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

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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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

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Conclusions: inhibitor (WMD=11.44 and p<0.001), fibrinopeptide-A (WMD=4.13 and p=0.01)); and endothelial markers (von Willebrand factor (WMD=27.01 and p<0.001) and soluble thrombomodulin (WMD=3.92 and p<0.001)) with AF. The levels of coagulation, fibrinolytic, and endothelial markers have been reported to be significantly higher in AF patients than in SR patients.

MeSH Keywords: Atrial Fibrillation • Blood Coagulation Disorders • Fibrinolysis

Full-text PDF: http://www.basic.medscimonit.com/abstract/index/idArt/902558

Background

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

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hemostatic 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 subacute *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 ranges 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 *p* value <0.1 for Q test or I^2 >50% indicated significant heterogeneity among the studies. Heterogeneity among trials was accounted for by applying a random effect model when indicated. Sample weighting assigned studies with larger sample sizes and more weight, and reduced the effect of sampling error because sampling error generally decreases as the sample size increases. The presence of publication bias was evaluated using the Begg tests. Results were considered statistically significant at 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 (I^2=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 the AF group and 2.78 g/L in the SR group (details in Tables 1 and 2). Pooled analysis showed 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 (I^2=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 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 (I^2=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

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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
Amdur [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
Oneal (with comorbidities) [14]	2015	USA	Cohort	63	820	65	64	22	43	58	38	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	52.29	58.06	64	19	12	Combined	8
Chen (with comorbidities) [16]	2014	China	Cohort	107	100	59.4	52.29	64.4	64	26	12	Combined	8
Schnabel [17]	2014	Germany	Cohort	161	4837	64.9	55.2	59	50	ND	ND	ND	9
Wei-Hong Ma [18]	2014	China	Cohort	55	50	59	57	74.5	70	100	100	ND	8
Xu (without comorbidities) [19]	2014	China	Cohort	57	58	65.9	67.8	50.9	50	50.9	15.5	ND	7
Xu (with comorbidities) [19]	2014	China	Cohort	57	58	68.95	67	52.6	50	49.1	15.5	ND	7
Distelmaier [20]	2014	USA	Case-control	66	132	73.5	73.5	61	61	ND	ND	ND	7
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

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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
Adamsson Eryd [26]	2011	Sweden	Cohort	667	5364	47.8	46.7	100	100	ND	ND	ND	9
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
Letsas (PAF) [30]	2010	Greece	Case-control	45	48	67.5	61.3	62	56	ND	ND	Paroxysmal	9
Letsas (permanent) [30]	2010	Greece	Case-control	41	48	71.9	61.3	63	56	ND	ND	Permanent	9
Gartner [31]	2008	Austria	Case-control	222	28	64.5	54.4	63	68	55	40	ND	6
Targonski (PAF and PeAF) [32]	2008	Poland	Case-control	26	30	70.3	56.7	65.4	70	84.6	83.3	Combined (PAF and PeAF)	8
Targonski (Permanent) [32]	2008	Poland	Case-control	43	30	69.9	68.7	62.8	70	48.8	83.3	Permanent	8
Marcus [33]	2008	USA	Case-control	46	925	74	66	94	81	ND	ND	ND	9
Blann [34]	2007	UK	Case-control	54	28	65	64	64.8	60.7	60	0	ND	6
Topaloglu (disease control) [35]	2007	Turkey	Case-control	18	28	37	32	ND	ND	ND	ND	ND	6
Topaloglu (healthy control) [35]	2007	Turkey	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
Turgut (disease control) [37]	2006	Turkey	Case-control	26	29	67.42	64.8	30.8	58.6	38.5	20.7	ND	8
Turgut (healthy control) [37]	2006	Turkey	Case-control	26	20	67.42	65.7	30.8	57.1	38.5	0	ND	8
Heeringa [38]	2006	UK	Cohort	162	324	78	77	51	51	ND	ND	ND	8
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
Hatzinikolaou-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	53	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

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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
Li-saw-Hee [58]	1999	UK	Case-control	25	25	60	58	20	20	ND	ND	ND	6
Roldan [59]	1998	Spain	Case-control	36	20	62	62	62	ND	0	0	ND	7
Tsai [50]	1998	Taiwan	Case-control	73	38	65	63	75.3	73.6	11	0	ND	6
Minamino [61]	1997	Japan	Case-control	45	45	63	63	73.3	73.3	ND	ND	ND	6
Kahn [62]	1997	Canada	Case-control	50	31	ND	65	ND	38.7	0	0	ND	7
Sohara [63]	1997	Japan	Case-control	21	9	59.1	59.1	71.4	ND	0	0	Paroxysmal	6
Lip (PAF) [64]	1996	UK	Case-control	30	158	60.8	58.9	60	55.6	0	0	Paroxysmal	8
Lip (chronic) [64]	1996	UK	Case-control	56	158	64.7	58.9	57.14	55.6	0	0	ND	8
Lip [65]	1996	UK	Case-control	51	26	70.4	ND	ND	ND	0	0	ND	6
Mitusch [66]	1996	Germany	Case-control	69	28	72	70	42	60.7	0	0	ND	7
Nagao [67]	1995	Japan	Case-control	17	19	81.5	78.4	47.05	42.1	0	0	ND	8
Lip [68]	1995	UK	Case-control	87	158	63	59.3	50.6	56	ND	ND	ND	7
Sohara [69]	1994	Japan	Case-control	13	9	60	ND	76.9	ND	0	0	Paroxysmal	6
Kumagai [70]	1990	Japan	Case-control	73	21	64	61	53.4	42.9	0	0	ND	7
Gustafsson (with stroke) [71]	1990	Sweden	case-control	20	40	77	77	ND	ND	0	0	ND	8
Gustafsson (without stroke) [71]	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
Occurrence of AF		
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 PAI: AF: 47.9±2.5 *vs.* SR: 13.52±3.57
Yusuf (healthy control) [11]	TAT and PAI	TAT: AF: 15.37±1.87 *vs.* SR: 9.07±1.22 PAI: AF: 26.72±3.37 *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

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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: 27.95±1.65 *vs.* SR: 24.07±3.12 vWF: AF: 172.75±10.75 *vs.* SR: 121.75±5.25
Borgi [13]	D-dimer	D-dimer: AF: 590±506 *vs.* SR: 225.26±112.95
Oneal (with comorbidities) [14]	Fibrinogen	Fibrinogen: AF: 0.42±0.10 *vs.* SR: 0.41±0.11
Oneal (with comorbidities) [14]	Fibrinogen	Fibrinogen: AF: 0.41±0.07 *vs.* SR: 0.38±0.10
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	D-dimer: AF: 660±60 *vs.* SR: 270±20 Fibrinogen: AF: 2.63±0.07 *vs.* SR: 2.57±0.12
Chen (with comorbidities) [16]	D-dimer and Fibrinogen	D-dimer: AF: 350±20 *vs.* SR: 270±20 Fibrinogen: AF: 2.62±0.05 *vs.* SR: 2.57±0.12
Schnabel [17]	Fibrinogen	Fibrinogen: AF: 4.11±0.35 *vs.* SR: 3.47±0.23
Wei-Hong Ma [18]	vWF	vWF: AF: 166±46 *vs.* SR: 141±24
Xu (without comorbidities) [19]	D-dimer and Fibrinogen	D-dimer: AF: 379.5±48 *vs.* SR: 98.5±5 Fibrinogen: AF: 3.64±0.89 *vs.* SR: 2.62±0.5
Xu (with comorbidities) [19]	D-dimer and Fibrinogen	D-dimer: AF: 398.25±54.75 *vs.* SR: 98.5±5 Fibrinogen: AF: 3.68±0.62 *vs.* SR: 2.62±0.5
Distelmaier [20]	Fibrinogen	Fibrinogen: AF: 4±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: 125.2±10.4 *vs.* SR: 86.8±14
Berge [22]	tPA	tPA: AF: 15.2±1.8 *vs.* SR: 15.2±1
Acevedo [23]	TAT and sTM	TAT: AF: 0.054±0.23 *vs.* SR: 0.002±0.003 sTM: AF: 52.2±111 *vs.* 44±13
Zorlu [24]	D-dimer	D-dimer: AF: 1351.75±497.75 *vs.* SR: 644.25±113.8
Alonso (White) [25]	Fibrinogen and vWF	Fibrinogen: AF: 3.19±0.64 *vs.* SR: 2.95±0.61 vWF: AF: 124.5±46.4 *vs.* SR: 111.3±42.6
Alonso (African-American) [25]	Fibrinogen and vWF	Fibrinogen: AF: 3.32±0.76 *vs.* SR: 3.18±0.71 vWF: AF: 148.9±67.5 *vs.* SR: 132.4±55.6
Adamsson Eryd [26]	Fibrinogen	Fibrinogen: AF: 3.6±0.8 *vs.* SR: 3.5±0.8
Fu [27]	Fibrinogen and vWF	Fibrinogen: AF: 3.3±0.9 *vs.* SR: 3±0.6 vWF: AF: 116.5±37.4 *vs.* SR: 105.6±29.8
Hou (disease control) [28]	D-dimer and vWF	D-dimer: AF: 327±96 *vs.* SR: 231±83 vWF: AF: 132±38 *vs.* SR: 126±36
Hou (healthy control) [28]	D-dimer and vWF	D-dimer: AF: 327±96 *vs.* SR: 208±80 vWF: AF: 132±38 *vs.* SR: 113±37
Schnabel [29]	D-dimer and Fibrinogen	D-dimer: AF: 451.5±56 *vs.* SR: 321±43.6 Fibrinogen: AF: 3.52±0.15 *vs.* SR: 3.31±0.15
Letsas (PAF) [30]	Fibrinogen	Fibrinogen: AF: 3.74±1.03 *vs.* SR: 3.6±0.89
Letsas (permanent) [30]	Fibrinogen	Fibrinogen: AF: 4.12±0.99 *vs.* SR: 3.6±0.89
Gartner [31]	D-dimer	D-dimer: AF: 929.3±105.1 *vs.* SR: 457.3±108.8
Targonski (PAF and PeAF) [32]	Fibrinogen	Fibrinogen: AF: 3.39±0.67 *vs.* SR: 3.6±0.76
Targonski (Permanent) [32]	Fibrinogen	Fibrinogen: AF: 3.91±0.77 *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

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

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: 5.82±1.79 PAI: AF: 1.05±0.97 *vs.* SR: 1.16±0.7 vWF: AF: 134.9±68 *vs.* SR: 115.7±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 (with cerebral ischemic) [36]	Fibrinogen	Fibrinogen: AF: 3.68±1.04 *vs.* SR: 3.07±0.3
Cecchi (without 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: 3.47±1.1 PF1-2: AF: 2.83±0.89 *vs.* SR: 2.33±0.8
Turgut (healthy control) [37]	Fibrinogen and PF1-2	Fibrinogen: AF: 3.64±0.86 *vs.* SR: 2.51±0.61 PF1-2: AF: 2.83±0.89 *vs.* SR: 1.94±0.64
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±650 *vs.* SR: 390±280 vWF: AF: 133.1±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: 1.04±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: 0.82±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: 4.5±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: 675.75±151.75 *vs.* SR: 659.5±185.5 Fibrinogen: AF: 2.9±0.7 *vs.* SR: 2.6±0.5

