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Review Article

Glycoprotein IIIa PIA1/A2 polymorphisms not associated with risk of ischemic stroke: a meta-analysis and systematic literature review

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Abstract: Objective: The aim of this study was to assess association of glycoprotein IIIa gene PIA1/A2 polymorphisms with risk of ischemic stroke. Methods: All case-control studies associating glycoprotein IIIa PIA1/A2 polymorphisms with risk of ischemic stroke were retrieved from PubMed, Embase, Web of Science, and Cochrane Library databases. Data were extracted, reviewed, and meta-analyzed using Revman 5.2 software. Results: A total of 1,517 studies were reviewed. The 25 included studies comprised of 6,351 cases and 7,737 controls. Data revealed that there were no statistical significances between glycoprotein IIIa PIA1/A2 polymorphisms and stroke (OR=1.03; 95% CI=0.87, 1.22; *P*=0.74). Furthermore, subgroup analysis revealed no statistical significance between glycoprotein IIIa PIA1/A2 polymorphisms and stroke risk in different ethnicities and regions, such as in Europeans (OR=0.96; 95% CI=0.79, 1.15; *P*=0.64), Asians (OR=1.34; 95% CI=0.69, 2.61; *P*=0.39), North Americans (OR=0.98; 95% CI=0.76, 1.26; P=0.85), or other groups (OR=0.97; 95% CI=0.83, 1.14; *P*=0.74). According to TOAST parting line in the stroke subgroup analysis, glycoprotein IIIa gene PIA1/A2 polymorphisms had no statistical significance in causes of stroke, such as large artery atherosclerosis (OR=1.97; 95% CI=0.82, 4.76; *P*=0.13), small artery occlusion (OR=1.10; 95% CI=0.78, 1.55; *P*=0.59), cardiac embolism (OR=0.85; 95% CI=0.64, 1.14; *P*=0.27), or in all groups (OR=1.21, 95% CI=0.84, 1.75; *P*=0.31). Furthermore, there was no statistical significance between glycoprotein IIIa PIA1/A2 polymorphisms and stroke risk in different age subgroups (with a cut-off point at 45 years old (OR=0.96; 95% CI=0.72, 1.27; *P*=0.78). Conclusion: Glycoprotein IIIa PIA1/A2 polymorphisms are not associated with risk of ischemic stroke in terms of race, region, or age.

Keywords: Platelet glycoprotein IIIa, gene polymorphisms, stroke, integrin-beta 3

Introduction

Stroke is a vascular disease caused by poor blood flow into the brain, resulting in brain cell death. According to its etiology, there are two major types of stroke, ischemic and hemorrhagic. Ischemic stroke is a heterogeneous multifactorial disease caused by blockage of cerebral blood circulation, resulting in brain tissue ischemia, hypoxia, and necrosis [1]. To date, ischemic stroke is the most common type of cerebrovascular disease, accounting for 70% of all brain vascular diseases, becoming the second leading cause of death globally [2]. For example, approximately 6.9 million people suffered from ischemic strokes in 2013 [1]. In China alone, epidemiological studies have shown that there are three million new cases of stroke each year with characteristics of high morbidity, mortality, and disability [3]. The effective prevention strategy is to reduce occurrence, recurrence, and death of patients after stroke. Antiplatelet drugs are frequently used for stroke prevention, while aspirin or other nonsteroidal anti-inflammatory drugs can reduce risk of ischemic stroke by 25% [4]. However, clinical studies have shown that patients with previous ischemic stroke, while taking aspirin, continued to endure a high recurrence rate, reaching up to 17.7% [1]. Thus, a better understanding of its etiology, molecular mechanisms, and prevention could help to effectively prevent and treat ischemic stroke. Currently, there are four different causes of blocked blood flow into the brain: thrombosis, embosis, systemic hypoperfusion (such as shock), and cerebral venous

