[J Tokyo Wom Med Univ
84 (Extra) E42～E48 (2014)]

Review

The Usefulness of New Anticoagulant Drugs for Patients with Cardioembolic Stroke

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(Accepted October 30, 2013)

In multiple large clinical trials, novel oral anticoagulants (NOAC) have clearly showed superiority in both efficacy and safety in comparison to standard warfarin therapy in patients with nonvalvular atrial fibrillation (NVAF). However it is not easy to compare the new drugs, because of the many differences in patients' characteristics and study protocols. In this review, we compare the efficacy and safety of NOACs using data limited to include only that for secondary prevention sub-analyses.

We evaluated the published data of large scale randomized multi-center trials involving NOACs for prevention of stroke and systemic embolism in patients with NVAF. For each of these trials, we collected results of subanalyses for secondary prevention to compare the efficacy and safety.

We found five large clinical trials involving NOACs: RE-LY (dabigatran), ROCKET AF and J-ROCKET AF (rivaroxaban), and AVERROES and ARISTOTLE (apixaban).

The rate of the primary efficacy endpoint was lower in the J-ROCKET AF study than in other trials. The rate of the primary endpoint in other trials appears similar. Major bleeding rates in the high dose group (150 mg × 2) of the RE-LY study appeared higher as compared to other trials. The rate of intracranial hemorrhage among NOACs was almost double in the AVERROES study as compared to the others, whereas overall rates of hemorrhagic stroke were very low in all trials, with the low-dose dabigatran group (110 mg × 2) being the lowest.

In conclusion, all NOACs seem to be equally effective and superior in safety when compared to well-controlled warfarin anticoagulation for secondary prevention of stroke in patients with NVAF. In patients with previous stroke or TIA, differences in outcomes of trials involving NOACs do not appear to be significant.

Key Words: cardioembolic stroke, atrial fibrillation, anticoagulant therapy, warfarin, novel oral anticoagulants

Introduction

Cardioembolic stroke due to nonvalvular atrial fibrillation (NVAF) is the most critical type of ischemic stroke with poor prognoses. Anticoagulant therapy with warfarin had been the only preventative therapeutic option for decades, whereas the rate of hemorrhagic complications, namely intracranial hemorrhage is high, especially among Asian patients[1].

Newly developed anticoagulant agents (novel oral anticoagulant: NOAC) have showed lowered rates of hemorrhage than warfarin. It can be expected that the utility of NOACs brings greater benefit for secondary stroke prevention. Each NOAC has a similar pharmacological profile. It is therefore difficult to compare the clinical efficacy in a real world setting. Dosage and time of administration may strongly influence clinical outcomes. Patient backgrounds and study protocol may have also an influence on endpoint results in large scale clinical trials. Thus, in comparing results of clinical trials involving NOAC therapy, it is necessary to account for differences of patient backgrounds and patient characteristics.

For this review, we compared efficacy and safety of three NOACs using data limited to include only those of secondary prevention cases[2].