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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: 2.8±0.7 *vs.* SR: 2.6±0.4
Wang [50]	Fibrinogen, tPA and PAI	Fibrinogen: AF: 3.15±0.76 *vs.* SR: 3.03±0.63 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: 2.7±0.8 *vs.* SR: 2.5±0.6 vWF: AF: 106±26 *vs.* SR: 101±30
Li-saw-Hee (permanent) [51]	Fibrinogen and vWF	Fibrinogen: AF: 3.1±0.9 *vs.* SR: 2.5±0.6 vWF: AF: 143±47 *vs.* SR: 101±30
Feng [52]	Fibrinogen, tPA, PAI and vWF	Fibrinogen: AF: 3.33±0.53 *vs.* SR: 3.28±0.65 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: 142±46.2 *vs.* SR: 137±43.4
Topcuoglu [53]	PF1-2, TAT, tPA and PAI	PF1-2: AF: 2.29±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: 21.16±12.72 PAI: AF: 37.05±22.32 *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±23.75 Fibrinogen: AF: 3.81±1.09 *vs.* SR: 2.68±0.8 AT-III: AF: 99.9±15.8 *vs.* SR: 103.7±7.1 tPA: AF: 20.37±7.8 *vs.* SR: 9.8±3.21 PAI: AF: 15.2±6.2 *vs.* SR: 9.3±4.8 vWF: AF: 164.04±43.8 *vs.* SR: 93.44±33.04 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: 2.85±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: 542.02±147.4 AT-III: AF: 58.4±32.75 *vs.* SR: 14.85±4.8 tPA: AF: 1.94±0.34 *vs.* SR: 2.34±0.14 PAI: AF: 43.77±8.62 *vs.* SR: 31.37±9.3
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: 10.25±1.1 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]	D-dimer, Fibrinogen, vWF and sTM	D-dimer: AF: 54±26 *vs.* SR: 32±20 Fibrinogen: AF: 4.2±0.6 *vs.* SR: 3.1±0.6 vWF: AF: 149±24 *vs.* SR: 103±30 sTM: AF: 27±10 *vs.* SR: 40±12
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±79.46 *vs.* SR: 10.35±2.9 tPA: AF: 2.31±0.9 *vs.* SR: 2.88±1.58 PAI: AF: 42.78±22.85 *vs.* SR: 8.8±5.04 Plasmin-antiplasmin: AF: 275.31±151.69 *vs.* SR: 232.5±65.7
Tsai [50]	PF1-2 and Fibrinopeptide-A	PF1-2: AF: 4.74±0.49 *vs.* SR: 2.99±0.24 Fibrinopeptide-A: AF: 6±1.3 *vs.* SR: 1.4±0.3

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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: 141.7±208.6 *vs.* SR: 67.2±31.6 Fibrinogen: AF: 2.62±0.65 *vs.* SR: 2.25±0.37 TAT: AF: 6.68±5.11 *vs.* SR: 3.11±1.86
Lip (PAF) [64]	D-dimer and Fibrinogen	D-dimer: AF: 96.75±21.75 *vs.* SR: 77.5±8.33 Fibrinogen: AF: 3.15±0.24 *vs.* SR: 2.6±0.19
Lip (chronic) [64]	D-dimer and Fibrinogen	D-dimer: AF: 149.5±37.5 *vs.* SR: 77.5±8.33 Fibrinogen: AF: 3.82±0.28 *vs.* SR: 2.6±0.19
Lip [65]	D-dimer	D-dimer: AF: 241.25±56.75 *vs.* SR: 103±22
Mitusch [66]	D-dimer, Fibrinogen, PF1-2, TAT, tPA and PAI	D-dimer: AF: 788±76 *vs.* SR: 405±46 Fibrinogen: AF: 4.5±0.2 *vs.* SR: 3.1±0.3 PF1-2: 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±0.5 *vs.* SR: 7.2±0.5 PAI: 57.9±4.3 *vs.* SR: 47.7±4.9
Nagao [67]	D-dimer and TAT	D-dimer: AF: 366.3±211.3 *vs.* SR: 147.2±60.9 TAT: AF: 13.81±14.51 *vs.* SR: 3.47±2.52
Lip [68]	D-dimer, Fibrinogen and vWF	D-dimer: AF: 105.25±23.8 *vs.* SR: 77±8.3 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	D-dimer: AF: 78.6±48.2 *vs.* SR: 67.2±31.7 Fibrinogen: AF: 2.4±0.31 *vs.* SR: 2.25±0.3 TAT: AF: 4.7±3.2 *vs.* SR: 3.1±1.9
Kumagai [70]	D-dimer	D-dimer: AF: 150±19 *vs.* SR: 61±3
Gustafsson (with stroke) [71]	D-dimer, Fibrinogen, Fibrinopeptide-A and vWF	D-dimer: AF: 279.4±78.12 *vs.* SR: 169.12±34.3 Fibrinogen: AF: 4.4±0.2 *vs.* SR: 3.82±0.22 Fibrinopeptide-A: AF: 5.75±1.25 *vs.* SR: 4.25±0.7 vWF: AF: 17.75±2.25 *vs.* SR: 14.75±1.27
Gustafsson (without stroke) [71]	D-dimer, Fibrinogen, Fibrinopeptide-A and vWF	D-dimer: AF: 258.25±67 *vs.* SR: 169.12±34.3 Fibrinogen: AF: 4.5±0.35 *vs.* SR: 3.82±0.22 Fibrinopeptide-A: AF: 4.67±0.5 *vs.* SR: 4.25±0.7 vWF: AF: 17.87±2.62 *vs.* SR: 14.75±1.27
Occurrence of stroke in AF patients		
Skov [72]	D-dimer and Fibrinogen	D-dimer: Stroke: 240±135 *vs.* without stroke: 250±63 Fibrinogen: Stroke: 3.63±0.34 *vs.* without stroke: 3.77±0.36
Zabczyk [73]	D-dimer, Fibrinogen, PAI and sTM	D-dimer: Stroke: 306±164.4 *vs.* without stroke: 234±106.5 Fibrinogen: Stroke: 3.24±0.27 *vs.* without stroke: 3.32±0.22 PAI: Stroke: 28.35±7.33 *vs.* without stroke: 20.3±6.1 sTM: Stroke: 7.37±0.87 *vs.* without stroke: 3.27±0.32
Cecchi [36]	Fibrinogen	Fibrinogen: Stroke: 3.68±1.04 *vs.* without stroke: 4.36±1.22
Loffredo [74]	Fibrinogen	Fibrinogen: Stroke: 3.63±1.06 *vs.* without stroke: 3.14±0.78
Topcuoglu [53]	PF1-2, TAT, tPA and PAI	PF1-2: Stroke: 2.68±2.84 *vs.* without stroke: 2.29±1.25 TAT: Stroke: 43.88±44.45 *vs.* without stroke: 10.07±6.04 tPA: Stroke: 25.42±27.23 *vs.* without stroke: 23.93±10.17 PAI: Stroke: 53.39±32.91 *vs.* without stroke: 37.05±22.32
Soncini [75]	PF1-2 and TAT	PF1-2: Stroke: 2.65±0.53 *vs.* without stroke: 1.41±0.17 TAT: Stroke: 26.05±9.22 *vs.* without stroke: 11.18±4.5

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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: 291.5±156.3 *vs.* without stroke: 275.5±134 Fibrinogen: Stroke: 4.4±0.2 *vs.* without stroke: 4.5±0.35 AT-III: Stroke: 0.92±0.04 *vs.* without stroke: 0.91±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
Occurrence of Thromboembolism events in AF patients		
Zabczyk [73]	D-dimer, Fibrinogen and sTM	D-dimer: TE: 311±134 *vs.* without TE: 234±105.5 Fibrinogen: TE: 3.4±0.15 *vs.* without TE: 3.35±0.25 sTM: TE: 6.05±1.25 *vs.* without TE: 3.20±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
Pongratz [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±1.32 *vs.* without TE: 4.56±1.64
Kumagi [70]	D-dimer	D-dimer: TE: 196±73 *vs.* without TE: 140±19

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 (I^2=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 (I^2=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 (I^2=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 (I^2=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 (I^2=99.6%; heterogeneity p<0.001).

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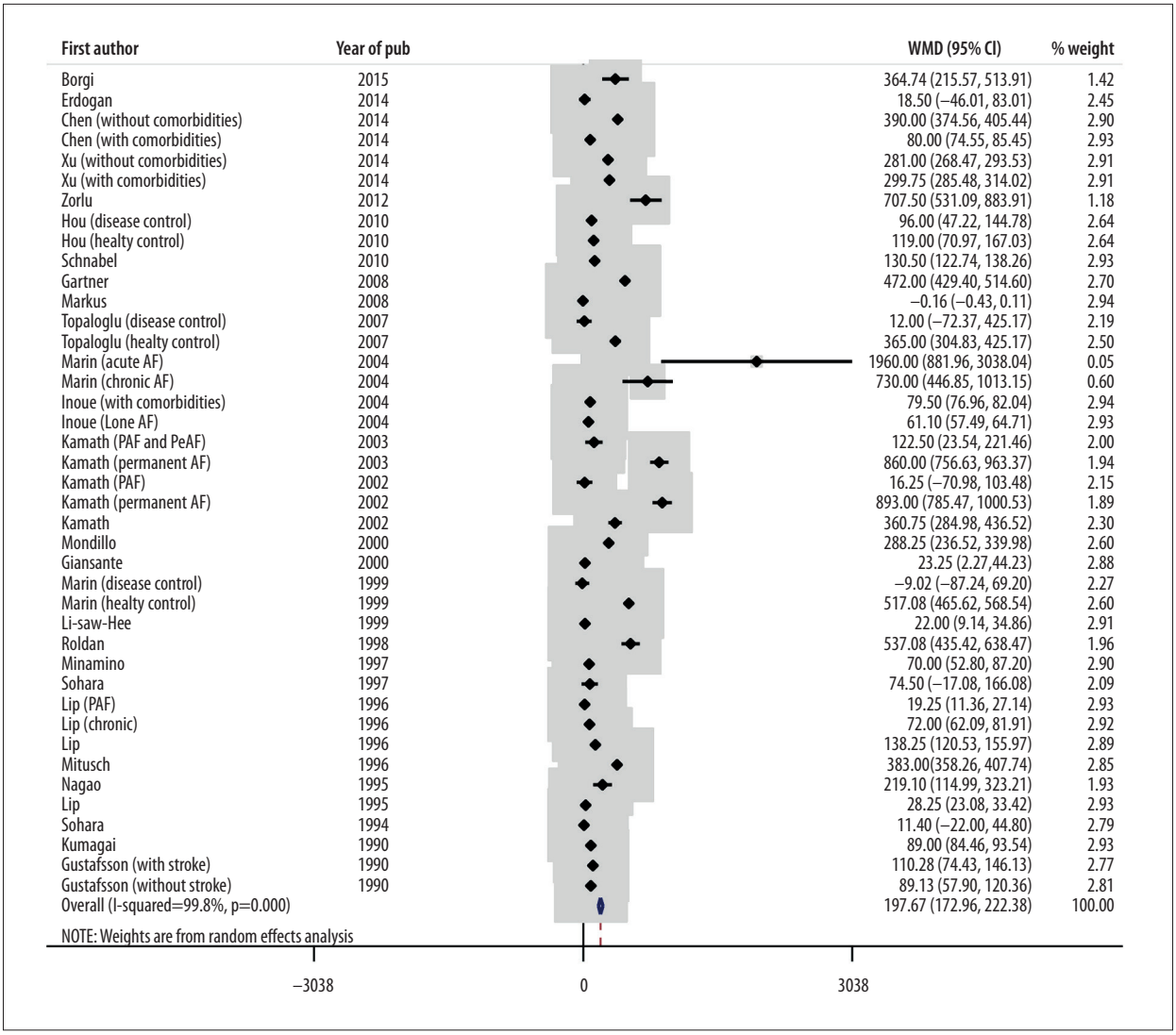

Figure 1. Forest plot of weighted mean difference (WMD) for association between level of D-dimer and occurrence of AF.

