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Low-Dose NOACs Versus Standard-Dose NOACs or Warfarin on Efficacy and Safety in Asian Patients with NVAF: A Meta-Analysis

META-ANALYSIS

ABSTRACT

Background: The meta-analysis of randomized controlled trials has illustrated that the efficacy of low-dose non-vitamin K antagonist oral anticoagulants is inferior compared with standard-dose non-vitamin K antagonist oral anticoagulants, though they are still frequently prescribed for Asian patients with non-valvular atrial fibrillation. We aimed to further investigate the efficacy and safety of low-dose non-vitamin K antagonist oral anticoagulants by carrying out a meta-analysis of all relevant randomized controlled trials and cohort studies.

Methods: Cochrane Central Register of Controlled Trials, Embase, and MEDLINE were systematically searched from the inception to September 9, 2021, for randomized controlled trials or cohorts that compared the efficacy and/or safety of low-dose non-vitamin K antagonist oral anticoagulants in Asian patients with non-valvular atrial fibrillation. The primary outcomes were stroke and major bleeding, and the secondary outcomes were mortality, intracranial hemorrhage, and gastrointestinal hemorrhage. Hazard ratios and 95% CIs were estimated using the random-effect model.

Results: Nineteen publications involving 371 574 Asian patients with non-valvular atrial fibrillation were included. Compared with standard-dose non-vitamin K antagonist oral anticoagulants, low-dose non-vitamin K antagonist oral anticoagulants showed comparable risks of stroke (hazard ratio, 1.18; 95% CI 0.98 to 1.42), major bleeding (hazard ratio, 1.00; 95% CI 0.83 to 1.21), intracranial hemorrhage (hazard ratio, 1.13; 95% CI 0.92 to 1.38), and gastrointestinal hemorrhage (hazard ratio, 1.07; 95% CI 0.87 to 1.31), though had a higher risk of mortality (hazard ratio, 1.34; 95% CI 1.05 to 1.71). Compared with warfarin, low-dose non-vitamin K antagonist oral anticoagulants were associated with lower risks of stroke (hazard ratio, 0.73; 95% CI 0.67 to 0.79), mortality (hazard ratio, 0.69; 95% CI 0.60 to 0.81), major bleeding (hazard ratio, 0.62; 95% CI 0.51 to 0.75), intracranial hemorrhage (hazard ratio, 0.48; 95% CI 0.33 to 0.69), and gastrointestinal hemorrhage (hazard ratio, 0.78; 95% CI 0.65 to 0.93).

Conclusion: Low-dose non-vitamin K antagonist oral anticoagulants were superior to warfarin, and comparable to standard-dose non-vitamin K antagonist oral anticoagulants considering risks of stroke, major bleeding, intracranial hemorrhage, and gastrointestinal hemorrhage. Further, high qualified studies are warranted.

Keywords: Atrial fibrillation, NOACs, warfarin, meta-analysis

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INTRODUCTION

Non-valvular atrial fibrillation (NVAF) is a common cardiac arrhythmia worldwide, which can cause ischemic stroke and systemic embolism, seriously endangers the health of global elder patients.[1] For few decades, warfarin was prescribed to prevent ischemic stroke from atrial fibrillation (AF) by decreasing the production of several clotting proteins that rely on vitamin K.[2] However, the adherence to warfarin is severely affected by the frequent international normalized ratio (INR) monitoring, drug-drug interactions, and drug-food interactions.[3] In recent years, the approval of non-vitamin K antagonist oral anticoagulants (NOACs), which directly inhibit the critical factors of the coagulation cascade, provided new anticoagulant strategies for the patients with NVAF.

A meta-analysis including five randomized controlled trials (RCTs) and 6177 patients assessed the efficacy and safety of standard-dose NOACs, low-dose NOACs, and warfarin in Asian patients with NVAF.[4] It revealed that low-dose NOACs were inferior to standard-dose NOACs in the efficacy with a higher risk of stroke, and had no superior efficacy than warfarin; standard-dose NOACs were superior to warfarin in the efficacy and safety with less stroke, mortality, intracranial hemorrhage (ICH), and major bleeding.[4] However, low-dose NOACs are still frequently prescribed for Asian patients with NVAF. Low-dose NOACs were prescribed for 22%, 26%, and 31% of patients in Japan,[5] Taiwan,[6] and Korea,[7] respectively. RCTs were performed under optimized conditions, strict inclusion and exclusion criteria, which might not fully reflect real-world conditions. Moreover, RCTs enroll a small, non-representative subset of patients and overlook the important interactions between the patients and the real world, which may affect the outcomes.[8] Real-world cohort studies, which enroll patients with broad-spectrum baseline characteristics, may provide a more comprehensive picture of the clinical practice.[8] Therefore, we aimed to further investigate the efficacy and safety of low-dose NOACs in Asian patients with NVAF by carrying out a meta-analysis of all relevant RCTs and cohort studies.

METHODS

This meta-analysis was prepared according to the PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-analysis) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines.[9,10]

Search Strategy and Study Selection

Cochrane Central Register of Controlled Trials (from inception to September 9, 2021), MEDLINE (from inception to September 9, 2021), and Embase (from inception to September 9, 2021) were systematically searched. Details of the search strategy are illustrated in Supplementary Table S1.

The inclusion criteria were as follows: (1) studies involved lose-dose NOACs and standard-dose NOACs or warfarin; (2) the target population was Asian patients with NVAF; (3) studies included efficacy (stroke and mortality) or safety outcomes (major bleeding, ICH, and gastrointestinal hemorrhage [GH]); (4) the study type was the cohort or RCT. And the exclusion criteria were as follows: (1) patients with valvular AF or receiving NOACs after catheter ablation; (2) studies published in the forms of conference abstracts, letters, or protocols; (3) for the same data source or overlapping data reported in more than one study, the other studies were excluded apart from the most comprehensive data with the longest follow-up period. References of included studies and relevant meta-analyses were screened for additional eligible studies as well.

Definitions of Low-Dose NOACs, Standard-Dose NOACs, and Warfarin

Definitions were in accordance with the included studies. Standard-dose NOACs and warfarin were defined as dabigatran 150 mg b.i.d., rivaroxaban 20 mg q.d., apixaban 5 mg b.i.d., edoxaban 60 mg q.d., and INR of 2.0-3.0.[11] Low-dose NOACs were defined as dabigatran 110 mg b.i.d., rivaroxaban 15/10 mg q.d., apixaban 2.5 mg b.i.d., and edoxaban 30 mg q.d.[7] And for patients with creatinine clearance rate (CrCl) of 30-50 mL/min, age ≥ 70 years old, and a prior history of bleeding, standard-dose dabigatran was defined as 110 mg b.i.d.;[12,13] for patients with CrCl of 15-50 mL/min, standard-dose rivaroxaban was defined as 10 mg q.d.;[14,15] for patients with any 2 of the following characteristics: ≥80 years old, body weight <60 kg, and serum creatinine level (Cr) ≥ 1.5 mg/dL, standard-dose apixaban was defined as 2.5 mg b.i.d.;[16,17] for patients with CrCl of 15-50 mL/min or body weight <60 kg, standard-dose edoxaban was defined as 30 mg q.d.[18]

Data Extraction and Quality Assessment

The primary efficacy outcome was stroke, and the secondary efficacy outcome was mortality (all-cause mortality). The primary safety outcome was major bleeding, defined as fatal bleeding or bleeding in a critical site, and the secondary safety outcomes were ICH and GH.

Two reviewers independently screened titles and abstracts of the retrieved studies to exclude those which did not explore questions of interest, and then independently screened full texts of the remaining studies to identify those which met all the inclusion criteria. We manually checked the reference list of each acquired article for relevant studies. For each included study, two reviewers independently extracted the characteristics of the included studies and patients, as well as outcome measures as predefined. Discrepancies were resolved by discussing with the third reviewer.

Bias risks of RCTs were assessed with the Cochrane Collaboration's tool[19] and cohort studies with the Newcastle-Ottawa quality assessment scale.[20] The publication bias was quantitatively assessed by the Begg's[21] and Egger's tests,[22] $P < .05$ was taken as statistically significant. Two reviewers assessed the risks of bias independently and in duplicate. Any disagreements were resolved in consultation with the supervisor.

Data Synthesis and Statistical Analysis

Intention-to-treat analysis (ITT) results were used wherever possible. If ITT results were not available, we used the data that the author reported. All analyses were performed by Stata 16.0 (StataCorp, College Station, TX, 77845, USA). Hazard ratios (HRs) and corresponding 95% CIs were

HIGHLIGHTS

- The first meta-analysis of low-dose non-vitamin K antagonist oral anticoagulants (NOACs) including both randomized controlled trials and cohort studies.
- Low-dose NOACs were comparable to standard-dose NOACs and superior to warfarin.
- Low-dose NOACs might be prescribed effectively and safely for Asian patients with non-valvular atrial fibrillation.

estimated using the random-effect model. The heterogeneity among studies was assessed by I^2 with <25%, 25-50%, and >50% indicating low, moderate, and a high degree of heterogeneity, respectively. Meta-regression analyses were performed to examine possible sources of the heterogeneity in the data.

Subgroup meta-analyses were performed by stratifying the study type into RCTs and cohort studies to explore different effects of experiment types. Most cohort studies used the propensity score matching (PSM) method to balance the confounding factors between groups, so we enrolled the adjusted cohort studies and RCTs to perform subgroup meta-analyses and minimize the heterogeneity. For all comparisons in this meta-analysis, $P < .05$ was taken as statistically significant.

RESULTS

Studies Identification and Characteristics

A total of 2846 publications were identified through the database search. After the study screening process, 19 studies consisting of 16 cohort studies and 3 RCTs were included (Figure 1).

In general, there were 371 574 patients in all included studies. Of which, 152 893 patients were involved in the standard-dose group, including 48 118 patients receiving NOACs and 104 775 patients receiving warfarin, and 218 681 patients were included in the low-dose NOACs group. The baseline characteristics of included studies are shown in Table 1. The detailed previous medical history and group contents of included studies are illustrated in Supplementary Tables S2 and S3.

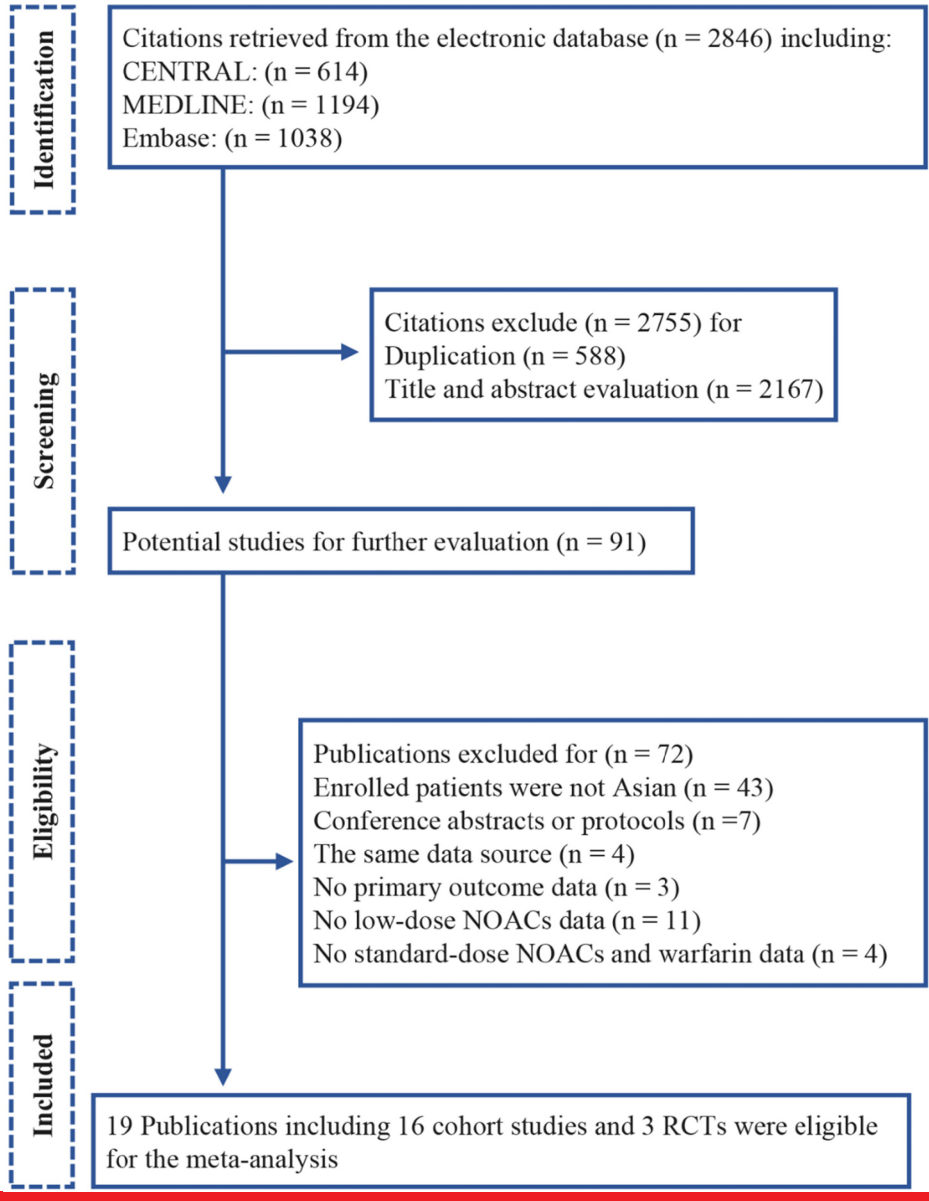

Figure 1. Flow chart for the selection of included studies.

