Low-Dose NOACs Versus Standard-Dose NOACs or Warfarin on Efficacy and Safety in Asian Patients with NVAF: A 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 371574 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

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. 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. 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, Taiwan, and Korea, 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. Real-world cohort studies, which enroll patients with broad-spectrum baseline characteristics, may provide a more comprehensive picture of the clinical practice. 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. 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. 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 tool19 and cohort studies with the Newcastle-Ottawa quality assessment scale.20 The publication bias was quantitatively assessed by the Begg’s21 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 whenever 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...
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.](image-url)
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/m²) | CHA2DS2-VASc | HAS-BLED | CrCl (mL/min) |
|----------------------|-----------------|------------|-----------------|------------------|-------------|-------------|-------------|-------------------|-------------|--------------|----------|---------------|
| Murata N, 2019⁵       | 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 |
|                      |                 |            |                 | Standard dose    | 749         | 63.3 ± 9.4  | 23.0        | 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, 2021⁶         | 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, 2018²⁵        | Taiwan          | Cohort     | PSM             | Low dose         | 26000       | 78.0 ± 10.0 | 48.0        | NR                | NR          | 4.02 ± 1.29  | 2.98 ± 0.92 | NR            |
|                      |                 |            |                 | Warfarin         | 16000       | 78.0 ± 10.0 | 48.0        | NR                | NR          | 4.01 ± 1.28  | 2.99 ± 0.90 | NR            |
| Yu HT, 2018²⁶         | Korea           | Cohort     | PSM             | Low dose         | 3016        | 72.8 ± 9.1  | 48.0        | 5.0³              | NR          | 4.90 ± 1.80  | NR        | NR            |
| Chan YH, 2018²⁷       | Taiwan          | Cohort     | PSM             | Standard dose²⁶  | 6307        | 76.0 ± 10.0 | 45.0        | 35.2              | NR          | 3.89 ± 0.84  | 2.96 ± 0.61 | NR            |
|                      |                 |            |                 | Low dose         | 47392       | 76.0 ± 10.0 | 46.0        | NR                | NR          | 3.89 ± 0.88  | 2.97 ± 0.61 | NR            |
| Kwon CH, 2016²⁸       | Korea           | Cohort     | NR              | Standard dose²⁸  | 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         | 97          | 83.2 ± 3.1  | 59.3        | NR                | 23.7 ± 3.6  | 4.70 ± 1.40  | 2.40 ± 0.90 | 53.1 ± 17.4  |
| Akagi Y, 2019²⁹       | Japan           | Cohort     | NR              | Standard dose²⁹  | 187         | 70.8 ± 10.8 | 34.2        | NR                | 192 ± 1.33³ | NR          | 69.4 ± 25.3 |
|                      |                 |            |                 | Low dose         | 488         | 74.7 ± 9.5  | 38.2        | 36.0              | NR          | 4.60 ± 1.70  | NR        | NR            |
| Yu HT, 2020⁷          | Korea           | Cohort     | PSM             | Standard dose²⁷  | 32400       | 69.8 ± 9.5  | 38.2        | 36.0              | NR          | 4.60 ± 1.70  | NR        | NR            |
|                      |                 |            |                 | Low dose         | 16757       | 70.7 ± 7.9  | 39.0        | NR                | 4.50 ± 1.80 | NR          | NR        | NR            |
| Cho MS, 2019³⁰        | Korea           | Cohort     | PSM             | Low dose         | 29695       | 73.8 ± 8.8  | 49.1        | 15.0              | 24.6 ± 2.9  | 3.60 ± 1.20  | 2.50 ± 0.90 | NR            |
| Jeong HK, 2019³¹      | Korea           | Cohort     | PSM             | Low dose         | 10409       | 70.8 ± 11.0 | 46.0        | 24.4 ± 2.8        | 3.50 ± 1.20  | 2.60 ± 1.00  | 85.4      |
|                      |                 |            |                 | Warfarin         | 414         | 71.4 ± 10.5 | 36.7        | 12.0              | 3.30 ± 1.80  | 2.10 ± 1.80  | 87.0      |
| Kohsaka S, 2020³²     | Japan           | Cohort     | PSM             | Low dose         | 17481       | 76.2 ± 10.6 | 38.9        | 28.9              | NR³          | 3.80 ± 1.90  | 3.80 ± 2.10 | NR            |
|                      |                 |            |                 | Warfarin         | 19059       | 76.1 ± 11.9 | 38.8        | NR                | NR          | NR          | NR        | NR            |

