Predictive Role of Coagulation, Fibrinolytic, and Endothelial Markers in Patients with Atrial Fibrillation, Stroke, and Thromboembolism: A Meta-Analysis, Meta-Regression, and Systematic Review

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Background:
The pathophysiological mechanism associated with the higher prothrombotic tendency in atrial fibrillation (AF) is complex and multifactorial. However, the role of prothrombotic markers in AF remains inconclusive.

Material/Methods:
We conducted a meta-analysis of observational studies evaluating the association of coagulation activation, fibrinolytic, and endothelial function with occurrence of AF and clinical adverse events. A comprehensive subgroup analysis and meta-regression was performed to explore potential sources of heterogeneity.

Results:
A literature search of major databases retrieved 1703 studies. After screening, a total of 71 studies were identified. Pooled analysis showed the association of coagulation markers (D-dimer (weighted mean difference (WMD)=197.67 and p<0.001), fibrinogen (WMD=0.43 and p<0.001), prothrombin fragment 1-2 (WMD=0.53 and p<0.001), antithrombin III (WMD=23.90 and p=0.004), thrombin-antithrombin (WMD=5.47 and p=0.004)); fibrinolytic markers (tissue-type plasminogen activator (t-PA) (WMD=2.13 and p<0.001), plasminogen activator
Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia in the general population and is associated with a high risk of developing morbidities such as hemodynamic instability, thromboembolism, stroke, hospital re-admissions, and increasing health care costs [1]. AF alone is associated with a 1.5% to 1.9% increase in risk of mortality in both sexes across a wide range of ages [2]. Moreover, the situation is likely to worsen since the number of people with AF is expected to double by 2050 [2]. AF is linked to a 5-fold increased risk of cerebrovascular events, and approximately 20% of strokes are related to AF [3].

Recently, researchers have suggested several important mechanisms for the occurrence of AF, including oxidative stress reactions and systemic inflammation [4]. The pathophysiological mechanism associated with the higher prothrombotic tendency in AF is highly complex and multifactorial [5]. Virchow’s triad regarding prothrombotic state, including changed blood flow (arterial stasis), abnormalities in vessel wall, and coagulant alternations in the hemostatic balance, may play an important role in the occurrence of supraventricular arrhythmia [6].

Various studies have reported the association of hemostatic markers with the occurrence of AF. However, so far, the data from these studies are largely inconclusive. The present systematic review with meta-analysis sought to determine the strength of evidence for evaluating the role of coagulation activation, fibrinolytic, and endothelial function in the occurrence of AF and related consequent outcomes such as thromboembolism and stroke.

**Material and Methods**

**Literature search**

A systematic and comprehensive literature search was conducted in electronic databases (Medline/PubMed, Embase, Web of Science, and Google Scholar) from their inception through 5 August 2016 to identify relevant studies on the association of coagulation, fibrinolytic, and endothelial functional assessment with the occurrence of AF and related consequent clinical adverse events, including thromboembolism and stroke. Predefined search terms were: coagulation [“fibrinogen”, “D-dimer”, “prothrombin fragment 1-2”, “antithrombin III”, “thrombin-antithrombin”], fibrinolytic [“tissue-type plasminogen activator”, “plasminogen activator inhibitor”, “alfa-2 antiplasmin”, “fibrinopeptide-A”, “urokinase-type plasminogen activator”, “plasmin-antiplasmin”], endothelial function [“von Willebrand factor”, “soluble thrombomodulin”], and “atrial fibrillation”. No limitations were imposed on language, time of publication, or sample size of studies. All retrieved references of the included studies and recent published review articles and meta-analyses were also reviewed to determine additional studies not indexed in major databases.

**Study selection**

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

**Data extraction and outcome measures**

Three investigators (S.A.-H-S, A.W., and A.S.) extracted the data independently, and discrepancies were resolved via a consensus standardized abstraction checklist used for recording data in each enrolled study. Disagreements were resolved through discussion with senior authors (A.F.-P, G.B.Z, and H.C.). Author’s name, year of publication, country, design of study, procedure, sample size, mean age, sex, coexistent cardiovascular disease and risk factors, anticoagulants, type of AF, and details of
hemosstatic markers were extracted. For exploration of heterogeneity among trials, subgroup analyses of disparities in the patients’ characteristics were performed for (1) year of publication (before 2000 vs. after 2000); (2) geographic area (Asia, Europe, Africa, North-America, South-America, and Oceania); (3) design of the study (case-control vs. cohort); (4) number of patients (≤300 vs. >300); (5) mean age (≤60 years vs. >60 years); (6) percentage of males (≤70% vs. >70%); (7) diabetes (≤30% vs. >30%); (8) hypertension (≤70% vs. >70%); (9) myocardial infarction (≤20% vs. >20%); (10) AF-classification (acute and sub-acute vs. chronic); (11) type of AF (paroxysmal, persistent, permanent); and (12) anticoagulation (code-1: no patient received anticoagulants in both groups, code-2: all participants were anticoagulated in both groups, code-3: range of percentages between both groups more than 50%, code-4: range of percentages between both groups less than 50%, code-5: anticoagulation information was not available in both groups, and code-6: anticoagulation information was not available in 1 group only).

Homogenization of extracted data

The suitable form of data for analyzing was mean ± standard deviation (SD). For studies that reported interquartile range instead of the range, we estimated means according to [minimum+maximum+2(median)]/4 and SD according to (maximum-minimum)/4 for groups with sample sizes up to about 70 and (maximum-minimum)/6 for sample sizes more than 70 [7].

Quality assessment and statistical analysis

Two investigators (L.M. and M.G.) independently assessed the quality of studies by using the Newcastle-Ottawa scale [8]. The total scores ranged from 0 (worst quality) to 9 (best quality) for case-control or cohort studies. Data were analyzed by STATA software version 11.0 utilizing METAN and METABIAS modules. The pooled effect size measured was weighted mean difference (WMD) with 95% CI for non-categorical data. Heterogeneity was assessed using I². Pooled analysis was performed for studies with a p-value <0.05.

Results

Literature search strategy and included studies

The literature search retrieved 1703 studies from screened databases, of which 1527 (89.6%) were excluded after detailed evaluation in the initial review due to either redundant information (n=1095), insufficient reporting of endpoints of interest (n=398), or reporting of non-matched data according to mean ± SD or median [minimum-maximum] (n=34); 176 potentially relevant full-text articles were reviewed, and a total of 71 studies were finally included in the meta-analysis (Supplementary Table 1).

Association of coagulation markers with AF

D-dimer

A total of 7954 cases were included from 41 studies. Patient populations in the included studies ranged from 22 to 3120 patients. Of 7954 cases, 2269 were allocated to AF group and 5685 to the SR group. Mean D-dimer levels were 520.05 µg/mL in AF group and 249.28 µg/mL in SR group (details in Tables 1 and 2). Pooled assessment effect analysis revealed that the mean D-dimer level was significantly higher in patients with AF than in patients with SR with WMD of 197.67 (95% CI: 172.96–222.38; p<0.001, Figure 1) using a random effect model. Significant heterogeneity was observed among the studies (I²=99.8%; heterogeneity p<0.001).

Fibrinogen

A total of 43174 cases were included from 58 studies. Patient populations of the included studies ranged from 22 to 11 107 patients. Of 43 174 cases, 5583 were allocated to AF group and 37 591 to the SR group. Mean level of fibrinogen was 3.24 g/L in AF group and 2.78 g/L in SR group (details in Tables 1 and 2). Pooled assessment effect analysis revealed that fibrinogen level was significantly higher in patients with AF compared to those with SR with WMD of 0.43 (95% CI: 0.36–0.51; p<0.001, Figure 2) using a random effect model. There was significant heterogeneity among the studies (I²=98.4%; heterogeneity p<0.001).

Prothrombin fragment 1-2 (PF 1-2)

A total of 1047 cases were included from 9 studies, of which 694 cases were allocated to the AF group and 353 to the SR group. The mean level of PF 1-2 was 1.88 nmol/mL in the AF group and 1.35 nmol/mL in the SR group (details in Tables 1 and 2). Pooled analysis revealed that PF 1-2 was significantly higher in the AF group than in patients with SR with WMD of 0.53 nmol/mL (95% CI: 0.33-0.73; p<0.001, Figure 3) using a random effect model. There was significant heterogeneity among the studies (I²=99.5%; heterogeneity p<0.001).

Antithrombin III (AT-3)

A total of 300 patients were included from 6 studies. Of them, 153 cases were allocated to the AF group and 147 cases to the
Table 1. Characteristics of included studies for meta-analysis of association of biomarkers 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 |
|--------------|------|---------|--------|------|------|--------|--------|---------|---------|-------|-------|------------|-----|
| Negreva [9]  | 2016 | Bulgaria| Cohort | 51   | 52   | 59.84  | 59.5   | 50.9    | 50      | 0      | 0     | Paroxysmal | 6   |
| Amdu [10]    | 2016 | USA     | Cohort | 642  | 3120 | 60.8   | 57     | 53.8    | 55.3    | 48.6   | 42    | ND         | 9   |
| Yusuf (disease control) [11] | 2015 | India  | Case-Control | 35   | 30   | 31.86  | 31.14  | 45.7    | 40      | 0      | 0     | ND         | 8   |
| Yusuf (healthy control) [11] | 2015 | India  | Case-Control | 35   | 30   | 28.97  | 31.14  | 37.1    | 40      | 0      | 0     | ND         | 8   |
| Drabik (persistent) [12] | 2015 | Poland | Case-Control | 47   | 50   | 60.8   | 59.4   | 65.9    | 64      | 38.3   | 26    | Persistent | 8   |
| Drabik (PAF) [12] | 2015 | Poland | Case-Control | 41   | 50   | 60.6   | 59.4   | 46.3    | 64      | 51.2   | 26    | Paroxysmal | 8   |
| Borgi [13]   | 2015 | Tunis  | Case-Control | 50   | 19   | 61.8   | ND     | 42      | ND      | ND     | ND    | Combined   | 7   |
| Oneal (with comorbidities) [14] | 2015 | USA    | Cohort | 79   | 568  | 71     | 68     | 44      | 64      | 47     | 42    | ND         | 9   |
| Erdogan [15] | 2014 | Turkey | Case-Control | 34   | 33   | 70.5   | 68.6   | 47.05   | 51.5    | 66.6   | 0     | Permanent  | 9   |
| Chen (without comorbidities) [16] | 2014 | China | Cohort | 62   | 100  | 55.1   | 52.9   | 58.06   | 64      | 19     | 12    | Combined   | 8   |
| Wei-Hong Ma [18] | 2014 | China | Cohort | 107  | 100  | 59.4   | 52.9   | 64.4    | 64      | 26     | 12    | Combined   | 8   |
| Xu (without comorbidities) [19] | 2014 | China | Cohort | 55   | 50   | 59     | 57     | 74.5    | 70      | 100    | 100   | ND         | 8   |
| Xu (with comorbidities) [19] | 2014 | China | Cohort | 55   | 50   | 65.9   | 67.8   | 50.9    | 50      | 50.9   | 15.5  | ND         | 7   |
| Distelmaier [20] | 2014 | USA    | Case-Control | 66   | 132  | 73.5   | 73.5   | 61      | 61      | ND     | ND    | ND         | 9   |
| Scridon (PAF) [21] | 2013 | France | Case-Control | 52   | 17   | 56     | 55     | 81      | 76      | 100    | 0     | Paroxysmal | 7   |
| Scridon (persistent) [21] | 2013 | France | Case-Control | 36   | 17   | 55     | 55     | 81      | 76      | 100    | 0     | Persistent | 7   |
| Berge [22]   | 2013 | Norway | Cohort | 63   | 126  | 75     | 75     | 71.4    | 70.6    | 8      | 33    | Combined   | 9   |
| Acevedo [23] | 2012 | Chile  | Case-Control | 130  | 20   | 67     | ND     | ND      | ND      | 0      | 0     | Combined   | 8   |
| Zorlu [24]   | 2012 | Turkey | Cohort | 31   | 119  | 72     | 67     | 64      | 60      | 0      | 0     | ND         | 8   |
| Alonso (White) [25] | 2012 | USA    | Cohort | 976  | 10131| 57.3   | 54.1   | 58.4    | 46.1    | 0      | 0     | ND         | 9   |
| Alonso (African-American) [25] | 2012 | USA    | Cohort | 233  | 3518 | 56.2   | 53.4   | 44.6    | 37.8    | 0      | 0     | ND         | 9   |
Table 1 continued. Characteristics of included studies for meta-analysis of association of biomarkers 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 |
|--------------|------|---------|--------|------|------|--------|--------|---------|---------|-------|-------|------------|-----|
| Adamsson     | 2011 | Sweden  | Cohort | 667  | 5364 | 47.8   | 46.7   | 100     | 100     | ND    | ND    | ND         | 9   |
| Eyd [26]     |      |         |        |      |      |        |        |         |         |       |       |            |     |
| Fu [27]      | 2011 | China   | Case-control | 90  | 79  | 54.1   | 54.8   | 70      | 57      | 22     | 0     | Combined   | 8   |
| Hou (disease control) [28] | 2010 | China  | Case-control | 26  | 26  | 65.2   | 64.5   | 57.6    | 57.6    | 7.6    | 11.5  | ND         | 8   |
| Hou (healthy control) [28] | 2010 | China  | Case-control | 26  | 26  | 65.2   | 65.4   | 57.6    | 57.6    | 7.6    | 0     | ND         | 8   |
| Schnabel [29] | 2010 | USA    | Cohort | 209  | 2911 | 66.3   | 57.8   | 60      | 45      | ND    | ND    | ND         | 9   |
| Marin (chronic AF) | 2006 | Italy  | Case-control | 18  | 28  | 37     | 32     | ND      | ND      | ND    | ND    | ND         | 6   |
| Marin (acute AF) | 2006 | Italy  | Case-control | 18  | 20  | 37     | 35     | ND      | ND      | ND    | ND    | ND         | 6   |
| Cecchi (with cerebral ischemic) [36] | 2006 | Italy  | Case-control | 62  | 130 | 75     | 72     | 61.2    | 59.2    | 100    | 0     | ND         | 6   |
| Cecchi (without cerebral ischemic) [36] | 2006 | Italy  | Case-control | 94  | 130 | 74     | 72     | 59.5    | 59.2    | 100    | 0     | ND         | 6   |
| Roldan [39]  | 2005 | Spain   | Case-control | 191 | 74  | 72     | ND     | 51.3    | ND      | 100    | 62.2  | ND         | 7   |
| Marin (acute AF) [40] | 2004 | Spain  | Case-control | 24  | 24  | 64     | 63     | 50      | 50      | 16.6   | 0     | ND         | 8   |
| Marin (chronic AF) [40] | 2004 | Spain  | Case-control | 24  | 24  | 64     | 63     | 45.8    | 50      | 41.6   | 0     | ND         | 8   |
| Inoue (with comorbidities) [41] | 2004 | Japan  | Case-control | 159 | 92  | ND     | ND     | ND      | ND      | ND    | ND    | ND         | 7   |