Table 1. Patient Baseline Characteristics of Included Studies

Author (Study), Year	Region	Study Type	Adjusted Method	Group	Sample Size	Age (Years)	Female (%)	Follow-Up (Months)	BMI (kg/m^2)	CHA_2DS_2-VASc	HAS-BLED	CrCl (mL/min)
Murata N, 2019[5]	Japan	Cohort	PSM	Standard dose	746	66.9 ± 9.0	21.6	43.6	25.0 ± 4.0	2.42 ± 1.39	1.16 ± 0.85	84.1 ± 27.5
				Low dose	369	71.2 ± 8.2	29.0		24.5 ± 3.8	2.88 ± 1.39	1.25 ± 0.78	70.1 ± 21.2
Wakamatsu Y, 2020[23]	Japan	Cohort	NR	Standard dose	749	63.3 ± 9.4	23.0	25.7	24.7 ± 3.7	2.10 ± 1.50	0.80 ± 0.80	76.7 ± 23.8
				Low dose	216	64.8 ± 9.5	34.3		24.2 ± 3.4	2.40 ± 1.60	0.90 ± 0.80	73.3 ± 22.3
Ohno J, 2021[24]	Japan	Cohort	PSM	Standard dose	907	66.0 ± 10.0	23.3	26.5	25.0 ± 4.0	2.74	2.27	82.8
				Low dose	338	70.0 ± 10.0	34.9		24.0 ± 4.0	3.23	2.54	73.5
Lee HF, 2018[25]	Taiwan	Cohort	PSM	Low dose	26 000	78.0 ± 10.0	48.0	NR	NR	4.02 ± 1.29	2.98 ± 0.92	NR
				Warfarin	16 000	78.0 ± 10.0	48.0			4.01 ± 1.28	2.99 ± 0.90	
Yu HT, 2018[26]	Korea	Cohort	PSM	Low dose	3016	72.8 ± 9.1	48.0	5.0[c]	NR	4.90 ± 1.80	NR	NR
				Warfarin	3016	72.6 ± 9.9	46.7			4.80 ± 2.00		
Chan YH, 2018[27]	Taiwan	Cohort	PSM	Standard dose[a]	6307	76.0 ± 10.0	45.0	35.2	NR	3.89 ± 0.84	2.96 ± 0.61	NR
				Low dose[a]	47 392							
				Warfarin	19 375	76.0 ± 10.0	46.0			3.89 ± 0.88	2.97 ± 0.61	
Kwon CH, 2016[28]	Korea	Cohort	NR	Standard dose[a]	51	84.2 ± 3.5	60.1	24.9	24.4 ± 3.6	4.70 ± 1.40	2.60 ± 1.00	51.0 ± 13.9
				Low dose[a]	97							
				Warfarin	145	83.2 ± 3.1	59.3		23.7 ± 3.6	4.70 ± 1.40	2.40 ± 0.90	53.1 ± 17.4
Akagi Y, 2019[29]	Japan	Cohort	NR	Standard dose[a]	187	70.8 ± 10.8	34.2	NR	NR	1.92 ± 1.33[b]	NR	69.4 ± 25.3
				Low dose[a]	488							
Yu HT, 2020[7]	Korea	Cohort	PSM	Standard dose	32 400	69.8 ± 9.5	38.2	36.0	NR	4.60 ± 1.70	NR	NR
				Low dose	16 757	70.7 ± 7.9	39.0			4.50 ± 1.80		
Cho MS, 2019[30]	Korea	Cohort	PSM	Low dose	29 695	73.8 ± 8.8	49.1	15.0	24.6 ± 2.9	3.60 ± 1.20	2.50 ± 0.90	NR
				Warfarin	10 409	70.8 ± 11.0	46.0		24.4 ± 2.8	3.50 ± 1.20	2.60 ± 1.00	
Jeong HK, 2019[31]	Korea	Cohort	PSM	Low dose	414	71.4 ± 10.5	36.7	12.0	NR	3.30 ± 1.80	NR	85.4
				Warfarin	804	70.4 ± 10.2	39.6			3.40 ± 1.80		87.0
Kohsaka S, 2020[32]	Japan	Cohort	PSM	Low dose	17 481	76.2 ± 10.6	38.9	28.9	NR[d]	3.80 ± 1.90	NR	NR
				Warfarin	19 059	76.1 ± 11.9	38.8			3.80 ± 2.10		

(*Continued*)

Table 1. Patient Baseline Characteristics of Included Studies (*Continued*)

Author (Study), Year	Region	Study Type	Adjusted Method	Group	Sample Size	Age (Years)	Female (%)	Follow-Up (Months)	BMI (kg/m^2)	CHA_2DS_2-VASc	HAS-BLED	CrCl (mL/min)
Kohsaka S, 2017[33]	Japan	Cohort	PSM	Low dose	6726	75.8 ± 10.0	38.9	NR	23.3 ± 4.5	3.30 ± 1.60	NR	NR
				warfarin	6726	76.2 ± 10.5	38.0		23.1 ± 4.2	3.40 ± 1.60		
Lai CL, 2018[34]	Taiwan	Cohort	PSM	Low dose	1489	88.4 ± 2.9	48.6	6.6	NR	3.80 ± 1.30	NR	NR
				Warfarin	1497	88.7 ± 3.1	54.8			3.80 ± 1.20		
Lee SR, 2019[35]	Korea	Cohort	PSM	Standard dose	5196	71.2 ± 8.1	45.1	30.0	24.7 ± 3.3	3.50 ± 1.60	NR	82.5 ± 37.5
				Low dose	5777	72.1 ± 8.4	44.9		24.5 ± 3.5	3.60 ± 1.60		81.5 ± 49.6
				Warfarin	5777	72.2 ± 8.9	46.5		24.5 ± 3.4	3.70 ± 1.80		81.3 ± 41.3
Chan YH, 2019[36]	Taiwan	Cohort	PSM	Low dose	60 212	74.7 ± 10.7	42.6	16.0	NR	3.60 ± 0.70	2.60 ± 0.50	NR
				Warfarin	19 761	74.6 ± 10.7	43.3			3.60 ± 0.80	2.70 ± 0.50	
RE-LY, 2013[37]	Asia	RCT		Standard dose[a]	933	68.0 ± 9.8	36.2	24.0[c]	NR	2.20 ± 1.10[b]	NR	65.3 ± 22.1
				Low dose[a]	923							
				Warfarin[a]	926							
J-ROCKET AF, 2012[38]	Japan	RCT		Low dose	639	71.0	17.1	30.0	NR	3.27[b]	NR	NR
				Warfarin	639	71.2	21.8			3.22[b]		
ENGAGE AF-TIMI 48, 2016[39]	Asia	RCT		Standard dose[a]	642	70.1 ± 8.7	28.0	NR	NR	2.90 ± 1.00[b]	NR	NR
				Low dose[a]	652							
				Warfarin[a]	641							

Values are shown as mean ± SD or n; BMI, body mass index; CrCl, creatinine clearance rate; NR, not reported; PSM, propensity score matching; RCT, randomized controlled trial.
[a] Means characteristics are the composite of low-dose and standard-dose groups.
[b] Means the $CHADS_2$ score.
[c] Means values are shown as the median.
[d] Means values are shown as the category.

Risks of Bias Assessments

Results of bias assessments are summarized in Supplementary Tables S4-S6. Overall, all included RCTs and most cohort studies reported low risks of bias. While Wakamatsu et al[23] (2020), Kwon et al[28] (2016), and Akagi et al[29] (2019) didn't balance the confounding factors between groups, which had risks of comparability bias. Lee et al[25] (2018), Akagi et al[29] (2019), and Kohsaka et al[33] (2017) did not report the length of follow-up, and most cohort studies did not show the lost follow-up rate, which had risks of outcome bias. In addition, there was no publication bias for this meta-analysis by the Begg's and Egger's tests, except for the risk of ICH ($P = .005$, Egger's test) in the comparison of low-dose NOACs versus warfarin.

Low-Dose NOACs versus Standard-Dose NOACs

For efficacy outcomes, there was no significant difference between low-dose NOACs and standard-dose NOACs for the risk of stroke (HR = 1.18, 95% CI 0.98 to 1.42, $I^2 = 42.3\%$). However, low-dose NOACs were associated with a slightly higher risk of mortality (HR = 1.34, 95% CI 1.05 to 1.71, $I^2 = 79.1\%$) compared with standard-dose NOACs. For safety outcomes, the risks of major bleeding (HR = 1.00, 95% CI 0.83 to 1.21, $I^2 = 46.2\%$), ICH (HR = 1.13, 95% CI 0.92 to 1.38, $I^2 = 2.9\%$), and GH (HR = 1.07, 95% CI 0.87 to 1.31, $I^2 = 34.4\%$) were similar between two groups. And the results of subgroup meta-analyses were also the same as the overall except for the higher risk of stroke (HR = 1.90, 95% CI 1.32 to 2.74, $I^2 = 0\%$) and comparable risk of mortality (HR = 1.18, 95% CI 0.92 to 1.52, $I^2 = 0\%$) in RCTs (Figure 2). Details of subgroup meta-analyses are illustrated in Supplementary Figures S1-S5.

Low-Dose NOACs versus Warfarin

For efficacy outcomes, compared with warfarin, low-dose NOACs were associated with lower risks of stroke (HR = 0.73, 95% CI .67 to 0.79, $I^2 = 9.6\%$) and mortality (HR = 0.69, 95% CI 0.60 to 0.81, $I^2 = 78.7\%$). For safety outcomes, in the low-dose NOACs group, the risks of major bleeding (HR = 0.62, 95% CI 0.51 to 0.75, $I^2 = 73.5\%$), ICH (HR = 0.48, 95% CI 0.33 to 0.69, $I^2 = 77.1\%$), and GH (HR = 0.78, 95% CI 0.65 to 0.93, $I^2 = 36.1\%$) were lower compared with warfarin. And the results of subgroup meta-analyses were similar to the overall except for comparable risks of stroke (HR = 0.81, 95% CI 0.56 to 1.15, $I^2 = 34.4\%$), mortality (HR = 0.83, 95% CI 0.57 to 1.22, $I^2 = 52.6\%$), and GH (HR = 0.76, 95% CI 0.48 to 1.22, $I^2 = 0\%$) in RCTs (Figure 3). Details of subgroup meta-analyses are shown in Supplementary Figures S6-S10.

Adjusted Subgroup Meta-Analyses

To minimize the heterogeneity and obtain more reliable results, adjusted subgroup meta-analyses including RCTs and cohort studies with PSM were performed. Results of all outcomes were consistent with the overall meta-analysis. Details of adjusted subgroup meta-analyses are illustrated in Supplementary Figures S11-S16.

Meta-regression Analyses

No significant correlations were observed in most efficacy and safety outcomes. However, in the comparison of low-dose NOACs versus standard-dose NOACs, a significant correlation was found between mortality and heart failure ($P = .023$), with HR decreasing as the heart failure percent of included patients increased (Supplementary Figure S17); another significant predictor of HR was found

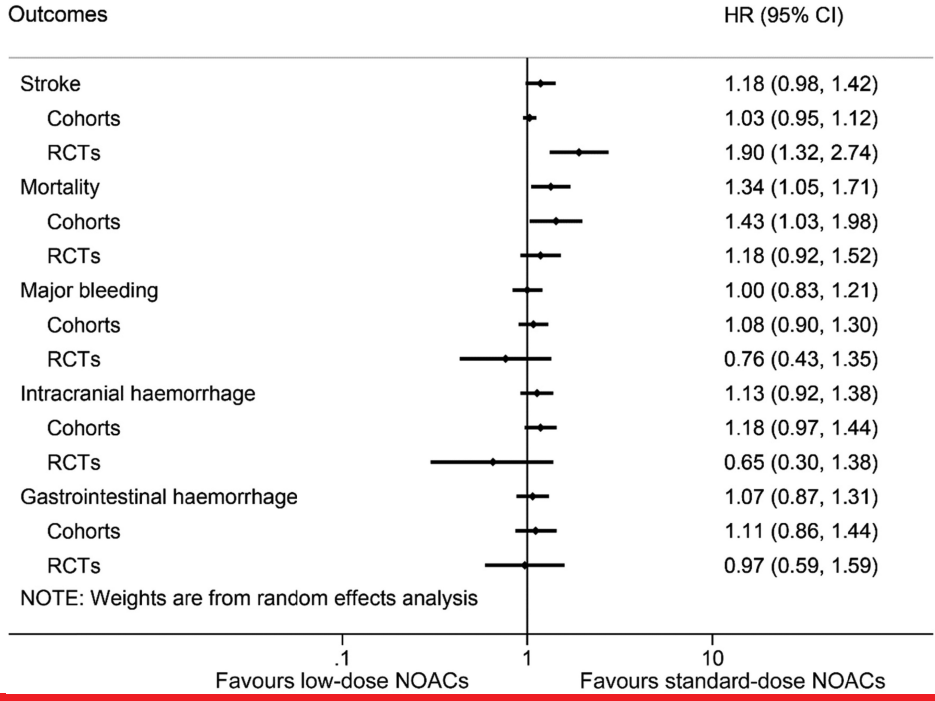

Figure 2. Meta-analysis of the efficacy and safety for low-dose NOACs versus standard-dose NOACs. HR, hazard ratio; RCTs, randomized controlled trials.

