Meta-Analysis Evaluating the Efficacy and Safety of Low-Intensity Warfarin for Patients >65 Years of Age With Non-Valvular Atrial Fibrillation

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Nonvalvular atrial fibrillation (NVAF) is the most common arrhythmia. It is of a high disability and death rate, and seriously affects quality of life. Although New oral anticoagulants (NOACs) are recommended for anticoagulation therapy of atrial fibrillation, they are not widely used for the high cost and limited availability. Warfarin is effective and economical. The risk of thromboembolism and anticoagulant hemorrhage is higher in patients >65 years with NVAF. So, it is of great clinical significance to explore the optimal anticoagulation intensity of warfarin in patients >65 years of China, and other ethnicities. Some studies suggested that low-intensity international normalized ratio (INR) has similar antithrombotic efficacy comparing to standard-intensity INR, whereas bleeding risk was significantly reduced. But others showed conflicting results. We pooled the efficacy and safety data of low- and standard-intensity warfarin therapy for patients over 65 years with NVAF by meta-analysis, as to evaluate optimal INR intensity of warfarin therapy in patients over 65 years. We identified 18 studies providing data of 2105 patients receiving anticoagulation therapy with warfarin. On meta-analysis (odds ratio [OR] [95% confidence interval {CI}]), low-intensity INR conferred similar efficacy to standard intensity INR on all thrombosis (1.28 [0.90 to 1.81]), stroke (1.09 [0.67 to 1.77]), other thromboembolism ([peripheral and pulmonary embolism] 2.26 [0.89 to 5.79]), and all cause death (1.38 [0.94 to 2.02]). Low-intensity INR conferred better safety profile than standard intensity INR in major bleeding (intracranial and gastrointestinal hemorrhage) (0.32 [0.19 to 0.52]), minor bleeding (gum, nasal cavity and conjunctival hemorrhage, skin ecchymosis, hematuria, hemoptysis) (0.30 [0.20 to 0.45]), and all bleeding (0.30 [0.22 to 0.40]). In conclusion, low-intensity INR (1.5 to 2.0) of warfarin therapy is as effective as standard intensity INR (2.0 to 3.0) therapy in reducing thromboembolic risk in patients>65 years with NVAF, and has a safer profile of bleeding. **(Am J Cardiol 2021;142:74−82)**

Chronic atrial fibrillation (AF) is the most common arrhythmia. The incidence of AF in general population is 1% to 2%, and there are about 30 million to 100 million AF patients worldwide.[1] About 70% AF patients are aged over 65. AF tends to cause serious complications such as cardiac insufficiency and thromboembolism, especially stroke, which seriously affects patients' quality of life, significantly increases the rate of disability and death. Nonvalvular atrial fibrillation (NVAF) increases year-by-year, it accounted for 65.2% of AF.[2] The use of warfarin anticoagulant therapy to prevent thromboembolism in patients with chronic AF has become a regular method and been widely accepted. The risk of thromboembolism and anticoagulant hemorrhage is higher in patients >65 years with NVAF. It is of great practical significance for figuring out the optimal international normalized ratio (INR) intensity of warfarin to preserve its adequate anticoagulating effect and limit its adverse effects in patients >65 years. However, it is still controversial that INR should be set at standard intensity 2.0 to 3.0 or low intensity 1.5 to 2.0 in patients >65 years with NVAF. In order to summarize the existing evidences and draw credible conclusions, we conducted a meta-analysis on the available trials to reevaluate the optimal INR target of warfarin in anticoagulation therapy in patients >65 years with NVAF.

Methods

All studies reporting anticoagulation therapy of NVAF in patients >65 years published before May 2020 were identified by the comprehensive computer-based search of

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PubMed, Cochrane, EmBase, Web of Science, Chinese BioMedical, Global Health, and BIOSIS Previews databases. The following terms were used for search: Atrial fibrillation, nonvalvular, warfarin, anticoagulation. Hand searches for related articles were also performed. All the searches were conducted without language restriction. Reference lists of the retrieved articles were also reviewed to ensure to no eligible study missed.

Studies with an INR (1.5 to 2.0, low-intensity anticoagulation) and (2.0 to 3.0, standard-intensity anticoagulation) were included. Exclusion criteria were as follows: (1) There was no relevant data of thromboembolism or bleeding between groups; (2) the target INR beyond 1.5 to 3.0; (3) the age was under 65; (4) rheumatic valvular disease or mechanical heart valve implantation; and (5) combination treatment with aspirin or other antiplatelet agents.

Xiaoqu Cheng and Jian Kuang collected the studies. Fengguang Kang and Yougang Ma extracted data independently and performed the main analyses. Weiyi Mai corrected the collected data. All the data were extracted using a standardized data-collection form. Information was recorded as follows: Last name of the first author, year of publication, geographical location, study design, INR target range, embolism, bleeding, all-cause mortality, duration of the follow-up period, and number of participants. The quality of enrolled studies was assessed by Peijian Liu and Zhuocheng Mai, and the following elements were considered: Study design, characteristics of the studied population, assessment of outcome, duration of follow-up, and statistical control for potential confounding factors. Any disagreement was resolved by a discussion. All the data were extracted from published results. There was no TTR related data in the included literature. Fengguang Kang, Yougang Ma, and Weiyi Mai completed the manuscript.

Meta-analysis was performed as our previous report.[3] In brief, heterogeneity of effect size across studies was quantified by the I^2-statistic and tested by a Cochrane Q-test with a significance level of $p < 0.1$, rather than 0.05.[4] Pooled effect size was estimated by Mantel-Haenszel fixed-effects model if no significant heterogeneity existed. Otherwise, the DerSimonian-Laird random-effects model was adopted. Potential publication bias was assessed by Egger's test and Begg's funnel plot was produced.[5]

To further investigate the effects and the safety of warfarin anticoagulant therapy in patients >65 years with NVAF, subgroup analyses according to ages and geographical locations were performed. The results were expressed in odd ratios (OR) and corresponding 95% confidence interval [CI] for thrombosis events and each separated outcome in forest plot figures. The comparison was made to estimate the efficacy and safety of low-intensity INR versus standard-intensity INR as well as the data was combined to estimate the pooled OR with 95% CIs.

