

Minimizing the risk of hemorrhagic stroke during oral anticoagulant therapy for atrial fibrillation: The neurologist's perspective

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ABSTRACT

Until recently, warfarin has been the gold standard for reducing stroke risk and mortality in patients with atrial fibrillation (AF). The key goals of antithrombotic treatment are the primary and secondary prevention of ischemic stroke and systemic embolism while minimizing the risk of major bleeds. While highly effective, warfarin has several limitations that have led to well-documented underutilization and suboptimal care by both physicians and patients. Recently, two classes of novel oral anticoagulants (NOACs) have emerged that may overcome some of the clinical challenges associated with warfarin use: the oral direct thrombin inhibitors (dabigatran) and the oral direct factor Xa inhibitors (rivaroxaban, apixaban). Most recently, the US Food and Drug Administration approved edoxaban in January 2015 and a European Medicines Agency approval application was filed for edoxaban in 2014) [1]. As clinical experience and outcomes research continue to accumulate for NOACs, practical approaches for their clinical use and optimizing patient outcomes continue to evolve.

Keywords: atrial fibrillation, hemorrhagic stroke, anticoagulant therapy, NOAC, oral direct thrombin inhibitors, oral direct Xa inhibitors

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INTRODUCTION

By current estimates, approximately 1–2% of the world population suffers from AF [1–3], translating to an estimated 2.5–5 million people in the United States (US) and 4.5–6 million people in Europe [4,5]. As an age-dependent condition, one in four adults over age 40 will develop AF at some point in their life [6]. Due to increasing population size, worldwide prevalence is predicted to at least double in the next decades [1,2,7].

Stroke is a frequent and severe complication of AF. AF is an independent risk factor for the severity and risk of recurrent ischemic stroke [8], and carries about the same risk whether the AF is clinically significant or not [9]. AF is implicated in approximately 15–20% of all strokes [7] and these strokes are generally more severe, more disabling, and more frequently lethal compared to strokes from other etiologies [1,10]. Ischemic stroke is the most common stroke type overall, accounting for 85% of all strokes with the remaining 10–15% representing intracerebral hemorrhage [11,12]. Approximately half of the global burden of stroke is due to hemorrhagic stroke, because cerebral hemorrhages are so highly fatal [13].

History of a prior stroke has been identified as the strongest risk factor for recurrent stroke, conveying an average risk of 10% per year for recurrent stroke in patients with AF [1]. In fact, the sub-group analysis of patients with

a history of prior stroke or TIA participating in the ENGAGE AF-TIMI trial (edoxaban) found that those with a prior stroke or TIA had an approximately twice a higher baseline risk of stroke (ischemic or hemorrhagic) or systemic embolic event (SEE) than patients with no prior stroke/TIA [14]. Therefore, the secondary prevention of stroke is a key issue for neurologists caring for patients with AF.

In antithrombotic therapy, patient outcomes can be optimized through the following strategies: accurate assessment of stroke and bleeding risks; individualized selection and tailoring of the most appropriate oral anticoagulant agent; increased understanding of pharmacokinetic/dynamic effects of these drugs; and awareness of strategies to minimize bleeding risks [10].

ASSESSMENT OF FUTURE RISK

Various stratification schemes exist to assist in determining the future risk of ischemic stroke; these schemes vary in complexity and number of risk factors included. CHADS₂ (congestive heart failure, hypertension, age ≥75, diabetes, stroke/TIA/systemic embolism) has historically been used to calculate points (0–6) that determine an adjusted stroke rate and stratify patients into low, intermediate, or high groups; the higher the total points, the higher the risk of stroke [2].

The more recently developed CHA₂DS₂-VASc score incorporates additional clinically relevant non-major risk factors (e.g., age, gender, vascular disease) into the CHADS₂ [1]. Both European and US guidelines now recommend use of the CHA₂DS₂-VASc score to assess the individual stroke risk in patients with AF [3,6]. The main advantage of the CHA₂DS₂-VASc score is the ability to identify and differentiate low risk patients with much better precision, than the CHADS₂ score, which is an important advantage for primary prevention [1,2,6].