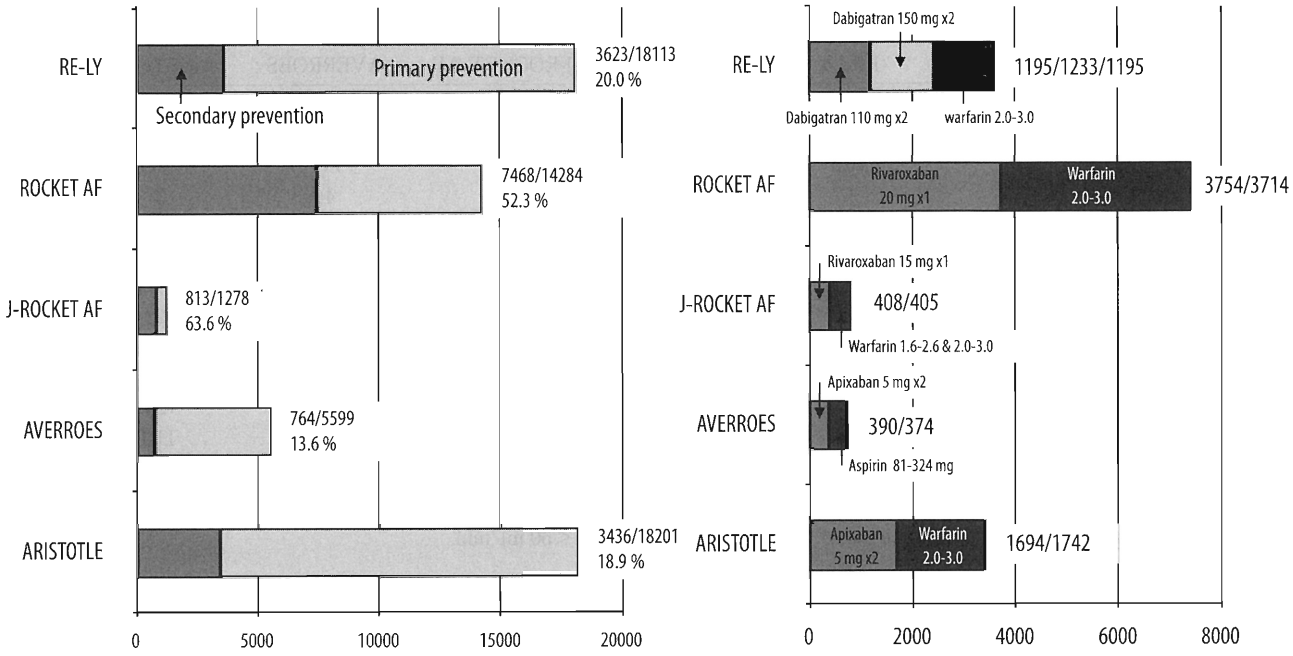

Fig. 1 Prevalence of patients with previous stroke or TIA history in various clinical trials
RE-LY: Randomized evaluation of long-term anticoagulation therapy, ROCKET AF: Rivaroxaban once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation, J-ROCKET AF: Japanese rivaroxaban once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation, AVERROES: Apixaban versus acetylsalitylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment, ARISTOTLE: Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation.

Subjects

We evaluated the published data of large scale (n＞1,000) randomized multi-center trials of NOACs for prevention of stroke and systemic embolism in patients with NVAF. For each of these trials, we collected results of sub-analyses for secondary prevention to compare the efficacy and safety of each NOAC.

Through August 2013, we found five large clinical trials involving NOACs: RE-LY (dabigatran)[3], ROCKET AF[4] and J-ROCKET AF (rivaroxaban)[5], and AVERROES[6] and ARISTOTLE (apixaban)[7]. The J-ROCKET AF trial was conducted only in Japan and all subjects were Japanese. The ROCKET AF and AVERROES studies did not include any Japanese patients. The distribution of secondary prevention subjects for each trial is shown in Fig. 1[8)~14)].

Analysis

Although we achieved some consistency in terms of background by evaluating results only for secondary prevention cases, there still exist some differences among trial settings. For this review, we intentionally only compared the event rates from each study and did not execute additional statistical analysis for the comparison.

Table 1 shows the residual differences which should be considered in a comparative analysis. The ROCKET AF study provided the largest number of patients meeting the secondary prevention criteria (approx. 3,800), followed by RE-LY (approx. 2,400), ARISTOTLE (approx. 1,700), and J-ROCKET AF and AVERROES (both approx. 400). In the AVERROES trial, more than 80% of patients had no history of stroke, and the actual number of secondary prevention cases was less than that of J-ROCKET AF.

