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Platelets Cellular and Functional Characteristics in Patients with Atrial Fibrillation: A Comprehensive Meta-Analysis and Systematic Review

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1 Alexander Weymann*
ABCDEFG 2 Sadeq Ali-Hasan-Al-Saegh*
ABCDEFG 3,4 Anton Sabashnikov*
ABCDEFG 3 Aron-Frederik Popov*
ABCDEFG 2 Seyed Jalil Mirhosseini
ABCDEFG 5 Luis Nombela-Franco
ABCDEFG 6 Luca Testa
ABCDEFG 2 Mohammadreza Lotfaliani
ABCDEFG 3,4 Mohamed Zeriouh
ABCDEFG 7 Tong Liu
ABCDEFG 8 Hamidreza Dehghan
ABCDEFG 9 Senol Yavuz
ABCDEFG 10,11,12 Michel Pompeu Barros de Oliveira Sá
ABCDEFG 13 William L. Baker
ABCDEFG 14 Jae-Sik Jang
ABCDEFG 7 Mengqi Gong
ABCDEFG 15 Umberto Benedetto
DGG 1 Pascal M. Dohmen
ABCDEFG 16 Fabrizio D'Ascenzo
ABCDEFG 17 Abhishek J. Deshmukh
ABCDEFG 18,19 Giuseppe Biondi-Zoccai
DE 20 Hugh Calkins
DE 21 Gregg W. Stone
Integrated Meta-Analysis of Cardiac Surgery and Cardiology-Group [IMCSC-Group]

1 Department of Cardiac Surgery, University Hospital Oldenburg, European Medical School Oldenburg-Groningen, Carl von Ossietzky University Oldenburg, Oldenburg, Germany
2 Cardiovascular Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
3 Department of Cardiothoracic Transplantation and Mechanical Circulatory Support, Royal Brompton and Harefield NHS Foundation Trust, Harefield Hospital, Harefield Middlesex, U.K.
4 Department of Cardiothoracic Surgery, University Hospital Cologne, Cologne, Germany
5 Instituto Cardiovascular, Hospital Universitario Clínico San Carlos, Madrid, Spain
6 Department of Cardiology, IRCCS Pol. S. Donato, S. Donato Milanese, Milan, Italy
7 Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, P.R. China
8 Department of Health Technology Assessment, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran
9 Department of Cardiovascular Surgery, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey
10 Division of Cardiovascular Surgery of Pronto Socorro Cardiológico de Pernambuco – PROCAPE, Recife, Brazil
11 University of Pernambuco – UPE, Recife, Brazil
12 Nucleus of Postgraduate and Research in Health Sciences of Faculty of Medical Sciences and Biological Sciences Institute (FCM/ICB), Recife, Brazil
13 University of Connecticut/Hartford Hospital Evidence-Based Practice Center, Hartford, CT, U.S.A.
14 Department of Cardiology, Busan Paik Hospital, Inje University College of Medicine, Busan, Korea
15 Bristol Heart Institute, University of Bristol, School of Clinical Sciences, Bristol, U.K.
16 Division of Cardiology, Department of Medical Sciences, Città della Salute e della Scienza Hospital, University of Turin, Turin, Italy
17 Mayo Clinic Heart Rhythm Section, Cardiovascular Diseases, Mayo Clinic, Rochester, MN, U.S.A.
18 Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy
19 Department of AngioCardioNeurology, IRCCS Neuromed, Pozzilli, Italy
20 Department of Cardiology, Johns Hopkins Medical Institutions, Baltimore, MD, U.S.A.
21 New York Presbyterian Hospital, Columbia University Medical Center, New York, NY, U.S.A.

* These authors contributed equally in this project

Corresponding Author: Seyed Jalil Mirhosseini, e-mail: dr.mirhosseini.imcsc@gmail.com
Contact to IMCSC-Group: www.imcsc-group.com, e-mail: info@imcsc-group.com
Source of support:

Background: This systematic review with meta-analysis aimed to determine the strength of evidence for evaluating the association of platelet cellular and functional characteristics including platelet count (PC), MPV, platelet distribution width (PDW), platelet factor 4, beta thromboglobulin (BTG), and p-selectin with the occurrence of atrial fibrillation (AF) and consequent stroke.

Material/Methods: We conducted a meta-analysis of observational studies evaluating platelet characteristics in patients with paroxysmal, persistent and permanent atrial fibrillations. A comprehensive subgroup analysis was performed to explore potential sources of heterogeneity.

Results: Literature search of all major databases retrieved 1,676 studies. After screening, a total of 73 studies were identified. Pooled analysis showed significant differences in PC (weighted mean difference (WMD)=–26.93 and

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p<0.001), MPV (WMD=0.61 and *p*<0.001), PDW (WMD=–0.22 and *p*=0.002), BTG (WMD=24.69 and *p*<0.001), PF4 (WMD=4.59 and *p*<0.001), and p-selectin (WMD=4.90 and *p*<0.001).

Conclusions: Platelets play a critical and precipitating role in the occurrence of AF. Whereas distribution width of platelets as well as factors of platelet activity was significantly greater in AF patients compared to SR patients, platelet count was significantly lower in AF patients.

MeSH Keywords: **Atrial Fibrillation • Blood Coagulation • Platelet Count**

Full-text PDF: http://www.basic.medscimonit.com/abstract/index/idArt/902557

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Background

As the most prevalent cardiac arrhythmia in the general population, atrial fibrillation (AF) is associated with a high risk of developing morbidities, such as thromboembolism, stroke and neurologic injury, major and minor organ injury or failure, and hospital re-admissions resulting in significantly increased health care costs [1–3]. Moreover, this situation might even exacerbate, since the number of AF patients is expected to double by 2050 [3].

The pathophysiological mechanism of increased prothrombotic tendency in patients with AF is highly intricate and multifactorial [4]. The association of increased platelet activity with atherosclerotic disease has been well documented [5]. Activated platelets have numerous vasoactive and prothrombotic factors [5,6]. Mean platelet volume (MPV) is a marker of platelet activation and function reflecting platelet size and changes either in terms of platelet stimulation or the rate of platelet production [6]. Virchow's triad on prothrombotic state including arterial stasis, vessel wall abnormalities, and coagulant alternations in the hemostatic balance may play a major role in the development of supraventricular arrhythmia [7]. Platelets represent an important part of hemostatic balance and can directly affect prothrombotic state.

Various studies have reported the association of hemostatic markers with the occurrence of AF. However, so far the data from the studies have been largely inconclusive. This systematic review with meta-analysis aimed to determine the strength of evidence for evaluating the association of platelet cellular and functional characteristics including platelet count, MPV, platelet distribution width (PDW), platelet factor 4, beta thromboglobulin (BTG), and p-selectin with the occurrence of AF and consequent stroke.

Material and Methods

Literature search

A comprehensive literature search was conducted in electronic scientific databases (Medline/PubMed, Web of Science, Embase, and Google Scholar) from their inception through August 10, 2016 to identify relevant studies on the association of platelet cellular and functional characteristics with the occurrence of AF and consequent stroke. Predefined search terms were as follows: "platelet count", "mean platelet volume", "platelet distribution width", "platelet factor 4", "beta thromboglobulin", "P-selectin", and "atrial fibrillation" or "supraventricular arrhythmia". No restrictions were applied regarding language, time of publication, or sample size of studies. To assess additional studies not indexed in common databases, all retrieved references of the enrolled studies, recent published review articles, and meta-analyses were also checked.

Study selection

Studies were included in the analysis when they met the following criteria: 1) human subjects; 2) cohort or case-control studies; 3) the study investigated the comparison between AF-cases and non-AF-population in terms of platelet biomarkers; 4) the study compared patients with and without stroke focusing on biomarkers. Abstracts without peer-review or from congress presentations only, as well as gray literature were not included.

Data extraction and outcome measures

Three investigators (S.A-H-S, S-J.M, and A.S) independently extracted the data. Discrepancies were resolved by a consensus standardized abstraction checklist used for recording data in each included study. Disagreements were discussed and resolved by senior authors (A.F-P, A.W, G.B.Z, and H.C). Author's name, year of publication, country, design of study, sample size, mean age, gender, coexistent cardiovascular diseases and risk factors, such as diabetes mellitus, hypertension and history of

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myocardial infarction, percentage of used anti-coagulants, type of AF, and details of platelet markers were extracted. For exploration of heterogeneity among trials, subgroup analyses of disparities in the patients' characteristics were performed for 1) the era of publication (before 2000 versus after 2000); 2) geographical area (Asia, Europe, Africa, North-America, South-America, and Oceania); 3) study design (case-control versus cohort); 4) size of patient cohort (≤300 versus >300); 5) mean age (≤60 years versus >60 years); 6) percentage of male patients (≤70% versus >70%); 7) presence of diabetes (≤30% versus >30%); 8) presence of hypertension (≤70% versus >70%); 9) history of cigarette smoking (≤0% versus >30%); 10) presence of myocardial infarction (≤20% versus >20%); 11) use of cardiovascular drugs, such as diuretics, angiotensin converting enzyme inhibitors, statins and beta-blockers (for each: ≤70% versus >70%); 12) AF-classification (chronic versus non-chronic; duration of AF ≥6 months and ≥1 attempt of electrical cardioversion to restore normal sinus rhythm were considered chronic AF and patients with duration of AF ≤6 months were considered non-chronic AF); 13) type of AF [paroxysmal (spontaneous termination of the arrhythmia within 7 days of its onset), persistent (sustained arrhythmia beyond 7 days), permanent (efforts to restore normal sinus rhythm have either failed or been forgone)]; and 12) anticoagulation (code-1: patients did not receive anticoagulants in both groups, code-2: all participants received anticoagulants in both groups, code-3: range of percentages between both groups >5 0%, code-4: range of percentages between both groups <50%, code-5: no information available about anticoagulation in both groups, and code-6: anticoagulation information not available for one group only).

Homogenization of extracted data

Continuous data were expressed as mean ± standard deviation (SD). For studies reporting interquartile ranges, the mean was estimated according to [minimum+maximum+2(median)]/4 and SD was calculated based on (maximum–minimum)/4 for groups with sample sizes of n ≤70 and (maximum–minimum)/6 for sample sizes of >70 [8].

Quality assessment and statistical analysis

The Newcastle-Ottawa scale was independently used by two investigators (S.A-H-S and M.G) to assess the quality of studies [9]. Total scores ranged from 0 (worst quality) to 9 (best quality) for case-control or cohort studies. Data were analyzed by STATA 11.0 using METAN and METABIAS modules. For non-categorical data, pooled effect size measured was weighted mean difference (WMD) with 95% CI. A p value <0.1 for Q test or I^2 >50% showed significant heterogeneity among the studies. Heterogeneity among trials was examined by applying a random effect model when indicated. Publication bias was assessed using the Begg tests. A p value <0.05 was considered statistically significant.

Results

Literature search strategy and included studies

A total of 1,676 studies were retrieved from the literature search and screened databases, of which 1,005 studies (59.9%) were excluded after meticulous evaluation during the first review due to either unnecessary information (n=710), inadequate report of endpoints of interest (n=265) or report of non-matched data based on mean ±SD or median [minimum-maximum] (n=30). In total, 671 potentially relevant full-text articles were reviewed, and finally 73 studies were analyzed in the meta-analysis (Supplementary Table 1).

Association of platelet characteristics with AF

Platelet count

A total of 6,255 cases were selected from 45 studies, of which 2,964 were allocated to the AF group and 3,291 to the SR group. Patient populations in the selected studies ranged from 27 to 621 patients. Mean platelet count was 237.3×10^9/L in AF group and 240.04×10^9/L in SR (Tables 1, 2). Using a random effect model, pooled assessment effect analysis indicated that the mean platelet count was significantly lower in patients with AF than in patients with SR with WMD of –26.93 (95% CI: –28.35 to –25.51; p<0.001, Figure 1). Significant heterogeneity was observed among the studies (I^2=93.5%; heterogeneity p<0.001).

MPV

A total of 3,609 cases were included from 19 studies, of which 1,646 were allocated to the AF group and 1,963 to the SR. Patient populations of the included studies ranged from 57 to 621 patients. Mean level of MPV was 9.22 FL in the AF group and 8.40 FL in the SR group (Tables 1, 2). Pooled analysis revealed that MPV level was significantly higher in patients with AF compared to those with SR with WMD of 0.61 (95% CI: 0.56 to 0.65; p<0.001, Figure 2) using a random effect model. There was a significant heterogeneity among the studies (I^2=94.3%; heterogeneity p<0.001).

PDW

A total of 1,117 cases were included from three studies, of which 290 were allocated to the AF group and 827 to the SR group. Using a random effect model, pooled analysis revealed that PDW was statistically lower in the AF group than in the SR group with WMD of –0.22 (95% CI: –0.37 to –0.08; p=0.002, Supplementary Figure 1). There was significant heterogeneity among the studies (I^2=87.4%; heterogeneity p<0.001)

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Table 1. Characteristics of included studies for meta-analysis of association of platelets characteristics and AF.

