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Efficacy and Safety of Non-Vitamin K Antagonist Oral Anticoagulants vs. Warfarin in Japanese Patients With Atrial Fibrillation

– Meta-Analysis –

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Background: Non-vitamin K antagonist oral anticoagulants (NOAC) have been developed as alternatives to warfarin. Until recently, the latter was the standard oral anticoagulant for patients with non-valvular atrial fibrillation (NVAF). The efficacy and safety of NOAC in Japanese patients with NVAF has been investigated in small trials or subgroups from global randomized control trials (RCT).

Methods and Results: We conducted a systematic review and meta-analysis of RCT, to compare the efficacy and safety of NOAC to those of warfarin in Japanese patients with NVAF. Published research was systematically searched for RCT that compared NOAC to warfarin in Japanese patients with NVAF. Random-effects models were used to pool efficacy and safety data across RCT. Three studies, involving 1,940 patients, were identified. Patients randomized to NOAC had a decreased risk for stroke and systemic thromboembolism (relative risk [RR], 0.45; 95% CI: 0.24–0.85), with a non-significant trend for lower major bleeding (RR, 0.66; 95% CI: 0.29–1.47), intracranial bleeding (RR, 0.46; 95% CI: 0.18–1.16) and gastrointestinal bleeding (RR, 0.52; 95% CI: 0.25–1.08).

Conclusions: NOAC are more efficacious than warfarin for the prevention of stroke and systemic embolism in Japanese patients with NVAF. The present findings offer clinicians a more comprehensive picture of NOAC as a therapeutic option to reduce the risk of stroke in Japanese NVAF patients.

Key Words: Atrial fibrillation; Japanese; Meta-analysis; Non-vitamin K antagonist oral anticoagulant; Stroke prevention

Until recently, warfarin was the standard oral anticoagulant for patients with non-valvular atrial fibrillation (NVAF). More recently, the non-vitamin K antagonist oral anticoagulants (NOAC) have been introduced, and are increasingly preferred in treatment guidelines.

Editorial p???

The NOAC are categorized, on the basis of their targets, as direct thrombin (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban and edoxaban). Recently, 4 large phase III randomized controlled trials (RCT), the Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY) trial,[1] the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF),[2] the Apixaban for Reduction of Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial,[3] and the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial,[4] have examined the long-term use of NOAC.

Although these trials showed that all 4 NOAC are at least as effective and safe with regard to the primary endpoint compared with warfarin, their outcomes in Japanese patients remains unclear. We therefore performed a systematic review and meta-analysis to examine the long-term efficacy and safety of NOAC compared with warfarin in preventing stroke and

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Table 1. Baseline Characteristics of RCT

Characteristics	Trial				
	RE-LY[9]	J-ROCKET AF[10]		ARISTOTLE[11]	
	Overall†	Rivaroxaban	Warfarin	Apixaban	Warfarin
Randomized (n)	326	639	639	161	175
Mean follow-up (years)	1.3	1.37	1.32	2.0	1.75
Age (years)	71.2	71	71.2	69.5 (±8.51)	69.8 (±8.43)
Male (%)	76.7	82.9	78.2	77.6	79.4
$CHADS_2$ score (mean ± SD)	2.2	3.27	3.22	2.0 (±1.11)	2.0 (±1.15)
0–1 (%)	31.3	0	0	41.6	41.1
2 (%)	34	15.2	18	26.1	30.9
≥3 (%)	34.7	84.8	82	32.3	28.0
Prior stroke/TIA (%)	33.1	63.8	63.4	24.8	26.9
Congestive heart failure (%)	31	41.3	40.2	18.0	23.4
ASA use (%)	35.9	38	34.7		
INR control (2.0–3.0) (%)	57.6		Age ≥70: 74, Age <70: 51.8		62.9

†Both arms of dabigatran (110 mg, n=107; 150 mg, n=111) and warfarin (n=108). ASA, acetylsalicylic acid; $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and previous stroke/transient ischemic attack (double); INR, International normalized ratio; RCT, randomized controlled trial; TIA, Transient ischemic attack.

systemic embolism in Japanese patients with NVAF.