A sensitivity analysis, which investigated the influence of a single study on the overall risk estimated by omitting one study in each turn, was used to test the stability of the pooled results. The study was performed in accordance with the PRISMA statement.[6] All analyses were performed by using STATA version 12.0 and graph of quality assessment was produced by Revman 5.3.

Results

With separated search strategy in each database, a total of 1,029 articles that potentially pertinent were retrieved. By reviewing titles and abstracts, irrelevant studies, case reports, and reviews were excluded. Finally, 72 studies were identified for further considerations. Of these, 54 studies were further excluded mainly due to the age of patients included was less than 65 years old (53 studies), or INR ranged 1.6 to 2.5 (one study). Therefore, 18 studies including 2,105 patients (1,058 in low-intensity INR and 1,047 in standard intensity INR) met the inclusion criteria, which were used in the later analysis.[7–24] The flow diagram of searching and screening publications were listed in Figure 1.

Characteristics of the included studies were presented in Table 1. Overall, enrolled trials were published from 2006 to 2020, including Chinese and Italy studies (only China and Italy met the inclusion criteria mentioned above), and ranging from 48 to 267 in sample size. One study was retrospective in design and the rest were prospective ones (Table 1).

All the included studies were low in attrition bias, whereas most studies were with low in detection and reporting bias, and more than a half of the studies were with low to unclear bias in selection, performance, and other bias (Figure 2).

Overall, the event rate of thromboembolism was 7.75% (76/981) and 6.19% (60/969) in populations of low and standard INR of warfarin respectively. Pooled analysis including all the studies was firstly performed and results from fixed-effects model showing a roughly equivalent effect on reducing rates of thromboembolism in low intensity and standard intensity anticoagulation with warfarin (OR = 1.28, 95% CI: 0.90 to 1.81, Figure 3). No heterogeneity was observed among studies (I^2= 0% and Q-test p = 0.62). This result showed that the initial analysis supports the opinion that low- and standard-intensity

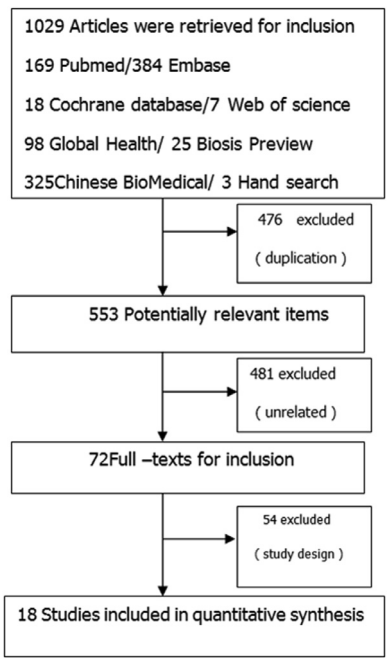

Figure 1. PRISMA flow diagram. PRISMA indicates preferred reporting items for systematic reviews and meta-analyses.

Table 1.
Characteristics of the included studies

Study	Location	Study design	INR range	Follow-up period (years)	Samle size	Thrombosis treatment/control	Minor bleeding treatment/control	Major bleeding treatment/control	All-cause death treatment/control
He et al., 2006[7]	China	prospective	1.5-2.0/2.1-3.0	3.1	99	2/1	1/7	0/0	0/0
Wang et al., 2008[8]	China	prospective	1.5-2.0/2.0-3.0	2.6	60	1/0	unclear	unclear	0/0
Zheng et al., 2008[9]	China	Prospective	1.5-2.0/2.1-3.0	2.0	48	0/0	0/0	0/2	unclear
Huang et al., 2010[10]	China	retrospective	1.5-2.0/2.0-3.0	3.0	160	15/6	3/7	0/1	10/5
Pengo et al., 2010[11]	Italy	prospective	1.5-2.0/2.0-3.0	5.1	267	11/14	0/0	13/21	78/70
Tang et al., 2011[12]	China	prospective	1.6-2.0/2.0-3.0	1.0	180	4/3	5 /12	0/6	2/2
Wu et al., 2012[13]	China	prospective	1.5-2.0/2.1-3.0	2.0	161	5/4	0/0	2/10	3/4
Huang et al., 2012[14]	China	prospective	1.6-2.0/2.0-3.0	1.5	107	0/0	0/4	0/4	unclear
Pu et al., 2015[15]	China	prospective	1.5-2.0/2.0-3.0	1.0	192	5/4	6/13	0/4	3/3
Qin et al., 2015[16]	China	prospective	1.5-2.1/2.2-3.0	2.0	120	2/1	5/12	1/4	unclear
Wang et al., 2015[17]	China	prospective	1.6-2.0/2.0-3.0	unclear	84	3/2	2/7	0/0	unclear
Yuan et al., 2016[18]	China	prospective	1.5-2.0/2.0-3.0	1.0	120	2/1	1/8	1/2	unclear
Wu et al., 2016[19]	China	prospective	1.6-2.0/2.1-3.0	2.0	56	5/3	6/13	0/2	unclear
Guan et al., 2017[20]	China	prospective	1.6-2.0/2.0-3.0	1.0	123	3/3	4/10	1/4	unclear
Huang et al., 2017[21]	China	prospective	1.5-2.0/2.0-3.0	2.0	120	4/5	2/8	1/3	unclear
Sun et al., 2017[22]	China	prospective	1.5-2.0/2.0-3.0	1.0	88	10/3	unclear	unclear	4/0
Ye et al., 2019[23]	China	prospective	1.6-2.0/2.1-3.0	2.0	60	2/3	unclear	unclear	0/0
Meng et al., 2020[24]	China	prospective	1.5-2.0/2.1-3.0	1.0	60	1/6	unclear	unclear	unclear

anticoagulation with warfarin had similar effects on reducing thromboembolism events.

