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

**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
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

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 change 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
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 >50%, 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 META-BIAS 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 I² >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 237.3×10^12/L in AF group and 240.04×10^12/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 (I²=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 than in patients with SR with WMD of 0.82 (95% CI: 0.63 to 0.98; p<0.001, Figure 1). Significant heterogeneity was observed among the studies (I²=92.4%; 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 (I²=87.4%; heterogeneity p<0.001)
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   | 64      | 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   | 46.6    | 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   |
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 |
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 |
**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: 272±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] |
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]<br>MPV [AF: 8.26±0.63 vs. SR: 7.63±0.68]<br>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]<br>MPV [AF: 8.99±0.65 vs. SR: 9.14±0.98] |
| Sonmez [32] | PC | PC [AF: 231±60 vs. SR: 247±83] |
| Ulu [33] | PC, MPV | PC [AF: 236.4±63.9 vs. SR: 233.3±86.2]<br>MPV [AF: 11.47±0.93 vs. SR: 10.37±1.07] |
| Turgut [34] | PC | PC [AF: 241±64 vs. SR: 265±84] |
| Jaremo (healthy control) [35] | PC | PC [AF: 241±64 vs. SR: 265±84]<br>P-selectin [AF: 102±53 vs. 74±44] |
| Jaremo (disease control) [35] | PC, P-selectin | PC [AF: 241±64 vs. SR: 265±84]<br>P-selectin [AF: 102±53 vs. 74±44] |
| Berge [36] | PC, P-selectin | PC [AF: 230±7.5 vs. SR: 261.25±4.16]<br>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]<br>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]<br>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]<br>MPV [AF: 9.7±0.9 vs. SR: 8.6±1.3] |
| Feng [41] | PC, MPV | PC [AF: 213±82.5 vs. SR: 217.6±81.7]<br>MPV [AF: 9.95±1.32 vs. SR: 9.0±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]<br>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]<br>MPV [AF: 7.6±1.4 vs. SR: 7.8±0.9]<br>P-selectin [AF: 61±7 vs. SR: 55.2±6.8] |
| Choudhury (healthy control) [47] | PC, MPV, P-selectin | PC [AF: 259.9±66.3 vs. SR: 266.9±56.1]<br>MPV [AF: 7.6±1.4 vs. SR: 7.4±0.97]<br>P-selectin [AF: 61±7 vs. SR: 40.7±5.25] |
| Colkesen [48] | PC, MPV | PC [AF: 242±73 vs. SR: 236±53]<br>MPV [AF: 10±2 vs. SR: 8.3±1.5] |
### 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±4 vs. SR: 50.75±6.75] |
| 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: 175.35±11.55 vs. SR: 161.7±8.4]  
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: 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: 92.13±11.02 vs. SR: 71.98±10.5]  
P-selectin [AF: 39±10 vs. SR: 36±11] |
| 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±6.54 vs. SR: 55.72±22.02] |
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 group. 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. A total of 1,781 patients were included from 22 studies, of which 1,043 were allocated to the AF group and 738 to the SR group.

### 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 group. 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). Using a random effect model, pooled analysis showed that the level of BTG was significantly higher in the AF group compared to the SR group with WMD of 24.69 (95% CI: 24.07 to 25.32; \( p < 0.001 \)) (Figure 5). Significant heterogeneity was observed among the studies (I\(^2\)=98.6%; 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 level of PF4 was 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 16.65 ng/mL (95% CI: 4.36 to 5.45; \( p < 0.001 \), Figure 3) with considerable heterogeneity among the studies (I\(^2\)=97.6%; 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 18.01 ng/mL (95% CI: 4.36 to 5.45; \( p < 0.001 \)) (Figure 4). 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 \( p < 0.001 \)) was significantly higher in patients with stroke 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 \( p = 0.21 \)) 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.
**Figure 1.** Forest plot of weighted mean difference (WMD) for association between platelet count and occurrence of AF.
### Figure 2. Forest plot of weighted mean difference (WMD) for association between level of mean platelet volume and occurrence of AF.