Methods

Search Strategies

PubMed, CINAHL and Scopus were searched for abstracts and papers, together with published bibliographies, and the Cochrane library. The following search terms were used: (oral anticoagulants OR oral thrombin inhibitors OR oral factor Xa inhibitors OR dabigatran OR rivaroxaban OR apixaban OR edoxaban OR Japanese) AND atrial fibrillation. The electronic search was restricted to peer-reviewed journals published between 2004 and July 2014. Clinical trial databases and relevant reviews were hand searched for potentially relevant studies not identified in the electronic database search.

Study Selection and Outcomes

The PRISMA statement for reporting systematic reviews and meta-analyses of RCT[5] was used for the method of the present study. Criteria for selection of trials for inclusion were (1) RCT; (2) randomized subjects to warfarin or to NOAC; and (3) included Japanese patients with NVAF. Conference abstracts and presentations were excluded, because their results may not be final, and such publications undergo more limited peer review. To assess the long-term efficacy and safety of these agents, only RCT with follow-up >1 year were included. The main efficacy outcome of interest was a composite endpoint of stroke and systemic embolism. The main safety outcome of interest was major bleeding. Other safety outcomes were intracranial bleeding and gastrointestinal (GI) bleeding.

Data Extraction

Data were extracted by 2 reviewers independently and disagreements were resolved by consensus or, if necessary, by a third party. Data extracted from each RCT included patient- and study-level characteristics as well as outcomes. Extracted patient and study-level characteristics, included mean age, gender distribution, mean congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and previous stroke/transient ischemic attack (double) ($CHADS_2$) score, proportion of patients with relevant comorbidities present at baseline, and international normalized ratio (INR; Table 1).

Quality Assessment

Quality assessment was performed using the Cochrane Collaboration's risk of bias tool.[6]

Statistical Analysis

Analyses were done using Review Manager 5.3 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Summary estimates were calculated as relative risk (RR) using the random effects model based on DerSimonian and Laird's meta-analytic statistical method.[7] The random effects model was chosen in view of the significant methodologic heterogeneity seen between the different studies. For meta-analyses, Cochran's chi-squared test and the I^2 statistic were quantified.[6,8] Cochran's chi-squared test assesses whether the observed differences in results may be due to chance alone, and a low P-value suggests the presence of significant statistical heterogeneity. The I^2 statistic is an alternative test that provides a measure of the inconsistency of the studies' results. It describes the percentage of total variation across the studies that is due to statistical heterogeneity rather than chance.[6] Although it is difficult to give thresholds for the significance of the I^2 statistic, I^2 was also ascertained, where I^2 represents an estimate of the degree of inconsistency among studies, with scores of 25%, 50%, and 75% representing, respectively, low, moderate, or high inconsistency.[8] In all analyses, $P<0.05$ was considered significant. Because of the lack of sufficient data, funnel-plot analyses could not be done for the correction for publication bias.

Results

The search strategy yielded 6,688 citations (Figure 1). Of these, 6,634 were excluded by title or abstract, and 54 studies were retrieved for detailed evaluation.

Three trials that met the inclusion criteria were identified and included in the present study. Two trials, the RE-LY subanalysis and the Japanese Rivaroxaban Once Daily Oral Di-

