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References

[1] Mozaffarian D, Benjamin EG, Go AS, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation*. January 26, 2016;133(4):e38-e360.

[2] Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. *Am J Cardiol*. December 1, 2009;104(11):1534-1539.

[3] Packer DL, Kowal RC, Wheelan KR, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol*. April 23, 2013;61(16):1713-1723.

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WILEY CLINICAL CARDIOLOGY

CLINICAL INVESTIGATIONS

Atrial fibrillation and risk of cardiovascular events and mortality in patients with symptomatic peripheral artery disease: A meta-analysis of prospective studies

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Background: Atrial fibrillation (AF) is associated with adverse outcomes in terms of survival and morbidity. Peripheral artery disease (PAD) and AF share several common risk factors and often coexist. Whether AF has a prognostic role in patients with PAD has not been extensively studied.

Hypothesis: AF is associated with major adverse cardiac events (MACE) and mortality in symptomatic PAD patients.

Methods: Using MEDLINE and Scopus, we searched for studies published before December 2016 that evaluated cardiovascular outcomes based on the presence/absence of AF in a prospective manner with a follow-up period of ≥12 months. The outcomes were reported using a random-effects model, and heterogeneity was assessed using the I^2 statistic. Sensitivity analyses were performed to test the contribution of each study to the overall results.

Results: Six prospective studies (Newcastle-Ottawa score range, 7–9) with 14 656 patients were included in the final analysis (age range, 66–70 years; median follow-up, 1.4 years). Our pooled analysis found a significant association between AF and mortality (odds ratio: 2.52, 95% confidence interval: 1.91-3.34, I^2 = 32.6%), without evidence of publication bias (P = 0.63). Meta-analysis showed a significant impact of AF on MACE (odds ratio: 2.54, 95% confidence interval: 1.78-3.63, I^2 = 74.3%), without detected publication bias (P = 0.08).

Conclusions: AF is associated with increased risk of mortality and MACE in symptomatic PAD.

KEYWORDS

Atrial Fibrillation, Cardiovascular Events, Meta-Analysis, Mortality, Peripheral Artery Disease

1 | INTRODUCTION

Atrial fibrillation (AF) and peripheral artery disease (PAD) are quite prevalent in the aging population and often coexist.[1] They share many common risk factors, including hypertension (HTN), diabetes mellitus (DM) and obesity, and are both associated with increased cardiovascular (CV) mortality and ischemic CV events.[1] Vascular disease was found to increase the risk of AF and complications associated with AF.[2] Recently, vascular disease (including myocardial infarction [MI], aortic plaque, and PAD) was included in the CHA_2DS_2-VASc (congestive heart failure, HTN, age ≥ 75 years, DM, prior stroke, vascular disease, age 65–74 years, sex category) risk score, thus underlining the importance of PAD as a prognostic factor in patients with AF.[3]

Although systematic reviews and meta-analyses undoubtedly showed the association of AF with increased risk of mortality in patients with coronary artery disease (CAD),[4,5] the prognostic implication of AF in PAD was not extensively studied. Therefore, we performed a comprehensive systematic review and meta-analysis of available studies to assess the prognostic effect of AF to predict risk of major adverse cardiovascular events (MACE) and mortality in patients with symptomatic PAD.

2 | METHODS

2.1 | Search strategy

During the conduct of this meta-analysis, we followed Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[6] We

performed a systematic literature search of MEDLINE and Scopus for all studies published between January 1993 and December 2016 without language restriction, using the following medical subject headings: "atrial fibrillation," "peripheral artery disease," "peripheral vascular disease," "critical limb ischemia," "cardiovascular outcome," and "mortality." Additional studies were identified by manual search of references of original studies or review studies.

2.2 | Study inclusion and outcomes

We included prospective cohort studies that evaluated the prognostic impact of AF on all-cause mortality and/or MACE (composite endpoint of MI, stroke, and death) in patients with symptomatic PAD (intermittent claudication and/or critical limb ischemia [CLI]) with a follow-up period of ≥12 months. All patients were categorized based on the presence or absence of AF (electrocardiographic evidence of arrhythmia) at the time of enrollment, and clinical outcomes of AF patients were compared with non-AF patients.

