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Association of factor XIII Val34Leu polymorphism and coronary artery disease: A meta-analysis

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Abstract

Background: *Factor XIII plays an important role in the stabilization of the linkage between fibrins and in the pathophysiology of coronary artery disease (CAD). The association between factor XIII Val34Leu polymorphism and CAD risk remains controversial.*

Methods: *We conducted a meta-analysis of 36 studies involving 26,940 cases and 34,694 controls. Subgroup analyses were performed with division of data into disease (myocardial infarction [MI], CAD without MI), age, and sex.*

Results: *Factor XIII Val34Leu polymorphism was significantly associated with ove all CAD risk (odds ratio [OR] = 1.09, 95% confidence interval [CI] = 1.03–1.06, p = 0.004) and MI risk (OR = 1.15, 95% CI 1.07–1.25, p = 0.0003), but not with CAD without MI risk (OR = 1.00, 95% CI 0.87–1.15, p = 0.96). In the subgroup analysis by age and sex, there was no association between Val34Leu polymorphism and CAD.*

Conclusions: *This meta-analysis found that factor XIII Val34Leu polymorphism was associated with CAD risk, especially MI, but not with CAD without MI. In addition, age and sex did not affect the relationship between factor XIII Val34Leu polymorphism and CAD risk.* (Cardiol J 2017; 24, 1: 74–84)

Key words: factor XIII A Val34Leu, coagulation, coronary artery disease, myocardial infarction, meta-analysis

Introduction

Coronary artery disease (CAD) is the leading cause of death worldwide. Approximately 85.6 million American adults suffer from coronary vascular disease and around 30% of all deaths in 2013 were caused by CAD [1]. Although CAD mortality has decreased in recent years, it still remains high. CAD is a multifactorial disease with a complex pathophysiology generated by the combined effects of genes and the environment. Improvement of environmental factors can reduce the rate of CAD prevalence and mortality, but genetic factors remain a problem in CAD. A number of genetic risk factors have been found to predispose individuals to CAD, and the coagulation factor XIII gene, factor XIII, has been extensively studied.

Factor XIII plays an important role in the stabilization of linkages between fibrins and in the pathophysiology of CAD [2, 3]. Factor XIII consists of two types of subunits (A_2 and B_2). Factor XIII-A consists of two active A subunits, and factor XIII-B consists of inhibitory/carrier B subunits. Factor XIII-A, which shows transglutaminase activity,

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strengthens fibrin polymers and protects them from degradation by the fibrinolytic machinery [4]. Many studies have investigated the association between factor XIII-A gene polymorphisms and susceptibility to CAD, especially myocardial infarction (MI). Most studies have focused on one single-nucleotide polymorphism (SNP), which was Val34Leu.

In 2014, two meta-analytical studies were published on the association between factor XIII Val34Leu polymorphism and MI. Chen et al. [5] analyzed 29 studies and showed that factor XIII Val34Leu polymorphism may be associated with the risk of MI, and Wang et al. [6] analyzed 12 studies and showed the same result. However, the association between overall CAD and factor XIII Val34Leu polymorphism has not been analyzed since 2007 [7]. The results of a meta-analysis by Voko et al. [7] suggest that factor XIII Val34Leu polymorphism also affects susceptibility to CAD. In the present study, we performed a meta-analysis of all eligible studies to assess the relationship of factor XIII Val34Leu polymorphism with risk of CAD.

Methods

Identification of eligible studies and data extraction

A literature search was performed for studies examining the association between factor XIII Val34Leu and CAD. The PUBMED and EMBASE citation databases were used to identify available articles in which the factor XIII Val34Leu polymorphism was analyzed in patients with CAD (up to May 2016). The search terms used were as follows: coronary artery disease, myocardial infarction, angina, ischemic heart disease, factor XIII or F13A1, polymorphism, and mutation or variant. References in identified studies were also investigated to identify additional studies not indexed by PUBMED or EMBASE. Studies were included in this meta-analysis if 1) they were case-control studies that determined the distribution of factor XIII Val24Leu polymorphism; 2) they contained original data; and 3) they provided sufficient data to calculate odd ratios (ORs). No restrictions were set on race, language, ethnicity, or geographic area. We excluded the following: 1) studies with overlapping data; 2) studies in which the number of null and wild-type genotypes or alleles could not be ascertained; and 3) studies with only an abstract. We extracted author, year of publication, ethnicity of the study population, demographics, number of cases and controls, and allele frequency of factor XIII Val34Leu polymorphism.

