

Indirect comparison of nonvitamin K oral anticoagulants and left atrial appendage occlusion

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Background: Anticoagulation is important in atrial fibrillation (AF) patients to reduce the occurrence of thrombotic events. We evaluated the efficacy and safety of percutaneous left atrial appendage occlusion (LAAO) as an alternative to systemic anticoagulation through an indirect comparative analysis.

Methods: An indirect comparative analysis of nonvitamin K oral anticoagulants (NOACs) and LAAO was conducted. Comparisons were made using data from four landmark randomized clinical trials (RE-LY, ROCKET-AF, ARISTOTLE, and PROTECT AF). Using warfarin as the common comparator, an indirect comparison was performed using data from each trial, and the relative risk was calculated between NOACs and LAAO.

Results: NOACs and LAAO showed similar results for the reduction of stroke and systemic embolism, with a non-statistically significant trend favoring NOACs (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.37–1.46 for dabigatran; HR, 0.99; 95% CI, 0.50–1.92 for rivaroxaban; HR, 0.89; 95% CI, 0.45–1.74 for apixaban). Significantly fewer major bleeding and procedure-related complications were found in patients treated with apixaban compared with LAAO (HR, 0.45; 95% CI, 0.26–0.75). Cardiovascular death occurred more frequently in patients administered NOACs than in patients with LAAO (HR, 2.28; 95% CI, 1.03–5.10 for dabigatran; HR, 2.41; 95% CI, 1.09–5.42 for rivaroxaban; HR, 2.40; 95% CI, 1.10–5.36 for apixaban).

Conclusions: The rate of all-cause death was similar between NOACs and LAAO. Compared with LAAO, NOACs led to a nonsignificant numerical decrease in stroke and embolism in AF patients. Significantly fewer safety events occurred in patients treated with apixaban. LAAO significantly reduced cardiovascular death.

Keywords: Atrial fibrillation; Stroke; Anticoagulants; Atrial appendage

INTRODUCTION

Atrial fibrillation (AF) is the most common type of complex arrhythmia, and stroke is a serious complication [1]. Ischemic stroke secondary to AF has a poorer prognosis than stroke due to other causes [2]; therefore, stroke prevention

in AF patients is important. Warfarin reduces the risk of stroke but increases the risk of bleeding [3]. Despite strong evidence of the clinical efficacy of warfarin, underuse and inadequate anticoagulation are quite common [4]. The limitations associated with warfarin have led to an extensive search for alternative strategies. First, for systemic anticoag-

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ulation, several nonvitamin K oral anticoagulants (NOACs) were developed to replace warfarin and approved for clinical use [5-7]. All NOACs showed non-inferiority in primary efficacy for stroke and systemic embolism prevention, and dabigatran (150 mg twice daily) and apixaban showed superiority over warfarin. In terms of safety, dabigatran (110 mg twice daily) and apixaban caused less major bleeding than warfarin. Second, percutaneous left atrial appendage occlusion (LAAO) was developed as a local treatment [8,9] because approximately 90% of strokes can be attributed to thrombus formation in the left atrial appendage when a source can be identified in nonvalvular AF [10]. The local LAAO strategy showed non-inferiority to warfarin regarding the primary efficacy endpoint of stroke, systemic embolism, and cardiovascular death [11]. Although NOACs and LAAO are different strategies (i.e., the former involves systemic anticoagulation with a drug and the latter involves local treatment using a device), the target population of both modalities is AF patients at high thrombotic risk [12,13]. In the absence of head-to-head trials, an adjusted indirect method allows comparison of two treatments using a common comparator (e.g., warfarin) in randomized controlled trials (RCTs) [14,15]. An indirect comparison of each NOAC has previously been published and has been helpful for clinical decision-making and generating further hypotheses [16]. In the present study, an indirect comparison between NOACs and LAAOs regarding the efficacy and safety endpoints was performed.

METHODS

RCTs in which the treatment consisted of NOACs (random-

ized evaluation of long-term anticoagulation therapy [RE-LY], rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in AF [ROCKET-AF], and apixaban for reduction in stroke and other thromboembolic events in AF [ARISTOTLE]) or LAAO (Watchman left atrial appendage system for embolic protection in patients with AF [PROTECT AF]) versus warfarin in patients with AF were included in the present study. Two studies were double-blind (ROCKET-AF, ARISTOTLE) and the other two studies were open-label (RE-LY, PROTECT AF). In all trials, the data were analyzed based on the intention-to-treat principle. The main efficacy and safety endpoints from the trials were reviewed for comparability and consistency of definitions (Table 1). In contrast to large pharmaceutical trials involving over 50,000 patients, only two randomized trials of LAAO have been published to date [8,17]. The recent PREVAIL trial compared LAAO and warfarin; however, this trial was not included due to the lack of published data (specifically, the number of major bleeding events and all-cause deaths) [17]. Regarding the RE-LY trial, the group treated with 110 mg of dabigatran was excluded for comparability and simplicity of the analysis. Regarding the PROTECT AF trial, the longer follow-up results published recently were used in the present study [11].