2.3 | Data extraction and quality assessment

Study selection and data extraction were conducted independently by 2 investigators (MV, AVP). Any disagreements or differences in the data extraction between the 2 authors were harmonized by consensus after rechecking the source data. Study quality was assessed using the validated Newcastle-Ottawa Scale for assessment of nonrandomized and observational studies, and studies were evaluated based on subject selection, comparability of study groups, and assessment of the outcome.[7] Completed database contained the following data: name of the first author; year of publication; country of origin; study design; total number of patients in each study; the number of patients with AF; the proportion of patients with HTN, DM, CAD, and CLI; medical treatment (ie, the use of anticoagulants, antiplatelet drugs, statins, and angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin II receptor blockers [ARBs]); the percentage of patients who died and experienced MACE in each group (with and without AF); the follow-up period; conduction of multivariate analysis; and confounding factors. The studies included symptomatic PAD patients suffering from CLI together with patients with intermittent claudication. One study reported the values of ankle-brachial index.[8]

2.4 | Statistical analysis

Meta-analysis of outcome was reported using a random-effects model, and pooled odds ratio (OR) was reported with 95% confidence interval (CI). Statistical heterogeneity was assessed using the Cochrane Q test and I^2 statistic. Statistically significant heterogeneity was considered present at $P < 0.10$ and $I^2 > 50\%$. The Begg and Mazumdar rank correlation test was used to assess the risk for publication bias. Sensitivity analyses were performed by excluding trials 1 at a time to test the contribution of each study to the pooled estimates. Analyses were conducted using statistical software StatsDirect version 3.0.165 (StatsDirect Ltd., England, United Kingdom).

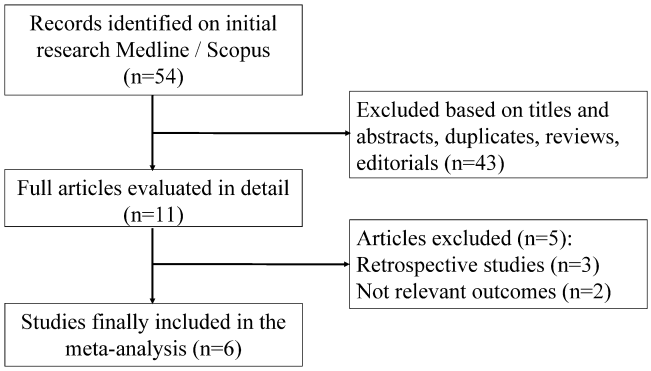

FIGURE 1 Study flow diagram for meta-analysis of AF and PAD outcomes. Abbreviations: AF, atrial fibrillation; PAD, peripheral artery disease

3 | RESULTS

3.1 | Selected studies and baseline characteristics

A total of 54 citations were obtained from electronic search. After reading titles and abstracts, followed by review of potentially relevant studies, 6 prospective studies were included in final analysis,[8–13] including a total of 14 656 patients (Figure 1). A median follow-up period was 1.4 years (range, 1.0–2.0 years). The study characteristics are listed in Table 1. The mean age of the population was 68 years (range, 66–70 years); 69% (range, 59%–85%) were males; 71% (range, 36%–87%) had HTN; 48% (range, 21%–59%) had CAD; and 42% (range, 31%–54%) had DM. Three studies[9,12,13] reported the prevalence of patients with CLI, which on average was 22% (range, 18%–42%). The average prevalence of AF among PAD patients was 11.4% (range, 8.0%–17.9%). $CHADS_2$ (congestive heart failure, HTN, age > 75 years, DM, stroke) scores differed between groups with and without AF (2.51 vs 2.01, respectively). Both groups were comparable in the use of statins (73% vs 77%) and ACEIs/ARBs (75% vs 70%), with more frequent use of anticoagulants (55% vs 8%) and less frequent use of antiplatelet drugs (58% vs 87%) in the AF group (Table 1). The combined use of anticoagulants and antiplatelet medications in patients with AF was reported in 3 studies[9,11,12] and was on average 16% (range, 8%–30%). Multivariate statistical analysis was performed in 5 studies.[8–11,13] Three studies reported the cause of death,[9,11,13] and CV death comprised 62% (range, 52%–67%). Using the Newcastle-Ottawa scoring system, the median score for included studies was 8 (range, 7–9).