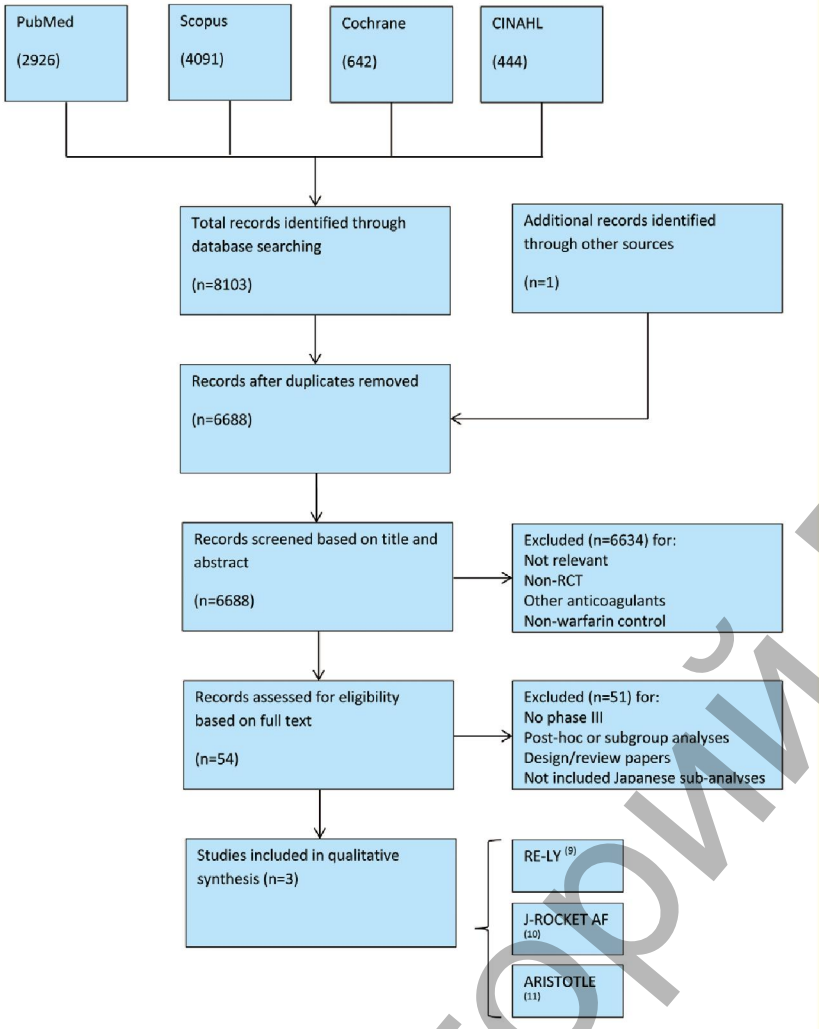

Figure 1. PRISMA diagram of selection process for articles included in the meta-analysis. RCT, randomized controlled trial.

rect Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (J-ROCKET) trial,[9,10] were published as an original report. The Japanese data in ARISTOTLE were not published, but can be found in the US Food and Drug Administration reviews.[11]

No additional studies were identified from Cochrane systematic reviews, manual searches of the reference lists of retrieved reports, relevant reviews, or clinical trial databases. The 3 included trials assessed the relative efficacy and safety of an NOAC, either dabigatran, rivaroxaban, apixaban, compared with warfarin in Japanese AF patients.

Study Quality

The risk of bias in the 3 randomized studies was low (**Table 2**).[9–11] The J-ROCKET AF trial was not powered to test efficacy hypotheses, and efficacy endpoints were evaluated in the per-protocol groups.

Study Characteristics

Table 1 lists the patient characteristics of each study. In the RE-LY trial, 326 patients with Japanese NVAF were randomized to 1 of 3 treatment arms: dabigatran 110 mg twice daily, dabigatran 150 mg twice daily, or warfarin. Both doses were used in the present analysis. In the ARISTOTLE trial, 336 patients with Japanese NVAF were randomized to either apixaban 5 mg twice daily or to warfarin. J-ROCKET AF trial compared a 15-mg per day dose of rivaroxaban to warfarin in 1,278 Japanese patients with NVAF.

These 3 trials randomized a total of 1,940 patients, as follows: 1,018 to NOAC and 922 to warfarin. The mean length of follow-up ranged from 1.3 to 2.0 years, and the average age ranged from 69.5 to 71.2 years. Mean $CHADS_2$ score was between 2.0 and 3.27. Male subjects constituted 76.7–82.9% of the study groups, and the INR control (2.0–3.0) of warfarin constituted approximately 60% of the study groups, excluding the group aged <70 years in J-ROCKET AF trial (51.8%).