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### Table 1 continued. Characteristics of included studies for meta-analysis of association of biomarkers 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 (Lone AF) [41] | 2004 | Japan | Case-control | 87  | 19  | ND     | ND     | ND      | ND      | ND    | ND    | ND         | 7   |
| Conway [42] | 2004 | UK     | Case-control | 106 | 41  | 69     | 67     | 63      | 61      | 86    | 0     | Permanent   | 6   |
| Hatzinikolaou-Kotsakou (PAF) [43] | 2004 | Greece | Case-control | 18  | 17  | 59     | 59     | 72.2    | 82.3    | ND    | ND    | Paroxysmal  | 8   |
| Kotsakou (persistent) [43] | 2004 | Greece | Case-control | 17  | 17  | 61     | 59     | 64.7    | 82.3    | ND    | ND    | Persistent  | 8   |
| Hatzinikolaou-Kotsakou (permanent) [43] | 2004 | Greece | Case-control | 20  | 17  | 64     | 59     | 70      | 82.3    | ND    | ND    | Permanent   | 8   |
| Conway [44] | 2004 | UK     | Case-control | 37  | 37  | 67     | 68     | 72.9    | 67.5    | ND    | ND    | Persistent  | 6   |
| Kamath (PAF and PeAF) [45] | 2003 | UK     | Case-control | 31  | 31  | 61     | 66     | 61.3    | 41.9    | 0     | 0     | Combined (PAF and PeAF) | 6   |
| Kamath (permanent AF) [45] | 2003 | UK     | Case-control | 93  | 31  | 66     | 66     | 63.4    | 41.9    | 0     | 0     | Permanent   | 6   |
| Marin [46] | 2003 | Spain  | Case-control | 48  | 32  | 71     | 70     | 63      | 47      | 38    | 9     | ND         | 7   |
| Conway [47] | 2003 | UK     | Cohort    | 162 | 324 | 78     | 77     | 51.2    | 50.9    | 0     | 0     | ND         | 8   |
| Kamath (PAF) [48] | 2002 | UK     | Case-control | 29  | 29  | 61     | 65     | 55.17   | 41.3    | 37.9  | 0     | Paroxysmal  | 7   |
| Kamath (permanent AF) [48] | 2002 | UK     | Case-control | 87  | 29  | 65     | 65     | 63.2    | 41.3    | 37.9  | 0     | Permanent   | 7   |
| Kamath [49] | 2002 | UK     | Case-control | 93  | 50  | 70     | 70     | 62.4    | 64      | 0     | 0     | ND         | 6   |
| Wang [50] | 2002 | Taiwan | Cohort    | 15  | 3159| 66.1   | 53.9   | 56.6    | 46.7    | ND    | ND    | ND         | 9   |
| Li-saw-Hee (PAF) [51] | 2001 | UK     | Case-control | 23  | 20  | 65     | 63     | 69.6    | 85      | 69.6  | 0     | Paroxysmal  | 8   |
| Li-saw-Hee (PeAF) [51] | 2001 | UK     | Case-control | 23  | 20  | 65     | 63     | 69.5    | 85      | 100   | 0     | Persistent  | 8   |
| Li-saw-Hee (permanent) [51] | 2001 | UK     | Case-control | 23  | 20  | 67     | 63     | 69.5    | 85      | 100   | 0     | Permanent   | 8   |
| Feng [52] | 2001 | USA    | Case-control | 47  | 167 | 62     | 62.3   | 74.5    | 72.5    | 76.6  | ND    | ND         | 8   |
| Topcuoglu [53] | 2000 | Turkey | Case-control | 15  | 21  | 61.9   | 62.8   | 66.6    | 57.14   | 0     | 0     | ND         | 6   |
| Mondillo [54] | 2000 | Italy  | Case-control | 45  | 35  | 67.6   | 66.3   | 80      | 85.7    | 55    | 0     | Permanent   | 7   |
| Giansante [55] | 2000 | Italy  | Case-control | 35  | 70  | 64     | 63     | 54.2    | 57.14   | 0     | 0     | Paroxysmal  | 7   |
| Li-saw-Hee [56] | 2000 | UK     | Case-control | 52  | 60  | 68     | 66     | 80      | 75      | 0     | 0     | ND         | 6   |
| Marin (disease control) [57] | 1999 | Spain  | Case-control | 18  | 24  | 56     | 51     | 22.2    | 12.5    | 0     | 0     | ND         | 6   |
| Marin (healthy control) [57] | 1999 | Spain  | Case-control | 18  | 20  | 56     | ND     | 22.2    | ND      | 0     | 0     | ND         | 6   |
### Table 1 continued. Characteristics of included studies for meta-analysis of association of biomarkers 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 |
|---------------------|------|---------|---------------|------|------|--------|--------|---------|---------|-------|-------|------------|-----|
| Li-saw-Hee          | 1999 | UK      | Case-control  | 25   | 25   | 60     | 58     | 20      | 20      | ND     | ND     | ND         | 6   |
| Roldan              | 1998 | Spain   | Case-control  | 36   | 20   | 62     | 62     | ND      | 0       | 0      | ND     | 7           |    |
| Tsai                | 1998 | Taiwan  | Case-control  | 73   | 38   | 65     | 63     | 75.3    | 73.6    | 11      | 0      | ND         | 6   |
| Minamino            | 1997 | Japan   | Case-control  | 45   | 45   | 63     | 63     | 73.3    | 73.3    | ND      | ND     | ND         | 6   |
| Kahn                | 1997 | Canada  | Case-control  | 50   | 31   | ND     | 65     | ND      | 38.7    | 0       | 0      | ND         | 7   |
| Sohara              | 1997 | Japan   | Case-control  | 21   | 9    | 59.1   | 59.1   | 71.4    | ND      | 0       | 0      | Paroxysmal | 6   |
| Lip (PAF)           | 1996 | UK      | Case-control  | 30   | 158  | 60.8   | 58.9   | 60      | 55.6    | 0       | 0      | Paroxysmal | 8   |
| Lip (chronic)       | 1996 | UK      | Case-control  | 56   | 158  | 64.7   | 58.9   | 57.14   | 55.6    | 0       | 0      | ND         | 8   |
| Lip                 | 1996 | UK      | Case-control  | 51   | 26   | 70.4   | ND     | ND      | ND      | 0       | 0      | ND         | 6   |
| Mitsusch            | 1996 | Germany | Case-control  | 69   | 28   | 72     | 70     | 42      | 60.7    | 0       | 0      | ND         | 7   |
| Nagao               | 1995 | Japan   | Case-control  | 17   | 19   | 81.5   | 78.4   | 47.05   | 42.1    | 0       | 0      | ND         | 8   |
| Lip                 | 1995 | UK      | Case-control  | 87   | 158  | 63     | 59.3   | 50.6    | 56      | ND      | ND     | ND         | 7   |
| Sohara              | 1994 | Japan   | Case-control  | 13   | 9    | 60     | ND     | 76.9    | ND      | 0       | 0      | Paroxysmal | 6   |
| Kumagai             | 1990 | Japan   | Case-control  | 73   | 21   | 64     | 61     | 53.4    | 42.9    | 0       | 0      | ND         | 7   |
| Gustafsson (with stroke) | 1990 | Sweden | case-control  | 20   | 40   | 77     | 77     | ND      | ND      | 0       | 0      | ND         | 8   |
| Gustafsson (without stroke) | 1990 | Sweden | case-control  | 20   | 40   | 77     | 77     | ND      | ND      | 0       | 0      | ND         | 8   |

### Table 2. Information about markers and these levels in each study.

| First author        | Markers | Levels |
|---------------------|---------|--------|
| Negreva [9]         | sTM     | sTM: AF: 6.5±0.4 vs. SR: 4.48±0.28 |
| Amdur [10]          | Fibrinogen | Fibrinogen: AF: 4.3±1.1 vs. SR: 4.1±1.2 |
| Yusuf (disease control) [11] | TAT and PAI | TAT: AF: 22.65±2.35 vs. SR: 9.07±1.22 |
| Yusuf (healthy control) [11] | TAT and PAI | PAI: AF: 47.9±2.5 vs. SR: 13.52±3.57 |
| Drabik (persistent) [12] | Fibrinogen, tPA, PAI, and vWF | Fibrinogen: AF: 3.32±0.27 vs. SR: 3.12±0.32 |
|                      |         | tPA: AF: 12.8±1.8 vs. SR: 9.4±2.1 |
|                      |         | PAI: AF: 28.1±1.35 vs. SR: 24.07±3.12 |
|                      |         | vWF: AF: 171±8 vs. SR: 121.75±5.25 |
### Table 2 continued. Information about markers and these levels in each study.

| First author | Markers                        | Levels                                           |
|--------------|--------------------------------|--------------------------------------------------|
| Drabik (PAF) [12] | Fibrinogen, tPA, PAI, and vWF | Fibrinogen: AF: 3.25±0.25 vs. SR: 3.12±0.32  
|               |                                | tPA: AF: 11.9±2.5 vs. SR: 9.4±2.1              
|               |                                | PAI: AF: 27.9±1.65 vs. SR: 24.07±3.12       
|               |                                | vWF: AF: 172.7±10.75 vs. SR: 121.7±5.25       |
| Borgi [13]   | D-dimer                        | D-dimer: AF: 590±506 vs. SR: 225.6±112.95       |
| O'Neal (with comorbidities) [14] | Fibrinogen | Fibrinogen: AF: 0.42±0.10 vs. SR: 0.41±0.11       |
| Erdogan [15] | D-dimer and Fibrinogen         | D-dimer: AF: 204.7±159.2 vs. SR: 186.2±105.6     |
|               |                                | Fibrinogen: AF: 2.74±0.63 vs. SR: 2.27±0.51      |
| Chen (without comorbidities) [16] | D-dimer and Fibrinogen | Fibrinogen: AF: 2.63±0.07 vs. SR: 2.57±0.12      |
| Chen (with comorbidities) [16] | D-dimer and Fibrinogen | Fibrinogen: AF: 3.25±0.25 vs. SR: 3.12±0.32      |
| Schnabel [17] | Fibrinogen                     | Fibrinogen: AF: 4.11±0.35 vs. SR: 3.47±0.23       |
| Xu (without comorbidities) [19] | D-dimer and Fibrinogen | Fibrinogen: AF: 3.64±0.89 vs. SR: 2.62±0.5        |
| Xu (with comorbidities) [19] | D-dimer and Fibrinogen | Fibrinogen: AF: 3.64±0.89 vs. SR: 2.62±0.5        |
| Distelmaier [20] | Fibrinogen                  | Fibrinogen: AF: 4.1±0.27 vs. SR: 4.11±0.23       |
| Scridon (PAF) [21] | vWF                           | vWF: AF: 107.5±9.4 vs. SR: 86.8±14               |
| Scridon (persistent) [21] | vWF                           | vWF: AF: 125±14.0 vs. SR: 86.8±14                |
| Borpe [22]   | tPA                           | tPA: AF: 15.2±1.8 vs. SR: 15.2±1.8               |
| Acevedo [23] | TAT and sTM                    | TAT: AF: 0.05±0.23 vs. SR: 0.00±0.003             |
| Zorlu [24]   | D-dimer                        | D-dimer: AF: 1351.7±497.75 vs. SR: 644.2±113.8   |
| Alonso (White) [25] | Fibrinogen and vWF | Fibrinogen: AF: 3.19±0.64 vs. SR: 2.95±0.61   |
| Alonso (African-American) [25] | Fibrinogen and vWF | Fibrinogen: AF: 3.19±0.64 vs. SR: 2.95±0.61   |
| Fu [27]      | Fibrinogen                     | Fibrinogen: AF: 3.3±0.98 vs. SR: 3.4±0.8         |
| Hou (disease control) [28] | D-dimer and vWF | D-dimer: AF: 327±96 vs. SR: 231±83               |
| Hou (healthy control) [28] | D-dimer and vWF | D-dimer: AF: 327±96 vs. SR: 231±83               |
| Schnabel [29] | D-dimer and Fibrinogen         | D-dimer: AF: 451.5±56 vs. SR: 321±43.6           |
| Letsas (PAF) [30] | Fibrinogen                     | Fibrinogen: AF: 3.7±1.03 vs. SR: 3.6±0.89       |
| Letsas (permanent) [30] | D-dimer                        | D-dimer: AF: 4.12±0.99 vs. SR: 3.6±0.89         |
| Targonski (PAF and PeAF) [32] | Fibrinogen | Fibrinogen: AF: 3.39±0.67 vs. SR: 3.6±0.76       |
| Targonski (Permanent) [32] | Fibrinogen | Fibrinogen: AF: 3.39±0.67 vs. SR: 3.6±0.76       |
| Marcus [33]  | D-dimer                        | D-dimer: AF: 392±91 vs. SR: 408±72               |
| Blann [34]   | vWF                            | vWF: AF: 180±86 vs. SR: 109±62                  |
| First author | Markers | Levels |
|--------------|---------|--------|
| Topaloglu (disease control) [35] | D-dimer, Fibrinogen, AT-III, tPA, PAI and vWF | D-dimer: AF: 384±130 vs. SR: 372±160 Fibrinogen: AF: 2.89±0.71 vs. SR: 2.82±0.37 AT-III: AF: 98.6±11.1 vs. SR: 97.9±21.2 tPA: AF: 8.89±3.5 vs. SR: 5.8±2.19 PAI: AF: 1.05±0.97 vs. SR: 1.16±0.7 vWF: AF: 134.9±68 vs. SR: 115±53.4 |
| Topaloglu (healthy control) [35] | D-dimer, Fibrinogen, AT-III, tPA, PAI and vWF | D-dimer: AF: 384±130 vs. SR: 19±8.3 Fibrinogen: AF: 2.89±0.71 vs. SR: 2.3±0.47 AT-III: AF: 98.6±11.1 vs. SR: 82.8±8.6 tPA: AF: 8.89±3.5 vs. SR: 7.3±3.7 PAI: AF: 1.05±0.97 vs. SR: 1.24±0.65 vWF: AF: 134.9±68 vs. SR: 75.1±17 |
| Cecchi (without cerebral ischemic) [36] | Fibrinogen | Fibrinogen: AF: 3.68±1.04 vs. SR: 3.07±0.3 |
| Cecchi (with cerebral ischemic) [36] | Fibrinogen | Fibrinogen: AF: 4.36±1.22 vs. SR: 3.07±0.3 |
| Turgut (disease control) [37] | Fibrinogen and PF1-2 | Fibrinogen: AF: 3.64±0.86 vs. SR: 3.07±0.3 |
| Turgut (healthy control) [37] | Fibrinogen and PF1-2 | Fibrinogen: AF: 3.64±0.86 vs. SR: 2.51±0.61 |
| Heeringa [38] | Fibrinogen and vWF | Fibrinogen: AF: 2.32±0.7 vs. SR: 2.32±0.9 vWF: AF: 144±32 vs. SR: 138±40.2 |
| Roldan [39] | PF1-2 | PF1-2: AF: 1.41±0.15 vs. SR: 1.05±0.09 |
| Marin (acute AF) [40] | D-dimer, vWF and sTM | D-dimer: AF: 2350±2680 vs. SR: 390±280 vWF: AF: 137±36.9 vs. SR: 86.7±33.2 sTM: AF: 12.1±4.1 vs. 5.9±2.7 |
| Marin (chronic AF) [40] | D-dimer, vWF and sTM | D-dimer: AF: 1120±630 vs. SR: 390±280 vWF: AF: 131±25 vs. SR: 86.7±33.2 sTM: AF: 11.8±4.6 vs. 5.9±2.7 |
| Inoue (with comorbidities) [41] | D-dimer and PF1-2 | D-dimer: AF: 158.6±9.2 vs. SR: 79.1±10.3 PF1-2: AF: 0.98±0.05 vs. SR: 1.0±0.04 |
| Inoue (Lone AF) [41] | D-dimer and PF1-2 | D-dimer: AF: 92.1±6.7 vs. SR: 31±7.4 PF1-2: AF: 0.79±0.06 vs. SR: 0.8±0.05 |
| Conway [42] | Fibrinogen and vWF | Fibrinogen: AF: 2.65±0.17 vs. SR: 2.72±0.28 vWF: AF: 132±26 vs. SR: 125±21 |
| Hatzinikolaou-Kotsakou (PAF) [43] | Fibrinogen and vWF | Fibrinogen: AF: 3.3±0.9 vs. SR: 2.4±0.8 vWF: AF: 119±0.9 vs. SR: 104±22 |
| Hatzinikolaou-Kotsakou (persistent) [43] | Fibrinogen and vWF | Fibrinogen: AF: 3.8±0.4 vs. SR: 2.4±0.8 vWF: AF: 129±19 vs. SR: 104±22 |
| Hatzinikolaou-Kotsakou (permanent) [43] | Fibrinogen and vWF | Fibrinogen: AF: 4.3±0.6 vs. SR: 2.4±0.8 vWF: AF: 158±15 vs. SR: 104±22 |
| Conway [44] | Fibrinogen and vWF | Fibrinogen: AF: 2.83±0.25 vs. SR: 2.67±0.27 vWF: AF: 130±25 vs. SR: 126±21 |
| Kamath (PAF and PeAF) [45] | D-dimer and Fibrinogen | D-dimer: AF: 760±195 vs. SR: 637.5±202.5 Fibrinogen: AF: 2.9±0.7 vs. SR: 2.6±0.4 |
| Kamath (permanent AF) [45] | D-dimer and Fibrinogen | D-dimer: AF: 1497.5±368.3 vs. SR: 637.5±202.5 Fibrinogen: AF: 2.7±0.6 vs. SR: 2.6±0.4 |
| Marin [46] | PF1-2 | PF1-2: AF: 1.61±0.31 vs. SR: 0.94±0.1 |
| Conway [47] | Fibrinogen and vWF | Fibrinogen: AF: 0.8±0.29 vs. SR: 0.79±0.3 vWF: AF: 144±32 vs. SR: 138±32 |
| Kamath (PAF) [48] | D-dimer and Fibrinogen | D-dimer: AF: 675.7±151.7 vs. SR: 659.5±185.5 Fibrinogen: AF: 2.9±0.7 vs. SR: 2.6±0.5 |
### Table 2 continued. Information about markers and these levels in each study.