3.2 | Quantitative data synthesis

In pooled analysis, there was a significant association between AF and mortality (OR: 2.52, 95% CI: 1.91-3.34; Figure 2A). The analysis of pooled studies showed a low to moderate heterogeneity (I^2 = 32.6%, Cochran Q = 5.93, P = 0.20), without evidence of publication bias (P = 0.63). None of the studies had a significant impact on the overall OR or the statistical significance (Table 2).

Meta-analysis of studies that reported MACEs showed a significant impact of AF on CV outcomes (OR: 2.54, 95% CI: 1.78-3.63; Figure 2B). Significant heterogeneity was observed across the studies (I^2 = 74.3%, Cochran Q = 15.58, P = 0.004), without detected publication bias (P = 0.08).

TABLE 1 Characteristics of studies included in meta-analysis

Author, Year	Country	No. of Patients	Mean Age, y	Male Sex, %	Follow-up, y	AF, %	HTN, %	CAD, %	DM, %	CLI, %	$CHADS_2$ Score, AF/non-AF	Anticoagulants, AF/Non-AF, %	Antiplatelets, AF/Non-AF, %	Statins, AF/Non-AF, %	ACEI/ ARB, AF/Non-AF, %	MACE, AF/Non-AF, %	Mortality, AF/Non-AF, %	NOS, 0–9	Confounders
Aguilar, 2012	Spain	1308	66	74	1.3	12.4	69	NR	39	20.3	NR	64/7	36/90	68/81	81/74	19/7	11/4	7	–
Conway, 2004	United Kingdom	388	70	59	1.4	8.0	36	21	31	NR	NR	NR	NR	NR	NR	NR	56/33	7	Age, sex, CAD
Goto, 2008	Japan	7716	69	64	1.0	11.5	82	59	44	NR	2.79/ 2.16	53/7	58/81	81/83	75/73	8/5	6/4	8	Age, sex, DM, HTN, HLP, smoking
Sanclemente, 2014	Spain	1270	66	85	1.2	11.7	68	23	45	18.0	NR	NR	NR	NR	NR	32/12	15/6	9	Age, sex, DM, CAD, CKD, medications
Vrsalovic, 2016	Croatia	319	70	66	2.0	17.9	87	41	54	42.0	2.64/ 1.99	100/6	94/96	41/55	63/68	49/19	NR	8	Age, sex, CAD, CLI, CKD, DM, HTN, HLP, smoking, medications
Winkel, 2010	Netherlands	3655	68	75	1.8	10.4	53	39	37	NR	2.1/1.9	52/10	63/96	61/63	73/61	13/6	6/2	8	Age, sex, DM, HTN, CAD, stroke, smoking

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; $CHADS_2$, congestive HF, HTN, age > 75 years, DM, stroke; CKD, chronic kidney disease; CLI, critical limb ischemia; DM, diabetes mellitus; HF, heart failure; HLP, hyperlipidemia; HTN, hypertension; MACE, major adverse cardiovascular events; NOS, Newcastle-Ottawa score; NR, not reported.

4 | DISCUSSION

The prognostic role of AF, although well established in ischemic heart disease, was not comprehensively examined in PAD patients. According to our meta-analysis, the coexistence of PAD and AF identified high-risk patients for MACE and mortality.

PAD is a marker of advanced atherosclerotic disease.[14,15] Because involvement of multiple vascular territories (and frequently associated CAD) is often present in PAD patients, these patients have an increased risk for CV ischemic events and CV death.[16] They represent a population at high CV risk that is comparable to individuals with previous MI, coronary revascularization, and other arterial revascularization procedures.[14] Consequently, current guidelines recommend that PAD patients receive optimal medical treatment (ie, antiplatelet therapy and lipid-lowering agents [statins]), together with smoking cessation and ACEIs, as they substantially reduce the likelihood of adverse CV outcomes.[14] At the same time, according to guidelines, patients with AF and stable vascular disease (arbitrarily defined as being free from any acute ischemic event or repeat revascularization for >1 year) should be managed with oral anticoagulants alone, without antiplatelet therapy.[17] In our meta-analysis, both groups of patients were comparable in the use of statins and ACEI/ARBs. Less frequent use of antiplatelet drugs was reported in the AF group of patients (58% vs 87%), 55% of AF patients received anticoagulation treatment, and the combined use of anticoagulants and antiplatelet medications averaged at 16%. Thus, the above-mentioned treatment differences could be, at least in part, responsible for the increased CV risk in PAD patients with AF.