Data Synthesis

Efficacy outcome analyses included only composite endpoint of stroke and systemic embolism due to the small number of events when divided into each endpoint, for example, ischemic stroke, hemorrhagic stroke and systemic embolism. In each trial, NOAC were found to be at least non-inferior to

Table 2. Risk of Bias†

	RE-LY[9]	J-ROCKET AF[10]	ARISTOTLE[11]
Random sequence generation	L	L	L
Allocation concealment	L	L	L
Blinding of participants and personnel	L	L	L
Blinding of outcomes assessment	L	L	L
Incomplete outcome data	L	L	L
Selective outcome reporting	L	L	L
Other bias (ITT)	L	H‡	L

†Assessed using the Cochrane Collaboration's bias assessment tool. ‡J-ROCKET AF trial was not powered to test efficacy hypotheses. Efficacy endpoint was evaluated in the per-protocol groups and consequently was at risk for bias that potentially could have affected its results. H, high; ITT, intention to treat; L, low.

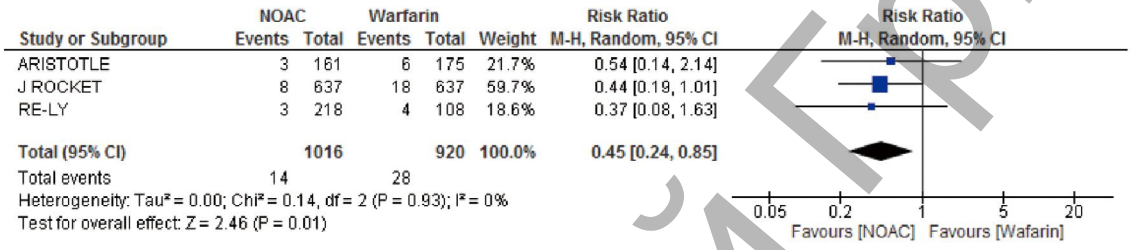

Figure 2. Stroke or systemic thromboembolism events. The RE-LY trial was designed to compare 2 fixed doses of dabigatran (150 mg and 110 mg) with warfarin. Each dose had similar risks for stroke or systemic embolism compared with warfarin (dabigatran 150 mg: RR, 0.24; 95% CI: 0.03–2.14; dabigatran 110 mg: RR, 0.50; 95% CI: 0.09–2.70). NOAC, non-vitamin K antagonist oral anticoagulant.

warfarin for the composite endpoint of stroke and systemic embolism (**Figure 2**).

When data were pooled across RCT, patients randomized to NOAC had a significant 55% RR reduction for the composite endpoint of stroke and systemic embolism compared with those randomized to warfarin (RR, 0.45; 95% CI: 0.24–0.85).

The safety outcome analyses included major bleeding, intracranial bleeding and GI bleeding (**Figure 3**). In each analysis, dabigatran and rivaroxaban had similar risk for major bleeding compared to warfarin, while apixaban demonstrated superiority for this outcome. For intracranial bleeding data and GI bleeding, the 3 NOAC had similar risk compared to warfarin.

In meta-analyses, the NOAC had a non-significant trend towards lower risk for major bleeding (RR, 0.66; 95% CI: 0.29–1.47), intracranial bleeding (RR, 0.46; 95% CI: 0.18–1.16) and GI bleeding (RR, 0.52; 95% CI: 0.25–1.08), when compared to warfarin.

Discussion

The present systematic review and meta-analysis was designed to compare the efficacy and safety of NOAC with that of warfarin in patients with AF. We found that NOAC significantly reduced the risk of stroke and systemic embolism compared with warfarin, but had a non-significant trend for benefit with respect to major bleeding, intracranial bleeding and GI bleeding. Thus, the present results support the use of NOAC as an alternative to warfarin for long-term anticoagulation therapy in Japanese patients with NVAF.

