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Impact of the *CYP4F2* gene polymorphisms on the warfarin maintenance dose: A systematic review and meta-analysis

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Abstract. Warfarin is an oral anticoagulant with significant interpatient variability in dosage. A large number of studies have confirmed that the individual warfarin dose is mainly affected by the cytochrome P450 complex subunit 2C9 and vitamin K epoxide reductase complex subunit 1. However, the association between cytochrome P450 4F2 (*CYP4F2*) gene polymorphisms and warfarin dosage in the Asian population remains controversial. To investigate the impact of the *CYP4F2* polymorphism rs2108622 (p.V433M) on warfarin dose requirement, a systematic review and meta-analysis were conducted. According to the strict inclusion and exclusion criteria set, a comprehensive literature search was performed, and the studies published before August 5, 2015 were searched for in PubMed, EMBASE and the China National Knowledge Infrastructure databases. The references were checked by two independent reviewers. The association between the warfarin maintenance dose and *CYP4F2* polymorphism was analyzed. Twenty-two studies were included in the meta-analysis. Compared with the *CYP4F2* genotype CC, carriers of the CT and TT genotypes required a 9 [95% confidence interval (CI): 6.0-13.0] and 20% (95% CI, 13.0-27.0) higher warfarin dose, respectively. In the combined analysis, T carriers (CT+TT) required an 11% (95% CI, 8.0-14.0) higher warfarin dose compared to the CC genotype. In addition, there was a 10% (95% CI, 5.0-15.0) higher warfarin dose in TT carriers compared to the CT genotype (all P<0.05). The results of the meta-analysis suggest that the effects of the *CYP4F2* polymorphism on individual warfarin dose have a statistically significant difference, and the effect degree is variable in the subgroups. Further studies are expected to explore whether the pharmacogenetics model including the *CYP4F2* polymorphism can strengthen the prediction of warfarin dose.

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Introduction

Warfarin is a commonly oral anticoagulant, mainly used clinically in the treatment of thromboembolic diseases, such as atrial fibrillation (AF) and deep venous thrombosis (DVT); however, the existence of high interpatient variability in drug dosage may increase the risk of bleeding or thrombosis. Studies indicated that individual warfarin dose was influenced by a host of factors, including genetic and environmental factors. Genetic factors are one of the main reasons for the individual difference in warfarin maintenance dosage. Previous studies have also suggested that cytochrome P450 complex subunit 2C9 (*CYP2C9*) and vitamin K epoxide reductase complex subunit 1 (*VKORC1*) polymorphisms, age, weight and body surface area can explain ~50% of the influence on warfarin dose requirement (1-6). Therefore, there remains a 50% uncertainty of the other factors to be further explored.

The cytochrome P450 4F2 (*CYP4F2*) gene, consisting of 13 exons and 12 introns and encoding 520 amino acid residues, is located on chromosome 19p13.12 in humans. Studies have shown that there are numerous single-nucleotide polymorphisms (SNPs) in the *CYP4F2* gene open reading frame, such as rs2108622, rs2074901 and rs2189784. Genome-wide association studies identified that the SNP associated with warfarin dose is *CYP4F2* p.V433M (rs2108622) in exon 11 (7). VKOR is mainly encoded by *CYP4F2*, which reduces VK1 by metabolizing VK1 to hydroxy VK1. Studies have also demonstrated that carriers of the *CYP4F2* p.V433M variant allele have a reduced capacity to metabolize VK1, and therefore, a higher warfarin dose was required to elicit the same anticoagulant response (8).

Since Caldwell *et al* (9) reported for the first time in 2008 that *CYP4F2* gene variants would change the warfarin maintenance dose in patients, an increasing number of research results regarding the correlation between the *CYP4F2* gene polymorphism and warfarin dose have been published. However, the findings are inconsistent, particularly for Asian patients (10-15). In 2012, two results of meta-analyses showed that the *CYP4F2* gene polymorphism was associated with the

warfarin maintenance dosage (16,17). However, as they all focused on the studies of European and American populations, the impact of the *CYP4F2* genotype on warfarin dose in the Asian population has not been investigated adequately. Furthermore, following the publication of these 2 meta-analyses, new research results regarding the association between the *CYP4F2* polymorphism and warfarin maintenance dose in Asian patients remains inconsistent. Thus, the aim of the present study was to investigate the effect of the *CYP4F2* genotype on warfarin maintenance dose in the Asian population by a meta-analysis.

Materials and methods

Search strategy of the literature. The literature search was conducted in PubMed, EMBASE and China National Knowledge Infrastructure databases (until August 5, 2015). There was no limitation in the date of publication or language. The search keywords were (warfarin* OR coumarin) AND (gene OR genotype OR genetics OR allele* OR polymorphism* OR variant* OR pharmacogenetics) AND (*CYP4F2*). Under the circumstances of missing data or ambiguity, the authors were contacted for additional information.