Subgroup analysis was presented in Figure 3. The subgroup analysis revealed that the stroke rate was 5.2% (36/691) and 4.82% (33/685) in populations of low-intensity and standard-intensity INR respectively. The analysis showing a roughly equivalent effect on reducing rates of stroke in low-intensity and standard-intensity anticoagulation with warfarin (OR = 1.09, 95% CI: 0.67 to 1.77, Figure 3). The event rate of other thromboembolism (including peripheral and pulmonary embolism) was 3.94% (14/355) and 1.72% (6/349) in populations of low- and standard-intensity INR. The analysis showing a roughly equivalent effect on reducing events of other thromboembolism in low- and standard-intensity anticoagulation with warfarin (OR = 2.26, 95% CI: 0.89 to 5.79, Figure 3). The event rate of all thromboembolism was similar in populations of low and standard intensity INR either in China (OR = 1.44, 95% CI: 0.97 to 2.12) or Italy (OR = 0.75, 95% CI: 0.33 to 1.71), and the total meta-OR is 1.28, 95% CI is 0.90 to 1.81. The event rate of all thromboembolism was similar in populations of low- and standard-intensity INR either in relative younger (65 to 74 years) (OR = 1.79, 95% CI: 0.83 to 3.86) or elder (above 75 years) (OR = 1.16, 95% CI: 0.78 to 1.73), and the total meta-OR is 1.28, 95% CI is 0.90 to 1.81 (Figure 6).

The all-cause mortality was 20.2% (87/522) and 16.7% (106/526) in populations of low- and standard-intensity anticoagulation with warfarin respectively. Pooled analysis including all the studies was firstly performed and results from fixed-effects model showing a roughly equivalent effect on reducing all-cause mortality with low- and standard-intensity INR of warfarin (OR =1.38, 95% CI: 0.94 to 2.02, Figure 4). Mild heterogeneity was observed among studies (I^2= 0% and Q-test p = 0.53).

The major bleeding (including gastrointestinal and intracranial hemorrhage) rate was 2.29% (19/829) and 7.27% (60/825) in populations of low and standard INR of warfarin respectively. Pooled analysis including all the studies was firstly performed and results from fixed-effects model showing a beneficial effect of low-intensity INR target, which reducing 68% major bleeding (OR = 0.32, 95% CI: 0.19 to 0.52, Figure 5). No heterogeneity was observed among studies (I2= 0% and Q-test p = 0.94).

The minor bleeding (including gum, nasal cavity and conjunctival hemorrhage, skin ecchymosis, hematuria, hemoptysis) rate was 5.11% (35/684) and 14.92% (101/677) in low and standard INR therapy respectively. Pooled analysis including all the studies was firstly performed and results from fixed-effects model showing a beneficial effect of low-intensity INR target, which reducing 70% minor bleeding (OR = 0.30, 95% CI: 0.20 to 0.45, Figure 5). No heterogeneity was observed among studies (I^2= 0% and Q-test p = 0.97).

Overall, all bleeding (including major and minor bleeding) rate was 6.14% (65/1058) and 17.9% (188/1047) in populations of low and standard INR of warfarin respectively. Pooled analysis including all the studies was firstly performed and results from fixed-effects model showing a beneficial effect of low-intensity INR target, which reducing 70% all bleeding (OR = 0.3, 95% CI: 0.22 to 0.40,

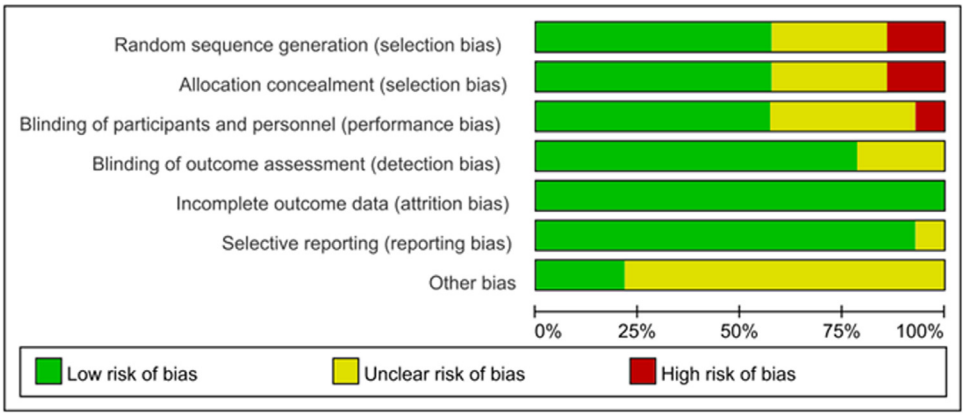

Figure 2. Quality assessments of included studies.