Statistical analysis

Prior to pooling the studies for meta-analysis, the Hardy-Weinberg equilibrium (HWE) was assessed in the control groups of each study. Chi-square test was used to determine whether the observed frequency of genotypes in the control population conformed to HWE expectations. A two-sided p value > 0.05 was considered consistent with the HWE. Statistical analyses were performed using Review Manager 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014). We performed meta-analyses using 1) allelic contrast, 2) homozygote contrast, and 3) recessive and 4) dominant models. The strength of the association between factor XIII Val34Leu polymorphism and CAD risk was measured by OR and 95% confidence interval (CI). Heterogeneity statistics (I^2), overall effect (Z score), and p value were calculated. The effect of heterogeneity was quantified using I^2, which ranges from 0% to 100% and represents the proportion of between-study variability attributable to heterogeneity rather than chance [8]. The I^2 values of 25%, 50%, and 75% were nominally considered low, moderate, and high estimates, respectively. With an I^2 value < 25% or p value of heterogeneity > 0.10, a fixed effect model was selected for Mantel-Haenszel statistics. Otherwise, a random-effect model was used [9]. A funnel plot test was used to assess publication bias and was set at $p < 0.10$. To evaluate disease-, age-, and sex-specific effects, subgroup analyses were performed based on disease status, age, and sex. Early-onset MI was defined as a cardiac event occurring before the age of 45 years.

Results

Studies included in the meta-analysis

Electronic and manual searches identified 156 applicable studies, and 42 were selected for a full-text review based on the title and abstract details. Three studies were excluded due to duplicate data, and other three studies were excluded because they were meta-analytical studies between factor XIII Val24Leu polymorphism and CAD or MI. A total of 36 studies met the inclusion criteria, and separate comparisons were considered in the present meta-analysis, which included 26,940 cases and 34,694 controls [2, 10–44] (Table 1). There were 25 studies performed in European populations, 3 studies in Asian populations, 6 studies in North American populations, 1 study in a South American population, and 1 study in an African population. The present meta-analysis included overall CAD including

Table 1. Characteristics of the case-control studies included in the meta-analysis.

First author	Year	Country	Age of patient	Gender	Case	Control	Disease	Adjusted covariates	Unadjusted covariates
Alkhiary	2015	Egypt	< 40	Mixed	104	40	MI/UA	Age, sex, DM, thrombophilia, history of HD, drug abuse	BMI, family history, smoking, HTN, hyperlipidemia
Güler	2014	Turkey	NA	F	96	72	CSX	Age, sex, HTN, DM, hyperlipidemia, abnormal echocardiography, PVD, CRF, hepatic failure, thyroid dysfunction	Smoking
Onrat	2012	Turkey	< 45/≥ 45	Mixed	200	72	MI	NA	NA
Guella	2011	Italy	< 45	Mixed	3760	3760	MI	Age, sex, cultural background, geographical origin	DM, HTN, smoking, BMI, hyperlipidemia
Jin	2011	China	NA	Mixed	390	406	MI/CAD without MI	Age, sex, BMI, HTN, DM	Cholesterol, smoking
Shaffer	2011	USA	36–65	M/F	1304	1250	MI	Age, sex, BMI, smoking, DM, hyperlipidemia, family history	HTN
Silvain	2011	France	< 45	Mixed	484	484	MI	Age, sex, DM, HTN, history of CVD	Smoking, family history, BMI, hyperlipidemia
Bronic	2009	Croatia	55–70	Mixed	484	276	MI/CAD without MI	BMI	Age, sex, smoking, DM, HTN, hyperlipidemia
Siegerink	2009	Nether-lands	18–50	F	436	1494	MI	Age, ethnicity, oral contraceptive use	HTN, DM, hyperlipidemia, smoking
Bereczky	2008	Hungary	NA	Mixed	1920	604	MI/CS	NA	NA
Rallidis	2008	Greece	< 36	Mixed	322	242	MI	Age, sex, HTN	Smoking, hyperlipidemia, fibrinogen
Mannila 1	2007	Sweden	45–70	M/F	2320	3006	MI	Age, sex, HTN (female), IL-6 (female)	Physical inactivity, smoking, WHR, HTN (male), hyperlipidemia, fibrinogen, IL-6 (male)
Smith	2007	USA	30–79	Mixed	1712	5376	MI	Age, sex, race, HTN, BMI	Smoking, DM, hyperlipidemia, CHF, TIA
Boekholdt	2006	UK	40–79	Mixed	1796	3160	CAD	Age, sex	BMI, smoking, DM, HTN, hyperlipidemia, fibrinogen
Hancer	2006	Turkey	18–60 (≤ 50/> 50)	Mixed	330	260	MI	Age, BMI, DM, HTN	Sex, smoking, hyperlipidemia
Mannila 2	2006	Sweden	< 60	Mixed	774	774	MI	Age, sex, smoking, hyperlipidemia	BMI, fibrinogen, IL-6
Roldan	2005	Spain	< 45	Mixed	562	1060	MI	Age, HTN, DM	Sex, smoking, hyperlipidemia

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Table 1. (cont.) Characteristics of the case-control studies included in the meta-analysis.