Figure 1 demonstrates the difference between the ability of these scores to assess risk and highlights the superior performance of CHA₂DS₂-VASc. The CHA₂DS₂-VASc score also plays a role in secondary prevention for patients with AF who have had an ischemic event (TIA or stroke); these patients will automatically have a score ≥ 2 , an indication for anticoagulant therapy for most patients [3,6].

Figure 1. The value of the CHA₂DS₂-VASc score for refining stroke risk stratification in patients with a CHADS₂ score 0–1

MANAGEMENT

For patients with valvular AF, the general recommendation of the European and U.S. guidelines is to use a vitamin K antagonist (VKA) [3,15]. In patients with nonvalvular AF, aspirin is no longer recommended for patients with a CHA₂DS₂-VASc score of zero. For the remainder of patients with nonvalvular AF and CHA₂DS₂-VASc score ≥ 2 , anticoagulation therapy is recommended unless major contraindications exist [2,3,6].

The European Society of Cardiology (ESC) guidelines recommendations are more specific, and recommend the use of novel oral anticoagulants (NOACs) in the event of inadequate control of anticoagulation with VKA. Anticoagulation with VKA in NVFA should be performed with the target INR range of 2.0–3.0. This is assessed by the time in treatment range. The ESC guidelines also advise the use of NOACs, rather than VKAs, when initiating oral anticoagulation therapy because of the clinical net benefit, efficacy, and safety [3,7].

THE OPTIONS

Abundant data support oral anticoagulant (OAC) therapy with VKAs is effective in the primary and secondary prevention in patients with AF compared to placebo or control; VKAs have been shown to reduce future ischemic events by 64% and all-cause mortality by 26% compared to placebo [16,17]. Nevertheless, there are disadvantages with vitamin K antagonists. These include the need for frequent dose adjustments, labile INR's, the narrow therapeutic range, and multiple interactions with other drugs and food. All of these factors have contributed to a need to develop alternatives [7].

Recently, two classes of novel oral anticoagulants have emerged that may overcome some of the clinical challenges associated with warfarin use: the oral direct thrombin inhibitors (dabigatran) and the oral direct factor

Xa inhibitors (rivaroxaban, apixaban, edoxaban (the US Food and Drug Administration approved edoxaban in January 2015 and a European Medicines Agency approval application was filed for edoxaban in 2014) [2]. Figure 2 demonstrates key differences between the 4 NOACs.

Figure 2. Key Pharmacokinetic and Pharmacodynamics of the New Oral Anticoagulants (NOACs)

Over a period of several years, starting with the RE-LY trial investigating Dabigatran, and then ROCKET, ARISTOTLE, and most recently ENGAGE AF-TIMI 48, the effectiveness of NOACs compared to warfarin have been well studied in approximately 70,000 patients in these four randomized trials [1]. Figure 3 summarizes the findings of these trials. All of the clinical trials included varying percentages of patients with prior stroke or TIA, i.e., the secondary prevention population.

Figure 3. Synopsis of the results of Phase III studies investigating NOACs versus warfarin in patients with nonvalvular AF

One can conclude from these trials that the NOACs are at least as effective as warfarin providing protection against ischemic stroke [3,6,7,10,14,18–24]. Another important point that consistently emerged across these trials is that the NOACs reduced the risk of both intracranial hemorrhages and including intracerebral hemorrhage (ICH) by about 50%, compared to vitamin K antagonists [7,10]. Moreover, in a meta-analysis by Ruff et al. found NOACs also demonstrated a favorable pattern for all major bleeding events compared to warfarin [24].

Figure 4. Summary of the key stroke prevention advantages of the NOACs vs. warfarin

It is important to note that observational studies and databases from clinical practice evaluating the risk of intracerebral hemorrhage during treatment with dabigatran compared to warfarin have demonstrated results consistent with those shown in the randomized clinical trials [25].

Evidence from Trials and Shortcomings in Real-World Practice

Despite very solid data from clinical trials and clear stroke prevention guidelines, evidence suggests that what is happening in the real world differs from recommendations [26]. Analysis of the Canadian Stroke Network (2009) demonstrated patients with AF who had experienced a stroke were receiving suboptimal care; 29% were not receiving antithrombotics, 31% were receiving aspirin, and/or clopidogrel—of the 40% that were receiving VKA at the time of the stroke, only 10% were within treatment range [27]. Data from the European Heart Survey indicate there is anticoagulation overuse in patients with very low scores; however, rates of anticoagulation use did not increase in those patients at higher risk who should have received anticoagulation [28].

