Meta-analysis of Stroke and Bleeding Risk in Patients with Various Atrial Fibrillation Patterns Receiving Oral Anticoagulants

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Oral anticoagulation therapy (OAT) is a mainstay for stroke prevention in atrial fibrillation (AF) patients. However, whether the risks of stroke/systemic embolic events (SEE) and bleeding events are affected by the type, duration, and frequency of AF in patients receiving OAT has been previously debated. We aimed to determine the risk of stroke/SEE and bleeding events associated with paroxysmal AF compared to persistent or permanent AF among patients who received OAT. Comprehensive literature searches of the Cochrane Library, PubMed/MEDLINE, and EMBASE databases were conducted from inception to July 2018. In total, 495 records were retrieved, of which 6 phase III randomized controlled trials (RCTs) focusing on the efficacy and safety of OAT in AF patients were ultimately evaluated and included. Among 70,447 AF patients, 15,028 (21.3%) patients had paroxysmal and 55,419 (78.7%) had persistent or permanent AF. Compared to persistent or permanent AF, the incidence of stroke/SEE was lower in paroxysmal AF patients (risk ratio [RR] 0.79, 95% confidence interval [CI] 0.71 to 0.88, P <0.00001, I^2 = 0%). Overall, all-cause mortality was also lower in paroxysmal AF than in persistent or permanent AF patients (RR 0.72, 95% CI 0.66 to 0.79, P <0.00001, I^2 =0%). Annualized major bleeding rates were similar across AF types (RR 1.06, 95% CI 0.96 to 1.17, P = 0.22, I^2= 35%). In conclusion, in patients with moderate-to-high risk of stroke receiving anticoagulation, those with paroxysmal AF have a lower risk of stroke, systemic embolism, and mortality but similar risk of major hemorrhage compared to persistent or permanent AF patients. **(Am J Cardiol 2019;123:922−928)**

Atrial fibrillation (AF) is associated with increased mortality and morbidity, mainly as a result of thromboembolic complications.[1] The risk of thromboembolism for individuals with AF is correlated with increases in the $CHADS_2$ and CHA_2DS_2-VASc scores.[2−5] The distinction between paroxysmal and persistent or permanent AF has not been used to guide the choice of stroke prophylaxis, as it remains unclear whether the pattern of AF affects the risk of thromboembolism. Several studies[6−8] have suggested a lower risk of stroke in patients with paroxysmal AF than in those with persistent or permanent AF. In contrast, other studies have reported a comparable stroke risk for paroxysmal and persistent or permanent AF.[9−13] Therefore, all AF patients who are at moderate-to-high risk of stroke, regardless of the AF type, are recommended to receive oral anticoagulation therapy (OAT), based on the clinical subtype of AF, according to the most recent guidelines.[14] Given that reports have rarely focused on whether patients with paroxysmal, persistent, or permanent AF will receive more benefit from OAT, the present study, which is based on pooled data from 6 phase III clinical trials, aims to determine the risk of stroke/systemic embolic events (SEE) and bleeding events associated with paroxysmal versus persistent or permanent AF in patients who received OAT.

Methods

Comprehensive literature searches of the Cochrane Library, PubMed/MEDLINE, and EMBASE databases were performed, from inception to July 2018, using the following search terms: “atrial fibrillation”, “paroxysmal”, “intermittent”, “sustained”, “persistent”, and “permanent”. The electronic search was specified for peer-reviewed journals, and additional data not identified in the electronic database were collected from other data resources, particularly original data that were absent in the published articles. We also performed an additional search of the references of studies that were retrieved. Specifically, we contacted the corresponding authors to obtain original data that were not reported in the published articles.

The following inclusion criteria were used for study selection: (1) Types of studies: RCTs focusing on the

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efficacy and safety of OAT in patients with various types of AF; (2) Types of participants: AF patients at moderate-high risk of stroke; (3) Types of interventions: OAT including warfarin or new oral anticoagulants (NOACs); (4) Types of outcome measures: efficacy endpoints of stroke/SEE or all-cause mortality. The safety endpoints were major bleeding, all bleeding, or both. The exclusion criteria were as follows: (1) Duplicated reports on the same cohort; (2) Certain publication types, such as conference abstracts, letters, comments, case reports, observational cohort studies, and editorials; (3) Studies not published in English; (4) Data presented for a treatment that was not an anticoagulant.

All studies retrieved by the search strategy were independently screened by 2 reviewers (W.Z. and Y.X.). The initial prescreening was performed by reading the titles and abstracts to select studies for further data extraction. Secondary selection was conducted by comprehensively reviewing the full text to determine whether the efficacy and safety outcomes of OAT and the patterns of AF were reported. Articles meeting the eligibility criteria were selected after review of the full text.