In the indirect analysis, treatment effectiveness was assumed to be the same across all trials used in the comparison. The primary efficacy endpoint for all trials, except for PROTECT AF, was stroke and systemic embolism. In the PROTECT AF trial, the primary efficacy endpoint was a composite of stroke, systemic embolism, and cardiovascular death. For comparability of the safety endpoint, major

Table 1. Summary of the included trials

Variable	RE-LY ^{a)} (n=12,098)	ROCKET-AF (n=14,264)	ARISTOTLE (n=18,201)	PROTECT AF (n=707)
Key inclusion criteria	Nonvalvular AF, CHADS ₂ ≥1	Nonvalvular AF, CHADS ₂ ≥2	Nonvalvular AF, CHADS ₂ ≥1	Nonvalvular AF, CHADS ₂ ≥1
Study group	Dabigatran (150 mg twice daily)	Rivaroxaban (20 mg daily)	Apixaban (5 mg twice daily)	LAAO (Watchman)
Control group (TTR)	Warfarin (64%)	Warfarin (55%)	Warfarin (66%)	Warfarin (66%)
Follow-up (yr), median	2.4	1.9	1.8	2.3

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; ARISTOTLE, apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation; PROTECT AF, Watchman left atrial appendage system for embolic protection in patients with atrial fibrillation; AF, atrial fibrillation; CHADS₂, congestive heart failure, hypertension, age ≥75years, diabetes mellitus, stroke (2 points); LAAO, left atrial appendage occlusion; TTR, time in therapeutic range.

^{a)}Patients who received 110 mg of dabigatran were excluded.

bleeding and procedure-related complications were formed into a composite. The network is shown in Fig. 1. The results of intention-to-treat analyses were used throughout.

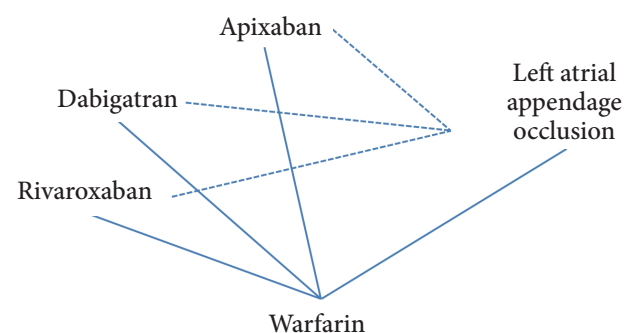


Fig. 1. Evidence network of the four reported randomized controlled trials of new oral anticoagulant and left atrial appendage occlusion in patients with nonvalvular atrial fibrillation at risk of stroke. The dashed lines represent indirect comparisons from the present study.

The present study was a meta-analysis, and approval by the institutional committee was therefore not required.

RESULTS

Baseline characteristics

The clinical trials compared in the present study are summarized in Table 1. All trials included a high-risk population of patients with nonvalvular AF. The ROCKET-AF trial enrolled a population at higher risk of stroke (CHADS₂ score ≥2) than the other trials (CHADS₂ score ≥1). CHADS₂ stands for congestive heart failure (C), hypertension (H), age ≥75 years (A), diabetes mellitus (D), stroke (2 points; S₂). The average time in therapeutic range among the warfarin-treated patients was similar. Patients' baseline characteristics are summarized in Table 2. The mean age of patients was broadly similar; however, there were fewer women in the PROTECT AF trial. Patients in the ROCKET-AF trial were at

Table 2. Baseline characteristics of patients in the included clinical trials

Baseline characteristic	RE-LY ^{a)} (n=12,098)	ROCKET-AF (n=14,264)	ARISTOTLE (n=18,201)	PROTECT AF (n=707)
Age (yr)	71.5±8.7	73 (65–78)	70 (63–76)	72.0±8.9
Male sex (%)	63.2	60.3	64.8	70.3
CHADS ₂ , mean	2.2	3.5	2.1	2.2
CHADS ₂ score (%)				
0–1	31.6	0	34.0	31.5
2	36.1	13.0	35.8	34.8
3–6	32.4	87.0	30.2	33.7
Prior stroke, TIA, systemic embolism (%)	20.1	54.9	19.4	18.5
Heart failure (%)	31.9	62.6	35.4	26.9
Prior myocardial infarction (%)	16.5	16.6	14.2	
Diabetes mellitus (%)	23.2	40.4	25.0	26.2
Hypertension (%)	78.9	90.3	87.5	89.5
Paroxysmal AF (%)	33.2	17.5	15.3	42.3
Use of warfarin (%)	49.4	62.3	57.2	98.7
Race/ethnicity (%)				
Asian	15.3	12.6	16.0	0.7
Black	NA	1.3	NA	1.6
White	NA	83.2	NA	91.5
Other	NA	3.0	NA	6.2

Values are presented as mean±standard deviation, median (range), or number.