First Author	Year	Country	Design	N-AF	N-SR	Age-AF	Age-SR	Male-AF	Male-SR	AC-AF	AC-SR	Type of AF	NOS
Karatas [20]	2016	Turkey	Case-control	40	581	65.7	56.4	70	75	100	100	ND	8
Drabik [21]	2015	Poland	Case-control	47	50	60.8	59.4	65.9	64	38.3	26	Persistent	9
Drabik [21]	2015	Poland	Case-control	41	50	60.6	59.4	46.3	64	51.2	26	Paroxysmal	9
Idriss [22]	2015	Egypt	Case-control	21	20	34.2	29.3	28.5	70	33.3	0	ND	7
Akdag [23]	2015	Turkey	Case-control	96	52	63.6	64.5	64	56	54.1	ND	Combined	9
Akyuz [24]	2015	Turkey	Case-control	40	50	63	61.5	72.5	72	20	14	Combined	7
Chavaria [25]	2015	USA	Case-control	40	250	70.6	60.7	65	84	ND	ND	ND	6
Erdogan [26]	2014	Turkey	Case-control	34	33	70.5	68.6	47	51.5	66.6	0	Permanent	9
Xu (without comorbidities) [27]	2014	China	Cohort	57	58	65.1	67	50.9	50	50.9	15.5	ND	7
Xu (with comorbidities) [27]	2014	China	Cohort	57	58	68.95	67	52.6	50	49.1	15.5	ND	7
Acet (PAF) [28]	2014	Turkey	Case-control	71	63	63	61.1	42	46	ND	ND	Paroxysmal	9
Acet (persistent and permanent) [28]	2014	Turkey	Case-control	63	63	64.6	61.1	41	46	ND	ND	Combined	9
Arik (with INR 2–3) [29]	2014	Turkey	Case-control	125	123	70.4	68.9	41.6	39.8	ND	ND	Permanent	8
Arik (with abnormal INR) [29]	2014	Turkey	Case-control	125	123	70	68.9	36	39.8	ND	ND	Permanent	8
Distelmaier [30]	2014	USA	Case-control	66	132	73.5	73.5	61	61	ND	ND	ND	7
Gungor [31]	2014	Turkey	Case-control	117	60	48.3	46.1	60.6	55	75.2	8.3	Combined	9
Sonmez [32]	2014	Turkey	Cohort	52	33	70	70	34.6	39.3	59.6	36.3	Persistent	7
Ulu [33]	2014	Turkey	Case-control	25	32	ND	ND	ND	ND	ND	ND	ND	7
Turgut [34]	2013	Turkey	Case-control	81	81	64	62	51	53	28	20	ND	7
Jaremo (healthy control) [35]	2013	Sweden	Cohort	58	24	69	66	79.3	54.1	12.06	0	ND	8
Jaremo (disease control) [35]	2013	Sweden	Cohort	58	72	69	74	79.3	56.9	12.06	41.6	ND	8
Berge [36]	2013	Norway	Cohort	63	126	75	75	71.4	70.6	8	33	Combined	9

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Table 1 continued. Characteristics of included studies for meta-analysis of association of platelets characteristics and AF.

First Author	Year	Country	Design	N-AF	N-SR	Age-AF	Age-SR	Male-AF	Male-SR	AC-AF	AC-SR	Type of AF	NOS
Ertas (without stroke) [37]	2013	Turkey	Case-control	87	24	69	38	44	58	58	ND	ND	6
Ertas (with stroke) [37]	2013	Turkey	Case-control	39	24	71	38	36	58	51	ND	ND	6
Sahin [38]	2013	Turkey	Case-control	72	72	65.1	64.7	48.2	51.3	ND	ND	Persistent	7
Tekin [39]	2013	Turkey	Case-control	107	112	74	73	31	40	ND	ND	ND	7
Turfan (without CVA) [40]	2013	Turkey	Cohort	77	58	63	56	57.4	51.7	44.3	0	ND	7
Turfan (with CVA) [40]	2013	Turkey	Cohort	63	58	69	56	52.4	51.7	41.3	0	ND	7
Feng [41]	2012	China	Case-control	185	189	65.9	65.7	62.7	60.8	76.8	83.1	Combined	8
Acevedo [42]	2012	Chile	Case-control	130	20	67	ND	ND	ND	0	0	Combined	ND
Hayashi [43]	2011	Japan	Case-control	14	13	53.1	62.8	93	92	100	100	Paroxysmal	7
Hayashi [43]	2011	Japan	Case-control	14	13	60.1	62.8	93	92	100	100	ND	7
Fu [44]	2011	China	Case-control	90	79	54.1	54.8	70	57	22	0	Combined	8
Hou (disease control) [45]	2010	China	Case-control	26	26	65.2	64.5	57.6	57.6	7.6	11.5	ND	8
Hou (healthy control) [45]	2010	China	Case-control	26	26	65.2	65.4	57.6	57.6	7.6	0	ND	8
Alberti [46]	2009	Italy	Case-control	17	34	68.1	60.8	94.1	23.5	0	0	Persistent	7
Choudhury (disease control) [47]	2008	UK	Case-control	121	71	62.58	64.04	76	72	37.2	47.4	ND	6
Choudhury (healthy control) [47]	2008	UK	Case-control	121	65	62.58	62.03	76	68	37.2	0	ND	6
Colkesen [48]	2008	Turkey	Case-control	103	87	63	45	55	21	50	14	Paroxysmal	8
Blann [49]	2008	UK	Case-control	54	28	65	64	64.8	60.7	60	0	ND	6
Topaloglu (disease control) [50]	2007	Turkey	Case-control	18	28	37	32	ND	ND	ND	ND	ND	6
Topaloglu (healthy control) [50]	2007	Turkey	Case-control	18	20	37	35	ND	ND	ND	ND	ND	6
Yip [51]	2006	Taiwan	Case-control	62	20	66.2	65.3	66.1	60	58.1	0	ND	7
Heeringa [52]	2006	UK	Cohort	162	324	78	77	51	51	ND	ND	ND	8

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Table 1 continued. Characteristics of included studies for meta-analysis of association of platelets characteristics and AF.

First Author	Year	Country	Design	N-AF	N-SR	Age-AF	Age-SR	Male-AF	Male-SR	AC-AF	AC-SR	Type of AF	NOS
Inoue (with comorbidities) [53]	2004	Japan	Case-control	159	92	ND	ND	ND	ND	ND	ND	ND	7
Inoue (lone AF) [53]	2004	Japan	Case-control	87	19	ND	ND	ND	ND	ND	ND	ND	7
Conway [54]	2004	UK	Case-control	106	41	69	67	63	61	86	0	Permanent	6
Conway [55]	2004	Turkey	Case-control	37	37	67	68	72.9	67.56	ND	ND	Persistent	6
Atalar (paroxysmal AF) [56]	2003	Turkey	Case-control	15	22	45	47	60	63.6	0	0	Paroxysmal	6
Atalar (permanent AF) [56]	2003	Turkey	Case-control	25	22	51	47	64	63.6	0	0	Permanent	6
Kamath [57]	2003	UK	Case-control	31	31	61	66	61.3	41.9	0	0	Combined	6
Kamath [57]	2003	UK	Case-control	93	31	66	66	63.4	41.9	0	0	Permanent	6
Kamath [58]	2002	UK	Case-control	29	29	61	65	55.17	41.3	37.9	0	Paroxysmal	7
Kamath [58]	2002	UK	Case-control	87	29	65	65	63.2	41.3	37.9	0	Permanent	7
Kamath [59]	2002	UK	Case-control	93	50	70	70	62.4	64	0	0	ND	6
Kamath [60]	2002	UK	Case-control	34	23	73	ND	20	ND	0	0	ND	6
Li-Saw-Hee [61]	2001	UK	Case-control	23	20	65	63	69.6	85	69.6	0	Paroxysmal	8
Li-Saw-Hee [61]	2001	UK	Case-control	23	20	65	63	69.6	85	100	0	Persistent	8
Li-Saw-Hee [61]	2001	UK	Case-control	23	20	67	63	69.6	85	100	0	Permanent	8
Mondillo [62]	2000	Italy	Case-control	45	35	67.6	66.3	80	85.7	55	0	Permanent	7
Li-Saw-Hee [63]	2000	UK	Case-control	52	60	68	66	80	75	0	0	ND	6
Li-Saw-Hee [64]	1999	UK	Case-control	25	25	60	58	20	20	ND	ND	ND	6
Minamino [65]	1999	UK	Case-control	28	28	64	64	71.4	71.4	7	14	ND	6
Minamino [66]	1997	Japan	Case-control	45	45	63	63	73.3	73.3	ND	ND	ND	6
Kahn [67]	1997	Canada	Case-control	50	31	ND	ND	ND	ND	0	0	ND	7
Sohara [68]	1997	Japan	Case-control	21	9	59.1	59	ND	ND	0	0	Paroxysmal	6

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Table 1 continued. Characteristics of included studies for meta-analysis of association of platelets characteristics and AF.

First Author	Year	Country	Design	N-AF	N-SR	Age-AF	Age-SR	Male-AF	Male-SR	AC-AF	AC-SR	Type of AF	NOS
Lip GY [69]	1996	UK	Case-control	51	26	70.4	ND	ND	ND	0	0	ND	6
Nagao [70]	1995	Japan	Case-control	17	19	81.5	78.4	47.1	47	0	0	ND	8
Sohara [71]	1994	Japan	Case-control	19	9	60	ND	76.9	ND	0	0	Paroxysmal	6
Gustafsson (with stroke) [72]	1990	Sweden	Case-control	20	40	77	77	ND	ND	0	0	ND	8
Gustafsson (without stroke) [72]	1990	Sweden	Case-control	20	40	77	77	ND	ND	0	0	ND	8
Yamauchi (without valvular heart disease) [73]	1986	Japan	Case-control	73	57	47	36	ND	89.5	0	0	ND	6
Yamauchi (with valvular heart disease) [73]	1986	Japan	Case-control	26	57	55	36	ND	89.5	0	0	ND	6

Table 2. Information about markers and their levels in each study.

First author	markers	Levels
Karatas [20]	PC, MPV, PDW	PC [AF: 230±69.3 *vs.* SR: 240±77.5] MPV [AF: 9.5±1.7 *vs.* SR: 8.7±1] PDW [AF: 13.9±1.7 *vs.* SR: 13.4±1.4]
Drabik [21]	PC, PF4	PC [AF: 202±20.5 *vs.* SR: 219±16.5] PF4 [AF: 66.1±10.25 *vs.* SR: 50.55±10.45]
Drabik [21]	PC, PF4	PC [AF: 210.25±15.75 *vs.* SR: 219±16.5] PF4 [AF: 62.72±7.95 *vs.* SR: 50.55±10.45]
Idriss [22]	P-selectin	P-selectin [AF: 85.9±42.1 *vs.* SR: 38±7.8]
Akdag [23]	PC, MPV	PC [AF: 265.5±73.4 *vs.* SR: 248.2±67.2] MPV [AF: 8.9±1.1 *vs.* SR: 7.8±1]
Akyuz [24]	PC, MPV	PC [AF: 277±79 *vs.* SR: 264±82] MPV [AF: 9.8±0.6 *vs.* SR: 8.4±0.6]
Chavaria [25]	PC	PC [AF: 242.2±54.1 *vs.* SR: 243.2±66.2]
Erdogan [26]	PC, MPV, P-selectin	PC [AF: 245.6±114.9 *vs.* SR: 238.4±66.6] MPV [AF: 7.82±1.2 *vs.* SR: 7.68±0.7] P-selectin [AF: 25.86±11.89 *vs.* SR: 23.95±8.49]
Xu (without comorbidities) [27]	PC, MPV	PC [AF: 205±31 *vs.* SR: 209±41] MPV [AF: 10.6±1.9 *vs.* SR: 8.7±0.8]
Xu (with comorbidities) [27]	PC, MPV	PC [AF: 206±42 *vs.* SR: 209±41] MPV [AF: 11.7±2 *vs.* SR: 8.7±0.8]
Acet (PAF) [28]	PC	PC [AF: 248.9±59 *vs.* SR: 259.8±95.9]
Acet (persistent and permanent) [28]	PC	PC [AF: 268±98 *vs.* SR: 259.8±95.9]
Arik (with INR 2-3) [29]	PC, MPV, PDW	PC [AF: 259±54.3 *vs.* SR: 255.75±41.5] MPV [AF: 7.56±0.63 *vs.* SR: 7.63±0.68] PDW [AF: 17.05±0.86 *vs.* SR: 17.52±0.71]

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Table 2 continued. Information about markers and their levels in each study.