| First author | Markers | Levels |
|--------------|---------|--------|
| Kamath (permanent AF) [48] | D-dimer and Fibrinogen | D-dimer: AF: 1552.5±398.3 vs. SR: 659.5±185.5  
Fibrinogen: AF: 2.7±0.6 vs. SR: 2.6±0.5 |
| Kamath [49] | D-dimer and Fibrinogen | D-dimer: AF: 1085±176.6 vs. SR: 724.25±240.75  
Fibrinogen: AF: 3.15±0.76 vs. SR: 3.0±0.63  
IPA: AF: 12.05±1.85 vs. SR: 8.25±0.96  
PAI: AF: 23.95±8.1 vs. SR: 19.05±4.1 |
| Wang [50] | Fibrinogen, tPA and PAI | D-dimer: AF: 1085±176.6 vs. SR: 724.25±240.75  
Fibrinogen: AF: 2.8±0.7 vs. SR: 2.6±0.5  
tPA: AF: 12.05±1.85 vs. SR: 8.25±0.96  
PAI: AF: 23.95±8.1 vs. SR: 19.05±4.1 |
| Li-saw-Hee (PAF) [51] | Fibrinogen and vWF | Fibrinogen: AF: 3.3±0.7 vs. SR: 2.5±0.6  
vWF: AF: 130±34 vs. SR: 101±30 |
| Li-saw-Hee (PeAF) [51] | Fibrinogen and vWF | Fibrinogen: AF: 3.3±0.7 vs. SR: 2.5±0.6  
vWF: AF: 130±34 vs. SR: 101±30 |
| Li-saw-Hee (permanent) [51] | Fibrinogen and vWF | Fibrinogen: AF: 3.3±0.7 vs. SR: 2.5±0.6  
vWF: AF: 130±34 vs. SR: 101±30 |
| Feng [52] | Fibrinogen, tPA, PAI and vWF | Fibrinogen: AF: 3.3±0.7 vs. SR: 2.5±0.6  
tPA: AF: 11.8±4 vs. SR: 10.5±3.9  
PAI: AF: 24.2±10.7 vs. SR: 25.7±17.3  
vWF: AF: 143±47 vs. SR: 137±43.4 |
| Topcuoglu [53] | PF1-2, TAT, tPA and PAI | PF1-2: AF: 2.9±1.25 vs. SR: 1.37±0.87  
TAT: AF: 10.07±6.04 vs. SR: 6.59±5.12  
tPA: AF: 23.93±10.17 vs. SR: 21.6±12.72  
PAI: AF: 37.05±12.32 vs. SR: 31.36±21.5 |
| Mondillo [54] | D-dimer, Fibrinogen, AT-III, tPA, PAI, vWF and sTM | D-dimer: AF: 458.5±175 vs. SR: 170.25±73.75  
Fibrinogen: AF: 3.8±1.09 vs. SR: 2.68±0.8  
AT-III: AF: 99.9±15.8 vs. SR: 103.7±13.1  
tPA: AF: 20.37±10.7 vs. SR: 9.81±3.21  
PAI: AF: 37.05±12.32 vs. SR: 31.36±21.5  
vWF: AF: 143±47 vs. SR: 137±43.4  
sTM: AF: 39.14±13.2 vs. SR: 26.86±14.6 |
| Giansante [55] | D-dimer and Fibrinopeptide-A | D-dimer: AF: 347±54 vs. SR: 323.75±46.75  
Fibrinopeptide-A: AF: 12.9±2 vs. SR: 8.2±0.57 |
| Li-saw-Hee [56] | Fibrinogen, vWF and sTM | Fibrinogen: AF: 2.9±0.9 vs. SR: 2.6±0.8  
vWF: AF: 137±27 vs. SR: 103±33  
sTM: AF: 52±17 vs. SR: 44±13 |
| Marin (disease control) [57] | D-dimer, AT-III, tPA and PAI | D-dimer: AF: 533±111.25 vs. SR: 15.92±6.07  
AT-III: AF: 58.4±32.75 vs. SR: 14.8±5.14  
tPA: AF: 1.94±0.34 vs. SR: 3.01±0.8  
PAI: AF: 43.77±8.62 vs. SR: 7.35±0.9 |
| Marin (healthy control) [57] | D-dimer, AT-III, tPA and PAI | D-dimer: AF: 533±111.25 vs. SR: 15.92±6.07  
AT-III: AF: 58.4±32.75 vs. SR: 14.8±5.14  
tPA: AF: 1.94±0.34 vs. SR: 3.01±0.8  
PAI: AF: 43.77±8.62 vs. SR: 7.35±0.9 |
| Li-saw-Hee [58] | Fibrinogen, vWF and sTM | Fibrinogen: AF: 2.9±0.9 vs. SR: 2.6±0.8  
vWF: AF: 137±27 vs. SR: 103±33  
sTM: AF: 52±17 vs. SR: 44±13 |
| Roldan [59] | D-dimer, Fibrinogen, AT-III, tPA, PAI and Plasmin-antiplasmin | D-dimer: AF: 549.38±311.16 vs. SR: 12.3±3.7  
Fibrinogen: AF: 3.69±0.81 vs. SR: 3.11±0.6  
AT-III: AF: 62.47±74.96 vs. SR: 10.35±2.9  
tPA: AF: 2.31±0.9 vs. SR: 2.88±1.58  
PAI: AF: 42.78±22.8 vs. SR: 8.8±5.04  
Plasmin-antiplasmin: AF: 275.3±151.69 vs. SR: 232.5±65.7 |
| Tsai [50] | PF1-2 and Fibrinopeptide-A | PF1-2: AF: 4.7±0±0.9 vs. SR: 2.99±0.24  
Fibrinopeptide-A: AF: 6±1.3 vs. SR: 1±0.3 |
Table 2 continued. Information about markers and these levels in each study.

| First author | Markers | Levels |
|--------------|---------|--------|
| Minamino [61] | D-dimer, Fibrinogen, tPA and PAI | D-dimer: AF: 160±55 vs. SR: 90±21  
Fibrinogen: AF: 2.55±0.9 vs. SR: 1.93±0.71  
tPA: AF: 12.05±5.4 vs. SR: 8.4±1.85  
PAI: AF: 62.12±33.07 vs. SR: 52±17.4 |
| Kahn [62] | Fibrinogen | Fibrinogen: AF: 3.7±0.8 vs. SR: 3.2±1.1 |
| Sohara [63] | D-dimer, Fibrinogen and TAT | D-dimer: AF: 161.7±208.6 vs. SR: 67±31.6  
Fibrinogen: AF: 2.55±0.9 vs. SR: 1.93±0.71  
tPA: AF: 12.05±5.4 vs. SR: 8.4±1.85  
PAI: AF: 62.12±33.07 vs. SR: 52±17.4 |
| Lip (PAF) [64] | D-dimer and Fibrinogen | Fibrinogen: AF: 3.7±0.8 vs. SR: 3.2±1.1 |
| Lip (chronic) [64] | D-dimer and Fibrinogen | Fibrinogen: AF: 3.7±0.8 vs. SR: 3.2±1.1 |
| Lip [65] | D-dimer | D-dimer: AF: 241.25±56.75 vs. SR: 103±22 |
| Mitsusch [66] | D-dimer, Fibrinogen, PF1-2, TAT, tPA and PAI | Fibrinogen: AF: 3.71±0.28 vs. SR: 2.6±0.12  
vWF: AF: 157.5±14.3 vs. SR: 109.25±11.16 |
| Nagao [67] | D-dimer and TAT | Fibrinogen: AF: 3.71±0.28 vs. SR: 2.6±0.12  
vWF: AF: 157.5±14.3 vs. SR: 109.25±11.16 |
| Lip [68] | D-dimer, Fibrinogen and vWF | Fibrinogen: AF: 3.71±0.28 vs. SR: 2.6±0.12  
vWF: AF: 157.5±14.3 vs. SR: 109.25±11.16 |
| Sohara [69] | D-dimer, Fibrinogen and TAT | Fibrinogen: AF: 3.71±0.28 vs. SR: 2.6±0.12  
vWF: AF: 157.5±14.3 vs. SR: 109.25±11.16 |
| Kumagai [70] | D-dimer | Fibrinogen: AF: 3.71±0.28 vs. SR: 2.6±0.12  
vWF: AF: 157.5±14.3 vs. SR: 109.25±11.16 |
| Gustafsson (with stroke) [71] | D-dimer, Fibrinogen, Fibrinopeptide-A and vWF | Fibrinogen: AF: 4.5±0.2 vs. SR: 3.1±0.3  
Fibrinopeptide-A: AF: 1.2±0.1 vs. SR: 1±0.1  
TAT: AF: 8.5±1.6 vs. SR: 2.5±0.3  
tPA: AF: 9.6±2.0 vs. SR: 7±2±0.5  
PAI: 57.9±4.3 vs. SR: 47.7±4.9 |
| Gustafsson (without stroke) [71] | D-dimer, Fibrinogen, Fibrinopeptide-A and vWF | Fibrinogen: AF: 4.5±0.2 vs. SR: 3.1±0.3  
Fibrinopeptide-A: AF: 1.2±0.1 vs. SR: 1±0.1  
TAT: AF: 8.5±1.6 vs. SR: 2.5±0.3  
tPA: AF: 9.6±2.0 vs. SR: 7±2±0.5  
PAI: 57.9±4.3 vs. SR: 47.7±4.9 |
| Occurrence of stroke in AF patients | | |
| Skov [72] | D-dimer and Fibrinogen | D-dimer: AF: 240±135 vs. without stroke: 250±63  
Fibrinogen: 3.6±0.34 vs. without stroke: 3.77±0.36 |
| Zabczyk [73] | D-dimer, Fibrinogen, PAI and sTM | D-dimer: Stroke: 270±134.4 vs. without stroke: 44±136.5  
Fibrinogen: Stroke: 3.2±0.27 vs. without stroke: 3.32±0.22  
PAI: Stroke: 28.3±7.33 vs. without stroke: 20±6.1  
sTM: Stroke: 7.37±0.87 vs. without stroke: 3.27±0.32 |
| Cecchi [36] | Fibrinogen | Fibrinogen: Stroke: 3.6±1.04 vs. without stroke: 4.36±1.22 |
| Topcuoglu [53] | PF1-2, TAT, tPA and PAI | PF1-2: Stroke: 2.6±2.84 vs. without stroke: 2.29±1.25  
TAT: Stroke: 43.8±44.45 vs. without stroke: 10±6.04  
tPA: Stroke: 25.4±27.3 vs. without stroke: 23.9±10.17  
PA: Stroke: 53.3±32.91 vs. without stroke: 37.0±22.32 |
| Soncini [75] | PF1-2 and TAT | PF1-2: Stroke: 2.6±0.53 vs. without stroke: 1.41±0.17  
TAT: Stroke: 26.0±9.22 vs. without stroke: 11.18±4.5 |
SR group. The mean level of AT-III was 79.39 in AF and 53.30 in SR (details in Tables 1 and 2). Pooled analysis revealed that the mean level of AT-III was significantly higher in the AF group compared to the SR group with WMD of 23.90 (95% CI: 7.51–40.29; p=0.004, Supplementary Figure 1) with significant heterogeneity (I²=94.2%; heterogeneity p<0.001).

**Thrombin-antithrombin (TAT)**

A total of 501 cases were included from 8 studies, of which 335 cases were allocated to the AF group and 166 to the SR group. The mean level of TAT was 10.22 ng/mL in the AF group and 4.61 ng/mL in the SR group (details in Tables 1 and 2). Pooled analysis revealed that level of TAT was significantly higher in the AF group compared to the SR group with WMD of 5.47 ng/mL (95% CI: 1.77–9.18; p=0.004, Supplementary Figure 2) using a random effect model. There was significant heterogeneity among the studies (I²=99.7%; heterogeneity p<0.001).

**Association of fibrinolytic markers with AF**

**Tissue-type plasminogen activator (t-PA)**

A total of 4326 cases were included from 14 studies. Patient populations of the included studies ranged from 36 to 3212 patients. From 4326 cases, 533 were allocated to the AF group and 3793 to the SR group. Mean level of t-PA was 10.97 ng/mL in the AF group and 8.61 ng/mL in the SR group (details in Tables 1 and 2). Pooled assessment analysis indicated that t-PA in patients with AF was significantly higher compared to those with SR with WMD of 2.13 (95% CI: 1.04–3.21; p<0.001, Figure 4) using a random effect model. Significant heterogeneity was observed among the studies (I²=98.3%; heterogeneity p<0.001).

**Plasminogen activator inhibitor (PAI)**

A total of 4267 cases were included from 15 studies, of which 540 cases were in the AF group and 3727 in the SR group. The mean level of PAI was 30.59 ng/mL in AF and 19.58 ng/mL in SR group (details in Tables 1 and 2). Pooled analysis revealed that the level of PAI was significantly higher in the AF group compared to the SR group with WMD of 11.44 ng/mL (95% CI: 6.83–16.05; p<0.001, Figure 5) with significant heterogeneity (I²=99.4%; heterogeneity p<0.001).

**Fibrinopeptide-A**

A total of 336 cases were included from 6 studies, whereas 148 cases were allocated to the AF group and 188 to the SR group. The mean level of fibrinopeptide-A was 7.33 ng/ml in AF and 3.18 ng/ml in SR (details in Tables 1 and 2). Pooled analysis showed that the level of fibrinopeptide-A was statistically higher in the AF group compared to SR with WMD of 4.13 ng/mL (95% CI: 0.67–7.60; p=0.01, Supplementary Figure 3) with significant heterogeneity (I²=99.6%; heterogeneity p<0.001).

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

| First author | Markers | Levels |
|--------------|---------|--------|
| Kahn [62]    | Fibrinogen and AT-III | Fibrinogen: Stroke: 3.8±0.9 vs. without stroke: 3.7±0.8 AT-III: Stroke: 1±0.14 vs. without stroke: 1±0.13 |
| Gustafsson [71] | D-dimer, Fibrinogen, AT-III, Fibrinopeptide-A and vWF | D-dimer: Stroke: 291.6±156.3 vs. without stroke: 275.5±134 Fibrinogen: Stroke: 4.4±0.2 vs. without stroke: 4.5±0.35 AT-III: Stroke: 0.2±0.04 vs. without stroke: 0.9±0.01 Fibrinopeptide-A: Stroke: 5.75±1.25 vs. without stroke: 4.67±0.57 vWF: Stroke: 17.1±2.2 vs. without stroke: 15.6±2.6 |
| Zabczyk [73] | D-dimer, Fibrinogen and sTM | D-dimer: TE: 31±134 vs. without TE: 234±105.5 Fibrinogen: TE: 3.4±0.15 vs. without TE: 3.3±0.25 sTM: TE: 6.05±1.25 vs. without TE: 3.2±0.35 |
| Roldan [76] | PF1-2 | PF1-2: TE: 1.37±0.4 vs. without TE: 1.31±0.33 |
| Feinberg [77] | PF1-2 | PF1-2: TE: 0.7±0.5 vs. without TE: 0.6±0.4 |
| Pontgratz [78] | Fibrinogen and AT-III | Fibrinogen: TE: 4.1±1.3 vs. without TE: 3.7±1.5 AT-III: TE: 99±13 vs. without TE: 105±22 |
| Black [79] | Fibrinogen | Fibrinogen: TE: 6.1±3.2 vs. without TE: 4.5±1.64 |
| Kumagi [70] | D-dimer | D-dimer: TE: 196±73 vs. without TE: 140±19 |
Association of endothelial markers with AF

**von Willebrand factor (vWF)**

A total of 18,057 cases were enrolled to the analysis from 32 studies, of which 2,607 cases were allocated to the AF group and 15,450 to the SR group. The mean level of vWF was 132.38 IU/dL in the AF group and 104.27 IU/dL in the SR group (details in Tables 1 and 2). Pooled analysis revealed a higher level of vWF in patients with AF than in patients with SR with WMD of 27.01 (95% CI: 19.79–34.23; p<0.001, Figure 6) using a random effect model. There was significant heterogeneity among the studies (I²=98.7%; heterogeneity p<0.001).