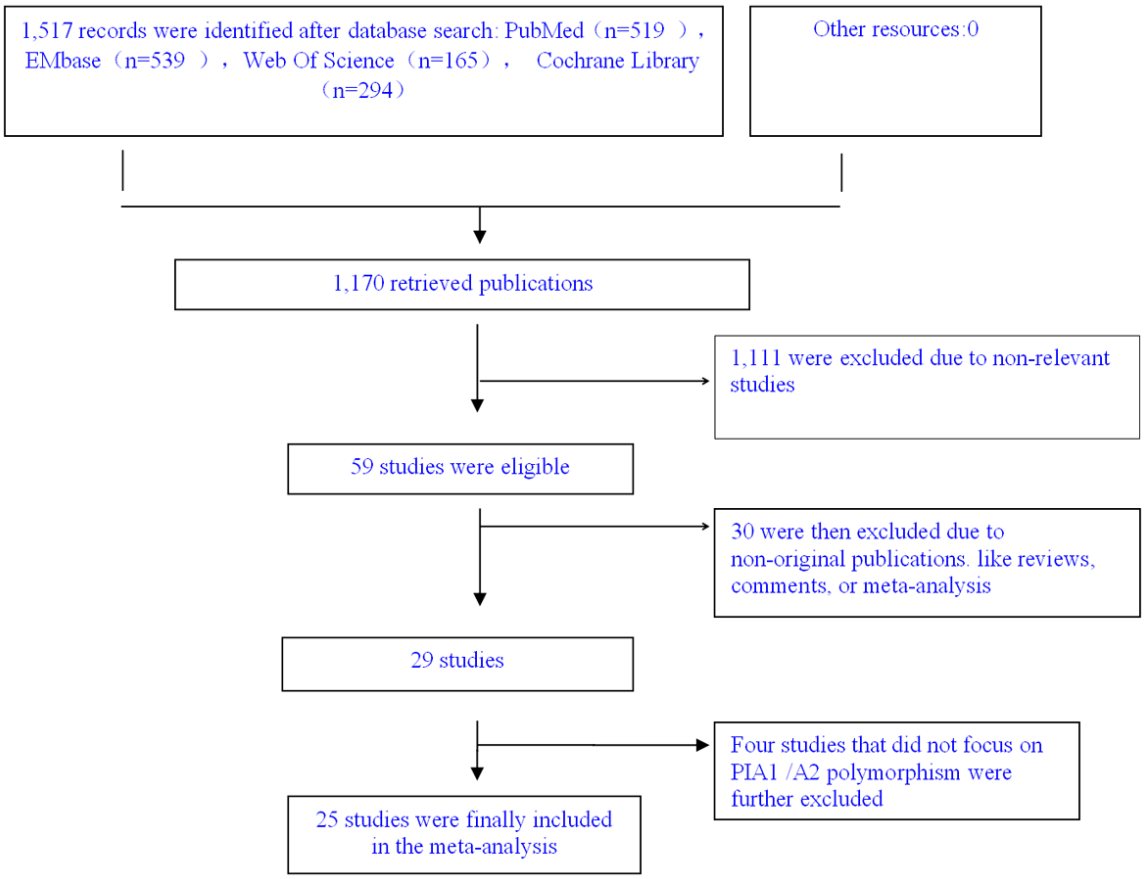

Figure 1. Flow diagram of the study design for inclusion and exclusion of studies in the present meta-analysis.

sinus thrombosis. Thus, a better understanding of the molecular mechanisms responsible for ischemic stroke could help to effectively prevent or treat ischemic stroke. With progress in genetic research, evidence has suggested that gene polymorphisms may play a significant role in aspirin resistance [5].

Polymorphisms of genes on platelets can influence the structure and expression levels of these proteins or enzymes, including GPIIb/IIIa, GPIa/IIa, GPVI, vWF, COX, P2Y1, P2Y12, or thromboxane A2 receptors [6]. However, the precise role of these genes and their genetic variations remains to be determined regarding development and progression of ischemic stroke. Glycoprotein IIa/IIIa (GPIIb/IIIa), also called integrin $\alpha_{IIb}\beta_3$, is the most abundant glycoprotein on the surface of platelets. *GP IIIa* polymorphisms encode PIA1 and PIA2. The *PIA2* gene is encoded by rs5918 and its polymorphism is associated with differential response to aspirin, possibly leading to incidence of thrombotic events [7, 8]. A recent study revealed that rs5918 was associated with acute myocardial infarction, heart disease, and thrombosis and that patients with rs5918 polymorphisms had a higher risk of atherosclerosis and ischemic stroke [6, 8]. However, such results remain controversial and inconsistent [9]. Therefore, the present study performed a meta-analysis to further determine association between *GPIIIa* polymorphisms and ischemic stroke risk, using published data. The aim of this study was to provide a genetic link to ischemic stroke risk.