First author	markers	Levels
Arik (with abnormal INR) [29]	PC, MPV, PDW	PC [AF: 238.75±41.16 *vs.* SR: 255.75±41.5] MPV [AF: 8.26±0.63 *vs.* SR: 7.63±0.68] PDW [AF: 17.50±1.13 *vs.* SR: 17.52±0.71]
Distelmaier [30]	PC	PC [AF: 202±14.75 *vs.* SR: 215±14.16]
Gungor [31]	PC, MPV	PC [AF: 249.4±59.4 *vs.* SR: 253.4±61.1] MPV [AF: 8.99±0.65 *vs.* SR: 9.14±0.98]
Sonmez [32]	PC	PC [AF: 231±60 *vs.* SR: 247±67]
Ulu [33]	PC, MPV	PC [AF: 236.4±63.9 *vs.* SR: 233.3±86.2] MPV [AF: 11.47±0.93 *vs.* SR: 10.37±1.07]
Turgut [34]	PC, MPV	PC [AF: 274±82 *vs.* SR: 253±83] MPV [AF: 9±0.2 *vs.* SR: 8.4±0.2]
Jaremo (healthy control) [35]	PC	PC [AF: 241±64 *vs.* SR: 260±78]
jaremo (disease control) [35]	PC, P-selectin	PC [AF: 241±64 *vs.* SR: 265±84] P-selectin [AF: 102±53 *vs.* 74±44]
Berge [36]	PC, P-selectin	PC [AF: 230±7.5 *vs.* SR: 261.25±4.16] P-selectin [AF: 31.2±3.72 *vs.* 31.52±2.05]
Ertas (without stroke) [37]	PC	PC [AF: 232±55 *vs.* 258±54]
Ertas (with stroke) [37]	PC	PC [AF: 240±82 *vs.* 258±54]
Sahin [38]	MPV	MPV [AF: 8.31±1.12 *vs.* SR: 7.99±1.39]
Tekin [39]	PC, MPV	PC [AF: 242±90 *vs.* SR: 243±67] MPV [AF: 9.49±1.08 *vs.* SR: 9.09±1.13]
Turfan (without CVA) [40]	PC, MPV	PC [AF: 264±94 *vs.* SR: 213±72] MPV [AF: 9.1±1 *vs.* SR: 8.6±1.3]
Turfan (with CVA) [40]	PC, MPV	PC [AF: 245±73 *vs.* SR: 213±72] MPV [AF: 9.7±0.9 *vs.* SR: 8.6±1.3]
Feng [41]	PC, MPV	PC [AF: 213.3±82.5 *vs.* SR: 217.6±81.7] MPV [AF: 9.95±1.32 *vs.* SR: 9.02±1.16]
Acevedo [42]	P-selectin	P-selectin [AF: 219±141 *vs.* 145±29]
Hayashi [43]	PC	PC [AF: 260±83 *vs.* 190±77]
Hayashi [43]	PC	PC [AF: 200±14 *vs.* 258±54]
Fu [44]	PC, P-selectin	PC [AF: 210±55.5 *vs.* SR: 221.1±51.1] P-selectin [AF: 33.4±7.4 *vs.* 29.2±6.5]
Hou (disease control) [45]	P-selectin	P-selectin [AF: 32±5 *vs.* 32±4.9]
Hou (healthy control) [45]	P-selectin	P-selectin [AF: 32±5 *vs.* 33±7]
Alberti [46]	PC	PC [AF: 185.6±10 *vs.* 243.3±9.5]
Choudhury (disease control) [47]	PC, MPV, P-selectin	PC [AF: 259.9±66.3 *vs.* SR: 261.1±63.4] MPV [AF: 7.6±1.4 *vs.* SR: 7.8±0.9] P-selectin [AF: 61±7 *vs.* SR: 55.25±6.8]
Choudhury (healthy control) [47]	PC, MPV, P-selectin	PC [AF: 259.9±66.3 *vs.* SR: 266.9±56.1] MPV [AF: 7.6±1.4 *vs.* SR: 7.4±0.97] P-selectin [AF: 61±7 *vs.* SR: 40.75±5.25]
Colkesen [48]	PC, MPV	PC [AF: 242±73 *vs.* SR: 236±53] MPV [AF: 10±2 *vs.* SR: 8.3±1.5]

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Table 2 continued. Information about markers and their levels in each study.

First author	markers	Levels
Blann [49]	P-selectin	P-selectin [AF: 72.5±7.5 *vs.* SR: 46.25±6.25]
Topaloglu (disease control) [50]	PF4	PF4 [AF: 115.39±7.56 *vs.* SR: 97.96±25.51]
Topaloglu (healthy control) [50]	PF4	PF4 [AF: 115.39±7.56 *vs.* SR: 6.95±2.49]
Yip [51]	PC	PC [AF: 204±57 *vs.* SR: 209±49]
Heeringa [52]	P-selectin	P-selectin [AF: 31.3±10.1 *vs.* SR: 31.8±13.1]
Inoue (with comorbidities) [53]	BTG, PF4	BTG [AF: 74.5±3.3 *vs.* SR: 43.9±3.3] PF4 [AF: 21.6±1.5 *vs.* SR: 14.7±1.9]
Inoue (lone AF) [53]	BTG, PF4	BTG [AF: 77±4.9 *vs.* SR: 46.3±5.5] PF4 [AF: 23.1±2.1 *vs.* SR: 17.7±3.1]
Conway [54]	P-selectin	P-selectin [AF: 53.5±4 *vs.* SR: 50.75±6.75]
Conway [55]	P-selectin	P-selectin [AF: 54.75±5.75 *vs.* SR: 51.25±6.25]
Atalar (paroxysmal AF) [56]	BTG, PF4	BTG [AF: 175.35±11.55 *vs.* SR: 161.7±8.4] PF4 [AF: 72.45±11.55 *vs.* SR: 56.7±12.6]
Atalar (permanent AF) [56]	BTG, PF4	BTG [AF: 191.1±14.7 *vs.* SR: 161.7±8.4] PF4 [AF: 81.9±12.6 *vs.* SR: 56.7±12.6]
Kamath [57]	PC, BTG, P-selectin	PC [AF: 280±81 *vs.* SR: 253±51] BTG [AF: 90.03±13.3 *vs.* SR: 71.98±10.5] P-selectin [AF: 38±6 *vs.* SR: 36±11]
Kamath [57]	PC, BTG, P-selectin	PC [AF: 264±75 *vs.* SR: 253±51] BTG [AF: 92.13±11.02 *vs.* SR: 71.98±10.5] P-selectin [AF: 39±10 *vs.* SR: 36±11]
Kamath [58]	PC, BTG, P-selectin	PC [AF: 279±73 *vs.* SR: 252±53] BTG [AF: 89.51±13.9 *vs.* SR: 66.93±8.13] P-selectin [AF: 38±11 *vs.* SR: 34±10]
Kamath [58]	PC, BTG, P-selectin	PC [AF: 266±76 *vs.* SR: 252±53] BTG [AF: 93.97±10.5 *vs.* SR: 66.93±8.13] P-selectin [AF: 39±10 *vs.* SR: 34±10]
Kamath [59]	PC, BTG	PC [AF: 253±77 *vs.* SR: 261±62] BTG [AF: 92.4±11.9 *vs.* SR: 69.3±10.5]
Kamath [60]	PC, BTG, P-selectin	PC [AF: 253±67 *vs.* SR: 270±49] BTG [AF: 88.2±16.8 *vs.* SR: 67.72±11.5] P-selectin [AF: 37±10 *vs.* SR: 36±9]
Li-Saw-Hee [61]	P-selectin	P-selectin [AF: 37±3 *vs.* SR: 36±4]
Li-Saw-Hee [61]	P-selectin	P-selectin [AF: 50.5±6.5 *vs.* SR: 36±4]
Li-Saw-Hee [61]	P-selectin	P-selectin [AF: 216.5±30.5 *vs.* SR: 36±4]
Mondillo [62]	BTG, PF4	BTG [AF: 80.11±31.29 *vs.* SR: 40.95±8.75] PF4 [AF: 6.82±1.68 *vs.* SR: 4.02±0.84]
Li-Saw-Hee [63]	P-selectin	P-selectin [AF: 205.25±47.75 *vs.* SR: 125.75±17.25]
Li-Saw-Hee [64]	BTG, P-selectin	BTG [AF: 34±6 *vs.* SR: 33±11] P-selectin [AF: 73±33 *vs.* SR: 144±78]
Minamino [65]	BTG	BTG [AF: 84±19.45 *vs.* SR: 43.22±8.32]
Minamino [66]	BTG	BTG [AF: 87.65±47.4 *vs.* SR: 55.72±22.02]

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Table 2 continued. Information about markers and their levels in each study.

First author	markers	Levels
Kahn [67]	PC	PC [AF: 230±98 *vs.* SR: 233±49]
Sohara [68]	BTG, PF4	BTG [AF: 38±27.3 *vs.* SR: 22.8±7.85] PF4 [AF: 16.4±18.2 *vs.* SR: 3.37±2.26]
Lip GY [69]	PC, BTG	PC [AF: 242±67 *vs.* SR: 224±63] BTG [AF: 187±30 *vs.* SR: 99.75±25.25]
Nagao [70]	BTG, PF4	BTG [AF: 43.8±23.2 *vs.* SR: 31.9±12.7] PF4 [AF: 9.06±7.04 *vs.* SR: 5.68±3.53]
Sohara [71]	BTG, PF4	BTG [AF: 31.1±29.9 *vs.* SR: 22.8±7.8] PF4 [AF: 9.8±15.9 *vs.* SR: 3.4±2.2]
Gustafsson (with stroke) [72]	PC, BTG, PF4	PC [AF: 179±18.5 *vs.* SR: 238.75±15.75] BTG [AF: 40.1±5.8 *vs.* SR: 25.47±2.62] PF4 [AF: 5.77±2.02 *vs.* SR: 2.55±0.45]
Gustafsson (without stroke) [72]	PC, BTG, PF4	PC [AF: 172.25±8.75 *vs.* SR: 238.75±15.75] BTG [AF: 36.25±2.75 *vs.* SR: 25.47±2.62] PF4 [AF: 3.77±1.07 *vs.* SR: 2.55±0.45]
Yamauchi (without valvular heart disease) [73]	BTG, PF4	BTG [AF: 49.4±35.8 *vs.* SR: 31.2±14] PF4 [AF: 18.6±27.2 *vs.* SR: 11.6±8.2]
Yamauchi (with valvular heart disease) [73]	BTG, PF4	BTG [AF: 64.1±52.8 *vs.* SR: 31.2±14] PF4 [AF: 34.1±45.5 *vs.* SR: 11.6±8.2]

BTG

A total of 1,781 patients were included from 22 studies, of whom 1,043 were allocated to the AF group and 738 to the SR. Mean level of BTG was 83.62 ng/mL in patients with AF and 58.72 ng/mL in those with SR (Tables 1, 2). Pooled analysis revealed that the mean level of BTG was significantly higher in AF patients compared to those with SR with WMD of 24.69 (95% CI: 24.07 to 25.32; $p<0.001$, Figure 3) with considerable heterogeneity among the studies ($I^2=97.6\%$; heterogeneity $p<0.001$).

PF4

A total of 1,220 cases were selected from 16 studies, of which 651 were allocated to the AF group and 569 to the SR group. Mean levels of PF4 were 41.43 ng/mL in the AF group and 24.78 ng/mL in the SR group (Tables 1, 2). Pooled analysis showed that the level of PF4 was remarkably higher in patients suffering AF compared to controls with WMD of 4.59 ng/mL (95% CI: 4.33 to 4.86; $p<0.001$, Figure 4) using a random effect model. There was significant heterogeneity among the studies ($I^2=99.6\%$; heterogeneity $p<0.001$).

P-selectin

A total of 2,725 cases were included from 24 studies, of which 1,469 were allocated to the AF group and 1,256 to the SR. Mean level of P-selectin was 69.52 ng/mL in the AF group and 51.51 ng/mL in the SR group (Tables 1, 2). Using a random effect model, pooled analysis showed that the level of P-selectin was significantly higher in the AF group compared to the SR group with WMD of 4.90 ng/mL (95% CI: 4.36 to 5.45; $p<0.001$, Figure 5). Significant heterogeneity was observed among the studies ($I^2=98.6\%$; heterogeneity $p<0.001$).

Association of platelet characteristics with the incidence of stroke in patients with AF

Five studies examined the association of platelet markers with stroke (Table 3). Platelet count and MPV were investigated in at least two studies which were included in the meta-analysis (Table 3). According to pooled assessment analysis, the level of MPV (number of studies=2, WMD of 0.97, 95% CI: 0.70 to 1.24; $p<0.001$ and $I^2=95\%\%$; heterogeneity $p<0.001$, Supplementary Figure 2) was significantly higher in patients with stoke compared to those without major cerebrovascular events. Pooled analysis showed that platelet count (number of studies=4, WMD of 7.23, 95% CI: –4.96 to 19.42; $p=0.245$ and $I^2=35.2\%\%$; heterogeneity $p=0.21$, Supplementary Figure 3) was not significantly different in patients with or without stroke.

Publication bias and subgroup analysis

Begg tests suggested that there might be publication bias for studies examining the levels of MPV and BTG (Supplementary Figures 4–8). Details of subgroup analysis are reported in Supplementary Tables 2 and 3.