Mean $CHADS_2$ scores for each trial ranged between 2.1 and 3.5 when considering the full sample populations, but when considering only secondary

Table 1 Baseline case characteristics of various clinical trials for secondary stroke prevention

	RE-LY	ROCKET AF	J-ROCKET AF	AVERROES	ARISTOTLE
Cases*	3,623/18,113	7,468/14,284	813/1,278	764/5,599	3,436/18,201
$CHADS_2$ mean*	3.5/2.1	3.9/3.5	3.5/3.3	3.8/2.1	3.7/2.1
Age mean	70.5	71	70.3	71.7	70.1
Women %	37	39	18	44	37
Warfarin naïve %	45	41	6	57	39
ASA at baseline	40	38	36	28	31
Target INR in age ≧70**	2.0-3.0 (2.6)	2.0-3.0	1.6-2.6	–	2.0-3.0 (2.6)
CKD Stage Ⅲ % ***	19****	19	20	36	22
Heart Failure %	21	51	21	NA	27
Hypertension %	77	85	71	81	83
Diabetes %	22	25	25	20	26
Efficacy endpoint analysis	ITT	OT	OT	ITT	ITT
Safety endpoint analysis	ITT	OT	OT	ITT	OT

*: subjects with secondary prevention/all study population, **: ( ) is the upper range of INR in Japanese patients, ***: creatinine clearance ≦60 ml/min, ****: creatinine clearance <50 ml/min.
ITT: intention to treat, OT: on treatment, NA: data not available.

prevention cases the range narrows from 3.5 to 3.9. In addition, we find a relatively lower percentage of male and warfarin naïve patients in the J-ROCKET AF study. Congestive heart failure patients in ROCKET AF and those with renal impairment in the AVERROES trial were more prevalent than in the other trials. We also noticed that the share of patients undergoing combination therapy with aspirin is about 10% lower at baseline in ARISTOTLE as compared to the other trials.

Differences in statistical analysis methods by trial raises further questions. The intention-to-treat (ITT) analysis is accepted as the strictest and ideal method when considering the efficacy in a clinical trial. In contrast, on-treatment (OT) analysis which only includes data during the period of study-medication administration is recommended for safety analyses. In the field of anticoagulant therapy, treatment options are still limited, thereby the more appropriate of the two methods remains a topic of discussion.

Results

Fig. 2 shows the annual rates of stroke and systemic embolism as the primary efficacy endpoint in all trials. The rates of ischemic stroke are shown separately in Fig. 3. Whereas none of the NOAC treatment arms could show statistical superiority compared to warfarin arms, the rate of the primary efficacy endpoint was lower in the J-ROCKET AF study than in other trials. The rate of the primary endpoint in other trials appeared similar, although we must take into account that analysis methods may contribute to differences. The event rate by OT analysis was usually lower than that by ITT analysis. Therefore, it is interesting to note that the primary efficacy endpoint rate in the ROCKET AF study for which the OT analysis was used, was the same as that in the trials analyzed by ITT.

In the J-ROCKET AF and ARISTOTLE trials, the efficacy outcome in the warfarin group was slightly worse than in the NOAC groups.

When limiting the endpoint to ischemic stroke, only J-ROCKET AF study could show statistical significance between the rivaroxaban and warfarin.

Regarding safety analysis, because the safety endpoint in the ROCKET AF and J-ROCKET AF trials included additional bleeding conditions not included in the other trials, we used a defined endpoint of "major bleeding" for comparison (Fig. 4). Low dose dabigatran and apixaban arms were successful in showing a statistically significant difference in major bleeding as compared to warfarin arms.

Furthermore we considered data for intracranial hemorrhage and hemorrhagic stroke separately (Fig. 5). Among the five studies, RE-LY and ARISTOTLE showed statistically significant differences between NOACs and warfarin in terms of both in-