| First Author | WMD (95% CI) | % Weight |
|--------------|-------------|----------|
| Karatas      | 0.80 (0.27, 1.33) | 0.76 |
| Akdag        | 1.10 (0.75, 1.45) | 1.77 |
| Akyuz        | 1.45 (1.15, 1.65) | 3.48 |
| Erdogan      | 0.14 (–0.33, 0.61) | 0.98 |
| Xu (without comorbidities) | 1.90 (1.37, 2.43) | 0.76 |
| Xu (with comorbidities) | 3.00 (2.44, 3.56) | 0.69 |
| Arik (with INR 2-3) | –0.07 (–0.23, 0.09) | 8.12 |
| Arik (with abnormal INR) | 0.90 (0.74, 1.06) | 8.12 |
| Gunogor      | –0.15 (–0.42, 0.12) | 2.87 |
| Ulu          | 1.10 (0.58, 1.62) | 0.80 |
| Turgut       | 0.60 (0.54, 0.66) | 57.02 |
| Sahin        | 0.32 (–0.09, 0.73) | 1.27 |
| Tekin        | 0.40 (0.11, 0.69) | 2.53 |
| Turfan (without CVA) | 0.50 (0.10, 0.90) | 1.34 |
| Turfan (with CVA) | 1.10 (0.70, 1.50) | 1.34 |
| Feng         | 0.93 (0.68, 1.18) | 3.41 |
| Choudhury (disease control) | –0.20 (–0.53, 0.13) | 2.04 |
| Choudhury (healthy control) | 0.20 (–0.14, 0.54) | 1.84 |
| Colkesen     | 1.70 (1.20, 2.20) | 0.87 |
| Overall (I-squared=94.3%, p=0.000) | 0.61 (0.56, 0.65) | 100.00 |

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

| First Author | WMD (95% CI) | % Weight |
|--------------|-------------|----------|
| Inoue (with comorbidities) | 30.60 (29.75, 31.45) | 54.13 |
| Inoue (lone AF) | 30.70 (28.02, 33.38) | 5.41 |
| Atalar (paroxysmal AF) | 13.65 (6.83, 20.47) | 0.84 |
| Atalar (permanent AF) | 29.40 (22.65, 36.15) | 0.85 |
| Kamath (PAF and persistent AF) | 18.05 (12.08, 24.02) | 1.09 |
| Kamath (permanent AF) | 20.21 (15.89, 24.53) | 2.08 |
| Kamath (PAF) | 22.58 (16.72, 28.44) | 1.13 |
| Kamath (Permanent AF) | 27.04 (23.35, 30.73) | 2.85 |
| Kamath | 23.10 (19.32, 26.88) | 2.71 |
| Kamath | 20.48 (13.13, 27.83) | 0.72 |
| Mondillo | 19.16 (28.57, 48.75) | 0.42 |
| Li-Saw-Hee | 1.00 (–3.91, 5.91) | 1.61 |
| Minamino (Year 1999) | 40.78 (32.94, 48.62) | 0.63 |
| Minamino (Year 1997) | 31.93 (16.66, 47.20) | 0.17 |
| Sohara | 15.20 (2.45, 27.95) | 0.24 |
| Lip GY | 87.25 (74.52, 99.98) | 0.24 |
| Nagao | 11.90 (–0.52, 24.32) | 0.25 |
| Sohara | 8.30 (–6.08, 22.68) | 0.19 |
| Gustafsson (with stroke) | 14.63 (11.96, 17.30) | 5.46 |
| Gustafsson (without stroke) | 10.78 (9.33, 12.23) | 18.40 |
| Yamauchi (without valvular heart disease) | 18.20 (9.22, 27.18) | 0.48 |
| Yamauchi (with valvular heart disease) | 32.90 (12.28, 53.52) | 0.09 |
| Overall (I-squared=9.6%, p=0.000) | 24.69 (24.07, 25.32) | 100.00 |
**Figure 4.** Forest plot of weighted mean difference (WMD) for association between level of platelet factor 4 and occurrence of AF.

| First Author | WMD (95% CI) | % Weight |
|--------------|--------------|----------|
| Drabik (persistent AF) | 15.55 (11.43, 19.67) | 0.41 |
| Drabik (PAF) | 12.17 (8.39, 15.95) | 0.49 |
| Topaloglu (disease control) | 17.43 (7.36, 27.50) | 0.07 |
| Topaloglu (healthy control) | 108.44 (104.78, 112.10) | 0.52 |
| Inoue (with comorbidities) | 6.90 (6.45, 7.33) | 34.12 |
| Inoue (lone AF) | 5.40 (3.94, 6.86) | 3.27 |
| Atalar (paroxysmal AF) | 15.75 (7.88, 23.62) | 0.11 |
| Atalar (permanent AF) | 25.20 (17.98, 32.42) | 0.13 |
| Mondillo | 2.80 (2.24, 3.36) | 21.98 |
| Sohara | 13.03 (5.11, 20.95) | 0.11 |
| Nagao | 3.38 (–0.32, 7.08) | 0.51 |
| Sohara | 6.40 (–0.91, 13.71) | 0.13 |
| Gustafsson (with stroke) | 3.22 (2.32, 4.12) | 8.71 |
| Gustafsson (without stroke) | 1.22 (0.73, 1.71) | 29.24 |
| Yamauchi (without valvular heart disease) | 7.00 (0.41, 13.59) | 0.16 |
| Yamauchi (with valvular heart disease) | 22.50 (4.88, 40.12) | 0.02 |
| Overall (I-squared=99.6%, p=0.000) | 4.59 (4.33, 4.86) | 100.00 |