(Continued)
| Author (Study), Year | Region | Study Type | Adjusted Method | Group | Sample Size | Age (Years) | Female (%) | Follow-Up (Months) | BMI (kg/m²) | CHA2DS2-VASc | HAS-BLED | CrCl (mL/min) |
|---------------------|--------|------------|----------------|------|-------------|-------------|------------|-------------------|-------------|--------------|-----------|----------------|
| Kohsaka S, 2017 | Japan | Cohort | PSM | Low dose | 6726 | 75.8 ± 10.0 | 38.9 | NR | 23.3 ± 4.5 | 3.30 ± 1.60 | NR | NR |
| Lai CL, 2018 | Taiwan | Cohort | PSM | Low dose | 1489 | 88.4 ± 2.9 | 48.6 | 6.6 | NR | 3.80 ± 1.30 | NR | NR |
| Lee SR, 2019 | 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 |
| Chan YH, 2019 | 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 |
| RE-LY, 2013 | Asia | RCT | PSM | Standard dose | 933 | 68.0 ± 9.8 | 36.2 | 24.0 | NR | 2.20 ± 1.10 | NR | 65.3 ± 22.1 |
| J-ROCKET AF, 2012 | Japan | RCT | Low dose | 639 | 71.0 | 171 | 30.0 | NR | 3.27 | NR | NR |
| ENGAGE AF-TIMI 48, 2016 | Asia | RCT | Low dose | 642 | 70.1 ± 8.7 | 28.0 | NR | NR | 2.90 ± 1.00 | NR | NR |

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 values are shown as the median.
c 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 al23 (2020), Kwon et al28 (2016), and Akagi et al29 (2019) didn’t balance the confounding factors between groups, which had risks of comparability bias. Lee et al25 (2018), Akagi et al29 (2019), and Kohsaka et al33 (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, P = 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, P = 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, P = 46.2%), ICH (HR = 1.13, 95% CI 0.92 to 1.38, P = 2.9%), and GH (HR = 1.07, 95% CI 0.87 to 1.31, P = 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, P = 0%) and comparable risk of mortality (HR = 1.18, 95% CI 0.92 to 1.52, P = 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 0.67 to 0.79, P = 9.6%) and mortality (HR = 0.69, 95% CI 0.60 to 0.81, P = 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, P = 73.5%), ICH (HR = 0.48, 95% CI 0.33 to 0.69, P = 77.1%), and GH (HR = 0.78, 95% CI 0.65 to 0.93, P = 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, P = 34.4%), mortality (HR = 0.83, 95% CI 0.57 to 1.22, P = 52.6%), and GH (HR = 0.76, 95% CI 0.48 to 1.22, P = 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.

| Outcomes                | HR (95% CI)            |
|-------------------------|------------------------|
| Stroke                  | 1.18 (0.98, 1.42)      |
| Cohorts                 | 1.03 (0.95, 1.12)      |
| RCTs                    | 1.90 (1.32, 2.74)      |
| Mortality               | 1.34 (1.05, 1.71)      |
| Cohorts                 | 1.43 (1.03, 1.98)      |
| RCTs                    | 1.18 (0.92, 1.52)      |
| Major bleeding          | 1.00 (0.83, 1.21)      |
| Cohorts                 | 1.08 (0.90, 1.30)      |
| RCTs                    | 0.76 (0.43, 1.35)      |
| Intracranial haemorrhage| 1.13 (0.92, 1.38)      |
| Cohorts                 | 1.18 (0.97, 1.44)      |
| RCTs                    | 0.65 (0.30, 1.38)      |
| Gastrointestinal haemorrhage | 1.07 (0.87, 1.31) |
| Cohorts                 | 1.11 (0.86, 1.44)      |
| RCTs                    | 0.97 (0.59, 1.59)      |