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; ARISTOTLE, apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation; PROTECT AF, Watchman left atrial appendage system for embolic protection in patients with atrial fibrillation; CHADS₂, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke (double weight); TIA, transient ischemic attack; AF, atrial fibrillation; NA, not available.

^{a)}Patients who received 110 mg of dabigatran were excluded.

Table 3. Efficacy and safety results of each trial

Variable	RE-LY ^{a)} (n=12,098)	ROCKET-AF (n=14,264)	ARISTOTLE (n=18,201)	PROTECT AF (n=707)
Stroke and systemic embolism	0.66 (0.53–0.82)	0.79 (0.66–0.96)	0.79 (0.66–0.95)	1.51 (0.65–0.92)
Major bleeding and procedure-related complications ^{b)}	0.93 (0.81–1.07)	1.04 (0.90–1.20)	0.69 (0.60–0.80)	1.53 (0.95–2.70)
Cardiovascular death	0.85 (0.72–0.99)	0.86 (0.74–0.99)	0.89 (0.76–1.04)	0.38 (0.18–0.85)
All-cause death	0.88 (0.77–1.00)	0.92 (0.82–1.03)	0.89 (0.80–0.99)	0.71 (0.46–1.28)

Values are presented as number (range). In the RE-LY trial, NOAC showed preventive effect on the occurrence of stroke and systemic embolism with HR 0.66 (0.53–0.82).

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; ARISTOTLE, apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation; PROTECT AF, Watchman left atrial appendage system for embolic protection in patients with atrial fibrillation.

^{a)}Patients who received 110 mg of dabigatran were excluded. ^{b)}Procedure-related complications consisted of serious pericardial effusion, device embolization, and procedure-related stroke.

higher risk of stroke based on the mean CHADS₂ score. In addition, there was a greater proportion of patients with a higher CHADS₂ score (3–6), previous stroke, heart failure, and diabetes. The prevalence of nonparoxysmal AF and previous warfarin use was significantly higher in patients included in the PROTECT AF trial; however, there were fewer Asian patients (Table S1).

Review of outcomes in each trial

The efficacy and safety endpoints of each trial are compared in Table 3. In contrast to a significant reduction in stroke and systemic embolism in NOAC trials, LAAO showed a tendency to increase events, while significantly reducing cardiovascular death. As previously published, the primary endpoint of the PROTECT AF trial was a composite of stroke, systemic embolism, and cardiovascular death; LAAO showed non-inferiority to warfarin therapy [8]. In the PROTECT AF trial, safety endpoints including major bleeding and procedure-related complications occurred at a higher rate in the LAAO group (hazard ratio [HR], 1.69; 95% confidence interval [CI], 1.01–3.19). However, in the NOAC trial, safety endpoints occurred at a similar rate in the NOAC and warfarin groups.

Indirect comparison of NOACs and LAAO

Indirect comparisons were performed for each NOAC versus LAAO. The results are summarized in Fig. 2. Regarding the reduction in stroke and systemic embolism, NOACs and LAAO were similar, but a non-statistically significant

trend favored NOACs compared with LAAO (HR, 0.74; 95% CI, 0.37–1.46 for dabigatran; HR, 0.99; 95% CI, 0.50–1.92 for rivaroxaban; HR, 0.89; 95% CI, 0.45–1.74 for apixaban). Major bleeding and procedure-related complications were significantly less common in patients treated with apixaban than in those who underwent LAAO (HR, 0.45; 95% CI, 0.26–0.75). Similarly, but not significantly, major bleeding and procedure-related complications tended to occur less often in patients treated with dabigatran (HR, 0.60; 95% CI, 0.35–1.01) or rivaroxaban (HR, 0.69; 95% CI, 0.40–1.15). Cardiovascular death occurred more often in patients who were administered NOACs than in those who underwent LAAO (HR, 2.28; 95% CI, 1.03–5.10 for dabigatran; HR, 2.41, 95% CI, 1.09–5.42 for rivaroxaban; HR, 2.40; 95% CI, 1.10–5.36 for apixaban). This finding was mainly due to the results of the PROTECT AF trial. The rate of all-cause death was similar between NOACs and LAAO (HR, 1.23; 95% CI, 0.72–2.07 for dabigatran; HR, 1.16; 95% CI, 0.67–1.99 for rivaroxaban; HR, 1.25; 95% CI, 0.74–2.09 for apixaban).