Material and methods

Literature search

Case-control studies associating glycoprotein IIIa PIA1/A2 polymorphisms with risk of ischemic stroke were retrieved from PubMed, Embase, Web of Science, and Cochrane Library databases, in July 2017, using the following

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

Study name	Country	Number	Origin of control	Genetic testing method	NOS	Genotype (IS/CO)		
		IS/CO				PIA1/A1	PIA1/A2	PIA2/A2
Carter 1998 [31]	England	505/402	PB	PCR	7	353/296	141/96	11/10
Carter 1999 [29]	England	515/423	PB	PCR	9	354/312	145/101	11/10
Lanni 2007 [18]	Italy	243/416	HB	PCR	6	143/267	87/129	13/19
Reiner 2000 [26]	America	36/346	PB	PCR	7	25/241	15/98	1/7
Rivera-García 2013 [14]	Mexico	200/200	NR	PCR	7	167/164	32/36	1/0
Saidi 2008 [15]	Tunisia	329/444	HB	PCR-SSP	8	47/124	209/274	73/46
Slowik 2004 [22]	Poland	377/572	PB	PCR	6	271/428	96/140	10/4
Szolnoki 2003 [23]	Caucasia	545/158	HB	PCR	7	368/123	167/33	10/2
Berge 2007 [19]	Norway	367/482	PB	PCR	6	287/361	69/114	7/7
Carlsson 1997 [34]	Spain	103/103	HB	PCR	7	73/77	29/25	1/1
Corral 1997 [33]	Spain	96/119	HB	PCR	6	38/81	42/31	7/16
Iniesta 1999 [28]	Spain	124/342	PB	PCR	8	84/40	239/103	
Kekornaki 1999 [27]	Greece	324/200	HB	PCR	7	271/169	53/31	
Konialis 2016 [12]	China	350/300	PB	PCR	7	332/289	11/18	
Lu 2014 [13]	Caucasia	640/627	PB	SSCP	9	468/452	131/129	10/19
Maguire 2011 [9]	England	150/150	PB	PCR	8	118/112	31/36	1/2
Meiklejohn 2001 [25]	America	209/704	PB	PCR	10	156/518	50/164	3/22
Ridker 1997 [32]	Holland	45/60	PB	PCR	8	35/44	8/16	2/0
Roldan 2008 [16]	Rome	115/180	HB	PCR	6	86/135	26/44	3/1
Rubattu 2005a [20]	Italy	294/286	HB	PCR	7	176/167	102/95	16/24
Rubattu 2005b [21]	Finland	234/326	PB	PCR	8	177/246	57/80	
van Goor 2002 [24]	America	65/122	PB	PCR	9	46/91	17/30	2/1
Wagner 1998 [30]	China	119/166	PB	NR	9	115/161	3/3	1/2
Zhang 2007 [17]	Germany	218/486	HB+PB	PCR	6	143/344	69/133	6/9

Notes: IS, ischemic stroke; CO, control; HB, hospital-based; PB, population-based; PCR, polymerase chain reaction sequence-specific primers; PCR-RFLP, polymerase chain reaction restriction fragment length polymorphism; SSCP, single-strand conformation polymorphism.

search terms: "stroke", "cerebrovascular", "glycoprotein IIIa", and "integrin beta3". All reviewed and assessed studies were in English. Specific Mesh words used for literature search were as follows: ["Stroke" [Mesh] or "Stroke" or "Cerebrovascular Disorders" [Mesh] or "Cerebrovascular"] and ["Platelet Glycoprotein GPIIb-IIIa Complex" [Mesh] or "glycoprotein III" or "Integrin beta3" [Mesh] or "Integrin beta3".

Inclusion and exclusion criteria

In the present meta-analysis, inclusion criteria were as follows: (1) case and control studies that associated GPIIIa gene polymorphisms with susceptibility to stroke risk; (2) studies having a firm diagnosis for ischemic stroke *vs.* normal health controls; (3) studies with outcome indicators of risk in cerebral infarction; and (4) studies with sufficient available data to calculate the odds ratio (OR) with corresponding 95% confidence interval (CI). In contrast, the exclusion criteria were as follows: (1) non-case-control studies; (2) studies on hemorrhagic stroke; (3) duplicate publications with overlapping cases; (4) studies with no available or reported data or have missing important data; and (5) reviews, meta-analyses, and other related publications.

Literature review, data extraction, and bias risk assessment

Two investigators (YZQ and NWX) independently reviewed the abstracts of each full-text report for eligibility. They extracted the following data from eligible studies (details are shown in **Figure 1**): (1) basic information, including research topic, name of the first author and publication journal, and date of publication; (2)

