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Prognostic value of von Willebrand factor in patients with atrial fibrillation

A meta-analysis

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Abstract

Background: Studies on the prognostic role of von Willebrand factor (vWF) in patients with atrial fibrillation (AF) are conflicting. This meta-analysis aimed to evaluate the association of elevated circulating vWF level with adverse outcomes in patients with AF.

Methods: PubMed and Embase were used to search literature through August 2017. Prospective observational studies that evaluated the association of elevated vWF level with major adverse cardiac events (MACEs) and all-cause mortality in patients with AF were deemed eligible. The MACEs included death, stroke/transient ischemic attack, heart failure, myocardial infarction, and systemic/peripheral embolism.

Results: A total of 6 studies were included this meta-analysis. Patients with AF with the highest vWF level were independently associated with greater risk of MACEs (risk ratio [RR] 2.20; 95% confidence intervals [CI] 1.61–3.01) and all-cause mortality (RR 1.63; 95% CI 1.39–1.91). Subgroup analysis showed that the prognostic role of higher vWF level was consistently observed in each defined subgroups.

Conclusion: Patients with AF with elevated vWF level are independently associated with a higher risk of MACEs and all-cause mortality. However, more well-designed prospective studies are needed to confirm these findings.

Abbreviations: AF = atrial fibrillation, CIs = confidence intervals, MACEs = major adverse cardiac events, NOS = Newcastle–Ottawa scale, RR = risk ratio, vWF = von Willebrand factor.

Keywords: all-cause mortality, atrial fibrillation, major adverse cardiac events, meta-analysis, von Willebrand factor

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia associated with increased global public health burden. The age-adjusted prevalence of AF was 596 per 100000 men and 373 per 100,000 women worldwide.[1] The estimated annual incidence of AF was 5.38 per 1000 person-years from Asian countries.[2] AF affects approximately 3.9 million Chinese populations aged over 60 years.[3] Patients with AF are at increased risk of morbidity due to stroke and thromboembolism.[4] These patients also have a high risk of all-cause mortality.[5] Therefore, identification of the prognostic biomarker is urgently needed in the care of patients with AF.

Abnormal coagulation, endothelial function, and platelet activation have been implicated in AF.[6,7] Von Willebrand factor (vWF), a glycoprotein mainly synthesized in endothelial cells as a response to endothelial damage/dysfunction,[8] plays a key role in platelet adhesion/aggregation and thrombus formation.[9] A well-designed meta-analysis[10] has demonstrated significantly higher circulating level of vWF in patients with AF than in sinus rhythm population. Increased vWF level has been recognized as an independent predictor of AF in the general population.[11] However, the prognostic role of vWF in patients with AF remains controversial. Several studies[12–14] failed to demonstrate an association between elevated vWF level and adverse outcomes in patients with AF. Moreover, the strength of predictive value of vWF varied significantly across these studies.

Currently, no previous meta-analysis has assessed the association of vWF level with adverse outcomes in patients with AF. The current meta-analysis sought to evaluate the predictive value of the vWF in patients with AF, in terms of major adverse cardiac events (MACEs) and all-cause mortality.

2. Materials and methods

2.1. Search strategy

A comprehensive literature search was conducted in PubMed and Embase databases from their inception to August 2017. Search keywords used to identify relevant articles were "von Willebrand Factor" OR "vWF" OR "hemostatic" AND "atrial fibrillation" AND "major adverse cardiac events" OR "mortality" OR "death". In addition, we also reviewed the reference lists of relevant articles to identify any additional studies. No limitation was imposed on language in the literature search. All literature searches were performed by 2 independent authors. This meta-analysis was

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conducted according to the checklist of the Meta-Analysis of Observational Studies in Epidemiology.[15] Ethical approval was not required because the present study reviewed the published studies.

2.2. Study selection

Inclusion criteria were the following: prospective studies enrolling patients with AF; baseline circulating vWF level as exposure; outcome of interests were MACEs and all-cause mortality; and provided multivariate-adjusted risk ratios (RRs) and 95% confidence intervals (CIs) for MACEs or all-cause mortality for the highest versus lowest category of vWF level. Exclusion criteria were studies provided risk estimate by continuous vWF level, and participants were not in the AF population.