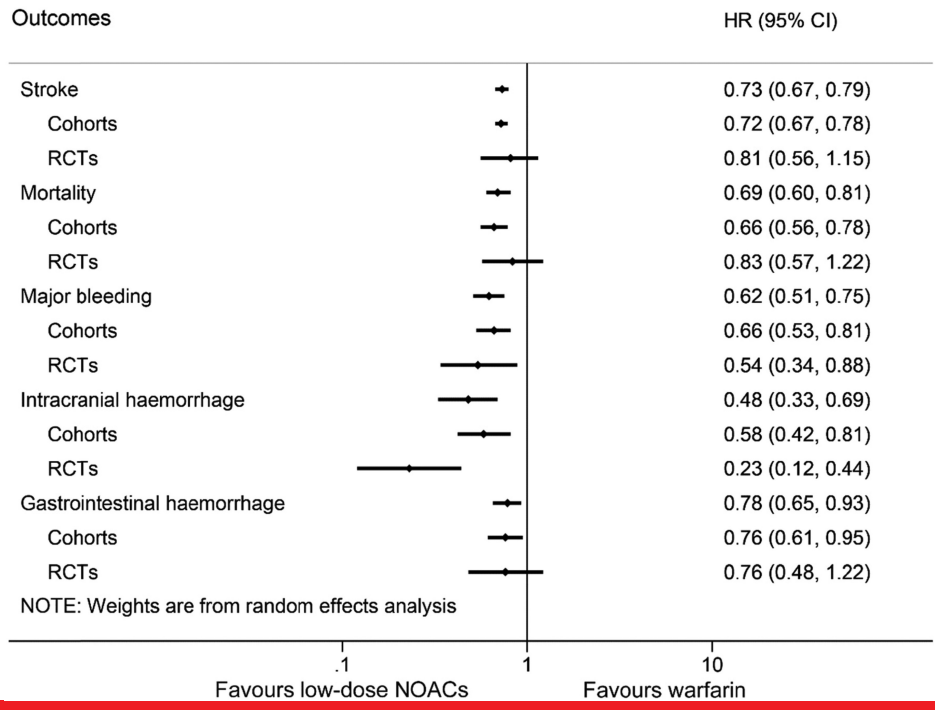

Figure 3. Meta-analysis of the efficacy and safety for low-dose NOACs versus warfarin. HR, hazard ratio; RCTs, randomized controlled trials.

between major bleeding and female ($P = .020$) as well, with HR increasing as the female percent of included patients ascended (Supplementary Figure S18). In the comparison of low-dose NOACs versus warfarin, potential influencing factors were observed between ICH, mean age ($P = .032$), and hypertension ($P = .038$), with HR increasing as the mean age of included patients ascended (Supplementary Figure S19) and HR decreasing as the hypertension percent of included patients increased, respectively (Supplementary Figure S20). Details of meta-regression analyses are illustrated in Supplementary Table S7.

To reduce the heterogeneity, subgroup meta-analyses stratified by the percent of heart failure, female, and hypertension (divided into high percent and low percent groups by the median) were performed, respectively. In general, all results were consistent with the overall meta-analysis. Details of subgroup meta-analyses are shown in Supplementary Figures S21-S23.

DISCUSSION

To our knowledge, this is the first meta-analysis including both cohort studies and RCTs for the efficacy and safety of low-dose NOACs. A previous meta-analysis in 2016 had tried to assess this by RCTs,[4] and the results indicated that: when compared with standard-dose NOACs, low-dose NOACs showed the inferior efficacy with a higher risk of stroke and similar safety; when compared with warfarin, low-dose NOACs showed the comparable efficacy and better safety. Even though the meta-analysis of RCTs is the highest level of evidence, results of cohorts may better represent the clinical practice with the additional real-world data. For example, the previous meta-analysis of RCTs solely enrolled patients of approximately 70 years old with the standard weight of roughly 66 kg.[4] These may not be generalizable to the under-represented patients, such as those with low weight, older age, or not yet represented in RCTs, so we performed this meta-analysis.

Our meta-analysis revealed that: when compared with standard-dose NOACs, low-dose NOACs had comparable risks of stroke and bleeding (including major bleeding, ICH, and GH), except for a slightly higher risk of mortality; when compared with warfarin, low-dose NOACs showed lower risks of stroke, mortality, and bleeding. The relatively higher age might explain the higher risk of mortality in the low-dose NOACs group: the mean age of low-dose NOACs group was approximately five years older than standard-dose NOACs group in the studies of Murata (2019),[5] Ohno (2021),[24] and Chan (2018).[27] As another study showed that the older patients with AF were faced with more comorbidities and death factors, would have a higher risk of mortality than younger patients,[40] which might eventually lead to the conflicting results. To validate our hypothesis, a subgroup meta-analysis excluding the above three studies was performed, and the result indeed indicated that low-dose NOACs showed a comparable risk of mortality compared with standard-dose NOACs (HR = 1.09, 95% CI 0.99 to 1.21, $I^2 = 0\%$) (Supplementary Figure S24). At the same time, the results of cohort study subgroups were consistent with the overall meta-analysis, and results of RCTs subgroups were similar to the previous meta-analysis, respectively. Most of our results were consistent with the previous meta-analysis of RCTs. However, the inclusion of cohort studies caused

some differences, such as the comparable risk of stroke and higher risk of mortality in the comparison of standard-dose NOACs, and lower the risks of stroke, mortality, and GH in the comparison of warfarin.[4]

As CHA_2DS_2-VASc and HAS-BLED scores were two important influence factors for the efficacy and safety of NOACs or warfarin, we tried to further interpret the results according to these. For low-dose NOACs versus standard-dose NOACs, CHA_2DS_2-VASc and HAS-BLED scores of the included patients ranged from 2.10 to 4.70, 0.80 to 2.96, respectively, which indicated that patients in this comparison were associated with high risk of stroke[41] and low or moderate risk of bleeding.[42] For low-dose NOACs versus warfarin, CHA_2DS_2-VASc and HAS-BLED scores of the included patients ranged from 3.30 to 4.90, 2.40 to 3.70, respectively, which illustrated that patients in this comparison were associated with the high risk of stroke[41] and moderate or high risk of bleeding[42] as well. As a result, we could further demonstrate that: (1) for the patients under the high risk of stroke with approximate CHA_2DS_2-VASc score of 2.0-5.0, and low or moderate risk of bleeding with approximate HAS-BLED score of 0.8-3.0, low-dose NOACs had the comparable efficacy and safety compared with standard-dose NOACs; (2) for the patients under the high risk of stroke with approximate CHA_2DS_2-VASc score of 3.0-5.0, and moderate or high risk of bleeding with approximate HAS-BLED score of 2.0-4.0, low-dose NOACs showed the superior efficacy and safety compared with warfarin.

Warfarin showed some therapeutic limitations in the clinical practice, whose effect was widely affected by food and drugs, and patients need to monitor the INR frequently to supervise the efficacy and risk of major bleeding.[43] Major bleeding can seriously affect the anticoagulation treatment, such as higher risks of stroke and mortality,[44] longer hospitalization,[45] and more healthcare resource utilization.[46] At the same time, patients taking warfarin often had less time within the therapeutic range.[47] Some meta-analyses had demonstrated that standard-dose NOACs could reduce the risks of stroke, mortality, major bleeding, and ICH compared to warfarin.[48-50] In this meta-analysis, low-dose NOACs were non-inferior to standard-dose NOACs and superior to warfarin. Thus, considering their excellence and convenience, low-dose NOACs might be an effective and safe alternative to warfarin in Asian patients with NVAF.

We need to note that the baseline characteristics of cohort studies may be diverse compared to RCTs. For some included studies, the mean age of low-dose NOACs group was approximately 5 years older than standard-dose NOACs or warfarin group, which led to the relatively lower CrCL and higher CHA_2DS_2-VASc and HAS-BLED scores.[5,24,27,30] Moreover, there were some heterogeneities in the previous medical history, including hypertension, diabetes, heart failure, vascular disease, stroke/transient ischemic attack (TIA), and major bleeding. Due to the broad-spectrum baseline characteristics, most cohort studies used the PSM method to adjust the data and minimize the heterogeneity. Adjusted subgroup meta-analyses including RCTs and cohort studies with PSM were performed as well, and the results were consistent with the overall meta-analysis.

What's more, meta-regression analyses indicated that the mean age, percent of heart failure, female, and hypertension captured a very substantial portion of the heterogeneity in the data, so subgroup meta-analyses stratified by those were performed to balance the confounding factors. Similarly, the results were consistent with the overall. Nonetheless, considering the relatively few studies and ineluctable heterogeneity in this meta-analysis, further well-designed prospective studies are required to validate these results.

Study Limitations

However, there were some potential limitations for our meta-analysis. Firstly, due to the limited number of the included studies and original composite results in most studies, we pooled all NOACs together even though rivaroxaban, apixaban, and edoxaban are the factor Xa inhibitors[51] while dabigatran is the thrombin inhibitor,[52] which was consistent with other meta-analyses and proved feasible and reliable.[4,53,54] This may not cause the significant bias, because they are all direct-acting oral anticoagulants inhibiting important factors in the coagulation cascade. Secondly, as it wasn't convenient to monitor the quality of warfarin routine usage, most included studies didn't report the level of time in therapeutic range (TTR). Many patients cannot reach the baseline TTR requirement in the clinical practice,[47] which might lead to the unexpected bias in the comparison of low-dose NOACs versus warfarin. And this limitation could be found in other meta-analyses involving warfarin.[53,54] However, the effectiveness of the treatment is ensured not only by the efficacy of potent drugs, but also patients' adherence to the therapy,[55] we should have a various and comprehensive view of this limitation. Thirdly, most enrolled studies were performed in Taiwan, Japan, or Korea, which might only represent East Asian patients rather than whole Asian patients.

CONCLUSIONS

Low-dose NOACs were superior to warfarin, and comparable to standard-dose NOACs in light of risks of stroke, major bleeding, ICH, and GH. Low-dose NOACs might be prescribed effectively and safely for Asian patients with NVAF. Considering limitations, further high qualified studies are warranted.

Availability of Data and Materials: All data generated or analyzed during this study are included in this published article and its supplementary information files.

Ethics Committee Approval: This is a meta-analysis and needs no ethical committee approval.

Peer-review: Externally peer-reviewed.

Author Contributions: Ze Li was responsible for the study design, literature search, data collection, data analysis, data interpretation, drafting and critical revision of the manuscript, and approval of the final submission. Yingming Zheng, Dandan Li, Xiaozhen Wang, Sheng Cheng, and Xiao Luo were responsible for the literature search and

data collection. Aiping Wen was responsible for the study concept and design, data interpretation, critical revision of the manuscript, approval of the final submission, integrity of the data, and accuracy of the data analysis.

Declaration of Interests: The authors declare that they have no competing interest.

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Table S1. Electronic Database Search Strategy
Cochrane Central Register of Controlled Trials
#1 atrial fibrillat* OR atrium fibrillat* OR atrial fibrillation in Title Abstract Keyword
#2 warfarin* OR acenocoumarol OR dicoumarol OR coumadin OR diphenadione OR 'vitamin k antagonist*' OR vka OR 'factor xa inhibitor*' OR antithrombin* OR anticoagul* OR xarelto OR apixaban OR eliquis OR 'dabigatran etexilate' OR edoxaban OR savaysa OR rivaroxaban OR dabigatran OR 'target specific oral anticoagulant*' OR 'target-specific oral anticoagulant*' OR tsoac* OR 'new oral anticoagulant*' OR 'novel oral anticoagulant*' OR noac* OR 'direct-acting oral anticoagulant*' OR 'direct acting oral anticoagulant*' OR 'direct oral anticoagulant*' OR doac in Title Abstract Keyword
#3 'low dose' OR 'micro dose' OR 'off label' OR underdosing OR underdose OR underdosed OR 'reduced dose' in All Text
#4 #1 and #2 and #3
Embase
1. 'atrial fibrillat*':ab,ti OR 'atrium fibrillat*':ab,ti OR 'atrial fibrillation':ab,ti 2. warfarin*:ab,ti OR acenocoumarol:ab,ti OR dicoumarol:ab,ti OR coumadin:ab,ti OR diphenadione:ab,ti OR 'vitamin k antagonist*':ab,ti OR vka:ab,ti OR 'factor xa inhibitor*':ab,ti OR antithrombin*:ab,ti OR anticoagul*:ab,ti OR xarelto:ab,ti OR apixaban:ab,ti OR eliquis:ab,ti OR 'dabigatran etexilate':ab,ti OR edoxaban:ab,ti OR savaysa:ab,ti OR rivaroxaban:ab,ti OR dabigatran:ab,ti OR 'target specific oral anticoagulant*':ab,ti OR 'target-specific oral anticoagulant*':ab,ti OR tsoac*:ab,ti OR 'new oral anticoagulant*':ab,ti OR 'novel oral anticoagulant*':ab,ti OR noac*:ab,ti OR 'direct-acting oral anticoagulant*':ab,ti OR 'direct acting oral anticoagulant*':ab,ti OR 'direct oral anticoagulant*':ab,ti OR doac:ab,ti 3. 'low dose':ab,ti OR 'micro dose':ab,ti OR 'off label':ab,ti OR underdosing:ab,ti OR underdose:ab,ti OR underdosed:ab,ti OR 'reduced dose':ab,ti 4. 1 and 2 and 3
MEDLINE
1. atrial fibrillat*[Title/Abstract] OR atrium fibrillat*[Title/Abstract] OR atrial fibrillation[Title/Abstract] 2. warfarin*[Title/Abstract] OR acenocoumarol[Title/Abstract] OR dicoumarol[Title/Abstract] OR coumadin[Title/Abstract] OR diphenadione[Title/Abstract] OR 'vitamin k antagonist*'[Title/Abstract] OR vka[Title/Abstract] OR 'factor xa inhibitor*'[Title/Abstract] OR antithrombin*[Title/Abstract] OR anticoagul*[Title/Abstract] OR xarelto[Title/Abstract] OR apixaban[Title/Abstract] OR eliquis[Title/Abstract] OR 'dabigatran etexilate'[Title/Abstract] OR edoxaban[Title/Abstract] OR savaysa[Title/Abstract] OR rivaroxaban[Title/Abstract] OR dabigatran[Title/Abstract] OR 'target specific oral anticoagulant*'[Title/Abstract] OR 'target-specific oral anticoagulant*'[Title/Abstract] OR tsoac*[Title/Abstract] OR 'new oral anticoagulant*'[Title/Abstract] OR 'novel oral anticoagulant*'[Title/Abstract] OR noac*[Title/Abstract] OR 'direct-acting oral anticoagulant*'[Title/Abstract] OR 'direct acting oral anticoagulant*'[Title/Abstract] OR 'direct oral anticoagulant*'[Title/Abstract] OR doac[Title/Abstract] 3. low dose' OR 'micro dose' OR 'off label' OR underdosing OR underdose OR underdosed OR 'reduced dose' 4. 1 and 2 and 3