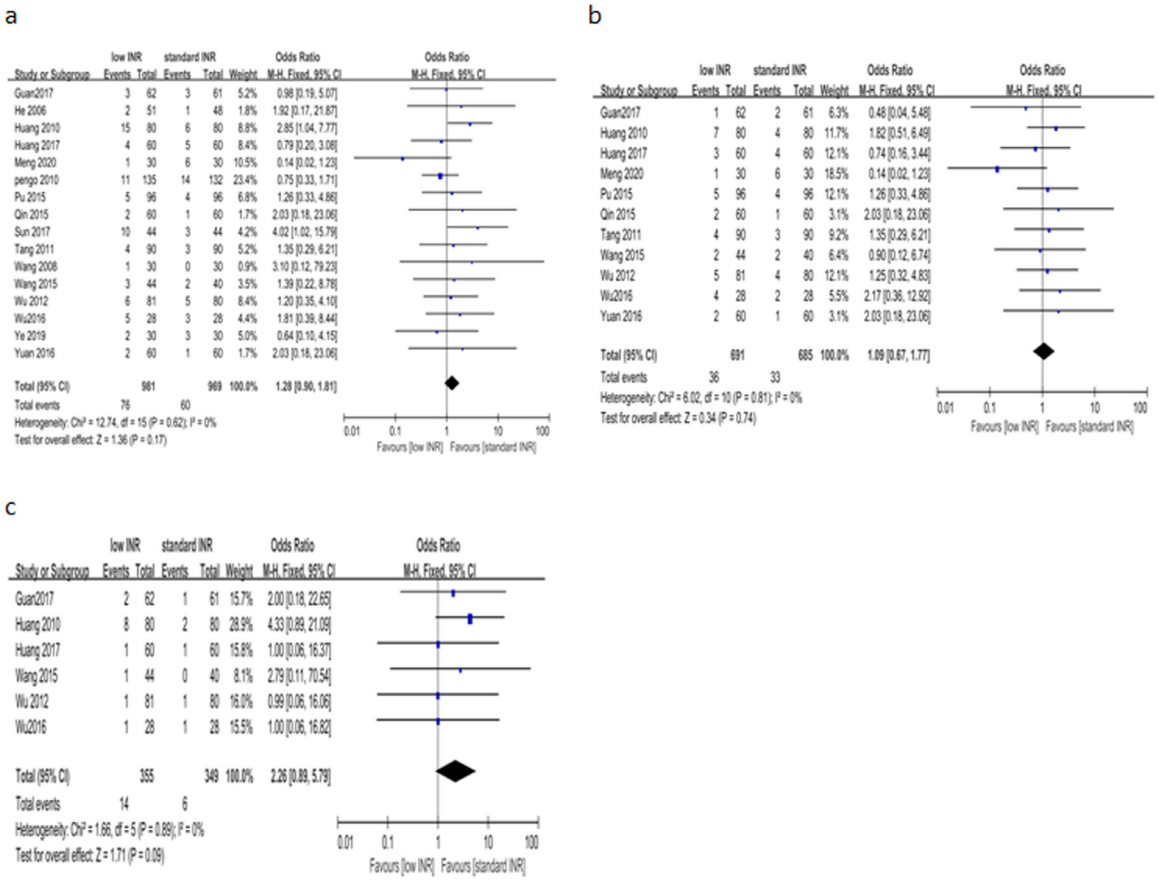

Figure 3. Meta-analysis of all the include studies on thrombosis events conferred by Warfarin anticoagulation. Estimated effect size was derived by Mantel-Haenszel fixed-effects model and heterogeneity text p-value was calculated by Cochrane Q-test. Size of the box represented weight of the study on the overall results. (a) All thrombosis; (b) stroke; (c) other thromboembolism: peripheral and pulmonary embolism.

Figure 5). No heterogeneity was observed among studies ($I^2 = 0\%$ and Q-test p = 0.48).

Subgroup analysis was presented in Figure 6, which revealed that the low-intensity warfarin reduced rate of the major bleeding either in younger (65 to 74 years) (OR = 0.22, 95% CI: 0.06 to 0.90) or elder(above 75 years) (OR = 0.34, 95% CI: 0.19 to 0.58), and the total meta-OR is 0.32, 95% CI is 0.19 to 0.52. The analysis also revealed that the low INR intensity warfarin therapy reduced minor bleeding rate either in younger (65 to 74 years) (OR = 0.3, 95% CI: 0.14 to 0.63) or elder (above 75 years) (OR = 0.3, 95% CI: 0.18 to 0.48), and the total meta-OR is 0.3, 95% CI is 0.20 to 0.45. Interestingly, all-bleeding rate in populations of low- and standard-intensity INR was not statistical difference in Italians (OR = 0.56, 95% CI: 0.27 to 1.18). In contrast, therapy of low-intensity INR of warfarin reduced

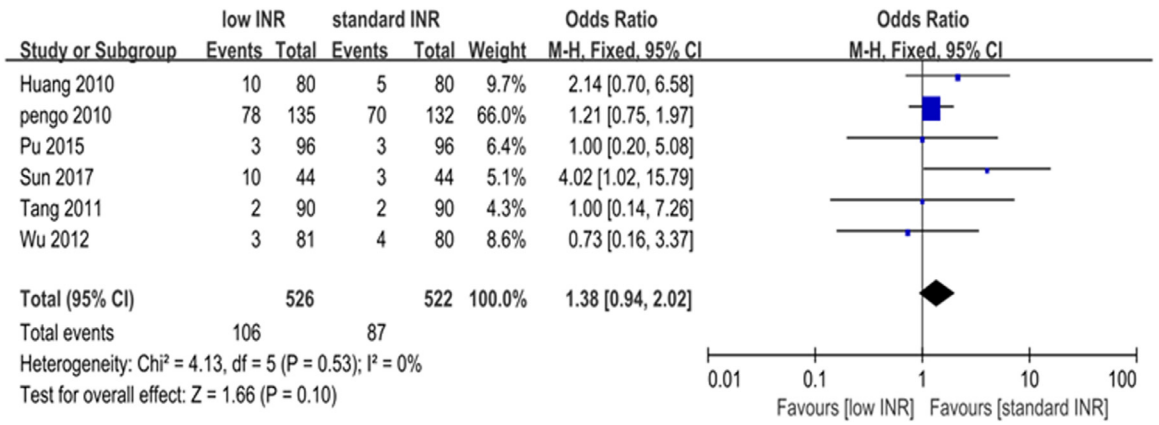

Figure 4. Meta-analysis of the included studies on all-cause mortality conferred by Warfarin anticoagulation. Methods used and meaning of symbols were the same as Figure 3.