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

| First Author | WMD (95% CI) | % Weight |
|--------------|--------------|----------|
| Idriss | 47.90 (28.57, 66.23) | 0.09 |
| Erdogan | 1.91 (1.03, 6.85) | 1.23 |
| Jaremo (disease control) | 28.00 (10.99, 45.01) | 0.10 |
| Berge | –0.32 (–1.31, 0.67) | 31.91 |
| Acedoa | 74.00 (46.63, 101.37) | 0.04 |
| Fu | 4.20 (2.10, 6.30) | 6.84 |
| Hou (disease control) | 0.00 (–2.72, 2.72) | 0.07 |
| Hou (healthy control) | –1.00 (–4.51, 2.51) | 2.75 |
| Choudhury (disease control) | 5.75 (1.74, 7.76) | 7.40 |
| Choudhury (healthy control) | 20.25 (18.47, 22.03) | 9.45 |
| Blann | 26.25 (23.19, 29.31) | 3.21 |
| Heeringa | –0.50 (–2.61, 1.61) | 6.75 |
| Conway | 2.75 (0.55, 4.95) | 6.20 |
| Conway | 3.50 (0.76, 6.24) | 4.01 |
| Kamath (PAF and persistent AF) | 2.00 (–2.41, 6.41) | 1.54 |
| Kamath (permanent AF) | 3.00 (–1.37, 7.37) | 1.57 |
| Kamath (PAF) | 4.00 (–1.41, 9.41) | 1.03 |
| Kamath (Permanent AF) | 5.00 (0.80, 9.20) | 1.70 |
| Kamath | 1.00 (–1.98, 5.98) | 1.21 |
| Li-Saw-Hee (PAF) | 1.00 (–1.14, 3.14) | 6.57 |
| Li-Saw-Hee (persistent AF) | 14.50 (11.32, 17.68) | 2.97 |
| Li-Saw-Hee (permanent AF) | 180.50 (167.91, 193.09) | 0.19 |
| Li-Saw-Hee (year: 2000) | 79.50 (65.81, 93.13) | 0.16 |
| Li-Saw-Hee (year: 1999) | –71.00 (–104.20, –37.80) | 0.03 |
| Overall (I-squared=98.6%, p=0.000) | 4.90 (4.36, 5.45) | 100.00 |
### 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...
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. Varastehavan et al. indicated that PWD 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, PWD 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 PWD 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.
Supplementary Files

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

| First Author                  | WMD (95% CI) | % Weight |
|-------------------------------|--------------|----------|
| Karatas                       | 0.50 (–0.04, 1.04) | 7.23     |
| Arik (with INR 2–3)           | –0.47 (–0.67, –0.27) | 54.58    |
| Arik (with abnormal INR)      | –0.02 (–0.25, 0.21) | 38.19    |
| Overall (I-squared=87.4%, p=0.000) | –0.23 (–0.37, –0.08) | 100.00   |

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

| First Author                  | WMD (95% CI) | % Weight |
|-------------------------------|--------------|----------|
| Bayar                         | 2.00 (1.48, 2.52) | 26.56    |
| Turfan & Arik (with abnormal INR) | 0.60 (0.28, 0.92) | 73.44    |
| Overall (I-squared=95.0%, p=0.000) | 0.97 (0.70, 1.24) | 100.00   |

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

| First Author                  | WMD (95% CI) | % Weight |
|-------------------------------|--------------|----------|
| Ertas                         | 8.00 (–20.21, 36.21) | 18.67    |
| Turfan                        | –19.00 (–46.67, 8.67) | 19.40    |
| Kahn                          | 23.00 (–19.08, 65.08) | 8.39     |
| Gustafsson                    | 14.00 (–2.66, 30.66) | 53.54    |
| Overall (I-squared=35.2%, p=0.201) | 7.23 (–4.96, 19.42) | 100.00   |
Supplementary Figure 4. Funnel plot for publication bias of studies investigating of platelet count.

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

Supplementary Figure 6. Fun funnel plot for publication bias of studies investigating of beta thromboglobulin.
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]

| Clinical outcomes and biomarkers | Platelet count | Mean platelet volume | Platelet distribution width | Beta thromboglobulin | Platelet factor 4 | P-selectin |
|----------------------------------|----------------|----------------------|---------------------------|----------------------|-------------------|-----------|
| [n]                              | 285            | 140                  | 11                        | 66                   | 54                | 115       |
| [n]                              | 252            | 125                  | 9                         | 51                   | 44                | 97        |
| [n]                              | 33 approved articles with totally 45 enrolled data for meta-analysis | 15 approved articles with totally 19 enrolled data for meta-analysis | 2 approved articles with totally 3 enrolled data for meta-analysis | 15 approved articles with totally 22 enrolled data for meta-analysis | 10 approved articles with totally 16 enrolled data for meta-analysis | 18 approved articles with totally 24 enrolled data for meta-analysis |