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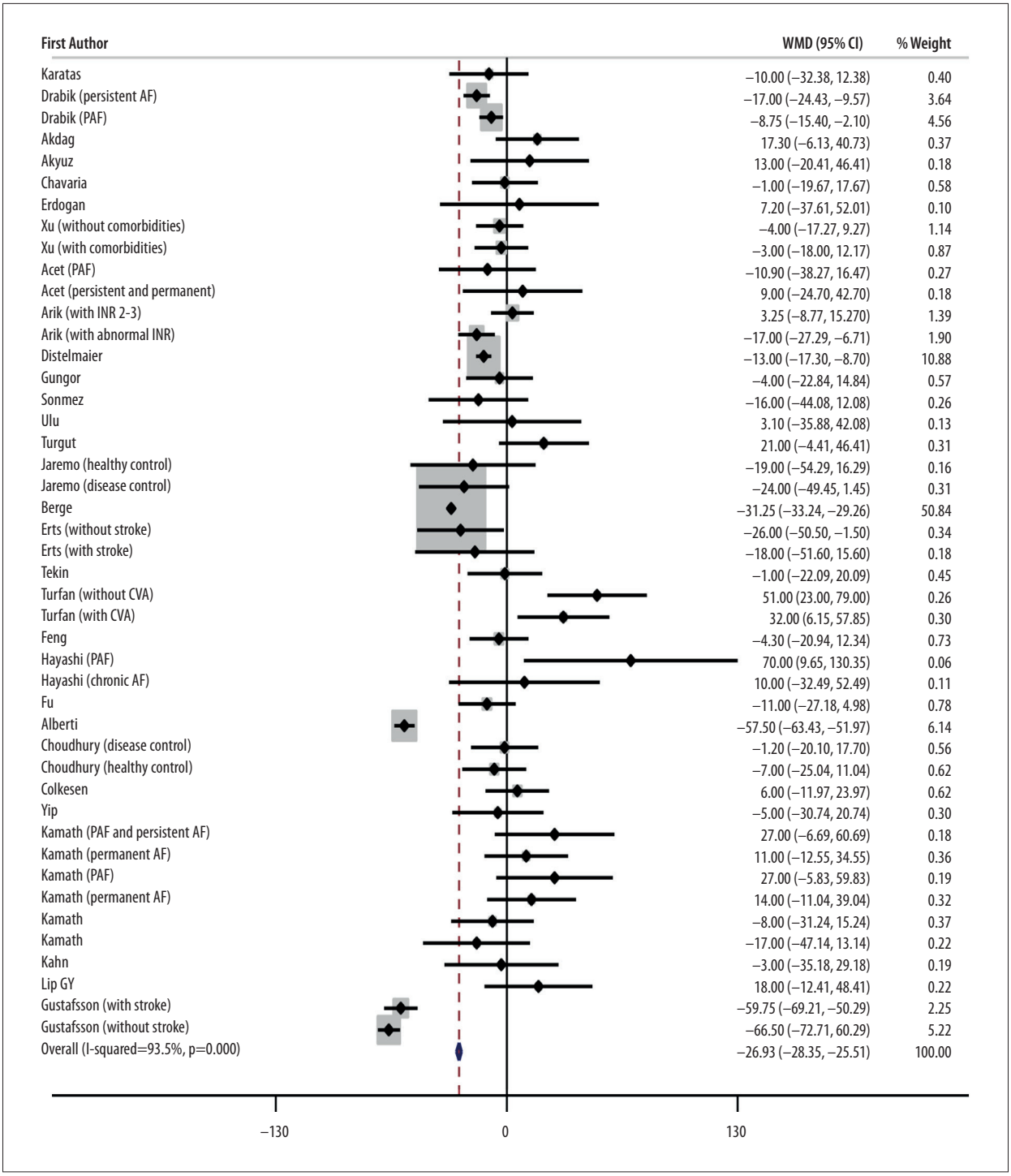

Figure 1. Forest plot of weighted mean difference (WMD) for association between platelet count and occurrence of AF.

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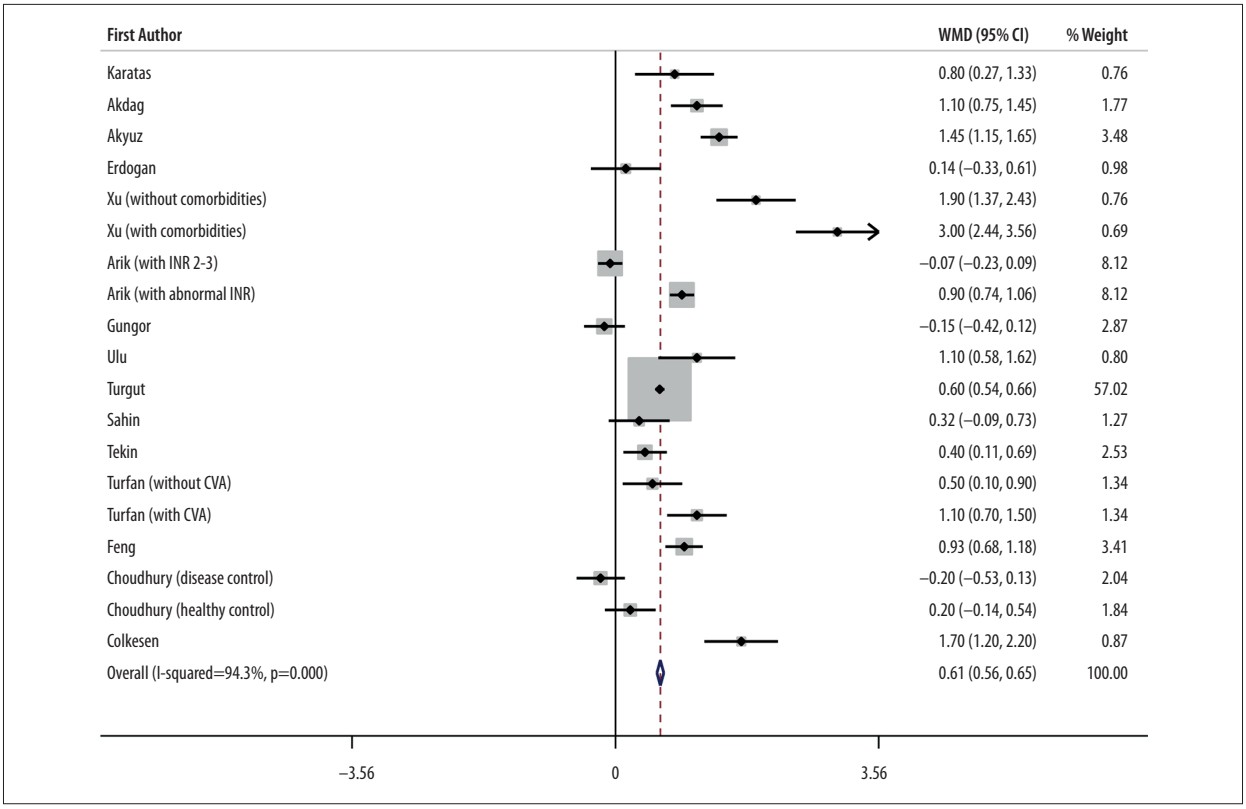

Figure 2. Forest plot of weighted mean difference (WMD) for association between level of mean platelet volume and occurrence of AF.

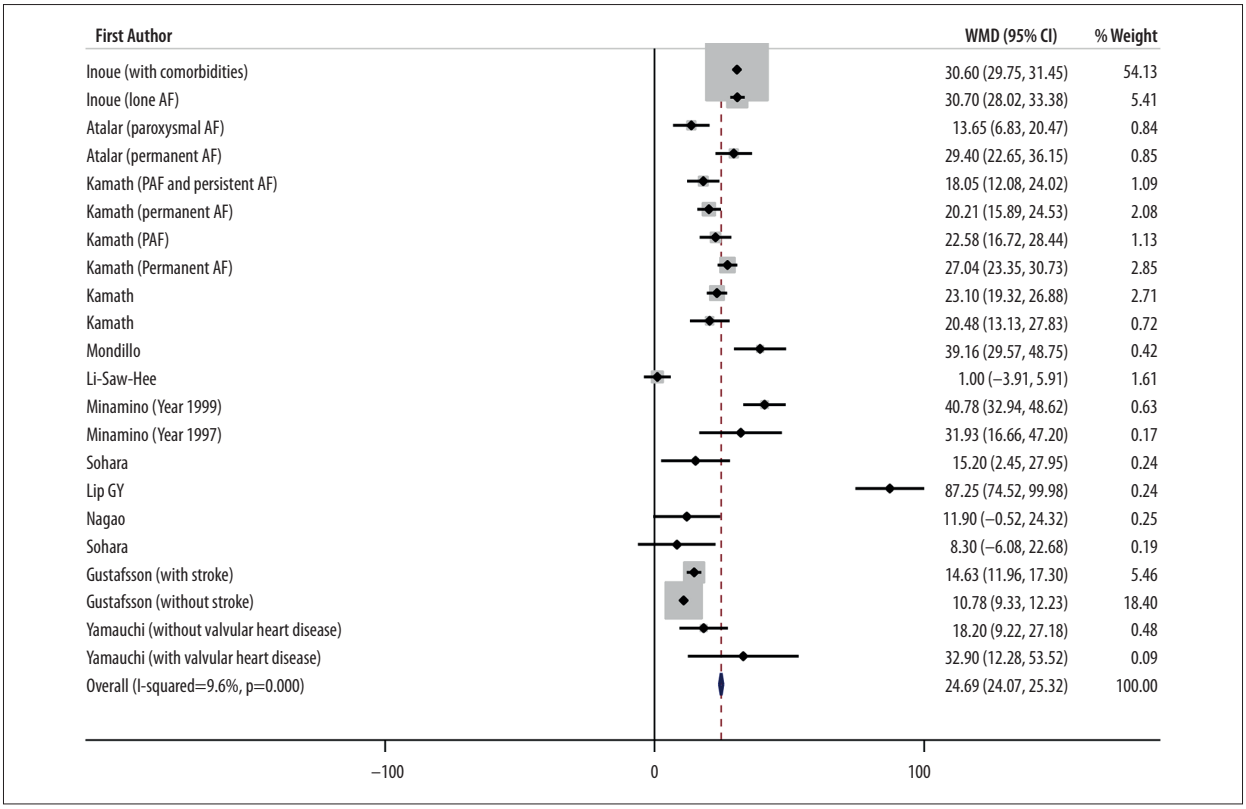

Figure 3. Forest plot of weighted mean difference (WMD) for association between level of beta thromboglobulin and occurrence of AF.

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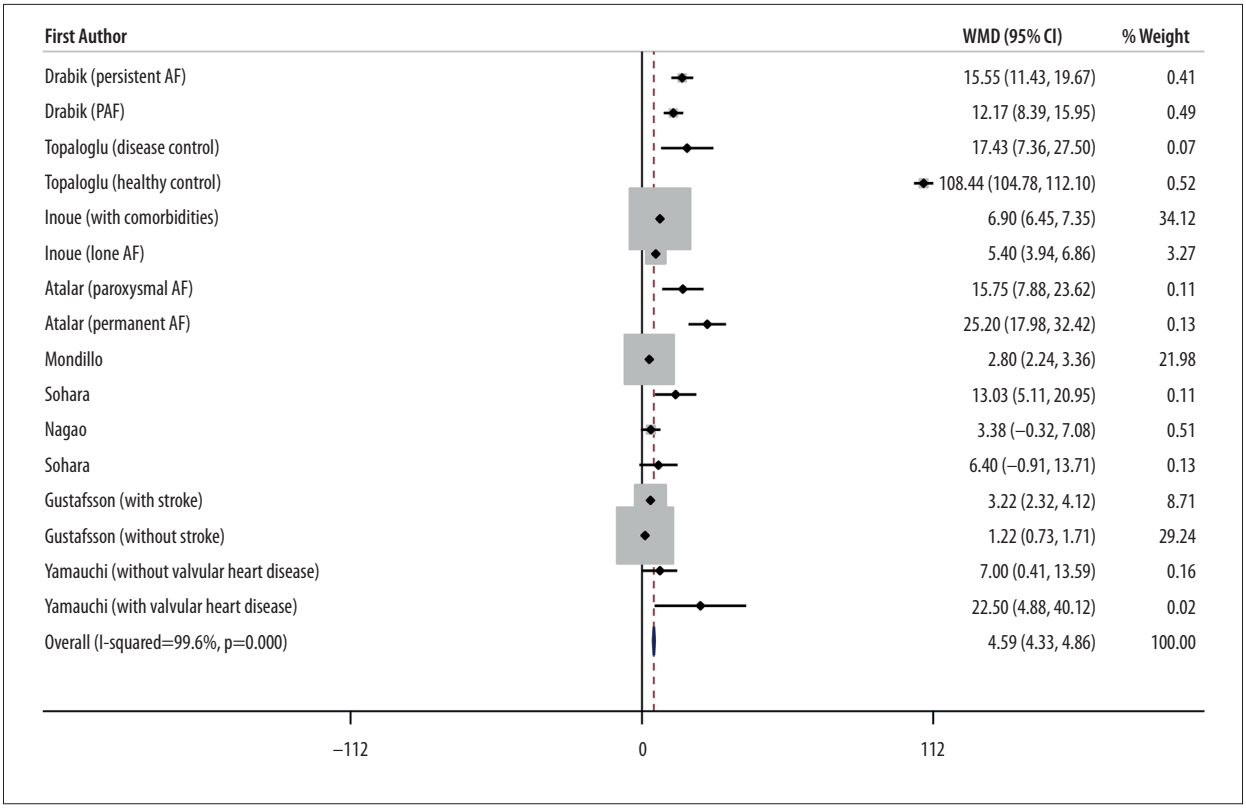

Figure 4. Forest plot of weighted mean difference (WMD) for association between level of platelet factor 4 and occurrence of AF.