First author	Year	Country	Age of patient	Gender	Case	Control	Disease	Adjusted covariates	Unadjusted covariates
Salazar--Sánchez	2005	Costa Rica	NA	Mixed	348	394	MI	Age, sex, oral contraceptive	BMI, fibrinogen, obesity, HTN, DM, smoking, hyperlipidemia, family history
Tu	2005	China	35–87	Mixed	126	260	MI	NA	NA
Feng	2004	China	NA	Mixed	390	406	MI/CAD without MI	Age, sex, BMI, HTN, DM	Hyperlipidemia, smoking
Martini	2004	Italy	20~47	Mixed	108	108	MI	Age, sex, smoking, BMI, HTN, hyperlipidemia, DM, family history	NA
Butt	2003	Canada	NA	Mixed	1000	1000	MI	NA	NA
Doggen	2003	Nether-lands	≤ 50/> 50	M	1428	1612	MI	Age, sex	NA
Mannuci	2003	Italy	< 45	Mixed	2420	2420	MI	Hyperlipidemia, alcohol, cocaine use, physical exercise	Smoking, DM, HTN, family history, BMI
Reiner 1	2003	USA	30–79	F	468	1442	MI	Age, race, oral contraceptive, BMI	Smoking, DM, HTN, hyperlipidemia
Aleksic	2002	USA	45–64	Mixed	846	958	CAD	NA	NA
Kakko	2002	Finland	< 62	Mixed	284	284	MI	Age, sex, smoking	BMI, hyperlipidemia, family history
Mills	2002	UK	19–51	M	250	370	CAD	HTN, hyperlipidemia, fasting glucose	Age, smoking, BMI, WHR, insulin resistance, fibrinogen
Reiner 2	2002	USA	18–44	F	136	690	MI	Age, premenopausal, oral contraceptive	Obesity, HTN, DM, hyperlipidemia
Gemmati	2001	Italy	30–80	Mixed	480	480	MI/CAD without MI	Age, sex, HTN, DM, hyperlipidemia, smoking	NA
Warner	2001	UK	49–65	Mixed	178	184	MI	Age, BMI, fibrinogen, hyperlipidemia, smoking, HTN, DM	Sex, WHR
Canavy	2000	France	18–65 (< 45/≥ 45)	Mixed	488	488	MI/VA	Age, sex, BMI, hyperlipidemia	NA
Corral	2000	Spain	34–85	Mixed	202	202	CAD	Age, sex, HTN, smoking, hyperlipidemia, DM	NA
Franco	2000	Brazil	25–55	Mixed	300	300	MI	Age, sex, race	Family history, HTN, DM, hyperlipidemia, BMI, smoking
Kohler	1999	UK	NA	Mixed	550	392	MI/CAD without MI	Age, fibrinogen, platelet count	Sex, hyperlipidemia, BMI
Wartiovaara	1999	Finland	< 69	M	252	688	MI	Age, BMI, smoking, hyperlipidemia	NA

BMI — body mass index; CAD — coronary artery disease; CHF — chronic heart failure; CRF — chronic renal failure; CS — coronary sclerosis; CSX — cardiac syndrome X; CVD — cardiovascular disease; DM — diabetes mellitus; F — female; HD — heart disease; HTN — hypertension; IL — interleukin; M — male; MI — myocardial infarction; NA — not available; PVD — peripheral vascular disease; TIA — transient ischemic attacks; UA — unstable angina; WHR — waist to hip ratio; VA — vasospastic angina

Table 2. Meta-analysis of association between the factor XIII Val34Leu polymorphism and coronary artery disease.

Population	Number of studies	Case	Control	Test of association			Test of heterogeneity		
				OR	95% CI	P	Model	P	I^2 (%)
Overall	36	26940	34694	1.09	1.03–1.16	0.004	R	0.003	44
MI	31	21168	29932	1.15	1.07–1.25	0.0003	R	0.0001	55
Without MI	9	2678	3164	1.00	0.05–0.96	0.96	F	0.28	18
Under 45	9	8098	9256	1.03	1.96–1.11	0.4	F	0.1	41
Over 45	7	4260	5020	0.90	0.75–1.08	0.25	R	0.08	47
Male	5	4268	5350	1.08	0.94–1.25	0.27	R	0.09	50
Female	6	2114	4954	1.09	0.97–1.24	0.15	F	0.13	41

CI — confidence interval; F — fixed effects model; MI — myocardial infarction; OR — odds ratio; R — random effects model

MI, unstable angina, coronary sclerosis, cardiac syndrome X, vasospastic angina, etc. A total of 9 studies were performed with patients younger than 45 years; among these, 2 studies also contained patients older than 45 years. Including these 2 studies, a total of 8 studies were performed in patients older than 45 years. Three studies included only male patients, 4 studies only females, and all other included both sexes. Two study analyses were performed separately based on sex.

Meta-analysis of the association between factor XIII Val34Leu polymorphism and coronary artery disease

A summary of the meta-analysis findings concerning associations between factor XIII Val-34Leu polymorphism and CAD is provided in Table 2. The meta-analysis of factor XIII Val34Leu polymorphism showed a significant association between CAD and the Val allele (OR = 1.09, 95% CI 1.03–1.06, p = 0.004; Fig. 1). A subgroup analysis by disease type (with MI or without MI) showed a significant association between MI and the Val allele (OR = 1.15, 95% CI 1.07–1.25, p = 0.0003; Fig. 2). However, no association was found between CAD without MI and the Val allele (OR = 1.00, 95% CI 0.87–1.15, p = 0.96). In the subgroup analysis by age, no association was found in either the younger population (OR = 1.03, 95% CI 0.96–1.11, p = 0.4) or older population (OR = 0.90, 95% CI 0.75–1.08, p = 0.25). In the subgroup analysis by sex, no association was found in males (OR = 1.08, 95% CI 0.94–1.25, p = 0.27) or females (OR = 1.09, 95% CI 0.97–1.24, p = 0.15).

