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CLINICAL RESEARCH
Atrial fibrillation

The association of coagulation and atrial fibrillation: a systematic review and meta-analysis

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Aims While atrial fibrillation (AF) is suggested to induce a prothrombotic state, increasing thrombotic risk, it is also hypothesized that coagulation underlies AF onset. However, conclusive evidence is lacking. With this systematic review and meta-analysis, we aimed to summarize and combine the evidence on the associations between coagulation factors with AF in both longitudinal and cross-sectional studies.

Methods and results We systematically searched for longitudinal cohort and cross-sectional studies investigating AF and thrombosis. For longitudinal studies, pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. For cross-sectional studies, we determined pooled standardized mean differences (SMDs) and 95% CIs. A total of 17 longitudinal and 44 cross-sectional studies were included. In longitudinal studies, we found significant associations between fibrinogen (HR 1.05, 95% CI 1.00–1.10), plasminogen activator inhibitor 1 (PAI-1) (HR 1.06, 95% CI 1.00–1.12), and D-dimer (HR 1.10, 95% CI 1.02–1.19) and AF incidence. In cross-sectional studies, we found significantly increased levels of fibrinogen (SMD 0.47, 95% CI 0.20–0,74), von Willebrand factor (SMD 0.96, 95% CI 0.28–1.66), P-selectin (SMD 0.31, 95% CI 0.08–0.54), ß-thromboglobulin (SMD 0.82, 95% CI 0.61–1.04), Platelet Factor 4 (SMD 0.42, 95% CI 0.12–0.7), PAI-1 (1.73, 95% CI 0.26–3.19), and D-dimer (SMD 1.74, 95% CI 0.36–3.11) in AF patients, as opposed to controls.

Conclusion These findings suggest that higher levels of coagulation factors are associated with prevalent and incident AF. These associations are most pronounced with prevalent AF in cross-sectional studies. Limited evidence from longitudinal studies suggests a prothrombotic state underlying AF development.

Keywords Coagulation • Atrial fibrillation • Thrombosis • Haemostasis • Tachyarrhythmia • Meta-analysis

What's new?

- Coagulation factors are related with atrial fibrillation (AF) presence, as well as suggest a prothrombotic state underlying its development.
- A positive feedback loop may stimulate AF development and progression, and may worsen AF prognosis.
- There is a lack of evidence from large longitudinal studies regarding coagulation and AF development. New research and replication are critical to improve AF risk assessment, prevention, and management.

Introduction

With a lifetime risk of over 22% in men and women at the age of 55, atrial fibrillation (AF) is a highly prevalent disease, expected to increase rapidly considering the ageing of the population.[1,2] This is especially relevant since AF patients are at an increased risk to develop stroke and heart failure, and have an increased risk of hospitalization and death.[3–6] Several risk factors for AF onset are already identified, including older age, male sex, and obesity.[7] While atrial remodelling is

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generally considered to be the underlying cause of AF, the exact pathways causing atrial remodelling are still largely unknown.[7–11] Previous studies suggest that a prothrombotic state is associated with prevalent AF, eventually leading to thrombotic events.[8] On the other hand, it is also suggested that coagulation underlies AF onset.[12–14] A possible mechanism underlying this association is immunothrombosis, as coagulation may increase local inflammation, stimulating atrial remodelling, and eventually AF development.[15–17] However, studies investigating the relation of coagulation with incidence AF are scarce and contradicting. Additionally, studies looking into the association of coagulation and AF presence investigate a limited amount of biomarkers, and these studies generally have small sample sizes. More conclusive evidence is warranted on the association of coagulation and AF, to improve knowledge on AF risk, AF prevention, and AF management.

We aimed to investigate the role of various markers of coagulation in the development and presence of AF. For this, we performed a systematic review and meta-analysis, summarizing and pooling all available evidence from both longitudinal and cross-sectional studies.

Methods

Data sources and study selection

The methods in this systematic review are described based on the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) Checklist[18] and the Prima-S extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews.[19] An exhaustive search strategy was developed by an experienced information specialist (WB) in Embase, optimized for sensitivity, and translated to other databases.[20] The search was carried out in Embase, Medline ALL via Ovid, Web of Science Core, and the Cochrane Central Register of Controlled Trial via Wiley. Additionally, the 200 most relevant references from Google Scholar were downloaded using Publish or Perish.[21] The original search was performed in February 2020, and last updated on January 26th, 2022.[22] The search strategies for Embase and Medline used relevant thesaurus terms from Emtree and Medical Subject Headings, respectively. Titles and abstracts from all databases were searched for the established search terms. The search contained terms for (1) haemostasis and coagulation factors, (2) AF, and (3) prediction, disease association, or prevalence. The full search strategies of all databases are available in Supplementary material online, Methods. Non-English articles and animal-only articles were excluded from the search results. The reference lists of retrieved non-included relevant articles and of the included studies have been scanned for references missed by the search.[23] No authors or subject experts were contacted and we did not browse unindexed journals in the field.

The references were imported into EndNote and duplicates were removed by the medical librarian.[24] All titles and abstracts were independently screened by at least two reviewers (M.J.T., S.G., or A.M.P.) in EndNote.[25] Any discrepancies in the verdict were resolved by discussion with the third reviewer. The quality of all studies was scored based on the Newcastle-Ottawa criteria.[26]

Inclusion and exclusion criteria

All studies investigating one or more biomarkers of coagulation in humans with AF and controls in sinus rhythm were included. The outcome of interest was defined as non-valvular AF or overall AF. Eligible study types were cross-sectional studies and longitudinal studies. All reviews, meta-analyses, case reports, and non-original studies were excluded. Additionally, studies investigating the biomarkers of interest in an uninterpretable method (for example tertiles) and studies investigating patients in acute cardiovascular settings or after cardiac surgery were removed. Lastly, if no English full text was available, the studies were also excluded from this systematic review. To avoid individuals being counted multiple times in the meta-analyses, if multiple studies investigating the same biomarker were conducted in the same study populations, the largest study was included. Additionally, biomarkers only investigated in one study were not included in meta-analyses.