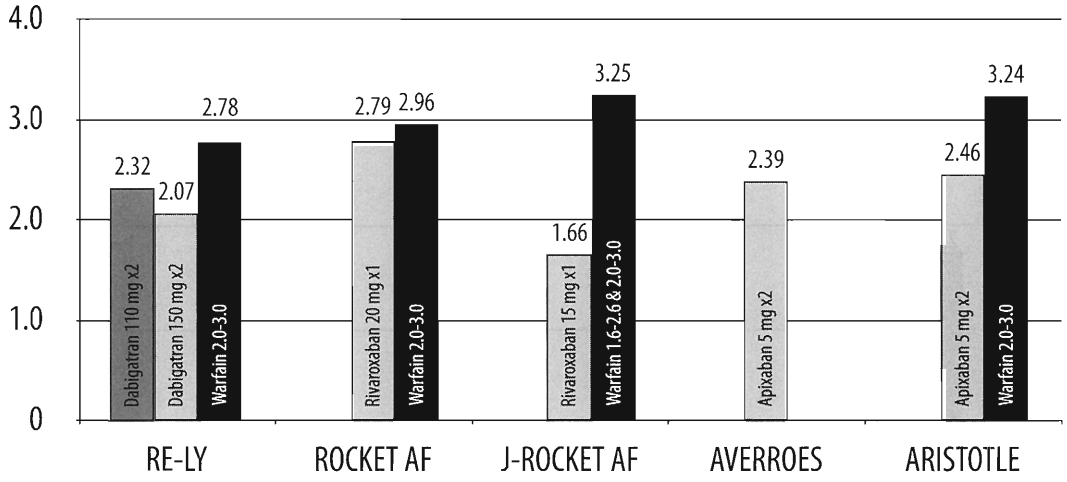

Fig. 2 Annual rates (%) of primary efficacy endpoint

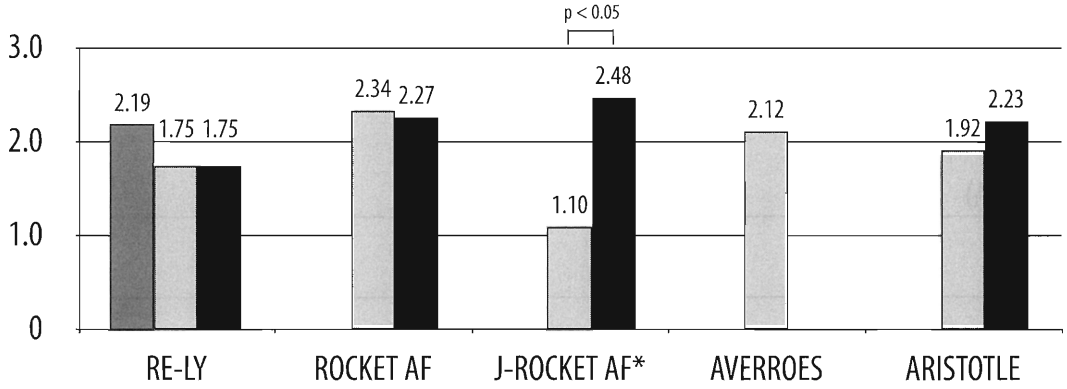

Fig. 3 Annual rates (%) of ischemic and unclassified stroke
*All cases in J-ROCKET AF were diagnosed as ischemic stroke.

tracranial hemorrhage and hemorrhagic stroke. Since safety outcomes in the RE-LY and AVERROES trials were analyzed using ITT, complication rates may have been slightly higher than those of other trials analyzed by the OT method. In the RE-LY study, overall rates of intracranial and hemorrhagic stroke using OT analysis were published but separate data for secondary prevention was not[15].

Major bleeding rates in the high dose group (150 mg × 2) of the RE-LY study appeared higher at more than 4.0%/year as compared to other trials. The rivaroxaban group in the J-ROCKET AF trial revealed the lowest rate of bleeding. Among warfarin groups in all trials, hemorrhage rates seemed to be higher in the RE-LY study whereas the warfarin group in the ROCKET AF study had the lowest rate. The definition of intracranial hemorrhage included hemorrhagic stroke, subdural hematoma, and in some studies, intraocular hemorrhage. The rate of intracranial hemorrhage among NOACs was almost double in the AVERROES study as compared to the others, whereas overall rates of hemorrhagic stroke were very low in all trials with the low-dose dabigatran group being the lowest.

