, including direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivarox-



**Figure 1.** Developmental history of anticoagulants.

aban, apixaban, and edoxaban) which have a more predictable anticoagulant effect allowing a fixed-dose regimen. Their therapeutic use for prevention of cardioembolic complications was validated in large phase III trials, demonstrating their non-inferiority and even superiority, in some cases, to warfarin [5–8]. Therefore, the use of NOACs is currently recommended by guidelines, along with VKAs, for stroke prevention in patients with non-valvular atrial fibrillation (NVAF). The risk of hemorrhage should also be assessed prior to starting an OAC drug. One of the validated risk scores is hypertension, renal or liver failure, stroke history, bleeding history, labile international normalized ratio (INR), age > 65 years, drugs predisposing to bleeding, and alcohol use (HAS-BLED). Bleeding risk assessment with HAS-BLED should not be used as an excuse not to prescribe OAC but rather to highlight those patients in whom caution with such treatment and regular review is warranted. Both VKA and NOACs have specific targets in the coagulation cascade (**Figure 2**). The INR is widely used for the measurement of anticoagulant effect of VKAs. However, the anticoagulant effect of NOACs cannot be measured with routine coagulation assays. While activated partial thromboplastin time (aPTT) is elevated in patients taking dabigatran and edoxaban, it is not correlated with the dose of the drug. Ecarin-clotting time (ECT), thrombin time (TT), and dilute thrombin time (dTT) assays



**Figure 2.** The coagulation cascade. VKA, vitamin K antagonist.

might be used for dabigatran's anticoagulant effect and anti-factor Xa assays for rivaroxaban and apixaban. However, these assays are not commercially available that restricts their use in most institutions. Although NOACs have clear advantages comparing warfarin, it may not be convenient for some patients. They were not studied in patients with severe renal failure (estimated glomerular filtration rate (GFR) <30 mL/min), and a dose reduction is recommended for patients with moderate renal failure (GFR: 30–50 mL/min). The use of NOACs in patients with mechanical heart valves is contraindicated. The RE-ALIGN (randomized, phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement) study showed that dabigatran was neither effective nor safe in patients with mechanical heart valves [8]. However, it was safe and effective in other types of valvular diseases such as mitral regurgitation, aortic regurgitation, aortic stenosis, tricuspid regurgitation, and mild mitral stenosis [9]. Thus the term “valvular AF” defines patients with mechanical heart valves and patients with mitral stenosis (mostly rheumatic) [10]. In this chapter, we will review the clinical use, real-world data, and reversal of anticoagulant effect of NOACs for stroke prevention in patients with NVAf as well as discuss the limitations of the new agents.

## 2. Direct thrombin inhibitors

Direct thrombin inhibitors act by inhibiting thrombin which converts fibrinogen to fibrin and activates platelets (**Figure 2**). Ximelagatran was the first-studied direct thrombin inhibitor for stroke prophylaxis in NVAf patients, but it was withdrawn from market because of safety concerns about hepatotoxicity.

### 2.1. Dabigatran

Dabigatran was the first-introduced NOAC into clinical practice. It was predominantly eliminated by kidneys; thus, a dose reduction was proposed for patients with renal failure [3]. The European Medical Agency (EMA) has approved two doses (110 and 150 mg) of dabigatran with a recommendation of dose reduction in older patients with renal failure. However, Food and Drug Administration (FDA) did not approve the 110 mg bid and approved 75 mg bid for patients with renal failure. FDA recommended the higher dose (150 mg bid) for most of the patients. Though it remains a controversial issue, FDA did not change its recommendations after a mini-sentinel [11]; however, a post hoc analysis of RE-LY trial showed better outcomes if European label was used [12]. Nevertheless, with the available data for both doses, dabigatran is an attractive alternative to warfarin in patients with NVAf. A meta-analysis of real-world data also showed similar efficacy compared to warfarin with less intracranial bleeding [13]. The authors concluded dabigatran should be used cautiously in older patients with a history of gastrointestinal bleeding.