We compared the Val/Val genotype and Val/Leu + Leu/Leu genotype in the overall CAD population and subgroups. There was a significant association between CAD and the Val/Val genotype (OR = 1.11, 95% CI 1.03–1.19, p = 0.006; Fig. 3). In the subgroup analysis, there was a significant association between MI and the Val/Val genotype in the CAD with MI group (OR = 1.18, 95% CI 1.08–1.30, p = 0.0003; Fig. 4). However, in the other subgroup analyses, there were no associations between disease and the Val/Val genotype. We also compared the Val/Val genotype and the Leu/Leu genotype in the overall CAD population and subgroups. Comparison of the Val/Val vs. LeuLeu genotypes of overall CAD (OR = 1.19, 95% CI 1.03–1.38, p = 0.02) and MI (OR = 1.27, 95% CI 1.06–1.52, p = 0.009) also showed a significant association, however other subgroups showed no associations.

Heterogeneity and publication bias

Some heterogeneity was found in the meta-analyses of the factor XIII Val34Leu polymorphisms (Table 2). For MI risk, there was significant heterogeneity in the Val allele (I^2= 55%, p = 0.0001; Table 3), and the Val/Val vs. Val/Leu + Leu/Leu genotype model (I^2 = 53%, p = 0.0003; Table 3). There was also significant heterogeneity in the Val/ /Val vs. Val/Leu + Leu/Leu genotype model in the group of subjects older than 45 years (I^2 = 67%, p = 0.006) and in the Val allele in males (I^2 = 50%, p = 0.09). All studies included in this meta-analysis satisfied the HWE. Publication bias was examined by a funnel plot (Fig. 5). The shape of the funnel plot was symmetrical, with 18 studies on the left side and 18 studies on the right side.

Discussion

In the current meta-analysis, we investigated the association between factor XIII Val34Leu