Data were extracted from each eligible study or calculated from the data presented, including the baseline characteristics of participants, interventions, comparisons, outcomes, and follow-up duration. The study endpoints included efficacy and safety outcomes. The primary efficacy endpoint for this analysis was stroke/SEE. The secondary efficacy endpoint was all-cause mortality. The safety endpoints for this analysis were major bleeding and all bleeding. If the event number was unavailable in the full text or by contacting the corresponding authors, it was calculated using the following formula: Event number = (Total patient number) × (Event rate [per 100 patient years]) × (Follow-up duration [years]). Discrepancies were resolved by consensus or, if necessary, through discussion or consultation with a third reviewer (L.Y.).

The methodological quality of the 6 included RCTs was evaluated using the Cochrane Collaboration Risk of Bias Tool,[15] with discrepancies resolved by consensus. Potential publication bias was evaluated by visually inspection of funnel plots[16] and by analytical appraisal based on the Begg adjusted-rank correlation test[17] and Egger's linear regression test.[18] According to the Begg or Egger methods for publication bias evaluation, a two-sided P value of 0.10 or less was regarded as indicating significance. Sensitivity analyses were performed by sequentially removing each study and reanalyzing the remaining dataset (producing a new analysis for each study removed) and by analyzing data from studies with moderate and low risk of bias. Both risk of bias and quality of included studies were independently evaluated by 2 reviewers (W.Z. and Y.X.).

Statistical analyses were performed using Review Manager Version 5.3, Stata and SPSS Statistics. The chi-square statistic and independent-samples t tests were used to assess the differences in the baseline characteristics of the 2 groups. The incidences of stroke/SEE, mortality, and major bleeding were measured as dichotomous outcome variables that were then compared between the different AF patterns. Subgroup analyses were conducted according to the type of OAT (NOACs and warfarin). The risk ratio (RR) was calculated and presented with the 95% confidence interval (CI) for summary estimates. Due to the heterogeneity among the included studies, appropriate statistical models were selected to ensure that the statistical data were estimated correctly. Cochran's chi-square test was performed, and the I^2 statistic was determined to evaluate the heterogeneity among included studies. Cochran's chi-square test was used to determine whether the observed difference may be due to chance alone. A low p value (cut-off of 0.10) indicated significant heterogeneity among different studies. The I^2 statistic describes the percentage of total variation across studies due to significant heterogeneity rather than random chance. An I^2 statistic greater than 75% suggests considerable heterogeneity among studies. Statistical significance was set at a P value <0.05.

Results

A total of 495 records were identified through the above-mentioned literature search strategy. After removing duplicates, we extracted 310 records for screening. Then, 275 were excluded by reviewing the title and abstract, and the full texts of the remaining 35 articles were retrieved for further review if they met the predetermined criteria. Finally, 6 eligible RCTs were identified and included in the present study.[7,8,19–23] With regard to the data of patients with different types of AF, subgroup analyses of 6 trials (ACTIVE W [Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events], SPORTIF [Stroke Prevention using an Oral Thrombin Inhibitor in atrial Fibrillation], RE-LY [Randomized Evaluation of Long-term Anticoagulation Therapy], ARISTOTLE [Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation], 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], ENGAGE-AF [Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombosis In Myocardial Infarction study 48]) were published in peer-reviewed journals[24–29] (Figure 1).

These studies were of high quality and are presented in Figure 2a. Visual inspection of the funnel plot (Figure 2b) showed a symmetrical shape, and quantitative evaluation

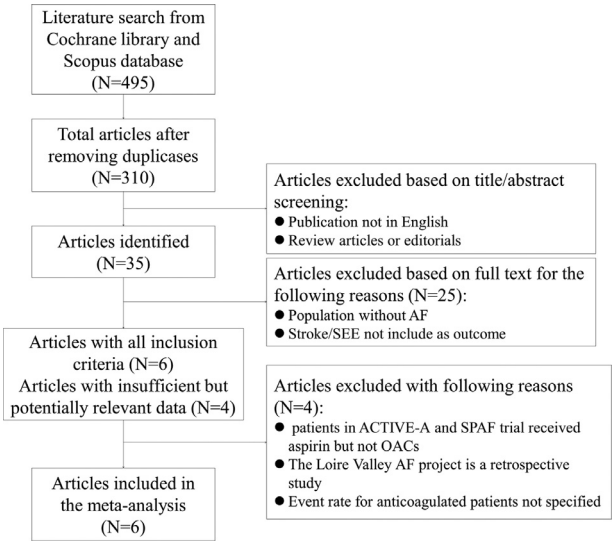

Figure 1. Study search diagram.