**Soluble thrombomodulin (sTM)**

A total of 591 cases were included from 7 studies. From all cases, 351 were allocated to the AF group and 240 to the SR group. The mean level of sTM was 25.96 ng/mL in the AF group and 22.04 ng/mL in the SR group (details in Tables 1 and 2). Pooled analysis indicated that sTM was significantly higher in the AF group compared to the SR group with WMD of 3.92 (95% CI: 0.53–7.32; p<0.001, Supplementary Figure 4) using a random effect model. There was significant heterogeneity among the studies (I²=91.2%; heterogeneity p<0.001).
META-ANALYSIS

Six studies reported the association of markers with thromboembolic events (Table 3). D-dimer, fibrinogen, and PF 1-2 levels were investigated in at least 2 studies and were included in the meta-analysis (Table 2). AT-III and sTM levels were investigated in at least 2 studies and were included in the meta-analysis (Table 2). AT-III and sTM levels were investigated in at least 2 studies and were included in the meta-analysis (Table 2).

**Related clinical adverse events of AF**

**Association of coagulation, fibrinolytic, and endothelial markers with thromboembolic events**

Six studies reported the association of markers with thromboembolic events (Table 3). D-dimer, fibrinogen, and PF 1-2 levels were investigated in at least 2 studies and were included in the meta-analysis (Table 2). AT-III and sTM levels were reported in only 1 study and thus were not included in the analysis. Pooled analysis revealed that the level of D-dimer (number of studies=2, WMD of 60.67, 95% CI: 28.61 to 92.73; p<0.001

![Figure 2](image-url)
and $I^2=0\%$; heterogeneity $p=0.59$, Supplementary Figure 5) was significantly higher in patients with thromboembolic events than in patients without thromboembolic events. Pooled analysis showed that the level of fibrinogen (number of studies=3, WMD of 0.61, 95% CI: −0.30 to 1.53; $p=0.19$ and $I^2=92.5\%$; heterogeneity $p<0.001$, Supplementary Figure 6), and the level of PF1-2 (number of studies=2, WMD of 0.08, 95% CI: −0.06 to 0.22; $p=0.18$ and $I^2=0\%$; heterogeneity $p=0.83$, Supplementary Figure 7).
Figure 7) were not significantly different whether they suffered from thromboembolic events or not.

Association of coagulation, fibrinolytic, and endothelial markers with stroke

Eight studies investigated the association of hemostatic markers with stroke (Table 3). D-dimer, fibrinogen, PF1-2, TAT, PAI, and AT-III were examined in at least 2 studies and were included in the meta-analysis (Table 2). Fibrinopeptide-A, tPA, vWF, and sTM levels were reported in only 1 study and were not included in the analysis. Pooled assessment analysis indicated that the level of PF 1-2 (number of studies=2, WMD of 1.06, 95% CI: 0.39 to 1.74; p=0.002 and I²=36.4%); heterogeneity p=0.21, Supplementary Figure 8), level of TAT (number of studies=2, WMD of 22.28, 95% CI: 4.16 to 40.39; p=0.016 and I²=74.5%); heterogeneity p<0.04, Supplementary Figure 9), and level of PAI (number of studies=2, WMD of 8.60, 95% CI: 4.12 to 13.09; p<0.001 and I²=0%; P-heterogeneity=0.36, Supplementary Figure 10) were significantly higher in patients with stroke as compared to patients without stroke. Pooled analysis showed that the levels of D-dimer (number of studies=3, WMD of 8.08, 95% CI: –3.28 to 48.96; p=0.69 and I²=4.7%); heterogeneity p=0.35, Supplementary Figure 11), fibrinogen (number of studies=6, WMD of 0.02, 95% CI: –0.22 to 0.25; p=0.88 and I²=79.9%); heterogeneity p<0.001, Supplementary Figure 12), and AT-III (number of studies=2, WMD of 0.01, 95% CI: –0.01 to 0.03; p=0.51 and I²=0%); heterogeneity p=0.39, Supplementary Figure 13) did not significantly differ between patients with stroke and patients without stroke.

Publication bias, subgroup analysis, and meta-regression

Begg’s tests suggested that there might be publication bias for studies examining levels of D-dimer, fibrinogen, AT-III, and vWF (Supplementary Figures 14–23). Extra details of each study, subgroup analysis, and meta-regression are presented in Supplementary Tables 2 and 3, respectively.

Discussion

For years, finding the pathophysiological mechanisms involved in AF has been an important research area in cardiology and cardiac surgery [80–83]. A proposed mechanism leading to an increased incidence of AF is coagulation and prothrombotic state [80–83]. Investigators believe that procoagulant and prothrombotic states might be more expressed in patients with chronic AF as compared to those with SR [80–83]. In the present study, we investigated a set of coagulation biomarkers to closely examine this possible pathophysiology of AF.

D-dimer is a byproduct of the degeneration of fibrin and reflects thrombin and fibrin turnover [84]. D-dimer is one of the
| First author (persistent) | Year of pub | WMD (95% Cl) | % weight |
|--------------------------|-------------|--------------|----------|
| Drabnik                  | 2015        | 49.25 (46.54, 51.96) | 3.56     |
| Drabik (PAF)             | 2015        | 51.00 (47.40, 54.60) | 3.54     |
| Wei-Hong Ma              | 2014        | 25.00 (11.14, 38.86) | 3.16     |
| Scridon (PAF)            | 2013        | 20.70 (13.57, 27.83) | 3.46     |
| Scridon (persistent)     | 2013        | 38.40 (30.93, 45.87) | 3.44     |
| Alonso (White)           | 2012        | 13.20 (10.17, 16.23) | 3.55     |
| Alonso (African-American)| 2012        | 16.50 (7.64, 25.36) | 3.39     |
| Fu                       | 2011        | 10.90 (7.06, 21.04) | 3.34     |
| Hou (disease control)    | 2010        | 6.00 (–14.12, 26.12) | 2.80     |
| Hou (disease control)    | 2010        | 19.00 (–1.39, 39.39) | 2.78     |
| Blann                    | 2007        | 71.00 (38.54, 103.46) | 2.08     |
| Topaloglu (healthy control) | 2007    | 19.20 (–17.92, 56.32) | 1.84     |
| Topaloglu (healthy control) | 2007    | 59.80 (27.51, 92.09) | 2.09     |
| Heeringa                 | 2006        | 6.00 (–0.59, 12.59) | 3.47     |
| Marin (acute AF)         | 2004        | 50.30 (30.44, 70.16) | 2.81     |
| Marin (chronic AF)       | 2004        | 46.40 (29.77, 63.03) | 3.01     |
| Conway                   | 2004        | 7.00 (–1.11, 15.11) | 3.42     |
| Hatzinikolaou-Kotsakou (PAF) | 2004    | 15.00 (4.53, 25.47) | 3.33     |
| Hatzinikolaou-Kotsakou (persistent) | 2004 | 25.00 (11.18, 38.82) | 3.16     |
| Hatzinikolaou-Kotsakou (permanent) | 2004 | 54.00 (41.65, 66.35) | 3.24     |
| Conway                   | 2004        | 4.00 (–6.62, 14.52) | 3.32     |
| Conway                   | 2003        | 6.00 (–0.04, 12.04) | 3.49     |
| Li-saw-Hee (PAF)         | 2001        | 29.00 (9.87, 48.13) | 2.86     |
| Li-saw-Hee (PeAF)        | 2001        | 5.00 (–10.58, 20.58) | 3.07     |
| Li-saw-Hee (permanent)   | 2001        | 42.00 (18.72, 65.28) | 2.61     |
| Feng                     | 2001        | 5.00 (–9.76, 19.76) | 3.11     |
| Mondillo                 | 2000        | 70.60 (53.76, 87.44) | 2.99     |
| Li-saw-Hee               | 2000        | 34.00 (22.88, 45.12) | 3.30     |
| Li-saw-Hee               | 1999        | 46.00 (30.94, 61.06) | 3.09     |
| Lip                      | 1995        | 48.25 (44.78, 51.72) | 3.55     |
| Gustafsson (with stroke) | 1990        | 3.00 (1.94, 4.06) | 3.57     |
| Gustafsson (without stroke) | 1990      | 3.12 (1.91, 4.33) | 3.57     |

Overall (I-squared=98.7%, p=0.000): 27.01 (19.79, 34.23) 100.00

NOTE: Weights are from random effects analysis.

**Figure 6.** Forest plot of weighted mean difference (WMD) for association between level of vWF and occurrence of AF.
surrogate markers for a hypercoagulable state which is one component of Virchow's triad [84]. The results of the present study revealed that the level of D-dimer was significantly higher in AF patients compared to those with SR. Generally, increased level of D-dimer is directly associated with an increased incidence of AF; however, it should be noted that there is a significant heterogeneity in our results. The subgroup analysis based on the year of publication, geographic area, design of the studies, age, sex, risk factors of diabetes and hypertension, number of cases, and chronic or non-chronic AF indicated that D-dimer was always considerably higher in AF groups compared with SR groups, despite heterogeneity among studies. A subgroup analysis reported that both paroxysmal and permanent AF had higher levels of D-dimer and the type of AF was not considered a factor of heterogeneity.

Fibrinogen is an acute-phase protein synthesized in the liver, and higher levels are associated with increased risk of cardiovascular diseases [85]. Our results also demonstrate that the level of fibrinogen was considerably higher in the AF group as compared to the SR group. A direct relationship between the level of fibrinogen and the incidence of AF was confirmed; however, this relationship was also associated with a justifiable heterogeneity. The analyses performed on coagulation markers PF1-2, TAT, and AT-III also indicated that the level of these markers was significantly higher in AF groups as compared to SR groups. The results of our study also showed that the type of AF could be a heterogeneity factor in the meta-analysis of D-dimer level. According to the analysis of the available data in our study, the level of D-dimer was strongly and directly related to the occurrence of thromboembolism in AF patients, while fibrinogen and PF1-2 were not. Other coagulation markers, in which no association with stroke and thromboembolism was reported, did not have sufficient data and thus no analysis was carried out.

Another proposed mechanism for the incidence of AF is fibrinolytic activity. PAI is a direct inhibitor of the plasminogen activation system, whereas its interaction with the adhesive glycoprotein plays a role in tissue remodeling [86].

### Table 3. Characteristics of included studies for meta-analysis of association of biomarkers and clinical adverse events related to AF.

| First Author | Country and year | Study design | Number | Mean age | AC in patients with adverse events | AC in patients without adverse events | Adverse events | NOS |
|--------------|------------------|--------------|--------|----------|-----------------------------------|--------------------------------------|----------------|-----|
| Skov [72]    | Denmark-2014     | Case-control | 179    | 71.6     | 100%                              | 100%                                 | Stroke         | 8   |
| Zabczyk [73] | Poland-2011      | Case-control | 62     | 78       | 81.8%                             | 72.5%                                | Stroke and thromboembolic event | 8   |
| Cecchi [36]  | Italy-2006       | Case-control | 156    | 74.4     | 100%                              | 100%                                 | Stroke         | 7   |
| Loffredo [74] | Italy-2005      | Case-control | 163    | 72.3     | 70%                               | 63.4%                                | Stroke         | 8   |
| Topcuoglu [53] | Turkey-2001 | Case-control | 39     | 63.6     | –                                 | –                                    | Stroke         | 7   |
| Somcini [75] | Italy-1998       | Case-control | 32     | 71.5     | –                                 | –                                    | Stroke         | 7   |
| Kahn [62]    | Canada-1997      | Case-control | 75     | 72.7     | 100%                              | 100%                                 | Stroke         | 7   |
| Gustafsson [71] | Sweden-1990  | Case-control | 40     | 70       | –                                 | –                                    | Stroke         | 8   |
| Roldan [76]  | Spain-2003       | Case-control | 191    | 72.3     | 100%                              | 100%                                 | Thromboembolic event | 8   |
| Feinberg [77] | UK-1999         | Cohort       | 726    | –        | –                                 | –                                    | Thromboembolic event | 8   |
| Pongratz [78] | Germany-1997    | Case-control | 60     | 65.7     | –                                 | –                                    | Thromboembolic event | 6   |
| Black [79]   | Australia-1993   | Case-control | 135    | –        | 50%                               | 28%                                  | Thromboembolic event | 8   |
| Kumagi [70]  | Japan-1990       | Case-control | 49     | –        | –                                 | –                                    | Thromboembolic event | 7   |
levels of PAI have been associated with an increased risk for coronary artery stenosis and acute coronary syndrome [86]. Our findings suggest a significant direct association between increased level of PAI and the incidence of AF, as patients with AF showed higher levels of PAI compared to those with SR.

Sorted analyses in terms of the year of publication, study design, number of cases, age, sex, diabetes, and hypertension indicated that the level of PAI in the AF group had constantly been higher than in the SR group. None of the above-mentioned criteria appeared to be a factor of heterogeneity. The results of this study predict that with the current heterogeneity in analysis on the level of PAI, history of MI and type of AF (chronic or non-chronic) could be considered factors of heterogeneity. Our results showed that the level of tPA in the AF group was considerably higher than in the SR group. There was a direct correlation between the incidence of AF and the level of tPA from laboratory and clinical studies, although statistically there was a notable heterogeneity. A subgroup analysis revealed that history of MI, type of AF, and geographical area may be considered factors of heterogeneity. Fibrinopeptide-A is also a marker of fibrinolytic activity, and we found that it was clearly higher in the AF group as compared to the SR group. However, we could not find factors of heterogeneity in the subgroup analysis. Owing to insufficient studies on alpha-2 antiplasmin, plasmin-antiplasmin, and urokinase-type plasminogen activator inhibitor, analyzing these markers was not feasible. Although based on the results, this fact is understandable and verifiable from laboratory and clinical studies, not finding a definite factor of heterogeneity of the results might be explained by the fact that other factors had affected the results of the published studies in recent years that have not been taken into account or not been reported on by their authors. Regarding the association of the level of PAI with stroke in AF patients, our results suggest a significant relationship between increased level of PAI and increased risk of stroke. Another mechanism which needs to be examined in AF patients is endothelial activity.

Increased levels of vWF have been found in inflammatory and atherosclerotic vascular diseases that are usually associated with damaged endothelium [87]. The pooled results of our study indicate that the level of vWF was significantly higher in AF patients as compared with the SR group. The results of subgroup analysis suggested that in all types of AF, including paroxysmal, persistent, and permanent, and also in terms of chronic or non-chronic AF, the level of vWF was statistically and clinically higher in the AF group. According to the subgroup analysis, geographic area, design of the studies, and number of cases could be defined as factors of heterogeneity. The findings of this study affirmed that STM, as another marker of endothelial activity, had a significant influence on the incidence of AF, as the level of STM considerably higher in AF patients compared with SR patients. Generally, increased endothelial activity appears to be associated with higher incidence of AF, which is confirmed statistically and through laboratory studies. We conducted a subgroup analysis based on cardiovascular risk factors, whereas one of the most significant cardiac risk factors affecting our results was history of MI. Also, DM, HTN, and smoking were not considered factors of heterogeneity.

Lip et al. argued that using anticoagulants could reduce the levels of D-dimer and PF1-2 in AF patients; therefore, differences in the use of anticoagulants in various studies might be considered confounding factors [68]. In this study, we defined codes for using anticoagulants. Performing a subgroup analysis, we found that on the levels of AT3, tPA, PAI, and STM, the available data about the status of using anticoagulants were confounding factors which possibly could play a part in the incidence of heterogeneity. Heterogeneity is higher in meta-analyses of non-experimental studies, which can be caused by several factors, such as: 1) many confounding factors, 2) less controlled bias, and 3) different definition of outcomes.

Meta-regression was performed on the levels of D-dimer, fibrinogen, PAI, and vWF that had greater number of studies than other markers and could be analyzed based on regression. According to the results of meta-regression on the level of D-dimer, difference in the design of studies, type of AF, and difference in geographical area of the study appeared to be factors of heterogeneity. For the level of fibrinogen, the year of publication (before or after 2000) and geographical area of the study were factors. For the level of vWF, difference in the design of studies and geographical area of the study were factors. For the level of PAI, difference in using anticoagulants was a factor.

Conclusions

Generally, considering the results of this study, we can strongly claim that prothrombotic state has a critical role as a precipitating mechanism in the incidence of AF and clinical complications of thromboembolism and stroke. The levels of coagulation, fibrinolytic, and endothelial markers have been reported to be significantly higher in AF patients than in SR patients. We believe that several other interventions may affect the association of these biomarkers with the incidence of AF; however, they have not been taken into account or mentioned in the series of past and recent studies. High heterogeneity is not the end of trying to find the relation between effective markers in predicting AF, but definitely points out that in future the authors are required to converge the quality of performing studies by observing the factors of heterogeneity and other confounding factors as described in the present study.
Finally, emphasizing the association of coagulation, fibrinolytic, and endothelial markers with the incidence of AF and its clinical outcomes, and defining the factors of heterogeneity using subgroup analysis and meta-regression, we believe that in meta-analysis of the relationship of the levels of biomarkers with the incidence of AF, there are real-world associations with heterogeneity. Efforts should be made to find and introduce these associations as well as factors of heterogeneity that affect the results.