DISCUSSION

The present study is the first to conduct an indirect comparison between NOACs and LAAO. The major findings of the present study are as follows: (1) compared with LAAO, a nonsignificant numerical decrease in stroke and embolism was found in patients treated with NOACs; (2) LAAO was associated with reduced cardiovascular mortality; and (3) NOACs and LAAO were similar in terms of all-cause death.

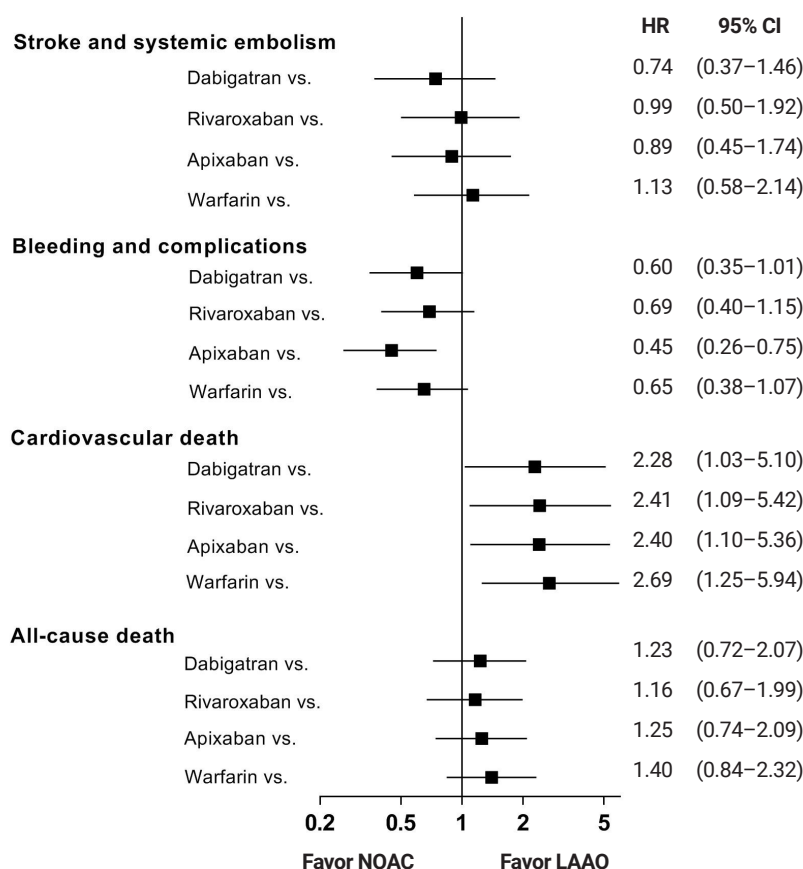


Fig. 2. New oral anticoagulants (NOACs) versus left atrial appendage occlusion (LAAO). The plot shows the hazard ratios (HRs) and 95% confidence intervals (CIs) for each outcome with NOACs versus LAAO estimated from the indirect comparisons.

Indirect comparison as an analytic method

Performing clinical trials for device evaluation is difficult due to the inherent risk of invasive procedures. Furthermore, greater complexity and cost limit the number and ability of patients to participate in trials. The application of indirect methods has increased in publications dealing with cardiovascular disease [18–22], and indirect methods are well-accepted despite the existence of many limitations, such as inter-trial population differences. The different trials examined in the present study were conducted in a similar population of patients with nonvalvular AF, which allowed for some degree of homogeneity. The efficacy and safety of NOACs and LAAO were evaluated in a systematic review and meta-analysis [23]; however, a comparative analysis was not performed. The present study conducted an indirect comparison of NOACs and LAAO due to the difficulty of direct comparison (Fig. 1).