In this review, we compare the efficacy and safety of both warfarin and NOACs for secondary stroke prevention in patients with NVAF. When we narrowed the data to that of patients having a previous history of stroke or TIA, differences among trial results tended subside as compared to those of the full trial populations. However, in either case, it was necessary to consider differences in study population backgrounds and protocol when evaluating results. In addition, in discussing only secondary prevention data, considerable statistical significance was lost due to a reduction the number of eligible

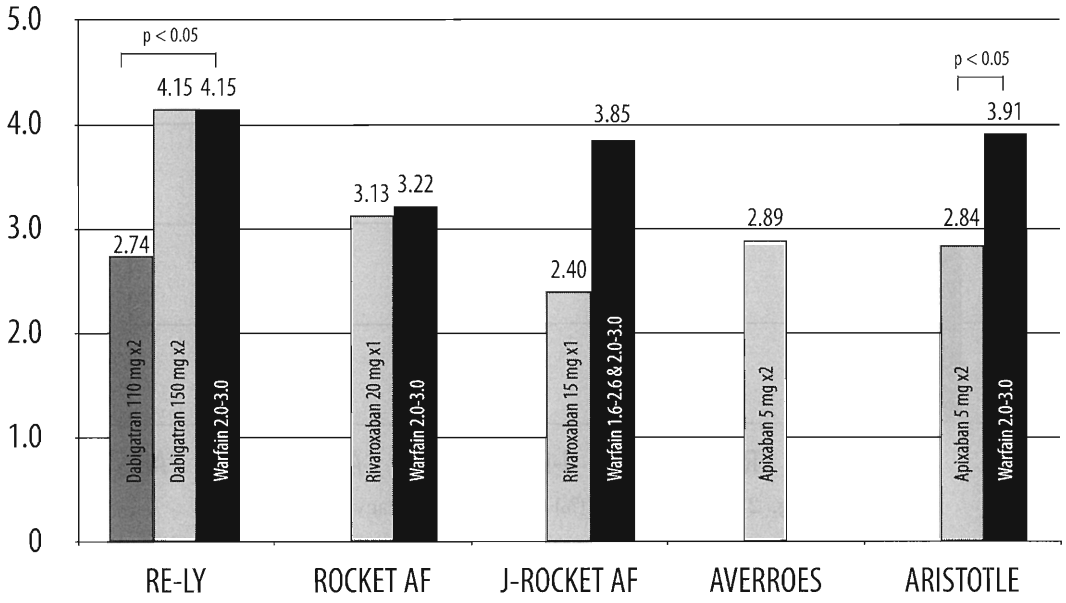

Fig. 4 Annual rates (%) of major bleeding

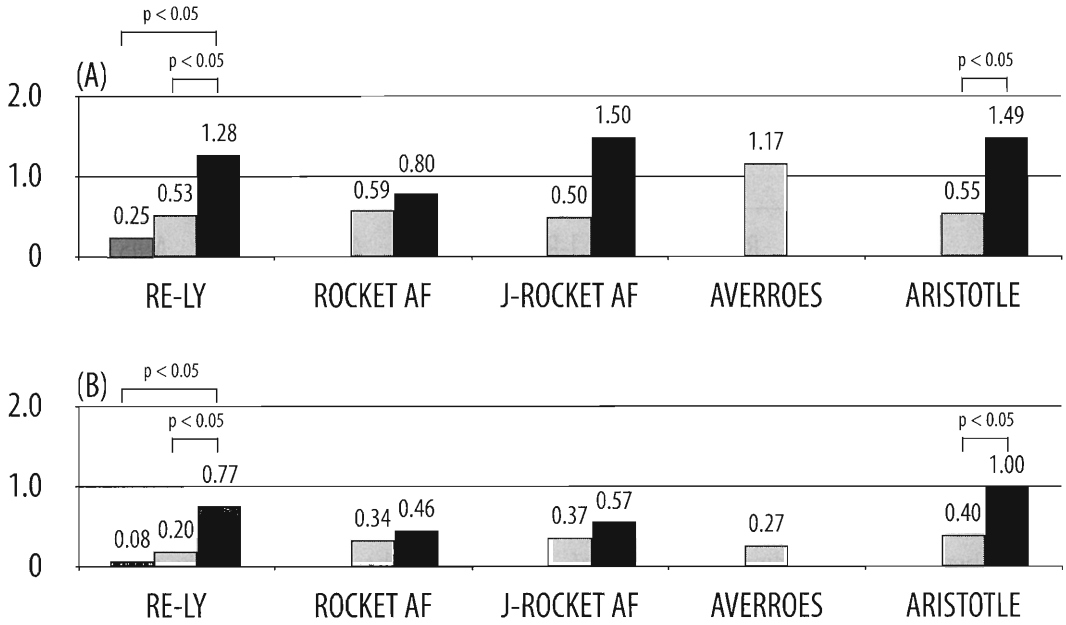

Fig. 5 Annual rates (%) of intracranial hemorrhage (A) and hemorrhagic stroke (B)

subjects.

Regarding the primary endpoint, we must emphasize that the primary "efficacy" endpoint in all studies included hemorrhagic stroke. While the occurrence of hemorrhagic stroke may strongly influence results especially in secondary prevention, rates were not greatly different among trials (Fig. 5B). In the J-ROCKET AF and ARISTOTLE trials, the rate of hemorrhagic stroke in the warfarin group was slightly higher than that of other trials. This may contribute to a more positive perspective of relative risk reduction.

The occurrence of ischemic stroke in the J-ROCKET AF trial seemed to be lower than that of the other trials, which may have been influenced in part by the OT analysis as previously discussed. We can confirm that the efficacy for secondary prevention of ischemic stroke were very similar—occurrence of around 2%/year—among all NOACs based on study protocols which included well con-

trolled warfarin therapy in the comparison group.