2.3. Data extraction and quality assessment

Using a standard data extraction form, 2 authors independently extracted the following data: author's surname, year of publication, country of origin, study design, sample size, gender, mean age or age range of participants, vWF cutoff value, definition of MACEs, number of adverse events, mean or median follow-up time, multivariate-adjusted risk estimate, and maximum adjusted covariates. Two authors independently assessed the study quality using the Newcastle–Ottawa scale (NOS) for the cohort studies.[16] Total NOS score ranged from 0 to 9 stars. Studies achieving ≥7 stars were deemed as good quality. Any discrepancy in data extraction and quality assessment was resolved through discussion.

2.4. Statistical analyses

Meta-analyses were conducted using a generic inverse variance approach with STATA Version 12.0 (Stata, College Station, TX). The pooled RR with 95% CI of MACEs or all-cause death was calculated for the highest versus the reference low category of vWF level. A pooled RR > 1 suggested a worse prognosis in patients with AF with increased vWF level. The presence of statistical heterogeneity across studies was tested using Cochran Q statistics and I^2 statistics. For $P < .10$ values of the Cochran Q statistic or I^2 statistic ≥ 50%, the assumption of heterogeneity was present and a random-effects model was selected. Subgroup analyses were planned for the length of follow-up, cutoff value of vWF, sample size, anticoagulated drugs, and form of AF. A leave-one-out sensitivity analysis was performed to examine the magnitude of influence of each study on pooled risk estimate. Begg rank correlation test and Egger regression test were used to detect publication bias.

3. Results

3.1. Search results and study characteristics

A total of 175 articles were identified from the initial literature search. We removed 156 articles after abstracts or titles were scanned, leaving 19 potentially relevant articles for full-text evaluation. After applying our predefined inclusion criteria, 13 articles were further removed. Thus, 6 studies[12,13,17–20] were finally included in the meta-analysis (Fig. 1).

Table 1 summarizes the baseline characteristics of the individual studies. All of these studies were published between 2003 and 2017. These studies were conducted in Germany,[12] Italy,[19] Spain,[20] Austria,[13] and United Kingdom.[17,18] A total of 4008 patients with AF were identified and analyzed. Individual study sample sizes varied from 269 to 1215, and the length of the follow-up ranged from 1.58 years to 7.0 years. Three studies[13,17,20] with 7 NOS stars were considered as good quality, and others[12,18,19] achieved 6 stars indicating moderate quality.

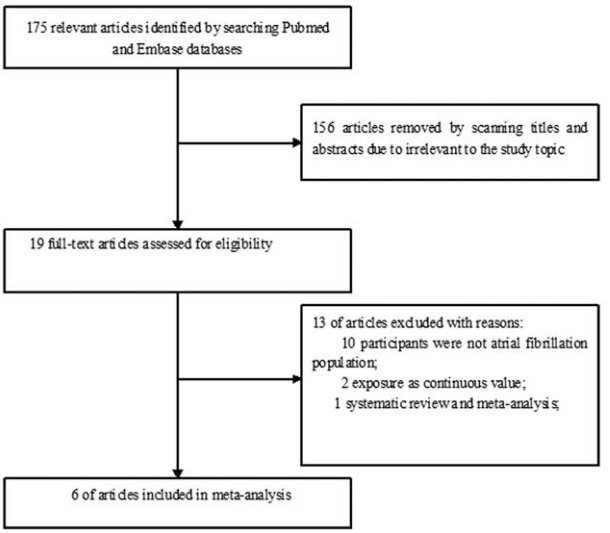

Figure 1. Flowchart of studies selection process.

3.2. Major adverse cardiac events

Six studies[12,13,17–20] reported the association of vWF level with MACEs. Meta-analysis showed that the pooled multivariate RR for MACEs was 2.20 (95% CI 1.61–3.01) for the highest versus the lowest category of vWF level in a random effect model (Fig. 2). A substantial heterogeneity between studies was observed ($I^2 = 66.9\%$; $P = .010$). There was no evidence of publication bias according to the results of Begg rank correlation test ($P = 1.000$) or Egger regression test ($P = .924$). A leave-one-out sensitivity analysis did not alter the statistical significance of the pooled risk estimate. A subgroup analysis showed that the association of the increased vWF level with MACEs was consistently observed in the length of follow-up, cutoff value of vWF, sample sizes, anticoagulated drugs, and form of AF subgroups (Table 2).