Study selection. The original studies published in full text were included. Reviews, case reports and editorials were excluded. In addition, the studies that were not of an Asian population, that did not include genotype frequencies or warfarin maintenance dose, and that did not include the indispensable information from the authors contacted were excluded. The following criteria were used to select the appropriate studies: i) Studies on Asian patients >18 years treated with warfarin; ii) *CYP4F2* genotyping performed in all patients or in a random selection of patients; and iii) warfarin maintenance dose (mean and standard deviation) available separately for CC, CT and TT genotypes or for the dominant model. There were no restrictions in the inclusion criteria with respect to patient demographic information.

Data extraction. Data of all the eligible studies were extracted and summarized independently by two reviewers. The recorded original information included the first author, the year of publication, country, the total sample size (the percentage of males), mean age, indication of warfarin, target international normalized ratio range, allele frequencies of *CYP4F2* and warfarin maintenance dose.

Quality score assessment. Two reviewers assessed the quality of the selected studies independently according to the Cochrane handbook and the criteria predefined by Little *et al* (18). The quality criteria were: i) Purpose of the study; ii) analytic validity of genotyping (types of samples used, timing of sample collection and analysis, genotyping method and quality control measures); iii) selection of the study subjects (geographic area, recruitment period, exclusion criteria, mean age and standard deviation or age range of study subjects, and the distribution by gender); and iv) statistical issues (methods of analysis used in reference and software used in the analysis). A study was graded as '++', '+' or '-' according to the satisfaction degree of the aforementioned criteria.

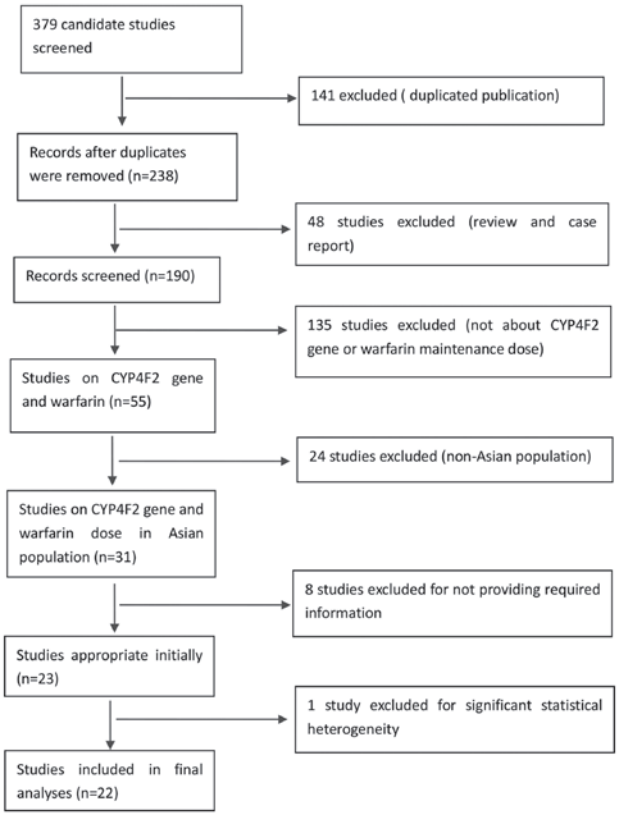

Figure 1. Flow diagram of the study selection procedure.

Statistical analysis. In order to eliminate any heterogeneity among different study populations, the maintenance dose of warfarin was normalized for each *CYP4F2* genotype group using the *CYP4F2* CC genotype as a reference. The normalization process was conducted by dividing the mean dose and associated standard deviations in each group by the mean maintenance dose in the *CYP4F2* CC group according to Lindh *et al* (19). Carriers of the CT or TT genotype were defined as 'T carriers'.

The association between the mean daily warfarin dose (MDWD) and *CYP4F2* gene polymorphisms was analyzed using the Review Manager 5.3 software (2014; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The normalized doses in the three genotype groups (CT, TT and T carriers) were compared with the CC genotype (reference group) by 3 meta-analyses. The TT genotype was compared with the CT genotype. The studies were weighted by the inverse variance method, and the effect of each *CYP4F2* genotype on the warfarin dose was defined as the mean difference (MD). The calculated MDs represent the relative differences in the maintenance dose due to the normalization procedure. The total weighted MD (WMD) is the sum of the WMD for each study. Z-test was employed to examine the effect of the *CYP4F2* SNP on MDWD, and $P<0.05$ was considered to indicate a statistically significant difference.

