

Where will Non-Vitamin K Oral Anticoagulants Stand beyond being Standard of Care in Anticoagulation Therapy?

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Abstract

Objective: Atrial fibrillation (AF) is the most common arrhythmia that increases risk of stroke by 4–5 fold. AF prevalence is approximately 1%–3% in the general population and increases with age. Until 2010, the standard of care (SoC) for prophylaxis of ischemic stroke was Vitamin K antagonists. Phase III randomized controlled trials (RCTs) of non-Vitamin K oral anticoagulants (NOACs) showed that NOACs have comparable or lower risk of stroke, systemic embolism, major bleeding, and death with warfarin in populations with nonvalvular AF (NVAF). Since then, results of these pivotal RCTs were confirmed by postmarketing studies and real-world data. In the last 8 years, they have been replacing warfarin as the SoC not only for preventing stroke in NVAF patients but also for patients with deep vein thrombosis, pulmonary embolism, and those who undergo hip or knee surgery. In recent years, there are emerging data on new clinical areas such as coronary and peripheral artery disease. In this article, it is attempted to review what has changed in the last 8–10 years in the management and prevention of stroke associated with NVAF and other thromboembolic situations and to foresee whether NOACs will be SoC and stand beyond being SoC in anticoagulation therapy. **Methods:** IMS data were obtained from IQVIA with a permission letter on request of Dr. Ergene. IQVIA grants permission to use the statements for the specified purpose (NOACs share in the total anticoagulation market and role of NOACs as the SoC in the near future) of peer-review publication by Dr. Ergene. **Conclusion:** NOACs are breakthrough in stroke prevention, and they will prevail eventually. It will take a few years; anticoagulation market will grow in favor of NOACs, and most probably, NOACs will reach over 50% standard unit market share. It is even more exciting to hear about new therapeutic areas and indications for these agents.

Keywords: Atrial fibrillation, oral anticoagulants, randomized controlled trials

INTRODUCTION

Atrial fibrillation (AF) is the most frequently encountered cardiac arrhythmia with a prevalence of 1%–3% in the general population, reaching 15% in elderly population. Therewithal, it also poses a 4–5-fold increased risk of ischemic stroke, which is increased for elderly patients and a 2-fold increased risk of all-cause mortality.^[1–4] On the other hand, AF is a disease with a high economic burden for both patients and healthcare providers.^[5] Because of these catastrophic consequences of AF, anticoagulation therapy is indispensable and the standard of care (SoC) for these patients for many years with Vitamin K antagonists (VKA) although some major drawbacks such as bleeding.^[6] Non-Vitamin K antagonists (NOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban have come a

long way to become standard therapy. Since 2010, all 4 NOACs have proven their efficacy and safety profile for the prevention of stroke in patients with nonvalvular AF (NVAF). The first evidences in terms of efficacy and safety were obtained with their phase III dose-adjusted, warfarin-controlled, randomized-controlled trials (RCTs). These pivotal trials demonstrated that similar or improved efficacy of NOACs compared with warfarin, in addition to reduced rates of intracranial and life-threatening bleeding.^[7–10] A meta-analysis published in 2014 showed that all NOACs had a favorable risk–benefit profile with a significant reduction in stroke,

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intracranial hemorrhage, and all-cause mortality, and with similar major bleeding as for warfarin.^[11] In the last 5 years, various and numerous real-world data confirmed these phase III clinical trial outcomes, especially in terms of combined endpoint of intracranial hemorrhage or ischemic stroke.^[12-14]