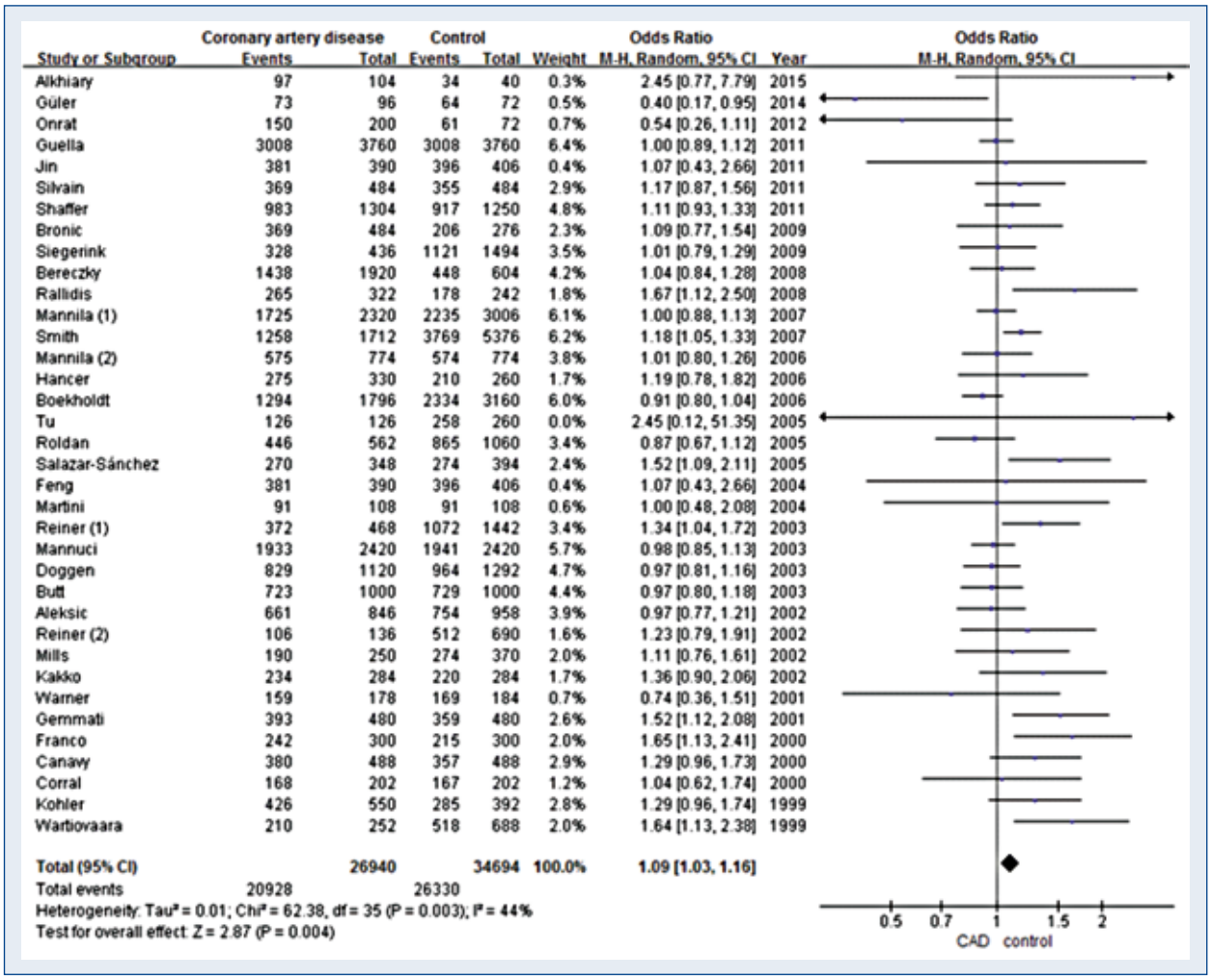

Figure 1. Odds ratio and 95% confidence interval (CI) of individual studies and pooled data for the association between the factor XIII Val allele and coronary artery disease (CAD).

polymorphism and CAD risk, including 26,940 cases and 34,694 controls. We found that the Val allele and Val/Val genotype showed increased risk of CAD. However, our meta-analyses did not show evidence of an association between factor XIII Val-34Leu polymorphism and CAD in any subgroup except MI. These results are in accord with previous meta-analyses [5–7]. However, Wang et al. [6] suggested that factor XIII Val34Leu polymorphism was significantly associated with MI risk in the subgroup analyses by age and sex.

In the subgroup analysis by disease, the present meta-analysis showed that factor XIII Val-34Leu polymorphism affected MI risk, but did not affect risk in CAD without MI, although the CAD without MI group was small (9 studies). CAD involves damage from plaque accumulating on the arterial wall. The buildup of plaque progressively hardens and narrows blood vessels, a process known as atherosclerosis [45]. MI, a severe complication of CAD, is commonly defined as a cardiomyocyte death due to a prolonged ischemia and increase in serum cardiac markers, such as troponin [46]. Both MI and CAD without MI are caused by atherosclerosis, but MI differs from CAD without MI in the existence of cardiac necrosis. We suspect that factor XIII has a function not only in blood coagulation, but also in healing of tissue damage.

Blood coagulation factor XIII has a key role in the terminal phase of the clotting cascade, which contributes to thrombotic events. Factor XII is composed of A and B subunits. Factor XIII is activated by thrombin proteolytically and, in the presence of calcium, dissociation of subunit B [47]. Activated factor XIII induces fibrin cross-linking via noncovalent binding of fibrin polymers. This process finally forms a stable clot that is resistant