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

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

Supplementary Table 1. Included and excluded studies.

|          | Std_Eff | Coef. | Std. Err. | t | P>|t| | [95% conf. Interval] |
|----------|---------|-------|-----------|---|----------|---------------------|
| slope    | –5.9970805 | .9492914 | .031   | 0.759  | ~1.73894 | 2.333108 |
| bias     | 4.563394  | 3.285383  | 1.39   | 0.187  | ~2.484128 | 11.61072 |

Begg's funnel plot with pseudo 95% confidence limits

Note: default 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
Pr > |z| (continuity corrected) = 0.50

Egger's Test

Std_Eff | Coef. | Std. Err. | t | P>|t| | [95% conf. Interval] |
|---------|-------|-----------|---|----------|---------------------|
| slope   | –5.966369 | .4598967 | –1.21 | 0.238   | ~1.50833 | .395264 |
| bias    | 5.536051  | 2.168015  | 2.56  | 0.018   | ~1.061663 | 10.05424 |
**Supplementary Table 2.** Extra details of characteristics of each study for exploration of heterogeneity factors.

| First Author | Geographic Area | Total N | Total age | Male | Diuretic | ACEI | Total Statin | Total Diuretic | Total ACEI | Total BB | AC-code | Chronic or not | CS |
|--------------|-----------------|---------|-----------|------|----------|------|--------------|--------------|------------|---------|---------|---------------|----|
| Karatas [20] | European        | 621     | 61.05     | 72.5 | 23       | ND   | ND           | ND           | ND         | 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    | 16.3    | 22    | ND           | ND           | ND         | ND      | 6      | ND           | 23.5 |
| Akuz [24]    | European        | 90      | 62.25     | 72.25 | 29      | 42.5  | 14.5         | ND           | 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      | 5      | 5             | 55.05 |
| Erdogan [26] | European        | 67      | 69.55     | 49.25 | 10      | 65    | ND           | ND           | 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 | 5 | Non-chronic | 21.5 |
| Acet (persistent and permanent) [28] | European | 126 | 62.85 | 43.5 | 21.5 | 24 | 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 | 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 | 35.5 | 4       | Non-chronic | ND |
| Ulu [33]     | European        | 57      | ND        | ND    | ND     | ND    | ND | ND | ND | ND | 5      | ND | 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 | 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 | 6 | ND | 2 |
| Ertas (with stroke) [37] | European | 63 | 54.5 | 47 | 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 | 4 | ND | 55.5 |
## Table 1: Summary Characteristics of Included Studies