On the other hand, AF itself is associated with elevated inflammatory biomarkers (C-reactive protein and interleukin-6), together with increased platelet activation, thrombin generation, and endothelial dysfunction.[18–20] So, it is plausible that AF in a patient with PAD predisposes them to a pro-inflammatory and prothrombotic state that may promote plaque destabilization and plaque rupture with consequent unfavorable CV events.

In line with our meta-analysis, AF was associated with almost a doubling in mortality in subjects from the original cohort of the Framingham Heart Study, even after adjustment for the preexisting CV conditions that were related to AF.[21] Moreover, the recently published meta-analysis revealed that AF was associated with a 71% increased risk of MI in patients free of CAD at baseline.[22]

AF and PAD share several common CV risk factors, including age, HTN, DM, and obesity.[1,2] Our analysis showed that $CHADS_2$ scores differed between groups with and without AF, suggesting a population at higher risk for ischemic events. So, the increased risk for CV events may be attributed to the comorbidities together with inflammation and increased prothrombotic activity associated with AF. Therefore, more attention should be paid to patients in whom coexistence of AF and PAD occurs, as they represent a vulnerable subgroup at a very high risk for adverse outcomes. In this way, AF in patients with PAD may serve as a surrogate marker of more severe disease with subsequent poor CV outcomes in terms of survival and morbidity.

The results of our systematic review and meta-analysis, which included high-quality prospective cohort studies, for the first time clearly showed the increased risk of all-cause mortality rates and MACE in patients with coexisting AF and symptomatic PAD. These findings are in

