Review

Frontiers of anticoagulation therapy for atrial fibrillation

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Summary In the management of atrial fibrillation (AF), stroke prevention has been proved to play a pivotal role in addition to therapy for concomitant diseases. And, hitherto, anticoagulation by warfarin has been the only effective choice that is known to decrease the stroke rate with ~70% risk reduction. Although the evidence has been rigid, there are many barriers not to make warfarin therapy pervasive. However, the principle of “KISS (keep it short and simple)” seems to alter our situations. Changing the complex pharmacology with warfarin into the simple pharmacology with new anticoagulants would lead us to a new paradigm, where the old book is now rewritten by a new language.

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Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias associated with increased mortality and morbidity. Recent studies have estimated the number of AF patients to be more than 1 million in Japan [1,2]. This figure was based on the number of patients with persistent and permanent AF, and therefore, AF patients including the paroxysmal type would equal to or exceed 2 million people in Japan.

Although the precise mechanisms of the association between AF and increased risk of death remain to be elucidated, AF is a strong independent risk factor for stroke [3,4], which should contribute to the increased mortality and morbidity. Cardiogenic cerebral infarction with AF is more severe than the other types of stroke [5], and this char-
acteristic would strengthen the position of stroke prevention in the management of AF patients. Randomized studies [6,7] including the recent J-RHYTHM study [8] in Japan support this clinical attitude. At present, there is no clinical evidence that pharmacological and non-pharmacological interventions to electrocardiograms (AF itself) improved the mortality and morbidity of AF patients. Therapy for concomitant diseases to AF and stroke prevention stratified by the stroke risks is the most important for the prognosis of AF patients. In this review, I would like to focus upon the role of new anticoagulants in AF management.

Gaps between evidence and the real world

Since the 1990s, numerous efforts have been made to identify an effective therapy for stroke prevention in AF patients. Before then, we encountered two troublesome clinical problems. One was regarding risk stratification, and the other the method for medical intervention. Many randomized clinical studies, their meta-analyses, and observational studies have solved these problems [9–11]. These studies apparently seemed to transform our complex clinical situations into a simple framework, which is composed of a simple tool of warfarin combined with a simple stratification of CHADS2 scoring system. Simplicity has been well known to be required for solving many social and personal problems, which is known as ”the principle of KISS (keep it short and simple).” Actually, this principle seemed to work well in stroke prevention in AF patients, as demonstrated by a study that the spread of antithrombotic therapy decreased the increasing rate of stroke in AF patients [12].

However, at the same time, we know well that the usage of warfarin is far from the ideal state that we anticipate. A meta-analysis revealed that, even in AF patients with a history of stroke/TIA, the prescription rate of warfarin reaches only ~50% [13]. Also in Japan, our hospital-based cohort study [14] and a multicenter study [15] reported a similar figure of warfarin prescription rates in AF patients with stroke risks. The underuse of warfarin in AF patients, which should be a theme for cardiologists to overcome, would lead to the fact that ~85% of AF patients experiencing stroke were not treated with warfarin prior to stroke.

Although efforts should be made to overcome this important problem, we know that there are many limitations in the widespread use of warfarin for all physicians and all AF patients. There is a big gap between the ideal image and our actual real world. The usage of warfarin causes many types of mental burdens to physicians, patients, and the families of the patients. For physicians, anxiety for major hemorrhages and inconvenience coming from strict dose titration would cause the underuse of warfarin. For patients, the frequent blood tests and limitations in everyday meals would lead to the reluctance to take warfarin. The limitations in meals affect also the patient’s family members who do not take warfarin. More than imagined, these factors, which apparently are trivial medical problems from academic viewpoints, would affect all the people related to AF and make a big gap between the evidence and the real world.