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 2607 cases were allocated to the AF group and 15450 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 (I^2=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 (I^2=91.2%; heterogeneity p<0.001).

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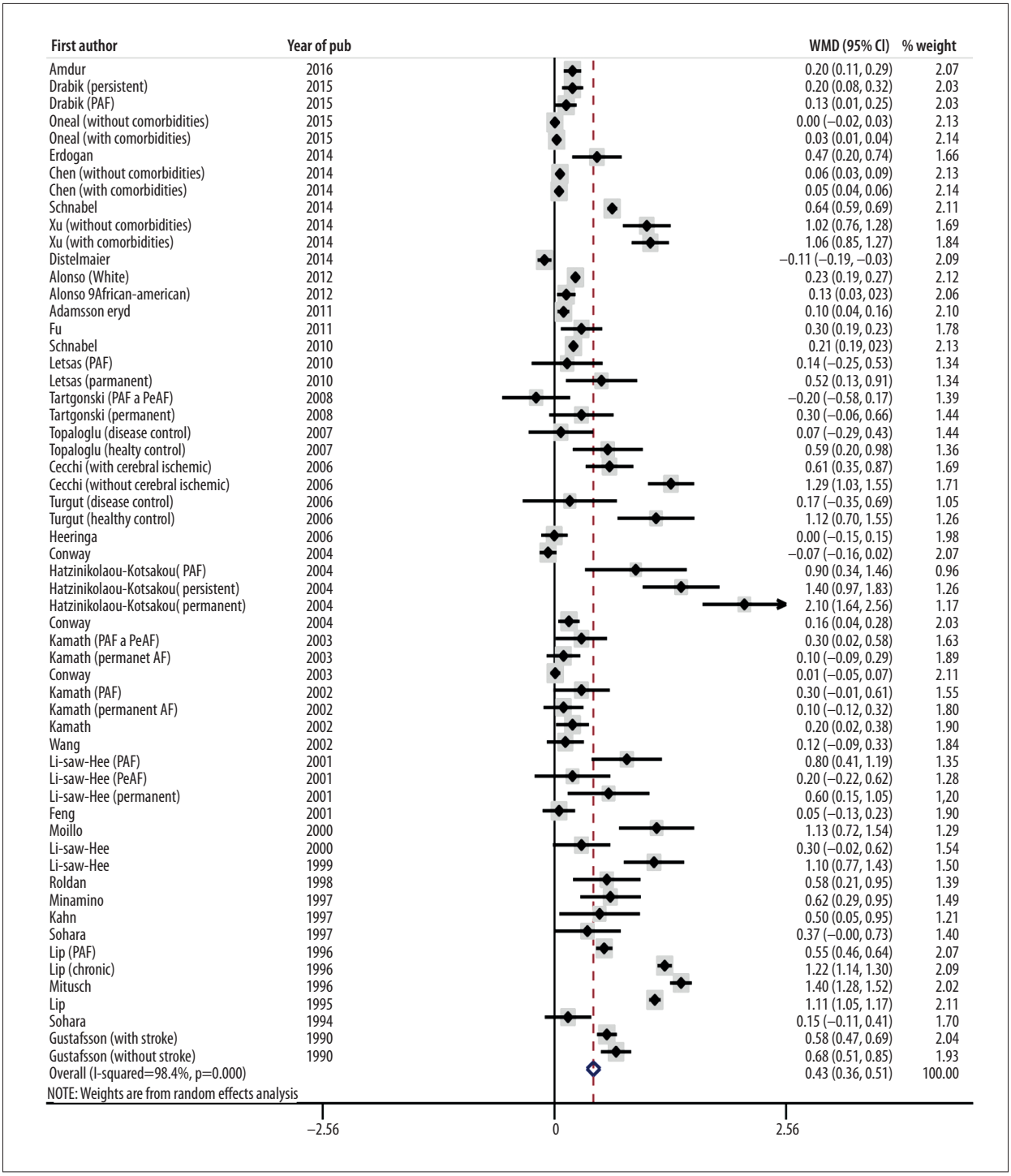

Figure 2. Forest plot of weighted mean difference (WMD) for association between level of fibrinogen and occurrence of AF.

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

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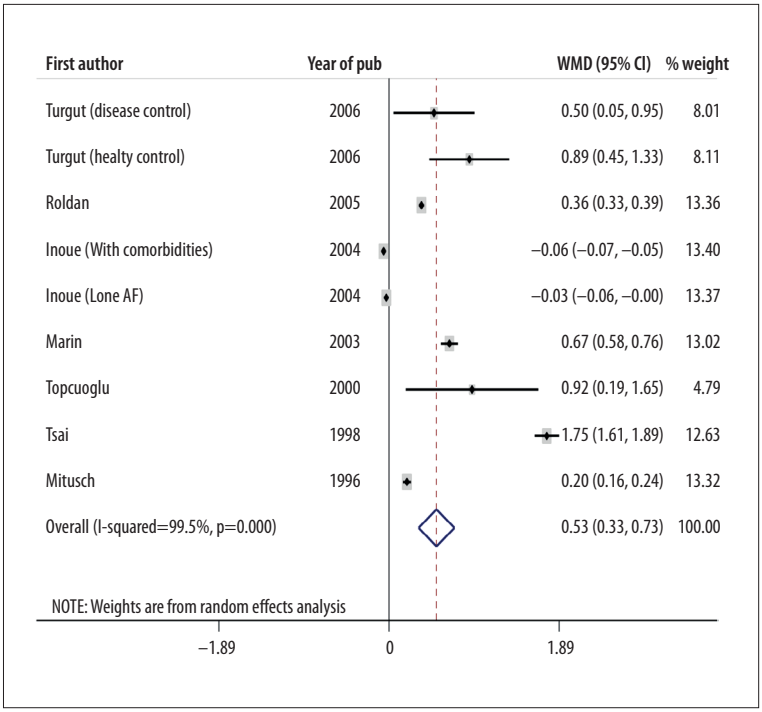

Figure 3. Forest plot of weighted mean difference (WMD) for association between level of PF1-2 and occurrence of AF.

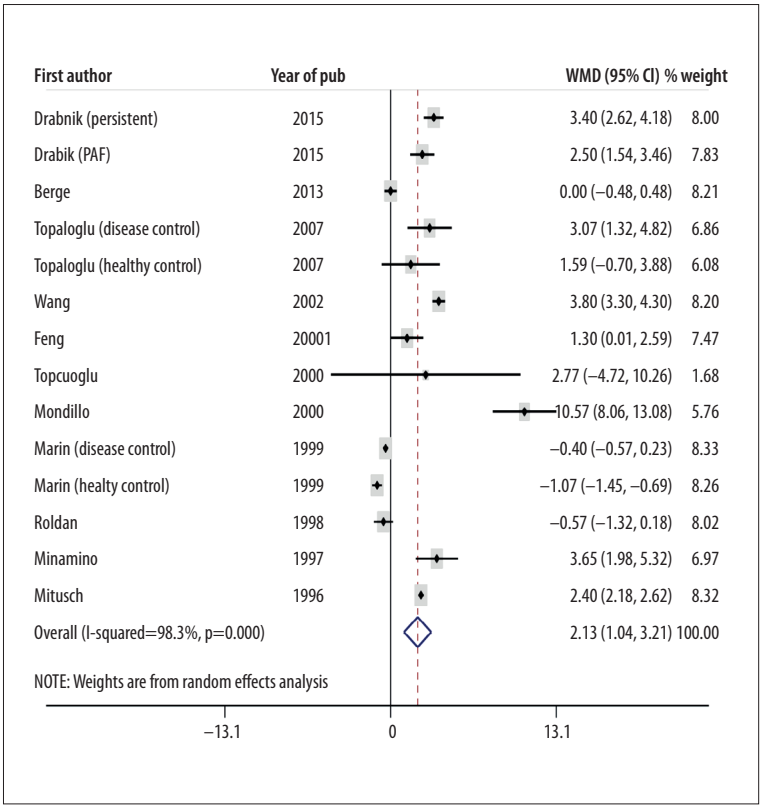

Figure 4. Forest plot of weighted mean difference (WMD) for association between level of t-PA and occurrence of AF.

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

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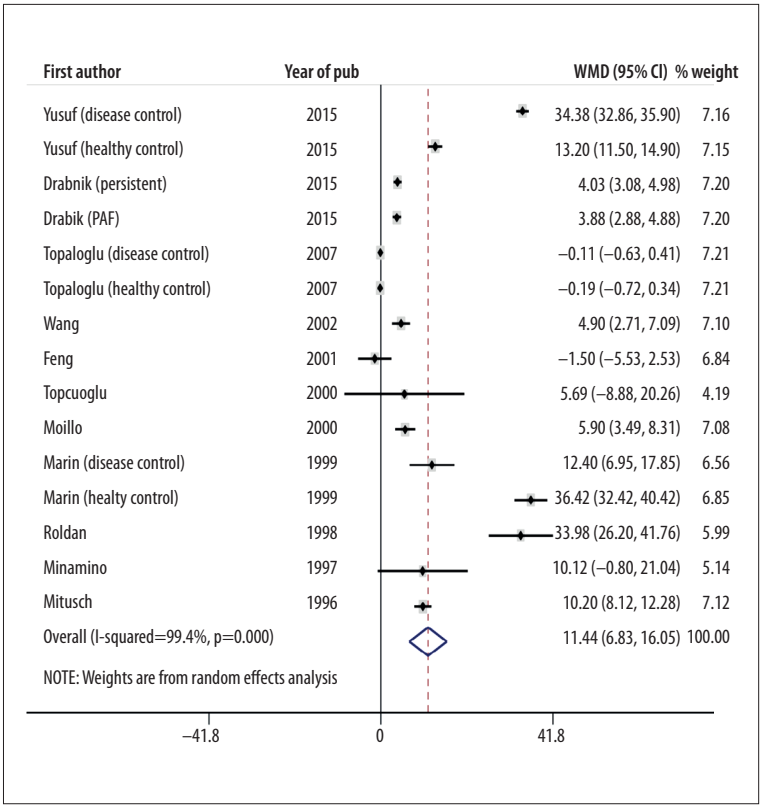

Figure 5. Forest plot of weighted mean difference (WMD) for association between level of PAI and occurrence of AF.