NOTE: Weights are from random effects analysis

Figure 2. Meta-analysis of the efficacy and safety for low-dose NOACs versus standard-dose NOACs. HR, hazard ratio; RCTs, randomized controlled trials.
between major bleeding and female (P = 0.020) 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 = 0.032), and hypertension (P = 0.038), 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, 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. 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 GHI), 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), Ohno (2021), and Chan (2018). 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, 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 CHA2DS2-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, CHA2DS2-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 stroke45 and low or moderate risk of bleeding.46 For low-dose NOACs versus warfarin, CHA2DS2-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 stroke44 and moderate or high risk of bleeding45 as well. As a result, we could further demonstrate that: (1) for the patients under the high risk of stroke with approximate CHA2DS2-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 CHA2DS2-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.44 Major bleeding can seriously affect the anticoagulation treatment, such as higher risks of stroke and mortality.44 longer hospitalization,46 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 CHA2DS2-VASc and HAS-BLED scores.51,52 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 inhibitors53 while dabigatran is the thrombin inhibitor,52 which was consistent with other meta-analyses and proved feasible and reliable.44-53,54 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.
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 underease 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 underease: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 underease OR underdosed OR 'reduced dose' OR 'reduced dose' |  |
| 4. 1 and 2 and 3 |  |
| Author (Study), Year | Group       | 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 | 87.0         | 41.0     | 13.0          | NR               | 23.0       | 2.0           |
|                      | Low-dose    | 87.0         | 40.0     | 13.0          |                 | 23.0       | 2.0           |
| Chang HK, 2016       | Standard-dose | 72.3         | 25.7     | 18.2          | NR               | 45.9       | NR            |
|                      | Low-dose    | 75.2         | 49.5     | 20.0          |                 | 37.9       |               |
| Akagi Y, 2019        | Standard-dose | 60.1         | 19.7     | 19.0          | NR               | 26.2       | NR            |
|                      | Low-dose    | 58.0         | 17.8     | 19.0          |                 | 26.2       | NR            |
| Yu HT, 2020          | Standard-dose | 94.5         | 31.4     | 60.4          | 279              | 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          |                 | NR         |               |
|                      | Warfarin    | 72.3         | 22.3     | 32.4          |                 | NR         |               |
| 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 | 71.2         | 25.1     | 36.3          | NR               | 24.2       | NR            |
|                      | Low-dose    | 79.5         | 39.0     | 41.3          | NR               | 63.8       | NR            |
|                      | Warfarin    | 79.5         | 37.1     | 40.2          |                 | 63.4       |               |
| 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 | 82.1         | 35.0     | 47.3          | NR               | 42.4       | NR            |
|                      | Low-dose    | 82.1         | 35.0     | 47.3          |                 | 42.4       |               |

NR, not reported; TIA, transient ischemic attack.

*Means characteristics are the composite of low-dose and standard-dose groups.
| Author (Study), Year | Standard-Dose | Low-Dose |
|---------------------|---------------|----------|
| Murata N, 2019      | Dabigatran    | Dabigatran 110 mg (b.i.d.) |
|                     | Rivaroxaban   | Rivaroxaban 10 mg (q.d.) |
|                     | Apixaban      | Apixaban 2.5 mg (b.i.d.) |
|                     | Edoxaban      | Edoxaban 30 mg (q.d.) |
| Wakamatsu Y, 2020   | Dabigatran    | Dabigatran 110 mg (b.i.d.) |
|                     | Rivaroxaban   | Rivaroxaban 10 mg (q.d.) |
|                     | Apixaban      | Apixaban 2.5 mg (b.i.d.) |
|                     | Edoxaban      | Edoxaban 30 mg (q.d.) |
| Ohno J, 2021        | Dabigatran    | Dabigatran 110 mg (b.i.d.) |
|                     | Rivaroxaban   | Rivaroxaban 10 mg (q.d.) |
|                     | Apixaban      | Apixaban 2.5 mg (b.i.d.) |
|                     | Edoxaban      | Edoxaban 30 mg (q.d.) |
| Akagi Y, 2019       | Dabigatran    | Dabigatran 110 mg (b.i.d.) |
| Yu HT 2020          | Dabigatran    | Dabigatran 110 mg (b.i.d.) |
|                     | Rivaroxaban   | Rivaroxaban 10/15 mg (q.d.) |
|                     | Apixaban      | Apixaban 2.5 mg (b.i.d.) |
|                     | Edoxaban      | Edoxaban 30 mg (q.d.) |
| Chan YH, 2018       | Dabigatran    | Dabigatran 110 mg (b.i.d.) |
|                     | Rivaroxaban   | Rivaroxaban 10/15 mg (q.d.) |
|                     | Apixaban      | Apixaban 2.5 mg (b.i.d.) |
| Chang HK, 2016      | Dabigatran    | Dabigatran 110 mg (b.i.d.) |
|                     | Rivaroxaban   | Rivaroxaban 15 mg (q.d.) |
| Lee SR, 2019        | Rivaroxaban   | Rivaroxaban 15 mg (q.d.) |
|                     | Warfarin      | Warfarin |
| 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    | Dabigatran 110 mg (b.i.d.) |
|                     | Warfarin      | Warfarin |
| ENGAGE AF-TIMI 48, 2016 | Edoxaban  | Edoxaban 30 mg (q.d.) |
|                     | Warfarin      | Warfarin |
| J-ROCKET AF, 2012   | Warfarin      | Rivaroxaban 10/15 mg (q.d.) |
| 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

| Comparison                          | Outcomes | Stroke (Begg's Test) | Stroke (Egger's Test) | Mortality (Begg's Test) | Mortality (Egger's Test) | Major Bleeding (Begg's Test) | Major Bleeding (Egger's Test) | ICH (Begg's Test) | ICH (Egger's Test) | GH (Begg's Test) | GH (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       | .926       | .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     |
| CHA2DS2-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     |
| CHA2DS2-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.