Warfarin is largely underused because of concerns over the need for systematic monitoring and the risk for bleeding associated with its use. In the Fushimi AF Registry, only 60% of patients with AF indicated for anticoagulation therapy were estimated to receive it.[12]

Similar to contemporary experience with warfarin, large Japanese registries have shown that only half of patients reached the therapeutic range of prothrombin time (PT)-INR.[12,13] These data highlight a substantial gap between the evidence-based guideline recommendation and everyday clinical practice. Thus, anticoagulation control as reflected by time in therapeutic range (TTR) in Japan tends to be low,[14] especially with the tendency to target INR 1.6–2.6 in elderly subjects.[14] Hence, there is an unmet need for new anticoagulants that can function as alternatives to warfarin for long-term thromboprophylaxis in AF.

Bleeding

Although warfarin has been shown to lower the risk for stroke and thromboembolism, it is associated with an increased risk for potentially life-threatening bleeding events.[15,16] Hemorrhagic complication is an important concern with anticoagulation therapy because it is associated with significant morbidity and mortality.

A previous report on patients with AF treated with warfarin demonstrated a 4-fold higher hazard ratio for intracranial hemorrhage in Asian compared with white patients.[17] Furthermore in a recent meta-analysis on the incidence of hemorrhagic stroke and major bleeding, the incidence was 2-fold higher in the Asian population compared to non-Asian patients.[18]