3.3. All-cause mortality

Four studies[12,13,18,20] reported the association of vWF level with all-cause mortality. As shown in Figure 3, there was no evidence of significant heterogeneity ($I^2 = 28.7\%$; $P = .024$) across the included studies. Meta-analysis showed that the pooled multivariate RR for all-cause mortality was 1.63 (95% CI 1.39–1.91) for the highest versus lowest category of vWF level in a fixed-effect model.

4. Discussion

This meta-analysis summarized the evidence to date regarding the association of elevated circulating vWF level with clinical adverse outcomes in patients with AF. The main findings of our meta-analysis indicated that patients with AF with elevated vWF level

Table 1

Characteristics of the included studies.

Author, y	Region	Patients (% men)	Age, y	vWF cutoff value	Definition of MACEs	Event number HR (95% CI)	Follow-up (y)	Maximum adjusted covariates	Overall no
Conway et al, 2003[17]	UK	Nonvalvular AF; 994 (75)	69 ± 9	Upper vs Lowest tertile; >158 IU/dL vs < 131 IU/dL	Ischemic stroke, MI, or vascular death	MACEs: 68; 2.5 (1.20–5.0)	2.0	Age, prior cerebral ischemia, hypertension, DM, and moderate to severe left ventricular dysfunction	7
Ehrlich et al, 2011[12]	Germany	Any type of AF; 278 (63)	71 ± 10	>0.7 U/mL	MI, stroke, peripheral embolism or death	MACEs: 88; 1.56 (0.94–2.57) Total death: 75; 1.46 (0.84–2.53);	2.67	Age, DM, left ventricular ejection fraction, metallomatrix protease-2, soluble vascular adhesion molecule-1, and CHA_2DS_2 score	6
Roldan et al, 2011[18]	UK	Permanent AF receiving oral anticoagulated drugs; 829 (50)	70–80	≥221 IU/dL	Stroke/TIA, embolic/ischemic peripheral embolism, ACS, HF, and cardiac death	MACEs: 95; 2.71 (1.78–4.13); Total death: 69; 2.03 (1.24–3.32);	2.27	Age, male, DM, previous stroke, HF, CAD, current smoking, renal impairment, hypercholesterolemia	6
Krishnamoorthy et al, 2013[19]	Italy	Nonvalvular AF; 423 (55.6)	72.7 ± 8.4	Upper vs Lowest tertile; >105 IU/dL vs <72 IU/dL	Stroke, MI, and all-cause death	MACEs: 94; 3.8 (2.63–5.57)	1.58	Age, sex, hypertension, diabetes, previous stroke, heart failure, smoker, statin treatment, vitamin K antagonists, and aspirin treatment.	6
Freynhofer et al, 2013[13]	Austria	Patients with AF; 269 (57.6)	60–78	>1434.92 mU/mL	TIA/stroke, nonfatal MI, thromboembolic complications	MACEs: 88; 1.54 (0.88–2.68) Total death: 82; 2.84 (1.49–5.44);	5.46	Age, heart failure, CAD, peripheral arterial disease, type of AF, and ADAMTS13	7
Garcia-Fernández et al, 2017[20]	Spain	Anticoagulated nonvalvular AF; 1215 (49)	71–81	>190 IU/dL for analyzing MACEs; >184 IU/dL for analyzing total death	Stroke/TIA, systemic/ peripheral embolism, ACS, HF, and cardiac death	MACEs: 226; 1.77 (1.35–2.32); Total death: 498; 1.53 (1.28–1.84);	7.0	Age, sex, hypertension, DM, HF, ischemic heart disease, smoking, dyslipemia, previous stroke, or bleeding, alcohol abuse, renal disease, hepatic disease, antiplatelet drugs, CHA_2DS_2-VASc score	7

ACS = acute coronary syndrome, AF = atrial fibrillation, CAD = coronary artery disease, CI = confidence interval, DM = diabetes mellitus, HF = heart failure, HR = hazard ratio, MACEs = major adverse cardiac events, MI = myocardial infarction, NOS = Newcastle–Ottawa scale, TIA = transient ischemic attack, vWF = von Willebrand factor.

were significantly increased risk of all-cause mortality and MACEs. Determination of vWF level may contribute to risk stratification among patients with AF. In addition, the presence of increased vWF level may be incorporated into clinical scores for AF risk stratification and treatment strategies.