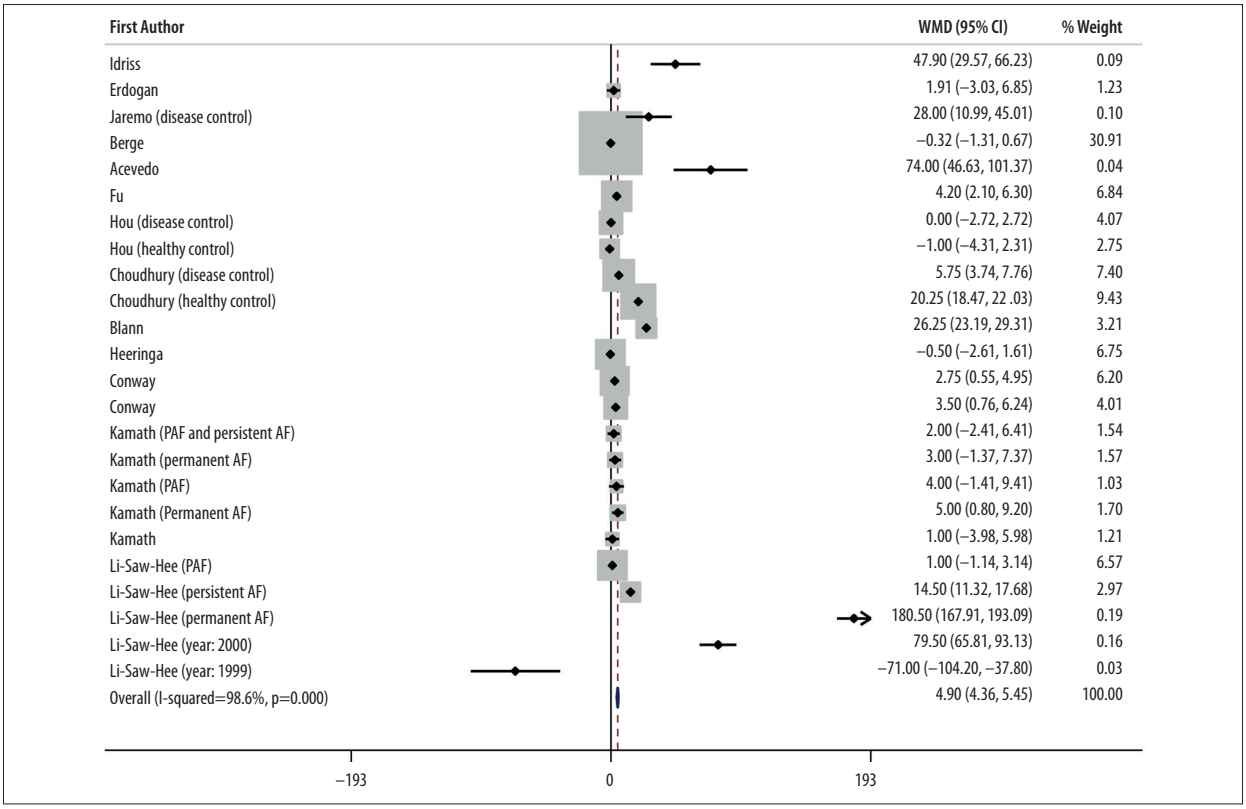

Figure 5. Forest plot of weighted mean difference (WMD) for association between level of P-selectin and occurrence of AF.

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Table 3. Included studies about relationship between platelet characteristics with clinical adverse events in patients with AF.

First Author	Country and year	Study design	Number	Mean age	AC in patients with adverse events	AC in patients without adverse events	Platelet markers
Bayar [74]	Turkey-2015	Case-control	90	65.3	–	–	MPV [AF: 11.1±1.3 *vs.* SR: 9.1±1]
Ertas [37]	Turkey-2013	Case-control	126	70	58	51	PC [AF: 240±82 *vs.* SR: 232±55]
Turfan [40]	Turkey-2013	Cohort	140	66	44.3	41.3	PC [AF: 245±73 *vs.* SR: 264±94] MPV [AF: 9.7±0.9 *vs.* SR: 9.1±1]
Kahn [67]	Canada-1997	Case-control	75	72.7	100%	100%	PC [AF: 253±82 *vs.* SR: 230±98]
Gustafsson [72]	Sweden-1990	Case-control	40	70	–	–	PC [AF: 188±37 *vs.* SR: 148±8.7] BTG [AF: 40.1±5.8 *vs.* SR: 36.25±2.75] PF4 [AF: 5.77±2.05 *vs.* SR: 3.77±1.07]

Discussion

The incidence of cardiovascular diseases has been dramatically increasing in developed and developing countries in recent decades [1]. AF represents one of the most critical and prevalent cardiac arrhythmias precipitating morbidity and mortality in short- and long-term periods of time and adversely affecting patient's quality of life [1,2]. Despite the wide range of investigations on diagnosis and treatment of AF conducted and published in recent years, the pathophysiology of this multifactorial disease is not completely understood [2]. Due to a number of complex mechanisms that are involved in the development of AF the current controversies regarding diagnosis and treatment of AF seem to be justifiable [2,3]. Among other things the mechanism of oxidation and release of free radical oxygen has been defined as one of the main precipitating mechanisms in development of AF [2]. Also, the Virchow's triad, which plays a critical role in predicting AF and includes arterial stasis, vessel wall abnormalities, and coagulant alternations in the hemostatic balance, indicates that prothrombotic state is another important pathophysiological mechanism of AF. However, the exact mechanism involving prothrombotic state in AF is ambiguous [6,7]. Nevertheless, it is known that platelets are involved in both thrombosis and inflammation becoming a key factor in pathogenesis of cardiovascular diseases [6]. In the present study, we attempted conducting a meticulous and multilateral investigation on platelets cellular and functional characteristics in patients with AF compared to patients with sinus rhythm. Our findings revealed that from statistical and clinical points of view, AF was significantly associated with reduced platelet count. However, an undeniable fact is that a considerable heterogeneity among the studies was present in this analysis. A subgroup analysis revealed that the type of AF (chronic or non-chronic) could probably be a factor of heterogeneity: there was an inverse relationship between the occurrence of AF and platelet count in non-chronic AF, while such an association was not observed in patients with chronic AF. On the other hand, reduced platelet count was not observed in paroxysmal and permanent AF, while this relationship only existed in persistent AF. In general, it can be concluded that the type of AF is one of the heterogeneity factors in platelet count analysis. Barura et al. reported that exposure to cigarette smoking could change the hemostatic process through multiple mechanisms including alteration of the function of endothelial cells, platelets, and coagulation factors [10]. However, our subgroup analysis demonstrated that platelet count was not significantly reduced in cigarette smokers with AF compared to smokers with SR, while lower platelet count was observed in non-smokers with AF compared to smokers with SR. This can be explained by the fact that cigarette smoking can disturb the actual platelet count via increasing aggregation and adhesion of the platelets [10]. In fact, we believe that the occurrence of AF is strongly associated with reduced platelet count while the type of AF, cigarette smoking, and the geographical area of the studies represent factors of heterogeneity.

MPV is also an important biomarker of platelet activity. Large platelets secrete many critical mediators of coagulation, inflammation, thrombosis, and atherosclerosis. A close relationship has been found between MPV and cardiovascular risk factors, such as diabetes mellitus, hypertension, and hypercholesterolemia [11,12]. The results of this study revealed that the average MPV was significantly higher in AF patients than in SR patients, thus implying the direct relationship between MPV and the risk of AF. According to our subgroup analysis, study sample size and diabetes mellitus could probably result in heterogeneity. Our findings also showed that levels of the platelet markers were notably higher in both chronic and non-chronic AF patients compared to the SR group. Interestingly, Sansanayudh et al. recently found an association between elevated MPV and CAD. Patients with CAD and slow coronary blood flow showed larger

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MPV compared to controls [13]. The mean difference in MPV in patients with an acute coronary event was higher than those with stable coronary disease [13]. They suggested that MPV might be used for risk stratification or to add diagnostic accuracy to the traditional risk stratification markers in patients with CAD [13].

PWD is a platelet biomarker and predictive factor in cardiovascular diseases. Varastehravan et al. indicated that PDW in patients with ST-segment elevation myocardial infarction could be used for prediction of ST-segment resolution and clinical outcomes [14]. According to the results of the present study, PDW was greater in patients with AF than those with SR and thus had a direct relationship to the risk of AF. However, due to the limited number of studies on PDW no subgroup analysis could be performed to examine heterogeneity factors. Nevertheless, our evidence shows that AF might be associated with both larger volume of platelets as well as distribution width.

Platelet activation is demonstrated by the release of platelet granules and their components into the circulation. BTG and platelet factor 4 (PF4) represent specific platelet proteins of alpha-granules, which can be secreted into surrounding medium during cell activation [15,16]. Based on the results of this study, increased levels of BTG might be also directly related to the risk of AF. Our subgroup analysis revealed the type of AF (chronic or non-chronic), history of CS, and gender as factors of heterogeneity. The present study also indicated that the level of PF4 was remarkably higher in AF patients compared to those with SR, while the level of BTG and PF4 were significantly increased compared to SR patients in both chronic and non-chronic AF as well as paroxysmal and permanent AF. Therefore, it can be suggested that platelet activity and release of specific proteins from their granules may also play a vital role in pathophysiology of AF.

P-selectin, an integral membrane glycoprotein of platelets and endothelial cells, is involved in the onset of atherosclerosis and cardiovascular diseases [17]. P-selectin functions as a cell adhesion molecule (CAM) on the surfaces of activated endothelial cells, which line the inner surface of blood vessels, and activated platelets. In unactivated endothelial cells, it is stored in α-granules [17]. The present study revealed that P-selectin marker was notably higher in AF patients compared to SR group. The subgroup analysis proposed the type of studies and the type of AF as factors of heterogeneity. In brief, cohort studies did not show any relationship between the level of P-selectin and occurrence of AF, whereas case-control studies strongly confirmed this relationship. It is necessary to mention that the number of cohort studies was remarkably less than case-control studies. Increased level of P-selectin was observed in both chronic and non-chronic AF in our meta-analysis. On the other hand, this association was found in persistent and permanent AF but not in paroxysmal AF. Overall, taking into account the evidence from the present study, platelet count and other biomarkers may considerably influence the development of AF underlying the role of platelets in pathophysiology of AF as well as the predictive function of platelet factors.

The results of our study showed that the level of MPV was obviously higher in AF patients with stroke as compared to AF patients without cerebrovascular events. However, we found no association between platelet count and the occurrence of stroke.

There is a hypothesis that cardiac risk factors might also affect the occurrence of AF. Feng et al. proposed a hypothesis that the relationship between hemostatic markers and AF became insignificant after stratifying based on cardiovascular disease status [18]. Our results showed that cardiac risk factors including diabetes, hypertension, and history of MI were not recognized as heterogeneity factors. However, it should be mentioned that an important cardiac risk factor affecting our results was cigarette smoking.

Lip et al. argued that using anticoagulants could reduce the level of hemostatic factors in AF patients, and consequently, differences in receiving anticoagulants in various studies could be considered as a factor of heterogeneity [19]. According to the results of our subgroup analyses of platelet count and level of MPV and PF4, differences in using anticoagulants could possibly play a considerable role in the occurrence of heterogeneity. It should also be noted that in our meta-analysis on non-experimental studies more heterogeneity was found which may be explained by the following reasons: 1) biases are less controlled, 2) more confounding factors, and 3) differences in defining outcomes. As a result, performing analysis on non-experimental studies, finding associations, effect size, and estimating heterogeneity as well as appropriate method for finding the factors of heterogeneity should be the aim of such meta-analyses.

Conclusions

In summary, considering the results of this study, we strongly state that platelets play a critical and precipitating role in the occurrence of AF as the volume and distribution width of platelets as well as the factors of platelet activity appeared to be significantly higher in AF patients compared to SR patients. On the other hand, AF was associated with lower platelet count. Therefore, emphasizing the potential predictive role of platelet factors in the occurrence of AF, we strongly recommend adding cellular and functional characteristics of platelets to the diagnostic criteria of AF in the future.

Declaration of interest

The authors declare that there is no conflict of interest.