| Study          | HR (95% CI)         | Weight |
|----------------|---------------------|--------|
| Cohorts        |                     |        |
| Murata N 2019  | 0.47 (0.19, 1.07)   | 4.05   |
| Wakamatsu Y 2020 | 1.16 (0.32, 4.23)   | 1.99   |
| Ohno J 2021    | 0.95 (0.49, 1.82)   | 6.61   |
| Lee SR 2019    | 1.16 (0.90, 1.51)   | 19.84  |
| Chan YH 2018   | 1.38 (1.01, 1.92)   | 16.52  |
| Akagi Y 2019   | 3.83 (0.49, 29.73)  | 0.83   |
| Yu HT 2020     | 0.99 (0.88, 1.11)   | 28.20  |
| Subtotal       | 1.08 (0.90, 1.30)   | 78.03  |

- RCTs
  - RE-LY: 1.01 (0.65, 1.56) | 11.84
  - ENGAGE AF-TIMI 48: 0.56 (0.34, 0.92) | 10.13
  - Subtotal (I-squared = 67.5%, p = 0.079): 0.76 (0.43, 1.35) | 21.97

- Overall (I-squared = 46.2%, p = 0.062): 1.00 (0.83, 1.21) | 100.00

**NOTE:** Weights are from random effects analysis.

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

| Study          | HR (95% CI)         | Weight |
|----------------|---------------------|--------|
| Cohorts        |                     |        |
| Murata N 2019  | 0.81 (0.26, 2.56)   | 3.06   |
| Wakamatsu Y 2020 | 0.38 (0.02, 7.11)   | 0.48   |
| Lee SR 2019    | 0.90 (0.58, 1.42)   | 19.36  |
| Chan YH 2018   | 1.58 (0.91, 2.70)   | 13.35  |
| Yu HT 2020     | 1.24 (0.97, 1.59)   | 56.72  |
| Subtotal       | 1.18 (0.97, 1.44)   | 92.96  |

- RCTs
  - RE-LY: 0.51 (0.15, 1.67) | 2.84
  - ENGAGE AF-TIMI 48: 0.77 (0.29, 2.04) | 4.20
  - Subtotal (I-squared = 0.0%, p = 0.599): 0.65 (0.30, 1.38) | 7.04

- Overall (I-squared = 2.9%, p = 0.403): 1.13 (0.92, 1.38) | 100.00

**NOTE:** Weights are from random effects analysis.
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.

| Study                | HR (95% CI)       | Weight |
|----------------------|-------------------|--------|
| High percent of heart failure (> 20%) |
| Yu HT 2020           | 1.07 (0.96, 1.20) | 67.14  |
| RE-LY                | 1.24 (0.92, 1.66) | 9.42   |
| ENGAGE AF-TIMI 48    | 1.05 (0.65, 1.67) | 3.78   |
| Lee SR 2019          | 1.19 (0.96, 1.45) | 19.66  |
| Subtotal (I-squared = 0.0%, p = 0.704) | 1.11 (1.01, 1.21) | 100.00 |
| Low percent of heart failure (≤ 20%) |
| Murata N 2019        | 1.78 (0.81, 3.92) | 5.89   |
| Wakamatsu Y 2020     | 0.43 (0.05, 3.45) | 0.85   |
| Ohno J 2021          | 2.09 (0.94, 4.64) | 5.77   |
| Chan YH 2018         | 2.04 (1.66, 2.50) | 87.49  |
| Subtotal (I-squared = 0.0%, p = 0.528) | 2.00 (1.65, 2.42) | 100.00 |

NOTE: Weights are from random effects analysis

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

| Study                | HR (95% CI)       | Weight |
|----------------------|-------------------|--------|
| High percent of female (> 35%) |
| Yu HT 2020           | 0.99 (0.88, 1.11) | 51.28  |
| RE-LY                | 1.01 (0.65, 1.56) | 9.89   |
| Lee SR 2019          | 1.16 (0.90, 1.51) | 22.52  |
| Chan YH 2018         | 1.38 (1.01, 1.92) | 16.32  |
| Subtotal (I-squared = 31.2%, p = 0.225) | 1.09 (0.94, 1.26) | 100.00 |
| Low percent of female (≤ 35%) |
| Murata N 2019        | 0.47 (0.19, 1.07) | 18.88  |
| Wakamatsu Y 2020     | 1.16 (0.32, 4.23) | 10.06  |
| Ohno J 2021          | 0.95 (0.49, 1.82) | 28.14  |
| Akagi Y 2019         | 3.83 (0.49, 29.73)| 4.40   |
| ENGAGE AF-TIMI 48    | 0.56 (0.34, 0.92) | 38.53  |
| Subtotal (I-squared = 28.0%, p = 0.235) | 0.74 (0.47, 1.15) | 100.00 |

NOTE: Weights are from random effects analysis
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.