Although dabigatran was well tolerated, prevalence of dyspepsia was increased compared to warfarin (11.8 % with 110 mg bid, 11.3 % with 150 mg bid, 5.8 % with warfarin). This side effect has been attributed to tartaric acid component in dabigatran etexilate capsule [14]. Although dabigatran has lower rates of drug-drug interaction, it has significant interaction with p-

glycoprotein inhibitors (e.g., ketoconazole, amiodarone, verapamil) and inducers (rifampin). A dose reduction was proposed for patients taking concomitant verapamil.

### 3. Factor Xa inhibitors

Factor Xa has an important role in the coagulation cascade (**Figure 2**). Currently there are three approved factor Xa inhibitors—rivaroxaban, apixaban, and edoxaban—and one under investigation betrixaban.

#### 3.1. Rivaroxaban

Rivaroxaban was the first-approved factor Xa inhibitor for stroke prophylaxis in NVAf. Rivaroxaban 15 mg od was given for patients with creatinine clearance 30–50 mL/min. It was found as effective as warfarin for stroke or systemic embolism prevention without an increase in major bleeding [7]. In addition, it was associated with less intracranial bleeding. Real-world analysis of rivaroxaban also revealed comparable bleeding rates with phase III trial with a significant heterogeneity in bleeding rates across studies [15]. A real-world analysis of rivaroxaban showed similar results comparing warfarin for safety and efficacy; however, venous thromboembolism (VTE) events were fewer in rivaroxaban patients [16]. Another real-world analysis showed that rivaroxaban may even be better in terms of hemorrhagic complications or at least as safe as warfarin [17]. Coleman et al. showed that rivaroxaban may be better for stroke prophylaxis in a German medical record study [18]. In conclusion, rivaroxaban was shown to be as effective and safe as warfarin in real-world data.

#### 3.2. Apixaban

Apixaban is a factor Xa inhibitor that has been approved for stroke prophylaxis in patients with NVAf. The risk of gastrointestinal bleeding was comparable between apixaban and warfarin, and apixaban showed a reduction in mortality rates [6]. Apixaban was also evaluated in patients who could not take warfarin in apixaban versus acetylsalicylic acid to prevent stroke (AVERROES) trial [19]. Apixaban was more effective and as safe as aspirin in stroke prophylaxis; thus, the study was prematurely terminated because of clear advantage of apixaban. The benefits of apixaban were consistent regardless of age with a greater absolute risk reduction in the elderly [20].

#### 3.3. Edoxaban

Edoxaban is a factor Xa inhibitor that has been approved for stroke prophylaxis recently. It has been tested in two different doses (30 and 60 mg) against warfarin [5]. The high dose of edoxaban was associated with a trend toward better efficacy versus warfarin for stroke and systemic embolism prophylaxis. A real-world modeling analysis also showed edoxaban 60 mg od might be superior to warfarin and 30 mg od dose [21]. The efficacy of edoxaban was decreased in patients with a creatine clearance <95 mL/min. Thus it is not recommended in these patients.

### 3.4. Betrixaban

Betrixaban is a factor Xa inhibitor with minimal renal excretion and a long half-life. It has minimal hepatic metabolism. Thus it could be used for patients with renal and hepatic impairment. The anticoagulant effect and safety of betrixaban were compared against warfarin in NVAF patients in a phase II study (EXPLORE-Xa) [22]. Betrixaban was well tolerated, and bleeding was lowest in betrixaban 40 mg group compared warfarin or betrixaban 60–80 mg. The study was primarily designed to assess safety of betrixaban, and it does not provide an information for the efficacy. The pharmacometric modeling suggests that 80 mg daily betrixaban has comparable anticoagulant effect to warfarin. The ongoing phase III trial (APEX) is currently investigating the protective effect of betrixaban in venous thromboembolism (VTE) against enoxaparin in acute medically ill patients. The topline results of the study showed betrixaban given once daily at a dose of 80 mg for 35–47 days was more effective than injectable enoxaparin given at a dose of 40 mg for 6–14 days [23]. There was no increase in major bleeding rates.