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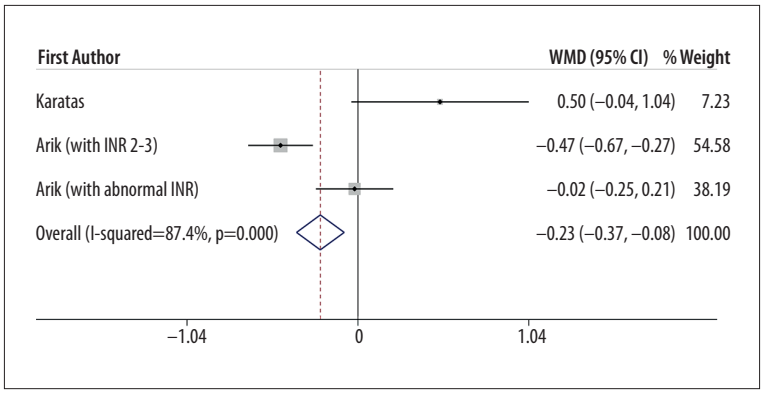
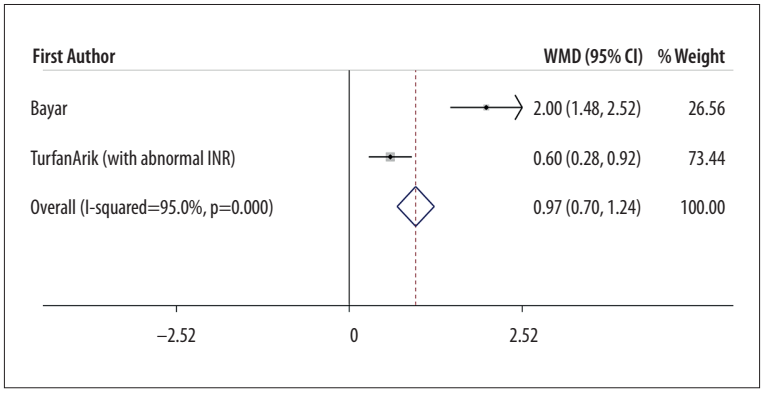
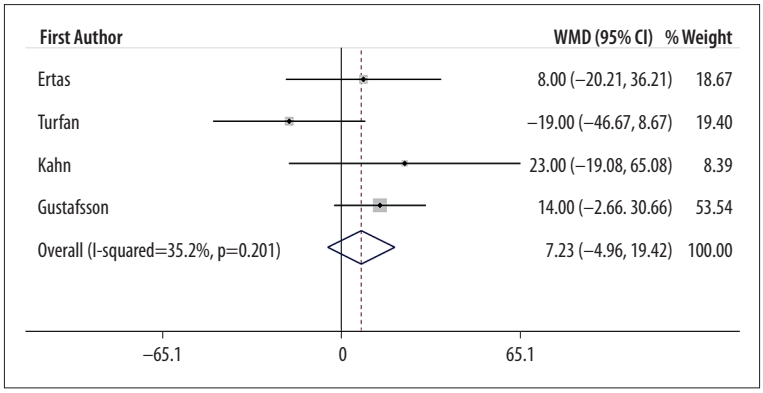
Supplementary Files



Supplementary Figure 1. Forest plot of weighted mean difference (WMD) for association between level of platelet distribution width and occurrence of AF.



Supplementary Figure 2. Forest plot of weighted mean difference (WMD) for association between level of mean platelet volume and occurrence of stroke.



Supplementary Figure 3. Forest plot of weighted mean difference (WMD) for association between level of platelet count and occurrence of stroke.

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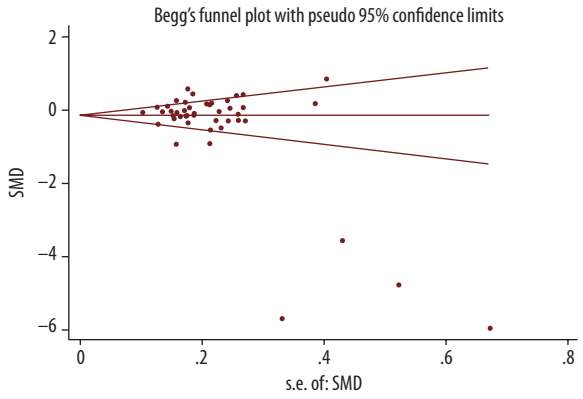

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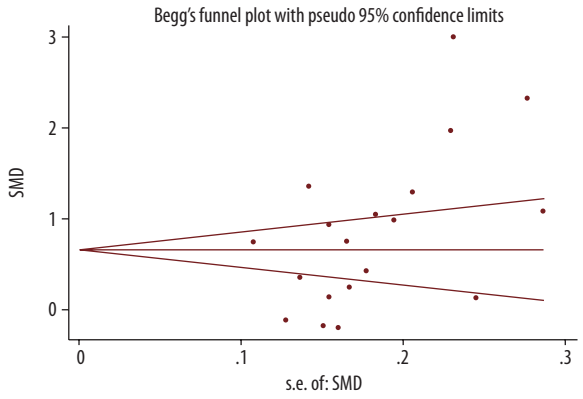
Note: defalut data input format (theta, se_thera) assumed.
Tests for Publication Bias
Begg's Test

adj. Kendall's Score (P-Q) = −148
Std. Dev. of Score = 102.23
Number of Studies = 45
z = −1.45
Pr > |z| = 0.148
z = 1.44 (continuity corrected)
Pr > |z| = 0.150 (continuity corrected)

Eggr's test

Std_Eff	Coef.	Std. Err.	t	P> |t|	[95% conf.	Interval]
slope	.0780889	.3098371	2.52	0.016	1560429	1.405735
bias	−5.12514	1.638633	−3.13	0.003	−8.429759	−1.820521

Supplementary Figure 4. Funnel plot for publication bias of studies investigating of platelet count.



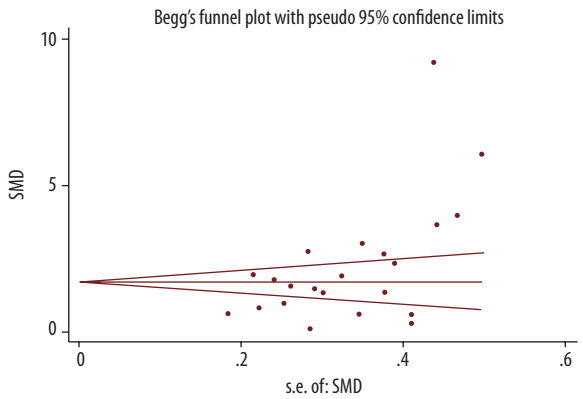
metabias _ES _seES, graph (begg)
Note: defalut data input format (theta, se_thera) assumed.
Tests for Publication Bias
Begg's Test

adj. Kendall's Score (P-Q) = 69
Std. Dev. of Score = 28.58
Number of Studies = 19
z = 2.41
Pr > |z| = 0.016
z = 2.38 (continuity corrected)
Pr > |z| = 0.017 (continuity corrected)

Eggr's test

Std_Eff	Coef.	Std. Err.	t	P> |t|	[95% conf.	Interval]
slope	−.6894023	.6131353	−1.12	0.276	−1.983005	.6042002
bias	8.427844	3.687688	2.29	0.035	.647502	16.20819

Supplementary Figure 5. Funnel plot for publication bias of studies investigating of mean platelet volume.



metabias _ES _seES, graph (begg)
Note: defalut data input format (theta, se_thera) assumed.
Tests for Publication Bias
Begg's Test

adj. Kendall's Score (P-Q) = 91
Std. Dev. of Score = 35.46
Number of Studies = 22
z = 2.57
Pr > |z| = 0.010
z = 2.54 (continuity corrected)
Pr > |z| = 0.011 (continuity corrected)

Eggr's test

Std_Eff	Coef.	Std. Err.	t	P> |t|	[95% conf.	Interval]
slope	−1.249722	1.062333	−1.18	0.253	−3.46571	.9662658
bias	10.50874	3.56853	2.94	0.008	3.064914	17.95256

Supplementary Figure 6. Funnel plot for publication bias of studies investigating of beta thromboglobulin.

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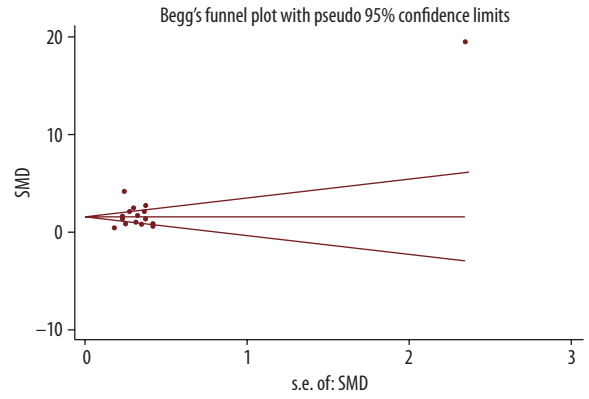


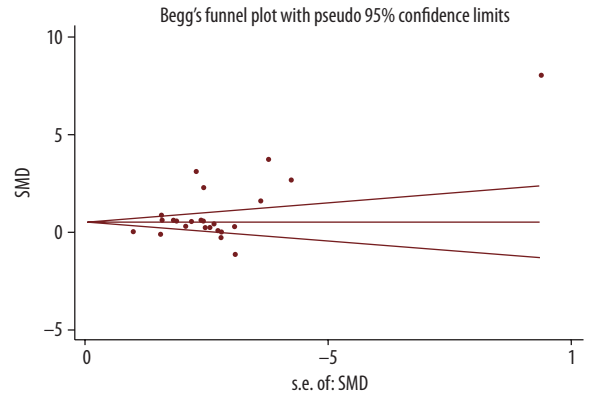
metabias _ES _seES, graph (begg)
Note: defalut data input format (theta, se_thera) assumed.
Tests for Publication Bias
Begg's Test

adj. Kendall's Score (P-Q) = 12
Std. Dev. of Score = 22.21
Number of Studies = 16
z = 0.54
Pr > |z| = 0.589
z = 0.50 (continuity corrected)
Pr > |z| = 0.620 (continuity corrected)

Eggr's test

Std_Eff	Coef.	Std. Err.	t	P> |t|	[95% conf.	Interval]
slope	.2970805	.9492914	0.31	0.759	−1.73894	2.333108
bias	4.563294	3.285838	1.39	0.187	−2.484128	11.61072

Supplementary Figure 7. Funnel plot for publication bias of studies investigating of platelet factor-4.



metabias _ES _seES, graph (begg)
Note: defalut data input format (theta, se_thera) assumed.
Tests for Publication Bias
Begg's Test

adj. Kendall's Score (P-Q) = 12
Std. Dev. of Score = 40.32
Number of Studies = 24
z = 0.30
Pr > |z| = 0.766
z = 0.27 (continuity corrected)
Pr > |z| = 0.785 (continuity corrected)

Eggr's test

Std_Eff	Coef.	Std. Err.	t	P> |t|	[95% conf.	Interval]
slope	−.5566369	.4589967	−1.21	0.238	−1.508538	.395264
bias	5.558051	2.168015	2.56	0.018	−1.061863	10.05424

Supplementary Figure 8. Funnel plot for publication bias of studies investigating of P-selectin.

Supplementary Table 1. Included and excluded studies.

Clinical outcomes and biomarkers	Studies were identified and screened [n]	Studies were excluded according to title, abstract or full text [n]	Studies were included [n]
Platelet count	285	252	33 approved articles with totally 45 enrolled data for meta-analysis
Mean platelet volume	140	125	15 approved articles with totally 19 enrolled data for meta-analysis
Platelet distribution width	11	9	2 approved articles with totally 3 enrolled data for meta-analysis
Beta thromboglobulin	66	51	15 approved articles with totally 22 enrolled data for meta-analysis
Platelet factor 4	54	44	10 approved articles with totally 16 enrolled data for meta-analysis
P-selectin	115	97	18 approved articles with totally 24 enrolled data for meta-analysis

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Supplementary Table 2. Extra details of characteristics of each study for exploration of heterogeneity factors.