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 I^2=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 I^2=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 I^2=0%; P-heterogeneity=0.36, Supplementary Figure 10) were significantly higher in patients with stoke 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: –32.80 to 48.96; p=0.69 and I^2=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 I^2=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 I^2=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

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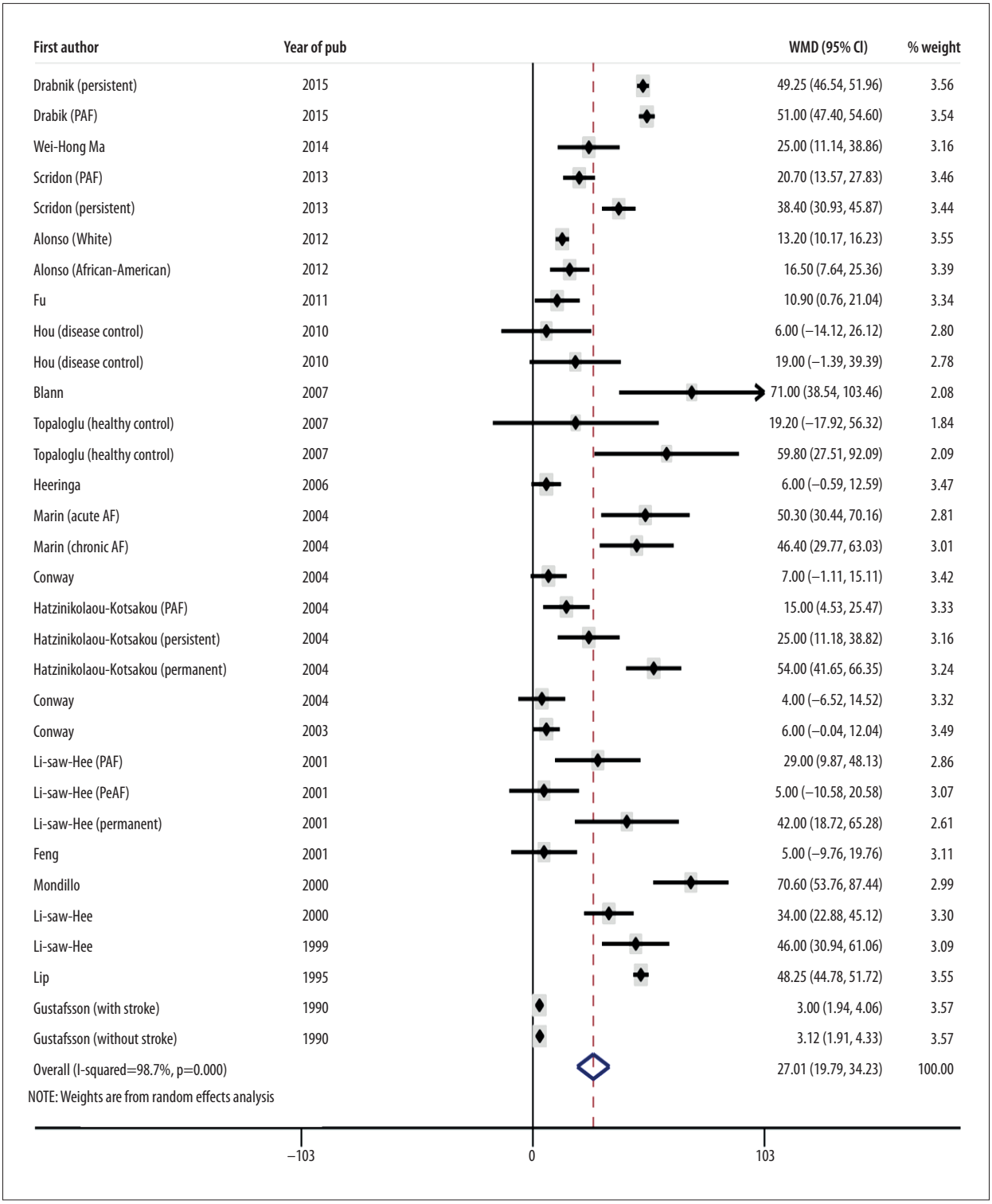

Figure 6. Forest plot of weighted mean difference (WMD) for association between level of vWF and occurrence of AF.

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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
Soncini [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

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]. Increased

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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 alfa-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.

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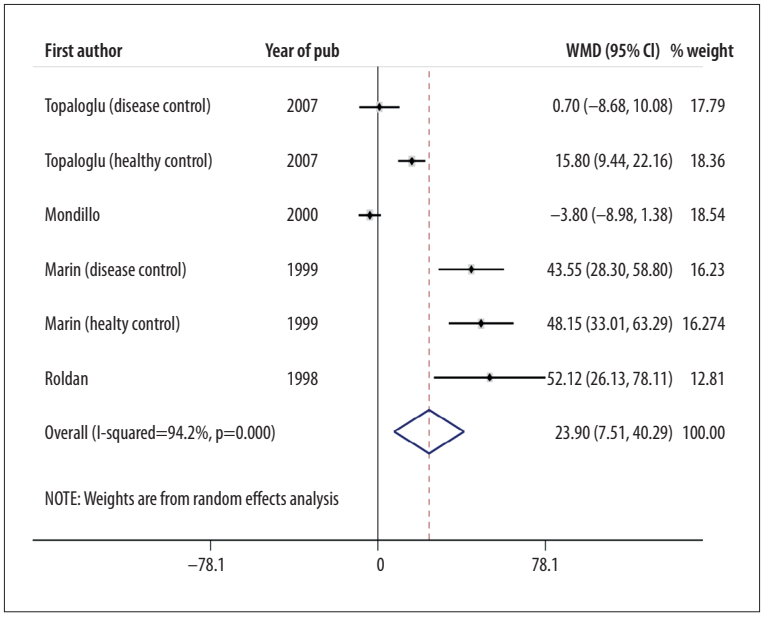
Finally, emphasizing the association of coagulation, fibrinolytic, and endothelial markers with the incidence of AF and its clinical outcomes, and defining the factors of heterogeneity using subgroup analysis and meta-regression, we believe that in meta-analysis of the relationship of the levels of biomarkers 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.

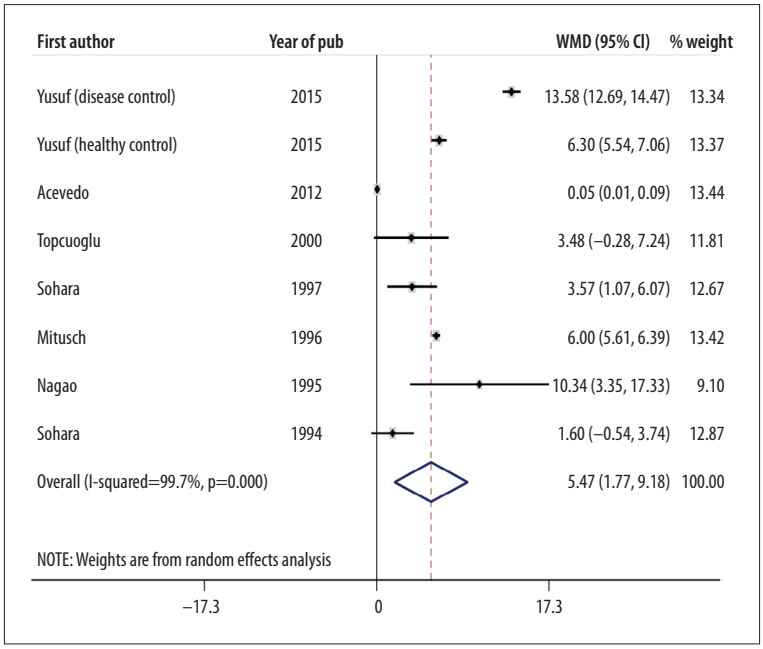
Declaration of interest

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.



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

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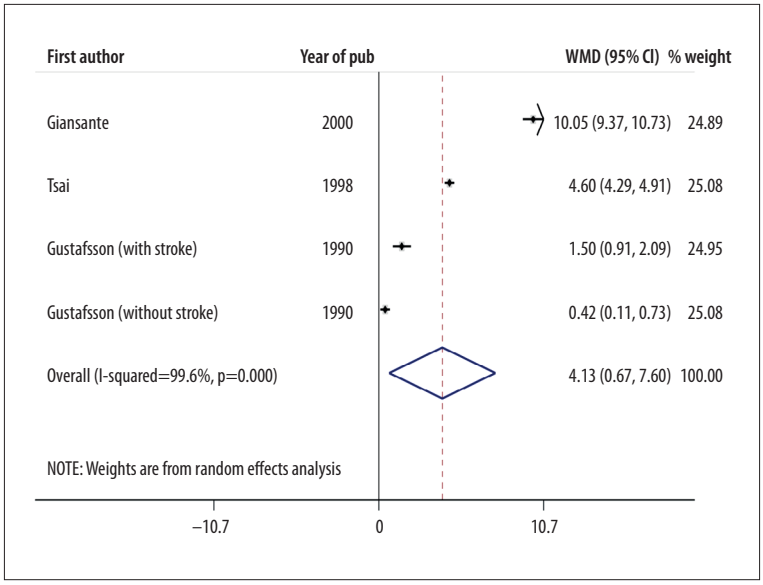
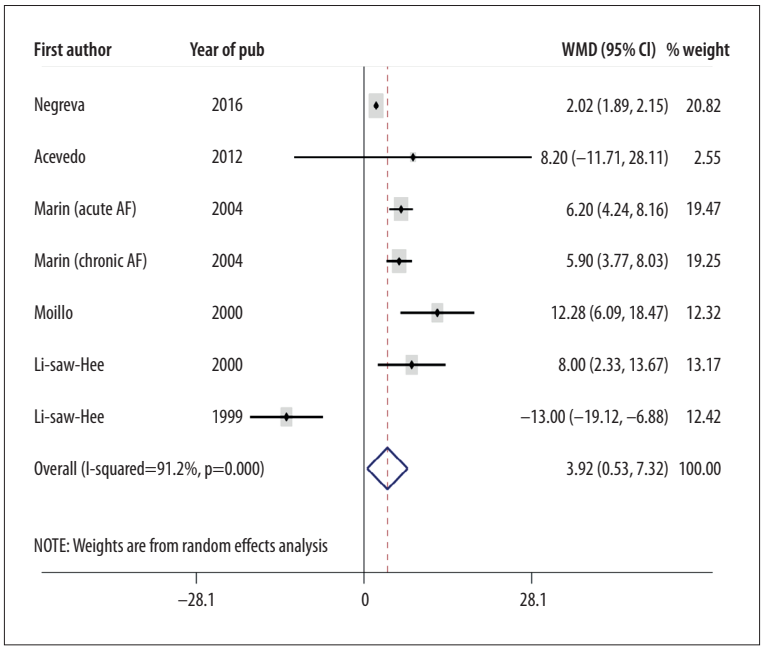


Supplementary Figure 3. Forest plot of weighted mean difference (WMD) for association between level of fibrinopeptide and occurrence of AF.