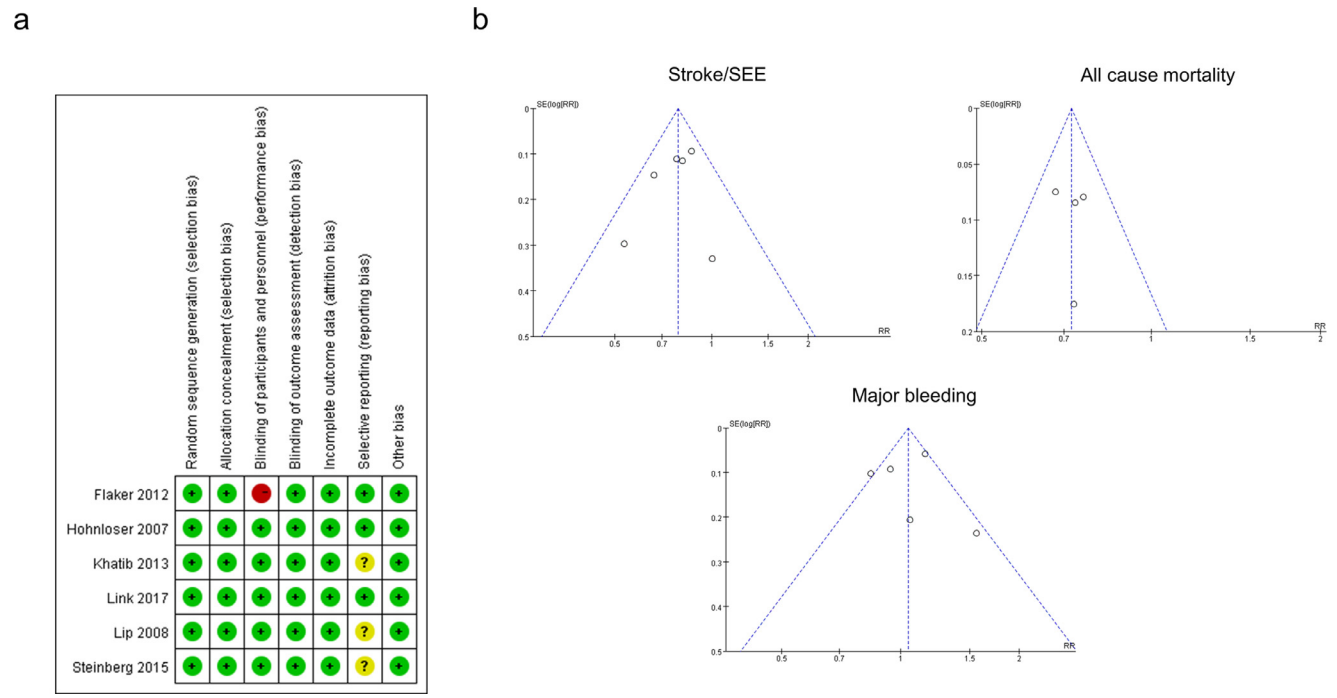

Figure 2. Methodological quality summary. (a) Risk of bias summary: review of author's judgments about each risk of bias item for each included study. + indicates low risk; − indicates high risk; ? indicates unclear risk. (b) Funnel plots show all studies included in the bias analysis.

suggested no significant publication bias (Egger's test [P = 0.433] or Begg's test [P = 0.452]).

The characteristics of the included studies are summarized in Table 1. Based on the data of 6 eligible trials, a total of 70,447 AF patients were enrolled, among which 15,028 (21.3%) patients had paroxysmal AF and 55,419 (78.7%) patients had persistent or permanent AF. Compared to patients with persistent or permanent AF, patients with paroxysmal AF were younger, more likely female and had a similar $CHADS_2$ score (Table 2).

The incidence rates of stroke/SEE, mortality and major bleeding in patients with paroxysmal or persistent/permanent AF treated with oral anticoagulants are shown in Table 3. Compared to patients with persistent or permanent AF, patients with paroxysmal AF were associated with a significant reduction in stroke/SEE incidence (2.75% vs 3.39%, RR = 0.79, 95% CI = 0.71 to 0.88, P <0.00001, I^2 = 0%) (Figure 3a) and all-cause mortality (6.48% vs 8.35%, RR 0.72, 95% CI 0.66 to 0.79, P <0.00001, I^2 = 0%) (Figure 3b) after receiving OAT. No significant heterogeneity was detected in the analysis of the efficacy outcomes.