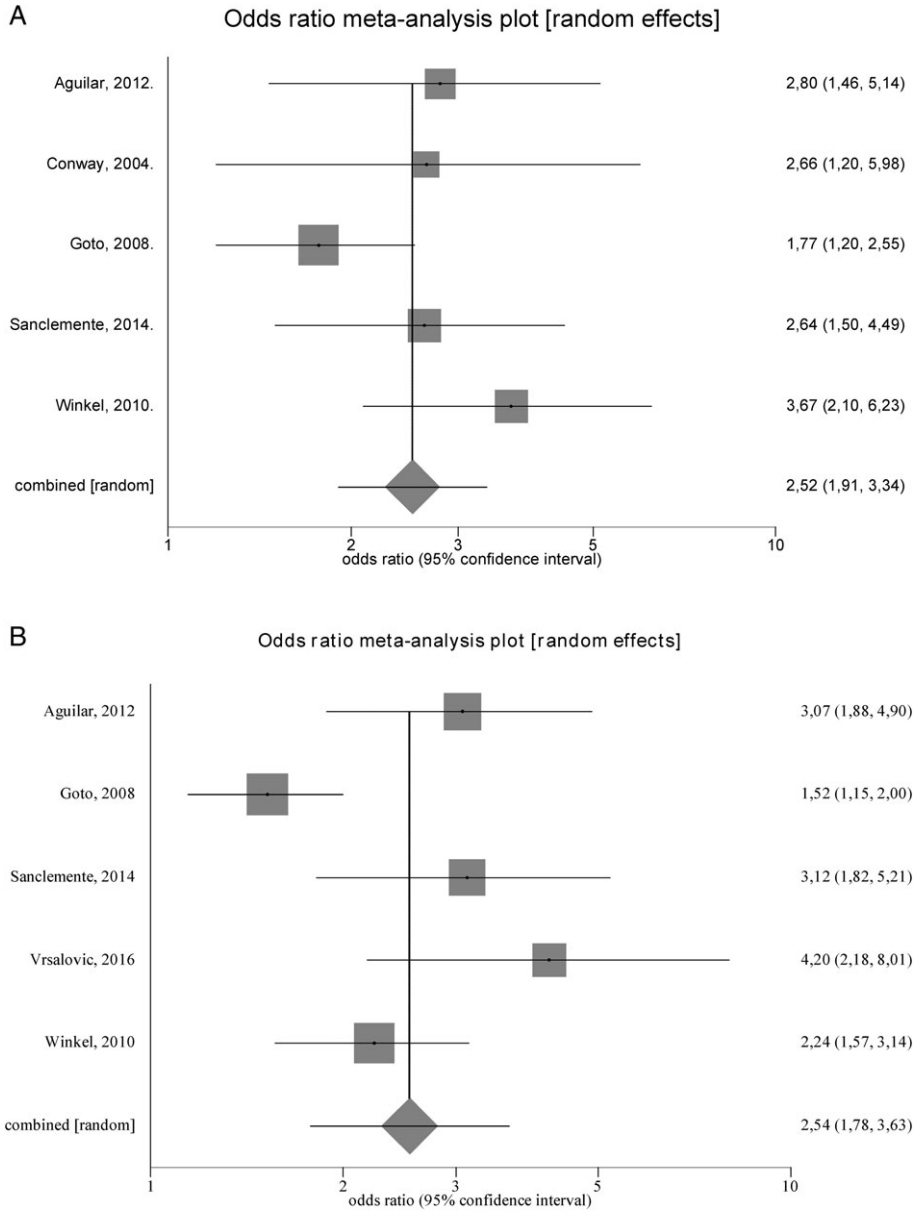

FIGURE 2 Meta-analysis (random-effects model) testing the prognostic impact of AF on (A) all-cause mortality and (B) MACE in patients with symptomatic PAD. Abbreviations: AF, atrial fibrillation; MACE, major adverse cardiac events; PAD, peripheral artery disease

TABLE 2 Sensitivity analyses excluding 1 study at a time

	MACE			Mortality		
Author, Year	**OR**	**95% CI**	**I^2, %**	**OR**	**95% CI**	**I^2, %**
Aguilar, 2012	2.44	1.61-3.69	77.1	2.50	1.77-3.55	47.1
Conway, 2004	–	–	–	2.54	1.81-3.56	48.9
Goto, 2008	2.86	2.22-3.69	21.7	2.97	2.24-3.94	0
Sanclemente, 2014	2.44	1.61-3.67	77.5	2.54	1.76-3.66	48.4
Vrsalovic, 2016	2.30	1.61-3.28	72.3	–	–	–
Winkel, 2010	2.69	1.64-4.42	80.7	2.21	1.73-2.83	0

Abbreviations: CI, confidence interval; MACE, major adverse cardiovascular events; OR, odds ratio.

line with previously published meta-analyses on the prognostic role of AF in CAD.[4,5,22] As warfarin and other vitamin K antagonists are known to increase vascular calcification and calcification of coronary arteries, future trials are needed to evaluate the potential benefit of direct oral anticoagulants in patients with atherosclerotic vascular disease and AF.[23]

Further prospective studies are needed to evaluate the prognostic role of AF in the whole spectrum of symptomatic and asymptomatic patients with peripheral vascular disease.

4.1 | Study limitations

Only patients who had symptomatic PAD of the lower extremities were included; therefore, asymptomatic patients and those with PAD of arteries other than lower-limb arteries were not evaluated in this systematic review.

Characteristics of patients with and without AF may very well differ, and thus the effect of AF may be confounded by other comorbidities.

The various types of AF (paroxysmal, persistent, permanent) were not differentiated in the included studies. The effect of AF type on CV outcomes in PAD patients needs further evaluation in future prospective clinical trials. The information about patients with asymptomatic episodes of AF or patients who may have developed AF during follow-up does not exist in the studies included in the meta-analysis.

5 | CONCLUSION

The results of this systematic review and meta-analysis showed that AF is associated with an increased risk of mortality and MACE in patients with symptomatic peripheral vascular disease.

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Conflicts of interest

The authors declare no potential conflicts of interest.