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

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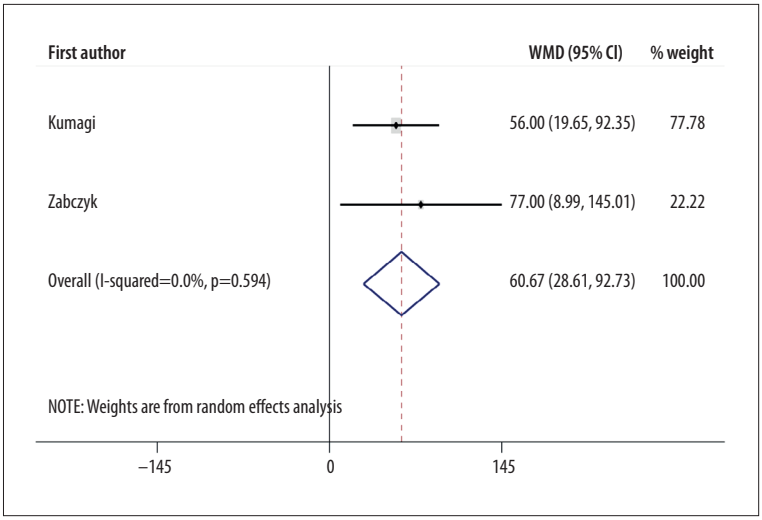
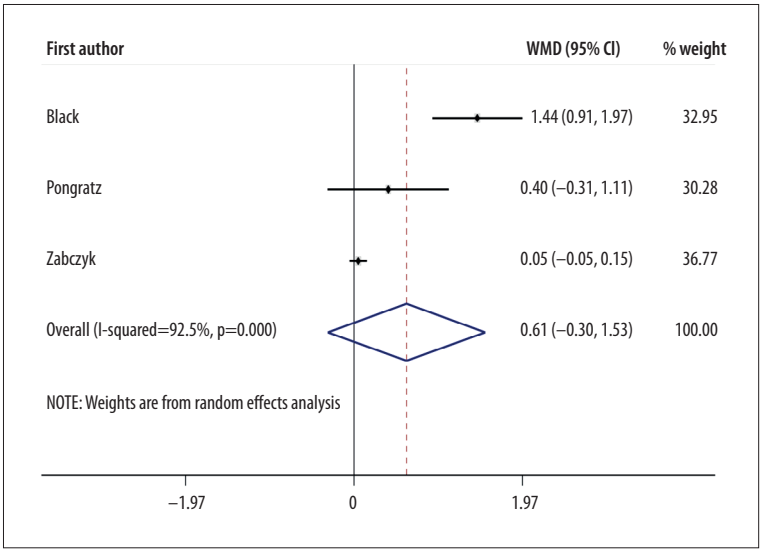
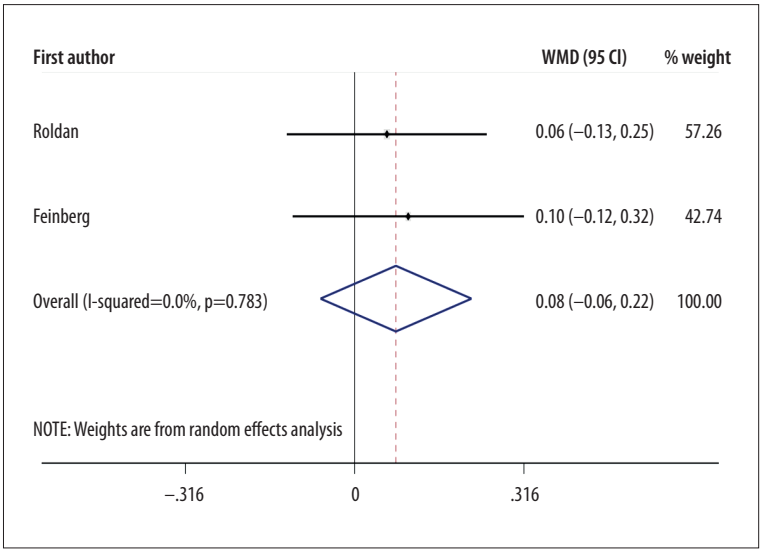


Supplementary Figure 5. Forest plot of weighted mean difference (WMD) for association between level of D-dimer and occurrence of thromboembolism.



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.

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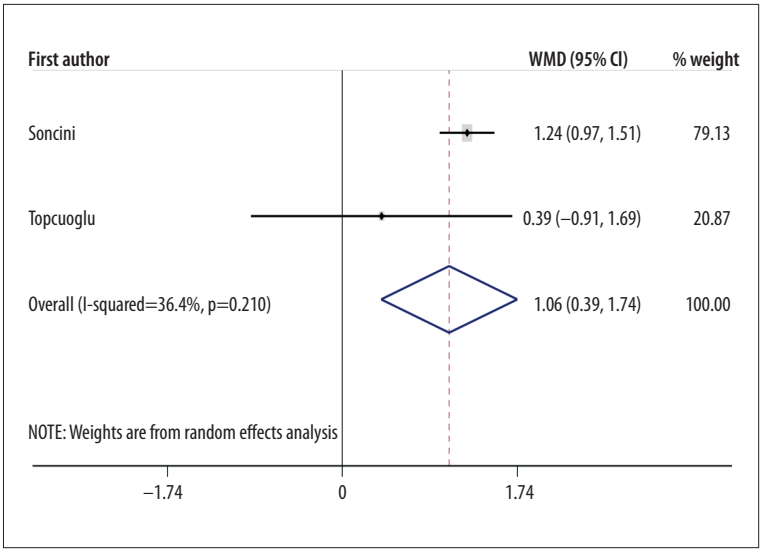
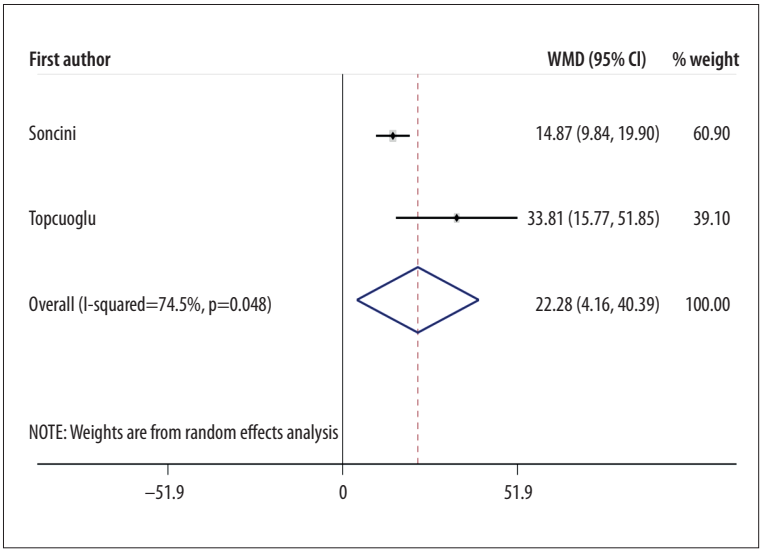
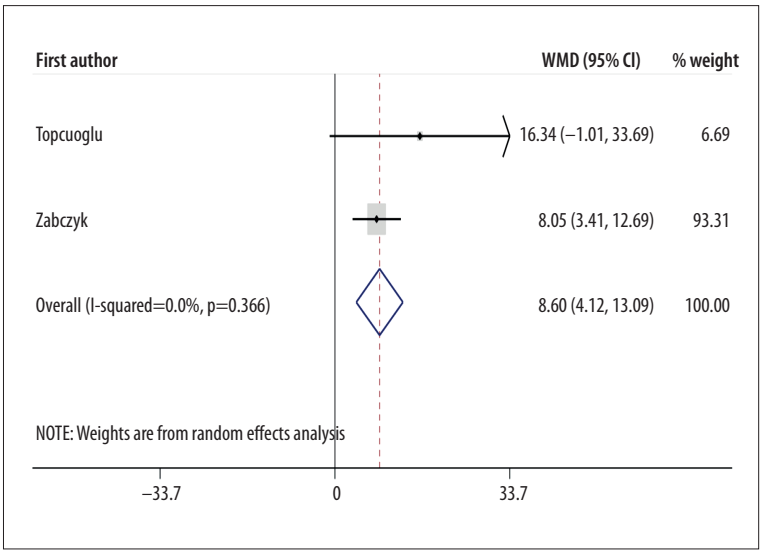


Supplementary Figure 8. Forest plot of weighted mean difference (WMD) for association between level of PF1-2 and occurrence of stroke.



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.

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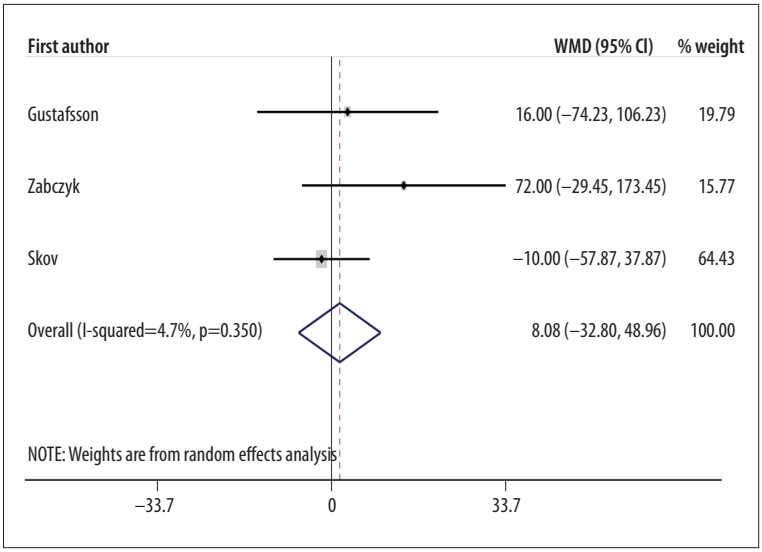
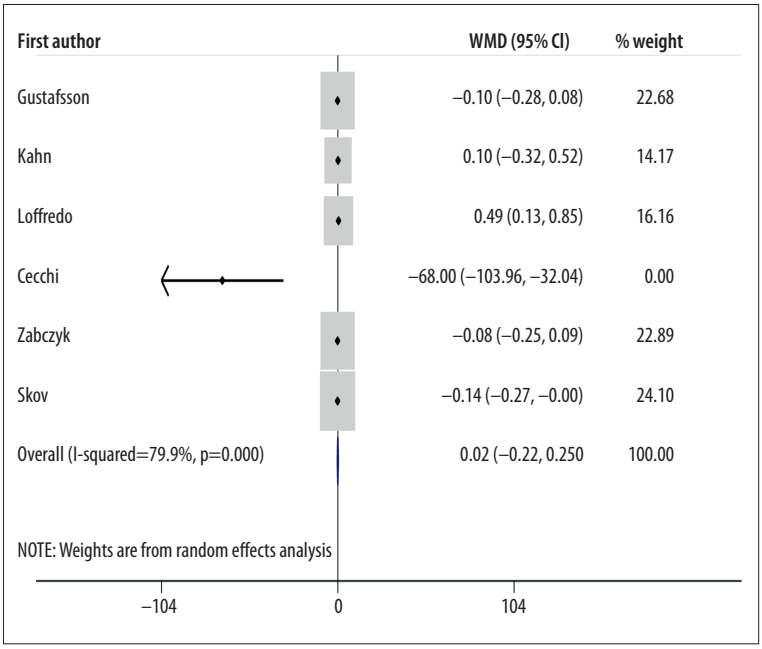


Supplementary Figure 11. Forest plot of weighted mean difference (WMD) for association between level of D-dimer and occurrence of stroke.



