# Chapter 1
# Secondary Prevention of Stroke with Atrial Fibrillation by New Oral Anticoagulants

**K. Kamiyama, T. Osato, and H. Nakamura**

**Abstract** We used the results of secondary prevention analyses for patients with a history of stroke or TIA in the large-scale RE-LY, ROCKET-AF (J-ROCKET-AF), and ARISTOTLE clinical trials to investigate the choice of new oral anticoagulants (NOACs) to prevent recurrent stroke. In light of these results, we concluded that dabigatran 150 mg BID should be the first-choice treatment for comparatively young patients with no apparent renal dysfunction, and apixaban for other patients, and that their efficacy and safety can be broadly guaranteed.

**Keywords** NVAF (non-valvular atrial fibrillation) • Previous stroke/TIA • Secondary prevention for stroke • Age • Creatinine clearance

## 1.1 Introduction

According to the results of previous large clinical trials [1–4], new oral anticoagulants (NOACs) showed equivalent or better results to standard anticoagulant treatment with warfarin for the prevention of stroke in patients with non-valvular atrial fibrillation (NVAF) in terms of both efficacy and safety. However, the enrollment criteria and analytical methods used varied somewhat among the studies, and a simple comparison of the results of the use of each drug is therefore inappropriate. There is, however, a need for information on how effective and safe the various NOACs with their different characteristics are in clinical practice.

In this chapter, we focus on the secondary prevention of cardiogenic cerebral embolism in patients with NVAF and discuss the choice of NOAC and treatment policy for preventing recurrent stroke on the basis of the results of subgroup analyses of patients with a history of stroke or TIA in large-scale clinical trials.

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## 1.2 Subgroup Analyses of NVAF Patients with a History of Stroke/TIA in Large-Scale Clinical Trials

Once patients with NVAF have experienced a TIA or cerebral infarction, their CHADS2 score increases to ≥2 points, and according to the Japanese guidelines on the management of atrial fibrillation [5], the use of an NOAC is recommended. The results of subgroup analyses of patients with a history of stroke/TIA have been reported from the RE-LY, ROCKET-AF, J-ROCKET-AF, and ARISTOTLE trials [6–9]. The methods of statistical analysis and the presentation used in each trial varied, meaning that a direct comparison cannot be made, but for the sake of simplicity, we quote and analyze the data in the form that they were reported.

### *1.2.1 A Subgroup Analysis of the RE-LY Trial in Patients with Atrial Fibrillation and Previous Stroke or TIA*

The RE-LY trial included 3623 patients with a history of stroke/TIA, accounting for approximately 20 % of the total enrollment. They included 1233 patients treated with dabigatran 110 mg BID, 1233 with dabigatran 150 mg BID, and 1195 with warfarin. The annual incidence of stroke was 2.23 %/year in the dabigatran 110 mg BID arm, 1.91 %/year in the dabigatran 150 mg BID arm, and 2.53 %/year in the warfarin arm, with no significant difference between dabigatran and warfarin. The annual incidence of ischemic or unknown stroke was 2.19 %/year in the 110 mg BID arm, 1.75 %/year in the 150 mg BID arm, and 1.75 %/year in the warfarin arm, with no significant difference between both doses and warfarin, although the rate tended to be somewhat higher in the 110 mg BID arm. For intracranial bleeding, the rates were 0.25 %/year in the 110 mg BID arm, 0.53 %/year in the 150 mg BID arm, and 1.28 %/year in the warfarin arm, with a significant difference between both BID arms and the warfarin arm. For major bleeding, the rates were 2.74 %/year in the 110 mg BID arm, 4.15 %/year in the 150 mg BID arm, and 4.15 %/year in the warfarin arm, with a significant difference for the 110 mg BID arm only [6].