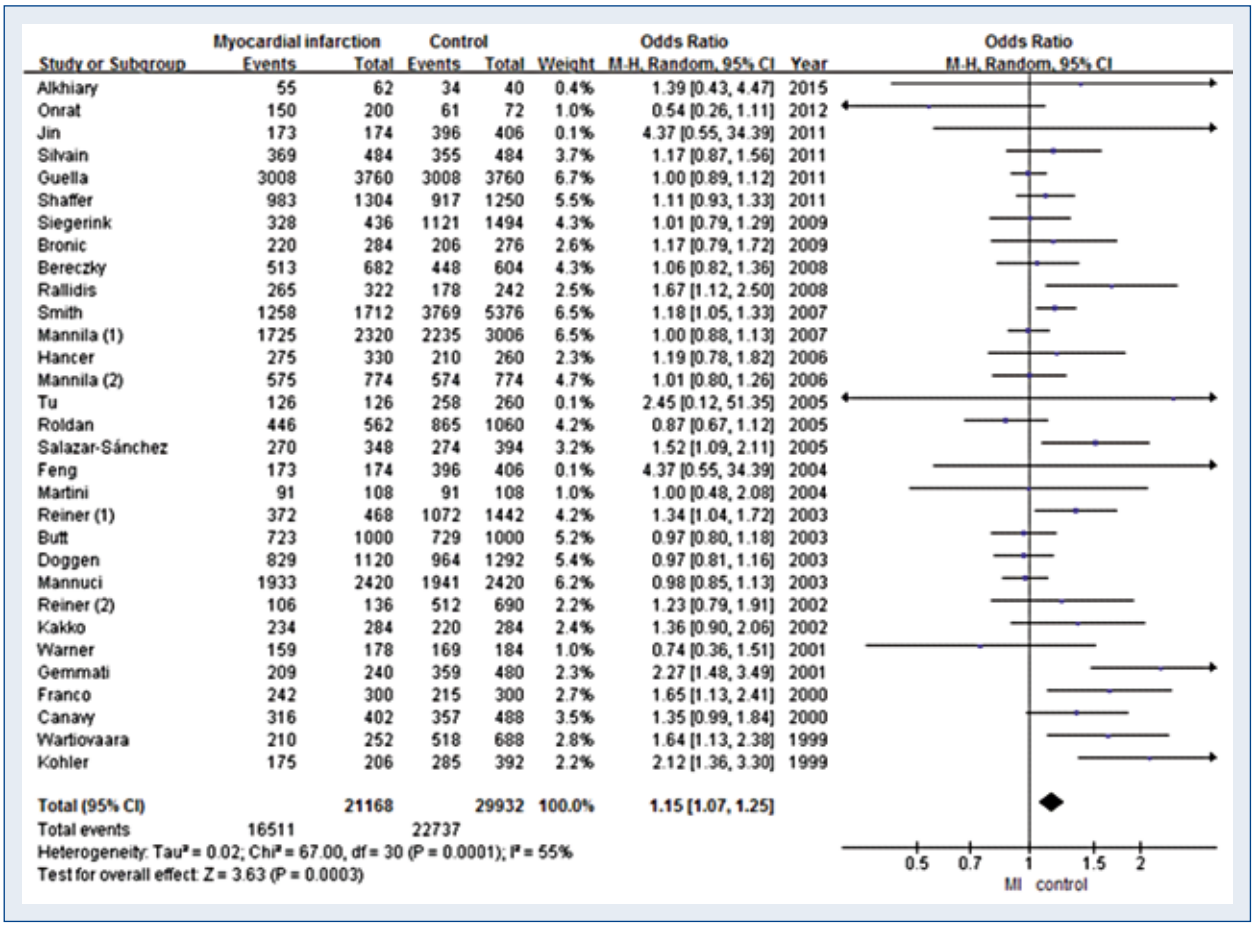

Figure 2. Odds ratio and 95% confidence interval (CI) of individual studies and data pooled for the association between the factor XIII Val allele and myocardial infarction (MI).

to shear forces and fibrinolysis [48]. The Val34Leu polymorphism in factor XIII A subunit is located in the activation peptide 3 amino acid residues upstream from the thrombin cleavage site [14]. The 34Leu variant increases activation rate by thrombin, alters fibrin structure *in vitro*, and influences fibrin cross-linking *in vivo* [47]. Compared to CAD without MI, a vulnerable plaque is a cruel character of MI. Thus, MI can be protected against by increases in factor XIII due to the 34Leu variant. However, it remains unclear whether the 34Leu variant protects against CAD without MI. The present meta-analysis also showed no association between CAD without MI and factor XIII Val34Leu polymorphisms.

In subgroup analyses by age or sex, there were no associations between CAD and factor XIII Val34Leu polymorphisms. It is possible that the influence of factor XIII Val34Leu polymorphism on CAD might be confounded by the presence of other unidentified causal genes involved in CAD development. Gene-gene interactions should be considered. Fibrinogen is an independent predictor of atherosclerotic disease including MI [49]. The factor XIII A 34Val allele is associated with an increase in fibrinogen concentrations, as is the fibrinogen Aα 312Ala allele. Fibrinogen Aα Thr312Ala polymorphism is also associated with fibrinogen concentration. High fibrinogen concentrations lead to formation of a fibrin clot, which is highly thrombogenic [50]. In addition, factor XIII B His95Arg polymorphism is associated with development of MI when inherited with factor XIII A Val34Leu polymorphism. The Arg95 allele reduces MI risk in the presence of the Leu34 allele [33]. Factor II 20210A and factor V leiden variants are also associated with MI risk, and Tyr2047Phe and Pro564Leu variants in the factor XIII A gene are associated atherosclerotic disease [18, 30]. Gene-environment interaction should also be considered. Fibrinogen concentrations are