| First Author | Geographic Area | Total N | Age (mean±SD) | DM | HTN | MI | Diuretic | ACEI | AT1 | Statin | BB | AC Code | Chronic or Not | CS |
|--------------|----------------|---------|---------------|----|-----|----|----------|------|------|--------|----|---------|----------------|----|
| Turfan [40]  | European       | 121     | 62.5±5       | ND | ND  | ND | ND       | ND   | ND   | ND     | ND | 4       | Non-chronic    | 50.6 |
| Feng [41]    | Asian          | 274     | 65.8±6       | ND | ND  | ND | ND       | ND   | ND   | 23     | ND | 4       | Non-chronic    | 53.6 |
| Acevedo [42] | South American | 150     | 57.9±9       | ND | ND  | ND | ND       | ND   | ND   | ND     | 1  | Non-chronic|               | ND |
| Weymann [43] | Asian          | 27      | 57.9±9       | ND | ND  | ND | ND       | ND   | ND   | 40.5   | 26 | ND      | 2 Non-chronic  | ND |
| Fu [44]      | Asian          | 192     | 63.1±7       | ND | ND  | ND | ND       | ND   | ND   | 21.15  | ND | 4       | Non-chronic    | 26.9 |
| Hou [45]     | Asian          | 52      | 64.8±5       | ND | ND  | ND | ND       | ND   | ND   | ND     | ND | 4       | Non-chronic    | ND |
| Alberti [46] | European       | 51      | 64.4±5       | ND | ND  | ND | ND       | ND   | ND   | ND     | ND | 4       | Non-chronic    | ND |
| Choudhury [47] | European   | 186     | 62.305±5     | ND | ND  | ND | ND       | ND   | ND   | ND     | ND | 4       | Non-chronic    | ND |
| Colkesen [48] | European     | 190     | 54±3         | ND | ND  | ND | ND       | ND   | ND   | 28     | ND | 4       | Non-chronic    | ND |
| Heeringa [50] | European     | 271     | 68.5±6       | ND | ND  | ND | ND       | ND   | ND   | ND     | ND | 4       | Non-chronic    | ND |
| Yip [51]     | Asian          | 82      | 63.75±5      | ND | ND  | ND | ND       | ND   | ND   | ND     | ND | 3       | Chronic        | ND |
| Hayashi [52] | Asian          | 486     | 77.5±5       | ND | ND  | ND | ND       | ND   | ND   | 23     | ND | 5       | Non-chronic    | 20.9 |
| Inoue [53]   | Asian          | 251     | ND           | ND | ND  | ND | ND       | ND   | ND   | ND     | 5  | ND      | Non-chronic    | ND |
| Conway [54]  | European       | 147     | 68±6         | ND | ND  | ND | ND       | ND   | ND   | ND     | ND | 3       | Chronic        | 16 |
| Conway [55]  | European       | 74      | 67.5±7       | ND | ND  | ND | ND       | ND   | ND   | 37     | ND | 5 Non-chronic|               | 16.2|
| Atalar [56]  | European       | 37      | 46±6         | ND | ND  | ND | ND       | ND   | ND   | 17.845  | ND | 1 Non-chronic|               | ND |
| Atalar [56]  | European       | 47      | 49±6         | ND | ND  | ND | ND       | ND   | ND   | 17.845  | ND | 1 chronic    |               | ND |
| Kamath [57]  | European       | 62      | 63.5±5       | ND | ND  | ND | ND       | ND   | ND   | ND     | 1  | Non-chronic|               | ND |
| Kamath [57]  | European       | 124     | 66±5         | ND | ND  | ND | ND       | ND   | ND   | ND     | 1  | Non-chronic|               | ND |
| Kamath [58]  | European       | 58      | 63±4         | ND | ND  | ND | ND       | ND   | ND   | ND     | 4  | Non-chronic|               | 5.15 |
| Kamath [59]  | European       | 116     | 63±5         | ND | ND  | ND | ND       | ND   | ND   | 17.845  | ND | 4 chronic    |               | 5.15 |
| Kamath [59]  | European       | 143     | 70±5         | ND | ND  | ND | ND       | ND   | ND   | ND     | ND | 1 Non-chronic|               | ND |
| Kamath [60]  | European       | 57      | 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      | 65        | 77.3       | 6.52     | 23.9      | ND       | ND             | ND         | ND           | ND       | 3        | Non-chronic   | 11.52 |
| Mondillo [62]            | European       | 80      | 66.95     | 82.85      | 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           | 1        | ND       | 3            | 13.3  |
| Li-Saw-Hee [64]          | European       | 50      | 59        | 20         | ND       | ND        | ND       | ND             | ND         | ND           | 5        | chronic |               | 20    |
| Minamino [65]            | European       | 56      | 64        | 71.4       | 21.5     | 25        | ND       | ND             | ND         | ND           | 4        | chronic |               | 37.5  |
| Minamino [66]            | Asian          | 90      | 63        | 73.3       | 12.5     | 23.5      | ND       | ND             | ND         | ND           | ND       | 1        | Non-chronic   | ND    |
| 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           | 1        | chronic |               | ND    |
| Nagao [70]               | Asian          | 36      | 79.95     | 47.05      | ND       | ND        | ND       | ND             | ND         | ND           | 12       | ND       |               | ND    |
| Sohara [71]              | Asian          | 28      | ND        | ND         | ND       | ND        | ND       | ND             | ND         | ND           | ND       | 1        | Non-chronic   | ND    |
| Gustafsson (with stroke) | European       | 60      | 77        | ND         | ND       | ND        | ND       | ND             | ND         | ND           | ND       | 1        | ND           | ND    |
| Gustafsson (without stroke) | 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 |
| Yamauchi (with valvular heart disease) [73] | Asian | 83 | 45.5 | ND | ND | ND | ND | ND | ND | ND | ND | 1 | ND |

**Supplementary Table 3. Subgroup-analysis**

| Subgroup                          | Studies (N) | WMD (95% CI)            | I-squared and Heterogeneity-p-value | 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           |                         |                                     |                |
| 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           | ~12.23 (~16.39 to ~8.08)  | 0.0% and 0.401 and 0.001               |                |
| South American                    | -           |                         |                                     |                |
| 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                |                |
### META-ANALYSIS

Weymann A. et al.: Platelets cellular and functional characteristics in patients with atrial fibrillation…
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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**              |             |                               |                                                                     |
| All of studies: after 2000            |             |                               |                                                                     |