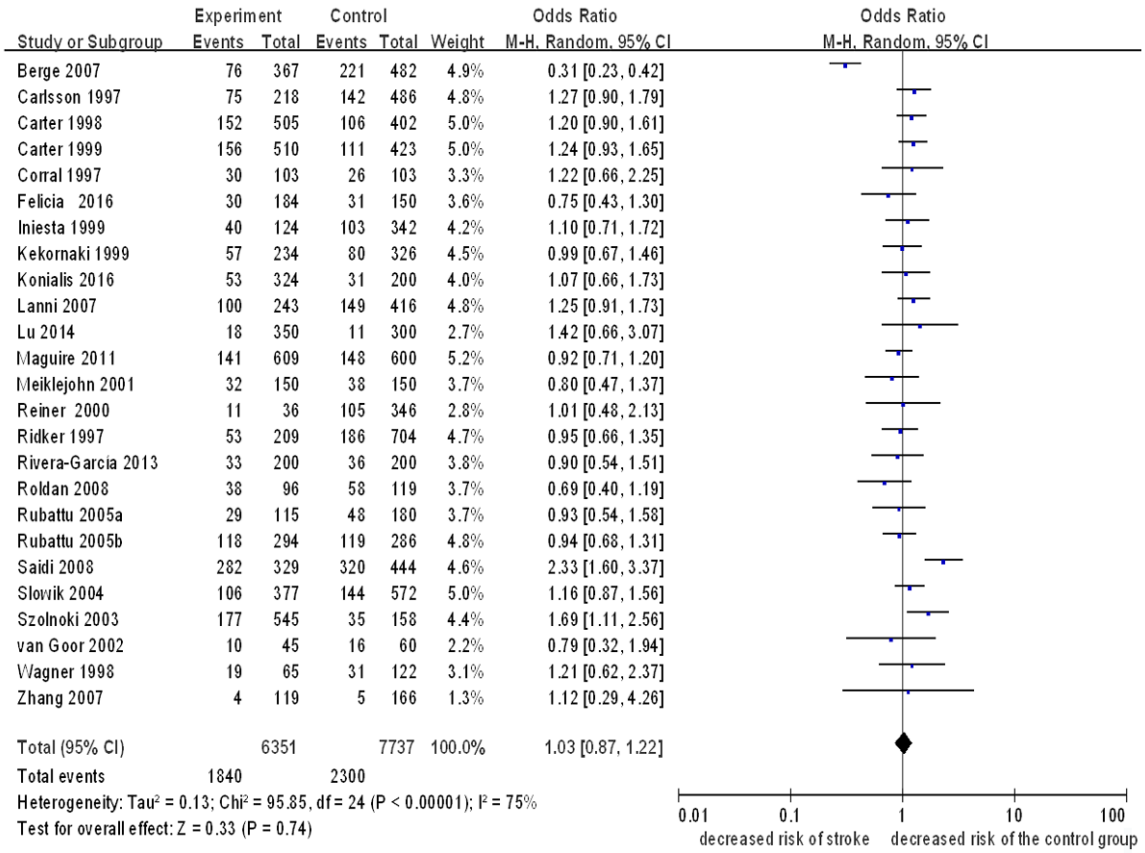

Figure 2. Forest plot of *GPIIIa* PIA1/A2 polymorphisms and association with risk for developing ischemic stroke.

key elements of study design and risk assessment; (3) information of study subjects including gender, age, country, ethnicity, and the number of cases and controls; and (4) gene identification, including methods of genotype identification and genotype distribution.

Quality assessment

After data were retrieved from eligible studies, methodological quality was first assessed using the Newcastle-Ottawa scale (NOS) for risk of bias. A NOS score of 9 stars was utilized and 6 stars or more was considered as high-quality research. These results were then checked and any discrepancy over quality scores was resolved by discussion among all investigators.

Statistical analysis

Association between *GPIIIa* polymorphisms and susceptibility to ischemic stroke was assessed using pooled ORs and their corresponding 95% CIs. Heterogeneity of the included studies was analyzed using X^2-test and the size of heterogeneity was determined by Cochran's Q statistic and I^2-metric. Meta-analysis was performed using a fixed effects model, when there was no statistical heterogeneity among studies. Otherwise, the random effects model was applied. Statistical significance was set at $P<0.05$. Potential publication bias was analyzed using Begg's funnel plot. All statistical analyses were performed using Revman 5.2 software (Cochrane Groups, London, UK).

Results

Study characteristics

Initially, a total of 1,517 articles were identified after the preliminary literature search. After reviewing titles and abstracts, 59 articles were included. After systematically reading the full texts, 25 studies satisfying the inclusion criteria were obtained [5, 10-32] (**Figure 1**). These 25 studies comprised of 6,351 patients with ischemic stroke and 7,737 controls. These studies are summarized in **Table 1**.