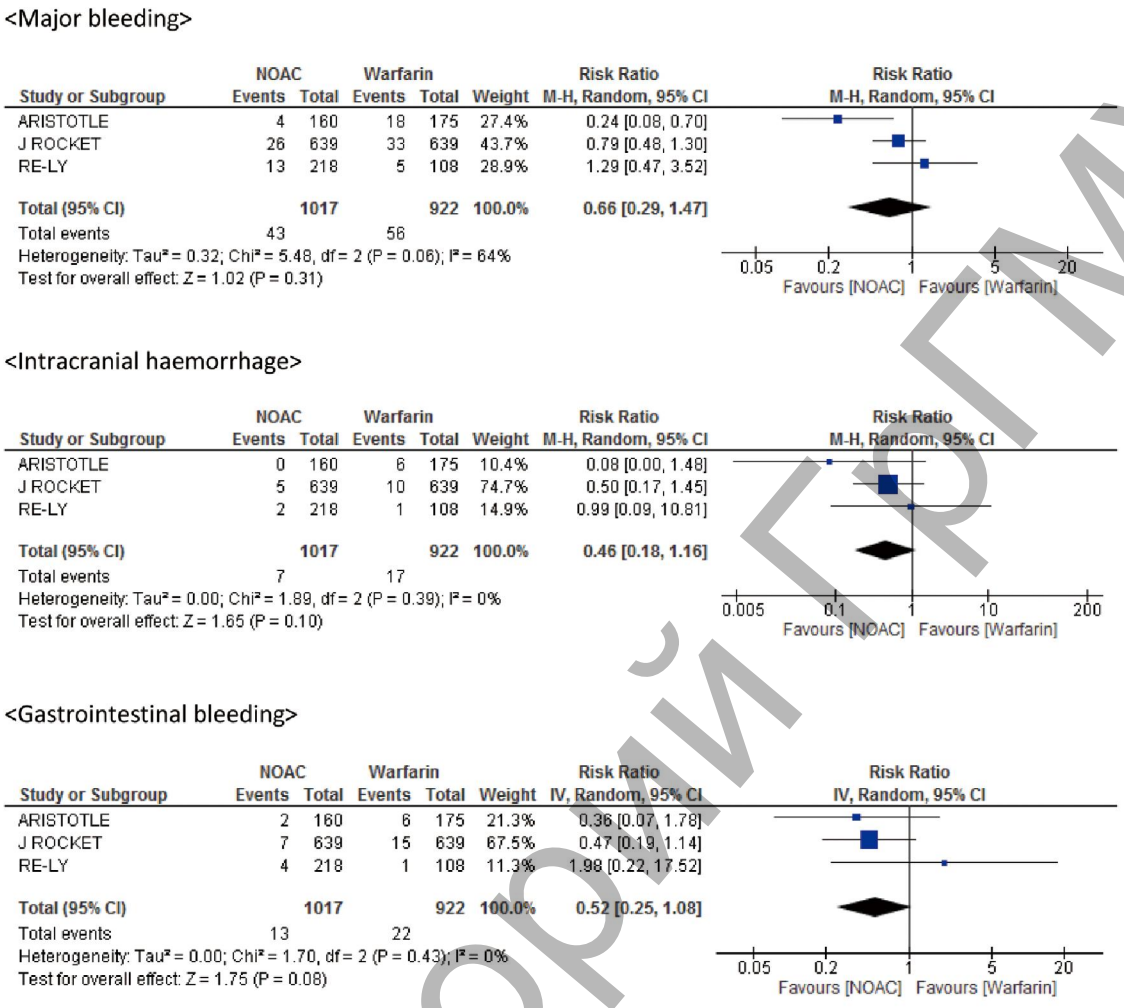

Figure 3. Major bleeding, intracranial hemorrhage and gastrointestinal bleeding. The RE-LY trial was designed to compare 2 fixed doses of dabigatran (150 mg and 110 mg) with warfarin. Each dose had similar risks compared with warfarin for major bleeding (dabigatran 150 mg: RR, 0.97; 95% CI: 0.29–3.27; dabigatran 110 mg: RR, 1.61; 95% CI: 0.55–4.78), intracranial hemorrhage (dabigatran 150 mg: RR, 0.97; 95% CI: 0.06–15.36; dabigatran 110 mg: RR, 1.01; 95% CI: 0.06–15.93) and gastrointestinal bleeding (dabigatran 150 mg: RR, 0.97; 95% CI: 0.06–15.36; dabigatran 110 mg: RR, 3.03; 95% CI: 0.32–28.65). NOAC, non-vitamin K antagonist oral anticoagulant.

It is possible that a racial or genetic factor is involved in this difference, which has been pointed out for years, but we should also consider other factors because no such differences were observed in a comparison between Asian and non-Asian patients receiving dabigatran. In the RE-LY substudy, the lower average INR and the low TTR in Asian patients may be the biggest reasons for the higher risks of both ischemic stroke and hemorrhagic stroke.[19] In a subanalysis of the RE-LY trial, the percentage of patients with a mean INR of 2–3 was 68.9% and 56.5% in non-Asian and Asian patients, respectively.

In the same way, the proportion of patients with a mean INR of 2–3 in Japanese patients was 57.6%, 51.8% and 62.9% in RE-LY, J-ROCKET (age <70 years) and ARISTOTLE trials, respectively. Together with a lower TTR in Asian countries compared to non-Asian countries,[18] these results suggest that Japanese patients are not receiving optimally managed warfarin therapy. Another reason is that most Japanese physicians adjusted the dose of warfarin to achieve a target PT-INR between 1.6 and 2.6, based on the latest JCS guidelines.[20] If the target PT-INR was set between 1.6 and 2.6, the TTR in Japanese patients taking warfarin was not low in practice.[14,21] Indeed, the TTR in elderly patients (≥70 years) in the J-ROCKET AF trial was 74%, and therefore, a lower TTR (especially PT-INR <2.0) in the 3 trials was not necessarily due to poor warfarin control or warfarin adherence but reflected what was recommended in Japanese guidelines. The data from the J-RHYTHM registry indicate that most INR outside the therapeutic range were below the therapeutic range that applied to patients aged <70 years (ie, <2.0), reflecting the tendency of Japanese physicians to favor lower levels of anticoagulation.[22]