Recent trials which have been conducted in the last couple of years promise wider use of NOACs in new therapeutic areas. One of these new areas is about the use of NOACs in patients with NVAF receiving antiplatelet therapy after percutaneous coronary intervention (PCI).^[15-17] Another area is uninterrupted anticoagulation during AF ablation. NOACs became an alternative to VKAs in these procedures.^[18,19] In the pathogenesis of acute coronary syndromes (ACSs), plaque disruption and factor Xa play a central role in activation of the coagulation cascade. For this purpose, low-dose rivaroxaban added to dual antiplatelet therapy (DAPT) was tested whether it will improve cardiovascular (CV) outcomes in patients with ACS.^[20] It revealed better CV outcomes in the cost of slightly increased risk of bleeding. It might be a new therapeutic option in high-risk ACS patients. In another recently published trial, low-dose rivaroxaban was tested instead of aspirin with P2Y12 inhibitor in ACS patients. It revealed the safety of rivaroxaban in this setting.^[21] In patients with chronic ischemic heart disease, proved antithrombotic strategy is antiplatelet therapy mainly with aspirin. A multicenter trial was conducted whether rivaroxaban alone or in combination with aspirin is more effective than aspirin alone to prevent the recurrence of CV events in patients with stable atherosclerotic disease.^[22] This study results with a paradigm shift to anticoagulant therapy in these patient population. Another new therapeutic area is venous thromboembolic disease. In the initial phase of the treatment only rivaroxaban 15 mg bid and apixaban 10 mg bid strategies which approved by regulatory authorities are alternative to VKAs.^[23-25] All of the four NOACs approved for remainder of treatment phase. Furthermore, a recently published trial showed benefits of rivaroxaban in extended therapy in chronic phase of venous thromboembolism instead of aspirin.^[26]

In summary, in the last 10 years, the development and widespread use of NOACs lead an abundant change and paradigm shift in many therapeutic and preventive areas of CV diseases. Hereafter, it seems that this conversion will expand in other therapeutic areas.

In this article, we tried to review what has changed in the last decade in the management and prevention of stroke associated with NVAF. We also reviewed the evidences which issued NOAC use in other thromboembolic and CV diseases to foresee whether NOACs will be SoC and stand beyond being SoC in anticoagulation therapy.

METHODS

IMS data were obtained from IQVIA with a permission letter on request of Dr. Ergene. IQVIA grants permission to use the statements for the specified purpose (NOACs share in the total anticoagulant market and role of NOACs as the SoC in the near

future) of peer-review publication by Dr. Ergene. The data are used in accordance with applicable laws and Turkish regulatory authority (Turkish Medicines and Medical Devices Agency).

RESULTS

IMS data of global anticoagulant market showed that trend for either the decrease in VKAs market share or the increase in NOACs market share is continuing in the period from 2014 to 2017 as VKAs decreased from 71.3% to 51.5%; on the contrary, NOACs increased from 16% to 35.7% from 2014 to 2017 [Figure 1].

DISCUSSION

The use of warfarin tends to decrease in the last years due to an increase in NOAC use for several reasons. Time in therapeutic range (TTR) adjustment for warfarin-treated patients is difficult and unpredictable because of its narrow therapeutic window, wide variability in anticoagulant effect, and food/drug interactions.^[27-31] TTR data obtained from the real world are much lower than retrieved from randomized controlled trials.^[32] The clinical practice guidelines extend the criteria for antithrombotic use and currently recommend NOACs over warfarin.^[33]

AF is the most frequent reason for using oral anticoagulant, whereas ACSs (either ST- or non-ST-elevation myocardial infarction or unstable angina) are the leading indication for PCI with stent implantation. Among ACS patients undergoing PCI, approximately 5%–21% of patients have concomitant AF.^[15] DAPT plus OAC treatment (triple therapy) that has been used in these patients as a standard treatment has a higher incidence of major bleeding than single antiplatelet plus oral anticoagulant therapy which was shown in WOEST trial.^[34] Therefore, one of the trial arm was planned as P2Y12 plus rivaroxaban 15 mg combination without aspirin therapy in phase III PIONEER AF-PCI trial. PIONEER AF-PCI is the first prospective