Statistical analyses

For longitudinal studies, pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with log-transformed HRs and 95% CIs using the generic inverse variance method. The most extensively adjusted model per study was included in the meta-analysis. Additionally, sensitivity analyses were performed by grouping the analyses into univariate models, simple multivariate models (adjusted for age, sex, race, and/or cohort), and complex multivariate analyses (additionally adjusted for cardiovascular risk factors).

For cross-sectional studies, means and standard deviation (SD) were extracted from the studies. If the median and interquartile range (IQR) were reported in the studies, the SD was manually calculated by dividing the IQR with 1.35, as explained in the Cochrane handbook of a systematic review.[27] Inverse variance weighting was used for pooling. Differences were reported as standardized mean difference (SMD) and 95% CIs. SMDs <0.2 are considered no effect, 0.2–0.5 as a small effect, 0.5–0.8 as an intermediate effect, and ≥0.8 as a large effect.

Due to the high probability of significant heterogeneity between the studies, random-effect models were used in the meta-analyses. Heterogeneity was assessed through I^2-statistics. If I^2 was above 75%, additional sensitivity analyses were performed to identify causes of heterogeneity. Publication bias was assessed visually through funnel plots. Statistical significance was considered at a two-tailed P-value ≤ 0.05. Data management and statistical analyses were performed in IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, New York, USA) and R: A language and environment for statistical computing, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study selection

10,335 manuscripts were collected for title and abstract screening. 236 (2.3%) studies were eligible for full-paper reading. We excluded studies with a study design other than cohort and case–control studies ($n = 60$), studies using populations in acute cardiovascular or surgical settings ($n = 34$), studies without the biomarkers of interest ($n = 56$), studies investigating other outcomes than non-valvular or overall AF as primary or secondary outcome ($n = 5$), studies with uninterpretable data (for example tertiles) ($n = 7$), and non-English full-text available studies ($n = 5$). Through reference checking, two additional studies were included. An overview of the study selection is depicted in *Figure 1*. Characteristics of the included studies are summarized in Supplementary material online, *Tables 1 and 2*.

Coagulation and AF in longitudinal studies

Fibrinogen

Nine population-based studies investigated the association of fibrinogen with incident AF, totalling 85 282 individuals (mean age 54.6

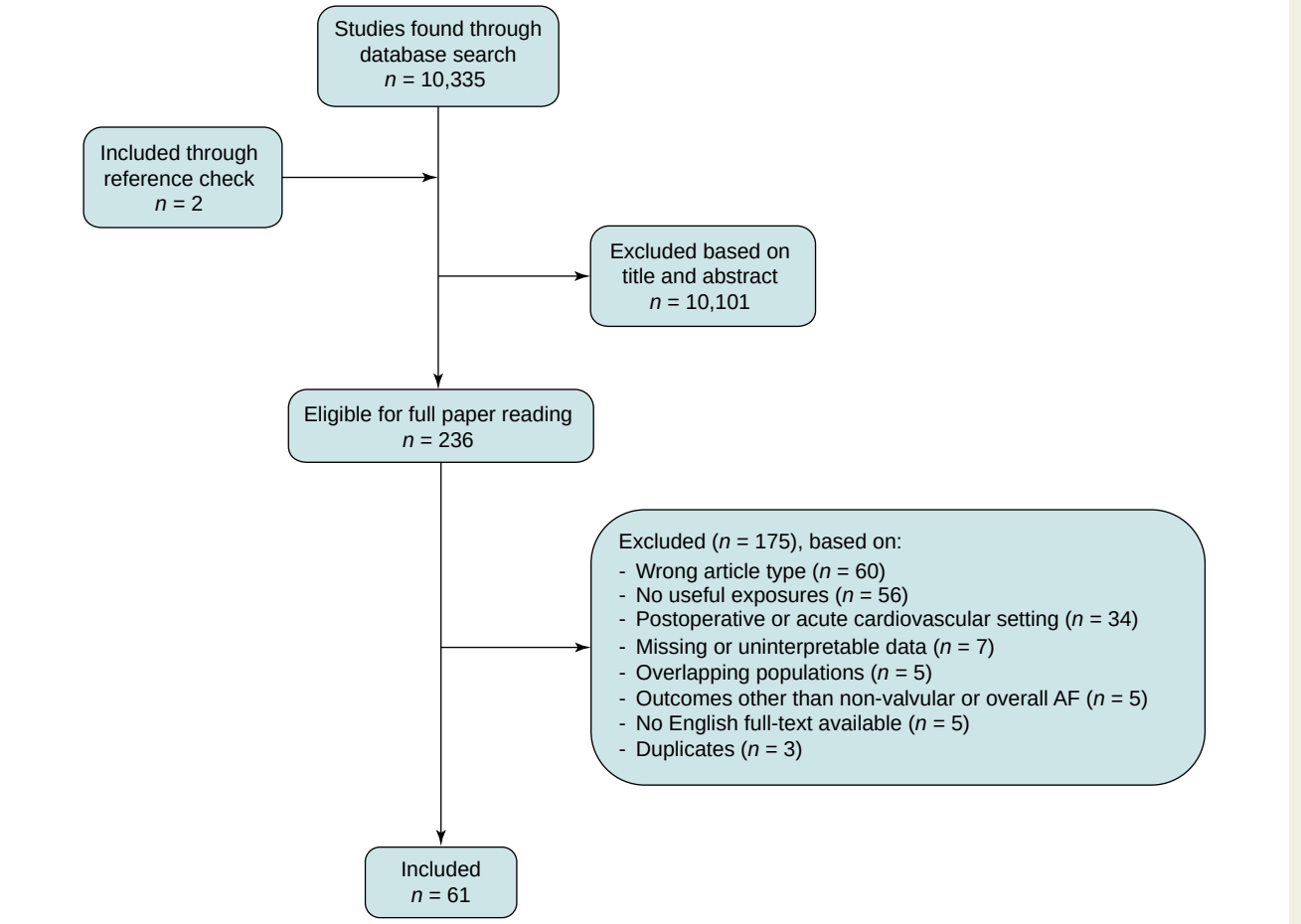

Figure 1 Flowchart of the inclusion and exclusion of studies. AF, atrial fibrillation; *n*, number.