### *1.2.2 A Subgroup Analysis of the ROCKET-AF Trial in Patients with Atrial Fibrillation and Previous Stroke or TIA*

The ROCKET-AF trial included 7468 patients with a history of stroke/TIA, accounting for approximately 52 % of total enrollment. They included 3754 patients treated with rivaroxaban and 3714 with warfarin. The annual incidence of stroke was 2.66 %/year in the rivaroxaban arm and 2.71 %/year in the warfarin arm, with no significant difference between the two arms. The annual incidence of ischemic or

unknown stroke was 2.34 %/year in the rivaroxaban arm and 2.27 %/year in the warfarin arm, with no significant difference for this endpoint either. The annual incidence of intracranial bleeding was 0.59 %/year in the rivaroxaban arm and 0.80 %/year in the warfarin arm, slightly lower in the rivaroxaban arm, although this difference was not significant. For major bleeding, the rates were 3.13 %/year in the rivaroxaban arm and 3.22 %/year in the warfarin arm, with no significant difference between the two arms for this parameter either [7].

The J-ROCKET-AF trial of Japanese subjects, who are believed to experience a higher rate of bleeding events as a result of the use of antithrombotics, was a safety validation trial with a smaller dose than the global trial. It included 813 patients with a history of stroke/TIA, accounting for approximately 64 % of the total. Tanahashi et al. carried out an analysis of patients with a history of stroke/TIA [8]. These are valuable data for Japanese patients, but the far lower enrollment compared with other large-scale clinical trials means they should be regarded as reference data. The analysis included 407 patients treated with rivaroxaban and 405 with warfarin. The annual incidence of stroke was 1.47 %/year in the rivaroxaban arm and 3.06 %/year in the warfarin arm, somewhat lower in the rivaroxaban arm, although this difference was not significant. For primary ischemic stroke, the rates were 1.10 %/year in the rivaroxaban arm and 2.48 %/year in the warfarin arm, also lower, but not significantly so. For major bleeding, the rates were 2.40 %/year in the rivaroxaban arm and 3.85 %/year in the warfarin arm, a difference that was also not significant. The endpoints of this particular trial were somewhat different from those of the other large-scale clinical trials, and it has therefore not been included in the forest plot for comparative analysis.

### *1.2.3 A Subgroup Analysis of the ARISTOTLE Trial Involving Patients with Atrial Fibrillation and Previous Stroke or TIA*

The ARISTOTLE trial included 3436 patients with a history of stroke/TIA, accounting for approximately 19 % of total enrollment. They included 1694 patients treated with apixaban and 1742 with warfarin. The annual incidence of stroke was 2.26 %/year in the apixaban arm and 3.17 %/year in the warfarin arm, making this the only reported analysis of secondary stroke prevention to find a significant reduction in the rate of recurrence of stroke in the apixaban arm. The annual incidence of ischemic or unknown stroke was 1.92 %/year in the apixaban arm and 2.23 %/year in the warfarin arm, somewhat lower in the apixaban arm, although this difference was not significant. The annual incidence of intracranial bleeding was 0.55 %/year in the apixaban arm and 1.49 %/year in the warfarin arm, significantly lower in the apixaban arm. Similarly, for major bleeding, the rates were 2.84 %/year in the apixaban arm and 3.91 %/year in the warfarin arm, also significantly lower in the apixaban arm [9].

### *1.2.4 A Subgroup Analysis of the ENGAGE AF-TIMI 48 Trial Involving Patients with Atrial Fibrillation and Previous Stroke or TIA*

The ENGAGE AF-TIMI 48 trial compared edoxaban 30 mg and 60 mg with warfarin [10] and showed that neither arm was inferior to warfarin and that this investigational drug suppressed major bleeding and cardiovascular death. As of March 2016, however, no analysis of secondary prevention for patients with a history of stroke/TIA has yet been published, and edoxaban has therefore been excluded from our analysis in this study.

### *1.2.5 Hazard Ratios in Each Trial Compared with Warfarin for the Secondary Prevention of Stroke*

We extracted data from the results of the subgroup analyses described above and summarized them as a forest plot. To investigate efficacy, we extracted data on stroke and cerebral infarction or stroke of unknown origin and calculated the hazard ratios compared with warfarin (Fig. 1.1). The efficacy of each drug was very similar to that of warfarin, but apixaban was more effective for preventing the recurrence of stroke. We also extracted data on intracranial bleeding and major bleeding in the same way as for our investigation of efficacy and calculated their hazard ratios (Fig. 1.2). This showed that both apixaban and dabigatran 110 mg BID were safer than warfarin.