In all 6 trials, major bleeding was mainly defined according to the criteria of the International Society on Thrombosis and Hemostasis. Annualized major bleeding rates were similar across AF types (RR 1.05, 95% CI 0.97 to 1.15, P = 0.67, I^2= 56%) (Figure 4). Due to the high heterogeneity among trials, subgroup analyses were conducted according to OAT (NOACs and warfarin). Similarly, no significant difference in major bleeding was observed between the paroxysmal and persistent or permanent AF

Table 1
Patient characteristics in the included studies

Study ID	Data source	Patients	N	Anticoagulation strategy	Comparison	Outcomes of interest	Median duration of follow-up
Hohnloser 2007	ACTIVE W	AF	3367	warfarin or combined antiplatelet therapy	paroxysmal vs sustained	stroke/SEE; bleeding	1.3 Y
Lip 2008	SPORTIF III and V	NVAF	7329	warfarin or ximelagatran	paroxysmal vs persistent	stroke; mortality; bleeding	≥18.6 M*
Flaker 2012	RE-LY	NVAF	18,107	Dabigatran, etexilate or warfarin	paroxysmal vs persistent and permanent	stroke/SEE; bleeding	2 Y
Khatib 2013	ARISTOTLE	NVAF	18,198	apixaban or warfarin	paroxysmal vs persistent and permanent	stroke/SEE; mortality; bleeding	1.8 Y
Steinberg 2015	ROCKET-AF	NVAF	14,062	rivaroxaban or warfarin	paroxysmal vs persistent	stroke/SEE; mortality; bleeding	1.9 Y
Link 2017	ENGAGE AF-TIMI 48	NVAF	9384	edoxaban or warfarin	paroxysmal vs persistent and permanent	stroke/SEE; mortality; bleeding	2.8 Y

N, Number of patients NA, not available Y, years M, months

* For SPORTIF III, the median follow-up was 17.9 months per patients (range 0−26 months); for SPORTIF V, the median follow-up was 20.1 months (range 0−31 months); and for the pooled analysis, the median follow-up was 18.6 months per patient (range 0−31 months).

Table 2
Baseline characteristics according to the types of atrial fibrillation (AF)

Variables	Paroxysmal AF (n = 6730)	Persistent/permanent AF (n = 36226)	*P* value
Age	70.10 ± 10	71.14 ± 9.5	0.000
Women	3030 (41.29%)	13,496 (34.65%)	0.000
CHADS2 score	2.52 ± 1.26	2.54 ± 1.23	0.203

groups (RR 1.06, 95% CI 0.96 to 1.17, $P = 0.22$, $I^2 = 35\%$), regardless of treatment with NOACs (RR 1.08, 95% CI 0.95 to 1.22, $P = 0.23$, $I^2 = 24\%$) or warfarin (RR 1.05, 95% CI 0.90 to 1.23, $P = 0.54$, $I^2 = 51\%$).

The significantly lower stroke/SEE (RR 0.79, 95% CI 0.71 to 0.88, $P < 0.0001$, $I^2 = 0\%$) and all-cause mortality (RR 0.72, 95% CI 0.66 to 0.79, $P < 0.00001$, $I^2 = 0\%$) rates in patients with paroxysmal AF than in those with persistent or permanent AF were confirmed by fitting with a random effect model. The sensitivity analysis performed by sequentially removing each study individually and reanalyzing the remaining dataset is shown in Table 4. The results were not affected by removal of any single study.

Discussion

The present study is the first to use a pooled analysis to determine whether paroxysmal AF exhibits a similar or lower stroke risk than persistent or permanent AF in patients receiving OAT. The most important finding of the present meta-analysis is that paroxysmal AF patients show significantly improved efficacy and a similar safety profile compared to persistent or permanent AF patients. Regarding efficacy outcomes, patients with paroxysmal AF were less likely to experience stroke or systemic embolic outcomes than persistent or permanent AF patients. In addition, the all-cause mortality of paroxysmal AF patients was lower. Regarding safety outcomes, major bleeding did not differ by AF pattern.