**Year of publication**

>2000  
≤2000  

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| 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                                           |
| 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                  |             |                                    |                                                                    |
| Medication: Diuretic           |             | No Data                           |                                                                    |
| Medication: ACEI               |             | No Data                           |                                                                    |
| >70%                           |             | No Data                           |                                                                    |
| Medication: Statin             |             | No Data                           |                                                                    |
| >70%                           |             | No Data                           |                                                                    |
| Medication: Beta-Blocker       |             | No Data                           |                                                                    |
| >70%                           |             | No Data                           |                                                                    |
| ≤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                              | –           | –                                 | –                                                                 |
### WMD (95% CI) and I-squared and Heterogeneity-p-value and Effect-p-value respectively

| Subgroup                        | Studies (N) | WMD (95% CI)        | I-squared and Heterogeneity-p-value | Effect-p-value |
|---------------------------------|-------------|---------------------|-------------------------------------|----------------|
| 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          |                |
| 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           | 6.75 (6.32 to 7.17)  | 51.5% and 0.054 and 0.001          |                |
| European                        | 9           | 3.25 (2.91 to 3.59)  | 99.8% and 0.001 and 0.001          |                |
| African                         | –           | –                   |                                     |                |
| North American                  | –           | –                   |                                     |                |
| South American                  | –           | –                   |                                     |                |
| Australia                       | –           | –                   |                                     |                |
| Design of study                 |             |                     |                                     |                |
| Cohort                          |             | All of studies are “case-control” | |                |
| Case-control                    |             | All of studies are “number less than 300 population”; | |                |
| 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          |                |
| 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          | Medication: ACEI | Medication: Statin | Medication: Beta-Blocker |
|-------------------|------------------|-------------------|-------------------------|
| >70%              | –                | –                 | –                       |
| ≤70%              | –                | –                 | –                       |
| Studies (N)       | 8                | 6                 | 10                      |
| WMD (95% CI)      | 5.25 (4.54 to 5.96) | 4.60 (3.87 to 5.34) | 3.67 (3.02 to 4.33)    |
| I-squared and Heterogeneity-p-value respectively | 98.9% and 0.001 and 0.001 | 98.8% and 0.001 and 0.001 | 98.0% and 0.001 and 0.001 |

Anti-coagulant status codes

| Type of AF          | Medication: ACEI | Medication: Statin | Medication: Beta-Blocker |
|---------------------|------------------|-------------------|-------------------------|
| AF                  | –                | –                 | –                       |
| Chronic             | 6                | 3.94 (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 |
| 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

| Subgroup          | Medication: ACEI | Medication: Statin | Medication: Beta-Blocker |
|-------------------|------------------|-------------------|-------------------------|
| >30%              | –                | –                 | –                       |
| ≤30%              | –                | –                 | –                       |
| Studies (N)       | 2                | 4.76 (2.68 to 6.84) | 95.4% and 0.001 and 0.001 |
| WMD (95% CI)      | 5.41 (4.55 to 6.27) | 98.8% and 0.001 and 0.001 |

References:

1. Macle L, Cairns J, Leblanc K et al: 2016 Focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. Can J Cardiol, 2016; 32(10): 1170–85
2. Ali-Hassan-Sayegh S, Mirhosseini SJ, Rezaeisadrabadi M et al: Antioxidant supplementations for prevention of atrial fibrillation after cardiac surgery: An updated comprehensive systematic review and meta-analysis of 23 randomized controlled trials. Interact Cardiovasc Thorac Surg, 2014; 18: 464–54
3. Mark L, Dani G, Vendrey R et al: Oral anticoagulant therapy and bleeding events with vitamin K antagonists in patients with atrial fibrillation in a Hungarian county hospital. Med Sci Monit, 2015; 21: 1181–93
4. Kornej J, Apostolakis S, Bollmann A, Lip GY: The emerging role of biomarkers in atrial fibrillation. Can J Cardiol, 2013; 29: 1181–93
5. Argan O, Ural D, Kozdag G et al: Associations between neutrophil gelatinase associated lipocalin, neutrophil-to-lymphocyte ratio, atrial fibrillation and renal dysfunction in chronic heart failure. Med Sci Monit, 2016; 22: 4765–72
6. Davi G, Patrono C: Platelet activation and atherothrombosis. N Engl J Med, 2007; 357: 2482–94
7. Brotman DJ, Deitcher SR, Lip GY, Matz dorff AC: Virchow’s triad revisited. South Med J, 2004; 97: 213–14
8. Hozo SP, Djulbegovic B, Hozo I: Estimating the mean and variance from the median, range, and the size of a sample. BMC Res Methodol, 2005; 5: 13
9. Wells GA SB, O’Connell D, Peterson J et al: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses, 2011. [Available: http://www.ohri.ca/programs/clinical_epidemiology/ suddf.asp]
10. Barua RS, Ambrose JA: Mechanisms of coronary thrombosis in cigarette smoke exposure. Arterioscler Thromb Vasc Biol, 2013; 33: 1460–47
11. Gasparyan AV, Ayvazyan L, Mikhailidis DP, Kitas GD: Mean platelet volume: A link between thrombosis and inflammation? Curr Pharm Des, 2011; 17: 47–58
12. Ünúbol M, Ahyan M, Güney E: The relationship between mean platelet volume with microalbuminuria and glycemic control in patients with type II diabetes mellitus. Platelets, 2012; 23: 475–80
13. Sansanayudh N, Anothaisintawee T, Muntham D et al: Mean platelet volume and coronary artery disease: A systematic review and meta-analysis. Int J Cardiol, 2014; 175: 433–40
14. Varasteh-Ravan HR, Ali-Hassan-Sayegh S, Shokraneh S et al: Relationship of admission mean platelet volume, platelet distribution width and white blood cells with ST resolution in patients with acute ST segment elevation myocardial infarction treated with streptokinase without history of previous cardiovascular surgery. Perspect Clin Res, 2013; 4: 125–29
15. Butkiewicz AM, Kemonia H, Dymicka-Piekarska V, Bychowsky J: Beta-thromboglobulin in platelets and unstable angina. Kardiol Pol, 2003; 58: 449–55
16. Resmi KR, Krishnan LC: Protease action and generation of beta-thromboglobulin-like protein followed by platelet activation. Thromb Res, 2002; 107: 23–29
17. Guo L, Sun G, Wang G et al: Soluble P-selectin promotes acute myocardial infarction onset but not severity. Mol Med Rep, 2015; 11: 2027–33
18. Feng D, D’Agostino RB, Silberschatz H et al: Hemostatic state and atrial fibrillation (The Framingham Offspring Study). Am J Cardiol, 2001; 87: 168–71
19. Lip GY, Lowe GD, Rumley A, Dunn FG: Increased markers of thrombogenesis in chronic atrial fibrillation: Effects of warfarin treatment. Br Heart J, 1995; 73: 527–33
20. Karataş MB, Çanga Y, İpek G et al: Association of admission serum laboratory parameters with new-onset atrial fibrillation after a primary percutaneous coronary intervention. Coron Artery Dis, 2016; 27: 128–34
META-ANALYSIS