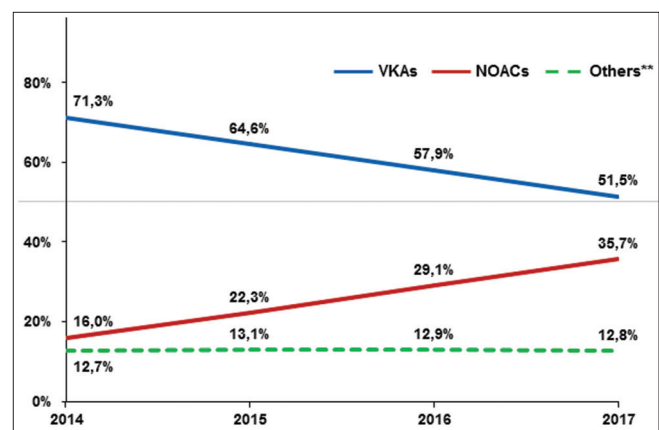


Figure 1: Global AC market volume shares in % (based on DoT*). Source: IQVIA MIDAS, Database: Current All 2017. *DoT = days of therapy, calculated based on volume in SU (standard units). DoT = SU (1 tablet per day) except for dabigatran and apixaban: DoT = SU divided by 2 (two tablets per day) (Adopted with permission from IQVIA Database)

study which evaluated two rivaroxaban dosing regimens. In addition to the above-mentioned dosing regimen, rivaroxaban 2.5 mg twice daily (BID) plus DAPT compared with VKA in patients with NVAF receiving concomitant antiplatelet therapy after PCI, to assess the relative risks of bleeding complications.^[15] Rivaroxaban is the first NOAC (versus VKA) which demonstrated significantly improved safety in this patient population. The reduced dose of rivaroxaban 15 mg OD plus single antiplatelet therapy could become a treatment option in this clinical scenario.^[15] Other NOACs also have interest in this therapeutic area. In the RE-DUAL PCI study which was recently announced, the safety of dabigatran 110 and 150 mg were compared with warfarin. Both dosing regimens showed significantly lower rates of major bleeding.^[16]

In patients with ACS, DAPT is used as standard therapy. Despite this treatment regimen, it is known that there is a residual CV risk.^[20] A residual CV risk may be due to the persistence of activation of the coagulation system and significant thrombin formation for several months after clinical stabilization. This may be explaining the rationale for the use of anticoagulant therapy to further reduce recurrent events.^[20] Although the benefits of adding warfarin to treatment have been shown in some studies during the last two decades, warfarin has not found a place in this therapeutic area due to the concern of increased bleeding.^[28,29,31,32] Recently, two different low doses of rivaroxaban in addition to DAPT were tested for CV outcomes and safety in ATLAS ACS 2-TIMI 51.^[20] Rivaroxaban showed a significant reduction in the primary efficacy endpoints of death from CV causes, myocardial infarction, or stroke in patients with a recent ACS and 2.5 mg dose also showed a survival benefit. Regarding safety, there was a nonsignificant slight increase in bleeding with 5 mg dose of rivaroxaban. Conversely, APPRAISE-2 trial which has evaluated apixaban, was prematurely terminated due to an excessive risk of intracranial hemorrhage and major bleeding with triple antithrombotic therapy without a benefit in the risk of recurrent ischemic events.^[35] Hereafter, the so-called “vascular dose” is proposed for the low dose of rivaroxaban in patients with ACS. ATLAS ACS-2 TIMI 51 findings demonstrate that increased thrombin activity may play a role in ACS and that NOACs such as rivaroxaban may be a useful option in this treatment regimen.^[20] On the other hand, aspirin which has shown benefit in terms of its antiplatelet effect inhibits only the thromboxane A₂-dependent pathway of platelet.^[36] Since aspirin has a limited antiplatelet effect, a factor Xa inhibitor instead of aspirin was tested in GEMINI study.^[21] In this study, it was aimed to assess the safety of using a low dose of the oral anticoagulant rivaroxaban instead of aspirin in patients treated with a P2Y₁₂ inhibitor (either clopidogrel or ticagrelor) in patients with ACS. The similar risk of TIMI non-CABG clinically significant bleeding with rivaroxaban versus aspirin was observed. In summary, low-dose rivaroxaban had similar risk of clinically significant bleeding as aspirin in patients with ACSs.^[21]