First Author	Geographic Area	Total N	Total age	Total male	Total DM	Total HTN	Total MI	Total Diuretic	Total ACEI	Total. Statin	Total BB	AC-code	Chronic or not	CS
Karatas [20]	European	621	61.05	72.5	23	45.5	ND	ND	ND	0	ND	2	Non-chronic	64
Drabik [21]	European	97	60.1	64.95	20	48.85	17.3	ND	52.25	53.15	60.6	4	Non-chronic	22.85
Drabik [21]	European	91	60	55.15	16.4	46.05	26.2	ND	54.05	47.45	57.25	4	Non-chronic	20
Idriss [22]	Africa	41	31.75	49.25	0	0	ND	ND	ND	ND	11.9	4	ND	34.5
Akdag [23]	European	148	64.05	60	16.5	22	ND	ND	ND	ND	ND	6	ND	23.5
Akyuz [24]	European	90	62.25	72.25	29	42.5	ND	14.5	20.75	32.5	23	4	ND	34.25
Chavaria [25]	North American	290	65.65	74.5	29.05	65.65	4.5	ND	ND	ND	ND	5	ND	55.05
Erdogan [26]	European	67	69.55	49.25	10	65	ND	18	53.5	10	43.3	3	chronic	6
Xu (without comorbidities) [27]	Asian	115	66.05	50.45	37.4	53.1	ND	ND	42.6	29.55	43.55	4	chronic	38.25
Xu (with comorbidities) [27]	Asian	115	67.975	51.3	36.5	57.5	ND	ND	40.8	26.05	40.95	4	chronic	31.25
Acet (PAF) [28]	European	134	62.05	44	16.5	18	ND	ND	ND	ND	ND	5	Non-chronic	21.5
Acet (persistent and permanent) [28]	European	126	62.85	43.5	21.5	24	ND	ND	ND	ND	ND	5	ND	28.5
Arik (with INR 2-3) [29]	European	248	69.65	40.7	6.05	68.95	ND	27	59.25	ND	59.7	5	chronic	13.7
Arik (with abnormal INR) [29]	European	248	69.45	37.9	6.85	65.35	ND	24.2	55.65	ND	61.3	5	chronic	12.1
Distelmaier [30]	North American	198	73.5	61	24	60.5	25	ND	ND	ND	ND	5	Non-chronic	ND
Gungor [31]	European	177	47.2	57.8	3.3	14.75	ND	ND	ND	ND	10.6	3	ND	23.15
Sonmez [32]	European	85	70	36.95	10.6	63.25	ND	14.1	47.15	15.4	35.55	4	Non-chronic	ND
Ulu [33]	European	57	ND	ND	ND	ND	ND	ND	ND	ND	ND	5	ND	ND
Turgut [34]	European	162	63	52	100	65.5	ND	6.5	23.5	18	16.5	4	chronic	41.5
Jaremo (healthy control) [35]	European	82	67.5	66.7	ND	ND	ND	ND	ND	ND	ND	4	ND	2.55
jaremo (disease control) [35]	European	130	71.5	68.1	12.75	43.75	9.1	28.65	26.25	25.05	55.9	4	ND	9.45
Berge [36]	European	189	75	71	8	48	ND	19	21	34.5	28	4	ND	ND
Ertas (without stroke) [37]	European	111	53.5	51	ND	ND	ND	ND	ND	ND	ND	6	ND	2
Ertas (with stroke) [37]	European	63	54.5	47	ND	ND	ND	ND	ND	ND	ND	6	ND	5
Sahin [38]	European	144	64.9	49.75	100	66.5	ND	ND	ND	ND	ND	5	Non-chronic	44.5
Tekin [39]	European	219	73.5	35.5	13.5	68.5	ND	ND	ND	ND	ND	5	chronic	19
Turfan (without CVA) [40]	European	135	59.5	54.55	ND	ND	ND	ND	ND	ND	ND	4	ND	55.5

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First Author	Geographic Area	Total N	Total age	Total male	Total DM	Total HTN	Total MI	Total Diuretic	Total ACEI	Total. Statin	Total BB	AC-code	Chronic or not	CS
Turfan (with CVA) [40]	European	121	62.5	52.05	ND	ND	ND	ND	ND	ND	ND	4	ND	50.6
Feng [41]	Asian	374	65.8	61.75	17.65	53.2	ND	23	41.95	44.85	42.5	4	ND	25.65
Acevedo [42]	South American	150	ND	ND	ND	ND	ND	ND	ND	ND	ND	1	Non-chronic	ND
Hayashi [43]	Asian	27	57.95	92.5	14.5	48.5	ND	ND	40.5	26	ND	2	Non-chronic	ND
Hayashi [43]	Asian	27	61.45	92.5	11.05	52	ND	ND	37	26	ND	2	chronic	ND
Fu [44]	Asian	169	54.45	63.5	ND	ND	ND	ND	ND	12.9	6.1	4	ND	42.45
Hou (disease control) [45]	Asian	52	64.85	57.6	ND	ND	ND	ND	40.3	ND	11.45	4	Non-chronic	26.9
Hou (healthy control) [45]	Asian	52	65.3	57.6	ND	ND	ND	ND	21.15	ND	7.65	4	Non-chronic	26.9
Alberti [46]	European	51	64.45	58.8	ND	ND	ND	ND	ND	ND	ND	1	Non-chronic	ND
Choudhury (disease control) [47]	European	192	63.31	74	10.5	66.4	ND	33.15	55.7	46.5	43.7	4	ND	ND
Choudhury (healthy control) [47]	European	186	62.305	72	4.1	31.8	ND	17.75	26.85	14.45	21.9	4	ND	ND
Colkesen [48]	European	190	54	38	18.5	41.5	ND	ND	ND	28	ND	4	Non-chronic	ND
Blann [49]	European	82	64.5	62.75	ND	27	ND	16.5	19	ND	18.5	3	ND	12.6
Topaloglu (disease control) [50]	European	46	34.5	ND	ND	ND	ND	ND	ND	ND	ND	5	ND	ND
Topaloglu (healthy control) [50]	European	38	36	ND	ND	ND	ND	ND	ND	ND	ND	5	ND	ND
Yip [51]	Asian	82	65.75	63.05	ND	ND	ND	ND	ND	ND	ND	3	chronic	ND
Heeringa [52]	European	486	77.5	51	17.5	25	22.5	31.65	ND	ND	16.55	5	ND	20.9
Inoue (with comorbidities) [53]	Asian	251	ND	ND	ND	ND	ND	ND	ND	ND	ND	5	ND	ND
Inoue (lone AF) [53]	Asian	106	ND	ND	ND	ND	ND	ND	ND	ND	ND	5	ND	ND
Conway [54]	European	147	68	62	7.5	26.5	ND	ND	ND	ND	ND	3	chronic	16
Conway [55]	European	74	67.5	70.23	12.95	37	1.85	ND	ND	ND	ND	5	Non-chronic	16.2
Atalar (paroxysmal AF) [56]	European	37	46	61.8	0	35.9	ND	ND	ND	ND	17.845	1	Non-chronic	ND
Atalar (permanent AF) [56]	European	47	49	63.8	0	35.9	ND	ND	ND	ND	17.845	1	chronic	ND
Kamath [57]	European	62	63.5	51.6	ND	ND	ND	ND	ND	ND	ND	1	Non-chronic	ND
Kamath [57]	European	124	66	52.65	ND	ND	ND	ND	ND	ND	ND	1	chronic	ND
Kamath [58]	European	58	63	48.235	6.85	24.1	ND	ND	ND	ND	ND	4	Non-chronic	5.15
Kamath [58]	European	116	65	52.25	5.15	30.45	ND	ND	ND	ND	ND	4	chronic	5.15
Kamath [59]	European	143	70	63.2	5.35	29.565	ND	ND	ND	ND	ND	1	ND	ND
Kamath [60]	European	57	ND	ND	ND	ND	ND	ND	ND	ND	ND	1	ND	ND

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First Author	Geographic Area	Total N	Total age	Total male	Total DM	Total HTN	Total MI	Total Diuretic	Total ACEI	Total. Statin	Total BB	AC-code	Chronic or not	CS
Li-Saw-Hee [61]	European	43	64	77.3	2.15	10.85	ND	ND	ND	ND	ND	3	Non-chronic	13.65
Li-Saw-Hee [61]	European	43	64	77.3	2.15	13	ND	ND	ND	ND	ND	3	Non-chronic	11.52
Li-Saw-Hee [61]	European	43	65	77.3	6.52	23.9	ND	ND	ND	ND	ND	3	chronic	11.52
Mondillo [62]	European	80	66.95	82.85	ND	ND	ND	ND	ND	ND	ND	3	chronic	33.75
Li-Saw-Hee [63]	European	112	67	77.5	3.85	12.5	ND	ND	ND	ND	ND	1	ND	13.3
Li-Saw-Hee [64]	European	50	59	20	ND	ND	ND	ND	ND	ND	ND	5	chronic	20
Minamino [65]	European	56	64	71.4	21.5	25	ND	ND	ND	ND	19.5	4	chronic	37.5
Minamino [66]	Asian	90	63	73.3	12.5	23.5	ND	ND	ND	ND	14.5	5	chronic	39
Kahn [67]	North American	81	ND	ND	ND	ND	ND	ND	ND	ND	ND	1	ND	ND
Sohara [68]	Asian	30	59.05	ND	ND	ND	ND	ND	ND	ND	ND	1	Non-chronic	ND
Lip GY [69]	European	77	ND	ND	ND	ND	ND	ND	ND	ND	ND	1	chronic	ND
Nagao [70]	Asian	36	79.95	47.05	ND	ND	ND	ND	ND	ND	ND	1	ND	ND
Sohara [71]	Asian	28	ND	ND	ND	ND	ND	ND	ND	ND	ND	1	Non-chronic	ND
Gustafsson (with stroke) [72]	European	60	77	ND	ND	ND	ND	ND	ND	ND	ND	1	ND	ND
Gustafsson (without stroke) [72]	European	60	77	ND	ND	ND	ND	ND	ND	ND	ND	1	ND	ND
Yamauchi (without valvular heart disease) [73]	Asian	130	41.5	ND	ND	ND	ND	ND	ND	ND	ND	1	ND	ND
Yamauchi (with valvular heart disease) [73]	Asian	83	45.5	ND	ND	ND	ND	ND	ND	ND	ND	1	ND	ND

Supplementary Table 3. Subgroup-analysis

Subgroup	Studies (N)	WMD (95% CI)	I-squared and Heterogeneity-p-value and Effect-p-value respectively
		Platelet count	
Year of publication			
>2000	41	–24.04 (–25.52 to –22.56)	91.1% and 0.001 and 0.001
≤2000	4	–60.67 (–65.22 to –55.62)	92.8% and 0.001 and 0.001
Geographic area			
Asian	7		13.8% and 0.324 and 0.284
European	35	–3.88 (–10.98 to 3.21)	94% and 0.001 and 0.001
Africa	-	–30.05 (–31.59 to –28.50)	–
North American	3	–	0.0% and 0.401 and 0.001
South American	-	–12.23 (–16.39 to –8.08)	–
Australia	-		–
Design of study			
Cohort	8	–29.32 (–31.25 to –27.40)	91.6% and 0.001 and 0.001
Case-control	37	–24.10 (–26.20 to –22.01)	93.8% and 0.001 and 0.001

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Subgroup	Studies (N)	WMD (95% CI)	I-squared and Heterogeneity-p-value and Effect-p-value respectively
Number of population			
>300	2	–6.33 (–19.68 to 7.02)	0.0% and 0.689 and 0.353
≤300	43	–27.16 (–28.59 to –25.74)	93.7% and 0.001 and 0.001
Mean Age			
>60 years	34	–27.90 (–29.34 to –26.46)	94.5% and 0.001 and 0.001
≤60 years	7	–0.76 (–9.25 to 7.12)	76.7% and 0.001 and 0.860
Male			
>70%	8	–29.82 (–31.76 to –27.88)	85.8% and 0.001 and 0.001
≤70%	31	–16.15 (–18.44 to –13.86)	90.6% and 0.001 and 0.001
Diabetes mellitus			
>30%	1	21.00 (–4.40 to 46.40)	–
≤30%	28	–22.68 (–24.24 to –21.12)	88.3% and 0.001 and 0.001
Hypertension			
>70%	–	–	–
≤70%	29	–22.52 (–24.07 to –20.96)	88.4% and 0.001 and 0.001
History of MI			
>20%	2	–11.74 (–15.35 to –8.13)	9.7% and 0.293 and 0.001
≤20%	3	–15.44 (–22.10 to –8.77)	31.1% and 0.234 and 0.001
Medication: Diuretic			
>70%	–	–	–
≤70%	11	–28.43 (–30.31 to –26.56)	88.1% and 0.001 and 0.001
Medication: ACEI			
>70%	–	–	–
≤70%	17	–25.60 (–27.33 to –23.88)	89.6% and 0.001 and 0.001
Medication: Statin			
>70%	–	–	–
≤70%	18	–25.90 (–27.64 to –24.15)	88.4% and 0.001 and 0.001
Medication: Beta-Blocker			
>70%	–	–	–
≤70%	17	–25.40 (–27.11 to –23.68)	89.3% and 0.001 and 0.001
Anti-coagulant status codes			
1	9	–54.79 (–58.44 to –51.15)	93.4% and 0.001 and 0.001
2	3	1.69 (–17.11 to 20.53)	67.3% and 0.047 and 0.860
3	3	–3.15 (–17.55 to 11.23)	0.0% and 0.890 and 0.667
4	19	–25.27 (–27.00 to –23.53)	90.9% and 0.001 and 0.001
5	8	–10.84 (–14.41 to 7.24)	38.3% and 0.124 and 0.001
6	3	–6.34 (–21.47 to 8.77)	70.8% and 0.033 and 0.411
AF			
Chronic	12	–2.15 (–7.34 to 3.02)	35.6% and 0.106 and 0.414
Non-chronic	11	–21.73 (–24.45 to –19.01)	95.5% and 0.001 and 0.001
Type of AF			
Paroxysmal	5	–5.29 (–11.24 to 0.64)	67.8% and 0.015 and 0.081
Persistent	3	–41.86 (–46.34 to –37.38)	97.4% and 0.001 and 0.001
Permanent	5	–4.55 (–11.58 to 2.46)	64.6% and 0.023 and 0.204
Cigarette smoking			
>30%	9	2.31 (–4.14 to 8.77)	67.3% and 0.002 and 0.482
≤30%	17	–9.11 (–12.70 to –5.52)	46.6% and 0.018 and 0.001
Mean platelet volume			
Year of publication			
>2000		All of studies: after 2000	
≤2000			