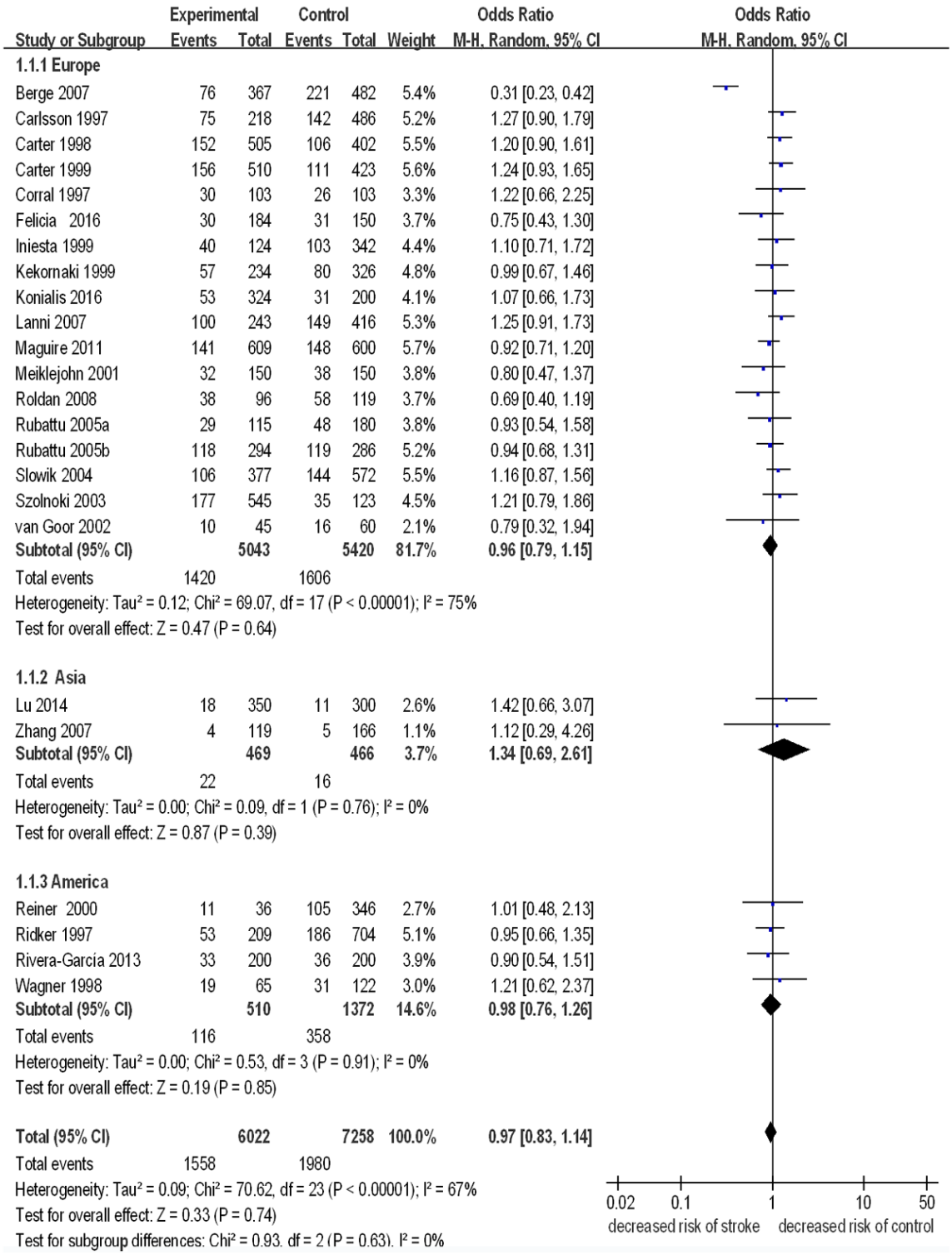

Figure 3. Association of *GPIIIa* PIA1/A2 polymorphisms with risk of ischemic stroke stratified by different regions and populations.

Meta-analysis

No association of GPIIIa polymorphisms with stroke susceptibility: GPIIIa PIA1/A2 polymorphisms and association with risk of ischemic stroke were assessed in these 25 case and control studies. First, the heterogeneity test was performed, with no heterogeneity observed