The present results also show that use of NOAC does not increase the overall risk for major bleeding, intracranial bleeding and GI bleeding compared with warfarin in Japanese pa-

Table 3. Comparison of Stroke and Bleeding Events

Events/Drugs	Japanese patients†		Global patients‡	
	%/year	n	%/year	n
Stroke/systemic thromboembolism				
Dabigatran 150	0.67	1/111	1.11	134/6,076
Dabigatran 110	1.38	2/107	1.54	183/6,015
Rivaroxaban¶	1.26	11/637	2.1	269/7,131
Apixaban	0.87	3/161	1.27	212/9,120
Major bleeding				
Dabigatran 150	3.33	5/111	3.31	399/6,076
Dabigatran 110	5.53	8/107	2.87	342/6,015
Rivaroxaban¶	3	26/639	3.6	395/7,131
Apixaban	1.26	4/160	2.13	327/9,088
Intracranial bleeding				
Dabigatran 150	0.67	1/111	0.32	39/6,076
Dabigatran 110	0.69	1/107	0.23	27/6,015
Rivaroxaban¶	§	5/639	0.5	55/7,131
Apixaban	0	0/160	0.33	52/9,088
Gastrointestinal bleeding				
Dabigatran 150	0.67	1/111	1.85	223/6,076
Dabigatran 110	2.11	3/107	1.36	162/6,015
Rivaroxaban¶	§	7/639	3.15	224/7,131
Apixaban	0.63	2/160	0.76	118/9,088

†Dabigatran data were derived from the RE-LY trial (sub-analysis),[9] those for rivaroxaban from the J-ROCKET AF trial[10] and those for apixaban from the ARISTOTLE trial (sub-analysis).[11] ‡Dabigatran data were derived from the RE-LY trial,[1,23] and those for apixaban from the ARISTOTLE trial,[3] whereas the rivaroxaban data were derived from the ROCKET AF trial[2] (excluded Japanese patients). ¶Rivaroxaban 15 mg in Japanese patients and rivaroxaban 20 mg in global patients. §No %/year was listed.

tients with AF. Major bleeding and intracranial bleeding rates of all 3 NOAC in Japanese sub-analysis tended to be lower compared with the warfarin group, consistent with the main results from global trials. GI bleeding rates of the NOAC group in both the RE-LY (Japanese subanalysis) and J-ROCKET AF trial tended to be lower than that of the warfarin group,[9,10] whereas in the main RE-LY and ROCKET AF trial results, GI bleeding occurred more frequently in the NOAC group than the warfarin group (**Table 3**).[1,2,23] This discrepancy in the rate of GI bleeding between Japanese patients and global patients might be attributable to ethnic difference in GI bleeding, or to health-care divergence by country in the endoscopic diagnosis/treatment of GI tract diseases, and different patient awareness of GI bleeding.

What are the future directions? NOAC are expected to overcome the limitations of warfarin, and to improve patient outcome. In fact, the use of NOAC is recommended in patients with $CHADS_2$ score ≥1, according to the latest Japanese guidelines. Thus, the use of NOAC should be determined by an evidence-based medicine, so as to avoid underuse and under-dosage.

Study Limitations

The present study has potential limitations. First, there was heterogeneity between the 3 trials and residual confounding may be apparent from differences in patient demography, comorbidities, and the concomitant use of cardiovascular prevention strategies. Those 3 trials also investigated different oral anticoagulant drugs, and some of the between-study differences may be due to these. Second, patients taking warfarin in the J-ROCKET AF trial had a target INR 1.6–2.6, while target INR was 2.0–3.0 in the other 2 trials. Thus, there was heterogeneity between the included trials, although similar variability was not likely to apply to the NOAC because of their fixed dose. Thus, we used random effects models that account for between-study heterogeneity. Third, half of the study patients included in this meta-analysis were derived from the J-ROCKET AF trial, which was not powered to test for efficacy. The efficacy endpoint was also evaluated in the per-protocol study groups and, consequently, was at risk for bias that could have affected its results. Nonetheless, the significance of this study is that it shows evidence for the efficacy and safety of NOAC in Japanese AF patients.