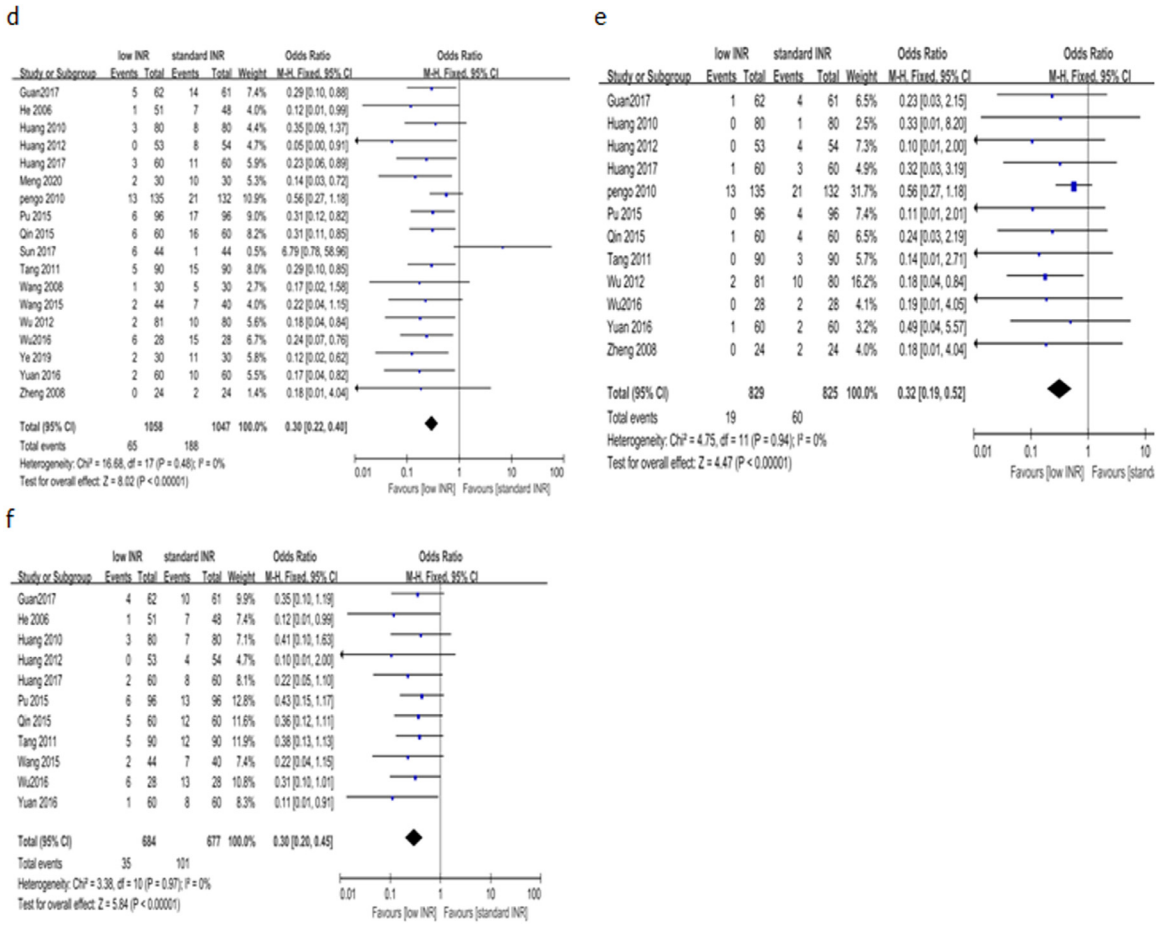

Figure 5. Meta-analysis of the included studies on bleeding events conferred by Warfarin anticoagulation. Methods used and meaning o symbols wer the same as Figure 3. (d) All bleeding events; (e) major bleeding; (f) minor bleeding.

all-bleeding rate than that of standard one in China ethnicity (OR = 0.26, 95% CI: 0.19 to 0.36), and the total meta-OR is 0.3, 95% CI is 0.22 to 0.40. The analysis indicated the elder population of east-Asian would experience more all-bleeding events than Italians under standard INR.

Furthermore, we performed sensitivity analysis to examine the intensity of the conclusion and results, we found that the beneficial effects of reducing minor and major bleeding of low-intensity INR were not influenced, which remained to be significant by omitting any of the included study; and in terms of antithrombotic effect, the low-intensity INR was equivalent to standard intensity INR, which were also not influenced, remained to be significant by omitting any of the included study. These results implied