Indexed in: [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Subgroup	Studies (N)	WMD (95% CI)	I-squared and Heterogeneity-p-value and Effect-p-value respectively
Geographic area			
Asian	3	1.37 (1.16 to 1.58)	95.9% and 0.001 and 0.001
European	16	0.56 (0.51 to 0.61)	93.1% and 0.001 and 0.001
Africa	–	–	–
North American	–	–	–
South American	–	–	–
Australia	–	–	–
Design of study			
Cohort	4	1.37 (1.14 to 1.60)	94.7% and 0.001 and 0.001
Case-control	15	0.57 (0.52 to 0.62)	93.6% and 0.001 and 0.001
Number of population			
>300	2	0.90 (0.67 to 1.13)	0.0% and 0.666 and 0.001
≤300	17	0.59 (0.54 to 0.64)	94.9% and 0.001 and 0.001
Mean Age			
>60 years	15	0.61 (0.56 to 0.66)	94.8% and 0.001 and 0.001
≤60 years	3	0.33 (0.13 to 0.54)	95.2% and 0.001 and 0.001
Male			
>70%	4	0.67 (0.50 to 0.83)	95.6% and 0.001 and 0.001
≤70%	14	0.59 (0.54 to 0.64)	94.7% and 0.001 and 0.001
Diabetes mellitus			
>30%	2	0.59 (0.53 to 0.65)	42.3% and 0.188 and 0.001
≤30%	14	0.60 (0.52 to 0.67)	95.8% and 0.001 and 0.001
Hypertension			
>70%	–	–	–
≤70%	16	0.59 (0.55 to 0.64)	95.1% and 0.001 and 0.001
History of MI		Studies have not data about history of myocardial infarction	
Medication: Diuretic			
>70%	–	–	–
≤70%	8	0.57 (0.52 to 0.62)	95.5% and 0.001 and 0.001
Medication: ACEI			
>70%	–	–	–
≤70%	10	0.60 (0.55 to 0.65)	96.4% and 0.001 and 0.001
Medication: Statin			
>70%	–	–	–
≤70%	10	0.66 (0.61 to 0.72)	95.1% and 0.001 and 0.001
Medication: Beta-Blocker			
>70%	–	–	–
≤70%	11	0.58 (0.53 to 0.63)	96.4% and 0.001 and 0.001
Anti-coagulant status codes			
1	–	–	–
2	1	0.80 (0.26 to 1.33)	–
3	2	–0.07 (–0.31 to 0.16)	8.7% and 0.295 and 0.530
4	10	0.67 (0.62 to 0.73)	95.1% and 0.001 and 0.001
5	5	0.43 (0.33 to 0.53)	94.6% and 0.001 and 0.001
6	1	1.10 (0.75 to 1.45)	–
AF			
Chronic	7	0.58 (0.53 to 0.63)	96.6% and 0.001 and 0.001
Non-chronic	3	0.85 (0.58 to 1.13)	88.6% and 0.001 and 0.001
Type of AF			
Paroxysmal	1	1.70 (1.20. to 2.19)	–
Persistent	1	0.32 (–0.09 to 0.73)	–
Permanent	3	0.39 (0.28 to 0.51)	97.1% and 0.001 and 0.001

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Subgroup	Studies (N)	WMD (95% CI)	I-squared and Heterogeneity-p-value and Effect-p-value respectively
Cigarette smoking			
>30%	8	0.68 (0.62 to 0.74)	94.7% and 0.001 and 0.001
≤30%	7	0.45 (0.36 to 0.54)	94.8% and 0.001 and 0.001
		BTG	
Year of Publication			
>2000	11	29.31 (28.57 to 30.04)	88.6% and 0.001 and 0.001
≤2000	11	12.67 (11.49 to 13.85)	95.5% and 0.001 and 0.001
Geographic area			
Asian	8		77% and 0.001 and 0.001
European	14	30.31 (29.51 to 31.11)	96.2% and 0.001 and 0.001
Africa	–	15.91 (14.92 to 16.91)	–
North American	–	–	–
South American	–	–	–
Australia	–		–
Design of study			
Cohort		All of studies are “case-control”	
Case-control			
Number of population			
>300		All of studies are “number less than 300 population”	
≤300			
Mean Age			
>60 years	11	15.79 (14.74 to 16.84)	94.2% and 0.001 and 0.001
≤60 years	6	13.01 (9.94 to 16.08)	90.1% and 0.001 and 0.001
Male			
>70%	3	39.01 (33.37 to 44.65)	0.0% and 0.600 and 0.001
≤70%	9	19.98 (18.28 to 21.68)	90.9% and 0.001 and 0.001
Diabetes mellitus			
>30%	–	–	–
≤30%	7	25.36 (23.30 to 27.42)	80.8% and 0.001 and 0.001
Hypertension			
>70%	–	–	–
≤70%	7	25.36 (23.30 to 27.42)	80.8% and 0.001 and 0.001
History of MI		No Data	
Medication: Diuretic		No Data	
Medication: ACEI			
>70%		No Data	
≤70%			
Medication: Statin			
>70%		No Data	
≤70%			
Medication: Beta-Blocker			
>70%	–	–	–
≤70%	4	27.17 (23.22 to 31.12)	89.1% and 0.001 and 0.001
Anti-coagulant status codes			
1	14	14.70 (13.63 to 15.78)	93.6% and 0.001 and 0.001
2	–	–	–
3	1	39.16 (29.56 to 48.75)	–
4	3	27.83 (24.92 to 30.73)	85.5% and 0.001 and 0.001
5	4	29.83 (29.03 to 30.63)	97.8% and 0.001 and 0.001
6	–	–	–

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Subgroup	Studies (N)	WMD (95% CI)	I-squared and Heterogeneity-p-value and Effect-p-value respectively
AF			
Chronic	8	24.21 (22.11 to 26.30)	96.7% and 0.001 and 0.001
Non-chronic	5	17.74 (14.40 to 21.08)	31.3% and 0.213 and 0.001
Type of AF			
Paroxysmal	4	17.60 (13.57 to 21.63)	48.3% and 0.121 and 0.001
Persistent	–	–	–
Permanent	4	25.90 (23.39 to 28.40)	80.5% and 0.002 and 0.001
Cigarette smoking			
>30%	3	39.01 (33.37 to 44.65)	0.0% and 0.600 and 0.001
≤30%	3	18.64 (16.00 to 21.27)	97.2% and 0.001 and 0.001
Platelet factor 4			
Year of Publication			
>2000	9	6.38 (6.04 to 6.72)	99.8% and 0.001 and 0.001
≤2000	7	1.78 (1.36 to 2.20)	81.6% and 0.001 and 0.001
Geographic area			
Asian	7		51.5% and 0.054 and 0.001
European	9	6.75 (6.32 to 7.17)	99.8% and 0.001 and 0.001
Africa	–	3.25 (2.91 to 3.59)	–
North American	–	–	–
South American	–	–	–
Australia	–		–
Design of study			
Cohort		All of studies are “case-control”	
Case-control			
Number of population			
>300		All of studies are “number less than 300 population”	
≤300			
Mean Age			
>60 years	6	2.27 (1.93 to 2.61)	94.6% and 0.001 and 0.001
≤60 years	7	58.31 (55.83 to 60.80)	99.6% and 0.001 and 0.001
Male			
>70%	1	2.80 (2.23 to 3.36)	–
≤70%	5	11.60 (9.55 to 13.66)	89.3% and 0.001 and 0.001
Diabetes mellitus			
>30%	–	–	–
≤30%	4	15.25 (12.79 to 17.72)	69.6% and 0.020 and 0.001
Hypertension			
>70%	–	–	–
≤70%	4	15.25 (12.79 to 17.72)	69.6% and 0.020 and 0.001
History of MI			
>20%	1	15.55 (11.43 to 19.67)	–
≤20%	1	12.17 (8.38 to 15.95)	–
Medication: Diuretic		No Data	
Medication: ACEI			
>70%	–	–	–
≤70%	2	13.71 (10.92 to 16.50)	28.7% and 0.236 and 0.001
Medication: Statin			
>70%	–	–	–
≤70%	18	13.71 (10.92 to 16.50)	28.7% and 0.236 and 0.001
Medication: Beta-Blocker			
>70%	–	–	–
≤70%	4	15.25 (12.79 to 17.72)	69.6% and 0.020 and 0.001

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Subgroup	Studies (N)	WMD (95% CI)	I-squared and Heterogeneity-p-value and Effect-p-value respectively
Anti-coagulant status codes			
1	9	1.90 (1.48 to 2.32)	90.6% and 0.001 and 0.001
2	–	–	–
3	1	2.80 (2.23 to 3.36)	–
4	2	13.71 (10.92 to 16.50)	28.7% and 0.236 and 0.001
5	4	8.18 (7.75 to 8.61)	99.9% and 0.001 and 0.001
6	–	–	–
AF			
Chronic	2	2.93 (2.37 to 3.49)	97.3% and 0.001 and 0.001
Non-chronic	5	13.07 (10.71 to 15.43)	23.9% and 0.262 and 0.001
Type of AF			
Paroxysmal	4	11.86 (8.98 to 14.75)	6.1% and 0.363 and 0.001
Persistent	1	15.50 (11.43 to 19.67)	–
Permanent	1	2.93 (2.37 to 3.49)	97.3% and 0.001 and 0.001
Cigarette smoking			
>30%	1	2.80 (2.23 to 3.36)	–
≤30%	2	13.71 (10.92 to 16.50)	28.7% and 0.236 and 0.001
		P-selectin	
Year of Publication			
>2000	23	4.92 (4.37 to 5.47)	98.6% and 0.001 and 0.001
≤2000	1	–71.00 (–104.1 to –37.80)	–
Geographic area			
Asian	3	1.90 (0.42 to 3.38)	78.9% and 0.009 and 0.012
European	19	5.30 (4.71 to 5.89)	98.8% and 0.001 and 0.001
Africa	1	47.90 (29.57 to 66.22)	–
North American	–	–	–
South American	1	74.0 (46.63 to 101.36)	–
Australia	–		–
Design of study			
Cohort	3	–0.27 (–1.16 to 0.61)	81.2% and 0.005 and 0.547
Case-control	21	8.04 (7.35 to 8.74)	98.6% and 0.001 and 0.001
Number of population			
>300	1	–0.50 (–2.61 to 1.61)	–
≤300	23	5.29 (4.72 to 5.86)	98.6% and 0.001 and 0.001
Mean Age			
>60 years	19	4.95 (4.38 to 5.53)	98.8% and 0.001 and 0.001
≤60 years	3	4.46 (2.38 to 6.54)	95.2% and 0.001 and 0.001
Male			
>70%	8	5.42 (4.72 to 6.12)	99.5% and 0.001 and 0.001
≤70%	14	4.09 (3.19 to 4.99)	95.5% and 0.001 and 0.001
Diabetes mellitus			
>30%	–	–	–
≤30%	15	4.70 (4.08 to 5.31)	99.0% and 0.001 and 0.001
Hypertension			
>70%	–	–	–
≤70%	16	5.54 (4.93 to 6.15)	99.0% and 0.001 and 0.001
History of MI			
>20%	1	–0.50 (–2.61 to 1.61)	–
≤20%	2	4.11 (1.41 to 6.82)	87.1% and 0.005 and 0.003
Medication: Diuretic			
>70%	–	–	–
≤70%	7	5.24 (4.53 to 5.96)	99.0% and 0.001 and 0.001

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Subgroup	Studies (N)	WMD (95% CI)	I-squared and Heterogeneity-p-value and Effect-p-value respectively
Medication: ACEI			
>70%	–	–	–
≤70%	8	5.25 (4.54 to 5.96)	98.9% and 0.001 and 0.001
Medication: Statin			
>70%	–	–	–
≤70%	6	4.60 (3.87 to 5.34)	98.8% and 0.001 and 0.001
Medication: Beta-Blocker			
>70%	–	–	–
≤70%	10	3.67 (3.02 to 4.33)	98.0% and 0.001 and 0.001
Anti-coagulant status codes			
1	5	5.46 (2.88 to 8.03)	97.2% and 0.001 and 0.001
2	–	–	–
3	6	9.20 (7.99 to 10.42)	99.5% and 0.001 and 0.001
4	10	4.19 (3.50 to 4.87)	98% and 0.001 and 0.001
5	3	0.81 (–0.85 to 2.47)	91.4% and 0.001 and 0.342
6	–	–	–
AF			
Chronic	6	5.94 (4.28 to 7.60)	99.4% and 0.001 and 0.001
Non-chronic	8	3.09 (1.94 to 4.23)	92.2% and 0.001 and 0.001
Type of AF			
Paroxysmal	2	1.40 (–0.58 to 3.39)	2.1% and 0.312 and 0.166
Persistent	2	8.17 (6.10 to 10.25)	96.2% and 0.001 and 0.001
Permanent	5	6.13 (4.47 to 7.79)	99.5% and 0.001 and 0.001
Cigarette smoking			
>30%	2	4.76 (2.68 to 6.84)	95.4% and 0.001 and 0.001
≤30%	15	5.41 (4.55 to 6.27)	98.8% and 0.001 and 0.001

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