## 4. Comparison of real-world data and phase III trials

Large phase III trials showed a comparable effect and better safety profile of NOACs for stroke thromboprophylaxis. However, these studies included highly selected patients without severe comorbidities with strict follow-up procedures. In addition all the patients in these trials were OAC indicated. However, observational studies showed OAC use was 60–80 % in real-world settings [24–27]. Another concern regarding OAC therapy is the appropriate use. Inappropriate use might be up to 87 % in warfarin and 47 % in NOACs [28, 29]. The efficacy and safety of NOACs were confirmed in observational studies. Danish registry compared the safety and efficacy of dabigatran against warfarin [30]. Both 110 and 150 mg bid doses of dabigatran were as effective as warfarin for stroke prophylaxis, and 110 mg bid but not 150 mg bid was associated with lower rates of gastrointestinal bleeding. A recent meta-analysis also showed similar stroke rates with dabigatran comparing warfarin and lower intracranial bleeding with an elevated risk for gastrointestinal bleeding [24]. Xarelto® on prevention of stroke and non-central nervous system systemic embolism in patients with non-valvular atrial fibrillation (XANTUS) trial with rivaroxaban showed better efficacy and safety profile in a real-world dataset [31]. A propensity score-matched study also showed the efficacy and safety of rivaroxaban in real-world data [32]. These observations showed NOACs are safe and effective treatment options for stroke prevention in NVAF patients. However, a recent real-world database study from the USA revealed a 4.4-fold increase in the use of reduced dose of apixaban comparing ARISTOTLE trial [33].

## 5. Reversal agents

One of the main difficulties with NOACs is the lack of specific reversal agents. Despite the lower rates of hemorrhage with NOACs comparing warfarin, a hemorrhagic complication that

needs medical support may occur with NOACs. While a minor bleeding might be solved with supportive care, specific medications should be used for major bleedings. Perioperative management for patients on NOAC may also be challenging especially in emergency situations. Activated charcoal should be administered if the drug has recently been taken. Hemodialysis is an option for patients on dabigatran. Tranexamic acid and aminocaproic acid are also nonspecific agents that can be used to control bleeding. Fresh frozen plasma is not an option; however, prothrombin plasma concentrates (PCC) especially four-factor PCC are more useful. However, there has been an unmet need for specific reversal agents until idarucizumab's FDA approval. Idarucizumab is a monoclonal antibody that was approved for reversal of dabigatran's anticoagulant effect. Andexanet alfa is a specific antidote of factor Xa inhibitors, and ciraparantag is a universal reversal agent.

### **5.1. Idarucizumab**

Idarucizumab is a monoclonal antibody fragment that specifically binds to dabigatran and antagonizes its effect at a 1:1 ratio. Its half-life is 45 min and thus it may require repeat infusion. The effect of idarucizumab was shown by measuring dTT and ECT which are specific for dabigatran activity. The efficacy and safety of idarucizumab were evaluated in RE-VERSE AD (a study of the reversal effects of idarucizumab on active dabigatran) phase III trial, and a 5 g intravenous infusion was found safe and effective [34]. In 35 patients with major bleeding, hemostasis was restored at a median of 11.4 h, and in 36 patients who underwent urgent procedure, normal hemostasis was reported in 33, mildly abnormal in 2, and moderately abnormal in 1 patient. Idarucizumab was approved by FDA for the reversal of dabigatran's anticoagulant effect. It does not have prolonged effect, and dabigatran can be restarted after 24 h.

### **5.2. Andexanet alfa**

Andexanet alfa is a recombinant factor Xa inhibitor antidote. It specifically binds to factor Xa inhibitors thus reduces their unbound concentrations. It has been studied in animal and human studies and reversed anticoagulant effect of rivaroxaban, apixaban, and edoxaban [35, 36]. The effect of andexanet alfa disappears in the absence of a maintenance infusion. Consistent with the half-life of andexanet alfa, the anticoagulant effect reversal was comparable with placebo after 2 h cessation of infusion. Levels of D-dimer and prothrombin fragments 1 and 2 were elevated in patients receiving andexanet alfa; however, this was not associated with clinical thrombotic events [36]. Andexanet alfa is a potential universal antidote for factor Xa inhibitors.