At the beginning of the last decade, it was determined that DAPT was more effective yet with more bleeding events

compared to single acetylsalicylic acid therapy in CURE study.^[36] On the other hand, the combination of warfarin and aspirin has shown improved efficacy profile with an increased bleeding rate. Subsequently, ATLAS ACS-2 TIMI 51 study showed improved CV outcomes with an acceptable safety profile with rivaroxaban 2.5 mg bid plus DAPT. The results of this study inspired COMPASS trial; it was conducted whether rivaroxaban alone or in combination with aspirin is more effective than aspirin alone to prevent the recurrence of CV events in patients with stable atherosclerotic disease. One of the most important features of this study was that it was the most comprehensive phase III study conducted in almost 27000 patients who have coronary artery and/or peripheral artery disease, and the study was terminated early due to the overwhelming efficacy since it has met its primary endpoint significantly ahead of time. According to the results of this study, although the rate of major bleeding was higher with the combination of rivaroxaban 2.5 mg bid plus ASA than with aspirin alone as expected, a composite of CV death, stroke, or myocardial infarction was found lower. As a result, the net clinical benefit outcome was better.^[22]

Recent retrospective cohort study of Medicare beneficiaries sought to determine patterns of apixaban use and its associated outcomes in dialysis-dependent patients with end-stage renal disease (ESRD) and AF. The study showed that among patients with ESRD and AF on dialysis, apixaban use may be associated with a lower risk of major bleeding compared with warfarin, with a standard 5 mg twice a day dose also associated with reductions in thromboembolic and mortality risk.^[37] Recent ACC/AHA focused update paper issued apixaban and warfarin treatment in patients with ESRD with IIb recommendation level. However, its important to recognize that this study has only hypothesis generating not confirming fashion.^[38]

VKA has been the standard therapy for patients with a mechanical prosthetic valve, or bioprosthesis with AF. The Dabigatran versus Warfarin in Patients with Mechanical Heart Valves (RE-ALIGN) trial comparing dabigatran etexilate to warfarin was the only randomized controlled study in patients with mechanical valve prosthesis, but it was terminated prematurely because of an excess of thromboembolic and bleeding events among patients in the dabigatran group.^[39] To date, use of NOACs is contraindicated for AF patients with mechanical prosthetic valves. The hypothesis of eligibility of use of factor Xa inhibitors in mechanical heart valves was discussed in a recent published paper.^[40] The authors emphasize that 1 single trial with a single NOAC does not represent sufficient evidence for dismissing a therapeutic strategy, anticoagulation with NOACs and further experimentation should be conducted in this important area.

In the light of this overwhelming data related to NOACs that we tried to summarize, there are 3 basic questions that must be answered.

Can the NOACs be used in all indications for which warfarin is indicated? Starting from the release of the new agents in

the market, how has the dynamics changed for the global anticoagulant market? What is the future of NOACs in new indications and new therapeutic areas?

The answer of the first question is almost yes. According to clinical practice guidelines, other than severe mitral stenosis and prosthetic valves, NOACs can be used nearly in all indications that VKAs are indicated. In patients with NVAF when oral anticoagulation is indicated, clinical practice guidelines recommend NOACs in preference to a VKA.

The answer of the second question is more complicated and more related to the subject of this article. The answer is not straight forward due to confounding factors such as cost effectiveness and VKAs familiarity of healthcare providers. To what extent are the physicians aware of the benefits of NOACs over VKAs and how much do they adapt to these advantages. On the other hand, healthcare providers have some hesitation in their practice of anticoagulation with VKAs, mostly because of the concerns about bleeding.