Table 3
Incidence of the stroke/SEE, mortality, and bleeding in patients with paroxysmal or persistent/permanent atrial fibrillation (AF) treated with oral anticoagulants

		Event rates (per patient year)					
		Hohnloser 2007 (ACTIVE W)	Lip 2008 (SPORTIF)	Flaker 2012 (RE-LY)	Khatib 2013 (ARISTOTLE)	Steinberg 2015 (ROCKET-AF)	Link 2017 (ENGAGE AF-TIMI 48)
Stroke/SEE	paroxysmal AF;	1.5%	0.93%	1.32%	0.98%	1.73%	1.49%
	persistent/permanent AF	1.5%	1.73%	1.55%/1.49%	1.52%	2.18%	1.83%/1.95%
All-cause mortality	paroxysmal AF;	NA	2.62%	NA	2.81%	3.52%	3%
	persistent/permanent AF	NA	3.6%	NA	3.9%	4.78%	4.4%/4.4%
Major bleeding	paroxysmal AF;	3.2%	2.33%	3.57%	2.22%	3.31%	2.86%
	persistent/permanent AF	2%	2.16%	3.29%/2.29%	2.68%	3.55%	2.65%/2.73%

SEE, systemic embolic events; NA, not available

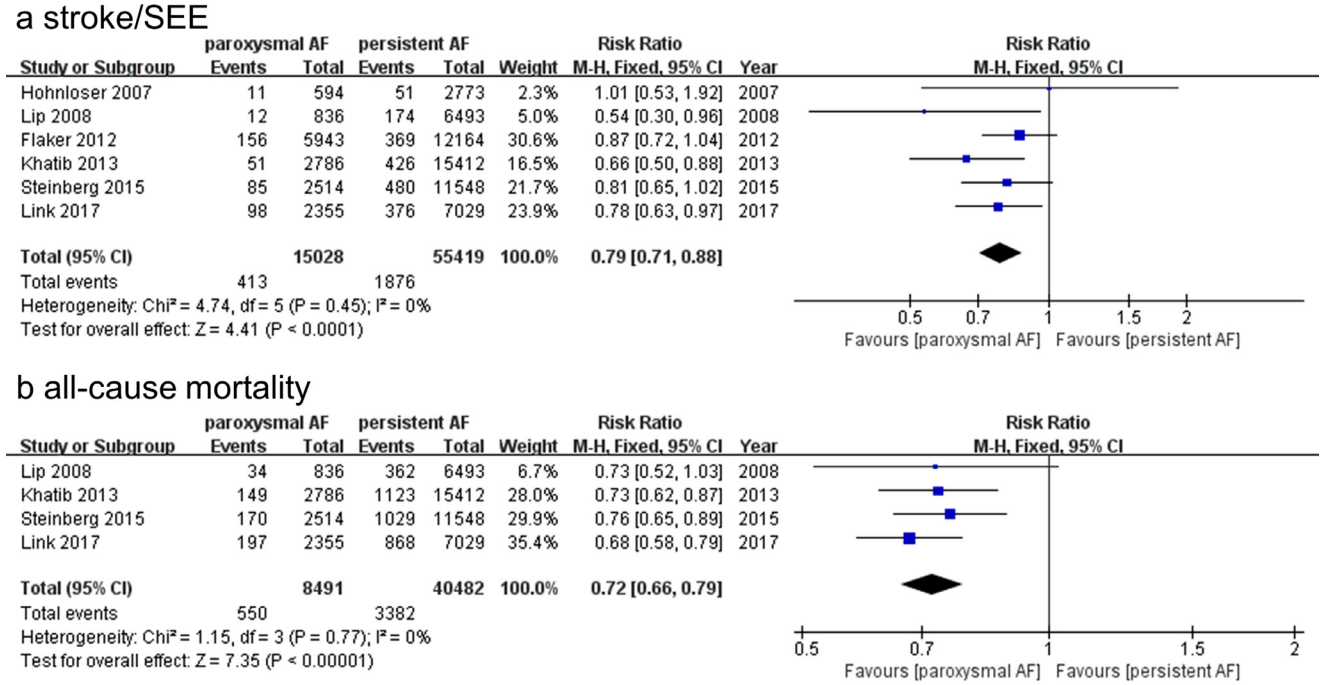

Figure 3. Forest plot of the comparative analysis of the incidence of efficacy outcomes for different types of atrial fibrillation (AF) patients. (a) Stroke/systemic embolism events (SEE), (b) all-cause mortality. $P < 0.05$ was considered statistically significant.