Table S2. Detailed Previous Medical History of Included Patients

Author (Study), Year	Group	Previous Medical History (%)					
		Hypertension	Diabetes	Heart Failure	Vascular Disease	Stroke/TIA	Major Bleeding
Murata N, 2019	Standard-dose	68.1	22.3	16.4	9.9	9.5	0.5
	Low-dose	71.3	22.2	17.9	14.4	7.6	1.4
Wakamatsu Y, 2020	Standard-dose	61.3	20.4	15.2	9.8	11.9	1.5
	Low-dose	62.5	17.6	17.1	13.9	12.5	2.3
Ohno, J 2021	Standard-dose	71.0	28.8	18.3	6.2	14.9	NR
	Low-dose	71.6	27.2	17.8	10.2	22.5	
Lee HF, 2018	Low-dose	86.0	39.0	14.0	NR	22.0	2.5
	Warfarin	86.0	39.0	14.0		21.0	2.0
Yu HT, 2018	Standard-dose	94.5	30.5	63.2	28.1	37.1	NR
	Low-dose	94.0	34.6	66.9	32.8	40.6	
	Warfarin	94.6	34.3	67.5	32.6	40.4	
Chan YH, 2018	Standard-dose[a]	87.0	41.0	13.0	NR	23.0	2.0
	Low-dose[a]						
	Warfarin	87.0	40.0	13.0		23.0	2.0
Chang HK, 2016	Standard-dose[a]	72.3	25.7	18.2	NR	45.9	NR
	Low-dose[a]						
	Warfarin	75.2	49.5	20.0		37.9	
Akagi Y, 2019	Standard-dose[a]	60.1	19.7	19.0	NR	26.2	NR
	Low-dose[a]						
Yu HT, 2020	Standard-dose	94.5	31.4	60.4	27.9	46.6	NR
	Low-dose	95.3	32.3	60.4	29.7	41.6	
Cho MS, 2019	Low-dose	87.8	45.5	20.5	11.5	21.1	NR
	Warfarin	86.7	48.4	22.8	12.8	27.3	
Jeong HK, 2019	Low-dose	53.5	24.1	5.7	NR	29.2	NR
	Warfarin	54.7	22.3	5.1		29.2	
Kohsaka S, 2020	Low-dose	54.9	30.0	37.1	NR	21.2	NR
	Warfarin	55.9	30.4	37.5		21.4	
Kohsaka S, 2017	Low-dose	53.8	28.9	35.3	6.6	22.3	NR
	Warfarin	54.0	28.2	35.4	6.2	22.6	
Lai CL, 2018	Low-dose	51.1	16.9	25.3	4.2	16.3	NR
	Warfarin	50.3	15.4	29.6	4.1	11.6	
Lee SR, 2019	Standard-dose	72.0	21.5	30.2	NR	NR	NR
	Low-dose	73.1	21.1	31.2			
	Warfarin	72.3	22.3	32.4			
Chan YH, 2019	Low-dose	84.1	38.1	11.1	NR	15.2	NR
	Warfarin	84.5	38.6	10.8		15.0	
RE-LY, 2013	Standard-dose[a]	71.2	25.1	36.3	NR	24.2	NR
	Low-dose[a]						
	Warfarin[a]						
J-ROCKET AF, 2012	Low-dose	79.5	39.0	41.3	NR	63.8	NR
	Warfarin	79.5	37.1	40.2		63.4	
ENGAGE AF-TIMI 48, 2016	Standard-dose[a]	82.1	35.0	47.3	NR	42.4	NR
	Low-dose[s]						
	Warfarin[a]						

NR, not reported; TIA, transient ischemic attack.
[a]Means characteristics are the composite of low-dose and standard-dose groups.

Table S3. Detailed Group Contents of Included Studies

Author (Study), Year	Standard-Dose	Low-Dose
Murata N, 2019	Dabigatran Rivaroxaban Apixaban Edoxaban	Dabigatran 110 mg (b.i.d.) Rivaroxaban 10 mg (q.d.) Apixaban 2.5 mg (b.i.d.) Edoxaban 30 mg (q.d.)
Wakamatsu Y, 2020	Dabigatran Rivaroxaban Apixaban Edoxaban	Dabigatran 110 mg (b.i.d.) Rivaroxaban 10 mg (q.d.) Apixaban 2.5 mg (b.i.d.) Edoxaban 30 mg (q.d.)
Ohno J, 2021	Dabigatran Rivaroxaban Apixaban Edoxaban	Dabigatran 110 mg (b.i.d.) Rivaroxaban 10 mg (q.d.) Apixaban 2.5 mg (b.i.d.) Edoxaban 30 mg (q.d.)
Akagi Y, 2019	Dabigatran	Dabigatran 110 mg (b.i.d.)
Yu HT 2020	Dabigatran Rivaroxaban Apixaban Edoxaban	Dabigatran 110 mg (b.i.d.) Rivaroxaban 10/15 mg (q.d.) Apixaban 2.5 mg (b.i.d.) Edoxaban 30 mg (q.d.)
Chan YH, 2018	Dabigatran Rivaroxaban Apixaban	Dabigatran 110 mg (b.i.d.) Rivaroxaban 10/15 mg (q.d.) Apixaban 2.5 mg (b.i.d.)
Chang HK, 2016	Dabigatran Rivaroxaban Warfarin	Dabigatran 110 mg (b.i.d.) Rivaroxaban 15 mg (q.d.)
Lee SR, 2019	Rivaroxaban Warfarin	Rivaroxaban 15 mg (q.d.)
Yu HT, 2018	Warfarin	Edoxaban 30 mg (q.d.)
Lee HF, 2018	Warfarin	Rivaroxaban 10/15 mg (q.d.)
Cho MS, 2019	Warfarin	Dabigatran 110 mg (b.i.d.) Rivaroxaban 10/15 mg (q.d.) Apixaban 2.5 mg (b.i.d.)
Jeong HK, 2019	Warfarin	Rivaroxaban 15 mg (q.d.)
Kohsaka S, 2017	Warfarin	Rivaroxaban 10/15 mg (q.d.)
Kohsaka S, 2020	Warfarin	Rivaroxaban 10/15 mg (q.d.)
Lai CL, 2018	Warfarin	Dabigatran 110 mg (b.i.d.)
Chan YH, 2019	Warfarin	Dabigatran 110 mg (b.i.d.) Rivaroxaban 10/15 mg (q.d.) Apixaban 2.5 mg (b.i.d.) Edoxaban 15/30 mg (q.d.)
RE-LY, 2013	Dabigatran Warfarin	Dabigatran 110 mg (b.i.d.)
ENGAGE AF-TIMI 48, 2016	Edoxaban Warfarin	Edoxaban 30 mg (q.d.)
J-ROCKET AF, 2012	Warfarin	Rivaroxaban 10/15 mg (q.d.)

Table S4. Results of Quality Assessment Using the Newcastle-Ottawa Scale for Cohort Studies

	Selection				Comparability	Outcome		
Author, Year	Representativeness of the Exposed Cohort	Selection of the Non-exposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Was Follow-Up Long Enough for Outcomes to Occur	Adequacy of Follow-Up of Cohorts
Murata N, 2019	★	★	★	★	★★	★	★	★
Wakamatsu Y, 2020	★	★	★	★	☆☆	★	★	☆
Ohno J, 2021	★	★	★	★	★★	★	★	☆
Lee HF, 2018	★	★	★	★	★★	★	☆	☆
Chang HK, 2016	★	★	★	★	☆☆	★	★	☆
Akagi Y, 2019	★	★	★	★	☆☆	★	☆	☆
Yu HT, 2020	★	★	★	★	★★	★	★	☆
Yu HT, 2018	★	★	★	★	★★	★	★	☆
Cho MS, 2019	★	★	★	★	★★	★	★	☆
Jeong HK, 2019	★	★	★	★	★★	★	★	☆
Kohsaka S, 2020	★	★	★	★	★★	★	★	☆
Kohsaka S, 2017	★	★	★	★	★★	★	☆	☆
Lai CL, 2018	★	★	★	★	★★	★	★	☆
Lee SR, 2019	★	★	★	★	★★	★	★	☆
Chan YH, 2018	★	★	★	★	★★	★	★	☆
Chan YH, 2019	★	★	★	★	★★	★	★	☆

Table S5. Results of Quality Assessment Using the Cochrane Collaboration's Tool for RCTs

Study, Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Sources of Bias
RE-LY, 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
J-ROCKET AF, 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
ENGAGE AF-TIMI 48, 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table S6. Results of Publication Bias Assessment Using the Begg's and Egger's Tests

	Outcomes									
	Stroke		Mortality		Major Bleeding		ICH		GH	
Comparison	Begg's Test	Egger's Test	Begg's Test	Egger's Test	Begg's Test	Egger's Test	Begg's Test	Egger's Test	Begg's Test	Egger's Test
Low-dose NOACs versus standard-dose NOACs	0.721	0.467	0.764	0.496	0.917	0.918	0.548	0.102	0.707	0.364
Low-dose NOACs versus warfarin	0.858	0.497	1.000	0.707	0.210	0.162	0.368	0.005	0.368	0.156

GH, gastrointestinal hemorrhage; ICH, intracranial hemorrhage.

Table S7. Results of Meta-regression Analyses for Interesting Outcomes

Low-Dose NOACs versus Standard-Dose NOACs

Variables	Stroke (*P*)	Mortality (*P*)	Major bleeding (*P*)	ICH (*P*)	GH (*P*)
Mean age	.826	.119	.106	.211	.257
Female	.948	.760	.020	.373	.160
BMI	.476	.272	.240	.908	NA
HBP	.932	.934	.991	.126	.110
DM	.513	.292	.929	.122	.793
HF	.743	.023	.394	.983	.069
Vascular disease	.436	.218	.574	.517	NA
Stroke/TIA	.554	.100	.749	.726	.172
Prior major bleeding	.486	.968	.282	.483	NA
CHA_2DS_2-VASc	.770	.861	.701	.345	.245
HAS-BLED	.340	.542	.630	.415	NA
CrCl	.309	.922	.786	.448	NA

Low-Dose NOACs versus Warfarin

Variables	Stroke (*P*)	Mortality (*P*)	Major bleeding (*P*)	ICH (*P*)	GH (*P*)
Mean age	.717	.155	.947	.032	.972
Female	.483	.375	.606	.341	.851
BMI	.342	NA	.341	NA	NA
HBP	.892	.747	.997	.038	.154
DM	.365	.667	.787	.972	.089
HF	.256	.927	.988	.962	.988
Vascular disease	NA	.654	.575	NA	NA
Stroke/TIA	.377	.723	.936	.461	.792
Prior major bleeding	NA	NA	NA	NA	NA
CHA_2DS_2-VASc	.132	.145	.631	.805	.561
HAS-BLED	.928	NA	.630	NA	NA
CrCl	.930	NA	.341	NA	NA

BMI, body mass index; CrCl, creatinine clearance rate; DM, diabetes mellitus; GH, gastrointestinal hemorrhage; HBP, hypertension; HF, heart failure; ICH, intracranial hemorrhage; NA, not available; TIA, transient ischemic attack.

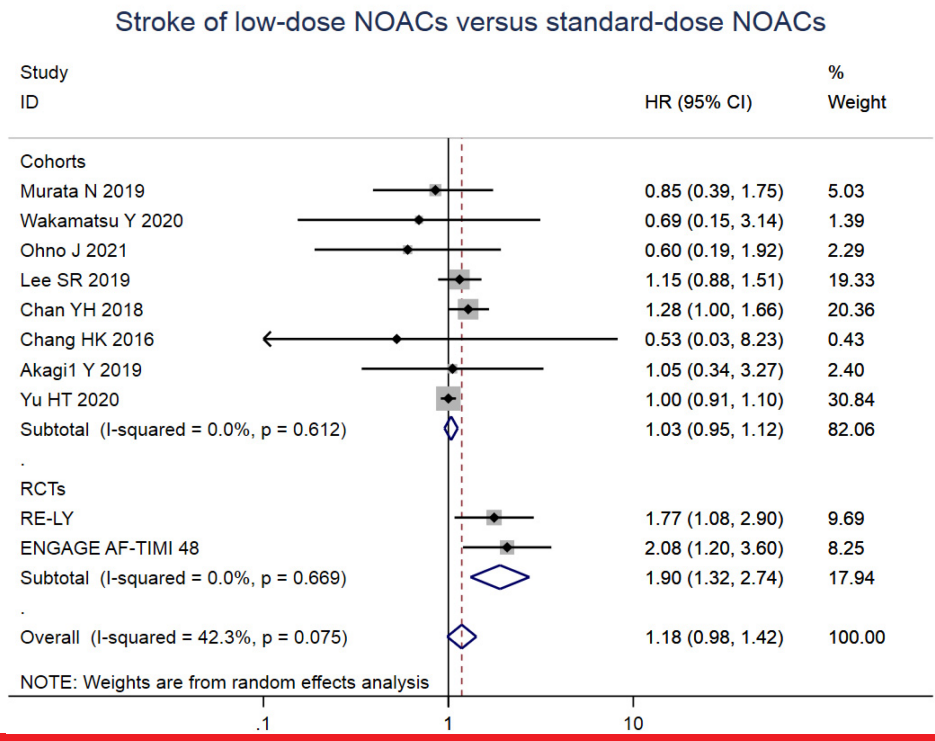

Figure S1. Pooled stroke of low-dose NOACs versus standard-dose NOACs. HR, hazard ratio; RCTs, randomized controlled trials.