**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 AT-III and occurrence of AF.

| First author                  | Year of pub | WMD (95% CI)       | % weight |
|------------------------------|-------------|--------------------|----------|
| Topaloglu (disease control)  | 2007        | 0.70 (–8.68, 10.08) | 17.79    |
| Topaloglu (healthy control)  | 2007        | 15.80 (9.44, 22.16) | 18.36    |
| Mondillo                     | 2000        | –3.80 (–8.98, 1.38) | 18.54    |
| Marin (disease control)      | 1999        | 43.55 (28.30, 58.80) | 16.23    |
| Marin (healthy control)      | 1999        | 48.15 (33.01, 63.29) | 16.274   |
| Roldan                       | 1998        | 52.12 (26.13, 78.11) | 12.81    |
| Overall (I-squared=94.2%, p=0.000) | 23.90 (7.51, 40.29) | 100.00 |

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

| First author                  | Year of pub | WMD (95% CI)       | % weight |
|------------------------------|-------------|--------------------|----------|
| Yusuf (disease control)      | 2015        | 13.58 (12.69, 14.47) | 13.34    |
| Yusuf (healthy control)      | 2015        | 6.30 (5.54, 7.06)   | 13.37    |
| Acevedo                      | 2012        | 0.05 (0.01, 0.09)   | 13.44    |
| Topcuoglu                    | 2000        | 3.48 (–0.28, 7.24)  | 11.81    |
| Sohara                       | 1997        | 3.57 (1.07, 6.07)   | 12.67    |
| Mitsch                       | 1996        | 6.00 (5.61, 6.39)   | 13.42    |
| Nagao                        | 1995        | 10.34 (3.35, 17.33) | 9.10     |
| Sohara                       | 1994        | 1.60 (–0.54, 3.74)  | 12.87    |
| Overall (I-squared=99.7%, p=0.000) | 5.47 (1.77, 9.18) | 100.00 |

**NOTE:** Weights are from random effects analysis.
Supplementary Figure 3. Forest plot of weighted mean difference (WMD) for association between level of fibrinopeptide and occurrence of AF.

Supplementary Figure 4. Forest plot of weighted mean difference (WMD) for association between level of sTM and occurrence of AF.
Supplementary Figure 5. Forest plot of weighted mean difference (WMD) for association between level of D-dimer and occurrence of thromboembolism.

Supplementary Figure 6. Forest plot of weighted mean difference (WMD) for association between level of fibrinogen and occurrence of thromboembolism.

Supplementary Figure 7. Forest plot of weighted mean difference (WMD) for association between level of PF1-2 and occurrence of thromboembolism.
Supplementary Figure 8. Forest plot of weighted mean difference (WMD) for association between level of PF1-2 and occurrence of stroke.

Supplementary Figure 9. Forest plot of weighted mean difference (WMD) for association between level of TAT and occurrence of stroke.

Supplementary Figure 10. Forest plot of weighted mean difference (WMD) for association between level of PAI and occurrence of stroke.
Supplementary Figure 11. Forest plot of weighted mean difference (WMD) for association between level of D-dimer and occurrence of stroke.

| First author | WMD (95% CI) | % weight |
|--------------|--------------|----------|
| Gustafsson   | 16.00 (−74.23, 106.23) | 19.79    |
| Zabczyk      | 72.00 (−29.45, 173.45) | 15.77    |
| Skov         | −10.00 (−57.87, 37.87) | 64.43    |
| Overall (I-squared=4.7%, p=0.350) | 8.08 (−32.80, 48.96) | 100.00   |

NOTE: Weights are from random effects analysis

Supplementary Figure 12. Forest plot of weighted mean difference (WMD) for association between level of fibrinogen and occurrence of stroke.

| First author | WMD (95% CI) | % weight |
|--------------|--------------|----------|
| Gustafsson   | −0.10 (−0.28, 0.08) | 22.68    |
| Kahn         | 0.10 (−0.32, 0.52) | 14.17    |
| Loffredo     | 0.49 (0.13, 0.85) | 16.16    |
| Cecchi       | −68.00 (−103.96, −32.04) | 0.00    |
| Zabczyk      | −0.08 (−0.25, 0.09) | 22.89    |
| Skov         | −0.14 (−0.27, −0.00) | 24.10    |
| Overall (I-squared=79.9%, p=0.000) | 0.02 (−0.22, 0.250) | 100.00   |

NOTE: Weights are from random effects analysis
Supplementary Figure 13. Forest plot of weighted mean difference (WMD) for association between level of AT-III and occurrence of stroke.

Supplementary Figure 14. Funnel plot for publication bias of studies investigating D-dimer.
META-ANALYSIS

Supplementary Figure 15. Funnel plot for publication bias of studies investigating fibrinogen.

Supplementary Figure 16. Funnel plot for publication bias of studies investigating PF1-2.

Supplementary Figure 17. Funnel plot for publication bias of studies investigating of TAT.
**Supplementary Figure 18.** Funnel plot for publication bias of studies investigating AT-III.

**Supplementary Figure 19.** Funnel plot for publication bias of studies investigating fibrinopeptide-A.

**Supplementary Figure 20.** Funnel plot for publication bias of studies investigating t-PA.
META-ANALYSIS

Supplementary Figure 21. Funnel plot for publication bias of studies investigating PAI.

Supplementary Figure 22. Funnel plot for publication bias of studies investigating vWF.

Supplementary Figure 23. Funnel plot for publication bias of studies investigating sTM.
**Supplementary Table 1.** Included, and excluded studies.

| Clinical outcomes and biomarkers | Studies were identified and screened [n] | Studies were excluded according to title, abstract or full text [n] | Studies were included [n] |
|----------------------------------|----------------------------------------|---------------------------------------------------------------|--------------------------|
| Fibrinogen                       | 315                                    | 275                                                           | 40 approved articles with totally 58 enrolled data for meta-analysis |
| D-dimer                          | 238                                    | 121                                                           | 30 approved articles with totally 40 enrolled data for meta-analysis |
| PF1-2                            | 86                                     | 79                                                            | 7 approved articles with totally 9 enrolled data for meta-analysis |
| AT-III                           | 98                                     | 94                                                            | 4 approved articles with totally 6 enrolled data for meta-analysis |
| TAT                              | 127                                    | 120                                                           | 7 approved articles with totally 8 enrolled data for meta-analysis |
| t-PA                             | 437                                    | 426                                                           | 11 approved articles with totally 14 enrolled data for meta-analysis |
| PAI                              | 91                                     | 80                                                            | 11 approved articles with totally 15 enrolled data for meta-analysis |
| Alpha-2 antiplasmin              | 18                                     | 18                                                            | -                         |
| Fibrinopeptide-A                 | 21                                     | 18                                                            | 3 approved articles with totally 4 enrolled data for meta-analysis |
| u-PA                             | 29                                     | 29                                                            | -                         |
| Plasmin-antiplasmin              | 22                                     | 21                                                            | 1 approved articles with |
| vWF                              | 185                                    |                                                               | 21 approved articles with totally 32 enrolled data for meta-analysis |
| sTM                              | 37                                     | 31                                                            | 6 approved articles with totally 7 enrolled data for meta-analysis |

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

| First Author                  | Geographic area | Total N | Total age | Total male | Total DM | Total HTN | Total MI | Total diuretic | Total ACEI | Total statin | Total BB | AC-code | Chronic or not | CS |
|-------------------------------|-----------------|---------|-----------|------------|----------|-----------|----------|----------------|------------|--------------|----------|----------|----------------|----|
| Negreva [9]                   | European        | 103     | 59.67     | 50.45      | 4.8      | 68.96     | ND       | ND             | 28.165     | 6.805        | 34.97    | 1        | Acute          | 14.5 |
| Amdur [10]                    | North America   | 3762    | 58.9      | 54.55      | 49.8     | 86.7      | ND       | 64.65          | 69.85      | ND           | 56.1     | 4        | No detection   | ND  |
| Yusuf (disease control) [11]  | Asian           | 65      | 31.5      | 42.85      | ND       | ND        | ND       | ND             | ND         | ND           | ND       | 1        | No detection   | ND  |
| Yusuf (healthy control) [11]  | Asian           | 65      | 30.055    | 38.55      | ND       | ND        | ND       | ND             | ND         | ND           | ND       | 1        | No detection   | ND  |
| Drabik (persistent) [12]      | European        | 97      | 60.1      | 64.95      | 20       | 48.85     | 17.35    | ND             | 52.25      | 53.15        | 60.6     | 4        | Acute          | 22.5 |
| Drabik (PAF) [12]             | European        | 91      | 60        | 55.15      | 16.4     | 46.05     | 26.65    | ND             | 54.05      | 47.45        | 57.25    | 4        | Acute          | 20  |
| Borgi [13]                    | Africa          | 69      | ND        | ND         | ND       | ND        | ND       | ND             | ND         | ND           | ND       | 5        | No detection   | ND  |
| O'Neal (with comorbidities) [14]| North America   | 647     | 69.5      | 54         | 32.5     | 70        | ND       | ND             | ND         | 29.5         | ND       | 4        | No detection   | 15  |
| O'Neal (with comorbidities) [14]| North America   | 883     | 64.5      | 32.5       | 29.5     | 54.5      | ND       | ND             | ND         | 30           | ND       | 4        | No detection   | 14  |
| 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 |
|--------------|-----------------|---------|-----------|------------|----------|-----------|----------|---------------|------------|-------------|---------|----------|----------------|----|
| Erdogan [15] | European        | 67      | 69.55     | 49.275     | 10       | 65        | ND       | 18            | 53.5       | ND          | 43.3    | 3        | Chronic         | 6  |
| Chen (without comorbidities) [16] | Asian          | 162     | 53.695    | 61.03      | 15       | 31.5      | ND       | ND            | ND         | ND          | ND      | 4        | Acute           | ND |
| Chen (with comorbidities) [16] | Asian          | 207     | 55.845    | 64.2       | 13.5     | 35.5      | ND       | ND            | ND         | ND          | ND      | 4        | Acute           | ND |
| Schnabel [17] | European       | 4998    | 60.05     | 54.5       | 10.15    | 61.95     | 8.3      | ND            | ND         | ND          | ND      | 5        | No detection    | 15.3 |
| Wei-Hong Ma [18] | Asian      | 105     | 59.5      | 72.25      | 0        | 100       | ND       | ND            | ND         | ND          | ND      | 2        | No detection    | ND |
| Xu (without comorbidities) [19] | Asian          | 115     | 66.85     | 50.45      | 37.4     | 53.1      | ND       | ND            | 42.6       | 29.55       | 43.55   | 4        | Chronic         | 38.5 |
| Xu (with comorbidities) [19] | Asian          | 115     | 67.975    | 51.3       | 36.5     | 57.5      | ND       | ND            | 40.8       | 26.05       | 40.95   | 4        | Chronic         | 31.2 |
| Distelmaier [20] | North America | 198     | 73.5      | 61         | 24       | 60.5      | 25       | ND            | ND         | ND          | ND      | 5        | Acute           | ND |
| Scridon (PAF) [21] | European    | 69      | 55.5      | 78.5       | 7        | 39.5      | ND       | ND            | 18.5       | 13.5        | ND      | 3        | Acute           | 13 |
| Scridon (persistent) [21] | European     | 53      | 55        | 78.5       | 7        | 35.5      | ND       | ND            | 24         | 15.5        | ND      | 3        | Acute           | 13 |
| Berge [22] | European       | 189     | 75        | 71         | 8        | 48        | ND       | 19            | 21         | 34.5        | 28      | 4        | No detection    | ND |
| Acevedo [23] | South America | 150     | ND        | ND         | ND       | ND        | ND       | ND            | ND         | ND          | ND      | 1        | No detection    | ND |
| Zorlu [24] | European       | 150     | 69.5      | 62         | 16       | 33        | ND       | ND            | 75.5       | ND          | 76      | 1        | No detection    | ND |
| Alonso (White) [25] | North America | 11107   | 55.7      | 52.25      | 12.05    | 34.85     | 6.6      | ND            | ND         | ND          | ND      | 1        | No detection    | 26.7 |
| Alonso (African-American) [25] | North America | 3751    | 54.8      | 41.2       | 26.05    | 63.65     | ND       | ND            | ND         | ND          | ND      | 1        | No detection    | 32 |
| Adamsson Eryd [26] | European      | 6031    | 47.25     | 100        | 4.8      | 6         | ND       | ND            | ND         | ND          | ND      | 5        | No detection    | 48 |
| Fu [27] | Asian          | 169     | 54.45     | 63.5       | ND       | ND        | ND       | ND            | 12.9       | 6.1         | ND      | 4        | No detection    | 42.5 |
| Hou (disease control) [28] | Asian       | 52      | 64.85     | 57.6       | 0        | ND        | ND       | ND            | 40.35      | ND          | 11.45   | 4        | Acute           | 26.9 |
| Hou (healthy control) [28] | Asian        | 52      | 65.3      | 57.6       | 0        | ND        | ND       | ND            | 21.15      | ND          | 7.65    | 4        | Acute           | 26.9 |
| Schnabel [29] | North America | 3120    | 62.05     | 52.5       | ND       | 38        | ND       | ND            | ND         | ND          | ND      | 5        | No detection    | ND |
| Letsas (permanent) [30] | European     | 89      | 66.6      | 59.5       | 11       | 63        | ND       | ND            | 52.5       | 13.5        | 35.5   | 5        | Chronic         | ND |
| Gartner [31] | Australia      | 250     | 59.45     | 65.5       | 9        | 48.5      | ND       | ND            | ND         | ND          | ND      | 4        | No detection    | ND |
| Targonski (PAF and PeAF) [32] | European     | 56      | 63.5      | 67.7       | 44.75    | 69.6      | ND       | 67.7          | 96.66      | 87.3        | 85.4   | 4        | 12.4            |     |
| Targonski (Permanent) [32] | European     | 73      | 69.3      | 66.4       | 33.3     | 72.2      | ND       | 78.05         | 90.85      | 70.6        | 89.2   | 4        | 11.3            |     |
| 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  |
|--------------|-----------------|---------|-----------|------------|----------|-----------|----------|----------------|------------|-------------|---------|----------|----------------|-----|
| Marcus [33]  | North America   | 971     | 70        | 87.5       | 22.5     | 65.5      | 52       | ND             | 57         | 59.5        | ND       | 5        | No detection  | 15  |
| Blann [34]   | European        | 92      | 3        | 66.5       | 16.5     | 67.9      | 27       | ND             | 168        | 17          | ND       | 18        | No detection  | 12.6|
| Topaloglu (disease control) [35] | European | 46      | 34.5     | ND         | 0        | 0         | ND       | ND             | ND         | ND         | ND       | ND       | No detection  | ND  |
| Topaloglu (healthy control) [35] | European | 38      | 36       | ND         | 0        | 0         | ND       | ND             | ND         | ND         | ND       | ND       | No detection  | ND  |
| Cecchi (with cerebral ischemic) [36] | European | 192     | 73.5     | 60.2       | 7.25     | 45.95     | ND       | 18.05         | 27.3       | 6.85        | 6.8      | 3        | No detection  | 30.1|
| Cecchi (without cerebral ischemic) [36] | European | 224     | 73       | 59.35      | 6.4      | 47.5      | ND       | 20.5          | 27.05      | 7.3         | 8.05     | 3        | No detection  | 25.9|
| Turgut (disease control) [37] | European | 55      | 66.11    | 44.7       | 17.4     | 67.6      | ND       | ND             | ND         | ND         | ND       | ND       | No detection  | ND  |
| Turgut (healthy control) [37] | European | 46      | 66.56    | 43.95      | 3.85     | 36.55     | ND       | ND             | ND         | ND         | ND       | ND       | No detection  | ND  |
| Heeringa [38] | European       | 486     | 77.5     | 51         | 17.5     | 25        | 22.5     | 31.65         | ND         | 16.55       | 5        | No detection  | 20.9 |
| Roldan [39]  | European       | 265     | 62.75    | 62.75      | 7.5      | 26.5      | ND       | ND             | ND         | ND         | ND       | ND       | No detection  | ND  |
| Marin (acute AF) [40] | European | 48      | 63.5     | 50         | 0        | 8.3       | 8.3      | ND             | 10.4       | ND         | 8.3      | 4        | Acute         | ND  |
| Marin (chronic AF) [40] | European | 48      | 63.5     | 47.9       | 14.55    | 12.5      | 6.25     | ND             | 6.25       | 4.15        | 4        | Chronic     | ND             |     |
| Inoue (with comorbidities) [41] | Asian | 251     | ND       | ND         | ND       | ND       | ND       | ND             | ND         | ND         | ND       | ND       | No detection  | ND  |
| Inoue (Lone AF) [41] | Asian | 106     | ND       | ND         | ND       | ND       | ND       | ND             | ND         | ND         | ND       | ND       | No detection  | ND  |
| Cecchi [42]  | European       | 197     | 66       | 62         | ND       | ND       | ND       | ND             | ND         | ND         | ND       | ND       | No detection  | ND  |
| Hatzinikolaou-Kotsakou (PAF) [43] | European | 35      | 59       | 77.25      | 8.3      | 13.85     | 13.85    | ND             | ND         | ND         | ND       | 5        | Acute         | 20.5|
| Hatzinikolaou-Kotsakou (persistent) [43] | European | 34      | 60       | 73.5       | 5.85     | 20.585    | 17.6     | ND             | ND         | ND         | ND       | 5        | Acute         | 20.8|
| Hatzinikolaou-Kotsakou (permanent) [43] | European | 37      | 61.5     | 76.15      | 5        | 22.5      | 15       | ND             | ND         | ND         | ND       | 5        | Chronic       | 24.2|
| Conway [44]  | European       | 74      | 67.5     | 70.2       | 9.45     | 27        | 1.35     | ND             | ND         | ND         | ND       | 5        | Acute         | 11.2|
| Kamath (PAF and PeAF) [45] | European | 62      | 63.5     | 51.6       | ND       | ND       | ND       | ND             | ND         | ND         | ND       | 1        | Acute         | ND  |
| Kamath (permanent AF) [45] | European | 124     | 66       | 52.65      | ND       | ND       | ND       | ND             | ND         | ND         | ND       | 1        | Chronic       | ND  |
| Marin [46]   | European       | 80      | 70.5     | 55         | 19.5     | 52        | 6.5      | ND             | ND         | ND         | ND       | 4        | Chronic       | ND  |
| Conway [47]  | European       | 486     | 77.5     | 51.05      | 8.3      | 10.595    | 8.6      | ND             | ND         | ND         | ND       | 1        | No detection  | 10.3|