The United States (US) health statistics showed that from 2001 to 2011, the relative rate of stroke death decreased by 35%.^[41] At that time, this decline was achieved by risk factor management such as controls of hypertension, diabetes, high cholesterol, and smoking cessation. However, the big step was AF management mostly by anticoagulation with VKAs. As NOACs were approved by European and US regulatory agencies in 2008, a contribution of NOAC use to this decline in stroke rate should not be negligible. Although some meta-analysis showed a 19% reduction in stroke and systemic embolism and significantly reduced all-cause mortality with NOACs compared to VKAs, there are no real-world data concerning this issue.^[11] Regarding to IMS, data of global anticoagulant market warfarin have declined from 87.5% to 72% through 2008–2014. In the same period, NOACs have reached 15.5% market share [Figure 2]. IMS data also show that same trend for either the decrease in VKAs market share or the increase in NOACs market share is continuing in the period from 2014 to 2017 as VKAs decreased from 71.3% to 51.5%; on the contrary, NOACs increased from 16% to 35.7% from 2014 to 2017. According to 2018 IQVIA Database, 50 million patients have been prescribed rivaroxaban since marketing launch.^[42] These data reveal that in the near future, NOACs will be the SoC in anticoagulation therapy.

The third question, what is the future of NOACs in new indications and new therapeutic areas? It is hard to answer this question also, at least now. There are substantial data about factor Xa inhibitor usage in acute and chronic ischemic atherosclerotic heart and peripheral arterial disease albeit only with rivaroxaban. Nevertheless, it is quite early to decide whether in these new therapeutic areas, we should use factor Xa inhibitor, namely rivaroxaban. However, the 2018 European Heart Rhythm Association practical guide recommend low-dose (2.5 mg bid) rivaroxaban in patients with ACS and for secondary prevention of atherothrombotic events in stable CAD in addition to aspirin.^[33] Consequently, U.S. Food and Drug Administration,

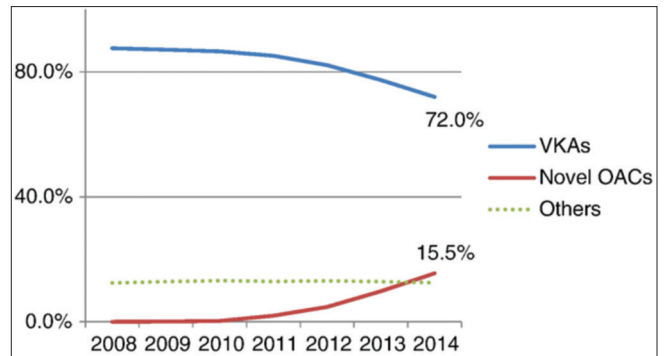


Figure 2: Global AC market volume shares in % (based on DoT*). Source: IMS MIDAS, Database: Current All 2014. *DoT = days of therapy, calculated based on volume in SU (standard Units) (Adopted with permission from IQVIA Database)

European Medicine Agency and Turkish Medicines and Medical Devices Agency (TITCK) have approved rivaroxaban to reduce the risk of major CV events, such as CV death, myocardial infarction and stroke, in people with chronic coronary, or peripheral artery disease. In the near future, medical society will continue discussing the controversial term “vascular dose” of rivaroxaban. We do not know whether there are “vascular doses” of other NOACs. Somehow, it is clear that there is a need for more randomized trials in this new therapeutic areas and new indications for anticoagulant drugs.

CONCLUSION

As the time pass by, numerous articles regarding the real-world data about NOACs appear on the medical literature. In general, the efficacy and safety of NOACs are confirmed by these real-world data. These drugs are breakthrough in stroke prevention, and they will prevail eventually. It will take a few years; anticoagulation market will grow in favor of NOACs, and most probably, NOACs will reach over 50% standard unit market share. It is even more exciting to hear about new therapeutic areas and indications for these agents.

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Conflicts of interest

The author has made a speech in the field of NOACs for Bayer, Daiichi Sankyo, Pfizer, and Boehringer Ingelheim. The author declares full independence from this funding as to the content of this article.

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