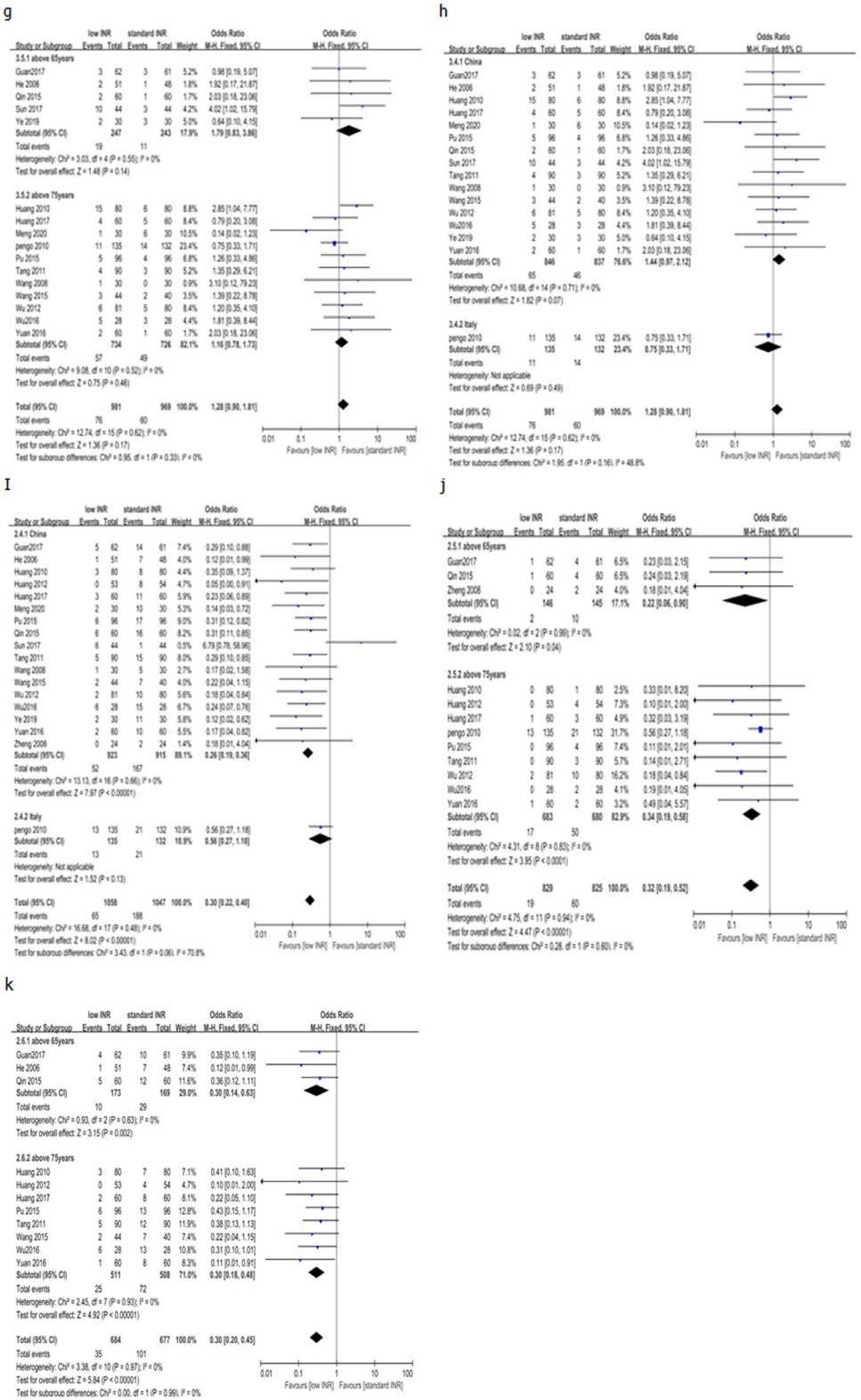

Figure 6. Subgroup analyses according to (g) thrombosis age; (h) thrombosis region; (i) bleeding region; (j) major bleeding age; (k) minor bleeding age. Methods used and meaning of symbols were the same as Figure 3.

that the effectiveness and safety of the low-intensity INR target in anticoagulation in patients >65 years with NVAF were stable and robust. Publication bias determined by Begg's test did not show a significant bias (Figure 7).

Discussion

NVAF is one of the most common arrhythmia in patients >65 years, which increasing the risk of stroke by 5 times.

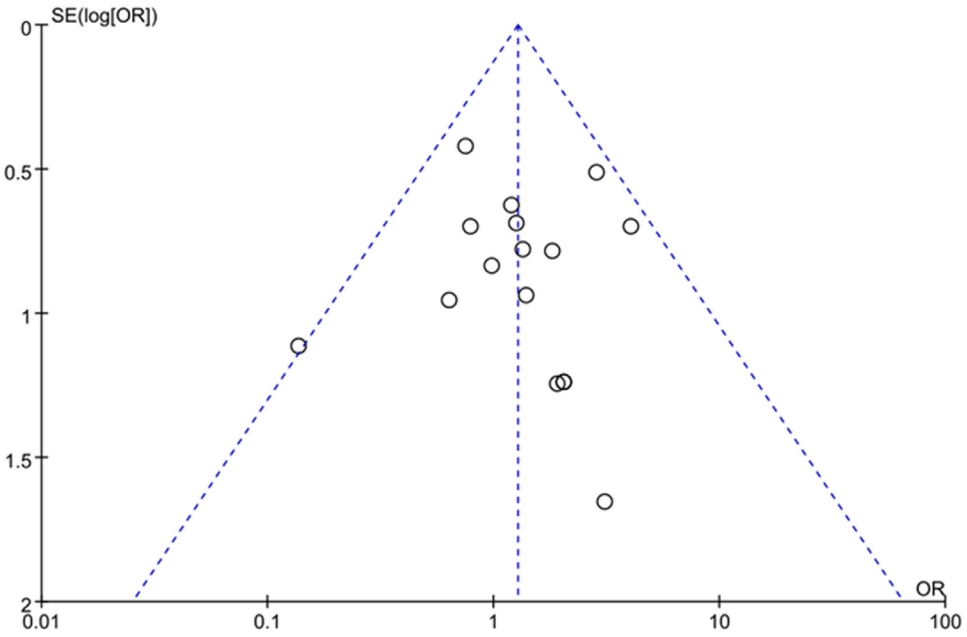

Figure 7. Publication bias of included studies. p-value was derived by Egger's test. Size of the circle indicated study weight.

Stroke not only increases the social disability burden, but also economic burden of public health and medical system.[25] It is of great significance to explore an optimal anticoagulation therapy for patients >65 years with NVAF. There have been many studies on anticoagulation therapy of AF, but patients' age was in a broad range. Studies on populations over 65 years in this field were limited. After screening, we found that only China and Italy had performed specific studies on this special population.