Conclusions

NOAC are more efficacious than warfarin for the prevention of stroke and systemic embolism in Japanese patients with NVAF. The present findings offer clinicians a more comprehensive picture of NOAC as a therapeutic option to reduce the risk of stroke in Japanese NVAF patients.

Disclosures

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bureau for Bayer, BMS/Pfizer, Boehringher Ingelheim, Daiichi-Sankyo, Medtronic and Sanofi Aventis.

References

1. 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.
2. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365:** 883–891.
3. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365:** 981–992.
4. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; **369:** 2093–2104.
5. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *J Clin Epidemiol* 2009; **62:** e1–e34, doi:10.1016/j.jclinepi.2009.06.006.
6. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327:** 557–560.
7. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7:** 177–188.
8. Higgins JP, Altman DG, Gotzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343:** d5928.
9. Hori M, Connolly SJ, Ezekowitz MD, Reilly PA, Yusuf S, Wallentin L. Efficacy and safety of dabigatran vs. warfarin in patients with atrial fibrillation: Sub-analysis in Japanese population in RE-LY trial. *Circ J* 2011; **75:** 800–805.
10. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation: The J-ROCKET AF study. *Circ J* 2012; **76:** 2104–2111.
11. Bristol-Myers K.K. Common Technical Document. http://www.info.pmda.go.jp/approvalSrch/PharmacySrchInit (accessed September 16, 2014).
12. Akao M, Chun YH, Esato M, Abe M, Tsuji H, Wada H, et al. Inappropriate use of oral anticoagulants for patients with atrial fibrillation. *Circ J* 2014; **78:** 2166–2172.
13. Inoue H, Okumura K, Atarashi H, Yamashita T, Origasa H, Kumagai N, et al. Target international normalized ratio values for preventing thromboembolic and hemorrhagic events in Japanese patients with non-valvular atrial fibrillation: Results of the J-RHYTHM Registry. *Circ J* 2013; **77:** 2264–2270.
14. Okumura K, Komatsu T, Yamashita T, Okuyama Y, Harada M, Konta Y, et al. Time in the therapeutic range during warfarin therapy in Japanese patients with non-valvular atrial fibrillation: A multicenter study of its status and influential factors. *Circ J* 2011; **75:** 2087–2094.
15. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest* 2008; **133:** 160s–198s.
16. Wysowski DK, Nourjah P, Swartz L. Bleeding complications with warfarin use: A prevalent adverse effect resulting in regulatory action. *Arch Intern Med* 2007; **167:** 1414–1419.
17. Shen AY, 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.
18. Chiang CE, Wang KL, Lip GY. Stroke prevention in atrial fibrillation: An Asian perspective. *Thromb Haemost* 2014; **111:** 789–797.
19. Hori M, Connolly SJ, Zhu J, Liu LS, Lau CP, Pais P, et al. Dabigatran versus warfarin: Effects on ischemic and hemorrhagic strokes and bleeding in Asians and non-Asians with atrial fibrillation. *Stroke* 2013; **44:** 1891–1896.
20. JCS Joint Working Group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013). http://www.j-circ.or.jp/guideline/pdf/JCS2013_inoue_h.pdf (accessed September 16, 2014).
21. Naganuma M, Shiga T, Sato K, Murasaki K, Hashiguchi M, Mochizuki M, et al. Clinical outcome in Japanese elderly patients with non-valvular atrial fibrillation taking warfarin: A single-center observational study. *Thromb Res* 2012; **130:** 21–26.
22. Atarashi H, Inoue H, Okumura K, Yamashita T, Kumagai N, Origasa H. Present status of anticoagulation treatment in Japanese patients with atrial fibrillation: A report from the J-RHYTHM Registry. *Circ J* 2011; **75:** 1328–1333.
23. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: An analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011; **123:** 2363–2372.