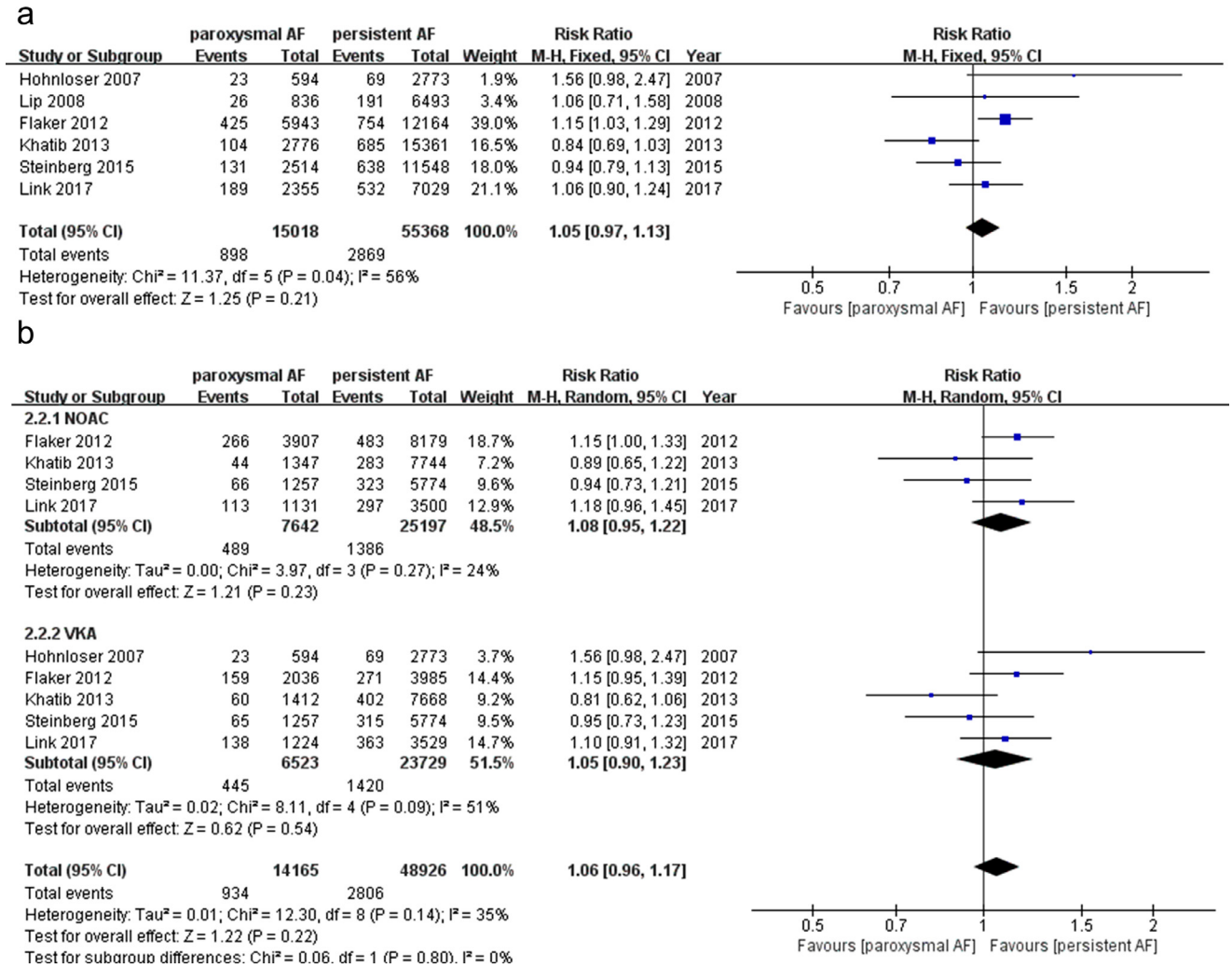

Figure 4. Forest plot of the comparative analysis of the incidence of safety outcomes in different types of AF patients. (a) Major bleeding events in different types of AF patients, (b) subgroup analyses for major bleeding events by type of AF patient, taking new oral anticoagulants (NOACs) or warfarin. P <0.05 was considered statistically significant.

Table 4
Sensitivity analysis

Excluded trial	Stroke/SEE		All-cause mortality		Major bleeding	
	RR (95% CI)	*P* value	RR (95% CI)	*p* value	RR (95% CI)	*P* value
Hohnloser 2007	0.78 (0.7−0.87)	<0.00001	NA	NA	1.01 (0.90, 1.15)	0.81
Lip 2008	0.80 (0.72−0.89)	<0.0001	0.72 (0.66,0.79)	<0.00001	1.04 (0.90, 1.20)	0.6
Flaker 2012	0.75 (0.66−0.86)	<0.0001	NA	NA	1.00 (0.87, 1.16)	1
Khatib 2013	0.81 (0.72−0.91)	0.0004	0.72 (0.65,0.79)	<0.00001	1.09 (0.98, 1.21)	0.13
Steinberg 2015	0.78 (0.69−0.88)	<0.0001	0.70 (0.63,0.78)	<0.00001	1.07 (0.92, 1.24)	0.41
Link 2017	0.79 (0.7−0.89)	0.0002	0.75 (0.67,0.83)	<0.00001	1.04 (0.88, 1.23)	0.67

RR, Risk ratio; 95% CI, 95% confidence interval; NA, not available.