years, 60.0% women), of whom 4164 (6.1%) developed AF.[13,28–35] The median follow-up from this set of studies ranged from 3.6 to 25.0 years. Combining all nine studies (*Figure* 2), our meta-analysis showed no significant association between fibrinogen and incident AF (HR 1.04, 95% CI 0.99–1.08). When combining the more extensively adjusted models, fibrinogen was minimally associated with the incidence AF (HR 1.05, 95% CI 1.00–1.10).[13,29–33,35] In contrast, grouping the studies using simple multivariable analyses resulted in no significant association (HR 1.08, 95% CI 0.97–1.21).[29,31,32,34,35] Similarly, combining the two univariable analyses, no significant associations were found (HR 1.08, 95% CI 0.90–1.29).[28,34]

Von Willebrand factor

Two studies (total $n = 21\,032$, AF events $n = 1938$, mean age 58.6 years, 55.6% women) investigated the relation between Von Willebrand factor (vWF) and incidence AF. Pooled, we found no significant association (HR 1.10, 95% CI 0.98–1.23).[29,35]

ADAMTS13

For a desintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) no statistical significant associations were found with incidence AF (HR 0.89, 95% CI 0.70–1.13), after combining the results of two studies (total $n = 8059$, AF events $n = 1078$, mean age 65.8 years, 56.3% women).[35,36]

P-selectin

The association of P-selectin and incidence AF was investigated by two studies (total $n = 3743$, AF events $n = 265$, mean age 59.9 years, 53.6% women).[34,37] The pooled effect of these studies showed no significant association of P-selectin with AF (HR 1.10, 95% CI 0.87–1.18).

Plasminogen activator inhibitor 1

The pooled effect of three studies (total $n = 14\,153$, AF events $n = 1197$, mean age 60.1 years, 51.4% women) showed significant association of plasminogen activator inhibitor 1 (PAI-1) and AF risk in complex multivariate models (HR 1.06, 95% CI 1.00–1.12).[33,38,39]

D-Dimer

Two studies (total $n = 9735$, AF events $n = 1084$, mean age 60.2 years, 53.2% women) examined the association of D-dimer with new-onset AF in complex multivariate models.[33,40] Pooled effect showed a significant association of D-dimer with AF incidence (HR 1.10, 95% CI 1.02–1.19).

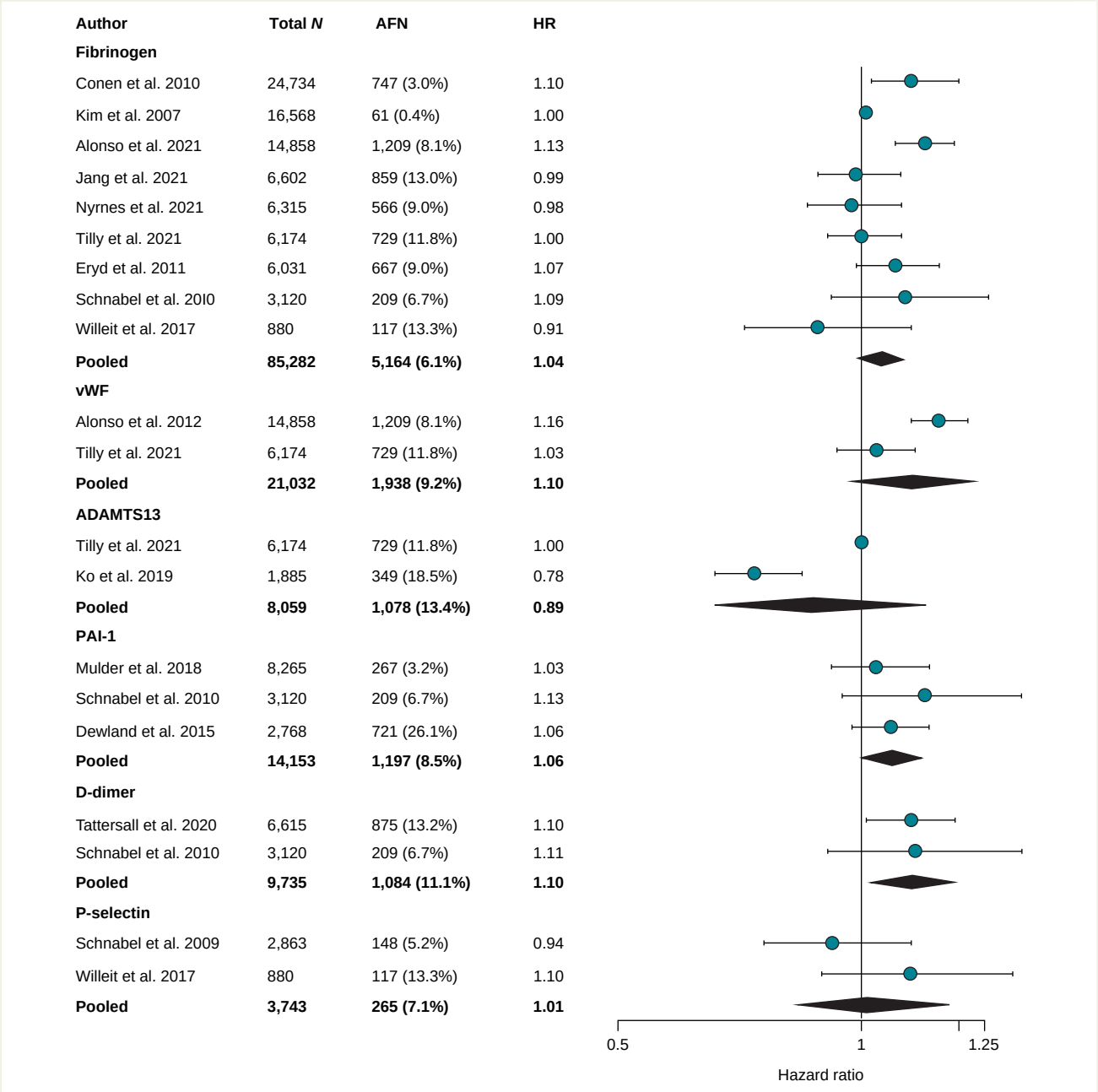

Figure 2 Forest plot of the associations between various coagulation biomarkers and incident AF in longitudinal studies. I^2 was 71.8% for fibrinogen, 83.9% for von Willebrand factor, 94.5% for ADAMTS13, 0.0% for PAI-1, 0.0% for D-dimer, and 40.4% for P-selectin. ADAMTS13, a desintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; AF, atrial fibrillation; HR, hazard ratio; *N*, number; PAI-1, plasminogen activator inhibitor 1.