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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 |
|--------------|----------------|---------|-----------|------------|----------|-----------|---------|---------------|------------|-------------|---------|---------|----------------|----|
| Kamath (PAF) [48] | European | 58 | 63 | 48.235 | 6.85 | 24.1 | 3.4 | ND | ND | ND | ND | 4 | Acute | 5.1 |
| Kamath (permanent AF) [48] | European | 116 | 65 | 52.25 | 5.15 | 30.45 | 6.85 | ND | ND | ND | ND | 4 | Chronic | 5.1 |
| Kamath [49] | European | 143 | 70 | 63.2 | ND | ND | ND | ND | ND | ND | ND | 1 | No detection | 5.9 |
| Wang [50] | Asian | 3212 | 60 | 51.65 | 23.65 | 40.6 | 3.65 | ND | ND | ND | ND | 5 | No detection | 32.6 |
| Li-saw-Hee (PAF) [51] | European | 43 | 64 | 77.3 | 2.15 | 10.85 | 6.5 | ND | ND | ND | ND | 3 | Acute | 13.4 |
| Li-saw-Hee (PeAF) [51] | European | 43 | 64 | 77.25 | 2.15 | 13 | 4.3 | ND | ND | ND | ND | 3 | Acute | 11.5 |
| Li-saw-Hee (permanent) [51] | European | 43 | 65 | 77.25 | 6.52 | 23.9 | 15.2 | ND | ND | ND | ND | 3 | Chronic | 11.5 |
| Feng [52] | North America | 214 | 62.15 | 73.5 | 12.85 | 36 | 23.25 | ND | ND | ND | ND | 6 | No detection | 16.1 |
| Topcuoglu [53] | European | 36 | 62.35 | 61.87 | 13.5 | 42.5 | ND | ND | ND | ND | ND | 1 | No detection | 20 |
| Mondillo [54] | European | 80 | 66.95 | 82.85 | ND | ND | ND | ND | ND | ND | ND | 3 | Chronic | 33.7 |
| Giansante [55] | European | 105 | 63.5 | 55.67 | 8.5 | 29.25 | ND | ND | ND | ND | ND | 1 | Acute | 35.6 |
| Li-saw-Hee [56] | European | 112 | 67 | 77.5 | 3.85 | 12.5 | 11.55 | ND | ND | ND | ND | 1 | Chronic | 13.3 |
| Marin (disease control) [57] | European | 42 | 53.5 | 17.35 | 0 | ND | ND | ND | ND | ND | ND | 1 | No detection | ND |
| Marin (healthy control) [57] | European | 38 | ND | ND | 0 | ND | ND | ND | ND | ND | ND | 1 | No detection | ND |
| Li-saw-Hee [58] | European | 50 | 59 | 20 | ND | ND | ND | ND | ND | ND | ND | 5 | Chronic | 20 |
| Roldan [59] | European | 56 | 62 | ND | 0 | ND | ND | ND | ND | ND | ND | 1 | Chronic | ND |
| Tsai [50] | Asian | 111 | 64 | 74.45 | ND | ND | ND | ND | ND | ND | ND | 4 | Chronic | ND |
| Minamino [61] | Asian | 90 | 63 | 73.3 | 12.5 | 23.5 | ND | ND | ND | ND | ND | 1 | Chronic | 13.5 |
| Kahn [62] | North America | 81 | ND | ND | ND | ND | ND | ND | ND | ND | ND | 1 | Chronic | ND |
| Sohara [63] | Asian | 30 | 59.1 | ND | ND | ND | ND | ND | ND | ND | ND | 1 | Acute | ND |
| Lip (PAF) [64] | European | 188 | 59.85 | 57.8 | ND | ND | ND | ND | ND | ND | ND | 1 | Acute | 30 |
| Lip (chronic) [64] | European | 214 | 61.8 | 56.37 | ND | ND | ND | ND | ND | ND | ND | 1 | Chronic | 33 |
| Lip [65] | European | 77 | ND | ND | ND | ND | ND | ND | ND | ND | ND | 1 | Chronic | ND |
| Mitsusch [66] | European | 97 | 71 | 51.35 | 25 | 67 | ND | ND | ND | ND | ND | 1 | No detection | ND |
| Nago [67] | Asian | 36 | 79.95 | 44.575 | ND | ND | ND | ND | ND | ND | ND | 1 | No detection | ND |
| Lip [68] | European | 245 | 61.15 | 53.3 | ND | ND | ND | ND | ND | ND | ND | 5 | Chronic | ND |
| Sohara [69] | Asian | 22 | ND | ND | ND | ND | ND | ND | ND | ND | ND | 1 | Acute | ND |
| Kumagai [70] | Asian | 94 | 62.5 | 48.15 | ND | ND | ND | ND | ND | ND | ND | 1 | Chronic | ND |
| Gustafsson (with stroke) [71] | European | 60 | 77 | ND | ND | ND | ND | ND | ND | ND | ND | 1 | No detection | 30 |
| Gustafsson (without stroke) [71] | European | 60 | 77 | ND | ND | ND | ND | ND | ND | ND | ND | 1 | No detection | 25 |
### Supplementary Table 3. Subgroup-analysis and meta-regression.