Both CHA_2DS_2 and CHA_2DS_2-VASc score, which are used to estimate the risk of stroke, do not consider the type of AF. If the risk of thromboembolism is substantially lower in paroxysmal AF patients, then the AF pattern may be important when determining a risk score to guide therapeutic decisions. Prior studies have shown conflicting results regarding whether paroxysmal AF patients have a lower risk of thromboembolism than those with persistent or permanent AF. Among patients treated with OAT in the SPORTIF, ARISTOTLE, ROCKET-AF, and ENGAGE AF-TIMI 48 trials, those with paroxysmal AF had a lower risk of stroke/SEE than persistent or permanent AF patients. In the ACTIVE W and RE-LY trials, however, the overall risk of stroke/SEE was similar in paroxysmal, persistent, and permanent AF patients. Our meta-analysis demonstrated that paroxysmal AF patients were less likely to

experience stroke or systemic embolic outcomes than persistent or permanent AF patients regardless of whether they have similar CHADS2 scores based on pooled data from the above RCTs. Given these results, it will be necessary to include AF pattern in the current risk scoring systems.

The present study implied that paroxysmal AF patients are more likely to benefit from OAT than those with persistent or permanent AF. This finding may be explained as follows: (1) The efficacy of OAT was significant in women. Compared to patients with persistent or permanent AF, paroxysmal AF patients were more likely to be female in the included studies. A prior meta-analysis assessed the efficacy of antithrombotic therapy in women and found that warfarin decreased the risk of stroke by 84% in women compared to 60% in men.[2] (2) Platelet activation, a key factor of thrombogenesis, was greater in permanent AF patients receiving therapeutic anticoagulation than in those with paroxysmal AF.[30] (3) AF burden, which is positively correlated with the risk of ischemic stroke in adults not taking OAT, was smaller in paroxysmal AF than in persistent or permanent AF.[31] It remains unknown whether paroxysmal AF is associated with a lower risk of thromboembolism due to sharing of underlying mechanisms, such as fibrosis and atrial dilatation, or whether the shorter time in AF is directly responsible.

Our study has some limitations. The baseline characteristics of different AF types were only based on 4 RCTs. However, the characteristics of patients in the 2 studies not included were consistent with the pooled patient characteristics in our meta-analysis. Patients with paroxysmal AF were younger, and more females were included in the RELY and ENGAGE AF-TIMI 48 trials. Moreover, some heterogeneity was observed for the major bleeding rates among trials. We performed subgroup analyses according to different types of OAT to reduce the heterogeneity, which was reflected by a decrease in I^2 from 56% to 35%. We also found that the slight difference in the definition of major bleeding among the 6 trials also contributed to the heterogeneity.

In conclusion, the present study shows that paroxysmal AF patients exhibited a similar safety and favorable efficacy profile compared to those with persistent or permanent AF.

Disclosures

The authors have no conflicts of interest to disclose.