Additional biomarkers

For β-thromboglobulin (HR 0.92, 95% CI 0.67–1.27),[41] platelet count (HR 0.90, 95% CI 0.73–1.10),[42] Factor VII (HR 0.94, 95% CI 0.88–1.00), Factor VIII (HR 1.17, 95% CI 1.10–1.23), Protein C (HR 1.05, 95% CI 0.98–1.05),[29] tissue plasminogen activator (TPA) (HR 1.03, 95% CI 0.97–1.10),[38] and soluble urokinase plasminogen activator receptor (HR 1.20, 95% CI 1.01–1.42)[43] only one study was available.

Coagulation and AF in cross-sectional studies

Fibrinogen

The association of fibrinogen and AF was investigated in 15 cross-sectional studies (1025 AF patients, 13 261 controls, mean age 56.4 years, 51.2% women).[44–58] Mean fibrinogen in AF patients ranged from 2.32 to 4.60 g/l, and from 2.26 to 4.08 g/l in controls, with higher fibrinogen levels in AF patients in 13 out of 15 studies. Pooled

results showed higher fibrinogen values in AF patients (SMD 0.47, 95% CI 0.20–0.74) than in controls, as depicted in *Figure 3*.

Von Willebrand factor

vWF was assessed in 16 studies (1439 AF patients, 4723 controls, mean age 58.0 years, 46.3% women).[45,48,50,51,53,54,56,59–67] vWF levels were higher in AF patients (mean 153.6%, range 116.5–210.3%) than in controls (mean 126.9%, range 89.0–153.2%). Pooled analysis showed that elevated vWF is significantly associated with AF (SMD 0.96, 95% CI 0.27–1.66). As visible in *Figure 3*, the results presented by Negreva *et al.*[64] were clear outliers. No explanation was found despite meticulous review of the studies. However, similar results were found in sensitivity analyses excluding this study.

P-selectin

The association of P-selectin and AF was assessed in 10 studies (871 AF patients, 793 controls, mean age 69.2 years, 39.6% women).[48,50–53,67–71] Mean P-selectin was 84.7 ng/ml for AF patients (range 31.2–219 ng/ml), and 43.3 ng/ml (range 29.2–145 ng/ml) in the control group. Overall, we found that AF was associated with elevated P-selectin, as compared with individuals without AF (SMD 0.31, 95% CI 0.08–0.54).

β-Thromboglobulin

Seven studies investigated β-thromboglobulin in relation to AF (358 AF patients, 299 controls, mean age 63.3 years, 35.5% women).[52,56,58,72–75] We found significantly higher values (SMD 0.82, 95% CI 0.61–1.04) for β-thromboglobulin in AF patients (mean 83.29 ng/ml, range 36.0–181.0) than in controls (mean 44.32 ng/ml, range 22.80–91.0 ng/ml).

Platelet factor 4

Platelet factor 4 was examined in four studies (192 AF patients, 216 controls, mean age range 61.2 years, insufficient data on sex).[56,58,72,73] In all studies platelet factor levels were higher in AF patients (mean 17.8 ng/ml, range 3.9–20.9 ng/ml) compared with the controls (mean 11.5 ng/ml, range 2.6–15.3 ng/ml). Meta-analysis showed a significantly elevated platelet factor 4 levels in AF patients (SMD 0.42, 95% CI 0.12–0.71) as compared with controls.

Platelet count

Fourteen studies examined platelet count in AF and controls (868 AF patients, 2269 controls, mean age 62.6 years, 39.5% women).[50,52,56,64,68,69,71,74,76–81] The mean platelet count in AF patients was 235×10^9/l (range $174–277 \times 10^9$/l), and 225×10^9 in controls (range $212–270 \times 10^9$). Pooled, we found no significant difference between the two groups (SMD −0.41, 95% CI −1.42 to 0.59).

Mean platelet volume

The relation of MPV with AF was investigated in three studies (264 AF patients, 202 controls, mean age 59.1 years, 41.0% women).[69,77,79] MPV was higher in AF patients (mean 8.9 fl, range 7.76–10.0 fl) than in controls (mean 8.0 fl, range 7.39–8.4 fl), but the pooled overall effect showed no significant difference (SMD 1.19, 95% CI −1.26 to 3.64).

Tissue factor

We included two studies with data on tissue factor (165 AF patients, 81 controls).[51,65] The studies were similar in mean age (64.6 and 62.6 years), but differed in sex ratio (37.4% and 51.5% women). Despite comparable methodology, the studies differed largely in tissue factor values in both AF (115 vs. 750 pg/ml) and healthy control patients (95 vs. 455 pg/ml), whereas the SMDs were similar (0.33 and 0.27). The meta-analysis showed no significant differences between AF patients and controls (SMD 0.31, 95% CI −0.06 to 0.67).

Factor VIII

Factor VIII levels were measured in 104 AF patients and 3211 controls in two studies (mean age 54.1 and 59.7 years, 53.2% and 49.5% women).[46,64] Pooled, Factor VIII levels were higher in AF patients than in controls (136.3% vs. 133.6%), albeit not significantly (SMD 12.10, 95% CI −88.0 to 112.2).