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REFERENCES

1. Olesen JB, Gislason GH, Torp-Pedersen C, et al. Atrial fibrillation and vascular disease—a bad combination. *Clin Cardiol.* 2012;35(suppl 1):15–20.
2. Ruff CT, Bhatt DL, Steg PG, et al; REACH Registry Investigators. Long-term cardiovascular outcomes in patients with atrial fibrillation and atherothrombosis in the REACH Registry. *Int J Cardiol.* 2014;170:413–418.
3. Olesen JB, Lip GY, Lane DA, et al. Vascular disease and stroke risk in atrial fibrillation: a nationwide cohort study. *Am J Med.* 2012;125:826.e13–826.e23.
4. Jabre P, Roger VL, Murad MH, et al. Mortality associated with atrial fibrillation in patients with myocardial infarction: a systematic review and meta-analysis. *Circulation.* 2011;123:1587–1593.
5. Erez A, Goldenberg I, Sabbag A, et al. Temporal trends and outcomes associated with atrial fibrillation observed during acute coronary syndrome: real-world data from the Acute Coronary Syndrome Israeli Survey (ACSIS), 2000–2013. *Clin Cardiol.* 2017;40:275–280.
6. Stroup DF, Berlin JA, Morton SC, et al; Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA.* 2000;283:2008–2012.
7. Wells GA, Shea B, O'Connell D, et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses*. Ottawa, Canada: Ottawa Health Research Institute; 1999. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed September 4, 2016.
8. Goto S, Bhatt DL, Röther J, et al; REACH Registry Investigators. Prevalence, clinical profile and cardiovascular outcomes of atrial fibrillation patients with atherothrombosis. *Am Heart J.* 2008;156:855–863.
9. Vrsalović M, Vučur K, Jelakovic B. Atrial fibrillation predicts cardiovascular outcome in hypertensive patients with symptomatic peripheral artery disease and preserved ejection fraction. *J Clin Hypertens (Greenwich).* 2016;18:953–954.
10. Conway DS, Lip GY. Comparison of outcomes of patients with symptomatic peripheral artery disease with and without atrial fibrillation (the West Birmingham Atrial Fibrillation Project). *Am J Cardiol.* 2004;93:1422–1425.
11. Winkel TA, Hoeks SE, Schouten O, et al. Prognosis of atrial fibrillation in patients with symptomatic peripheral arterial disease: data from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Eur J Vasc Endovasc Surg.* 2010;40:9–16.
12. Aguilar E, García-Díaz AM, Sánchez Muñoz-Torrero JF, et al; FRENA Investigators. Clinical outcome of stable outpatients with coronary, cerebrovascular or peripheral artery disease, and atrial fibrillation. *Thromb Res.* 2012;130:390–395.
13. Sanclemente C, Yeste M, Suarez C, et al. Predictors of outcome in stable outpatients with peripheral artery disease. *Intern Emerg Med.* 2014;9:69–77.
14. Tendera M, Aboyans V, Bartelink ML, et al; European Stroke Organisation, ESC Committee for Practice Guidelines. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *Eur Heart J.* 2011;32:2851–2906.
15. Vrsalović M, Vučur K, Car B, et al. C-reactive protein, renal function, and cardiovascular outcome in patients with symptomatic peripheral artery disease and preserved left ventricular systolic function. *Croat Med J.* 2015;56:351–356.
16. Vrsalović M, Vučur K, Vrsalović Presečki A, et al. Impact of diabetes on mortality in peripheral artery disease: a meta-analysis. *Clin Cardiol.* 2017;40:287–291.
17. Lip GY, Windecker S, Huber K, et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). *Eur Heart J.* 2014;35:3155–3179.
18. Gedikli O, Dogan A, Altuntas I, et al. Inflammatory markers according to types of atrial fibrillation. *Int J Cardiol.* 2007;120:193–197.
19. Akar JG, Jeske W, Wilber DJ. Acute-onset human atrial fibrillation is associated with local cardiac platelet activation and endothelial dysfunction. *J Am Coll Cardiol.* 2008;51:1790–1793.
20. Lim HS, Willoughby SR, Schultz C, et al. Effect of atrial fibrillation on atrial thrombogenesis in humans: impact of rate and rhythm. *J Am Coll Cardiol.* 2013;61:852–860.
21. Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation.* 1998;98:946–952.
22. Guo XY, Li N, Du X, et al. Atrial fibrillation is associated with an increased risk of myocardial infarction: insights from a meta-analysis. *Atherosclerosis.* 2016;254:1–7.
23. Osawa K, Nakanishi R, Win TT, et al. Rationale and design of a randomized trial of apixaban vs warfarin to evaluate atherosclerotic calcification and vulnerable plaque progression. *Clin Cardiol.* 2017. https://doi.org/10.1002/clc.22746.

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