21. Drablk L, Wokow P, Undas A: Denser plasma clot formation and impaired fibrinolysis in paroxysmal and persistent atrial fibrillation while on sinus rhythm: Association with thrombin generation, endothelial injury and platelet activation. Thromb Res, 2015; 136: 408–14

22. Idrissi NK, Blann AD, Sayed DM et al: Circulating endothelial cells and platelet micro particles in mitral valve disease with and without atrial fibrillation. Angiology, 2015; 66: 631–17

23. Akdag S, Simsek H, Sahin M et al: Association of epicardial adipose tissue thickness and inflammation parameters with CHA2DS2-VASc score in patients with nonvalvular atrial fibrillation. Ther Clin Risk Manag, 2015; 11: 1675–81

24. Akyüz A, Akkoyun DC, Değirmenci H, Alp R: Atrial fibrillation is associated with increased mean platelet volume and anepla hypognea index in patients with obstructive sleep apnea. Angiology, 2015, 66: 525–30

25. Chavarria N, Wong C, Hussain H et al: Persistent elevation of neutrophil/lymphocyte ratio associated with new onset atrial fibrillation following percutaneous coronary intervention for acute ST segment elevation myocardial infarction. J Thromb Thrombolysis, 2015; 39: 122–28

26. Erdogan D, Uysal BA, Aksoy F et al: Strict heart rate control attenuates prothrombotic state and platelet activity in patients with non-valvular permanent atrial fibrillation. Clin Hemorheol Microcirc, 2014; 56: 219–29

27. Xu XF, Jiang FL, Ou M, Zhang ZH: The association between mean platelet volume and chronic atrial fibrillation and the presence of thrombotic events. Blood Coagul Fibrinolysis, 2015; 26: S5–94

28. Acet H, Ertas F, Akı A et al: New inflammatory predictors for non-valvular atrial fibrillation: echocardiographic epicardial fat thickness and neutrophil to lymphocyte ratio. Int J Cardiovasc Imaging, 2014; 30: 81–89

29. Arık OZ, Ozkan B, Kutlu R et al: Relationship between platelet indices and international normalized ratio in patients with non valvular atrial fibrillation. Platelets, 2014; 25: 311–16

30. Distelmaier K, Mauer G, Gollaich G: Blood count in new onset atrial fibrillation after acute myocardial infarction – a hypothesis generating study. Indian J Med Res, 2014; 139: 579–84

31. Gündoğar B, Özcan K, Erdirli I et al: Elevated levels of RDW is associated with non-valvular atrial fibrillation. J Thromb Thrombolysis, 2014; 37: 251–10

32. Sonmez O, Ertem RV, Vatankulu MA et al: Novel fibro-inflammation markers in assessing left atrial remodeling in non-valvular atrial fibrillation. Med Sci Monit, 2014; 20: 463–70