Causes of the discrepancy between guidelines and real-life are multifactorial. Concerns over old age, risk of falls, patient adherence, and risk of bleeding all contribute. Bleeding risk is the main drawback to anticoagulants not being appropriately used [6,10,29]. Promising recent registry data from seven European countries suggest that adherence to

stroke prevention guidelines in AF is improving (Figure 5). anticoagulation rates in patients with $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$ are at 85.6% and 70.1% in those with $\text{CHA}_2\text{DS}_2\text{-VASc} = 1$ [30]. The use of VKAs is decreasing in favor of NOAC use, and baseline anticoagulation rates in patients with $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$ are at 85.6% and 70.1% in those with $\text{CHA}_2\text{DS}_2\text{-VASc} = 1$ [30].

Figure 5. Trends in the antithrombotic management of atrial fibrillation

THE BALANCING ACT

One of the key issues in clinical practice is balancing the benefits with the risks of anticoagulation therapy. Longitudinally, the increasing use of anticoagulants and of warfarin in patients with AF has been paralleled by an expected increase in the proportion of intracerebral hemorrhages being attributed to anticoagulant therapy [31,32]. This has been demonstrated by several data sources; both an American study and the Swedish Stroke Registry indicate that one out of six intracerebral hemorrhages is now related to anticoagulant therapy [33].

Figure 6 demonstrates data from a Swedish observational study done based on quality registers. The charts compare the mortality of patients based upon varying $\text{CHA}_2\text{DS}_2\text{-VASc}$ and HAS-BLED scores treated with anticoagulants versus no anticoagulants. While these observational data are not randomized trial data, they indicate that the risk of ischemic stroke is predominant over the risk of intracerebral hemorrhage and the prognosis is better in those patients treated with oral anticoagulants [34].

Figure 6. Trends in mortality for patients with atrial fibrillation receiving oral anticoagulation (OAC) vs. no OAC based upon varying $\text{CHA}_2\text{DS}_2\text{-VASc}$ and HAS-BLED scores

BLEEDING RISK

Intracerebral hemorrhage (ICH) is one of the most feared complications of anticoagulant therapy. In general, spontaneous ICH is a serious condition which is associated with a 3-month mortality of about 30%. ICH occurring in anticoagulated patients carries an even substantially worse prognosis. ICH related to OAC has larger hematoma volumes and a higher rate of hematoma expansion [32,35–37].

The HAS-BLED score is one of the more widely used tools to assess the baseline risk of a major bleeding event in patients receiving anticoagulation. One point is assigned for each positive finding on the following risk factors:

- Uncontrolled hypertension
- Abnormal renal function
- Abnormal liver function
- Stroke
- History of bleeding
- Labile INR
- Elderly (age > 65)

- Drugs (e.g., NSAIDs, aspirin, other antiplatelets) or alcohol use [1]

A HAS-BLED score ≥ 3 is indicative of a high risk of major bleeding event [1]. The HAS-BLED score needs to be used in combination with patients' $\text{CHA}_2\text{DS}_2\text{-VASc}$ scores to assess the overall risks and benefits of treatment. A high HAS-BLED score should not be used to exclude patients from oral anticoagulant therapy. Rather, it is meant to identify modifiable risk factors to decrease hemorrhage risk. Although data are not yet definitive, other possible risk factors for increased risk of bleeding during anticoagulation therapy include cerebral amyloid angiopathy, Asian or Mexican-American ethnicity, tobacco smoking, leukoaraiosis or microbleeds detected by brain CT/MRI, and APOE e II or IV genotype [38].

The core treatment with antiplatelet agents poses another concern as the combination of OAC with antiplatelets substantially increases the risk of major bleeding [3,6,7]. Analysis of the prospective PREvention of thromboembolic events-European Registry in Atrial Fibrillation (PREFER in AF) Registry found 95% of patients on dual therapy (i.e., antiplatelet + OAC) and 63.8% of patients on triple therapy (OAC + ASA+ clopidogrel), didn't have an accepted indication for therapy [39].