Need for alternative treatments and their comparison

The risk of stroke and systemic embolism is fivefold higher in patients with nonvalvular AF than in those with sinus rhythm [24]. In addition, thromboembolism occurring with AF is associated with a greater risk of recurrent stroke, more severe disability, and mortality [25]. Even silent AF is associated with stroke [24]. Although anticoagulants have been found to be effective in reducing thromboembolism, they have significant limitations that require monitoring, such as unpredictable response, food and drug interactions, and an increased risk of bleeding. Many patients at risk of thromboembolic events still have inadequate or no anticoagulation. Therefore, new alternative treatments for stroke prevention are needed for patients with AF. Recently, two interesting methods have emerged, NOACs and LAAO, which have shown positive results regarding effectiveness and safety in comparison with warfarin [5–8]. Careful consideration

Table 4. Suggested strategies in clinical situations in patients with nonvalvular atrial fibrillation

Variable	NOAC favored	LAAO favored
Preventive treatment of thrombotic event	Recurrent thrombus despite warfarin therapy Non-feasibility for an invasive procedure	Contraindication of anticoagulation Poor drug compliance Concurrent risk of thrombus and bleeding

NOAC, new oral anticoagulant; LAAO, left atrial appendage occlusion.

is required to balance the benefits and risks of bleeding in each patient with AF. The two alternative treatments have different mechanisms of reducing thromboembolism; thus, a comparison of both modalities is necessary to determine which option is the most suitable for each patient. Regarding stroke prevention in patients with AF, many clinical situations requiring alternatives to warfarin can occur, such as bleeding in patients with a high CHA₂DS₂-VASC score, stroke, or embolism even after adequate warfarin therapy, poor compliance with oral anticoagulation, and labile warfarin effects. CHA₂DS₂-VASC stands for congestive heart failure (C), hypertension (H), age ≥ 75 years (2 points; A₂), diabetes mellitus (D), stroke (2 points; S₂), vascular disease, age 65 to 74 years, female sex (VASC).

Indirect comparison of efficacy

Despite the limitations of an indirect comparison, several differential effects between NOACs and LAAO were observed for stroke prevention and death. NOACs were associated with a numerical but nonsignificant decrease in stroke and systemic embolism, as well as bleeding and procedure-related complications. The following could be inferred from the results of each trial: all NOACs were broadly effective in preventing stroke and systemic embolism (HR, 0.66–0.79) (Table 3). However, LAAO increased thrombotic events, but this increase was statistically nonsignificant (HR, 1.51; 95% CI, 0.65–3.92). In the PROTECT AF trial, LAAO significantly reduced cardiovascular death, which led to a nonsignificant decrease in all-cause death. Conversely, NOACs showed neutral effects on mortality, with HRs ranging from 0.88 to 0.92 (Table 3). In the present analysis, LAAO showed efficacy regarding mortality compared with NOACs (Fig. 2).

Clinical implications and limitations

Stroke in AF patients cannot always be prevented by warfa-

rin. Although NOACs and LAAO have been introduced into clinical practice, data from a direct comparison between NOACs and LAAO, as well as guidelines to determine the best strategy in clinical practice, are lacking. Based on the results of the present study, several suggestions could be made regarding this question (Table 4). However, this study has several limitations. First, all indirect comparisons have inherent limitations and cannot be substituted for head-to-head RCTs. In the present analysis, the common comparator was warfarin, and the quality of anticoagulation control was different among the four trials, particularly in the ROCKET-AF trial (which had a 55% average time in the therapeutic range) while the other three trials showed better warfarin control (with an average time in therapeutic range of approximately 64% to 66%). Thus, whether the results from indirect comparisons can be directly applied or this type of comparison is only useful for hypothesis generation is unclear. In addition, whether indirect comparisons can be used as the basis for direct comparisons might be difficult because the strategies are different. Second, the number of patients who underwent LAAO was significantly smaller than the number of patients who were administered NOACs. Unfortunately, the PREVAIL trial, which is one of the two randomized LAAO trials, could not be included due to the lack of published data on bleeding and mortality. In conclusion, NOACs tended to reduce stroke and systemic embolism, as well as bleeding and complications, although the results did not reach statistical significance. LAAO significantly reduced cardiovascular death compared with NOACs. These findings could be helpful for clinical decision-making; however, they should be confirmed in head-to-head RCTs.

SUPPLEMENTARY MATERIAL

Table S1. The number of patients in each group. Supplementary data are available at <https://doi.org/10.36011/cpp.2022.4.e1>.

ARTICLE INFORMATION

Ethical statement

Not applicable.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Author contributions

Conceptualization: SHK, SSH; Data curation: SHK, SSH; Formal analysis: SHK, SSH; Funding acquisition: SHK, SSH; Investigation: SHK, SSH; Methodology: SHK, SSH; Project administration: SHK, SSH; Resources: SHK, SSH; Software: SHK, SSH; Supervision: SHK, SSH; Validation: SHK, SSH; Visualization: SHK, SSH; Writing – original draft: SHK, SYP, SSH; Writing – review & editing: SHK, SSH, SYP.

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