Although according to the AF management of ESC in 2016, and the guidelines of AHA/ACC/HRS in 2019, New oral anticoagulants (NOACs) are recommended over warfarin (I, A), except for moderate to severe mitral stenosis or mechanical heart valve implantation,[26] there are some disadvantages of NOACs: (1) NOACs are not optimal anticoagulants in patients with severe renal impairment or on dialysis, which is common in patients >65 years with NVAF; (2) There is no effective monitoring indicators by conventional means(PT, APTT, INR), only guaranteed by anti-Ⅹa or anti-Ⅱa activity; (3) Although NOACs have antidotes, which are very expensive and not available widely; (4) The high price of NOACs make them difficult to be widely used in China and some countries. In UK, warfarin costs an average of £0.83 per month/patient, whereas the average monthly cost of NOACs is >£50/patient.[27] China has a huge population, and NVAF patients are far more than UK, it will bring huge economic burden to the country if all NVAF patients taking NOACs; (5) NOACs are not completely safer than warfarin on bleeding. A meta-analysis of 4 RCTs comparing efficacy and safety of NOACs versus warfarin found that NOACs to be inferior in terms of gastrointestinal bleeding events.[28]

The application of warfarin is mainly affected by the following reasons: (1) Some doctors are worrying too much about adverse effect of warfarin - hemorrhage and bleeding, which lead to the utilization of warfarin is seriously insufficient; (2) Stable control of INR within the target range, which is the key to improve the quality of anticoagulation to reduce clinical events. TTR is one of the most commonly quality control indicators. Patients with a TTR $\geq$ 65% had significant benefit. (3) Warfarin has ethnic difference in safety profile of bleeding. The interpretation may be involved the follows: (1) The vitamin K epoxide reductase complex subunit 1 gene (VKORC1) contains haplotype A and haplotype B. The frequency of group A haplotypes (predictive of a low warfarin dose) was significantly higher in the Asian-American population (89%), whereas it is only 37% in the European-American population ($p < 0.001$), which leads to a low dose of warfarin for Asian ethnicity. The frequency of group B haplotypes (predictive of a high warfarin dose) was significantly higher in the European-American population (58%), whereas it is only 10% in the Asian-American population ($p < 0.001$), which leads to a high dose of warfarin for European ethnicity; (2) Although warfarin is mainly metabolized by P4502C9 (CYP2C9), the mutation of CYP2C9 gene can slow down the metabolism of warfarin and prolong the half-life of warfarin, and increase the blood concentration of warfarin in vivo, which leads to stronger anticoagulant effect. However, CYP2C9 gene mutation did not explain all the difference of warfarin maintenance dose among different ethnicities,[29] and anticoagulating efficacy of warfarin is interfered by other factors, such as taking plenty green vegetable or Saddling fish, antibiotics.

So far, the optimal INR intensity of Chinese population is still not clear. Some scholars believe that low-intensity INR is suitable for patients >65 years with NVAF in China. But data of effects and safety of the low-intensity INR from the reports were inconsistent. To summary available information in this field, the meta-analysis of 18 studies involving 2105 participants supported that there was no significant difference between low-intensity INR(1.5 to 2.0) and standard intensity INR(2.0 to 3.0) in effect of

preventing both stroke and other thrombosis events and lowering all cause death rate. Whereas in terms of major bleeding, compared with standard intensity INR, low-intensity INR decreased major bleeding by 68%. Similarly, therapy of low INR intensity decreased minor bleeding by 70% compared with the standard intensity INR. The event rate of all thromboembolism was similar in populations of low- and standard-intensity INR either in younger (65 to 74 years) or elder (above 75 years). Furthermore, therapy of low-intensity warfarin reduced major and minor bleeding events either in younger (65 to 74 years), or elder (above 75 years) in all participants. In summary, therapy of low INR intensity of warfarin can preserve its adequate anticoagulating effect and limit its adverse effect in patients >65 years with NVAF, especially for whom over 75 years.

In a systematic review and meta-analysis of 14 studies, low-intensity warfarin anticoagulation was associated with a lower incidence of bleeding, including fatal and severe bleeding, whereas without increasing the risk of thromboembolism.[30] A total of 3,295 patients were enrolled, including 1,403 patients with INR target range of 1.5 to 2.0 (low anticoagulant intensity group) and 1,892 patients with INR target range of 2.0 to 3.0 (standard anticoagulant intensity group). The incidence of total bleeding in low anticoagulant group was significantly lower than the standard anticoagulation intensity group (RR = 0.47, 95% CI: 0.37 to 0.59, $p < 0.01$); There was no significant difference in the incidence of thromboembolism, ischemic stroke and mortality between the 2 groups (RR = 1.35, 95% CI: 1.00 to 1.84, P = 0.05; RR = 1.44, 95% CI: 1.01 to 2.05, p = 0.05; RR = 1.06, 95% CI: 0.85 to 1.31, p = 0.60). Although the results of previous study were consistent with our study, there was no age limit for the inclusion criteria of previous study, and no subgroup analysis for patients older than 65years were specifically analyzed. Therefore, the results of previous study couldn't be applied to patients >65 years with NVAF.

Some limitations of the current study should be noted. First, TTR is the key to the efficacy and safety of warfarin in AF patients. But there is no relevant data in the included studies, which may result in an incomplete evaluating the efficacy of warfarin. Second, patients' renal function also affected safety of warfarin, but there is little relevant data in the included studies, so it is difficult to perform a more accurate analysis. Third, most of the included studies had small sample size. Fourth, some studies only mentioned the word ''random'', but did not specify randomization method or scheme, so there was possibility bias. Fifth, the collected literatures are all published articles and there may be unpublished literatures, therefore, there might be a publication bias.

In conclusion, our meta-analysis showed that low-intensity INR of warfarin conferred similar efficacy to standard intensity INR on reducing stroke, other thromboembolism and all cause death, with a better safety profile than standard INR in all bleeding(major and minor bleeding). Low INR intensity of warfarin(1.5 to 2.0) would be a preferred warfarin therapy for the patients >65 years.