33. Ulu SM, Ozcicek G, Akı A et al: Mean platelet volume, in predicting sepsis in the elderly. Scand J Clin Lab Invest, 2013; 73: 326–32

34. Inoue H, Nozawa T, Okumura K et al: Prothrombotic activity is increased in patients with nonvalvular atrial fibrillation and risk factors for embolism. Chest, 2004; 126: 687–92

35. Conway DS, Buggins P, Hughes E, Lip GY: Relationship of interleukin-6 and C-reactive protein, and the prothrombotic state to transesophageal echocardiographic findings in atrial fibrillation. Am J Cardiol, 2004; 93: 1368–73, A6

36. Atalar E, Haznedaroglu IC, Akı C et al: Patients with paroxysmal atrial fibrillation and the effects of antithrombotic therapy. Eur Heart J, 2002; 23: 1788–95

37. Kamath S, Blann AD, Chin BS, Lip GY: Platelet activation, haemorheology and thrombogenesis in acute atrial fibrillation: A comparison with permanent atrial fibrillation. Heart, 2003; 89: 1093–95

38. Kamath S, Chin BS, Blann AD, Lip GY: A study of platelet activation in paroxysmal, persistent and permanent atrial fibrillation. Blood Coagul Fibrinolysis, 2002; 13: 627–36

39. Kamath S, Blann AD, Chin BS et al: A study of platelet activation in atrial fibrillation and the effects of antithrombotic therapy. Eur Heart J, 2002; 23: 1788–95

40. Kamath S, Blann AD, Caine GJ et al: Platelet P-selectin and beta-thromboglobulin levels in atrial fibrillation. Stroke, 2002; 33: 1237–42

41. Li-Saw-Hee FL, Blann AD, Gurney D, Lip GY: Plasma von Willebrand factor, fibrinogen and soluble P-selectin levels in paroxysmal, persistent and permanent atrial fibrillation. Effects of cardioversion and return of left atrial function. Eur Heart J, 2001; 22: 1741–47

42. Mondillo S, Sabatini L, Agricola E et al: Correlation between left atrial size, prothrombotic state and markers of endothelial dysfunction in patients with lone chronic nonhaemorrhagic atrial fibrillation. Int J Cardiol, 2000; 75: 227–32

43. Li-Saw-Hee FL, Blann AD, Lip GY: A cross-sectional and diurnal study of thrombogenesis among patients with chronic atrial fibrillation. J Am Coll Cardiol, 2000; 35: 1926–31

44. Minamino T, Kitakaze M, Asanuma H et al: Plasma adenosine levels and platelet activation in patients with atrial fibrillation. Am J Cardiol, 1999; 83: 194–98
66. Minamino T, Kitakaze M, Sato H et al: Plasma levels of nitrite/nitrate and platelet cGMP levels are decreased in patients with atrial fibrillation. Arterioscler Thromb Vasc Biol, 1997; 17: 3191–95
67. Kahn SR, Solymoss S, Flegel KM: Nonvalvular atrial fibrillation: Evidence for a prothrombotic state. CMAJ, 1997; 157: 673–81
68. Sohara H, Amitani S, Kurose M, Miyahara K: Atrial fibrillation activates platelets and coagulation in a time-dependent manner: A study in patients with paroxysmal atrial fibrillation. J Am Coll Cardiol, 1997; 29: 106–12
69. Lip GY, Lip PL, Zarifis J et al: Fibrin D-dimer and beta-thromboglobulin as markers of thrombogenesis and platelet activation in atrial fibrillation. Effects of introducing ultra-low-dose warfarin and aspirin. Circulation, 1996; 94: 425–31
70. Nagao T, Hamamoto M, Kanda A et al: Platelet activation is not involved in acceleration of the coagulation system in acute cardioembolic stroke with nonvalvular atrial fibrillation. Stroke, 1995; 26: 1365–68
71. Sohara H, Miyahara K: Effect of atrial fibrillation on the fibrino-coagulation system – study in patients with paroxysmal atrial fibrillation. Jpn Circ J, 1994; 58: 821–26
72. Gustafsson C, Blomback M, Britton M et al: Coagulation factors and the increased risk of stroke in nonvalvular atrial fibrillation. Stroke, 1990; 21: 47–51
73. Yamauchi K, Furui H, Taniguchi N, Sotobata I: Plasma beta-thromboglobulin and platelet factor 4 concentrations in patients with atrial fibrillation. Jpn Heart J, 1986; 27: 481–87
74. Bayar N, Arslan S, Cagirci G et al: Usefulness of mean platelet volume for predicting stroke risk in paroxysmal atrial fibrillation patients. Blood Coagul Fibrinolysis, 2015; 26: 669–72