This is the first meta-analysis that provided evidence for an independent association of elevated vWF level with all-cause mortality and MACEs in patients with AF. Previous meta-analysis[21] failed to show an association of higher vWF level with stroke event in patients with AF. Prognostic value of circulating vWF for the development of all-cause mortality and MACEs among patients with AF was demonstrated in our meta-analysis. Prognostic role of increased vWF level may be different in various subtype of AF. Subgroup analysis revealed that increased vWF level likely exhibited a stronger impact on MACEs in nonvalvular AF than any other form of AF. Our subgroup analysis also showed the association of increased vWF level with MACEs risk seemed to be stronger for longer follow-up. Also, vWF as a

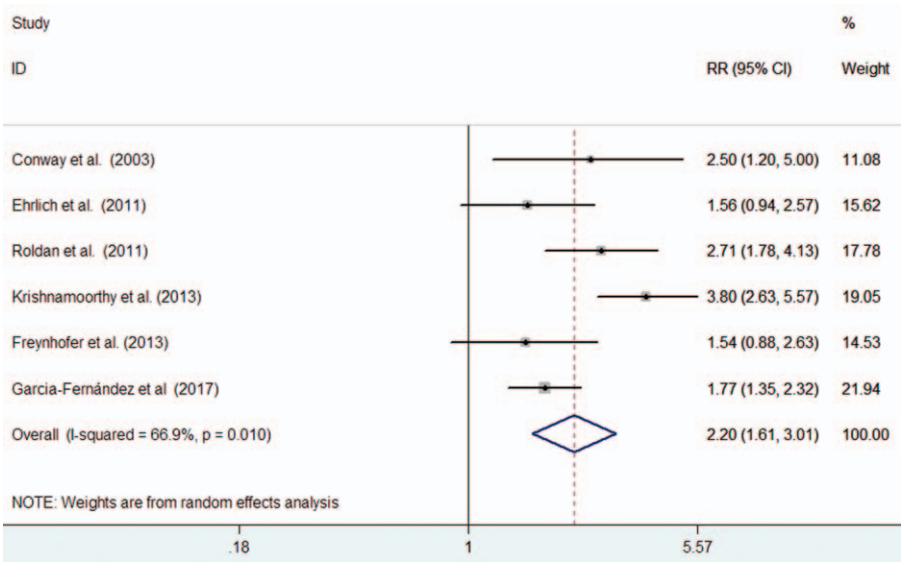

Figure 2. Forest plots showing pooled risk ratio (RR) with 95% confidence interval (CI) of major adverse cardiac events for the highest versus the lowest category of von Willebrand factor level.

Table 2

Subgroup analyses on major adverse cardiac events.

Subgroup	No of studies	Pooled RR	95% CI	Heterogeneity between studies
Type of AF				
Nonvalvular	3	2.54	1.46–4.40	$P=.005$; $I^2=81.0\%$;
Any type	3	1.92	1.30–2.83	$P=.149$; $I^2=47.5\%$
Sample size				
≥800	2	1.85	1.44–2.38	$P=.375$; $I^2=0.0\%$
<800	4	2.30	1.48–3.57	$P=.010$; $I^2=73.5\%$
Cutoff value of vWF				
Tertile	2	3.46	2.45–4.87	$P=.309$; $I^2=74.3\%$;
Single cutoff	4	1.87	1.47–2.38	$P=.248$; $I^2=27.3\%$
Follow-up duration, y				
≥5	2	1.72	1.35–2.20	$P=.655$; $I^2=0.0\%$;
<5	4	2.58	1.75–3.81	$P=.050$; $I^2=61.5\%$
Regular anticoagulant drugs				
Yes	2	2.12	1.40–3.21	$P=.095$; $I^2=64.1\%$;
No	4	2.22	1.35–3.66	$P=.011$; $I^2=73.0\%$

AF = atrial fibrillation, CI = confidence interval, RR = risk ratio, vWF = von Willebrand factor.

continuous variable was also predictive for all-cause mortality in patients with AF.[11]

Endothelial damage/dysfunction and inflammation are important pathologic alteration in AF.[22] vWF itself plays a pathogenetic role in atherogenesis and regulates the balance between hemostasis and thrombosis.[23] The increased risk of all-cause death and MACEs in AF may be correlated with the presence of a prothrombotic or hypercoagulable condition. Therefore, vWF could be considered as a potential clinical biomarker.