The next stage from complexity to simplicity

It would be useful to speculate on the origins of the mental burdens of warfarin to healthcare providers and patients. As mentioned above, most of the burdens would result from the instability of warfarin effects. The instability requires frequent blood testing, strict dose titration, limitations in meals, and also leads to the risk of major hemorrhages. What causes the instability of warfarin effects? The pharmacology of warfarin itself would be one of the reasons. Actually, the pharmacological actions of warfarin are very complex (Fig. 1). Warfarin causes multiple effects on the production of the 4 coagulation molecules (II, VII, IX, and X factors in the coagulation cascade), and the effects are indirect and affected by many factors including vitamin K intake, drug interactions, VKOR genotype, CYP genotype, and unknown factors. If this complex warfarin pharmacology produces the mental burdens, the rifts between the evidence and the real world would not be bridged only by warfarin and the educational activities by healthcare providers. The principle of “KISS” would again support the movement that the complex pharmacology should be improved into a simpler pharmacology with a new agent.

And now, we have a new tool, a direct thrombin inhibitor, dabigatran, for stroke prevention in AF patients and would have more tools of anti-Xa inhibitors [16–22]. The principle of “KISS” has seemed to produce new substitutes for warfarin. Because these drugs affect the coagulation cascade via a single molecule directly (Fig. 1), the drug effect would not vary from patient to patient and be affected by other environmental factors. This stability of drug effect would make it unnecessary to change the doses frequently by blood tests, to make limitations in meals, and to be too anxious for major hemorrhages. Not only for those reasons, the “KISS” principle would affect our medical practice more than expected. With these drugs, stroke prevention in AF patients would appear to be on the next stage from complexity inherent to warfarin to simplicity with direct inhibitors, a part of which is shown in a recent large-scale clinical trial [23].

New world opened by dabigatran

The RE-LY trial is a randomized controlled study comparing the efficacy and safety of a new anticoagulant, dabigatran, with a well-established agent, warfarin, for stroke prevention in AF patients [23]. The results of the study were immediately published in the New England Journal of Medicine, and also referenced by many reviews [16–22]. Therefore, this review does not refer to the results in detail. The study aimed to show the non-inferiority of dabigatran to warfarin, but it unexpectedly showed significant superiority of dabigatran (150 mg bid) without losing the safety profile. It shows clear dose-response relationships of dabigatran for stroke prevention and major hemorrhages, both of which are great concerns for all physicians.

This new pharmacological approach has opened a new paradigm. In addition to the scientific results that we could rely on, the RE-LY trial has rewritten the book on the common knowledge constructed by anticoagulation with warfarin. Before the trial, only the convenience was pur-
New anticoagulants

Figure 1  A schema showing the complex pharmacology of warfarin and the simple pharmacology of new anticoagulants. VK, vitamin K; VKOR, vitamin K epoxide reductase; CYP, cytochrome P450.

sued by the new drug, but the fruits are far beyond what we anticipated. The first fruit is the superiority of dabigatran to warfarin that has been the most effective drug for stroke prevention in AF for more than several decades. This is a truly innovative event. The second fruit is our renewed knowledge that the balance between stroke and hemorrhage differs among drugs, which should be very natural but has been obscured for a long time. When a drug shows a narrow range between the therapeutic and toxic doses, strict medical practice for stroke prevention might lead to increased rate of major hemorrhages (seesaw relationships), as shown in many clinical studies with warfarin [24,25]. However, when the range is wide, the drug could decrease the stroke rate without increasing the hemorrhage rate, and this would be the case with dabigatran. And, the last fruit is the mental freedom for physicians and patients from the "straitjacket", which includes frequent blood testing, dose titration, anxiety for hemorrhages, and so on. These fruits would make smaller our present gap of stroke prevention between the ideal and the real.

Moreover, a new paradigm would open a new strategy. During an era with warfarin, CHADS2 scoring system has been a well-fitted strategy for physicians and patients. The system could discriminate AF patients that warfarin effectively works upon, on the balance between stroke prevention and major hemorrhages. However, at present, we have a tool with a wider therapeutic range, dabigatran. Particularly, it is noteworthy that the rate of intracranial hemorrhages under dabigatran was almost the same as that without any anticoagulation therapy [23], although the precise mechanisms are still unknown. This fact alters the risk-benefit balance for stroke prevention. Without increase in intracranial hemorrhage, more AF patients could benefit from a new type of anticoagulation. This means the requirement of a new strategy fitted for the new anticoagulation therapy. A new guideline by the European Society of Cardiology in 2010 has clearly demonstrated this trend by presenting a new scoring system of CHA2DS2-VASc [26], which could be derived from the modification of CHADS2 score. In both scoring systems, AF patients with 2 points or more are strongly recommended to take anticoagulation for stroke prevention. Because more risks and more points have been included in the new scoring system, the same threshold score of 2 points would imply that the strategy has been modified to lower the threshold for stroke prevention with the new anticoagulation therapy (Fig. 2).