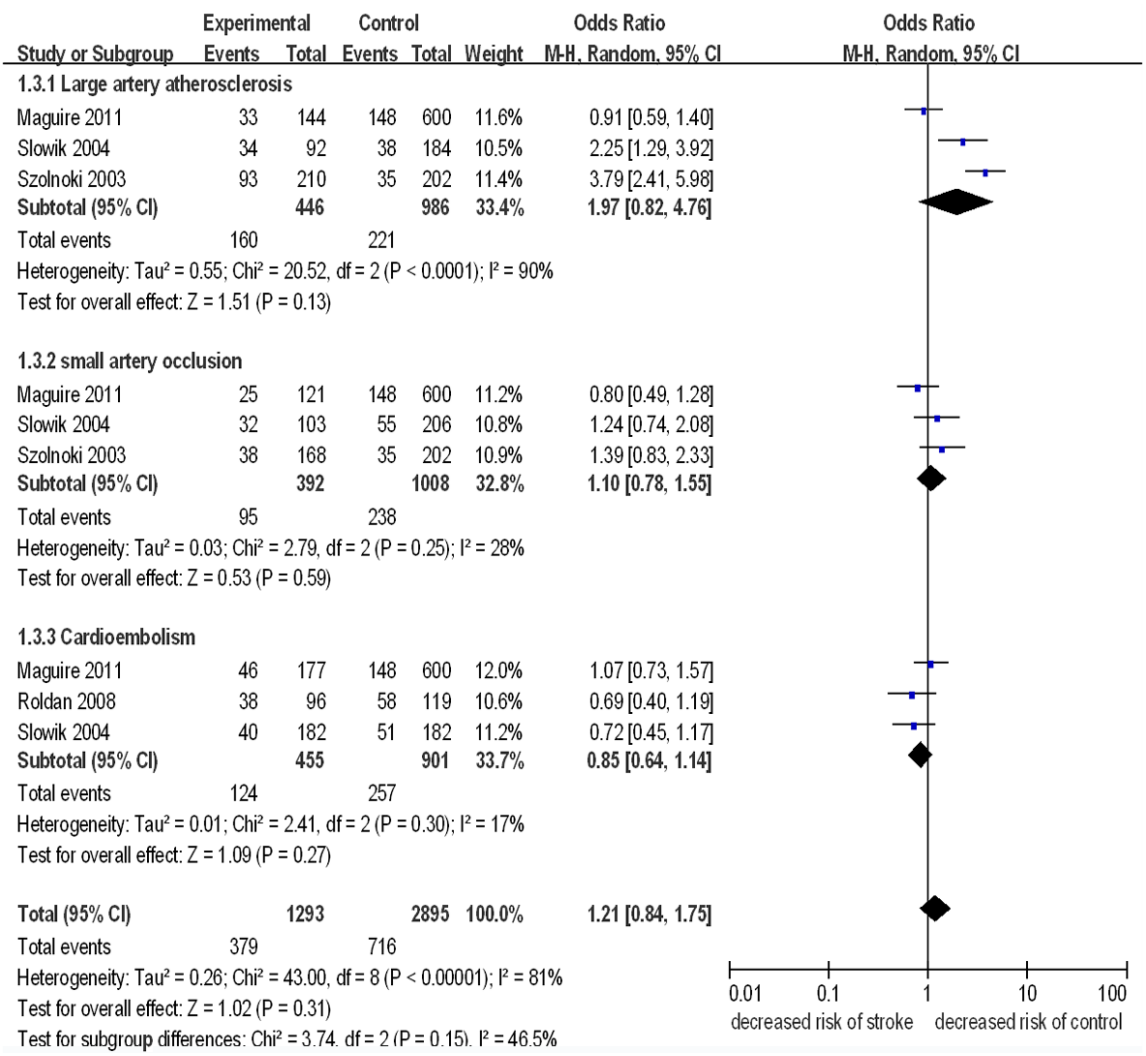

Figure 4. Association of *GPIIIa* PIA1/A2 polymorphisms with risk of ischemic stroke stratified by different etiologies of ischemic stroke using the forest plot.

among these studies (Z=0.33, I^2=75%). Therefore, the random effects model was used for meta-analysis. The present data revealed that *GPIIIa* PIA1/A2 polymorphisms did not alter the risk of cerebral infarction (OR=1.03; 95% CI=0.87, 1.22; P=0.74; **Figure 2**). Next, the association of *GPIIIa* polymorphisms with stroke susceptibility was further examined in different populations. In 18 of these included studies, no heterogeneity occurred (Z=0.47, I^2=75%). Hence, the random effects model was used for meta-analysis. For example, *GPIIIa* PIA1/A2 polymorphisms did not increase risk of ischemic stroke in a European population (OR=0.96; 95% CI=0.79, 1.15; *P*=0.64), while pooled OR was 1.34 (95% CI=0.65, 2.61; *P*=0.39) in Asian population (OR=0.97; 95% CI=0.83, 1.14; *P*=0.74) and in American population (**Figure 3**).