Thrombin–antithrombin complex

Two studies (151 AF patients, 29 controls, mean age 59.9 and 67.0 years, 23.3% and 46.0% women) assessed the association between thrombin–antithrombin complex (TAT) and AF.[58,70] In AF patients, the mean TAT values differed significantly (54.0 ± 237 and 6.7 ± 5.1 ng/l), whereas in control patients, the mean TAT was comparable (2.7 ± 3.3 and 3.1 ± 1.9 ng/l). Pooled analysis showed no significant difference between AF and controls (SMD 0.42, 95% CI −2.91 to 3.75).

Thrombomodulin

Thrombomodulin levels were compared in 396 AF patients and 179 controls over five studies (mean age 66.2 years, 38.1% women).[53,54,62,70,82] Mean (range) levels were 40.5 ng/ml (11.8–52.2 ng/ml) and 35.3 ng/ml (5.9–44.0 ng/ml), respectively. Pooled analysis showed no significant differences between AF patients and controls (SMD 0.48, 95% CI −0.48 to 1.44).

Tissue plasminogen activator

TPA was assessed in eight studies (370 AF patients, 6954 controls, mean age range 53.6–75.0 years, 17.5–55.4% women).[8,45,46,54,57,68,83,84] Through pooled analysis, we found no significant difference (SMD 2.42, 95% CI −2.02 to 6.85) in TPA value between AF (mean 11.43 ng/ml, range 2.31–20.37 ng/ml) and controls (mean 8.50 ng/ml, range 2.88–15.5 ng/ml). We performed a sensitivity analyses excluding the study by Negreva *et al.*,[83] based on the distinctly higher values without a clear cause. However, similar to vWF, the pooled estimates did not change.

PAI-1

Six studies contained data on PAI-1 and AF (240 AF patients, 6796 controls, mean age 55.5 years, 51.9% women).[45,46,54,57,84,85] AF patients had higher PAI-1 levels (mean 23.6 ng/ml, range 15.2–42.8 ng/ml) than the control group (mean 19.6 ng/ml, range 5.4–22.9 ng/ml). Meta-analysis showed a large difference between PAI-1 in AF patients and controls (SMD 1.73, 95% CI 0.26–3.19).

D-Dimer

Twelve studies included D-dimer in the analyses (523 AF patients, 535 controls, mean age 64.7 years, 38.3% women).[49,52,54,56–58,67,72,74,82,83,86] In AF patients, the mean D-dimer was 0.47 μg/ml (range 0.13–1.15 μg/ml), as opposed to 0.16 μg/ml (range 0.01–0.59 μg/ml) in controls. AF patients had significantly higher D-dimer levels than controls in the meta-analysis

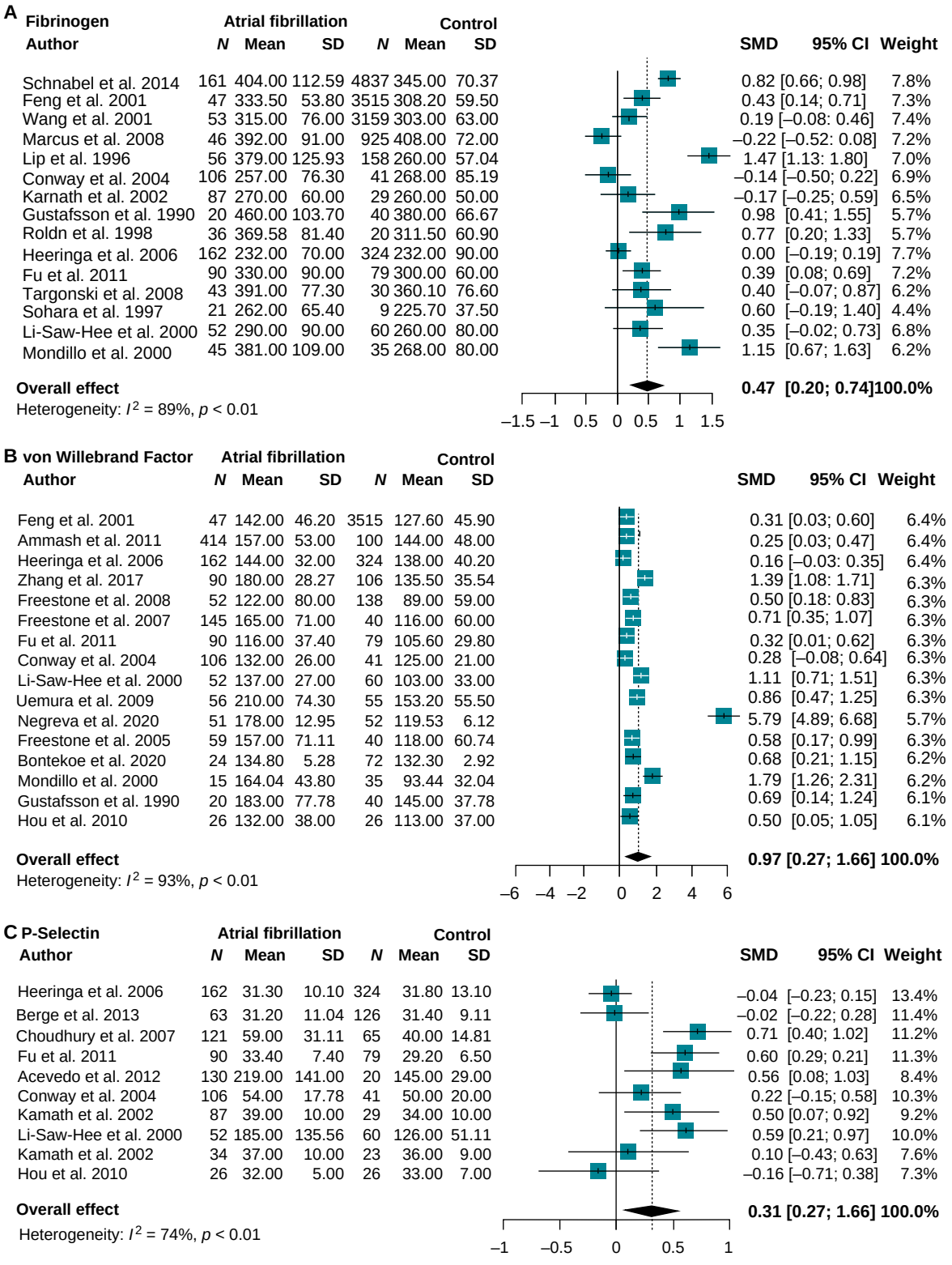

Figure 3 Forest plots of the associations between various coagulation biomarkers and AF presence in cross-sectional studies. (*A*) Fibrinogen; (*B*) von Willebrand Factor; (*C*) P-Selectin; (*D*) ß-thromboglobulin; (*E*) platelet factor 4; (*F*) platelet count; (*G*) thrombomodulin; (*H*) TPA. (*I*) PAI-1; (*J*) D-dimer. CI, confidence interval; *N*, number; PAI-1, plasminogen activator inhibitor 1; SD, standard deviation; SMD, standardized mean difference; TAT, thrombin–antithrombin complex; TPA, tissue plasminogen activator.