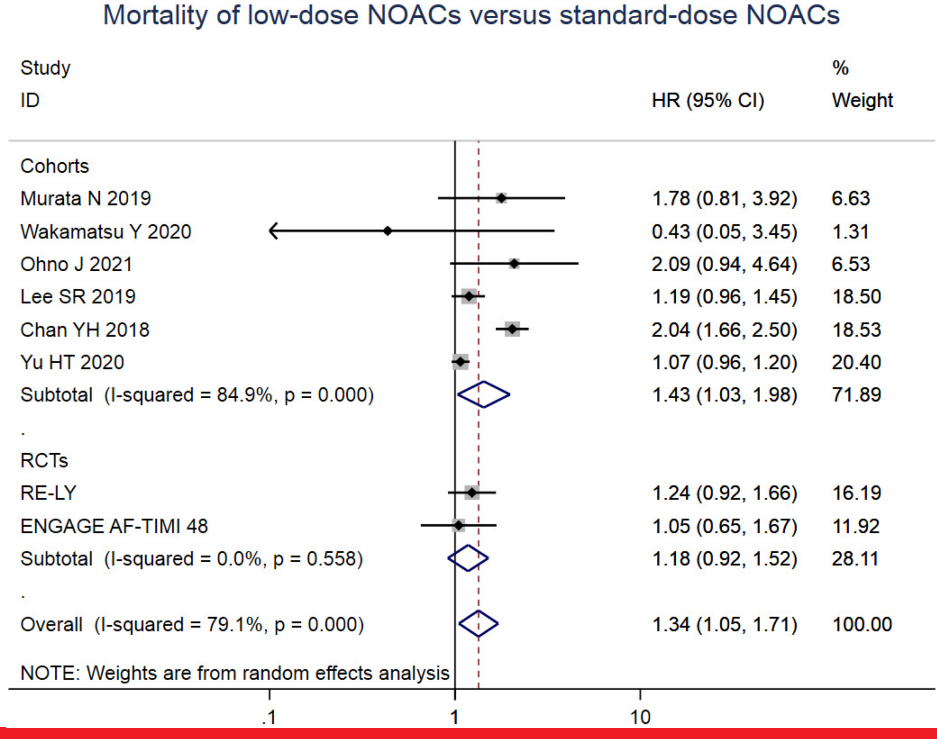

Figure S2. Pooled mortality of low-dose NOACs versus standard-dose NOACs. HR, hazard ratio; RCTs, randomized controlled trials.

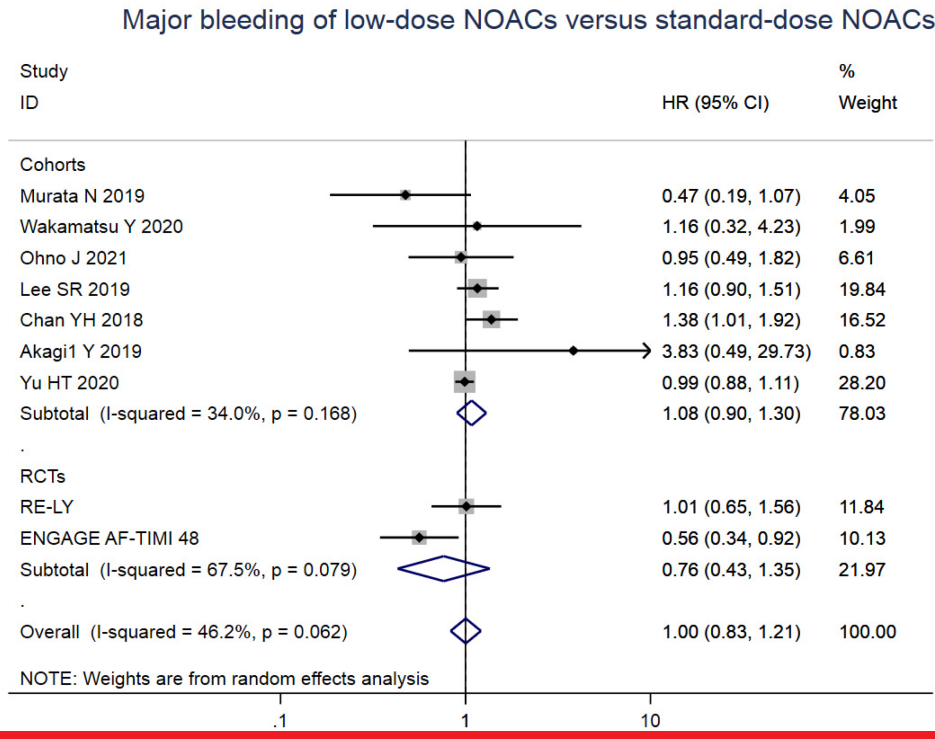

Figure S3. Pooled major bleeding of low-dose NOACs versus standard-dose NOACs. HR, hazard ratio; RCTs, randomized controlled trials.

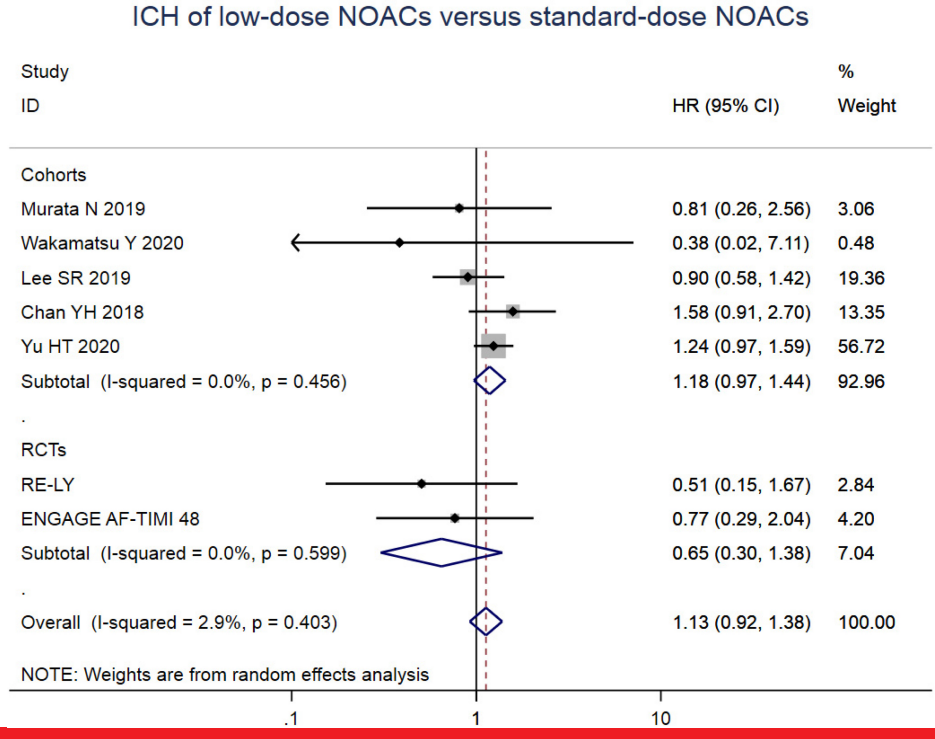

Figure S4. Pooled ICH of low-dose NOACs versus standard-dose NOACs. ICH, intracranial hemorrhage; HR, hazard ratio; RCTs, randomized controlled trials.

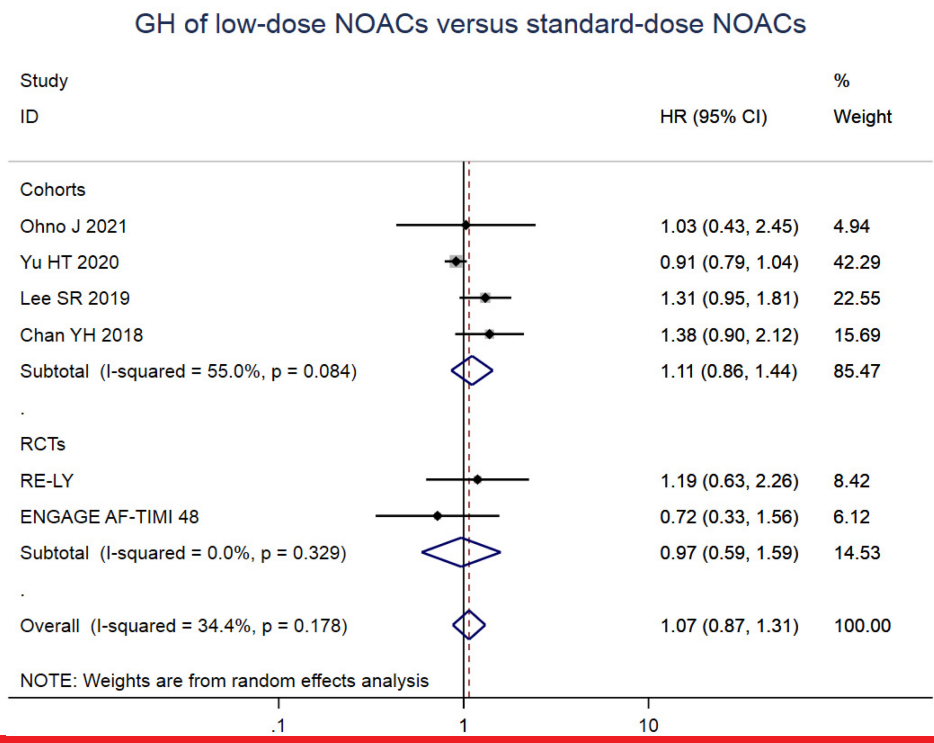

Figure S5. Pooled GH of low-dose NOACs versus standard-dose NOACs. HR, hazard ratio; GH, gastrointestinal hemorrhage; RCTs, randomized controlled trials.

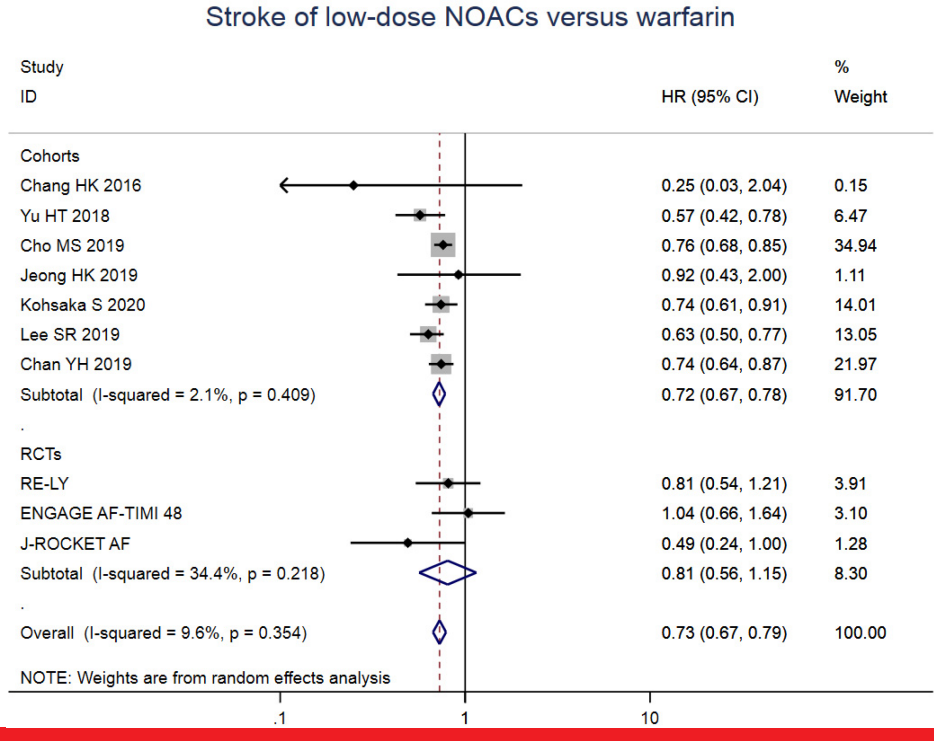

Figure S6. Pooled stroke of low-dose NOACs versus warfarin. HR, hazard ratio; RCTs, randomized controlled trials.

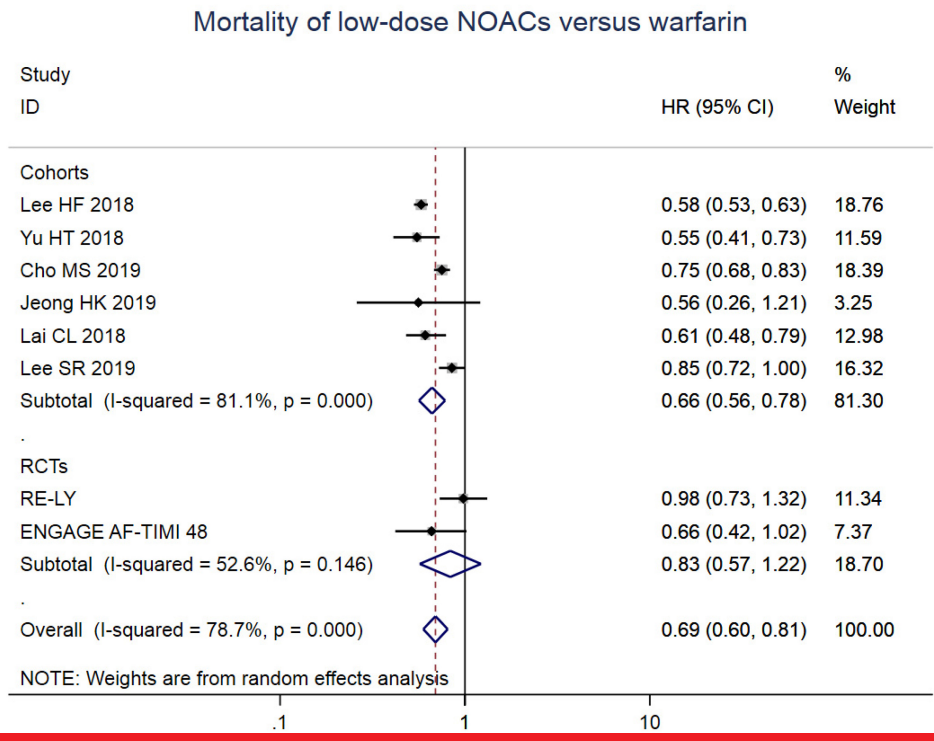

Figure S7. Pooled mortality of low-dose NOACs versus warfarin. HR, hazard ratio; RCTs, randomized controlled trials.