## 1.3 Should Efficacy or Safety Be Emphasized in the Secondary Prevention of Stroke?

The decision on which NOAC to use for secondary prevention of stroke in patients with NVAF is an extremely important issue in clinical terms. If the selection criteria are overcomplex, however, this reduces their convenience in clinical use, making them difficult to use as indicators. We therefore considered whether efficacy or safety should be prioritized on the basis of the data from the results of the above subgroup analyses of patients with a history of stroke/TIA, using age and creatinine clearance rate (Ccr) as the XY axes, and we propose simple NOAC selection criteria (Fig. 1.3).

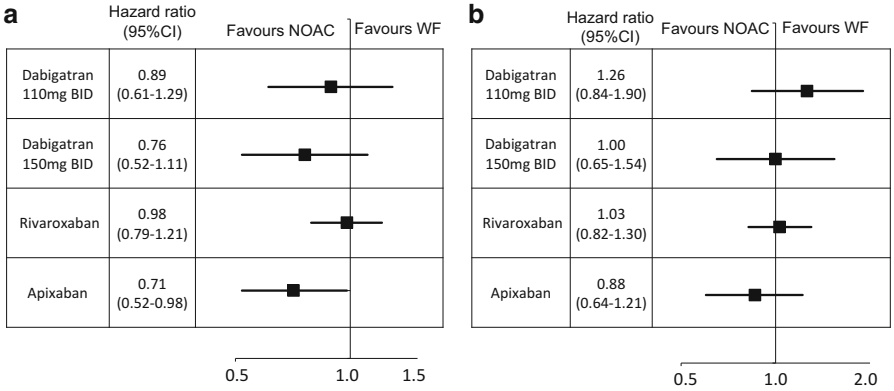


**Fig. 1.1** Main efficacy outcomes in patients with previous stroke or TIA among RCTs. (**a**) Stroke. (**b**) Ischemic stroke or unknown type stroke

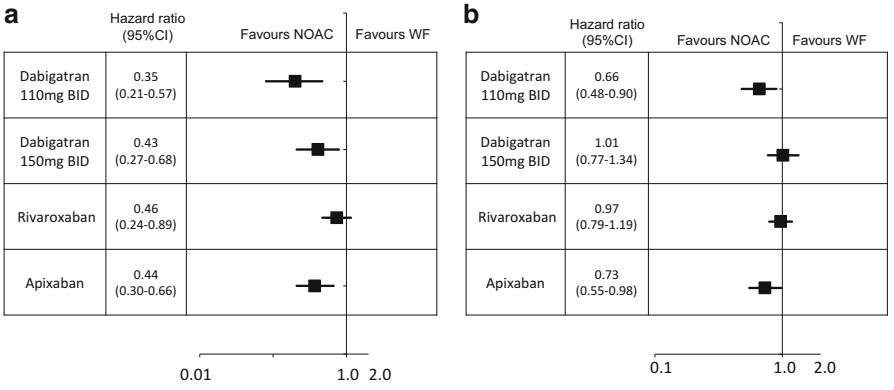


**Fig. 1.2** Main safety outcomes in patients with previous stroke or TIA among RCTs. (**a**) Intracranial hemorrhage. (**b**) Major bleeding

This graph has age as its horizontal axis and Ccr as its vertical axis. Ccr values of 30 mL/min and 50 mL/min are important cutoff values for adjusting the dose of each NOAC, and these two lines were therefore drawn as boundary lines. Three of the large-scale clinical trials had also included subgroup analyses by age with 75 years as the boundary, and another boundary line was therefore drawn at age 75 years.

Patients with Ccr >50 mL/min comprise a population with comparatively good renal function and a low rate of hemorrhagic events, and for these patients, efficacy may therefore be prioritized over safety. If Ccr is 30–50 mL/min, hemorrhagic events are a concern, and for this population, safety should be prioritized over efficacy.