STRATEGIES TO MINIMIZE THE RISK OF ICH

Strategies to minimize the risk of ICH include individualizing patients' anticoagulant therapy as well as identifying and managing modifiable risk factors. One of the most important ways to reduce the risk of intracerebral hemorrhage in patients receiving anticoagulation therapy is through good and consistent blood pressure control. The PROGRESS study demonstrated a 50% reduction in the incidence of intracerebral hemorrhage in patients, and a sub-group analysis of patients with atrial fibrillation and ischemic stroke showed approximately a 30% decrease in major vascular events and a 30% decrease in the risk of hemorrhagic stroke [40,41].

Studies have demonstrated patients on VKA who spend at least 70% of time within therapeutic range have a 79% reduced risk of stroke, compared to patients with a lower amount of time in the therapeutic range; thus, it is very important for INRs to be tightly controlled if patients are to receive the beneficial effects VKAs [42]. Based on studies showing a positive linear relationship between alcohol consumption and hemorrhagic stroke risk, patients at risk of ICH should be advised to consume very little or no alcohol [43]. Combination with antiplatelets should only be performed if clearly indicated. Double and particularly triple antithrombotic therapies substantially increase the bleeding risk by 1.5 to XX fold, respectively [3,7].

Given the better efficacy, safety, and convenience of NOACs compared with VKAs, guidelines now recommend NOAC instead of adjusted-dose VKA (INR 2-3) for most patients with AF in whom de novo therapy with OAC is indicated [44]. This recommendation has also rapidly entered clinical practice in most geographical regions and settings;

however, the evidence to routinely recommend one NOAC over another is currently not well established. The choice of a specific NOAC may be guided by individual patient characteristics such as kidney function, use of interacting drugs (such as antiarrhythmics), drug compliance, and individual dosing schedule preferences. Treatment with NOACs requires the pharmacological competence of the prescriber, as well as a well informed patient [6,45–47].

OPEN QUESTIONS

As evidence of and clinical experience with the use of OACs for stroke prophylaxis in patients with nonvalvular continue to accumulate, questions regarding their practical use still require further refinement [46]. For example, to date, the different NOACs have not been subject to comparative head to head efficacy and safety trials [1,3,6,10,14]. Additionally, clear guidance is sparse on how to safely “bridge” OAC therapy with VKA to parenteral anticoagulant for patients on who need to undergo invasive or surgical procedures with a high risk of bleeding [1,3,6,10]. However, on-going studies (e.g., BRIDGE—Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery) may help answer some of these questions [6]. Although, the ENGAGE AF-TIMI 48 established a safe way to transition patients from NOACs to VKAs [14], uncertainty surrounding how to implement this in clinical practice may still persist [1,3,10]. Lastly, robust evidence and guidance are becoming available at a rapid pace on how to best manage NOAC-related bleeding events as well as how and when to safely restart OAC therapy in patients who have experienced a hemorrhagic stroke or another severe bleeding event [1,3,10,47,48]. Data from the ENGAGE-AF TIMI study underline the importance of this challenging constellation: in patients surviving a major bleeding event, 61% were not restarted on an anticoagulant for the duration of the trial. Patients in the warfarin group suffered twice as many ischemic cardiovascular deaths and twice as many ischemic strokes in the warfarin group after anticoagulation had been interrupted and permanently discontinued [14].

CONCLUSION

AF is a growing global epidemic and cardiogenic embolism responsible for at least 15–20% of all strokes. Although ischemic stroke can be very effectively prevented by OAC, the major risk factors for ischemic stroke are also risk factors for bleeding [1]. Accordingly, physicians need to balance the benefits of anticoagulation therapy with the risks of bleeding. Numerous trials with VKAs and NOACs unanimously show the benefit of oral anticoagulation for stroke prevention in AF. Additionally, compared to VKAs, the NOACs reduce the risk of intracerebral hemorrhage by approximately 50% [7,10] and these findings are reflected in the clinical guidelines. Patient outcomes can be improved by thoughtful assessment of patients to identify and modify

risk factors, and by tailoring anticoagulation therapy to individual patient characteristics and preferences [7].