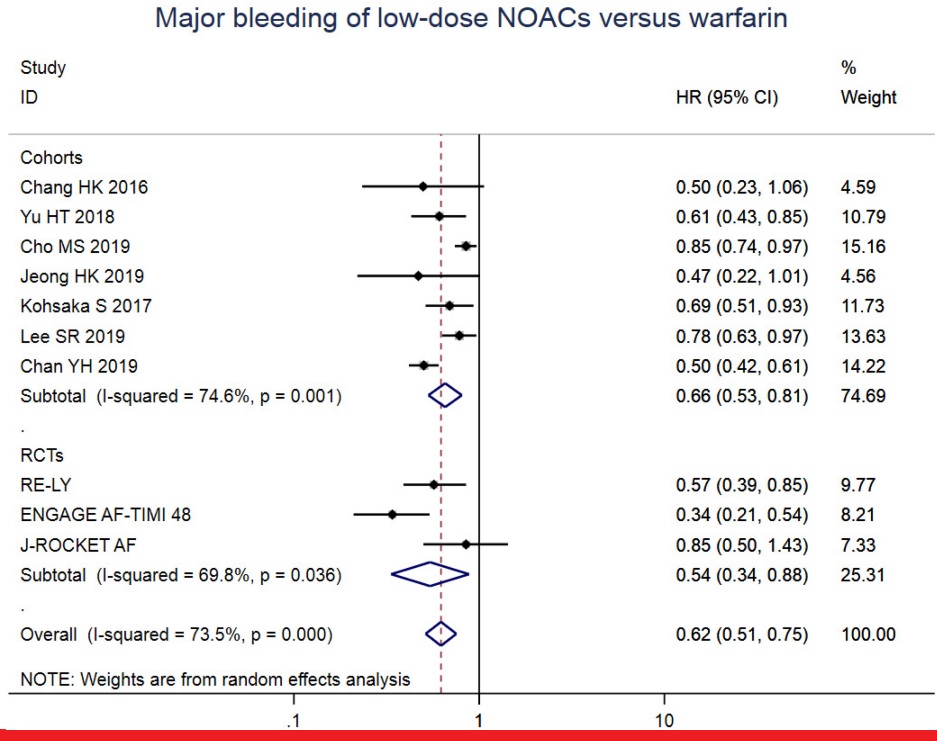

Figure S8. Pooled major bleeding of low-dose NOACs versus warfarin. HR, hazard ratio; RCTs, randomized controlled trials.

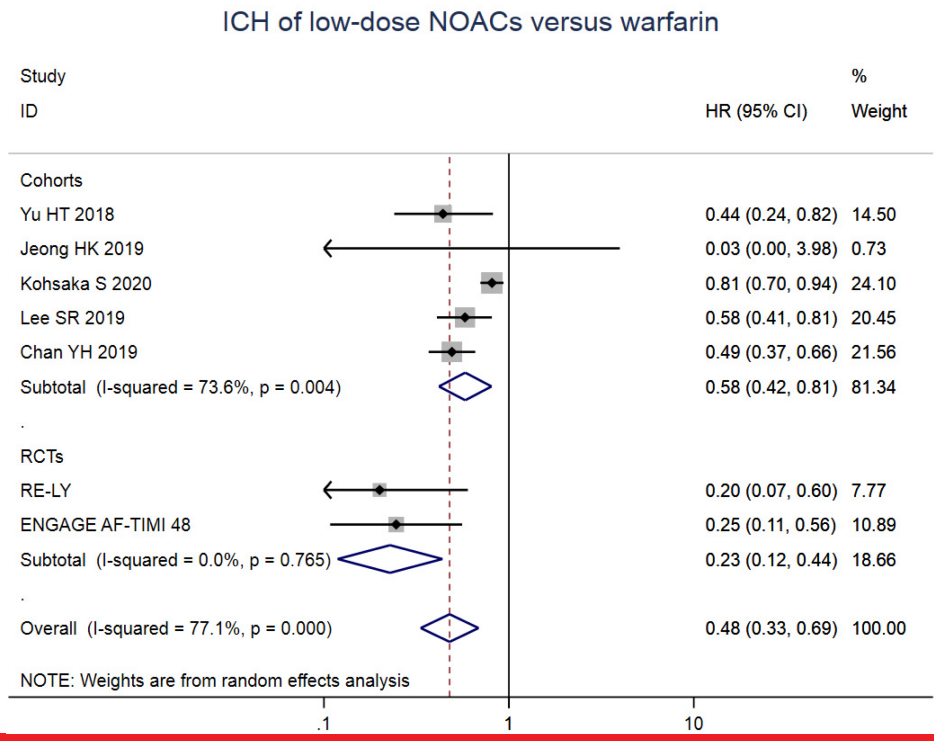

Figure S9. Pooled ICH of low-dose NOACs versus warfarin. HR, hazard ratio; ICH, intracranial hemorrhage; RCTs, randomized controlled trials.

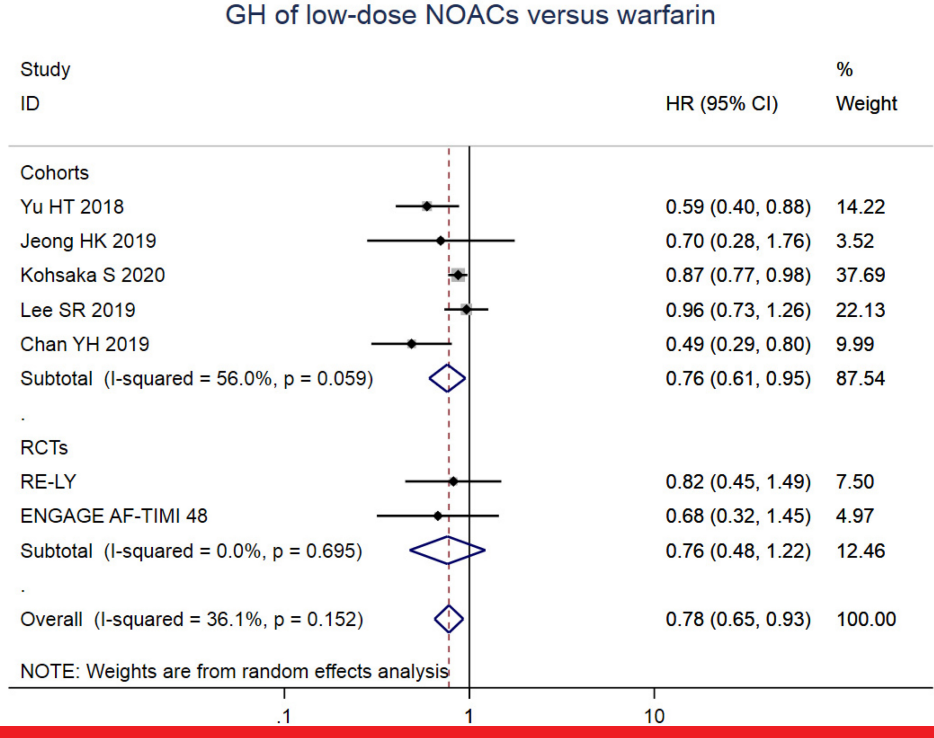

Figure S10. Pooled GH of low-dose NOACs versus warfarin. HR, hazard ratio; GH, gastrointestinal hemorrhage; RCTs, randomized controlled trials.

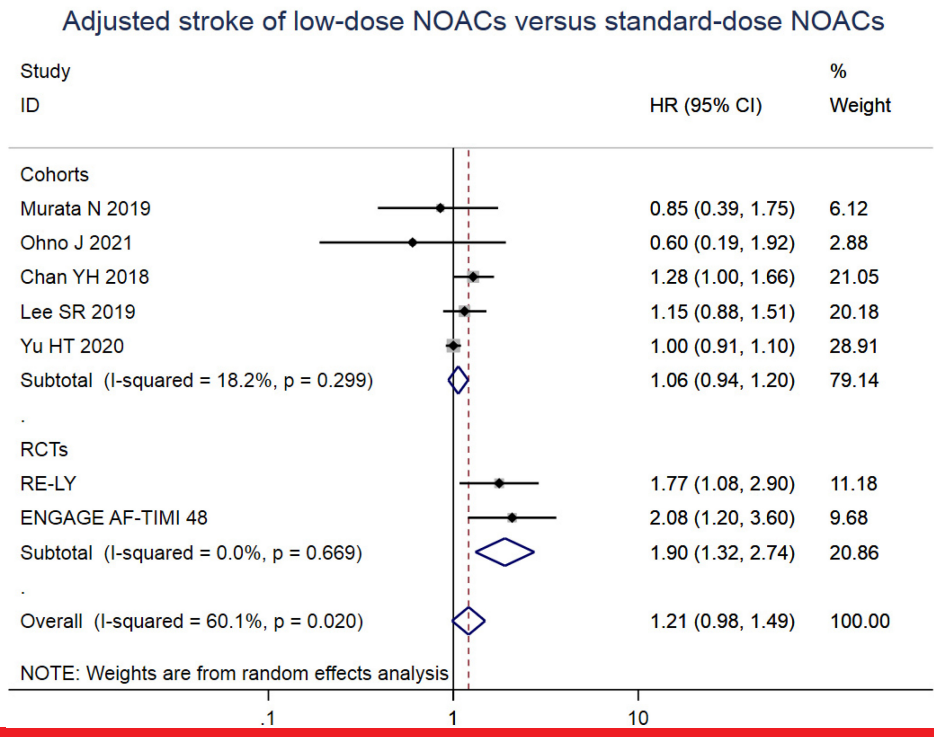

Figure S11. Pooled adjusted stroke of low-dose NOACs versus standard-dose NOACs. HR, hazard ratio; RCTs, randomized controlled trials.

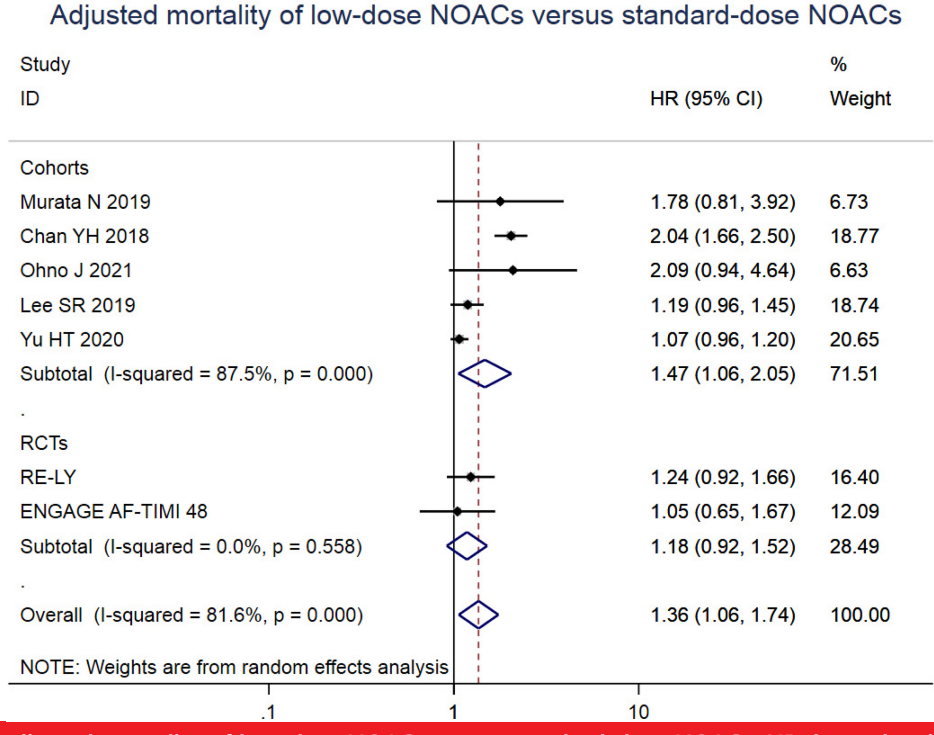

Figure S12. Pooled adjusted mortality of low-dose NOACs versus standard-dose NOACs. HR, hazard ratio; RCTs, randomized controlled trials.