In line with these included studies, the significant and independent association of increased circulating vWF level with adverse outcomes was also reported in the general and other specific disease populations. vWF was an independent predictor of all-cause death in the population of community dwelling Japanese,[24] diabetic, and nondiabetic patients.[25] In patients with angiographically proven coronary artery disease, vWF was independent predictors of future cardiovascular mortality.[26] Increased vWF level was predictive of adverse cardiovascular outcome and death during 1-year follow-up in acute coronary syndrome and stable angina pectoris patients.[27]

Several limitations of the current meta-analysis need to be considered. First, the number of studies available for meta-analyzes was relatively small and substantial heterogeneity was present across studies in pooling MACEs ($I^2=70.0\%$; $P=.005$). The source of heterogeneity may be correlated with the type of AF, follow-up length, cutoff value of vWF, or different definition of MACEs. Second, included studies used different cutoff value of vWF to define higher vWF level and this meta-analysis could not determine the optimal cutoff value of vWF for predicting adverse outcomes. Third, circulating vWF level was only measured at baseline, and repeat measurements during follow-up of patients would improve diagnostic accuracy. Fourth, circulating vWF level is affected by several factors including vWF polymorphisms, systemic inflammation, blood type, and ADAMTS13 activity.[28] Lack of adjustment for these residual confounding factors in the statistical model could have slightly overestimated the risk estimate. Finally, the patients with AF analyzed in the current

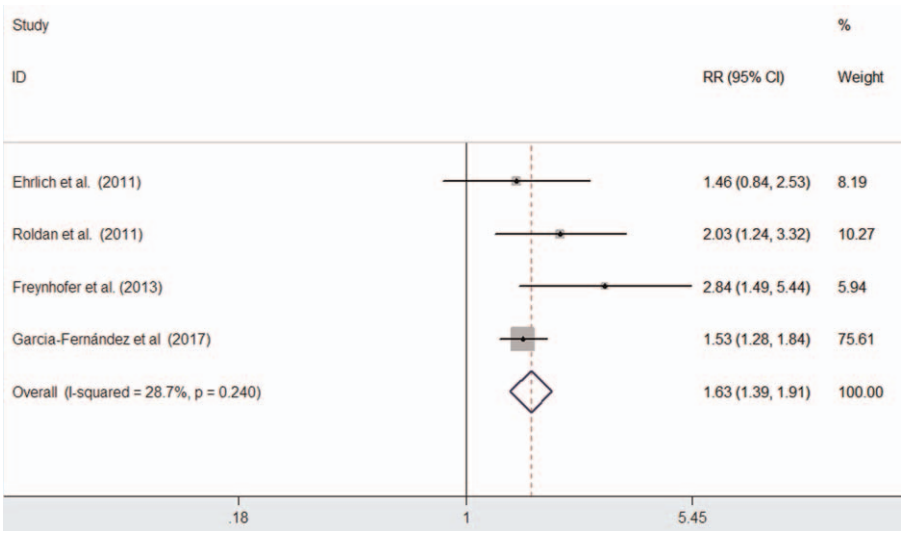

Figure 3. Forest plots showing pooled risk ratio (RR) with 95% confidence interval (CI) of all-cause mortality for the highest versus the lowest category of von Willebrand factor level.

meta-analysis were predominantly elderly people, so generation of our findings to the younger patients should be with caution.

5. Conclusion

Elevated vWF level at baseline is significantly associated with higher risk of MACEs and all-cause mortality in elderly patients with AF. This risk seems more pronounced in patients with nonvalvular AF. However, more well-designed prospective studies are needed to confirm these findings.

Author contributions

Conceptualization: Cheng Zhong.
Data curation: Minghua Xin, Lang He.
Formal analysis: Minghua Xin, Lang He.
Investigation: Minghua Xin, Lang He.
Methodology: Cheng Zhong, Minghua Xin.
Project administration: Cheng Zhong.
Resources: Minghua Xin.
Software: Guojian Sun.
Supervision: Cheng Zhong.
Validation: Cheng Zhong.
Writing – original draft: Guojian Sun.
Writing – review & editing: Farong Shen.

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