| Subgroup                          | Studies (N) | WMD (95% CI)              | I-squared and P-value respectively | P-value of meta-regression |
|----------------------------------|-------------|---------------------------|-------------------------------------|---------------------------|
| **D-dimer**                      |             |                           |                                     |                           |
| Year of publication              |             |                           |                                     |                           |
| >2000                            | 25          | 243.7 (209.1 to 278.2)    | 99.8% and 0.001                     | 0.845                     |
| ≤2000                            | 16          | 137.3 (103.6 to 171.1)    | 99.1% and 0.001                     |                           |
| Geographic area                  |             |                           |                                     |                           |
| Asian                            | 13          | 144.4 (108.8 to 180.1)    | 99.7% and 0.001                     |                           |
| European                         | 24          | 242.5 (199.4 to 285.7)    | 99% and 0.001                       |                           |
| Africa                           | 1           | 0.83 (0.28 to 1.38)       | –                                   | 0.008                     |
| North American                   | 2           | 65.11 (–62.93 to 193.1)   | 98.2% and 0.001                     |                           |
| South American                   | –           | –                         | –                                   |                           |
| Australia                        | 1           | 472 (429.3 to 514.6)      | –                                   |                           |
| Design of study                  |             |                           |                                     |                           |
| Cohort                           | 35          | 176.1 (153.7 to 198.4)    | 99.7% and 0.001                     | 0.001                     |
| Case-control                     | 6           | 290.2 (189.5 to 390.8)    | 99.8% and 0.001                     |                           |
| Number of population             |             |                           |                                     |                           |
| >300                             | 2           | 65.1 (–62.9 to 193.1)     | 99.9% and 0.001                     | 0.49                      |
| ≤300                             | 39          | 204.4 (179.9 to 229)      | 99.4% and 0.001                     |                           |
| Mean Age                         |             |                           |                                     |                           |
| >60 years                        | 26          | 226.7 (188.6 to 264.8)    | 99.7% and 0.001                     | 0.92                      |
| ≤60 years                        | 9           | 160.7 (77 to 244.4)       | 99.6% and 0.001                     |                           |
| Male                             |             |                           |                                     |                           |
| >70%                             | 3           | 113.7 (22.2 to 205.1)     | 98.9% and 0.001                     | 0.94                      |
| ≤70%                             | 26          | 227.8 (187.8 to 267.8)    | 99.6% and 0.001                     |                           |
| Diabetes mellitus                |             |                           |                                     |                           |
| >30%                             | 2           | 290 (271.6 to 308.4)      | 73.3% and 0.001                     | 0.47                      |
| ≤30%                             | 20          | 264.8 (205.7 to 323.8)    | 99.7% and 0.001                     |                           |
| Hypertension                     |             |                           |                                     |                           |
| >70%                             | 1           | 96.1 (47.2 to 144.7)      | –                                   | 0.96                      |
| ≤70%                             | 19          | 258.6 (194.7 to 321.9)    | 99.8% and 0.001                     |                           |
| History of myocardial infarction |             |                           |                                     |                           |
| >20%                             | 1           | –0.16 (–0.42 to 0.107)    | –                                   | 0.95                      |
| ≤20%                             | 4           | 761.7 (140.3 to 1383.2)   | 98.2% and 0.001                     |                           |
| Anti-coagulant status codes      |             |                           |                                     |                           |
| 1                                | 18          | 215.3 (172 to 258.6)      | 98.9% and 0.001                     | 0.015                     |
| 2                                | –           | –                         | –                                   |                           |
| 3                                | 2           | 154 (–110.2 to 418.4)     | 97.6% and 0.001                     | 0.91                      |
| 4                                | 11          | 331.3 (225.5 to 437.1)    | 99.6% and 0.001                     |                           |
| 5                                | 10          | 91.1 (56 to 126.3)        | 99.9% and 0.001                     |                           |
| 6                                | –           | –                         | –                                   |                           |
| AF                               |             |                           |                                     |                           |
| Chronic                          | 14          | 261.3 (208.9 to 313.8)    | 99.6% and 0.001                     | 0.015                     |
| Non-chronic                      | 11          | 104.7 (29.6 to 179.8)     | 99.4% and 0.001                     |                           |
| Type of AF                       |             |                           |                                     |                           |
| Paroxysmal                       | 5           | 19.6 (12.5 to 26.8)       | 0.0% and 0.78                       | 0.254                     |
| Persistent                       | –           | –                         | –                                   |                           |
| Permanent                        | 4           | 512.5 (135.3 to 889.8)    | 99% and 0.001                       |                           |
| Cigarette smoking                |             |                           |                                     |                           |
| >30%                             | 7           | 111.1 (106.1 to 116)      | 99.7% and 0.001                     | 0.132                     |
| ≤30%                             | 8           | –0.136 (–0.403 to 0.131)  | 98.3% and 0.001                     |                           |
| Subgroup                          | Studies (N) | WMD (95% CI) | I-squared and P-value respectively | P-value of meta-regression |
|----------------------------------|-------------|--------------|-------------------------------------|---------------------------|
| Fibrinogen                       |             |              |                                     |                           |
| Year of publication              |             |              |                                     |                           |
| >2000                            | 46          | 0.29 (0.24 to 0.35) | 96.1% and 0.001                      | 0.02                      |
| ≤2000                            | 12          | 0.75 (0.54 to 0.96)  | 96.4% and 0.001                      |                           |
| Geographic area                  |             |              |                                     |                           |
| Asian                            | 9           | 0.35 (0.24 to 0.47)  | 95% and 0.001                        |                           |
| European                         | 40          | 0.53 (0.38 to 0.68)  | 97.9% and 0.001                      |                           |
| Africa                           | –           | –            |                                     | 0.04                      |
| North American                   | 9           | 0.10 (0.02 to 0.19)  | 97.3% and 0.001                      |                           |
| South American                   | –           | –            |                                     |                           |
| Australia                        | –           | –            |                                     |                           |
| Design of study                  |             |              |                                     |                           |
| Cohort                           | 15          | 0.22 (0.15 to 0.29)  | 98.2% and 0.001                      | 0.44                      |
| Case-control                     | 43          | 0.52 (0.36 to 0.69)  | 97.4% and 0.001                      |                           |
| Number of population             |             |              |                                     |                           |
| >300                             | 11          | 0.15 (0.05 to 0.25)  | 98.4% and 0.001                      | 0.053                     |
| ≤300                             | 47          | 0.52 (0.39 to 0.64)  | 98% and 0.001                        |                           |
| Mean Age                         |             |              |                                     |                           |
| >60 years                        | 43          | 0.48 (0.37 to 0.59)  | 98.7% and 0.001                      | 0.94                      |
| ≤60 years                        | 13          | 0.26 (0.17 to 0.34)  | 95% and 0.001                        |                           |
| Male                             |             |              |                                     |                           |
| >70%                             | 13          | 0.56 (0.35 to 0.77)  | 93.9% and 0.001                      | 0.468                     |
| ≤70%                             | 37          | 0.40 (0.31 to 0.48)  | 99.9% and 0.001                      |                           |
| Diabetes mellitus                |             |              |                                     |                           |
| >30%                             | 6           | 0.40 (0.11 to 0.69)  | 96.5% and 0.001                      | 0.97                      |
| ≤30%                             | 37          | 0.35 (0.28 to 0.43)  | 97.3% and 0.001                      |                           |
| Hypertension                     |             |              |                                     |                           |
| >70%                             | 3           | 0.17 (0.004 to 0.35) | 87.1% and 0.001                      | 0.60                      |
| ≤70%                             | 40          | 0.36 (0.29 to 0.43)  | 97.5% and 0.001                      |                           |
| History of myocardial infarction |             |              |                                     |                           |
| >20%                             | 4           | 0.01 (~0.11 to 0.13) | 75.6% and 0.006                      | 0.58                      |
| ≤20%                             | 16          | 0.42 (0.26 to 0.58)  | 96.5% and 0.001                      |                           |
| Anti-coagulant status codes      |             |              |                                     |                           |
| 1                                | 16          | 0.45 (0.23 to 0.68)  | 98.5% and 0.001                      |                           |
| 2                                | –           | –            |                                     |                           |
| 3                                | 8           | 0.62 (0.19 to 1.05)  | 95.3% and 0.001                      | 0.26                      |
| 4                                | 16          | 0.20 (0.14 to 0.25)  | 92.7% and 0.001                      |                           |
| 5                                | 17          | 0.53 (0.33 to 0.73)  | 98.6% and 0.001                      |                           |
| 6                                | 1           | 0.05 (~0.13 to 0.23) | –                                     |                           |
| AF                               |             |              |                                     |                           |
| Chronic                          | 18          | 0.7 (0.42 to 0.97)   | 97.6% and 0.001                      | 0.23                      |
| Non-chronic                      | 16          | 0.24 (0.16 to 0.33)  | 92.6% and 0.001                      |                           |
| Type of AF                       |             |              |                                     |                           |
| Paroxysmal                       | 8           | 0.38 (0.18 to 0.58)  | 83.9% and 0.78                       | 0.43                      |
| Persistent                       | 4           | 0.42 (0.11 to 0.74)  | 90.2% and 0.001                      |                           |
| Permanent                        | 9           | 0.54 (0.21 to 0.87)  | 93.6% and 0.001                      |                           |
| Cigarette smoking                |             |              |                                     |                           |
| >30%                             | 11          | 0.51 (0.47 to 0.56)  | 98.3% and 0.001                      | 0.47                      |
| ≤30%                             | 26          | 0.09 (0.78 to 1.03)  | 96.5% and 0.001                      |                           |
| Subgroup                        | Studies (N) | WMD (95% CI)                  | I-squared and P-value respectively | P-value of meta-regression |
|--------------------------------|-------------|-------------------------------|-----------------------------------|----------------------------|
| **Prothrombotic Factor 1–2**   |             |                               |                                   |                            |
| Year of publication            |             |                               |                                   |                            |
| >2000                          | 7           | 0.79 (–0.39 to 1.98)          | 98.1% and 0.001                   | –                          |
| ≤2000                          | 2           | 0.97 (–0.54 to 2.49)          | 99.8% and 0.001                   | –                          |
| Geographic area                 |             |                               |                                   |                            |
| Asian                           | 3           | 0.52 (0.23 to 0.82)           | 99.7% and 0.001                   |                            |
| European                        | 6           | 0.47 (0.34 to 0.64)           | 94.8% and 0.001                   |                            |
| Africa                          | –           | –                             | –                                 | –                          |
| North American                  | –           | –                             | –                                 | –                          |
| South American                  | –           | –                             | –                                 | –                          |
| Australia                       | –           | –                             | –                                 | –                          |
| Design of study                 |             |                               |                                   |                            |
| Cohort                          |             |                               |                                   |                            |
| Case-control                    |             |                               |                                   |                            |
| Number of population            |             |                               |                                   |                            |
| >300                            | 1           | 0.36 (0.33 to 0.39)           | –                                 | –                          |
| ≤300                            | 8           | 0.46 (0.29 to 0.62)           | 99.2% and 0.001                   | –                          |
| Mean Age                        |             |                               |                                   |                            |
| >60 years                       | 6           | 0.82 (0.26 to 1.37)           | 99% and 0.001                     | –                          |
| ≤60 years                       | –           | –                             | –                                 | –                          |
| Male                            |             |                               |                                   |                            |
| >70%                            | 1           | 1.75 (1.61 to 1.88)           | –                                 | –                          |
| ≤70%                            | 5           | 0.58 (0.25 to 0.91)           | 95.5% and 0.001                   |                            |
| Diabetes mellitus               |             |                               |                                   |                            |
| >30%                            | –           | –                             | –                                 | –                          |
| ≤30%                            | 5           | 0.58 (0.25 to 0.91)           | 95.5% and 0.001                   |                            |
| Hypertension                    |             |                               |                                   |                            |
| >70%                            | –           | –                             | –                                 | –                          |
| ≤70%                            | 5           | 0.38 (0.17 to 0.59)           | 99.7% and 0.001                   |                            |
| History of myocardial infarction|             |                               |                                   |                            |
| >20%                            | 1           | 0.67 (0.57 to 0.76)           | –                                 | –                          |
| ≤20%                            | –           | –                             | –                                 | –                          |
| Anti-coagulant status codes     |             |                               |                                   |                            |
| 1                               | 2           | 0.46 (–0.21 to 1.42)          | 72.9% and 0.05                    |                            |
| 2                               | –           | –                             | –                                 | –                          |
| 3                               | –           | –                             | –                                 | –                          |
| 4                               | 5           | 0.84 (0.31 to 1.36)           | 99% and 0.001                     |                            |
| 5                               | 2           | –0.04 (–0.07 to 0.01)         | 77.1% and 0.03                    |                            |
| 6                               | –           | –                             | –                                 | –                          |
| AF                              |             |                               |                                   |                            |
| Chronic                         | 2           | 1.20 (0.15 to 2.26)           | 99.4% and 0.001                   | –                          |
| Non-chronic                     | –           | –                             | –                                 | –                          |
| Type of AF                      |             |                               |                                   |                            |
| Paroxysmal                      | –           | –                             | –                                 | –                          |
| Persistent                      | –           | –                             | –                                 | –                          |
| Permanent                       | –           | –                             | –                                 | –                          |
| Cigarette smoking               |             |                               |                                   |                            |
| >30%                            | –           | –                             | No Data                           | –                          |
| ≤30%                            | –           | –                             | –                                 | –                          |
| Subgroup                          | Studies (N) | WMD (95% CI)               | I-squared and P-value respectively | P-value of meta-regression |
|----------------------------------|-------------|---------------------------|------------------------------------|---------------------------|
| **Year of publication**          |             |                           |                                    |                           |
| >2000                            | 4           | 5.80 (–1.006 to 12.78)    | 99.7% and 0.001                    | –                         |
| ≤2000                            | 4           | 4.57 (1.77 to 7.36)       | 85.4% and 0.001                    | –                         |
| **Geographic area**              |             |                           |                                    |                           |
| Asian                            | 5           | 6.93 (2.18 to 11.68)      | 98.1% and 0.001                    | –                         |
| European                         | 2           | 5.46 (3.43 to 7.48)       | 41.4% and 0.19                     | –                         |
| Africa                           | –           | –                         | –                                  | –                         |
| North American                   | 1           | 0.05 (0.01 to 0.093)      | –                                  | –                         |
| South American                   | –           | –                         | –                                  | –                         |
| Australia                        | –           | –                         | –                                  | –                         |
| **Design of study**              |             |                           |                                    |                           |
| Cohort                           |             |                           |                                    | All of them are case–control |
| Case-control                     |             |                           |                                    |                           |
| **Number of population**         |             |                           |                                    |                           |
| >300                             |             |                           |                                    | All of them are less than 300 cases |
| ≤300                             |             |                           |                                    |                           |
| **Mean Age**                     |             |                           |                                    |                           |
| >60 years                        | 3           | 5.79 (3.63 to 7.96)       | 37.5% and 0.202                    | –                         |
| ≤60 years                        | 3           | 7.89 (2.09 to 13.68)      | 98.8% and 0.001                    | –                         |
| **Male**                         |             |                           |                                    |                           |
| >70%                             | –           | –                         | –                                  | –                         |
| ≤70%                             | 5           | 7.87 (4.43 to 11.32)      | 98.3% and 0.001                    | –                         |
| **Diabetes mellitus**            |             |                           |                                    |                           |
| >30%                             | –           | –                         | –                                  | –                         |
| ≤30%                             | 2           | 5.46 (3.43 to 7.48)       | 41.4% and 0.19                     | –                         |
| **Hypertension**                 |             |                           |                                    |                           |
| >70%                             | –           | –                         | –                                  | –                         |
| ≤70%                             | 2           | 5.46 (3.43 to 7.48)       | 41.4% and 0.19                     | –                         |
| **History of myocardial infarction** |         |                           |                                    | No Data                   |
| >20%                             | –           | –                         | –                                  | –                         |
| ≤20%                             |             |                           |                                    |                           |
| **Anti-coagulant status codes**  |             |                           |                                    | All of them are Code–1    |
| 1                                | –           | –                         | –                                  | –                         |
| 2                                | –           | –                         | –                                  | –                         |
| 3                                | –           | –                         | –                                  | –                         |
| 4                                | –           | –                         | –                                  | –                         |
| 5                                | –           | –                         | –                                  | –                         |
| 6                                |             |                           |                                    |                           |
| **AF**                           |             |                           |                                    |                           |
| Chronic                          | –           | –                         | –                                  | –                         |
| Non-chronic                      | 2           | 2.47 (0.55 to 4.39)       | 27.4% and 0.24                    | –                         |
| **Type of AF**                   |             |                           |                                    |                           |
| Paroxysmal                       | 5           | 2.47 (0.55 to 4.39)       | 27.4% and 0.24                    | –                         |
| Persistent                       | –           | –                         | –                                  | –                         |
| Permanent                        | –           | –                         | –                                  | –                         |
| **Cigarette smoking**            |             |                           |                                    |                           |
| >30%                             |             |                           |                                    | No sufficient data        |
| ≤30%                             |             |                           |                                    |                           |
| Subgroup               | Studies (N) | WMD (95% CI)                      | I-squared and P-value respectively | P-value of meta-regression |
|------------------------|-------------|----------------------------------|-----------------------------------|----------------------------|
| **Anti-thrombin III**  |             |                                  |                                   |                            |
| Year of publication    |             |                                  |                                   |                            |
| >2000                  | 3           | 4.26 (~8.76 to 17.28)            | 91% and 0.001                     | –                          |
| ≤2000                  | 3           | 46.78 (36.8 to 56.70)            | 0% and 0.833                      | –                          |
| Geographic area        |             |                                  |                                   |                            |
| Asian                  |             |                                  |                                   |                            |
| European               |             |                                  |                                   |                            |
| Africa                 |             |                                  | All of them are European          |                            |
| North American         |             |                                  |                                   |                            |
| South American         |             |                                  |                                   |                            |
| Australia              |             |                                  |                                   |                            |
| Design of study        |             |                                  |                                   |                            |
| Cohort                 |             |                                  |                                   |                            |
| Case-control           |             |                                  |                                   |                            |
| Number of population   |             |                                  |                                   |                            |
| >300                   |             |                                  | All of studies have less than 300 |                            |
| ≤300                   |             |                                  |                                   |                            |
| Mean Age               |             |                                  |                                   |                            |
| >60 years              | 2           | 22.65 (~32.07 to 77.37)          | 94.2% and 0.001                   | –                          |
| ≤60 years              | 3           | 18.96 (0.16 to 37.65)            | 91.1% and 0.001                   | –                          |
| Male                   |             |                                  |                                   |                            |
| >70%                   | 1           | –3.80 (~8.98 to 1.38)            | –                                 | –                          |
| ≤70%                   | 1           | 43.55 (28.29 to 58.80)          | –                                 | –                          |
| Diabetes mellitus      |             |                                  |                                   |                            |
| >30%                   |             |                                  |                                   |                            |
| ≤30%                   | 5           | 30.21 (11.99 to 48.42)          | 91.3% and 0.001                   | –                          |
| Hypertension           |             |                                  |                                   |                            |
| >70%                   |             |                                  |                                   |                            |
| ≤70%                   | 2           | 8.65 (~6.11 to 23.43)           | 85.3% and 0.009                   | –                          |
| History of myocardial infarction | | | No data | |
| >20%                   |             |                                  |                                   |                            |
| ≤20%                   |             |                                  |                                   |                            |
| Anti-coagulant status codes | | | | |
| 1                      | 3           | 46.78 (36.85 to 56.70)          | 0.0% and 0.833                    | –                          |
| 2                      |             |                                  |                                   |                            |
| 3                      | 1           | –3.80 (~8.98 to 1.38)           | –                                 | –                          |
| 4                      |             |                                  |                                   |                            |
| 5                      | 2           | 8.65 (~6.11 to 23.43)          | 85.3% and 0.009                   | –                          |
| 6                      |             |                                  |                                   |                            |
| AF                     |             |                                  |                                   |                            |
| Chronic                | 2           | 22.65 (~32.07 to 77.37)          | 94.2% and 0.001                   | –                          |
| Non-chronic            |             |                                  |                                   |                            |
| Type of AF             |             |                                  |                                   |                            |
| Paroxysmal             |             |                                  |                                   |                            |
| Persistent             |             |                                  |                                   |                            |
| Permanent              | 1           | –3.80 (~8.98 to 1.38)           | –                                 | –                          |
| Cigarette smoking      |             |                                  |                                   |                            |
| >30%                   |             |                                  | No sufficient data                |                            |
| ≤30%                   |             |                                  |                                   |                            |
| Subgroup                          | Studies (N) | WMD (95% CI)            | I-squared and P-value respectively | P-value of meta-regression |
|----------------------------------|-------------|-------------------------|-----------------------------------|----------------------------|
| **Fibrinopeptide-A**             |             |                         |                                   |                            |
| Year of publication              |             |                         |                                   |                            |
| >2000                            | 1           | 10.05 (9.37 to 10.72)   | –                                 | –                          |
| ≤2000                            | 3           | 2.17 (~0.72 to 5.07)    | 99.4% and 0.001                   | –                          |
| Geographic area                  |             |                         |                                   |                            |
| Asian                            | 1           | 4.60 (4.28 to 4.91)     | –                                 | –                          |
| European                         | 3           | 3.98 (~1.33 to 9.30)    | 99.7% and 0.001                   | –                          |
| Africa                           | –           | –                       | –                                 | –                          |
| North American                   | –           | –                       | –                                 | –                          |
| South American                   | –           | –                       | –                                 | –                          |
| Australia                        | –           | –                       | –                                 | –                          |
| Number of population             |             |                         |                                   |                            |
| >300                             | –           | –                       | –                                 | –                          |
| ≤300                             | –           | 4.60 (4.28 to 4.91)     | –                                 | –                          |
| Mean Age                         |             |                         |                                   |                            |
| >60 years                        | –           | 10.05 (9.37 to 10.72)   | –                                 | –                          |
| ≤60 years                        | –           | –                       | –                                 | –                          |
| Male                             |             |                         |                                   |                            |
| >70%                             | 1           | 4.60 (4.28 to 4.91)     | –                                 | –                          |
| ≤70%                             | 1           | 10.05 (9.37 to 10.72)   | –                                 | –                          |
| Diabetes mellitus                |             |                         |                                   |                            |
| >30%                             | –           | –                       | –                                 | –                          |
| ≤30%                             | 1           | 10.05 (9.37 to 10.72)   | –                                 | –                          |
| Hypertension                     |             |                         |                                   |                            |
| >70%                             | –           | –                       | –                                 | –                          |
| ≤70%                             | 1           | 10.05 (9.37 to 10.72)   | –                                 | –                          |
| History of myocardial infarction |             |                         |                                   |                            |
| >20%                             | –           | –                       | –                                 | –                          |
| ≤20%                             | –           | 4.60 (4.28 to 4.97)     | –                                 | –                          |
| Anti-coagulant status codes      |             |                         |                                   |                            |
| 1                                | 3           | 3.98 (~1.33 to 9.30)    | 99.7% and 0.001                   | –                          |
| 2                                | –           | –                       | –                                 | –                          |
| 3                                | –           | –                       | –                                 | –                          |
| 4                                | 1           | 4.60 (4.28 to 4.97)     | –                                 | –                          |
| 5                                | –           | –                       | –                                 | –                          |
| 6                                | –           | –                       | –                                 | –                          |
| AF                               |             |                         |                                   |                            |
| Chronic                          | 1           | 4.60 (4.28 to 4.97)     | –                                 | –                          |
| Non-chronic                      | 1           | 10.05 (9.37 to 10.72)   | –                                 | –                          |
| Type of AF                       |             |                         |                                   |                            |
| Paroxysmal                       | 1           | 10.05 (9.37 to 10.72)   | –                                 | –                          |
| Persistent                       | –           | –                       | –                                 | –                          |
| Permanent                        | –           | –                       | –                                 | –                          |
| Cigarette smoking                |             |                         |                                   |                            |
| >30%                             | 2           | 5.19 (4.78 to 5.63)     | 99.7% and 0.001                   | –                          |
| ≤30%                             | 1           | 0.42 (0.11 to 0.72)     | –                                 | –                          |
The table below summarizes the meta-regression results for various subgroups.