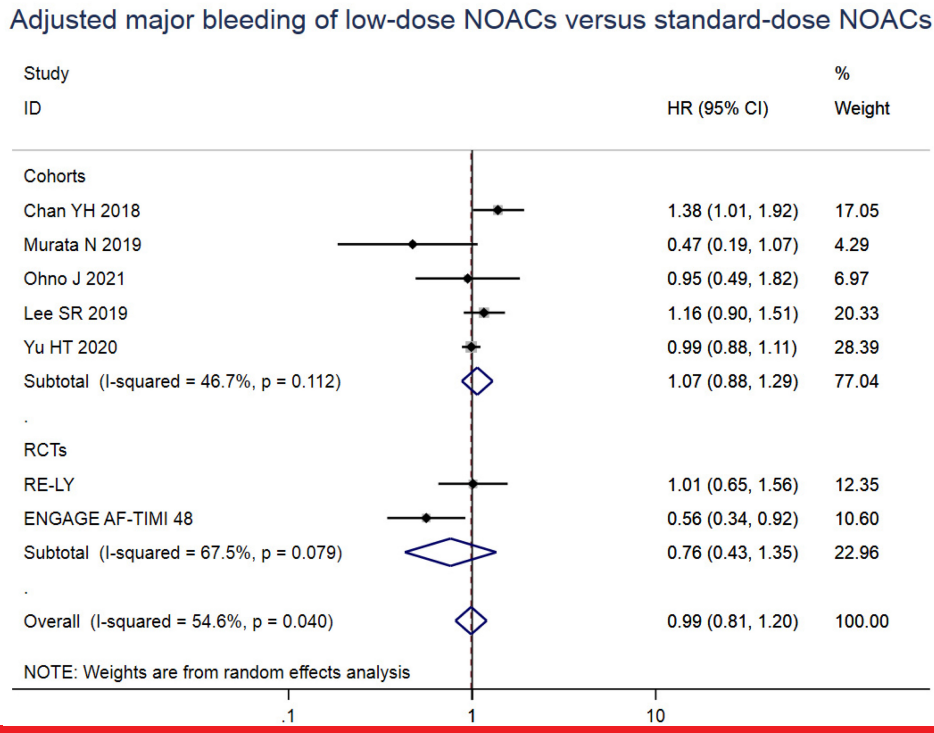

Figure S13. Pooled adjusted major bleeding of low-dose NOACs versus standard-dose NOACs. HR, hazard ratio; RCTs, randomized controlled trials.

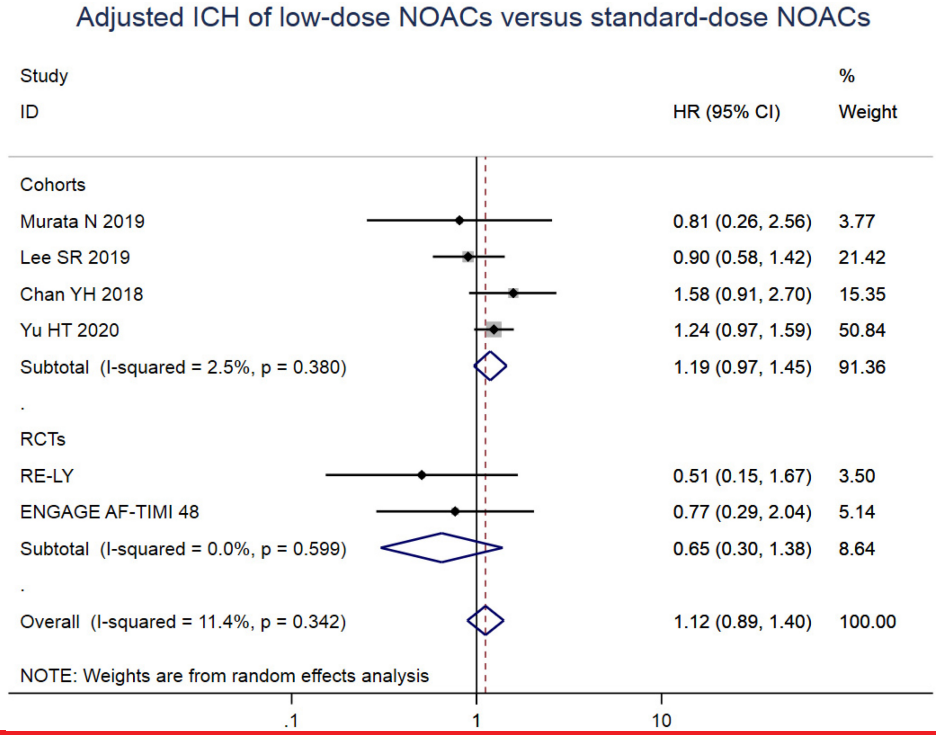

Figure S14. Pooled adjusted ICH of low-dose NOACs versus standard-dose NOACs. HR, hazard ratio; ICH, intracranial hemorrhage; RCTs, randomized controlled trials.

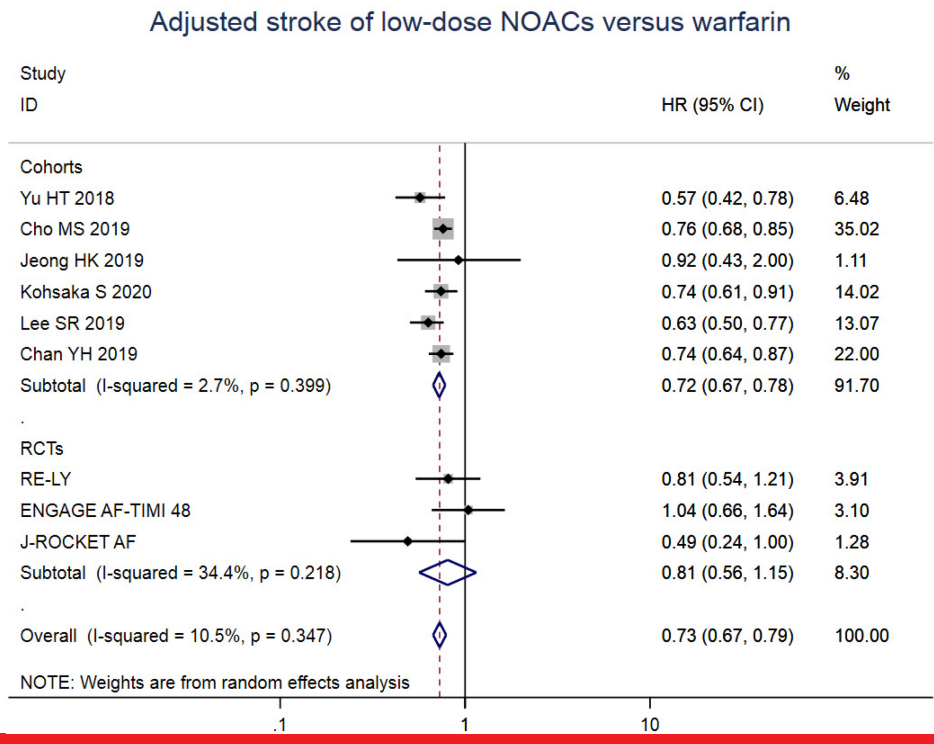

Figure S15. Pooled adjusted stroke of low-dose NOACs versus warfarin. HR, hazard ratio; RCTs, randomized controlled trials.

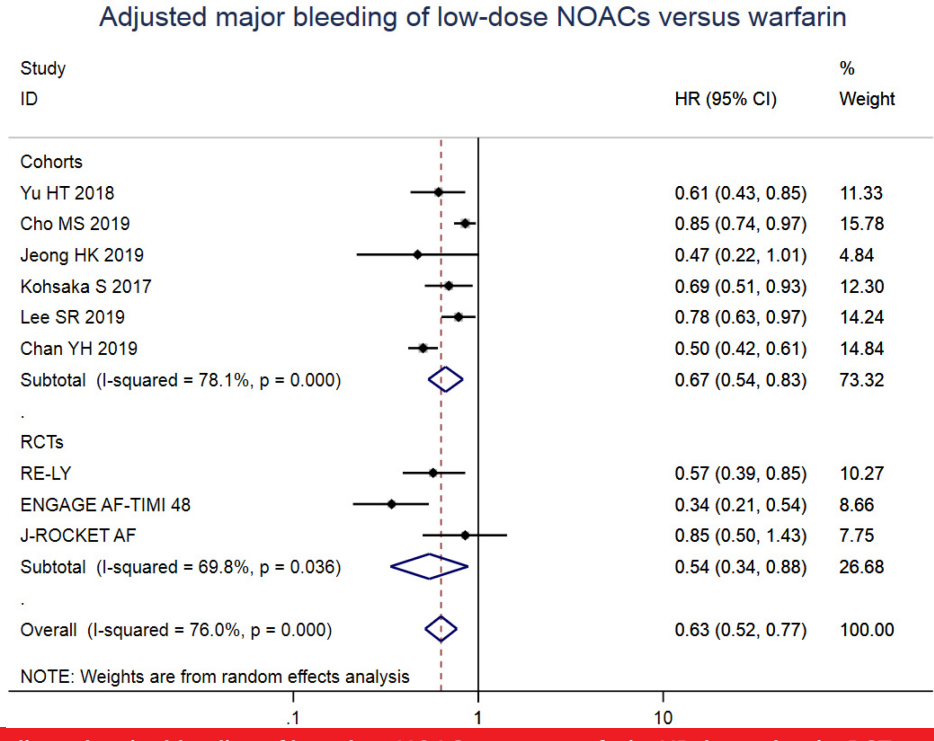

Figure S16. Pooled adjusted major bleeding of low-dose NOACs versus warfarin. HR, hazard ratio; RCTs, randomized controlled trials.

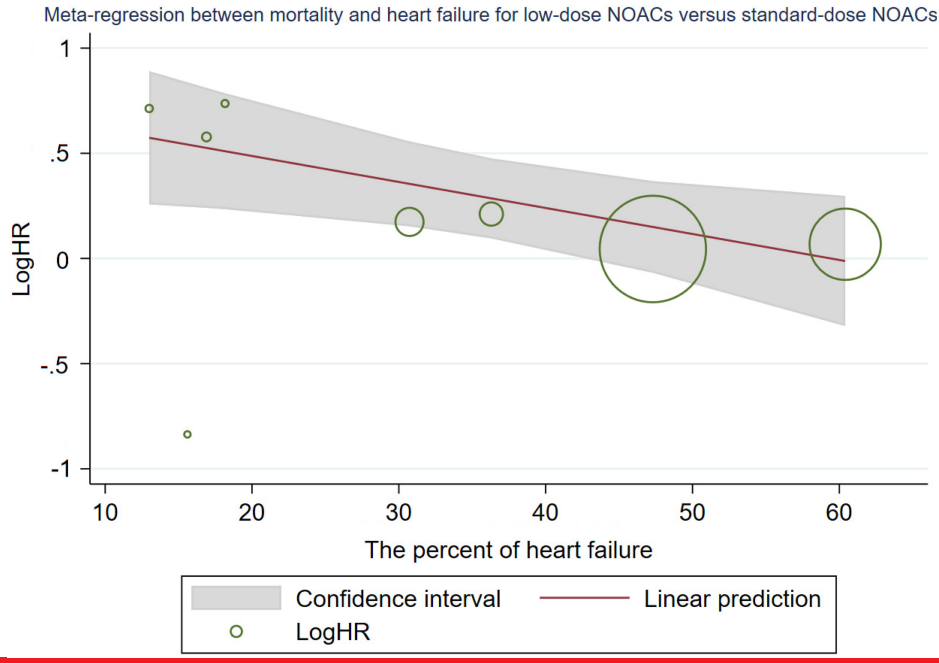

Figure S17. Result of meta-regression between mortality and heart failure for low-dose NOACs versus standard-dose NOACs. HR, hazard ratio.

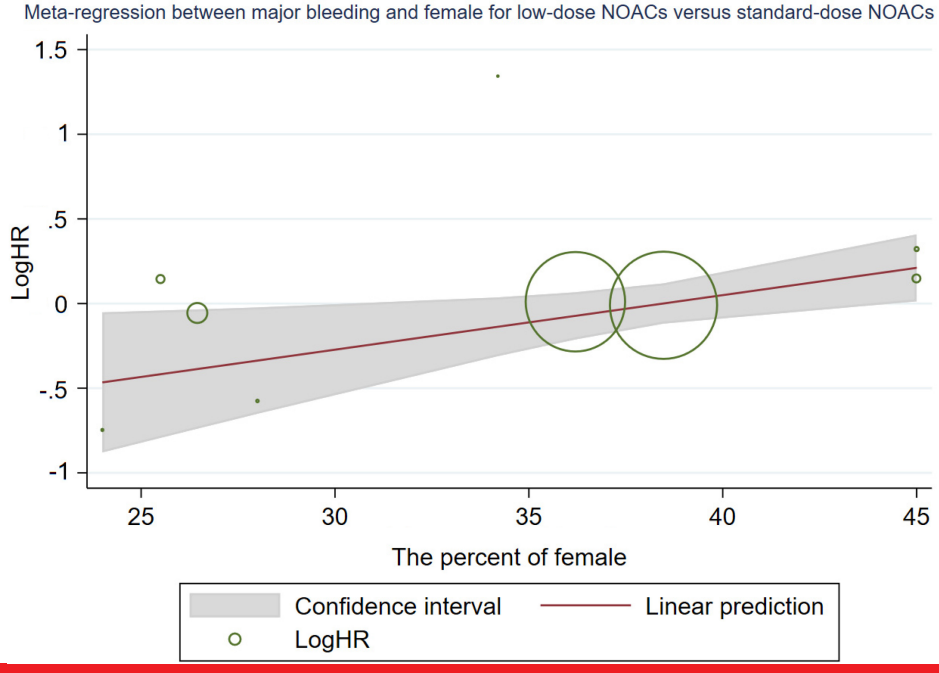

Figure S18. Result of meta-regression between major bleeding and female for low-dose NOACs versus standard-dose NOA. HR, hazard ratio.