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

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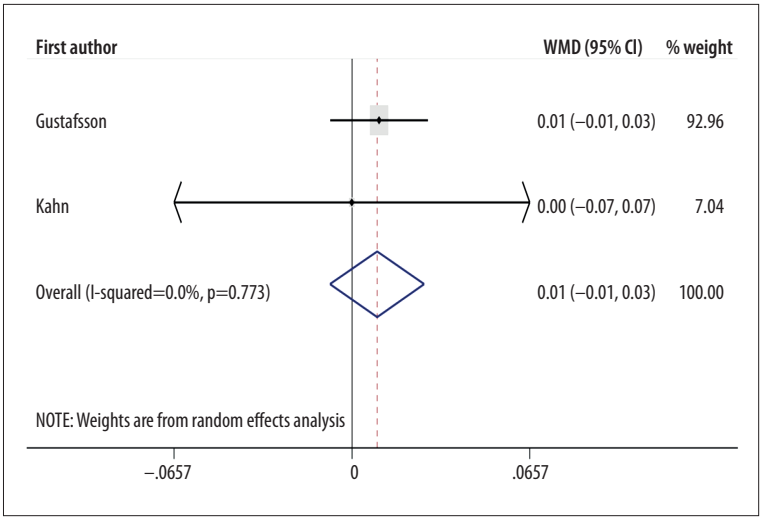
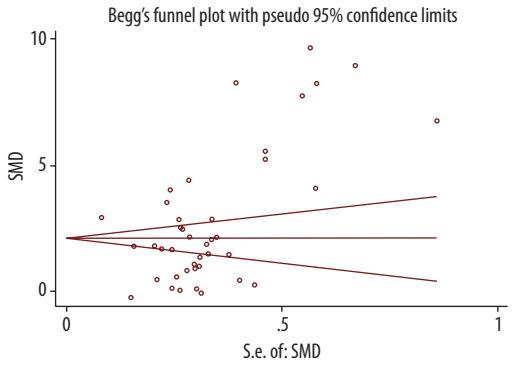


Supplementary Figure 13. Forest plot of weighted mean difference (WMD) for association between level of AT-III and occurrence of stroke.



Begg's Test
adj. Kendall's Score (P-Q)=234
Std. Dev. of Score=89.03
Number of Studies= 41
z=2.63
Pr>|z|=0.009
z=2.62 (continuity corrected)
Pr>|z|=0.009 (continuity corrected)

Egger's Test

Sta_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	1.425284	.5802146	2.46	0.019	.2516896	2.598879
bias	3.093823	2.300181	1.35	0.186	−1.558731	7.746378

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

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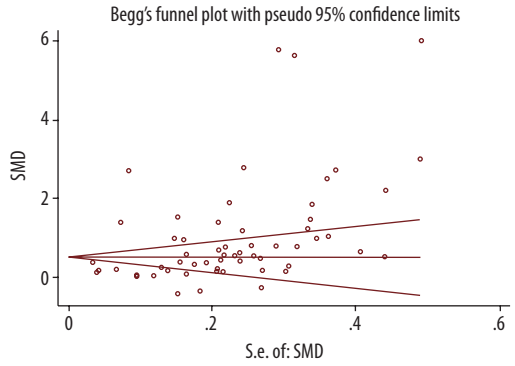
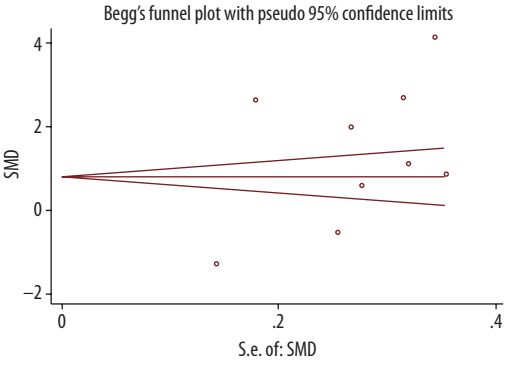


Begg's Test
adj. Kendall's Score (P-Q)=639
Std. Dev. of Score=149.08
Number of Studies= 58
z=4.29
Pr>|z|=0.000
z=4.28 (continuity corrected)
Pr>|z|=0.000 (continuity corrected)

Egger's Test

Sta_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.1869793	.1454879	1.29	0.204	−.104468	.4784267
bias	3.1442279	1.18126	2.91	0.005	1.075932	5.808627

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

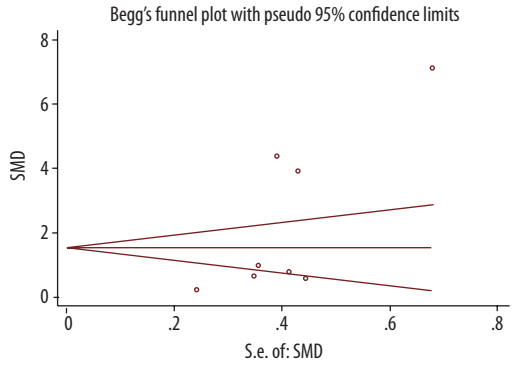


Begg's Test
adj. Kendall's Score (P-Q)=8
Std. Dev. of Score=9.59
Number of Studies= 9
z=0.83
Pr>|z|=0.404
z=0.73 (continuity corrected)
Pr>|z|=0.466 (continuity corrected)

Egger's Test

Sta_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	−2.018251	1.808457	−1.12	0.301	−6.294573	2.258071
bias	12.48991	7.593337	1.64	0.144	−5.465484	30.44529

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



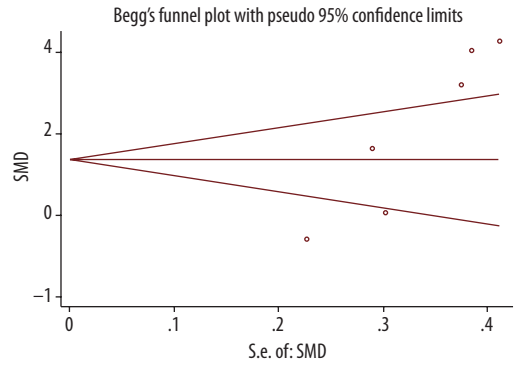
Begg's Test
adj. Kendall's Score (P-Q)=14
Std. Dev. of Score=8.08
Number of Studies= 8
z=1.73
Pr>|z|=0.083
z=1.61 (continuity corrected)
Pr>|z|=0.108 (continuity corrected)

Egger's Test

Sta_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	−3.289155	1.993073	−1.65	0.150	−8.166029	1.587719
bias	13.56598	5.394761	2.51	0.046	.3654726	26.76648

Supplementary Figure 17. Funnel plot for publication bias of studies investigating of TAT.

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

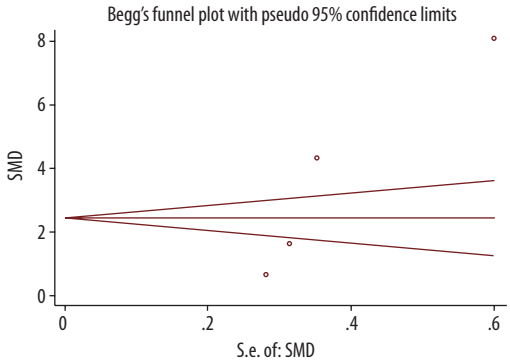


Begg's Test
adj. Kendall's Score (P-Q)=13
Std. Dev. of Score=5.32
Number of Studies= 6
z=2.44
Pr>|z|=0.015
z=2.25 (continuity corrected)
Pr>|z|=0.024 (continuity corrected)

Egger's Test

Sta_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	−3.396062	.7329126	−4.63	0.010	−5.430953	−1.36117
bias	13.40021	2.357966	5.68	0.005	6.853449	19.94697

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

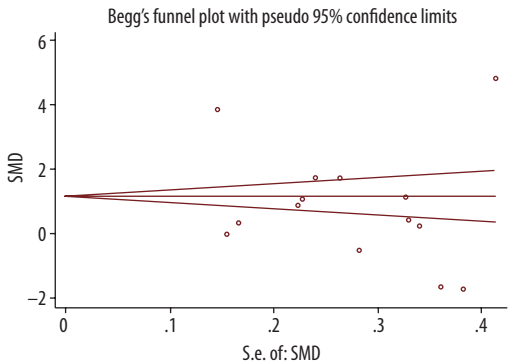


Begg's Test
adj. Kendall's Score (P-Q)=6
Std. Dev. of Score=2.94
Number of Studies= 4
z=2.04
Pr>|z|=0.042
z=1.70 (continuity corrected)
Pr>|z|=0.089 (continuity corrected)

Egger's Test

Sta_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	−5.672821	2.292648	−2.47	0.132	−15.53729	4.191648
bias	24.25936	6.653938	3.65	0.068	−4.370229	52.88894

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



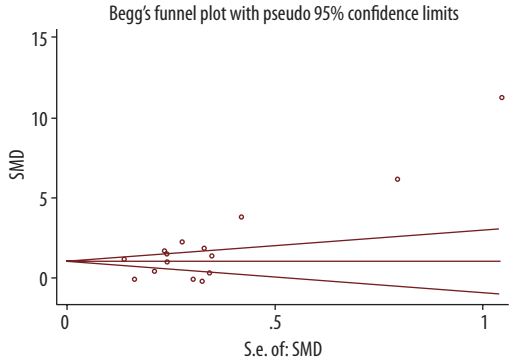
Begg's Test
adj. Kendall's Score (P-Q)=−9
Std. Dev. of Score=18.27
Number of Studies= 14
z=−0.49
Pr>|z|=0.622
z=0.44 (continuity corrected)
Pr>|z|=0.661 (continuity corrected)

Egger's Test

Sta_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	2.475661	1.365655	1.81	0.095	−.4998466	5.451168
bias	−5.899424	5.848912	−1.01	0.333	−18.64311	6.844261

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

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

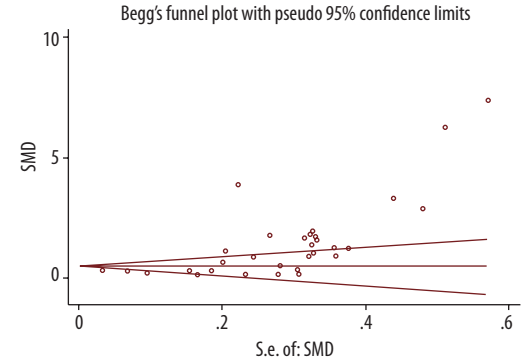


Begg's Test
adj. Kendall's Score (P-Q)=39
Std. Dev. of Score=20.21
Number of Studies= 15
z=1.93
Pr>|z|=0.054
z=1.88 (continuity corrected)
Pr>|z|=0.060 (continuity corrected)

Egger's Test

Sta_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	−.6120676	.6398518	−0.96	0.356	−1.994383	.7702482
bias	7.020544	2.508599	2.80	0.015	1.601045	12.44004

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

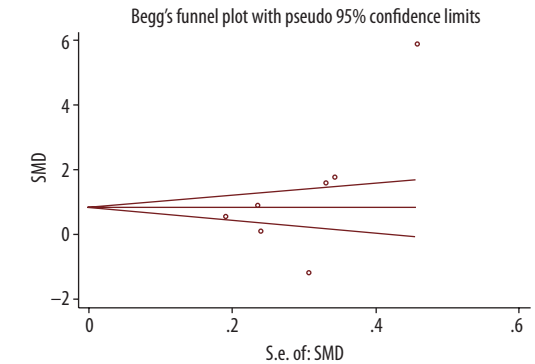


Begg's Test
adj. Kendall's Score (P-Q)=278
Std. Dev. of Score=61.67
Number of Studies= 32
z=4.51
Pr>|z|=0.000
z=4.49 (continuity corrected)
Pr>|z|=0.000 (continuity corrected)

Egger's Test

Sta_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.0402143	.1335247	0.30	0.765	−.2324794	.3129081
bias	4.428415	.9755097	4.54	0.000	2.436158	6.420672

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



Begg's Test
adj. Kendall's Score (P-Q)=11
Std. Dev. of Score=6.66
Number of Studies= 7
z=1.65
Pr>|z|=0.099
z=1.50 (continuity corrected)
Pr>|z|=0.133 (continuity corrected)

Egger's Test

Sta_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	−2.480094	1.95621	−1.27	0.261	−7.508691	2.548503
bias	12.52003	7.20912	1.74	0.143	−6.011597	31.05167

Supplementary Figure 23. Funnel plot for publication bias of studies investigating sTM.