Heterogeneity among studies was estimated by the Cochran's Q-statistic and I^2 tests. In the case of studies with statistical heterogeneity ($P<0.1$ or $I^2>50\%$), the random-effect model was selected. Otherwise, the fixed-effect model was used.

Table I. Characteristics of the included studies.

First author (year)	Ethnicities	Total, no. (% male)	Age, years	Indication for warfarin	INR target range	Genotype frequencies, %			Mean warfarin dose ± SD, mg/day				Quality score	(Refs.)
						CC	CT	TT	CC	CT	TT	CT+TT		
Lee (2009)	Chinese	235 (56.2)	63.0±12.8	AF, CVR, stroke, DVT, PE	1.7-3.0	58.3	36.2	5.5	2.90±1.35	2.98±1.49	2.63±0.77		++	(10)
Liang (2012)	Chinese	115 (61.7)	64.9±3.0	AF, HVR, DVT, PE	2.0-3.0	41.7	47.8	10.4	2.77±0.99	3.22±1.15	4.0±0.79		++	(11)
Li (2012)	Chinese	352 (34.9)	45.4±9.29	HVR	1.8-2.5	64.8	29.5	5.7	3.1±0.8	3.4±0.8	3.6±0.9		++	(12)
Liang (2013)	Chinese	300 (46.0)	47.9±12.5	NA	1.5-3.0	57.3	40.0	2.7	3.26±1.16	3.31±1.31	3.66±1.28		++	(13)
Li (2015)	Chinese	158 (28.5)	47.65±11.20	CVR	1.5-2.5	63.3	34.2	2.5	19.87±7.39[a]	22.21±6.40[a]	22.42±7.66[a]		++	(14)
Zhuang (2015)	Chinese	211 (46.9)	66.0±10.7	Stroke, other	1.5-3.0	57.3	42.7		2.71±0.80			2.82±0.72	+	(15)
Krishna (2014)	Indian	240 (36.7)	43.3±11.2	PVR, AF, DVT, stroke	2.0-3.5	38.3	48.8	12.9	4.0±1.5	4.9±2.3	6.3±2.5		++	(26)
Özer (2013)	Turkish	107 (49.5)	53.89±13.55	HVR, VT, AF, other	2.0-3.0	37.4	45.8	16.8	4.53±1.73	5.58±2.24	5.42±1.10		++	(27)
Hirai (2015)	Japanese	217 (65.9)	69	AF, HVR, DVT, PE, AFL	NA	53.0	36.9	10.1	2.94±1.19	2.90±1.10	3.46±1.42		++	(28)
Nakamura (2012)	Japanese	126 (51.6)	62.7	NA	NA	46.0	46.8	7.1	2.88±1.00			3.55±1.69	+	(29)
Lee (2012)	Korean	188 (33.0)	57.8±10.1	HVR	2.0-3.0	43.6	45.2	11.2	5.34±2.04	5.33±1.64	6.55±2.12		++	(30)
Singh (2011)	Asian	124 (56.5)	61	AF, DVT, PVR, PE, other	2.0-3.0	66.9	31.5	1.2	3.0±1.82			3.75±1.82	+	(31)
Cen (2010)	Chinese	222 (46.8)	45±12	HVR	1.5-3.0	51.8	41.4	6.8	2.9±1.1			3.2±1.1	+	(20)
Lou (2014)	Chinese	488 (44.7)	56.7±12.3	HVR, AF, PE	1.5-3.0	49.8	41.0	9.2	3.39±1.28	3.63±1.53	3.85±1.61		++	(21)
Zhang (2013)	Chinese	85 (63.5)	64.49±11.77	AF, PE, HVR, other	NA	49.1	43.5	7.4	2.63±0.72	2.81±0.87	3.10±1.35		++	(Unpublished)
Fang (2014)	Chinese	104 (NA)	56.8±12.4	AF, HVR, other	1.5-3.0	60.6	35.6	3.8	2.74±0.91	3.16±0.92	3.75±1.06		++	(Unpublished)
Tan (2012)	Chinese	317 (30.0)	45.2±10.5	HVR	1.7-3.0	63.4	33.8	2.8	3.04±1.00	3.48±1.06	3.54±0.84	3.49±1.04	++	(Unpublished)
Zhang (2012)	Chinese	197 (41.6)	52.92±11.76	HVR	1.5-2.8	58.4	37.1	4.6	2.51±0.82	2.74±0.96	3.20±1.22		++	(22)
Zhu (2012)	Chinese	260 (48.5)	67.2±13.1	AF	1.5-3.0	56.2	33.1	10.8	2.60±0.84	2.66±1.02	3.04±0.98		++	(23)
Yu (2014)	Chinese	100 (43.0)	46.69±9.73	HVR	1.5-2.5	59.0	33.0	8.0	3.01±0.78	3.66±0.99	3.87±1.26		++	(Unpublished)
Wang (2011)	Chinese	196 (40.8)	61.89±12.35	HVR, AF, DVT, PE, ACI	1.8-3.0	50.5	42.9	6.6	3.07±1.21	3.66±1.33	3.73±1.55		++	(24)
Zhang (2014)	Chinese	207 (51.21)	62.8±14.4	HVR, other	2.0-3.0	59.9	35.8	4.4	2.55±0.91	2.60±1.07	2.86±0.90		++	(25)