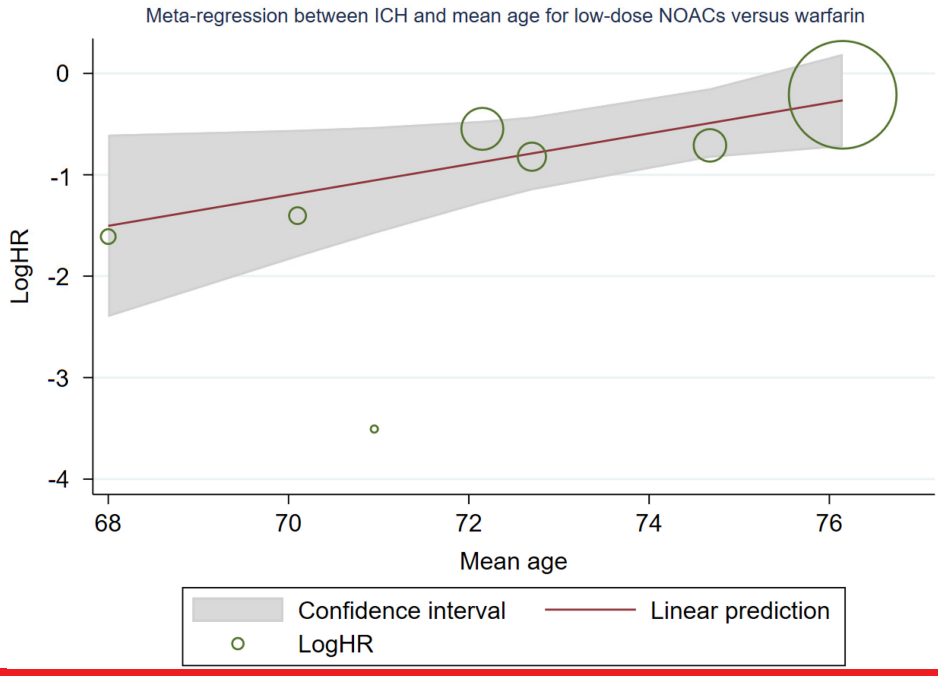

Figure S19. Result of meta-regression between ICH and mean age for low-dose NOACs versus warfarin. HR, hazard ratio; RCTs, randomized controlled trials.

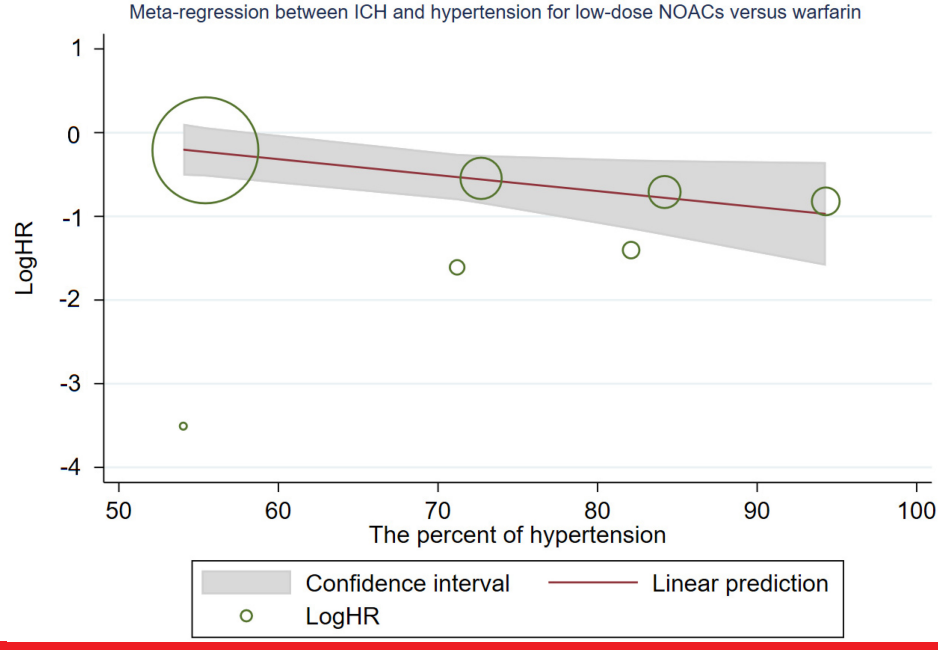

Figure S20. Result of meta-regression between ICH and hypertension for low-dose NOACs versus warfarin. HR, hazard ratio; RCTs, randomized controlled trials.

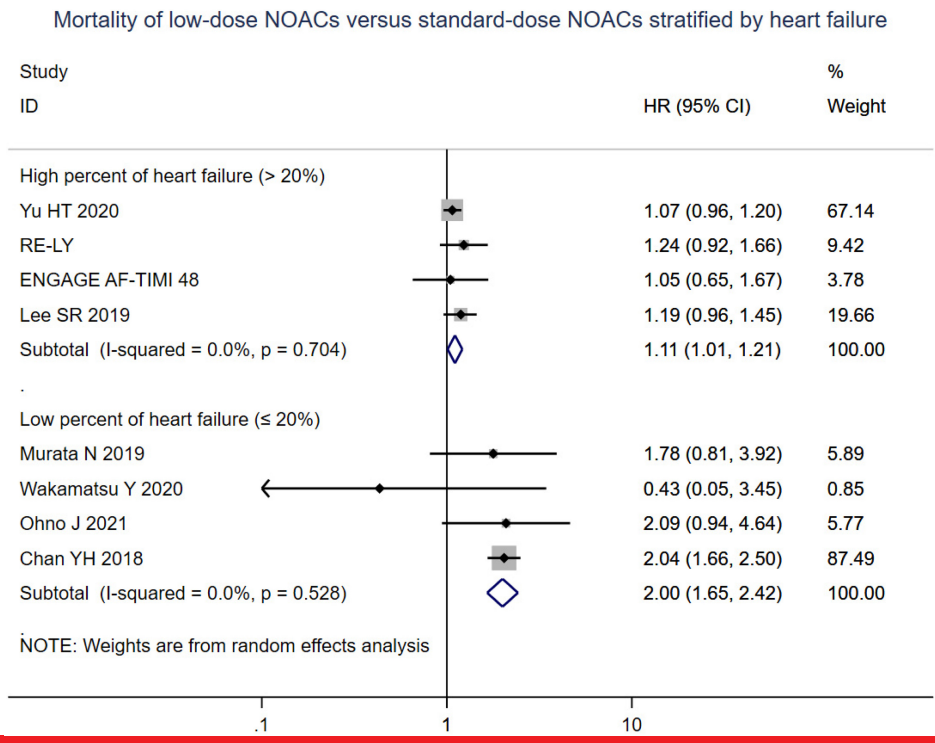

Figure S21. Pooled mortality of low-dose NOACs versus standard-dose NOACs stratified by heart failure. HR, hazard ratio.

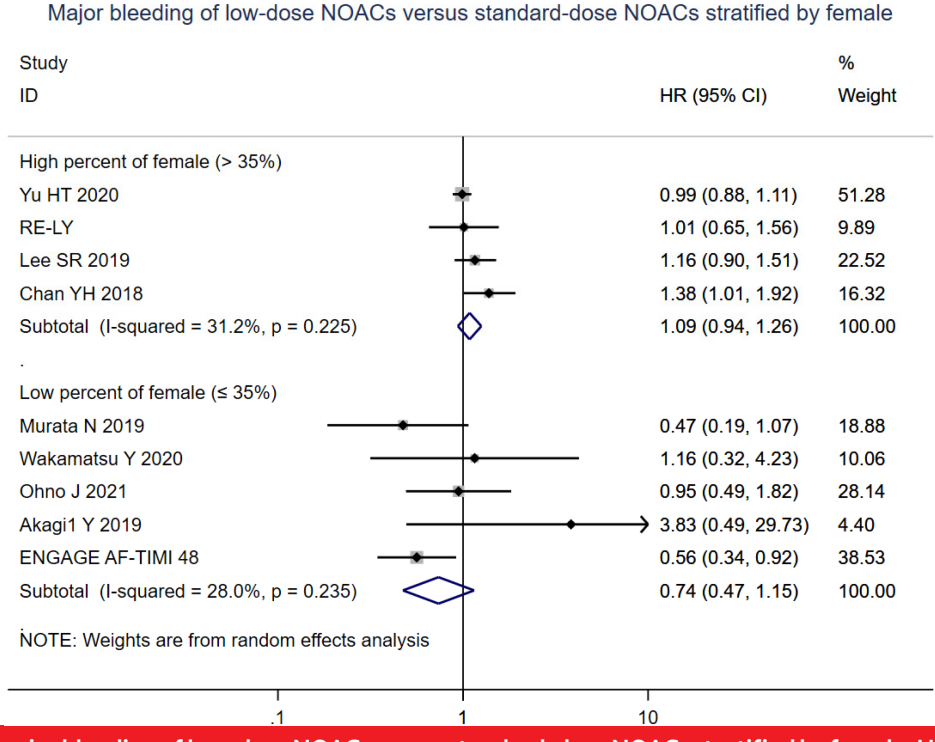

Figure S22. Pooled major bleeding of low-dose NOACs versus standard-dose NOACs stratified by female. HR, hazard ratio.

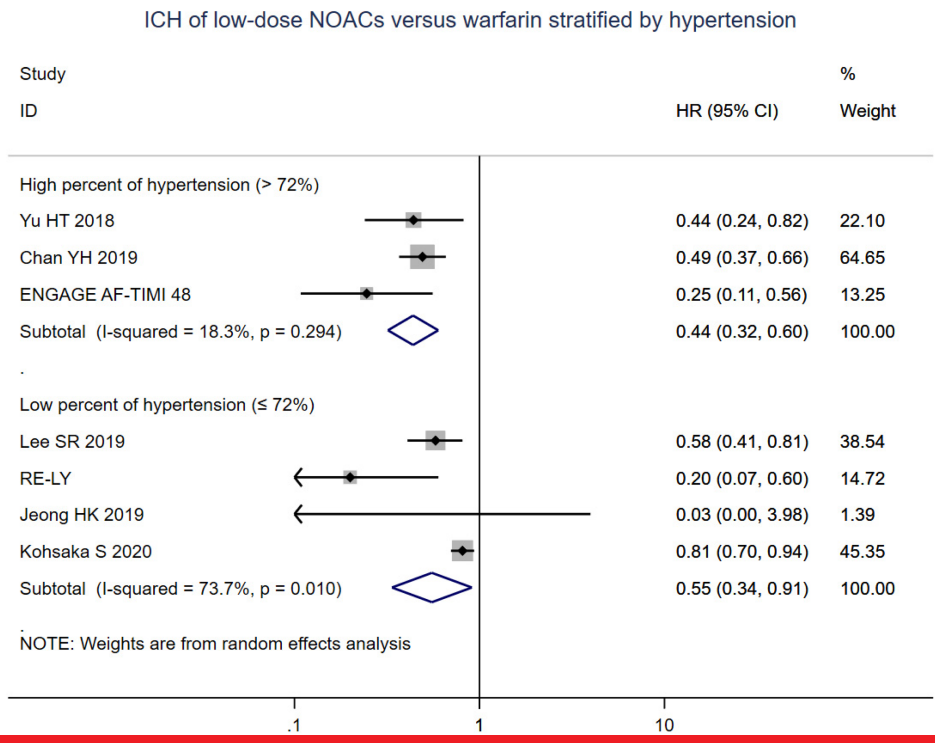

Figure S23. Pooled ICH of low-dose NOACs versus warfarin stratified by hypertension. ICH, intracranial hemorrhage; HR, hazard ratio.

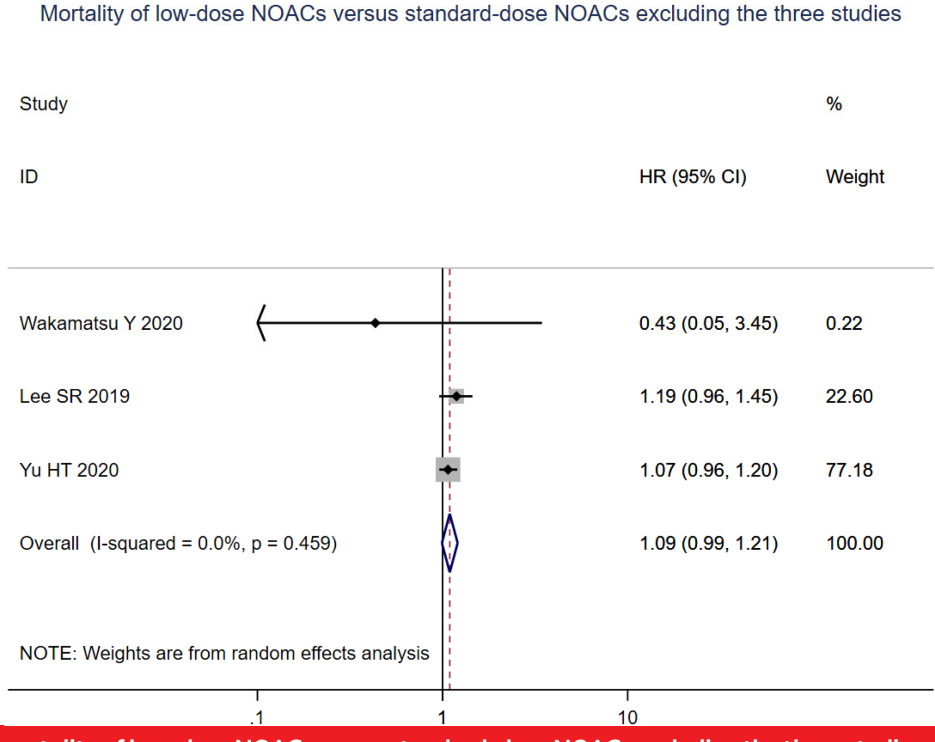

Figure S24. Pooled mortality of low-dose NOACs versus standard-dose NOACs excluding the three studies. HR, hazard ratio.