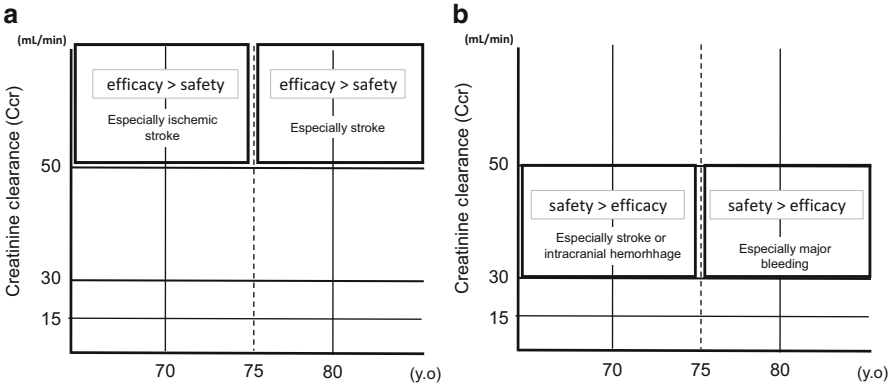


**Fig. 1.3** Important factors to consider from age and Ccr in selecting of NOACs. (**a**) Ccr of 51 or more ml/min. (**b**) Ccr of 30–50 ml/min

Patients aged <75 years with Ccr >50 mL/min thus comprise a comparatively young patient population with good renal function. For this group, an NOAC that is more effective in preventing ischemic stroke should therefore be chosen from the subgroup efficacy analyses. Patients aged ≥75 years with Ccr >50 mL/min are elderly, and because hemorrhagic events are a matter of some concern for this group, an NOAC that is more effective in preventing the recurrence of stroke should be chosen from the subgroup efficacy analyses.

For patients aged <75 years with Ccr 30–50 mL/min, efficacy and safety are of around equal importance, and an NOAC that is more effective in preventing the recurrence of stroke but has a lower rate of intracranial bleeding should be chosen. Patients aged ≥75 years with Ccr 30–50 mL/min form an elderly patient population with moderate or worse renal dysfunction, and an NOAC that is more effective in preventing major bleeding should be chosen from the subgroup safety analyses.

## 1.4 Choice of NOAC for Secondary Stroke Prevention Considered in Light of the Main Analyses and Subgroup Analyses of Large-Scale Clinical Trials (Fig. 1.4)

### *1.4.1 Patients Aged <75 Years with Ccr >50 mL/min*

For patients who fall into this category, efficacy in preventing the recurrence of cerebral infarction is the most important factor to consider. As described above, the secondary prevention analyses show that, at present, no NOAC is more effective than warfarin in preventing the recurrence of cerebral infarction. In the main analysis, however, dabigatran 150 mg BID was more effective in preventing cerebral infarction, and in light of this result, dabigatran 150 mg BID should be chosen as the first-choice medication. In Japan, decreasing the dose of dabigatran from 150 mg