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REFERENCES

1. Lopes RD, Crowley MJ, Shah BR, Melloni C, Wood KA, et al. Stroke Prevention in Atrial Fibrillation. Comparative Effectiveness Review No. 123. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I). In: 13-EHC113-EF APN, ed. Rockville, MD: Agency for Healthcare Research and Quality; August 2013.
2. Cove CL, Hylek EM. An updated review of target-specific oral anticoagulants used in stroke prevention in atrial fibrillation, venous thromboembolic disease, and acute coronary syndromes. *Journal of the American Heart Association*. 2013;2(5):e000136.
3. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation—developed with the special contribution of the European Heart Rhythm Association. *Europace*. 2012;14(10):1385–1413.
4. Cowell RP. Direct oral anticoagulants: integration into clinical practice. *Postgraduate Medical Journal*. 2014;90(1067):529–539.
5. Writing Group M, Lloyd-Jones D, Adams RJ, et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation*. 2010;121(7):e46–e215.
6. January C, Wann S, Alpert J, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;64(21):2246–2280.
7. Savelieva I, Camm AJ. Practical considerations for using novel oral anticoagulants in patients with atrial fibrillation. *Clinical Cardiology*. 2014;37(1):32–47.
8. Penado S, Cano M, Acha O, et al. Atrial fibrillation as a risk factor for stroke recurrence. *American Journal of Medicine*. 2003;114:5.
9. Page RL, Tillich TW, Connolly SJ, et al. Azimilide Supravent—tricular Arrhythmia Program (ASAP) Investigators. Asymptomatic or “silent” atrial fibrillation: frequency in untreated patients and patients receiving azimilide. *Circulation*. 2003;107:5.
10. Albert N. Use of novel oral anticoagulants for patients with atrial fibrillation: a systematic review and clinical implications. *Heart and Lung*. 2013;43(1):12.
11. Andersen KK, Olsen TS, Dehlendorff C, Kammergaard LP. Hemorrhagic and ischemic strokes compared: stroke severity, mortality, and risk factors. *Stroke*. 2009;40(6):2068–2072.
12. Truelsen T, Begg S, Mather C. The global burden of cerebrovascular disease. In: Organization WH, ed2000. World Health Organization (WHO). Available at: http://www.who.int/healthinfo/statistics/bod_cerebrovascular_diseases_stroke.pdf. Accessed march 24, 2015
13. Feigin V, Forouzanfar M, Roth G, et al. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 2014;383:10.
14. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *The New England Journal of Medicine*. 2013;369(22):2093–2104.
15. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. 2014;63(22):2438–2488.
16. Larsen TB, Potpara T, Dagres N, et al. Stroke and bleeding risk evaluation in atrial fibrillation: results of the European Heart Rhythm Association survey. *Europace*. 2014;16(5):698–702.