| Subgroup                          | Studies (N) | WMD (95% CI)          | I-squared and P-value respectively | P-value of meta-regression |
|-----------------------------------|-------------|-----------------------|------------------------------------|---------------------------|
| **Tissue plasminogen activator**  |             |                       |                                    |                           |
| Year of publication              |             |                       |                                    |                           |
| >2000                             | 9           | 3.095 (1.52 to 4.66)  | 95.5% and 0.001                    | –                         |
| ≤2000                             | 5           | 0.709 (~0.908 to 2.32)| 99.2% and 0.001                    |                           |
| Geographic area                   |             |                       |                                    |                           |
| Asian                             | 2           | 3.78 (3.30 to 4.26)   | 0.0% and 0.86                      |                           |
| European                          | 11          | 1.86 (0.69 to 3.03)   | 98.4% and 0.001                    |                           |
| Africa                            | –           | –                     | –                                   |                           |
| North American                    | 1           | 1.30 (0.013 to 2.58)  | –                                   |                           |
| South American                    | –           | –                     | –                                   |                           |
| Australia                         | –           | –                     | –                                   |                           |
| Design of study                   |             |                       |                                    |                           |
| Cohort                            | 2           | 1.89 (~1.82 to 5.62)  | 98.2% and 0.001                    | –                         |
| Case-control                      | 12          | 2.16 (0.98 to 3.34)   | 98.2% and 0.001                    |                           |
| Number of population              |             |                       |                                    |                           |
| >300                              | 1           | 3.80 (3.30 to 4.29)   | –                                   | –                         |
| ≤300                              | 13          | 1.95 (0.88 to 3.02)   | 98.1% and 0.001                    |                           |
| Mean Age                          |             |                       |                                    |                           |
| >60 years                         | 10          | 2.69 (1.56 to 3.83)   | 96.1% and 0.001                    | –                         |
| ≤60 years                         | 3           | 1.29 (~1.14 to 3.74)  | 88.8% and 0.001                    |                           |
| Male                              |             |                       |                                    |                           |
| >70%                              | 4           | 3.67 (0.40 to 6.94)   | 96.3% and 0.001                    | –                         |
| ≤70%                              | 6           | 2.34 (0.56 to 4.13)   | 99.2% and 0.001                    |                           |
| Diabetes mellitus                 |             |                       |                                    |                           |
| >30%                              | –           | –                     | –                                   | –                         |
| ≤30%                              | 13          | 1.60 (0.52 to 2.68)   | 98.3% and 0.001                    |                           |
| Hypertension                      |             |                       |                                    |                           |
| >70%                              |             |                       |                                    |                           |
| ≤70%                              | 10          | 2.41 (1.47 to 3.51)   | 93.5% and 0.001                    |                           |
| History of myocardial infarction  |             |                       |                                    |                           |
| >20%                              | 2           | 1.98 (0.81 to 3.14)   | 53.3% and 0.143                    | –                         |
| ≤20%                              | 2           | 3.68 (3.26 to 4.10)   | 0.0% and 0.396                     |                           |
| Anti-coagulant status codes       |             |                       |                                    |                           |
| 1                                 | 5           | 0.21 (~1.50 to 1.93)  | 99.1% and 0.001                    |                           |
| 2                                 | –           | –                     | –                                   | –                         |
| 3                                 | 1           | 10.57 (8.055 to 13.085)| –                                  | –                         |
| 4                                 | 3           | 1.94 (~0.36 to 4.26)  | 96.8% and 0.001                    |                           |
| 5                                 | 4           | 3.48 (2.76 to 4.19)   | 22.6% and 0.275                    |                           |
| 6                                 | 1           | 1.30 (0.013 to 2.58)  | –                                   | –                         |
| AF                                |             |                       |                                    |                           |
| Chronic                           | 3           | 4.43 (~1.25 to 10.12) | 97.6% and 0.001                    |                           |
| Non-chronic                       | 2           | 2.99 (2.11 to 3.87)   | 51% and 0.154                      |                           |
| Type of AF                        |             |                       |                                    |                           |
| Paroxysmal                        | 1           | 2.50 (1.53 to 3.46)   | –                                   | –                         |
| Persistent                        | 1           | 3.40 (2.62 to 4.17)   | –                                   | –                         |
| Permanent                         | 1           | 10.57 (8.055 to 13.085)| –                                  | –                         |
| Cigarette smoking                 |             |                       |                                    |                           |
| >30%                              | 2           | 4.05 (3.56 to 4.56)   | 96.3% and 0.001                    | –                         |
| ≤30%                              | 4           | 2.73 (2.18 to 3.27)   | 61.6% and 0.051                    |                           |
| Subgroup                        | Studies (N) | WMD (95% CI)                  | I-squared and P-value respectively | P-value of meta-regression |
|--------------------------------|-------------|-------------------------------|-------------------------------------|----------------------------|
|                                |             |                               |                                     |                            |
| **Plasminogen activator inhibitor** |             |                               |                                     |                            |
| **Year of publication**        |             |                               |                                     |                            |
| >2000                          | 10          | 6.69 (1.79 to 11.59)          | 99.5% and 0.001                    | 0.28                       |
| ≤2000                          | 5           | 20.72 (7.68 to 33.75)         | 97.4% and 0.001                    |                            |
| **Geographic area**            |             |                               |                                     |                            |
| Asian                          | 4           | 15.82 (0.49 to 31.14)         | 99.5% and 0.001                    |                            |
| European                       | 10          | 10.07 (6.93 to 13.21)         | 98.4% and 0.001                    |                            |
| Africa                         | –           | –                             |                                     | 0.30                       |
| North American                 | 1           | 1.009 (–3.05 to 5.07)         |                                     |                            |
| South American                 | –           | –                             |                                     |                            |
| Australia                      | –           | –                             |                                     |                            |
| **Design of study**            |             |                               |                                     |                            |
| Cohort                         | 1           | 4.490 (2.71 to 7.08)          |                                     | 0.97                       |
| Case-control                   | 14          | 11.28 (6.70 to 15.86)         | 99.4% and 0.001                    |                            |
| **Number of population**       |             |                               |                                     |                            |
| >300                           | 1           | 4.490 (2.71 to 7.08)          |                                     | 0.98                       |
| ≤300                           | 14          | 11.28 (6.70 to 15.86)         | 99.4% and 0.001                    |                            |
| **Mean Age**                   |             |                               |                                     |                            |
| >60 years                      | 9           | 6.99 (4.31 to 9.67)           | 91.7% and 0.001                    | 0.96                       |
| ≤60 years                      | 5           | 10.36 (2.19 to 18.52)         | 99.8% and 0.001                    |                            |
| **Male**                       |             |                               |                                     |                            |
| >70%                           | 1           | 36.42 (32.41 to 40.42)        |                                     | 0.18                       |
| ≤70%                           | 8           | 11.28 (3.14 to 19.42)         | 99.5% and 0.001                    |                            |
| **Diabetes mellitus**          |             |                               |                                     |                            |
| >30%                           | –           | –                             |                                     |                            |
| ≤30%                           | 12          | 8.93 (6.03 to 11.88)          | 98.1% and 0.001                    |                            |
| **Hypertension**               |             |                               |                                     |                            |
| >70%                           | –           | –                             |                                     |                            |
| ≤70%                           | 9           | 3.34 (1.30 to 5.39)           | 96% and 0.001                     |                            |
| **History of myocardial infarction** |         |                               |                                     |                            |
| >20%                           | 2           | 1.55 (–3.66 to 6.78)          | 84.5% and 0.011                    | 0.97                       |
| ≤20%                           | 2           | 4.16 (3.29 to 5.03)           | 0.0% and 0.474                    |                            |
| **Anti-coagulant status codes** |             |                               |                                     |                            |
| 1                              | 7           | 21.28 (11.09 to 31.47)        | 98.9% and 0.001                    |                            |
| 2                              | –           | –                             |                                     | 0.014                      |
| 3                              | 1           | 4.20 (1.09 to 7.31)           |                                     |                            |
| 4                              | 2           | 3.95 (3.27 to 4.64)           | 0.0% and 0.831                    |                            |
| 5                              | 4           | 1.08 (–0.357 to 2.534)        | 87.1% and 0.001                    |                            |
| 6                              | 1           | –1.50 (–5.53 to 2.53)         |                                     |                            |
| **AF**                         |             |                               |                                     |                            |
| Chronic                        | 3           | 16.58 (–1.97 to 35.14)        | 95.6% and 0.001                    | 0.97                       |
| Non-chronic                    | 2           | 3.80 (3.16 to 4.44)           | 0.0% and 0.448                    |                            |
| **Type of AF**                 |             |                               |                                     |                            |
| Paroxysmal                     | 1           | 3.88 (2.87 to 4.88)           |                                     | 0.26                       |
| Persistent                     | 1           | 4.03 (3.08 to 4.97)           |                                     |                            |
| Permanent                      | 1           | 5.90 (3.49 to 8.31)           |                                     |                            |
| **Cigarette smoking**          |             |                               |                                     |                            |
| >30%                           | 2           | 5.35 (3.73 to 6.97)           | 0.0% and 0.568                    | 0.95                       |
| ≤30%                           | 4           | 3.80 (3.13 to 4.48)           | 56.9% and 0.07                    |                            |
| Subgroup                      | Studies (N) | WMD (95% CI)          | I-squared and P-value respectively | P-value of meta-regression |
|-------------------------------|-------------|-----------------------|------------------------------------|---------------------------|
| von Willebrand Factor         |             |                       |                                    |                           |
| Year of publication           |             |                       |                                    |                           |
| >2000                         | 28          | 27.50 (19.43 to 35.56) | 96.3% and 0.001                    | 0.98                      |
| ≤2000                         | 4           | 23.67 (9.80 to 37.53)  | 99.5% and 0.001                    |                           |
| Geographic area                |             |                       |                                    |                           |
| Asian                         | 4           | 15.19 (7.19 to 23.19)  | 15.4% and 0.315                    |                           |
| European                      | 25          | 30.91 (22.26 to 39.56) | 99% and 0.001                      |                           |
| Africa                        | –           | –                     | –                                  | 0.01                      |
| North American                | 3           | 13.23 (10.42 to 16.04) | 0.0% and 0.423                    |                           |
| South American                | –           | –                     | –                                  |                           |
| Australia                     | –           | –                     | –                                  |                           |
| Design of study               |             |                       |                                    |                           |
| Cohort                        | 5           | 11.70 (6.62 to 16.78)  | 66.4% and 0.018                    | 0.05                      |
| Case-control                  | 27          | 29.97 (21.49 to 38.44) | 98.9% and 0.001                    |                           |
| Number of population          |             |                       |                                    |                           |
| >300                          | 4           | 10.32 (5.54 to 15.09)  | 63.8% and 0.041                    | 0.10                      |
| ≤300                          | 28          | 29.78 (21.48 to 38.08) | 98.8% and 0.001                    |                           |
| Mean Age                      |             |                       |                                    |                           |
| >60 years                     | 22          | 27.88 (18.70 to 37.07) | 99.1% and 0.001                    | 0.703                     |
| ≤60 years                     | 10          | 23.95 (16.11 to 31.79) | 85.4% and 0.001                    |                           |
| Male                          |             |                       |                                    |                           |
| >70%                          | 13          | 27.82 (18.23 to 37.41) | 87.9% and 0.001                    | 0.44                      |
| ≤70%                          | 15          | 28.74 (17.73 to 39.74) | 98% and 0.001                      |                           |
| Diabetes mellitus             |             |                       |                                    |                           |
| >30%                          | –           | –                     | –                                  |                           |
| ≤30%                          | 25          | 25.34 (16.93 to 33.76) | 95.6% and 0.001                    |                           |
| Hypertension                  |             |                       |                                    |                           |
| >70%                          | 2           | 16.95 (–1.44 to 35.35) | 57% and 0.127                     | 0.48                      |
| ≤70%                          | 24          | 27.42 (18.17 to 36.13) | 96.7% and 0.001                    |                           |
| History of myocardial infarction |           |                       |                                    |                           |
| >20%                          | 3           | 20.98 (–14.49 to 0.56.4) | 98.7% and 0.001                  | 0.97                      |
| ≤20%                          | 14          | 26.61 (14.62 to 38.60) | 97.2% and 0.001                    |                           |
| Anti-coagulant status codes   |             |                       |                                    |                           |
| 1                             | 6           | 9.66 (5.59 to 13.74)   | 93.5% and 0.001                    |                           |
| 2                             | 1           | 25 (11.14 to 38.85)    | –                                  |                           |
| 3                             | 8           | 33.09 (18.72 to 47.47) | 90.9% and 0.001                    | 0.81                      |
| 4                             | 7           | 34.96 (24.55 to 45.38) | 92.4% and 0.001                    |                           |
| 5                             | 9           | 30.16 (13.83 to 46.49) | 95.9% and 0.001                    |                           |
| 6                             | 1           | 5.0 (–9.75 to 19.75)   | –                                  |                           |
| AF                            |             |                       |                                    |                           |
| Chronic                       | 8           | 43 (29.03 to 56.97)    | 93% and 0.001                      | 0.65                      |
| Non-chronic                   | 12          | 26.73 (16.88 to 36.58) | 94.7% and 0.001                    |                           |
| Type of AF                    |             |                       |                                    |                           |
| Paroxysmal                    | 4           | 29.17 (7.99 to 50.34)  | 96.5% and 0.001                    | 0.75                      |
| Persistent                    | 5           | 25.02 (6.51 to 43.52)  | 96.1% and 0.001                    |                           |
| Permanent                     | 4           | 43.01 (10.43 to 75.59) | 95.6% and 0.001                    |                           |
| Cigarette smoking             |             |                       |                                    |                           |
| >30%                          | 4           | 3.53 (2.48 to 4.58)    | 95.8% and 0.001                    | 0.98                      |
| ≤30%                          | 21          | 14.60 (13.67 to 15.53) | 98.7% and 0.001                    |                           |
| Subgroup                       | Studies (N) | WMD (95% CI)     | I-squared and P-value respectively | P-value of meta-regression |
|-------------------------------|-------------|------------------|------------------------------------|---------------------------|
| Soluble thrombomodulin        |             |                  |                                    |                           |
| Year of Publication           |             |                  |                                    |                           |
| >2000                         | 6           | 4.36 (2.79 to 5.93) | 86.8% and 0.001                    | –                         |
| ≤2000                         | 1           | –13.0 (–19.12 to –6.87) |                                    |                           |
| Geographic area               |             |                  |                                    |                           |
| Asian                         | –           |                  |                                    |                           |
| European                      | 6           | 3.81 (0.35 to 7.27) | 92.6% and 0.001                    |                           |
| Africa                        | –           |                  |                                    |                           |
| North American                | –           |                  |                                    |                           |
| South American                | 1           | 1.81 (1.03 to 2.58) |                                    |                           |
| Australia                     | –           |                  |                                    |                           |
| Design of study               |             |                  |                                    |                           |
| Cohort                        | 1           | 2.02 (1.88 to 2.15) |                                    |                           |
| Case-control                  | 6           | 3.87 (0.31 to 7.43) | 90.6% and 0.001                    |                           |
| Number of population          |             |                  |                                    |                           |
| >300                          | All of studies have less than 300 cases |                  |                                    |                           |
| ≤300                          |             |                  |                                    |                           |
| Mean Age                      |             |                  |                                    |                           |
| >60 years                     | 4           | 6.04 (2.88 to 9.21) | 89.5% and 0.001                    | –                         |
| ≤60 years                     | 2           | –5.16 (–19.87 to 9.54) | 95.7% and 0.001                    | –                         |
| Male                          |             |                  |                                    |                           |
| >70%                          | 2           | 6.84 (0.02 to 13.65) | 86.8% and 0.001                    | –                         |
| ≤70%                          | 4           | 1.68 (–2.13 to 5.50) | 94.3% and 0.001                    | –                         |
| Diabetes mellitus             |             |                  |                                    |                           |
| >30%                          | –           |                  |                                    | –                         |
| ≤30%                          | 4           | 5.10 (2.03 to 8.17) | 91.2% and 0.001                    | –                         |
| Hypertension                  |             |                  |                                    |                           |
| >70%                          | –           |                  |                                    | –                         |
| ≤70%                          | 4           | 5.10 (2.03 to 8.17) | 91.2% and 0.001                    | –                         |
| History of myocardal infarction |         |                  |                                    |                           |
| >20%                          | 3           | 6.18 (4.78 to 7.58) | 0.0% and 0.794                    | –                         |
| ≤20%                          |             |                  |                                    | –                         |
| Anti-coagulant status codes   |             |                  |                                    |                           |
| 1                             | 3           | 4.36 (–0.52 to 9.25) | 56.9% and 0.09                     |                           |
| 2                             | –           |                  |                                    | –                         |
| 3                             | 1           | 12.28 (6.09 to 18.46) |                                    | –                         |
| 4                             | 2           | 6.02 (4.61 to 7.50) | 0.0% and 0.839                    |                           |
| 5                             | 1           | –5.27 (–19.76 to 9.21) |                                    | –                         |
| 6                             | –           |                  |                                    | –                         |
| AF                            |             |                  |                                    |                           |
| Chronic                       | 4           | 3.38 (–5.27 to 12.04) | 92.6% and 0.001                    | –                         |
| Non-chronic                   | 2           | 2.85 (1.52 to 4.17) | 88.7% and 0.001                    |                           |
| Type of AF                    |             |                  |                                    |                           |
| Paroxysmal                    | 1           | 2.02 (1.88 to 2.15) |                                    | –                         |
| Persistent                    | –           |                  |                                    | –                         |
| Permanent                     | 1           | 12.28 (6.09 to 18.46) |                                    |                           |
| Cigarette smoking             |             |                  |                                    |                           |
| >30%                          | 1           | 12.28 (6.09 to 18.46) |                                    | –                         |
| ≤30%                          | 3           | 2.01 (1.88 to 2.14) | 56.3% and 0.101                    |                           |
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