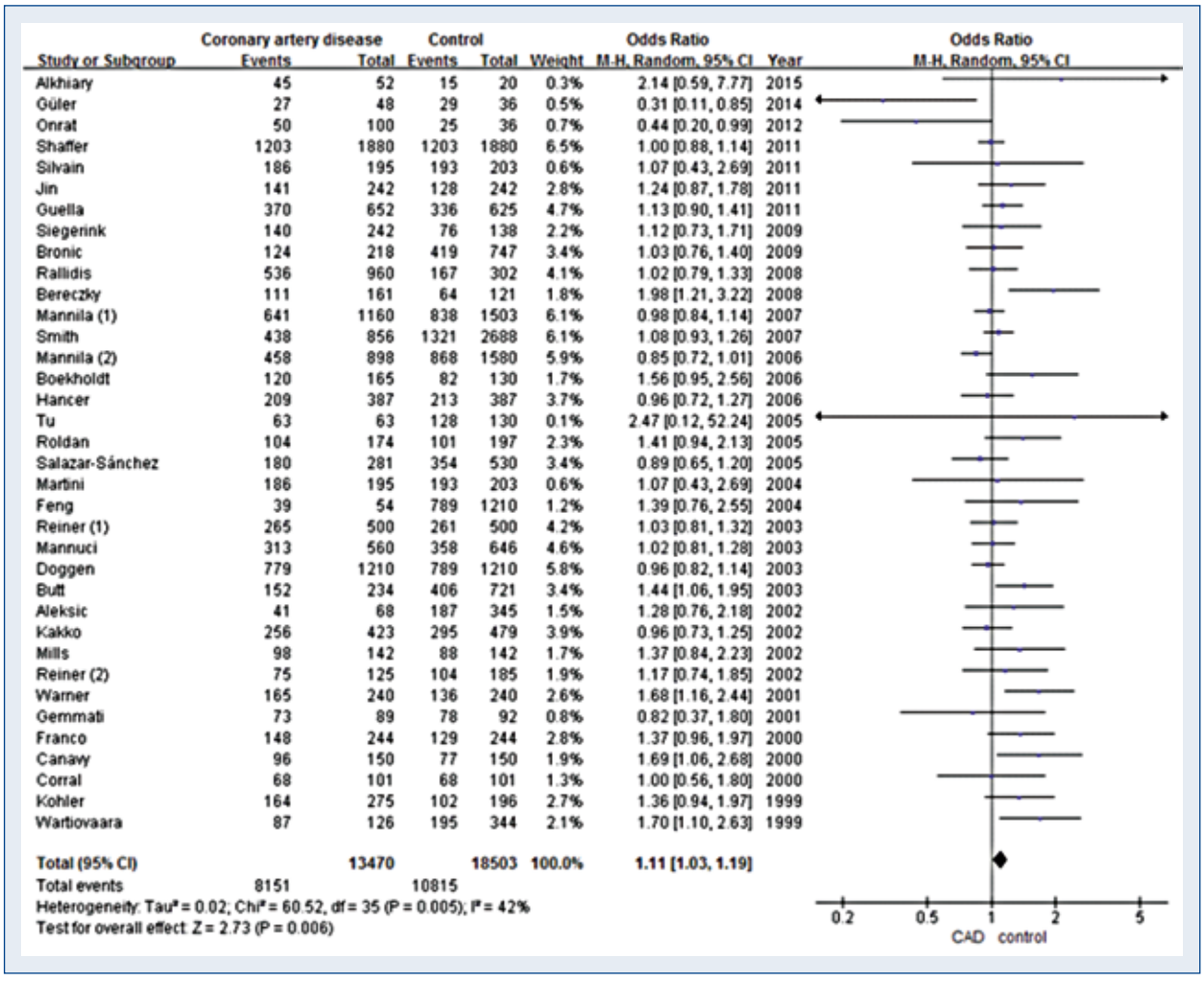

Figure 3. Odds ratio and 95% confidence interval (CI) of individual studies and data pooled for the association between the factor XIII Val/Val genotype and coronary artery disease (CAD).

associated with smoking, insulin resistance and physical activity [50]. The 34Leu allele is related to taking estrogen [48].

In recent years, another aspect of factor XIII has been identified in addition to blood coagulation. Factor XIII influences wound healing in several tissues, including cardiomyocytes, by exerting multiple plasma and cellular functions. Moreover, the proangiogenic function of factor XIII is directed by the interaction of vascular endothelial growth factor receptor 2 and integrin $\alpha V\beta_3$ on the cell membrane [51]. Certain studies showed that low factor XIIIA level correlated with a poor prognosis with regard to MI [52, 53]. Therefore, MI could be differently affected by this function of factor XIII compared to CAD without MI.

The present meta-analysis has several strengths. It included the largest number of studies. Previous meta-analyses included primarily Caucasians, however this meta-analysis contained other ethnicities including Asians. In addition, we used real gene polymorphism data in the meta-analysis rather than adjusted ORs, which could reduce the bias arising from adjustment.

Limitations of the study

As with any meta-analysis, there are a number of limitations that need to be considered. First, the proportion of studies with MI was too large. Among 36 studies, MI was included in 31 studies, which could overestimate the association between gene polymorphism and overall CAD. Second, although we sought to study gene effects in all ethnic groups, the majority of studies were conducted in Caucasian populations. Third, each study was not analyzed using uniform inclusion and exclusion criteria. Each