[a]Unit is mg/week. INR, international normalized ratio; CVR, cardiac valve replacement; HVR, heart valve replacement; AF, atrial fibrillation; PE, pulmonary embolism; PVR, prosthetic valve replace; DVT, deep vein thrombosis; VT, vein thrombosis; ACI, acute cerebral infarction; AFL, atrial flutter; NA, not available; SD, standard deviation.

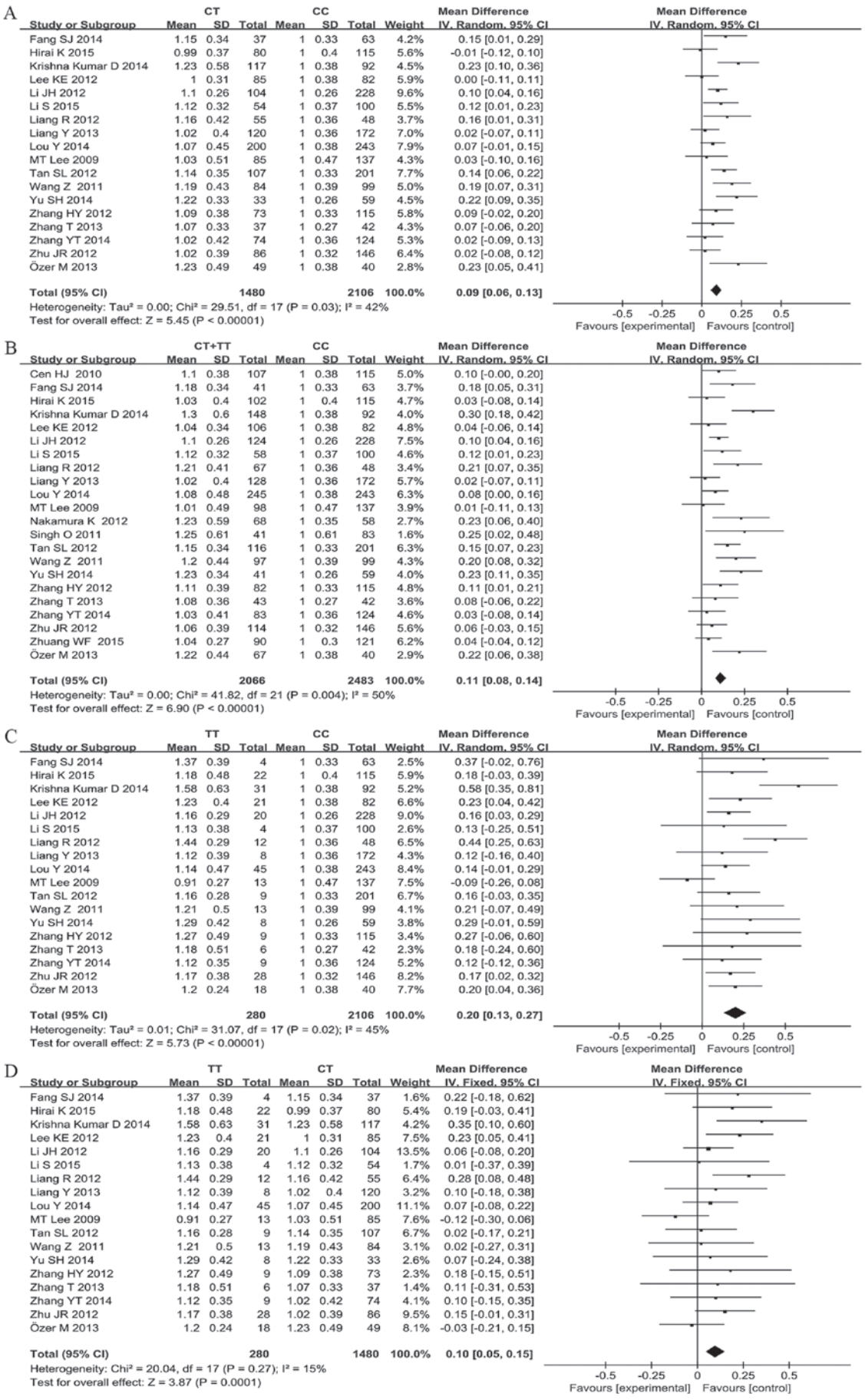

Figure 2. Forest plots for the association between the *CYP4F2* rs2108622 polymorphism and warfarin maintenance dose. The brackets represent 95% CI and the size of each box is proportional to the number of included patients. (A) CT vs. CC carriers. (B) T carriers (CT or TT) vs. CC carriers. (C) TT vs. CC carriers. (D) CT vs. TT carriers. SD, standard deviation of normalized warfarin doses associated with each genotype; CI, confidence interval.

Sensitivity analyses were performed by two methods. The first method removed studies one by one, and the second switched the meta-analysis between the fixed-effect model and random-effect model. Begg's funnel plot and Egger's linear regression test were applied to evaluate the publication bias with the use of STATA software version 12.0 (StataCorp LP, College Station, TX, USA), and P<0.05 was considered to indicate a statistically significant difference.

Subgroup analyses were carried out to identify the potential explanatory variables. The Chinese and non-Chinese Asian population studies were defined as two separate subgroups. As age was an important influence factor, the data was also divided into two according to the mean age of <60 years old and >60 years old. The main analysis was repeated separately in each subgroup.

Results

Literature selection. Fig. 1 shows the selection process of the eligible studies. A total of 379 candidate studies were included in the initial search. Following exclusion of the repeated and unfitted studies, 22 studies with a total of 4,549 patients conformed to the inclusion criteria for the qualitative data analysis.