### **5.3. Ciraparantag**

Ciraparantag is a small molecule that binds unfractionated and low-molecular-weight heparin. It binds to endogenous targets of anticoagulants that prevent their anticoagulant effect. It also binds to dabigatran and factor Xa inhibitors; thus, it has a wide range of action. The first human study with this drug reported effective and safe reversal of anticoagulant effect of edoxaban



within 10–30 min [37]. Ciraparantag is a promising universal reversal agent of anticoagulant effect.

## 6. Conclusion

The risk of ischemic stroke is increased in patients with AF. Recent guidelines for the evaluation of AF recommend OAC therapy for AF patients who had moderate to high risk of stroke. Although NOACs have clear advantages over warfarin, there are some concerns such as the lack of specific antidote, older patients, lower creatinine clearance, risk of gastrointestinal hemorrhage, and cost. Specific antidotes are under development—idarucizumab has already been approved—and lower doses of the drugs might be a solution for high-bleeding-risk-group patients. The phase III trials and real-world data indicated NOACs were as safe and effective as warfarin, while some studies showed better net clinical benefit with NOACs. The introduction of NOACs has led to an improvement in the management of patients with NVAf; however, there is need for great effort for the optimization of stroke prevention strategies in AF.

## Author details

Özcan Başaran\*, Volkan Doğan, Ibrahim Altun and Murat Biteker

\*Address all correspondence to: basaran\_ozcan@yahoo.com

Department of Cardiology, Faculty of Medicine, Muğla Sıtkı Koçman University, Muğla, Turkey

## References

- [1] Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults. JAMA [Internet]; 2001 May 9 [cited 2016 Apr 6]; 285(18):2370. Available from: <http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.285.18.2370>
- [2] Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med [Internet]. 2007 Jun 19 [cited 2016 Apr 6];146(12):857–67. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17577005>
- [3] Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. Eur

- Heart J [Internet]. 2012;33(21):2719–47. Available from: <http://eurheartj.oxfordjournals.org/content/33/21/2719.abstract>
- [4] Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation* [Internet]. 2008 Nov 11 [cited 2016 Apr 19];118(20):2029–37. Available from: <http://circ.ahajournals.org/cgi/doi/10.1161/CIRCULATIONAHA.107.750000>
- [5] Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* [Internet]. 2013;369:2093–104. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24251359>
- [6] Granger CB, Alexander JH, McMurray JJ V, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* [Internet]. 2011;365(11):981–92. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21870978>
- [7] Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* [Internet]. 2011;365(10):883–91. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21830957>
- [8] Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* [Internet]. 2013 Sep 26 [cited 2016 Apr 16];369(13):1206–14. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJMoa1300615>
- [9] Ezekowitz MD, Parise H, Nagarakanti R, Noack H, Brueckmann M, Clemens A, et al. comparison of dabigatran versus warfarin in patients with atrial fibrillation and valvular heart disease: the re-ly® trial. *J Am Coll Cardiol* [Internet]; 2014 Apr [cited 2016 Apr 16];63(12):A325. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0735109714603259>
- [10] Başaran Ö, Doğan V, Şahin C, Biteker M, Noseworthy PA, Yao X, et al. Non-vitamin K antagonist oral anticoagulants in valvular atrial fibrillation. *Int J Cardiol* [Internet]; 2016 Jun [cited 2016 Apr 17];212:357. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0167527316305502>
- [11] Southworth MR, Reichman ME, Unger EF. Dabigatran and postmarketing reports of bleeding. *N Engl J Med* [Internet]. 2013 Apr 4 [cited 2016 May 9];368(14):1272–4. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23484796>
- [12] Lip GYH, Clemens A, Noack H, Ferreira J, Connolly SJ, Yusuf S. Patient outcomes using the European label for dabigatran. A post-hoc analysis from the RE-LY database. *Thromb Haemost* [Internet]. 2014 May 5 [cited 2016 Apr 6];111(5):933–42. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24326736>
- [13] Romanelli RJ, Nolting L, Dolginsky M, Kym E, Orrico KB. Dabigatran versus warfarin for atrial fibrillation in real-world clinical practice: a systematic review and meta-