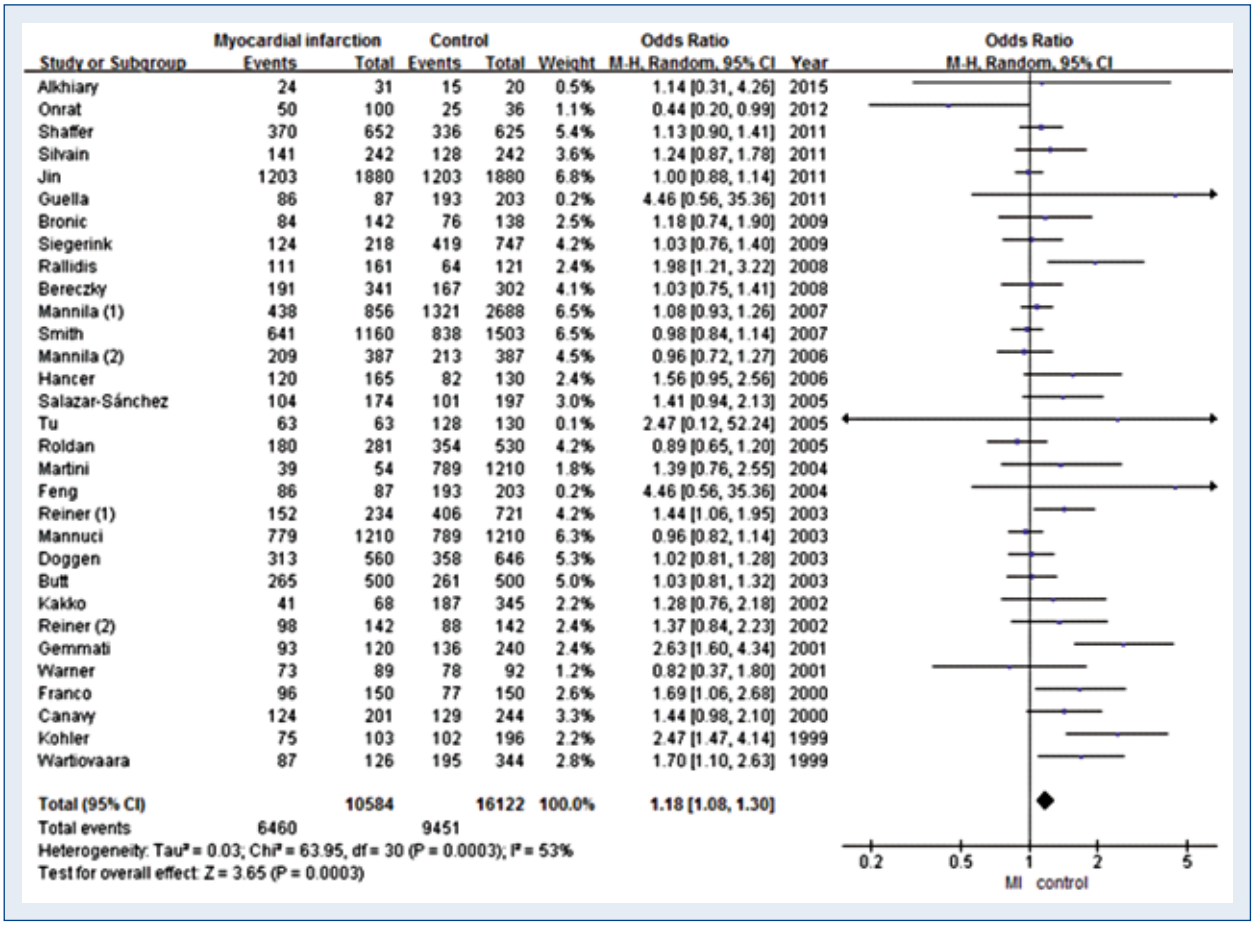

Figure 4. Odds ratio and 95% confidence interval (CI) of individual studies and data pooled for the association between the factor XIII Val/Val genotype and myocardial infarction (MI).

Table 3. Meta-analysis of association between the factor XIII Val34Leu polymorphism and myocardial infarction.

	Test of association			Test of heterogeneity		
	OR	95% CI	P	Model	P	I^2 (%)
V vs. L	1.15	1.07–1.25	0.0003	R	0.0001	55
VV vs. VL+LL	1.18	1.08–1.30	0.0003	R	0.0003	53
VV+VL vs. LL	1.21	1.02–1.43	0.003	R	0.02	39
VV vs. LL	1.27	1.06–1.52	0.009	R	0.009	44

CI — confidence interval; L — factor XIII Leu; OR — odds ratio; R — random effects model; V — factor XIII Val

study also differently defines MI, even though each definition of MI was mostly based on ischemic symptom, change of electrocardiography, and elevation of cardiac biomarkers. Fourth, in addition to Val34Leu polymorphism, the factor XIII A gene includes other genetic variants, such as tyr204Phe and Pro564Leu [18]. Fifth, due to the lack of the original data of the eligible studies, the evaluation of the effects of gene-gene or gene-environment interactions was limited, as well as the ability to perform subgroup analyses by age and sex. Sixth, all included studies were retrospective case-control studies, thus, we cannot exclude the possibility of undetected bias. Finally, publication bias is an important feature of meta-analyses, which we attempted to minimize by including studies in all languages.

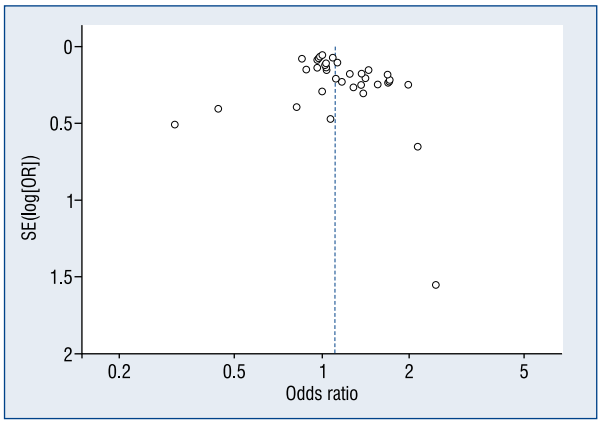

Figure 5. Funnel plot for coronary artery disease risk and factor XIII Val34Leu polymorphism.

Conclusions

In conclusion, this meta-analysis showed that factor XIII Val34Leu polymorphism was associated with CAD risk, especially with MI, but not with CAD without MI. In addition, age or sex did not affect the relationship between factor XIII Val34Leu polymorphism and CAD risk. However, some significant limitations exist in the interpretation of the result and the present meta-analysis should be interpreted with caution.

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Conflict of interest: None declared

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