Study characteristics. Table I expresses the characteristics of these 22 studies included in the meta-analysis. The publication years of the eligible studies ranged between 2009 and 2015. Among the included studies, the majority were of Chinese patients (10-15,20-25). Five studies were of non-Chinese populations (26-30) and one was for an Asian population (31). The main indications of warfarin were heart valve replacement, AF, DVT, pulmonary embolism and stroke.

Allele frequencies. There were 3,646 Chinese and 903 non-Chinese Asian patients included in the final analysis. On average, the frequencies of CC, CT and TT were 0.53, 0.39 and 0.08 in all the selected Asian patients. The frequencies of CC, CT and TT were 0.57, 0.37 and 0.06 in the Chinese patients and 0.44, 0.45 and 0.11, respectively, in the non-Chinese Asian patients. SPSS 18.0 (SPSS, Inc., Chicago, IL, USA) was used to assess the difference of allele frequencies between the two subgroups, and there was a significantly statistical difference (P<0.05).

Meta-analysis results. Fig. 2 shows the influence of each *CYP4F2* genotype on the warfarin maintenance dose. Compared with individuals with the homozygous CC genotype, warfarin doses in patients with genotype CT, TT and T carriers were significantly higher by 9 [95% confidence interval (CI), 6.0-13.0], 20 (95% CI, 13.0-27.0) and 11% (95% CI, 8.0-14.0), respectively (test for overall effect was P<0.05). Additionally, compared with the CT carriers, the TT carriers required a higher warfarin dose by 10% (95% CI, 5.0-15.0) with statistical significance (P<0.05).

Heterogeneity analysis. Only one meta-analysis showed no statistical heterogeneity (Cochran's Q test P=0.22, I^2 value 15%), and a fixed-effects model was used in the analysis. However, statistical heterogeneity was evident across the other meta-analyses in which the random-effects model was applied.

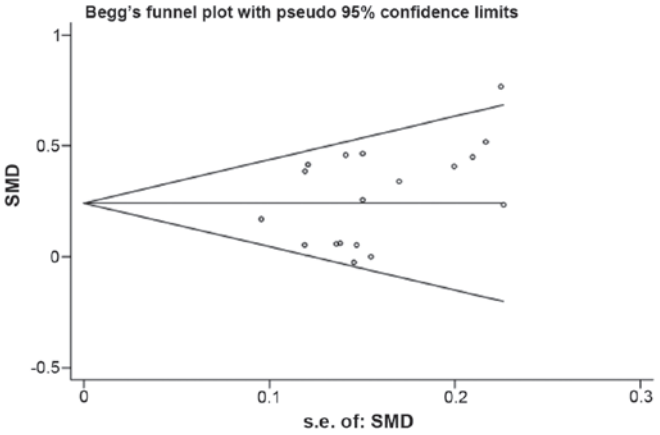

Figure 3. Funnel plot of the publication bias for the association between the *CYP4F2* rs2108622 polymorphism and warfarin maintenance dose. The solid horizontal line shows the summary effect estimate, for exhibiting the center of the plot in the absence of bias. The diagonal lines denote the 95% confidence limits.