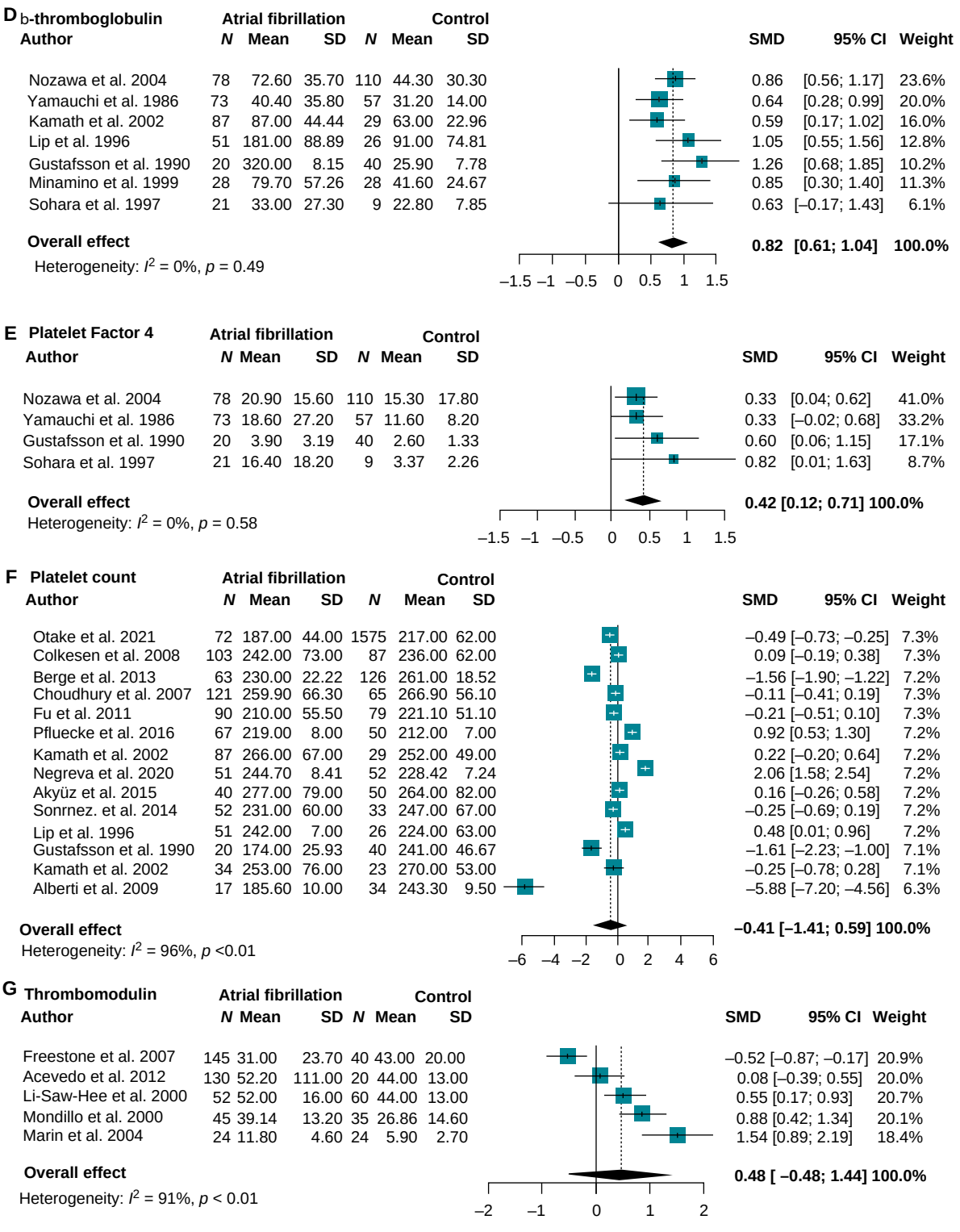

Figure 3 Continued

(SMD 1.74, 95% CI 0.36–3.11). As visualized in *Figure 3*, Roldan *et al.*[57] presented a disparate result as compared with the other studies, without an obvious cause. The pooled result of the sensitivity analyses showed similar tendencies after excluding Roldán *et al.*

Discussion

With this systematic review and meta-analysis, we aimed to identify markers of coagulation associated with AF incidence and AF