Disclosure

All the authors have nothing to disclose.

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH jr, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. *Circulation* 2014;129:837–847.
2. Zhou ZQ, Hu DY, Chen J, Zhang RH, Li GB, Zhao XL. An epidemiological survey of atrial fibrillation in China. *Chin J Intern Med* 2004; 43:491–494.
3. Kang FG, Liu PJ, Liang LY, Lin YQ, Xie SL, He Y, Liang BS, Zhang HF, Chen YX, Wang JF. Effect of pocket irrigation with antimicrobial on prevention of pacemaker pocket infection: a meta-analysis. *BMC Cardiovasc Disord* 2017;17:256–264.
4. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21. 1539−1538.
5. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–634.
6. Moher D, Liberati A, Tetzlaff J, Altman DG, Group PRISMA. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010;8:336–341.
7. He RL, Cheng GC, Hong Y, Wan QL. Effect of warfarin on anticoagulation in elderly patients with atrial fibrillation. *Chin J Misdiagn* 2006; 6:3347–3348.
8. Wang R, Yan H, Yan ZQ, Wang XX. Efficacy and safety of Warfarin in aged patients with nonvalvular atrial fibrillation. *Chin Heart J* 2008; 20:193–195.
9. Zheng HJ, Li AQ, Cui HL, Jin H, Wei Y, Zhu YX. Clinical analysis of warfarin low intensity anticoagulation in the elderly patients with permanent non valvular atrial fibrillation. *Chin J Pract Med* 2008;35:32–33.
10. Huang DJ, Gao L, He GH. Observation of anticoagulant therapy with different intensity in elderly patients with chronic non-valvular atrial fibrillation. *J Pract Med* 2010;26:4186–4187.
11. Pengo V, Cucchini U, Denas G, Davidson BL, Marzot F, Jose SP, Iliceto S. Lower versus standard intensity oral anticoagulant therapy (OAT) in elderly warfarin-experienced patients with non-valvular atrial fibrillation. *Cardiovas Bio Cell Signa* 2010;103:442–449.
12. Tang OS, Cheng YH, Chen LN, Chen ZL, Zhou HL, Tao F, Qin FM. Safety and efficacy of low intensity anticoagulant therapy in patients with atrial fibrillation over 80 years old. *Chin J Geriatr* 2011;30:118–120.
13. Wu J, Wang JH, Jiang SR, Xu J, Di Q, Zhou CW, Min XY, Pang SS, Wang H, Xu D, Guo Y. The efficacy and safety of low intensity warfarin therapy in Chinese elderly atrial fibrillation patients with high CHADS2 risk score. 11.
14. Huang JZ, Li HK, Lu YG, Fu CH, Yan H, Chen XG. Comparison of antithrombotic efficacy and safety of different doses of warfarin and aspirin in elderly patients with persistent atrial fibrillation. *South Chin J Cardiov Disea* 2012;18:357–359.
15. Pu QF, Jiao DL, Li FX. Efficacy and safety of low intensity anticoagulant therapy in elderly patients with atrial fibrillation. *Clin J Med Offic* 2015;43:969–973.
16. Qin PY, Zhou Q, Xuan CX. Effect of warfarin with different intensity on the prevention of ischemic stroke in elderly patients with nonvalvular atrial fibrillation. *Chin Youji Med J* 2015;43:252–253.
17. Wang HY, Yi X, Hu FH. The efficacy and safety of antithrombotic therapy with warfarin in elderly atrial fibrillation. *Chin Med J* 2015; 50:34–35.
18. Yuan QY, Xie JD, Shi L. Clinical observation of warfarin in the treatment of 80 years and older patients with atrial fibrillation. *Intern Med* 2016;11:842–844.
19. Wu JL. Efficacy and safety of low-intensity warfarin anticoagulation in patients over 75 years old with atrial fibrillation. *Treat Obser* 2016; 10:147–148.
20. Guan XH. Clinical effect and safety analysis of low-intensity warfarin in elderly patients with atrial fibrillation. *Master Thesis Dal Med Uni* 2017;10:1–36.
21. Huang FF, Tang YX, Zhang JF, Chen L. Comparison of efficacy and safety of warfarin anticoagulant with aspirin and clopidogrel in elderly patients with atrial fibrillation. *Clin Edu Gener Pract* 2017;15:673–675.
22. Sun Y. Comparison of different intensity anticoagulant therapy in the treatment of chronic atrial fibrillation in elderly patients with non-valvular disease. *Chin J of Public Health Eng* 2017;16:832–834.
23. Ye ZF, Ye QR, Lai XW. Long-term efficacy and prognosis of warfarin anticoagulation at different intensities in elderly patients with non-valvular atrial fibrillation. *J Clin Med Pract* 2019;23:55–58.

24. Meng QS, Tian S. Low anticoagulant warfarin in the treatment of elderly non valvular atrial fibrillation. *Med J ChinPeop Health* 2020;32:34–36.
25. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P. Heart disease and stroke statistics(2017 update): a report from the American Heart Association. *Circulation* 2017;135:e146–e603.
26. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2019;S0735-1097:30209–30218.
27. Burn J, Pirmohamed M. Direct oral anticoagulants versus warfarin: is new always better than the old? *Open Heart* 2018;5:e000712.
28. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials. *Lancet* 2014;383:955–962.
29. Peng Q, Huang SJ, Yu YJ, Zhou X. Association of CYP2C9 and VKORC1 gene polymorphisms with warfarin dosage in Chinese. *Med Gui* 2015;34:775–779.
30. Wang H, Xu XG, Huang PF, Wang CL. Efficacy and safety of warfarin with different anticoagulation intensities in treatment of nonvavular atrial fibrillation: meta-analysis. *Acad J Sec Mil Med Univ* 2016; 37:256–261.