Sensitive analysis and publication bias. The first method of sensitivity analysis was performed by deselecting each study one at a time. When deselecting the study of Luo *et al* (2013, unpublished data), the I^2 decreased from 74 to 42%, indicating that the study is the source of statistical heterogeneity. Further analysis showed that the heterogeneity may have been due to several design differences among the studies, including lower mean age and the definition of stable warfarin dose in the inclusion criteria. Following this, the study was excluded in the final analysis. Subsequently, the sensitivity was analyzed using the random-effect model, in which the results of the parameter analysis were in accordance with those using the fixed-effect model, suggesting that the results were stable.

Publication bias was evaluated by Begg's funnel plot and Egger's linear regression test. Fig. 3 showed the Begg's funnel plot of the main studies included in the meta-analysis. One study was outside the excepted 95% CI. The Egger regression test indicated no significant publication bias across the studies (t=1.65, P=0.119).

Subgroup analysis. Considering the multiple difference between Chinese and non-Chinese Asian populations, a subgroup analysis was performed and the results are presented in Fig. 4. Non-Chinese CT and TT carriers showed an ~1 and 12% larger effect on warfarin dose requirement compared to Chinese patients. Non-Chinese T carriers showed ~6% larger effect by comparison with Chinese patients. Fig. 5 shows the subgroup analyses of different age intervals. CT and TT carriers <60 years old showed an ~5 and 4% larger effect on warfarin dose requirement than that of patients >60 years. However, these differences were not significant (P>0.05).

Discussion

The incidence of thromboembolic disease ranks first among various diseases, showing an increasing tendency each year. New oral anticoagulants, such as rivaroxaban and apixaban, have the advantage of safe, effective and significant reduction