No association of GPIIIa polymorphism with the etiology of ischemic stroke: Results revealed that overall heterogeneity was observed (Z= 1.02, I^2=81%) among these included studies. Therefore, the random effects model was used to analyze the data. Three studies focused on cerebral atherosclerosis and results revealed that *GPIIIa* polymorphisms did not statistically alter the risk of cerebral atherosclerosis (OR=1.97, 95% CI=0.82, 4.76; *P*=0.13). The other three studies focused on small arterial occlusion, with results also revealing that GPIIIa polymorphisms did not alter the risk of small arterial occlusion (OR=1.10; 95% CI=0.78,

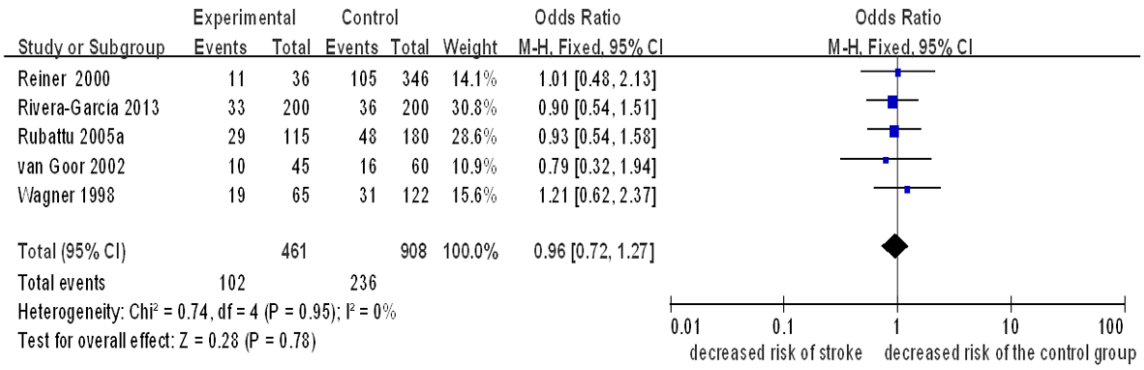

Figure 5. Association of *GPIIIa* PIA1/A2 polymorphisms with risk of ischemic stroke stratified by age of ischemic stroke patients using the forest plot.

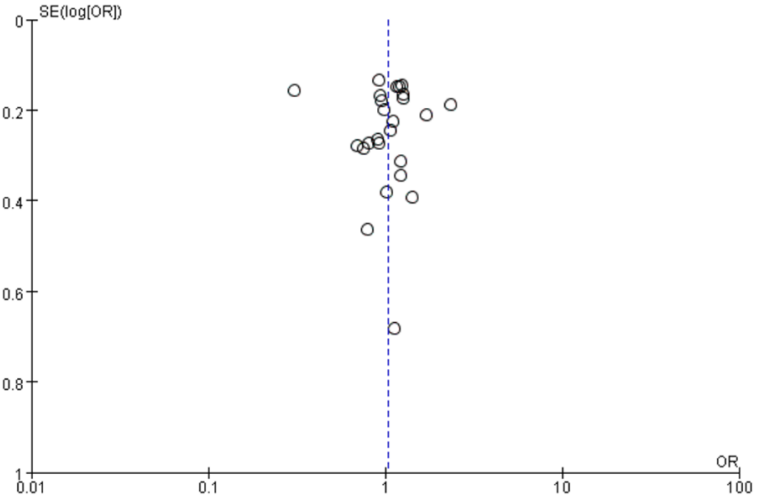

Figure 6. Funnel plot of publication bias.

1.55; *P*=0.59). Moreover, three studies focused on cardiac embolism and results revealed that *GPIIIa* po lymorphisms did not alter the risk of cardiogenic embolism (OR=0.85; 95% CI=0.64, 1.14; *P*=0.27; **Figure 4**).

Next, subgroup analysis, stratified by age of stroke patients, for association with GPIIIa polymorphisms was performed. Data revealed that there was no heterogeneity (Z=0.78, I^2=0%) in these studies. Therefore, meta-analysis was performed using the fixed effects model. Results revealed that *GPIIIa* polymorphisms did not alter the risk of cerebral infarction in young patients (OR=0.96; 95% CI=0.72, 1.27; *P*=0.78; **Figure 5**).

Publication bias

A funnel plot and Egger's linear regression test was used to assess any publication bias. It was found that the funnel plot was symmetrical in shape and Egger's tests provided statistical evidence of publication funnel plot symmetry. These analysis results did not show any evidence of publication bias (**Figure 6**).

