Thrombin Inhibitor or Factor Xa Inhibitor? – Opening of a New Era of Antithrombotic Management –

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice. At present, the prevention of thromboembolism is the most important objective in AF patients and the vitamin K antagonist, warfarin, is recommended as the first-line regimen.^{1,2} In the past half-century, as the only oral formula, warfarin has been widely prescribed for this purpose. In the early 1990s several large-scale clinical trials showed the superiority of warfarin over a number of antiplatelet preparations in preventing thromboembolism in patients with AF and since then, warfarin has become the gold standard. In clinical practice, however, its pharmacological features have many major limitations, such as its narrow therapeutic window, the slow onset and slow offset of its action, the attenuation of anticoagulation intensity by foods containing vitamin K, and the many drug–drug interactions that sometimes induce bleeding complications. Consequently, INR monitoring is needed. Among the most important issues are minimization of hemorrhagic complications and prevention of thromboembolism in AF patients. Recently, the clinical use of warfarin has begun to be widely discussed, especially the caution required in its use to avoid causing hemorrhage.

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In a recent issue of the Journal,³ a subanalysis of the RE-LY trial conducted in a Japanese population showed the superiority of dabigatran etexilate in both preventing ischemic stroke and significantly reducing bleeding complications, such as intracranial bleeding, as compared with an adjusted dose of warfarin. In this issue of the Journal,⁴ Ogawa et al report that the novel direct factor Xa inhibitor, apixaban, also caused less frequent major, or clinically relevant nonmajor, bleeding than an adjusted dose of warfarin. Their study, named ARISTOTLE-J, was a phase II randomized, partially blind, active controlled study in Japanese AF patients, that compared 3 treatment arms, using 2 different doses of apixaban and an adjusted dose of warfarin, respectively. Currently, phase III of the main study, known as the ARISTOTLE trial,⁵ which compares apixaban with warfarin, is being conducted on a worldwide scale. The findings of relatively small clinical studies suggest that both apixaban⁴ and dabigatran³ are more effective and safer than warfarin, and that these fixed-dose regimens do not require any drug monitoring. The favorable

Figure. Simplified schematic illustration of the site of action of anticoagulants. TF, tissue factor.

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outcomes in those reports suggest we are on the threshold of a new era of antithrombotic management. Early approval of these new drugs may well result in improvements in the management of AF patients.

To date, many multinational clinical studies have excluded Japan because of the difficulty in recruiting Japanese patients, and for them to be admitted into such studies, it is essential that the inconveniently long delay before a drug is approved in Japan be eliminated or minimized. With warfarin treatment, it is well known that racial differences lead to more frequent bleeding complications in Asian subjects.⁶ For this reason, we have long awaited approval of new drugs that appear likely to improve AF management, particularly in Asia.

The reason for the less frequent intracranial bleeding with these new agents appears to be that they do not affect factor VII, which plays an important role in repairing vascular injury, but is inhibited by warfarin. This process of repair occurs through the actions of factor VIIa, which induces tissue factor rapidly, repairs vascular injury and stimulates platelet aggregation (Figure). Therefore, the new factor Xa inhibitor, apixaban, as well as the thrombin inhibitor, dabigatran, may have significantly reduced the frequency of intracranial hemorrhage induced by warfarin in the RE-LY trial,⁷ and may do so also in the ARISTOTLE trial.⁵

It is well known that the hemorrhagic complications of warfarin occur more frequently in aged patients. In ARISTOTLE-J,⁴ hemorrhagic complications tended to occur also in aged patients on apixaban treatment. Approximately 25% of apixaban is eliminated by the kidneys, but the plasma concentrations of apixaban may depend less on renal function than in the case of dabigatran, of which 80% is eliminated renally.⁸