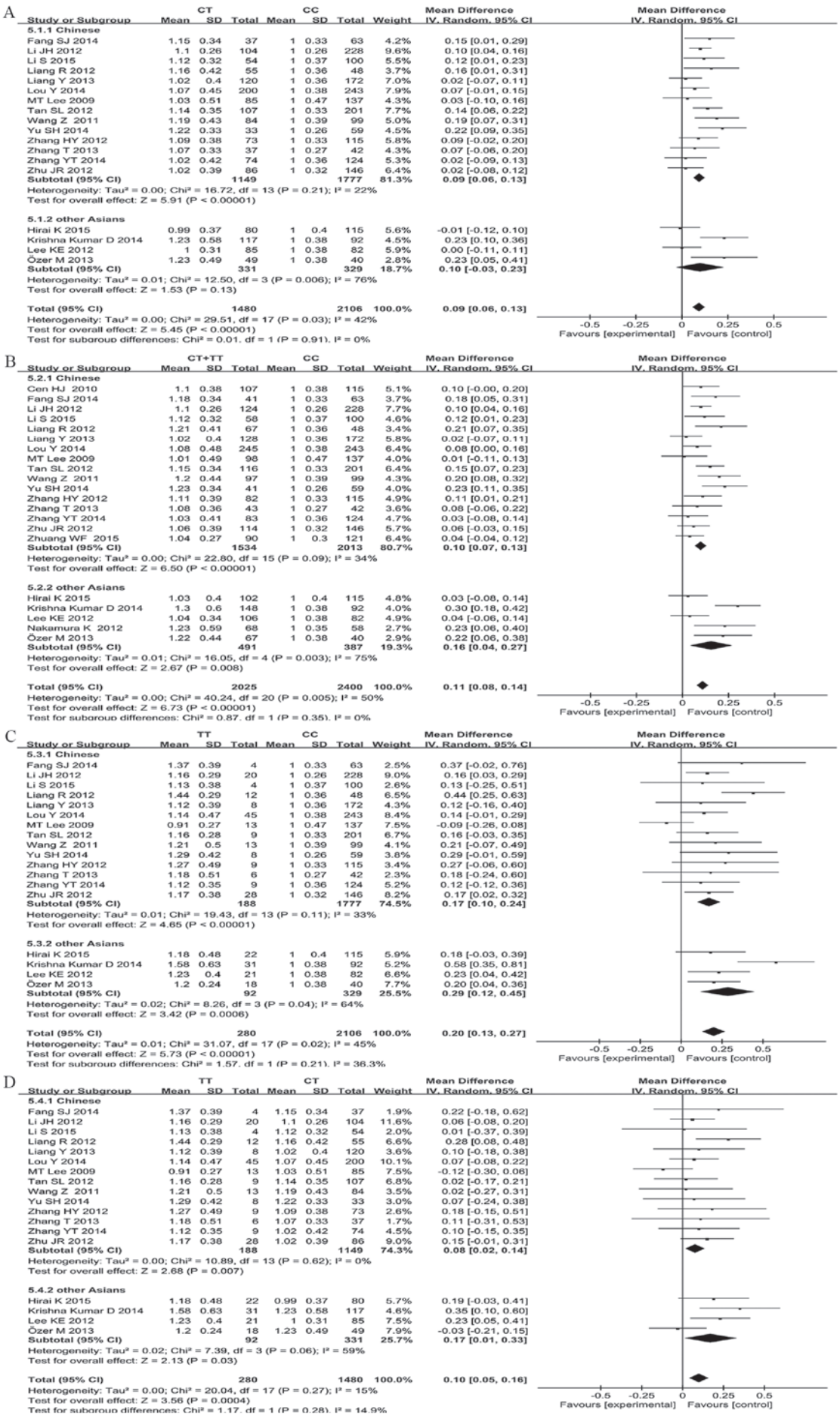

Figure 4. Forest plots of the subgroup analysis between Chinese and non-Chinese Asian populations. SD, standard deviation; CI, confidence interval.

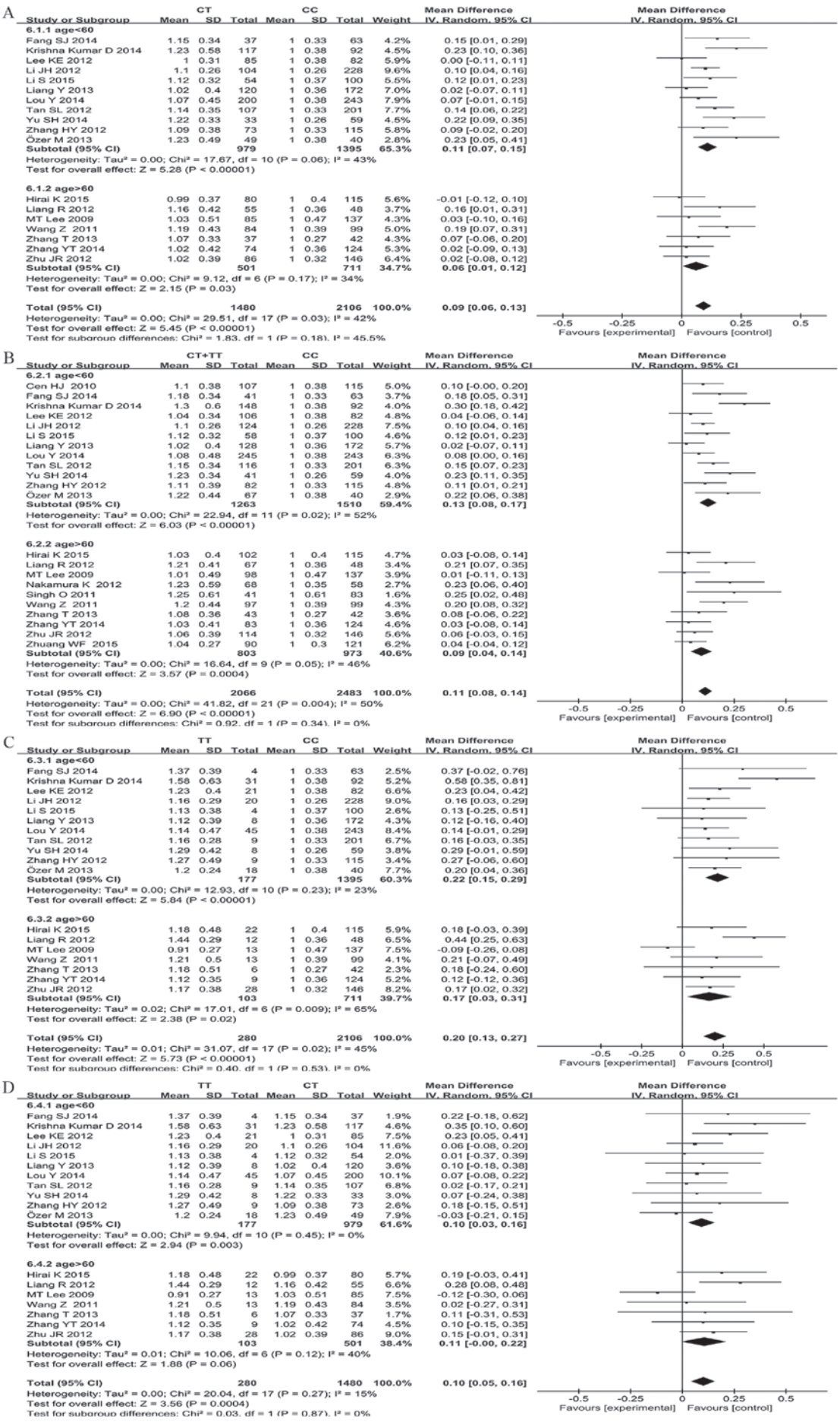

Figure 5. Forest plots of the subgroup analysis between ages <60 and >60 years old.