Discussion

GPIIIa can be found in platelets, as part of the integrin complex and as a receptor for fibrinogen and von Willebrand factor, in order to facilitate platelet activation such as platelet aggregation and endothelial adherence [33]. The function of GPIIIa proteins in the human body is to change the function of platelets. Weiss et al. previously revealed that *GPIIIa* PIA2 polymorphisms are an important risk factor for developing acute coronary syndrome [34], while Finnish et al. demonstrated that *GPIIIa* PIA2 polymorphisms could increase incidence of heart disease by four fold (OR=4.5, *P*=0.001), particularly in male patients (OR=6.4, *P*=0.0005) [35, 36]. Recently, a number of studies have focused on the association between *GPIIIa* polymorphisms and risk of developing ischemic stroke, primarily due to the similar pathogenesis of acute cerebrovascular disease and acute myocardial infarction [37]. For example, GPIa/IIa receptor density and function have been associated with *GPIa* polymorphisms (807C/T and 873G/A). Thus, the present meta-analysis was expected to provide a comprehensive summary of presently available evidence on association

between GPIIIa polymorphisms and susceptibility to ischemic stroke. Unfortunately, the meta-analysis results of these 25 studies suggest that *GPIIIa* polymorphisms are not statistically associated with risk of ischemic stroke in different populations and are not associated with the potential etiology of ischemic stroke. Thus, other factors could alter the function of platelets in the blood stream.

The present meta-analysis is consistent with data reported by Ridker et al., in which *GPIIIa* PIA2 polymorphisms did not increase incidence of thromboembolic events in a randomized double-blind controlled trial [35]. Furthermore, incidence of ischemic stroke has been predominant in elderly subjects. However, in recent years, incidence of stroke in younger people has also gradually increased [38]. Moreover, a case-control study conducted by Kathryn et al. demonstrated that *GPIIIa* PIA2 polymorphisms had no association with risk of ischemic stroke in young women [31]. Rivera-Garcia et al. also reported that *GPIII* PIA1/A2 polymorphisms were not directly correlated to early-onset stroke [23]. In addition, the present meta-analysis concludes that there is no association between GPIIIa polymorphisms and risk of cerebral infarction (OR=0.96; 95% CI=0.72, 1.27; *P*=0.78). Thus, further study is necessary to clarify the link between *GPIIIa* PIA2 polymorphisms and the function or expression of GPIIIa proteins in the human body.

Furthermore, the present meta-analysis revealed that there was no association between *GPIIIa* polymorphisms and ischemic stroke (OR=0.97; 95% CI=[P<0.05] 0.83, 1.4; *P*=0.74) in different ethnic groups and regions. It was also determined whether *GPIIIa* PIA2 polymorphisms were associated with different causes of ischemic stroke, finding that *GPIIIa* PIA2 gene polymorphisms are not statistically associated with occurrence of atherosclerosis (OR=1.97; 95% CI=0.82, 4.76; *P*=0.13) and cardiogenic embolism (OR=0.85, 95% CI=0.64, 1.14; P=0.27). Biologically, platelet-collagen receptor glycoprotein Ia/IIa plays a fundamental role in the regulation of platelet adhesion to brillar collagen [39]. This process leads to platelet activation and thrombus formation, contributing to the pathogenesis of thrombotic disease [33]. Atherosclerosis does significantly contribute to the pathophysiology of ischemic stroke, while GP receptors mediate the formation of platelet thrombi. In early lesions, and during vascular endothelial injuries under high shear, platelet receptor glycoprotein GP-IX-V mediates adhesion of platelets to the subendothelial matrix through reactive subendothelial matrix proteins such as the von Willebrand factor [40]. The platelet membrane GP Ia/IIa complex also promotes platelet binding to collagen while the GP IIb/IIIa platelet membrane complex interacts with fibrinogen. These processes further enhance platelet and endothelial adhesion, activation, and aggregation, resulting in thrombosis. However, it remains unknown how *GPIIIa* PIA2 polymorphisms alter the functions or expression of GPIIIa proteins in these processes, requiring further clarification and research.

There were some limitations to the present meta-analysis. For example, some unpublished articles and data were excluded from the present study. Although the funnel plot and Egger's test did not show any evidence of publication bias among these studies, bias still may have occurred. Furthermore, this analysis only included studies published in the English language, possibly resulting in language bias. Finally, subgroup analysis of stroke subtype with sufficient cases and controls might be necessary, as ischemic stroke is a multifactorial disease.

In summary, the present data reveals no association between *GPIIIa* PIA2 polymorphisms and risk of ischemic stroke, etiology, and age group in different populations, although there were several limitations to the study. These results remain significant concerning our understanding of risks for developing ischemic stroke. Further multi-center studies with larger sample sizes are necessary to validate this conclusion. Moreover, a future well-designed study involving more gene-environment and gene-gene interactions is required to explore multiple risk factors for ischemic stroke.

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Disclosure of conflict of interest

None.

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