Considering safety profiles, the rate of major bleeding in the high dose dabigatran group was higher than that of other NOACs. Rates of major bleeding revealed no major difference among NOACs, including that of low-dose dabigatran. The rate of major bleeding in the J-ROCKET AF study was slightly lower, which may be due to reduced dosage of rivaroxaban in Japanese patients (20 mg × 1 in the ROCKET AF and 15 mg × 1 in the J-ROCKET AF). The bleeding rate in the warfarin group of the J-ROCKET AF was relatively high despite a lower target INR. This may be due to ethnic differences between the J-ROCKET AF population and those of other trials.

Regarding intracranial hemorrhage, we must consider the distribution of hemorrhagic stroke cases. In the AVERROES study, nearly 75% of patients were classified as not having hemorrhagic stroke. This result may have been influenced by the inclusion criteria of AVERROES study, namely, "unsuitable patients for warfarin anticoagulation". We also must point out that in all trials, it is fortunate that almost half of intracranial hemorrhage cases were not hemorrhagic strokes. Many of these cases may be subdural hematoma, which is relatively benign and treatable.

Regarding the occurrence of hemorrhagic stroke, all NOACs showed a reduced rate as compared to warfarin. Low dose dabigatran in the RE-LY trial showed the lowest rate of hemorrhagic stroke, although clinicians must continue to consider safety as well as efficacy for treatment in every patient.

Conclusion

In conclusion, all NOACs seem to be equally effective and superior in safety compared to well-controlled warfarin anticoagulation for secondary prevention of stroke in patients with NVAF. In patients with previous stroke or TIA, differences in outcomes of trials involving NOACs do not appear to be meaningful.

Takehiko Nagao received the lecture fees from Bayer, Nippon Böhringer-Ingelheim. Shinichiro Uchiyama also received the lecture fees from Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Nippon Böhringer-Ingelheim and Pfizer.