- analysis. *Circ Cardiovasc Qual Outcomes* [Internet]. 2016 Mar [cited 2016 May 9];9(2):126–34. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26812933>
- [14] Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* [Internet]. 2009;361(12):1139–51. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19717844>
- [15] Weeda ER, White CM, Peacock WF, Coleman CI. Rates of major bleeding with rivaroxaban in real-world studies of nonvalvular atrial fibrillation patients: a meta-analysis. *Curr Med Res Opin* [Internet]. 2016 Mar 16 [cited 2016 May 18];1–4. Available from: <http://www.tandfonline.com/doi/full/10.1185/03007995.2016.1161610>
- [16] Laliberté F, Cloutier M, Nelson WW, Coleman CI, Pilon D, Olson WH, et al. Real-world comparative effectiveness and safety of rivaroxaban and warfarin in nonvalvular atrial fibrillation patients. *Curr Med Res Opin* [Internet]. 2014 Jul [cited 2016 May 18];30(7):1317–25. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24650301>
- [17] Beyer-Westendorf J, Förster K, Pannach S, Ebertz F, Gelbricht V, Thieme C, et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. *Blood* [Internet]. 2014 Aug 7 [cited 2016 May 18];124(6):955–62. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24859362>
- [18] Coleman CI, Antz M, Ehlken B, Evers T, Patel MR, Mahaffey KW, et al. REal-LIfe Evidence of stroke prevention in patients with atrial Fibrillation—the RELIEF study. *Int J Cardiol* [Internet]; 2016 Jan [cited 2016 May 18];203:882–4. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0167527315304769>
- [19] Connolly SJ, Eikelboom J, Joyner C, Diener H-C, Hart R, Golitsyn S, et al. Apixaban in Patients with Atrial Fibrillation. *N Engl J Med* [Internet]. 2011 Mar 3 [cited 2016 Apr 19];364(9):806–17. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJMoa1007432>
- [20] Halvorsen S, Atar D, Yang H, De Caterina R, Erol C, Garcia D, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. *Eur Heart J*. 2014 Jul 21;35(28):1864–72
- [21] Blann AD, Banerjee A, Lane DA, Torp-Pedersen C, Lip GYH. Net clinical benefit of edoxaban versus no treatment in a “real world” atrial fibrillation population: a modelling analysis based on a nationwide cohort study. *Int J Cardiol* [Internet]. 2015 Dec 15 [cited 2016 May 18];201:693–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26379097>
- [22] Connolly SJ, Eikelboom J, Dorian P, Hohnloser SH, Gretler DD, Sinha U, et al. Betrixaban compared with warfarin in patients with atrial fibrillation: results of a phase 2, randomized, dose-ranging study (Explore-Xa). *Eur Heart J* [Internet]. 2013 May [cited