17. Hart R, Pearce L, Aguilar M. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Annals of the Internal Medicine*. 2007;146(12):11.
18. Connolly SJ, Ezekowitz M, Yusuf S, Eikelboom JW, Oldgren J. Dabigatran versus Warfarin in patients with atrial fibrillation. *The New England Journal of Medicine*. 2009;361(12):13.
19. Connolly SJ, Eikelboom JW, C J, HC D, R H, et al. Apixaban in patients with atrial fibrillation. *The New England Journal of Medicine*. *New Engl J Med*. 2011;364:806-817.
20. Granger C, Alexander J, McMurray J, et al. Apixaban versus warfarin in patients with atrial fibrillation. *The New England Journal of Medicine*. 2011;365(11):12.
21. Patel M, Mahaffey K, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *The New England Journal of Medicine*. 2011;365(10):8.
22. Furie KL, Goldstein LB, Albers GW, et al. Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: a science advisory for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2012;43(12):3442-3453.
23. Goodman SG, Wojdyla DM, Piccini JP, et al. Factors associated with major bleeding events: insights from the ROCKET AF trial (rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *Journal of the American College of Cardiology*. 2014;63(9):891-900.
24. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *The Lancet*. 2014;383(9921):955-962.
25. Larsen TB, Rasmussen L, Skjoth F, Due K, Callreus T, et al. Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation. *Journal of the American College of Cardiology*. 2013;61(22):10.
26. Kim MH. Shared risk factors for anticoagulation in nonvalvular atrial fibrillation: a dilemma in clinical decision making. *Journal of the American College of Cardiology*. 2014;63(20):2148-2150.
27. Gladstone D, Bui E, Fang J, Laupacis A, Lindsay M, et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke* 2009;40(1):6.
28. Nieuwlaat R, Capucci A, Lip Gy, Olsson SB, Neiman FH, et al. Antithrombotic treatment in real-life atrial fibrillation patients: a report from the Euro Heart Survey on Atrial Fibrillation. *European Heart Journal*. 2006;27(9):3018.
29. Ferguson C, Inglis SC, Newton PJ, Middleton S, Macdonald PS, Davidson PM. Atrial fibrillation and thromboprophylaxis in heart failure: the need for patient-centered approaches to address adherence. *Vascular Health and Risk Management*. 2013;9:3-11.
30. Rincon, et al. Trends in antithrombotic management of AF: Abstract 86447. *ESC* 2014; 2014.
31. Veltkamp R, Horstmann S. Treatment of intracerebral hemorrhage associated with new oral anticoagulant use: the neurologist's view. *Clinics in Laboratory Medicine*. 2014;34(3):587-594.
32. Steiner T, Rosand J, Diringer M. Intracerebral hemorrhage associated with oral anticoagulant therapy. *Stroke*. 2006;37:7.
33. The Swedish Stroke Register: 2013. http://www.riksstroke.org/wp-content/uploads/2014/07/Strokerapport_AKUTTIA3man_LR.pdf
34. Friberg L, Rosenqvist M, Lindgren A, Terent A, Norrving B, Asplund K. High prevalence of atrial fibrillation among patients with ischemic stroke. *Stroke*. 2014;45(9):2599-2605.
35. Veltkamp R, Prabhakaran S. Critique of Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation trial. *Stroke* 2014;45(7):2151-2153.
36. Flaherty M, Tao H, Haverbusch M, et al. Warfarin use leads to larger intracerebral hematomas. *Neurology*. 2008;30(71):6.
37. Cucchiara B, Messe S, Sansing L, Kasner S, Lyden P, Investigators C. Hematoma growth in oral anticoagulant related intracerebral hemorrhage. *Stroke*. 2008;39(11):4.
38. Hart R, Tonarelli S, Pearce L. Avoiding central nervous system bleeding during antithrombotic therapy. *Stroke*. 2005;36:6.
39. De Caterina R, Ammentorp B, Darius H, et al. Frequent and possibly inappropriate use of combination therapy with an oral anticoagulant and antiplatelet agents in patients with atrial fibrillation in Europe. *Heart* 2014;100(20):11.
40. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *The Lancet*. 2001;358(9287):1033-1041.
41. Arima H, Hart R, Colman S, Chalmers J, Anderson C, et al. Perindopril-Based Blood Pressure-Lowering Reduces Major Vascular Events in Patients With Atrial Fibrillation and Prior Stroke or Transient Ischemic Attack. *Stroke*. 2005;36:6.
42. Gallagher A, Setakis E, Plumb J, Clemms A, van Staa T. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. *Thrombosis and Haemostasis*. 2011;106(106):10.
43. Reynolds K, Lewis B, Nolen J, Kinney G, Sathya T, He J. Alcohol consumption and risk of stroke: a meta-analysis. *JAMA*. 2003;289(5):10.
44. National Institute for Health and Care Excellence. Atrial fibrillation: the management of atrial fibrillation. NICE CLinical Guideline 180. guidance.nice.org.uk/cg180. August 2014.
45. Pokorney SD, Sherwood MW, Becker RC. Clinical strategies for selecting oral anticoagulants in patients with atrial fibrillation. *Journal of Thrombosis and Thrombolysis*. 2013;36(2):163-174.
46. Lessire S, Dincq AS, Douxfils J, et al. Preventive strategies against bleeding due to nonvitamin K antagonist oral anticoagulants. *BioMed Research International*. 2014;2014:616405.
47. Haas S, Bode C, Norrving B, Turpie AG. Practical guidance for using rivaroxaban in patients with atrial fibrillation: balancing benefit and risk. *Vascular Health and Risk Management*. 2014;10:101-114.
48. Hankey GJ, Norrving B, Hacke W, Steiner T. Management of acute stroke in patients taking novel oral anticoagulants. *International Journal of Stroke*. 2014;9(5):627-632.
49. Heidbuchel H, Verhamme P, Alings M, et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *European Heart Journal*. 2013;34(27):2094-2106.