New anticoagulants appearing

The RE-LY trial is not the end of this innovative era. Several new anticoagulants of anti-Xa inhibitors are coming to our clinical practice. These drugs include rivaroxaban, apixaban, and edoxaban. Recently, a global randomized controlled study, the ROCKET-AF study, has demonstrated the non-inferiority of rivaroxaban to warfarin for stroke pre-

![Figure 2](Image) A comparison of strategy between CHADS2 score and CHA2DS2-VASc score. In both scoring systems, AF patients with 2 points or more are recommended for anticoagulation therapy. Most patients categorized into 1 point in CHADS2 score would move to 2 points in the new CHA2DS2-VASc score.
vention of AF patients in a double-blinded fashion. The AVERROES study [27], comparing the effects of apixaban with aspirin in AF patients not suitable for warfarin, demonstrated the superiority of apixaban to aspirin as expected. On the assumption that the patient backgrounds in the AVERROES study were quite similar to those in the RE-LY trial, it is very promising that the annual rates of stroke and intracranial hemorrhage under apixaban were very similar to those observed under dabigatran. Edoxaban is a Japanese agent that is now under a global phase III trial of ENGAGE AF-TIMI 48 [28]. The drug has proved to be effective for prevention of venous thromboembolism [29]. These drugs are different from dabigatran in that they are direct anti-Xa inhibitors, and there are some other differences in their half-lives or metabolisms [30]. At present, it is unknown whether the different pharmacological and pharmacodynamic actions of several new anticoagulants would lead to different clinical outcomes in stroke prevention in AF patients. In the near future, clinical experiences with these direct thrombin and Xa inhibitors will open more progress and discussion.

Possible problems in the next stage

Not all things are good in this next stage with new anticoagulants, because there are some problems to be solved. The new drugs have been used in many AF patients enrolled in the clinical trials, but the information is still limited in our real-world AF patients. As compared with the long-accumulated experience with warfarin, we should know that we do not know everything about the new agents. Particularly with dabigatran, the number of Japanese AF patients that have taken the drug is too small.

The first concern is the antidote. With warfarin, our long experience provides several antidotes when patients are suffering from major hemorrhages under warfarin. They are vitamin K, fresh-frozen plasma, or activated recombinant factor VII. However, under new anticoagulants, there are no reliable methods known to reverse the anticoagulation. The second concern is regarding AF patients with renal insufficiency. The blood concentrations of the new anticoagulants are more or less dependent on renal secretion, which is a different characteristic from warfarin. Therefore, the safety profile of the drugs could not be applied to patients with severe renal dysfunction. The third concern is the adherence of AF patients to the new drugs. For better or worse, warfarin therapy could be monitored by physicians. This monitoring has supported the adherence of patients to warfarin. However, the efficacy of the new drugs is totally dependent upon the confidence between healthcare providers and patients. Although this situation is true for all medications other than warfarin, we could not predict the effects of switching from warfarin to the newer drugs at present.

The last point to mention is the medical costs, which should be taken into account from many viewpoints. These are drugs not for curing diseases, but for preventing diseases, and therefore patients should take them for all their lives. These are drugs not for rare diseases, but for a common disease, AF, which will be more prevalent in a society with increasingly aged people. We can easily predict the increasing demand of the drugs from a medical viewpoint. However, medical interventions for AF and its related diseases cannot be too expensive for society, where AF is merely one of the many medical problems. Therefore, the medical cost to our society should be a matter of discussion during the widespread introduction of the new anticoagulants. However, we have to walk on the new road because we have already known the innovation in AF management.

Disclosure statement

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