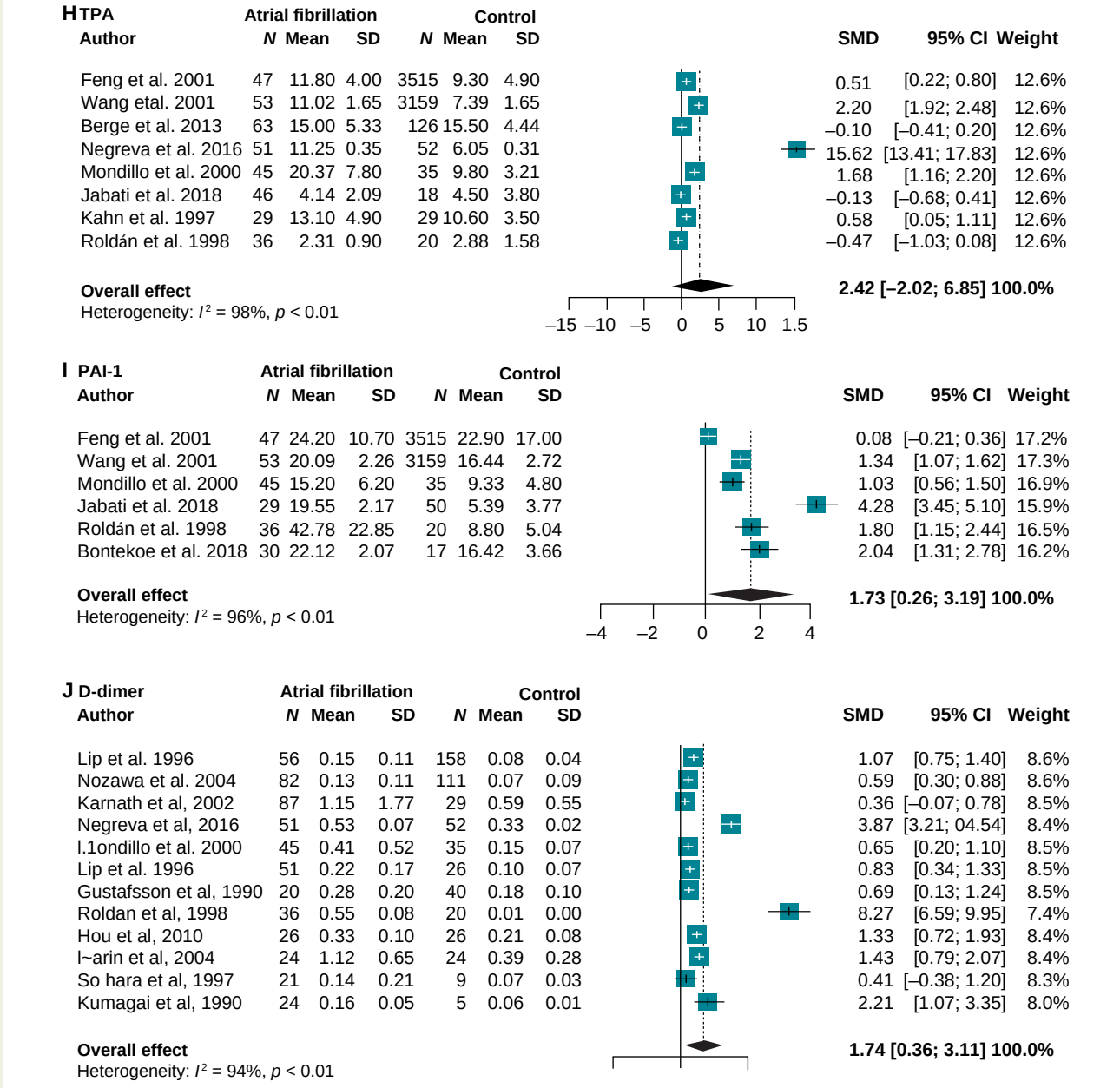

Figure 3 Continued

prevalence. In longitudinal studies, we found significant associations between fibrinogen, PAI-1, and D-dimer levels at baseline with AF incidence. Additionally, in cross-sectional studies, we found significant differences between AF patients and controls for fibrinogen, PAI-1, D-dimer, P-selectin, vWF, ß-thromboglobulin, and platelet factor 4. By investigating the association between coagulation and AF in longitudinal and cross-sectional studies separately, we strived to further clarify the direction in which coagulation and AF development and prognosis are dependent.

Our results give insight to the role of primary and secondary haemostasis, and fibrinolysis in the development of AF. Fibrinogen is an acute-phase reactant that indicates inflammatory processes or tissue damage, and has been associated with ischaemic heart disease in prior studies.[87,88] We found a borderline significant association between fibrinogen and AF incidence by combining studies with extensive multivariable models. However, after including models with less adjustments for confounding in the meta-analysis, this association attenuated. One possibility for this is that there are discrepancies in the quality of study designs between studies with more robust statistical models, and studies only investigating the associations in univariable models. On one hand, this suggests that fibrinogen is associated with new-onset AF, but other cardiovascular risk factors such as BMI or comorbidities may attenuate this association. On the other hand, it is possible that underlying confounders, if

not sufficiently corrected for, biased the association of fibrinogen with AF. PAI-1, a fibrinolysis inhibitor and established risk factor for atherosclerosis and thrombosis, was also significantly associated with AF incidence.[89] Increased PAI-1 causes decreased fibrinolysis, and thus a reduced degradation of thrombi. This could imply that coagulation, potentially promoted due to tissue damage or inflammation, is further sustained and perpetuated, as fibrinolysis is inhibited. PAI-1 is also associated with adiposity and inflammation, both of which may also contribute to AF development. To investigate the independent association between the role of PAI-1 in coagulation and AF, the studies investigating these associations all adjusted extensively for these potential confounders, such as BMI, sex, and medication use, mitigating the confounding role of adiposity and traditional cardiovascular risk factors. Lastly, we found a significant association of D-dimer, a marker of coagulation cascade activation, with incidence AF.[90] Increased D-dimer is associated with increased fibrin synthesis, and therefore increased coagulability. This implies that a hypercoagulable state underlies AF development, which is in line with the previously mentioned association between primary haemostasis and fibrinolysis. In contrast, vWF, ADAMTS13, and P-selectin were not significantly associated with AF. vWF and ADAMTS13 are inversely correlated with each other, and while a trend where higher vWF and lower ADAMTS13 levels are associated with increased AF risk, the pooled HR was non-significant. For P-selectin, the two studies contradicted each other. While this contradicts our hypothesis of the role of coagulation in AF development, these results could be due to low power, as only two studies investigated these associations. More evidence from large, prospective cohort studies is warranted before conclusive conclusions can be made on the associations between AF and these single markers of coagulation.