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

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
Oneal (with comorbidities) [14]	North America	647	69.5	54	32.5	70	ND	ND	ND	29.5	ND	4	No detection	15
Oneal (with comorbidities) [14]	North America	883	64.5	32.5	29.5	54.5	ND	ND	ND	30	ND	4	No detection	14

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

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	58	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		5	No detection	48
Fu [27]	Asian	169	54.45	63.5	ND	ND	ND	ND	ND	12.9	6.1	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 (PAF) [30]	European	93	64.4	59	6	60.5	ND	ND	43	15.5	34	5	acute	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	96.65	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

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

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	82	64.5	62.75	ND	27	ND	16.5	19	ND	18.5	3	No detection	12.6
Topaloglu (disease control) [35]	European	46	34.5	ND	0	0	ND	ND	ND	ND	ND	5	No detection	ND
Topaloglu (healthy control) [35]	European	38	36	ND	0	0	ND	ND	ND	ND	ND	5	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	4	No detection	ND
Turgut (healthy control) [37]	European	46	66.56	43.95	3.85	36.55	ND	ND	ND	ND	ND	4	No detection	ND
Heeringa [38]	European	486	77.5	51	17.5	25	22.5	31.65	ND	ND	16.55	5	No detection	20.9
Roldan [39]	European	265	ND	ND	ND	ND	ND	ND	ND	ND	ND	4	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	ND	4.15	4	Chronic	ND
Inoue (with comorbidities) [41]	Asian	251	ND	ND	ND	ND	ND	ND	ND	ND	ND	5	No detection	ND
Inoue (Lone AF) [41]	Asian	106	ND	ND	ND	ND	ND	ND	ND	ND	ND	5	No detection	ND
Conway [42]	European	147	68	62	7.5	26.5	13.5	ND	ND	ND	ND	3	chronic	16
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	4	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

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

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	14.5	5	Chronic	ND
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
Mitusch [66]	European	97	71	51.35	25	67	ND	ND	ND	ND	ND	1	No detection	ND
Nagao [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

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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	
2	–	–	–	
3	2	154 (–110.2 to418.4)	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	

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

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)	98.9% 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 0.103)	96.5% and 0.001	

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

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		All of them are case–control		
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%	–	–	–	–
≤20%	1	0.67 (0.57 to 0.76)	–	
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%				

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

Subgroup	Studies (N)	WMD (95% CI)	I-squared and P-value respectively	P-value of meta-regression
		Thrombin anti thrombin		
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 0.191	
Hypertension				
>70%	–	–	–	–
≤70%	2	5.46 (3.43 to 7.48)	41.4% and 0.191	
History of myocardial infarction				
>20%		No Data		
≤20%				
Anti-coagulant status codes				
1				
2				
3		All of them are Code–1		
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%				

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

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		All of them are case–control		
Case-control				
Number of population				
>300		All of studies have less than 300 cases		
≤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				
>20%		No data		
≤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	–	19.6 (12.5 to 26.8)	–	–
Persistent	–	–	–	
Permanent	1	–3.80 (–8.98 to 1.38)	–	
Cigarette smoking				
>30%		No sufficient data		
≤30%				

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

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 o 4.91)	–	
European	3	3.98 (–1.33 to 9.30)	99.7% and 0.001	
Africa	–	–	–	–
North American	–	–	–	
South American	–	–	–	
Australia	–	–	–	
Design of study				
Cohort		All of studies are case–control		
Case-control				
Number of population				
>300		All of studies have less than 300 cases		
≤300				
Mean Age				
>60 years		All of studies have total age higher than 60 years		
≤60 years				
Male				
>70%	1	4.60 (4.28 o 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%		No data		
≤20%				
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)	–	

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

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	

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

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	–	–	–	
3	1	4.20 (1.09 to 7.31)	–	0.014
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	

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

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	

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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 myocardial infarction				
>20%	–	–	–	–
≤20%	3	6.18 (4.78 to 7.58)	0.0% and 0.794	
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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References:

1. Macle L, Cairns J, Leblanc K et al: 2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. Can J Cardiol, 2016; 32(10): 1170–85
2. Fuster V, Rydén LE, Cannom DS et al: 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol, 2011; 57: e101–98
3. Albertsen IE, Rasmussen LH, Overvad TF et al: Risk of stroke or systemic embolism in atrial fibrillation patients treated with warfarin: A systematic review and meta-analysis. Stroke, 2013; 44: 1329–36
4. Ali-Hassan-Sayegh S, Mirhosseini SJ, Rezaeisadrabadi M et al: Antioxidant supplementations for prevention of atrial fibrillation after cardiac surgery: An updated comprehensive systematic review and meta-analysis of 23 randomized controlled trials. Interact Cardiovasc Thorac Surg, 2014; 18: 646–54
5. Kornej J, Apostolakis S, Bollmann A, Lip GY: The emerging role of biomarkers in atrial fibrillation. Can J Cardiol, 2013; 29: 1181–93
6. Brotman DJ, Deitcher SR, Lip GY, Matzdorff AC: Virchow's triad revisited. South Med J, 2004; 97: 213–14
7. Hozo SP, Djulbegovic B, Hozo I: Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol, 2005; 5: 13
8. Wells GA SB, O'Connell D, Peterson J et al: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. 2011. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
9. Negreva M, Georgiev S, Vitlianova K: Decreased activity of the protein C anticoagulant pathway in the early hours of paroxysmal atrial fibrillation. Clin Appl Thromb Hemost, 2016 [Epub ahead of print]
10. Amdur RL, Mukherjee M, Go A et al: Interleukin-6 is a risk factor for atrial fibrillation in chronic kidney disease: Findings from the CRIC study. PLoS One, 2016; 11(2): e0148189
11. Yusuf J, Goyal M, Mukhopadhyay S et al: Effect of heart rate control on coagulation status in patients of rheumatic mitral stenosis with atrial fibrillation – A pilot study. Indian Heart J, 2015; 67(Suppl. 2): S40–45
12. Drabik L, Wołkow P, Undas A: Denser plasma clot formation and impaired fibrinolysis in paroxysmal and persistent atrial fibrillation while on sinus rhythm: Association with thrombin generation, endothelial injury and platelet activation. Thromb Res, 2015; 136: 408–14
13. El Borgi W, Romdhane S, Sdiri W et al: [Measurement of d-dimers in nonvalvular atrial fibrillation. First prospective Tunisian study]. Ann Cardiol Angeiol (Paris), 2015; 64: 279–84 [in French]
14. O'Neal WT, Soliman EZ, Howard G et al: Inflammation and hemostasis in atrial fibrillation and coronary heart disease: The REasons for Geographic and Racial Differences in Stroke study. Atherosclerosis, 2015; 243: 192–9.
15. Erdogan D, Uysal BA, Aksoy F et al: Strict heart rate control attenuates prothrombotic state and platelet activity in patients with non-valvular permanent atrial fibrillation. Clin Hemorheol Microcirc, 2014; 56: 219–29
16. Chen Q, Yan Y, Zhang L et al: Effect of hyperthyroidism on the hypercoagulable state and thromboembolic events in patients with atrial fibrillation. Cardiology, 2014; 127: 176–82
17. Schnabel RB, Wild PS, Wilde S et al: Multiple biomarkers and atrial fibrillation in the general population. PLoS One 2014; 9: e112486
18. Ma WH, Sheng L, Gong HP et al: The application of vWF/ADAMTS13 in essential hypertension. Int J Clin Exp Med, 2014; 7: 5636–42
19. Xu XF, Jiang FL, Ou MJ, Zhang ZH: The association between mean platelet volume and chronic atrial fibrillation and the presence of thrombotic events. Biomed Rep, 2015; 3: 388–94
20. Distelmaier K, Maurer G, Goliasch G: Blood count in new onset atrial fibrillation after acute myocardial infarction – a hypothesis generating study. Indian J Med Res, 2014; 139: 579–84
21. Scridon A, Girerd N, Rugeri L et al: Progressive endothelial damage revealed by multilevel von Willebrand factor plasma concentrations in atrial fibrillation patients. Europace, 2013; 15: 1562–66
22. Berge T, Ulimoen SR, Enger S et al: Impact of atrial fibrillation on inflammatory and fibrinolytic variables in the elderly. Scand J Clin Lab Invest, 2013; 73: 326–33
23. Acevedo M, Corbalan R, Braun S et al: Biochemical predictors of cardiac rhythm at 1 year follow-up in patients with non-valvular atrial fibrillation. J Thromb Thrombolysis, 2012; 128: e113–18
24. Zorlu A, Akkaya E, Altay H et al: The relationship between Ddimer level and the development of atrial fibrillation in patients with systolic heart failure. J Thromb Thrombolysis, 2012; 33: 343–48
25. Alonso A, Tang W, Agarwal SK et al: Hemostatic markers are associated with the risk and prognosis of atrial fibrillation: the ARIC study. Int J Cardiol, 2012; 155: 217–22
26. Adamsson Eryd S, Smith JG, Melander O et al: Inflammation-sensitive proteins and risk of atrial fibrillation: A population-based cohort study. Eur J Epidemiol, 2011; 26: 449–55
27. Fu R, Wu S, Wu P, Qiu J: A study of blood soluble P-selectin, fibrinogen, and von Willebrand factor levels in idiopathic and lone atrial fibrillation. Europace, 2011; 13: 31–36
28. Hou J, Liang Y, Gai X et al: The impact of acute atrial fibrillation on the prothrombotic state in patients with essential hypertension. Clin Biochem, 2010; 43: 1212–15
29. Schnabel RB, Larson MG, Yamamoto JF et al: Relations of biomarkers of distinct pathophysiological pathways and atrial fibrillation incidence in the community. Circulation, 2010; 121: 200–7
30. Letsas KP, Weber R, Bürkle G et al: Pre-ablative predictors of atrial fibrillation recurrence following pulmonary vein isolation: The potential role of inflammation. Europace, 2009; 11: 158–63
31. Gartner W, Zierhut B, Mineva I et al: Brain natriuretic peptide correlates with the extent of atrial fibrillation-associated silent brain lesions. Clin Biochem, 2008; 41: 1434–39
32. Targonski R, Salczynska D, Sadowski J, Cichowski L: Relationship between inflammatory markers and clinical patterns of atrial fibrillation in patients with congestive heart failure. Kardiol Pol, 2008; 66: 729–36; discussion 737–39
33. Marcus GM, Whooley MA, Glidden DV et al: Interleukin-6 and atrial fibrillation in patients with coronary artery disease: Data from the Heart and Soul Study. Am Heart J, 2008; 155: 303–9
34. Blann AD, Choudhury A, Freestone B et al: Soluble CD40 ligand and atrial fibrillation: Relationship to platelet activation, and endothelial damage/dysfunction. Int J Cardiol, 2008; 127: 135–37
35. Topaloglu S, Boyaci A, Ayaz S et al: Coagulation, fibrinolytic system activation and endothelial dysfunction in patients with mitral stenosis and sinus rhythm. Angiology, 2007; 58: 85–91
36. Cecchi E, Marcucci R, Poli D et al: Hyperviscosity as a possible risk factor for cerebral ischemic complications in atrial fibrillation patients. Am J Cardiol, 2006; 97: 1745–48
37. Turgut N, Akdemir O, Turgut B et al: Hypercoagulopathy in stroke patients with nonvalvular atrial fibrillation: Hematologic and cardiologic investigations. Clin Appl Thromb Hemost, 2006; 12: 15–20
38. Heeringa J, Conway DS, van der Kuip DA et al: A longitudinal population-based study of prothrombotic factors in elderly subjects with atrial fibrillation: The Rotterdam Study 1990–1999. J Thromb Haemost, 2006; 4: 1944–49
39. Roldan V, Marin F, Martinez JG et al: Relation of interleukin-6 levels and prothrombin fragment 1+2 to a point-based score for stroke risk in atrial fibrillation. Am J Cardiol, 2005; 95: 881–82
40. Marín F, Roldán V, Climent VE et al: Plasma von Willebrand factor, soluble thrombomodulin, and fibrin D-dimer concentrations in acute onset nonrheumatic atrial fibrillation. Heart, 2004; 90: 1162–66
41. Inoue H, Nozawa T, Okumura K et al: Prothrombotic activity is increased in patients with nonvalvular atrial fibrillation and risk factors for embolism. Chest, 2004; 126: 687–92
42. Conway DS, Buggins P, Hughes E, Lip GY: Relationship of interleukin-6 and C-reactive protein to the prothrombotic state in chronic atrial fibrillation. J Am Coll Cardiol, 2004; 43: 2075–82
43. Hatzinikolaou-Kotsakou E, Kartasis Z, Tziakas D et al: Atrial fibrillation and hypercoagulability: Dependent on clinical factors or/and on genetic alterations? J Thromb Thrombolysis, 2003; 16: 155–61