- 2016 Apr 14];34(20):1498–505. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23487517>
- [23] Portola Pharmaceuticals Announces Topline Results from Phase 3 APEX Trial of Betrixaban for Prevention of Blood Clots in Acute Medically Ill Patients [Internet]. 2016. Available from: <http://investors.portola.com/phoenix.zhtml?c=198136&p=irol-news-roomArticle&ID=2150685>
- [24] Romanelli RJ, Nolting L, Dolginsky M, Kym E, Orrico KB. Dabigatran versus warfarin for atrial fibrillation in real-world clinical practice. *Circ Cardiovasc Qual Outcomes* [Internet]. 2016 Mar [cited 2016 Apr 19];9(2):126–34. Available from: <http://circoutcomes.ahajournals.org/lookup/doi/10.1161/CIRCOUTCOMES.115.002369>
- [25] Fumagalli S, Said SAM, Laroche C, Gabbai D, Marchionni N, Boriani G, et al. Age-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe. *JACC Clin Electrophysiol* [Internet]. 2015 Aug [cited 2016 Feb 3];1(4):326–34. Available from: <http://www.sciencedirect.com/science/article/pii/S2405500X15000936>
- [26] Huisman M V, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, et al. Antithrombotic treatment patterns in patients with newly diagnosed nonvalvular atrial fibrillation: the GLORIA-AF Registry, Phase II. *Am J Med* [Internet]. 2015 Dec [cited 2015 Dec 14];128(12):1306–13.e1. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26239094>
- [27] Basaran O. ReAl-life Multicenter Survey Evaluating Stroke prevention strategies in non-valvular atrial fibrillation (RAMSES study). *Anatol J Cardiol* [Internet]. 2016 [cited 2016 Apr 19]; Available from: [http://www.journalagent.com/anatoljcardiol/pdfs/AJC-04127-ORIGINAL\\_INVESTIGATION-BASARAN.pdf](http://www.journalagent.com/anatoljcardiol/pdfs/AJC-04127-ORIGINAL_INVESTIGATION-BASARAN.pdf)
- [28] Basaran O, Filiz Basaran N, Cekic EG, Altun I, Dogan V, Mert GO, et al. PRescriptiOn PAttERns of Oral Anticoagulants in Nonvalvular Atrial Fibrillation (PROPER study). *Clin Appl Thromb Hemost* [Internet]. 2015 Oct 30 [cited 2016 Apr 19]; Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26519049>
- [29] Bell AD, Gross P, Heffernan M, Deschaintre Y, Roux J-F, Purdham DM, et al. Appropriate use of antithrombotic medication in canadian patients with nonvalvular atrial fibrillation. *Am J Cardiol* [Internet]. 2016 Apr 1 [cited 2016 Apr 19];117(7):1107–11. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26879070>
- [30] Larsen TB, Rasmussen LH, Skjøth F, Due KM, Callréus T, Rosenzweig M, et al. Efficacy and safety of dabigatran etexilate and warfarin in 'real-world' patients with atrial fibrillation: a prospective nationwide cohort study. *J Am Coll Cardiol* [Internet]. 2013 Jun 4 [cited 2016 Apr 18];61(22):2264–73. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23562920>
- [31] Camm AJ, Amarenco P, Haas S, Hess S, Kirchhof P, Kuhls S, et al. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke

- prevention in atrial fibrillation. *Eur Heart J* [Internet]. The Oxford University Press; 2016 Apr 7 [cited 2016 Apr 19];37(14):1145–53. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26330425>
- [32] Laliberté F, Cloutier M, Nelson WW, Coleman CI, Pilon D, Olson WH, et al. Real-world comparative effectiveness and safety of rivaroxaban and warfarin in nonvalvular atrial fibrillation patients. *Curr Med Res Opin* [Internet]. 2014 Jul [cited 2016 Apr 19];30(7):1317–25. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24650301>
- [33] Nguyen E, White CM, Patel MR, Fields LE, Peacock WF, Crivera C, et al. Doses of apixaban and rivaroxaban prescribed in real-world United States cardiology practices compared to registration trials. *Curr Med Res Opin* [Internet]. 2016 Apr 1 [cited 2016 May 12];1–3. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27009372>
- [34] Pollack C V., Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for dabigatran reversal. *N Engl J Med* [Internet]. 2015 Aug 6 [cited 2016 Apr 14];373(6):511–20. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJMoa1502000>
- [35] Lu G, DeGuzman FR, Hollenbach SJ, Karbarz MJ, Abe K, Lee G, et al. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. *Nat Med* [Internet]; 2013 Mar 3 [cited 2016 Apr 13];19(4):446–51. Available from: <http://www.nature.com/doi/abs/10.1038/nm.3102>
- [36] Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med* [Internet]. 2015 Dec 17 [cited 2016 Apr 13];373(25):2413–24. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJMoa1510991>
- [37] Ansell JE, Bakhrin SH, Lauicht BE, Steiner SS, Grosso M, Brown K, et al. Use of PER977 to reverse the anticoagulant effect of edoxaban. *N Engl J Med* [Internet]. 2014 Nov 27 [cited 2016 Apr 13];371(22):2141–2. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJMc1411800>

IntechOpen