References

1) **Shen AY, Yao JF, Brar SS et al**: Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. J Am Coll Cardiol **50**: 309–315, 2007
2) **Diener HC, Easton JD, Hankey GJ et al**: Novel oral anticoagulants in secondary prevention of stroke. Best Pract Res Clin Haematol **26**: 131–139, 2013
3) **Connolly SJ, Ezekowitz MD, Yusuf S et al**: Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med **361**: 1139–1151, 2009
4) **Patel MR, Mahaffey KW, Garg J et al**: Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med **365**: 883–891, 2011
5) **Hori M, Matsumoto M, Tanahashi N et al**: Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation—the J-ROCKET AF study. Circ J **76**: 2104–2111, 2012
6) **Connolly SJ, Eikelboom J, Joyner C et al**: Apixaban in patients with atrial fibrillation. N Engl J Med **364**: 806–817, 2011
7) **Granger CB, Alexander JH, McMurray JJ et al**: Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med **365**: 981–992, 2011
8) **Diener HC, Connolly SJ, Ezekowitz MD et al**: Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. Lancet Neurol **9**: 1157–1163, 2010
9) **Hankey GJ, Patel MR, Stevens SR et al**: Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. Lancet Neurol **11**: 315–322, 2012
10) **Tanahashi N, Hori M, Matsumoto M et al**: Rivaroxaban versus Warfarin in Japanese Patients with Nonvalvular Atrial Fibrillation for the Secondary Prevention of Stroke: A Subgroup Analysis of J-ROCKET AF. J Stroke Cerebrovasc Dis 2013: doi: 10.1016/j.jstrokecerebrovasdis
11) **Diener HC, Eikelboom J, Connolly SJ et al**: Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomised trial. Lancet Neurol **11**: 225–231, 2012
12) **Eikelboom JW, Connolly SJ, Gao P et al**: Stroke risk and efficacy of apixaban in atrial fibrillation patients with moderate chronic kidney disease. J Stroke Cerebrovasc Dis **21**: 429–435, 2012
13) **Easton JD, Lopes RD, Bahit MC et al**: Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. Lancet Neurol **11**: 503–511, 2012
14) **Hohnloser SH, Hijazi Z, Thomas L et al**: Efficacy of apixaban when compared with warfarin in rela-

tion to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J **33**: 2821–2830, 2012
15) **Hart RG, Diener HC, Yang S et al**: Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: the RE-LY trial. Stroke **43**: 1511–1517, 2012

心原性脳塞栓症における新規経口抗凝固薬の有用性

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多くの大規模臨床研究により，非弁膜症性心房細動（nonvalvular atrial fibrillation：NVAF）症例の脳梗塞予防の領域において，新規経口抗凝固薬（novel oral anticoagulant：NOAC）は有効性，安全性の両面で標準治療法であるワルファリンによる抗凝固療法よりも優れた結果を実証した．しかし，各試験の適応症例選択やプロトコールの違いによって，各薬剤の臨床効果を比較するのは容易ではない．本総説では，脳梗塞二次予防に焦点をあて，各NOACの有効性，安全性の比較検討を試みた．

公表されている，NOACのNVAF症例における脳梗塞および全身塞栓症予防を目的とした大規模無作為化多施設臨床研究から，各試験の脳梗塞二次予防群のサブ解析を対象とした．

検索により，5つのNOACに関する大規模試験が該当した．すなわち，RE-LY試験（dabigatran），ROCKET AFおよびJ-ROCKET AF試験（rivaroxaban），そしてAVERROES試験とARISTOTLE試験（apixaban）である．

主要有効性エンドポイント発症率は他の試験に比較して，J-ROCKET AF試験が低い傾向があった．その他の試験の発症率は同レベルであった．大出血事象に関しては，RE-LY試験dabigatran高用量群（150 mg 1日2回）が他の試験より高い傾向にあった．頭蓋内出血はAVERROES試験が他の試験の2倍近い発症率であったが，脳内出血の頻度はすべての試験で大きな差異はなく，中ではRE-LY試験dabigatran低用量群（110 mg 1日2回）が他の試験より低めであった．

脳梗塞二次予防集団に限定しても，すべてのNOACはワルファリン治療薬と比較して，有効性において同等，安全性においては優れていると考えられた．各NOACによる差異に明らかなものは見いだせなかった．