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44. Conway DS, Buggins P, Hughes E, Lip GY: Relation of interleukin-6, C-reactive protein, and the prothrombotic state to transesophageal echocardiographic findings in atrial fibrillation. Am J Cardiol, 2004; 93: 1368–73, A1366
45. Kamath S, Blann AD, Chin BS, Lip GY: Platelet activation, haemorheology and thrombogenesis in acute atrial fibrillation: A comparison with permanent atrial fibrillation. Heart. 2003; 89: 1093–1095.
46. Marin F, Roldan V, Climent V et al: Is thrombogenesis in atrial fibrillation related to matrix metalloproteinase-1 and its inhibitor, TIMP-1? Stroke, 2003; 34: 1181–86
47. Conway DS, Heeringa J, Van Der Kuip DA et al: Atrial fibrillation and the prothrombotic state in the elderly: The Rotterdam Study. Stroke, 2003; 34: 413–17
48. Kamath S, Chin BS, Blann AD, Lip GY: A study of platelet activation in paroxysmal, persistent and permanent atrial fibrillation. Blood Coagul Fibrinolysis, 2002; 13: 627–36
49. Kamath S, Blann AD, Chin BS et al: A study of platelet activation in atrial fibrillation and the effects of antithrombotic therapy. Eur Heart J, 2002; 23: 1788–95
50. Wang TD, Chen WJ, Su SS et al: Increased levels of tissue plasminogen activator antigen and factor VIII activity in nonvalvular atrial fibrillation: Relation to predictors of thromboembolism. J Cardiovasc Electrophysiol, 2001; 12: 877–84
51. Li-Saw-Hee FL, Blann AD, Gurney D, Lip GY: Plasma von Willebrand factor, fibrinogen and soluble Pselectin levels in paroxysmal, persistent and permanent atrial fibrillation. Effects of cardioversion and return of left atrial function. Eur Heart J, 2001; 22: 1741–47
52. Feng D, D'Agostino RB, Silbershatz H et al: Hemostatic state and atrial fibrillation (the Framingham Offspring Study). Am J Cardiol, 2001; 87: 168–71
53. Topcuoglu MA, Haydari D, Ozturk S et al: Plasma levels of coagulation and fibrinolysis markers in acute ischemic stroke patients with lone atrial fibrillation. Neurol Sci, 2000; 21: 235–40
54. Mondillo S, Sabatini L, Agricola E et al: Correlation between left atrial size, prothrombotic state and markers of endothelial dysfunction in patients with lone chronic nonrheumatic atrial fibrillation. Int J Cardiol, 2000; 75: 227–32
55. Giansante C, Fiotti N, Miccio M et al: Coagulation indicators in patients with paroxysmal atrial fibrillation: effects of electric and pharmacologic cardioversion. Am Heart J, 2000; 140: 423–29
56. Li-Saw-Hee FL, Blann AD, Lip GY: A cross-sectional and diurnal study of thrombogenesis among patients with chronic atrial fibrillation. J Am Coll Cardiol, 2000; 35: 1926–31
57. Marín F, Roldán V, Monmeneu JV et al: Prothrombotic state and elevated levels of plasminogen activator inhibitor-1 in mitral stenosis with and without atrial fibrillation. Am J Cardiol, 1999; 84: 862–64, A869
58. Li-Saw-Hee FL, Blann AD, Goldsmith I, Lip GY: Indexes of hypercoagulability measured in peripheral blood reflect levels in intracardiac blood in patients with atrial fibrillation secondary to mitral stenosis. Am J Cardiol, 1999; 83: 1206–9
59. Roldan V, Marin F, Marco P et al: Hypofibrinolysis in atrial fibrillation. Am Heart J, 1998; 136: 956–60
60. Tsai LM, Chen JH, Tsao CJ: Relation of left atrial spontaneous echo contrast with prethrombotic state in atrial fibrillation associated with systemic hypertension, idiopathic dilated cardiomyopathy, or no identifiable cause (lone). Am J Cardiol, 1998; 81: 1249–52
61. Minamino T, Kitakaze M, Sato H et al: Plasma levels of nitrite/nitrate and platelet cGMP levels are decreased in patients with atrial fibrillation. Arterioscler Thromb Vasc Biol, 1997; 17: 3191–95
62. Kahn SR, Solymoss S, Flegel KM: Nonvalvular atrial fibrillation: Evidence for a prothrombotic state. CMAJ, 1997; 157: 673–81
63. Sohara H, Amitani S, Kurose M, Miyahara K: Atrial fibrillation activates platelets and coagulation in a time-dependent manner: A study in patients with paroxysmal atrial fibrillation. J Am Coll Cardiol, 1997; 29: 106–12
64. Lip GY, Lowe GD, Rumley A, Dunn FG: Fibrinogen and fibrin D-dimer levels in paroxysmal atrial fibrillation: evidence for intermediate elevated levels of intravascular thrombogenesis. Am Heart J, 1996; 131: 724–30
65. Lip GY, Lip PL, Zarifis J et al: Fibrin D-dimer and beta-thromboglobulin as markers of thrombogenesis and platelet activation in atrial fibrillation. Effects of introducing ultra-low-dose warfarin and aspirin. Circulation, 1996; 94: 425–31
66. Mitusch R, Siemens HJ, Garbe M et al: Detection of a hypercoagulable state in nonvalvular atrial fibrillation and the effect of anticoagulant therapy. Thromb Haemost, 1996; 75: 219–23
67. Nagao T, Hamamoto M, Kanda A et al: Platelet activation is not involved in acceleration of the coagulation system in acute cardioembolic stroke with nonvalvular atrial fibrillation. Stroke, 1995; 26: 1365–68
68. Lip GY, Lowe GD, Rumley A, Dunn FG: Increased markers of thrombogenesis in chronic atrial fibrillation: effects of warfarin treatment. Br Heart J, 1995; 73: 527–33
69. Sohara H, Miyahara K: Effect of atrial fibrillation on the fibrino-coagulation system – study in patients with paroxysmal atrial fibrillation. Jpn Circ J, 1994; 58: 821–26
70. Kumagai K, Fukunami M, Ohmori M et al: Increased intracardiovascular clotting in patients with chronic atrial fibrillation. J Am Coll Cardiol, 1990; 16: 377–80
71. Gustafsson C, Blomback M, Britton M et al: Coagulation factors and the increased risk of stroke in nonvalvular atrial fibrillation. Stroke, 1990; 21: 47–51
72. Skov J, Sidelmann JJ, Bladbjerg EM et al: Lysability of fibrin clots is a potential new determinant of stroke risk in atrial fibrillation. Thromb Res, 2014; 134: 717–22
73. Zabczyk M, Majewski J, Lelakowski J: Thromboembolic events are associated with prolonged clot lysis time in patients with permanent atrial fibrillation. Pol Arch Med Wewn, 2011; 121: 400–7
74. Loffredo L, Violi F, Fimognari FL et al: The association between hyperhomocysteinemia and ischemic stroke in patients with non-valvular atrial fibrillation. Haematologica, 2005; 90: 1205–11
75. Soncini M, Casazza F, Mattioli R et al: Hypercoagulability and chronic atrial fibrillation: The role of markers of thrombin generation. Minerva Med, 1997; 88: 501–5
76. Roldán V, Marín F, Blann AD et al: Interleukin-6, endothelial activation and thrombogenesis in chronic atrial fibrillation. Eur Heart J, 2003; 24: 1373–80
77. Feinberg WM, Pearce LA, Hart RG et al: Markers of thrombin and platelet activity in patients with atrial fibrillation: correlation with stroke among 1531 participants in the stroke prevention in atrial fibrillation III study. Stroke, 1999; 30: 2547–53
78. Pongratz G, Brandt-Pohlmann M, Henneke KH et al: Platelet activation in embolic and preembolic status of patients with nonrheumatic atrial fibrillation. Chest, 1997; 111: 929–33
79. Black IW, Chesterman CN, Hopkins AP et al: Hematologic correlates of left atrial spontaneous echo contrast and thromboembolism in nonvalvular atrial fibrillation. J Am Coll Cardiol, 1993; 21: 451–57
80. Colkesen Y, Acil T, Abayli B et al: Mean platelet volume is elevated during paroxysmal atrial fibrillation: A marker of increased platelet activation? Blood Coagul Fibrinolysis, 2008; 19: 411–14
81. Tan C, OuYang M, Kong D, Zhou X: Association between the left atrial and left atrial appendages systole strain rate in patients with atrial fibrillation. Med Sci Monit, 2016; 22: 4974–77
82. Hu X, Jiang J, Ma Y, Tang A: Novel P wave indices to predict atrial fibrillation recurrence after radiofrequency ablation for paroxysmal atrial fibrillation. Med Sci Monit, 2016; 22: 2616–23
83. Jia W, Qi X, Li Q: Association between Rs3807989 polymorphism in Caveolin-1 (CAV1) gene and atrial fibrillation: A meta-analysis. Med Sci Monit, 2016; 22: 3961–66
84. Boisclair MD, Ireland H, Lane DA: Assessment of hypercoagulable states by measurement of activation fragments and peptides. Blood Rev, 1990; 4: 25–40
85. Danesh J, Lewington S, Thompson SG et al: Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: An individual participant meta-analysis. JAMA, 2005; 294: 1799–809
86. Jankun J, Skrzypczak Jankun E: Yin and yang of the plasminogen activator inhibitor. Pol Arch Med Wewn, 2009; 119: 410–17
87. Hernández-Romero D, Marín F, Roldán V, Lip GY: Subclinical atherosclerotic endothelial damage as predictor for bleeding in anticoagulated atrial fibrillation patients. J Intern Med, 2012; 272: 409

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