The findings of this study suggest that coagulation is associated with AF development through multiple pathways of coagulation. A possible explanation for this is immunothrombosis, which comprises the complex interaction of the innate immune system and the coagulation system.[15–17] Prior studies found that markers of inflammation and endothelial damage, such as fibrinogen and vWF, underlie AF development and progression, but the exact pathophysiology remained unclear.[9,90–93] Therefore, it is unsure if the association is causally related, or if these biomarkers are also related to another process causally related to AF. The synergy between inflammation and coagulation, creating a hypercoagulable and hypofibrinolytic state, may lead to structural and biochemical changes, eventually resulting in AF.

AF presence was also significantly associated with multiple biomarkers of primary and secondary haemostasis, and fibrinolysis. Distinctly higher levels of indicators of platelet activation (ß-thromboglobulin and platelet factor 4), platelet aggregation (von Willebrand factor and P-selectin), as well as the aforementioned markers underlying a hypercoagulable and hypofibrinolytic state, were found in AF patients, as compared with healthy controls. These findings corroborate that AF further propels the haemostatic balance towards a prothrombotic state, by promoting not only hypercoagulability, but also hypofibrinolysis.[57]

Given these results, one might state our study underwrites the often phrased '*AF begets AF*'.[94] Immunothrombosis, as a potential underlying cause of increased coagulation, may stimulate AF development. Consequently, the restricted blood flow, atrial structural changes, and inflammatory processes related to AF further stimulate a prothrombotic state.[95–97] In other words, a hypercoagulable, inflammatory, and hypofibrinolytic state can promote AF development, which in turn further stimulates its own underlying pathophysiological pathways through a positive feedback loop.

However, despite our comprehensive search, it is clear that longitudinal population-based cohort studies investigating the association of coagulation and AF are lacking. With only two studies investigating vWF, ADAMTS13, P-selectin, and D-dimer, there remains a possibility of publication bias in our meta-analyses. In the cross-sectional meta-analyses, asymmetry and outliers were visually assessed through funnel plots, especially for vWF, platelet count, TPA, PAI-1, and D-dimer (see Supplementary material online, *Figures S1 and S2*). However, while funnel plots may assist in identifying publication bias, there have been increasing critiques on the added value.[98,99] Due to the low number of studies and the potential publication bias as depicted in the funnel plots, the results of this meta-analysis, especially in the longitudinal studies, must be interpreted with caution, and more studies investigating the relation of coagulation and AF are warranted. Population-based research and early recognition and prevention or people at risk are critical in the modern day society. Especially in large, longitudinal population-based studies, replication, resulting in the uncovering of supporting or contradicting evidence, can be crucial in risk stratification, even more so in different populations.

Besides the lack of studies investigating the role of coagulation biomarkers in AF development and AF presence, it is possible that single biomarkers are not sensitive or specific enough to accurately predict AF risk. Especially in a large, population-based study, subclinical elevation of single coagulation markers may not be strong enough to depict the elevated AF risk it is potentially associated with. However, combinations of biomarkers may give us a new insight. The International Society of Thrombosis and Haemostasis has previously developed a score to identify the degree of disseminated intravascular coagulation in individuals, using easy to test coagulation markers such as fibrinogen, D-dimer, and platelet count.[100] Our systematic review and meta-analysis suggest that other markers associated with primary and secondary haemostasis and fibrinolysis play a role in AF, and therefore could play a role in risk stratification and even AF prevention. We hope that our findings further stimulate researchers to assess these potential associations, opening the door to improved AF risk prediction, management, and prognosis. While we cannot reject the hypothesis of inflammation and coagulation preceding AF, coagulation is mostly increased after AF initiation. Additionally, the included studies were highly heterogeneous. While we carefully assessed the studies, and performed sensitivity analyses and step-by-step exclusion of potential causes, we were not able to significantly reduce the heterogeneity. To address this heterogeneity, we used random-effects models.

Conclusion

Higher levels of coagulation factors are associated with prevalent and incident AF. These associations are most pronounced with prevalent AF in cross-sectional studies. Limited evidence from longitudinal studies suggests a prothrombotic state underlying AF development.

These findings support the hypothesis of a prothrombotic and hypofibrinolytic state as both an underlying cause of AF, as well as further inducing atrial structural remodelling, in turn perpetuating AF.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author. Data from individual studies included in this systematic review and meta-analysis can be found in the respective references.

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EP CASE EXPRESS

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The scenic route: dilated left superior intercostal vein following acute left brachiocephalic venous obstruction

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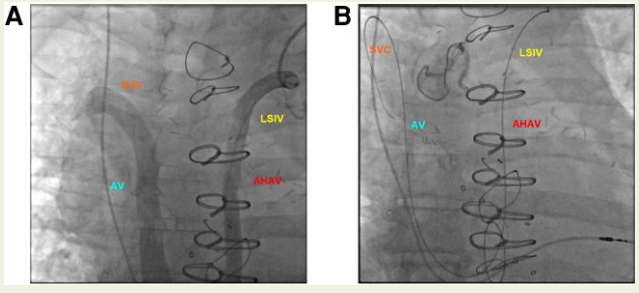
A 62-year-old man was scheduled for left-sided permanent pacemaker implantation for post-operative complete heart block. A peripheral venogram showed patency of the axillary and proximal subclavian veins. After access was obtained, the micropuncture wire did not follow the typical course expected of a left brachiocephalic vein. A venogram was therefore performed through a 5 Fr short sheath—this revealed a U-shaped course with eventual drainage into the superior vena cava (*Panels A* and *B*).



These represent a dilated left superior intercostal vein that drains into the accessory hemiazygous vein, followed by the azygous vein and finally the superior vena cava. The prominence of this vessel can occur with congenital or acquired obstruction of the proximal veins. In this case, a dialysis catheter-associated thrombus likely caused acute left brachiocephalic vein occlusion and consequent increase in collateral flow.

Pursuing left-sided device implantation was not deemed feasible, given the long and meandering venous course visualized. Hence, a dual-chamber pacemaker was implanted on the right side instead. The invasive electrophysiologist should be aware of these uncommon but impressive venous anomalies in the planning and execution of cardiac device implantations.

The full-length version of this report can be viewed at: https://www.escardio.org/Education/E-Learning/Clinical-cases/Electrophysiology.