in intracranial hemorrhage and no requirement for routine laboratory monitoring. However, they have the defects of higher drug prices and the absence of a suitable antidote. Currently, warfarin remains the primary anticoagulation drug for treatment of AF and other thromboembolic diseases. There is a large individual difference in warfarin dose requirement. Genetic variation shows a clinically important impact on stable warfarin dose. The association between *CYP2C9*, *VKORC1* and warfarin dose has been investigated in several meta-analysis (19,32-34), and the influence of these two genes on warfarin dose has been confirmed. Data showed that *CYP2C9* and *VKORC1* together with clinical factors such as age, weight and drug combination can explain only ~50% of warfarin dose variability, suggesting that 50% uncertain factors remain to be considered. Thus far, only *CYP2C9* and *VKORC1* as genetic factors are included in a multitude of pharmacogenetic models, and *CYP4F2* may have the third major influence among genetic factors. Studies regarding whether *CYP4F2* affects warfarin dose requirement are consecutive; however, the results of different studies are controversial, particularly for Asian population studies. One possible explanation could be that the sample size in these studies is too small. Therefore, summarizing the scattered sample data to analyze the association between *CYP4F2* and warfarin dose requirement in Asian populations is likely to get effectual results.

Although the findings regarding the correlation between the *CYP4F2* polymorphism and warfarin dose in the Asian population are inconsistent, the results of the present systematic review and meta-analysis showed a strong association between *CYP4F2* polymorphisms and warfarin maintenance dose. Using a systematic search strategy, 22 studies that met the prespecified eligibility criteria were selected. Carriers of the CT and TT genotypes required 9 and 20% higher warfarin doses compared to carriers of the CC genotype, respectively. Additionally, T carriers required a warfarin dose 11% higher than the CC genotype. Furthermore, TT carriers required a 10% higher warfarin dose compared to the CT group (all $P<0.05$).

With regard to the sensitivity analysis, following the exclusion of the study by Luo *et al*, any significant change or revision in findings was not identified, and the results of the parameter analysis using the random-effect model were in accordance with those using the fixed-effect model, so therefore, the meta-analysis results of the impact of *CYP4F2* genotype on warfarin dose requirements were considered stable and reliable.

Limdi *et al* (35) proposed that the effect of predictors including clinical and genetic factor on warfarin dose differs by ethnicities. In the subgroup analyses, minor but no significant differences were observed between the Chinese and non-Chinese population. The results were similar in different age ranges. However, the heterogeneity of the Chinese group was reduced compared with the undifferentiated patients, and there was a significant difference in the allele gene frequencies of *CYP4F2* between Chinese and non-Chinese Asian populations. The aforementioned results are indicative of a minor difference between the Chinese and non-Chinese patients. Due to the small number of non-Chinese Asian patients included in the present analysis, the results required further verification.

The systematic review and meta-analysis confirmed the association between warfarin and *CYP4F2* rs2108622 in the Asian population. The results will aid further research of pharmacogenetics model, and improve the antithrombotic therapy of warfarin. To the best of our knowledge, this is the first study to explore the association between *CYP4F2* and the warfarin stable dose solely for the Asian population. As opposed to the studies by Danese *et al* (16) and Liang *et al* (17), a statistical difference was observed between the CT and TT genotype, which may be an indication of a larger effect of *CYP4F2* on the warfarin dose in the Asian population.

There are several limitations to the present meta-analysis. Firstly, the data for warfarin mean maintenance dose in the meta-analysis was not adjusted for other predictors. Secondly, certain studies were not included in the meta-analysis due to the absence of sufficient data. Thirdly, data of certain non-Chinese Asian studies was unavailable, leading to a smaller number of studies for the non-Chinese Asian population.

More studies with larger sample sizes are required in the future to investigate the effect of *CYP4F2* on a stable warfarin dose requirement, particularly considering the adjustment for the *CYP2C9* and *VKORC1* genes.

In conclusion, the present meta-analysis provides evidence that *CYP4F2* rs2108622 may influence the maintenance dose of warfarin in the Asian population and can address the controversy that has emerged in recent years to a certain extent. However, whether the impact of *CYP4F2* on warfarin dose is clinically important requires further investigation.

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