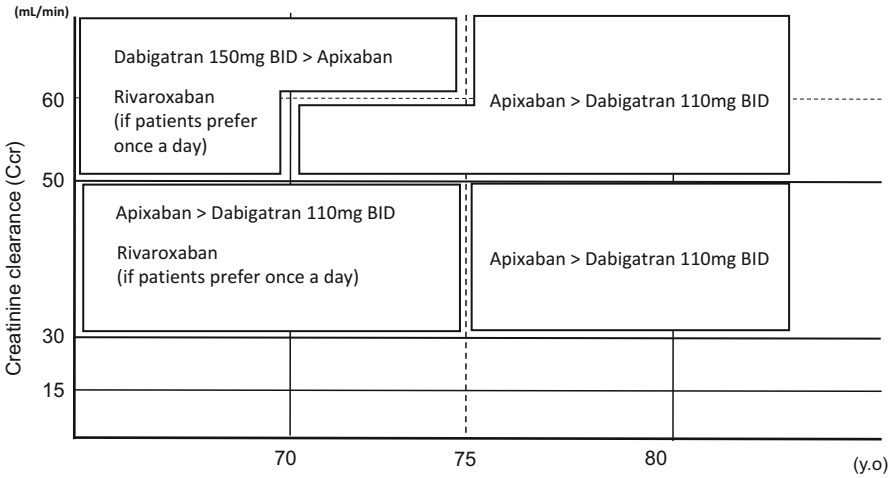


**Fig. 1.4** Our clinical guideline in selecting NOACs to patients with previous stroke or TIA

BID must be considered for patients aged ≥70 years. However, patients aged 70–75 years with comparatively good renal function and Ccr well over 50 mL/min (Ccr ≥60 mL/min) re regarded as being at low risk of bleeding, and dabigatran 150 mg BID may therefore be considered. Conversely, a dose of 110 mg BID should perhaps be chosen for patients aged 70–75 years with Ccr only slightly over 50 mL/min. The guidelines created for this category of patients have thus been displayed with *irregularities*. Apixaban should perhaps be considered as a second choice, given that in the secondary prevention analyses, it was the only drug to show greater efficacy than warfarin in preventing the recurrence of stroke. Rivaroxaban should be chosen for patients who prefer to take medication once a day.

### *1.4.2 Patients Aged ≥75 Years with Ccr >50 mL/min*

For patients who fall into this category, efficacy in preventing the recurrence of stroke is the most important aspect of efficacy to consider. In the subgroup analyses of patients with a history of stroke/TIA, apixaban was the only drug that was more effective than warfarin in preventing the recurrence of stroke, and it should therefore be chosen as the first-choice medication. Dabigatran 150 mg BID cannot be used by patients in this category, meaning that the second choice must be dabigatran 110 mg BID. For patients who request a medication that can be taken once a day, the only available choice is rivaroxaban, but the results of an analysis of patients aged ≥75 years in the J-ROCKET-AF trial showed that, in these patients, the rate of severe or clinically significant bleeding was somewhat higher for rivaroxaban than for warfarin. The choice in this case must be made cautiously, and we have not included it in the selection criteria [11].

### *1.4.3 Patients Aged <75 Years with Ccr 30–50 mL/min*

For patients in this category, efficacy in preventing intracranial bleeding is the most important safety-related factor, while preventing the recurrence of stroke is most important in terms of efficacy. Apixaban is more effective than warfarin in preventing intracranial bleeding, and it is also significantly more effective in preventing the recurrence of stroke, making it the first choice for patients in this category. As described in the previous section, dabigatran 150 mg BID cannot be used by patients in this category, meaning that the second choice must be dabigatran 110 mg BID. Rivaroxaban is chosen for patients who request a medication that can be taken once a day.

### *1.4.4 Patients Aged ≥75 Years with Ccr 30–50 mL/min*

For patients in this category, the most important safety-related factor is efficacy in preventing major bleeding. In the subgroup analyses of patients with a history of stroke/TIA, apixaban and dabigatran 110 mg BID were more effective in preventing major bleeding. Between these two, apixaban was also more effective in preventing recurrence of stroke and should perhaps therefore be the first-choice treatment. For many of the patients in this category, however, the dose of apixaban must be adjusted. Almost all data from the ARISTOTLE trial concerned 5 mg BID, and there were few data for 2.5 mg BID. Reliability is therefore considered to be low for a dose of 2.5 mg BID, and dabigatran 110 mg BID should be chosen for patients who require dose adjustment. With respect to rivaroxaban, as described earlier, for patients aged ≥75 years, the rate of severe or clinically significant bleeding was somewhat higher; for patients in this category, it must be administered with caution, and we have not included it in the selection criteria [11].

## 1.5 Studies of the Choice of NOAC for the Secondary Prevention of Stroke

Several studies have analyzed the question of which of three or four NOACs should be chosen for patients with a history of stroke/TIA in preventing the recurrence of stroke [12–16]. Some of these have recommended rivaroxaban on the grounds that the ROCKET-AF trial enrolled a large number of patients with a history of stroke/TIA. Others, however, have commented that apixaban should be recommended because many patients with a history of stroke/TIA are elderly or suffer from renal dysfunction, and the conclusions vary depending on the viewpoints of the different authors.

## 1.6 Conclusions

Based on the above results of the subgroup analyses of patients with a history of stroke/TIA, focusing on apixaban in the choice of NOAC for the secondary prevention of stroke enables both efficacy and safety to be broadly guaranteed. However, in clinical practice, this choice should be made cautiously in consideration of the characteristics of the different drugs and the condition of each individual patient.

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