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983–988.
2. Investigators TAF. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;154:1449–1457.
3. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864–2870.
4. Lip GY, Tse HF, Lane DA. Atrial fibrillation. *Lancet* 2012;379:648–661.
5. Lane DA, Lip GY. Use of the CHA(2)DS(2)-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. *Circulation* 2012;126:860–865.
6. Ganesan AN, Chew DP, Hartshorne T, Selvanayagam JB, Aylward PE, Sanders P, McGavigan AD. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur Heart J* 2016;37:1591–1602.
7. Bansilal S, Bloomgarden Z, Halperin JL, Hellkamp AS, Lokhnygina Y, Patel MR, Becker RC, Breithardt G, Hacke W, Hankey GJ, Nessel CC, Singer DE, Berkowitz SD, Piccini JP, Mahaffey KW, Fox KA. Efficacy and safety of rivaroxaban in patients with diabetes and nonvalvular atrial fibrillation: 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 Trial). *Am Heart J* 2015;170:675–682. e678.
8. Eisen A, Giugliano RP, Ruff CT, Nordio F, Gogia HS, Awasty VR, Henderson DA, Mercuri MF, Rutman H, Antman EM, Braunwald E. Edoxaban vs warfarin in patients with nonvalvular atrial fibrillation in the US Food and Drug Administration approval population: an analysis from the effective anticoagulation with Factor Xa next generation in atrial fibrillation-thrombolysis in myocardial infarction 48 (ENGAGE AF-TIMI 48) trial. *Am Heart J* 2016;172:144–151.
9. Aboaf AP, Wolf PS. Paroxysmal atrial fibrillation. A common but neglected entity. *Arch Intern Med* 1996;156:362–367.
10. Petersen P, Godtfredsen J. Embolic complications in paroxysmal atrial fibrillation. *Stroke* 1986;17:622–626.
11. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke prevention in atrial fibrillation investigators. *J Am Coll Cardiol* 2000;35:183–187.
12. Nieuwlaat R, Dinh T, Olsson SB, Camm AJ, Capucci A, Tieleman RG, Lip GY, Crijns HJ. Should we abandon the common practice of withholding oral anticoagulation in paroxysmal atrial fibrillation? *Eur Heart J* 2008;29:915–922.
13. Banerjee A, Taillandier S, Olesen JB, Lane DA, Lallemand B, Lip GY, Fauchier L. Pattern of atrial fibrillation and risk of outcomes: the Loire Valley Atrial Fibrillation Project. *Int J Cardiol* 2013;167:2682–2687.
14. European Heart Rhythm A, Heart Rhythm S, Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr., Jacobs AK, Adams CD, Anderson JL, Antman EM, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Zamorano JL. 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 the European Society of Cardiology Committee for practice guidelines (Writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation). *J Am Coll Cardiol* 2006;48:854–906.
15. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–560.
16. Wei A, Gu Z, Li J, Liu X, Wu X, Han Y, Pu J. Clinical Adverse effects of endothelin receptor antagonists: insights from the meta-analysis of 4894 patients from 24 randomized double-blind placebo-controlled clinical trials. *J Am Heart Assoc* 2016;5:1–16.
17. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–1101.
18. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–634.
19. Investigators AWGotAConnolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Pfeffer M, Hohnloser S, Yusuf S. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;367:1903–1912.
20. Albers GW, Diener HC, Frison L, Grind M, Nevinson M, Partridge S, Halperin JL, Horrow J, Olsson SB, Petersen P, Vahanian A. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA* 2005;293:690–698.
21. Olsson SB. Executive Steering Committee of the SIIII. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with nonvalvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet* 2003;362:1691–1698.
22. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Committee R-LS, Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–1151.

23. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L. Committees A, Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–992.
24. Hohnloser SH, Pajitnev D, Pogue J, Healey JS, Pfeffer MA, Yusuf S, Connolly SJ. Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W Substudy. *J Am Coll Cardiol* 2007;50:2156–2161.
25. Lip GY, Frison L, Grind M. Stroke event rates in anticoagulated patients with paroxysmal atrial fibrillation. *J Intern Med* 2008;264:50–61.
26. Flaker G, Ezekowitz M, Yusuf S, Wallentin L, Noack H, Brueckmann M, Reilly P, Hohnloser SH, Connolly S. Efficacy and safety of dabigatran compared to warfarin in patients with paroxysmal, persistent, and permanent atrial fibrillation: results from the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study. *J Am Coll Cardiol* 2012;59:854–855.
27. Al-Khatib SM, Thomas L, Wallentin L, Lopes RD, Gersh B, Garcia D, Ezekowitz J, Alings M, Yang H, Alexander JH, Flaker G, Hanna M, Granger CB. Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial. *Eur Heart J* 2013;34:2464–2471.
28. Steinberg BA, Hellkamp AS, Lokhnygina Y, Patel MR, Breithardt G, Hankey GJ, Becker RC, Singer DE, Halperin JL, Hacke W, Nessel CC, Berkowitz SD, Mahaffey KW, Fox KA, Califf RM, Piccini JP. Higher risk of death and stroke in patients with persistent vs paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. *Eur Heart J* 2015;36:288–296.
29. Link MS, Giugliano RP, Ruff CT, Scirica BM, Huikuri H, Oto A, Crompton AE, Murphy SA, Lanz H, Mercuri MF, Antman EM, Braunwald E. Stroke and mortality risk in patients with various patterns of atrial fibrillation: results from the ENGAGE AF-TIMI 48 Trial (effective anticoagulation with Factor Xa next generation in atrial fibrillation-thrombolysis in myocardial infarction 48). *Circ Arrhythm Electrophysiol* 2017;10:1–7.
30. Kamath S, Chin BS, Blann AD, Lip GY. A study of platelet activation in paroxysmal, persistent and permanent atrial fibrillation. *Blood Coagul Fibrinolysis* 2002;13:627–636.
31. Go AS, Reynolds K, Yang J, Gupta N, Lenane J, Sung SH, Harrison TN, Liu TI, Solomon MD. Association of burden of atrial fibrillation with risk of ischemic stroke in adults with paroxysmal atrial fibrillation: The KP-RHYTHM Study. *JAMA Cardiol* 2018;3:601–608.