More than 10 years ago, factor Xa inhibitors were anticipated to have better efficacy and a better safety profile than thrombin inhibitors, because of the relatively slow activation kinetics of factor Xa compared with those of thrombin, so their use should result in easier management of the balance between the therapeutic and bleeding actions.⁹ Two large clinical trials of antithrombotic treatment in patients with AF were conducted, one using a newly developed direct thrombin inhibitor, dabigatran,⁷ and the other the factor Xa inhibitor, apixaban.¹⁰ The report on the former showed the superiority of dabigatran over warfarin for reducing stroke and major bleeding, including intracranial hemorrhage,⁷ and finally, updated guidelines for the management of AF were published.¹¹ The latter report compared apixaban with aspirin, and there was a reduction of stroke and systemic embolism with apixaban, without causing major bleeding or intracranial hemorrhage.¹⁰ The limited amount of data obtained only from the reports of these large-scale trials suggests that dabigatran may possess a more potent antithrombotic effect than apixaban.

At present, there has not been a comparison of a factor Xa inhibitor with a direct thrombin inhibitor, and so the most suitable drug for each individual AF patient must be selected with reference to the available evidence.

This year, dabigatran has been released commercially for

clinical use in Japan. The advantages of this direct thrombin inhibitor are, firstly, a fixed dose that eliminates the need for monitoring; secondly, effectiveness superior to that of an adjusted dose of warfarin; and thirdly, clinical effects that are less affected by food intake or co-medication. This can be considered as the beginning of a new era, in which the best strategy for each AF patient must be chosen carefully.

The large clinical trial, ARISTOTLE,⁵ which comprises more than 18,000 patients with AF, is currently being conducted and we are looking forward to knowing the extent to which the primary endpoint can be met and by how much the hemorrhagic complications can be reduced. With the arrival of new anticoagulants, attention is given to their safety profiles in clinical practice in Japanese AF patients, and patients in whom warfarin is preferable may still be found, indicating the need to seek further appropriate strategies for AF patients.

References

1. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and European Society of Cardiology Committee for Practice Guidelines (Writing Committee to revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and Heart Rhythm Society. *Circulation* 2006; **114**: 700–752.
2. JCS Joint Working Group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2008): Digest version. *Circ J* 2010; **74**: 2479–2500.
3. Hori M, Connolly SJ, Ezekowitz MD, Reilly PA, Yusuf S, Wallentin L, et al. Efficacy and safety of dabigatran vs. warfarin in patients with atrial fibrillation. *Circ J* 2011; **75**: 800–805.
4. Ogawa S, Shinohara Y, Kanmuri K. Safety and efficacy of the oral direct Factor Xa inhibitor apixaban in Japanese patients with non-valvular atrial fibrillation: The ARISTOTLE-J Study. *Circ J* 2011; **75**: 1852–1859.
5. Lopes RD, Alexander JH, Al-Khatib SM, Ansell J, Diaz R, Easton JD, et al. Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial: Design and rationale. *Am Heart J* 2010; **159**: 331–339.
6. Shen AYJ, Yao JF, Brar SS, Jorgensen MB, Chen W. Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. *J Am Coll Cardiol* 2007; **50**: 309–315.
7. 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* 2009; **361**: 1139–1151.
8. Eikelboom JW, Weitz JI. Update on antithrombotic therapy. New anticoagulants. *Circulation* 2010; **121**: 1523–1532.
9. Samama MM, Walenga JM, Kaiser B, Fareed J. Specific factor Xa inhibitor. In: Verstraete M, Fuster V, Topol EJ, editors. Cardiovascular thrombosis: Thrombocardiology and thrombocardiology, 2nd edn. Philadelphia, Lippincott-Raven, 1998; 141–172.
10. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011; **364**: 806–817.
11. Wann IJ, Curtis AB, Ellenbogen KA, Estes NAM, Ezekowitz MD, Jackman WM, et al. 2011 ACCF/AHA/HRS focused update on management of patients with atrial fibrillation (update on dabigatran): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practical Guidelines. *Circulation* 2011; **123**: 1144–1150.