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Original Article

Higher circulating visfatin levels are associated with increased risk of atrial fibrillation and major adverse cardiovascular events in patients with acute ST-elevation myocardial infarction

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Abstract: Background: Circulating visfatin levels has reflected the long-term survival in patients with ST-elevation myocardial infarction myocardial infarction (STEMI). We postulated that higher visfatin would be linked to increased risk for atrial fibrillation (AF) and major adverse cardiovascular events (MACEs) in patients with STEMI treated with primary percutaneous coronary intervention (PPCI). Methods: Of the 604 patients with acute STEMI underwent the PPCI were enrolled in the study. ELISA was used to measure plasma visfatin concentrations. One-year MACEs and adverse events, were compared between patients with and without new-onset AF after PPCI, and using statistical analyses to respectively analyze the relationship between plasma visfatin level and MACEs, plasma visfatin level and new-onset AF. Results: Of the 604 patients, new-onset AF developed in 42 (6.95%). Compared with patients without AF after PPCI, patients with new-onset AF had higher 1-year rates of MACEs (30.95% vs 18.15%, P<0.05). Moreover, compared with patients with low plasma visfatin levels (visfatin ≤14.5 ng/ml), patients with higher plasma visfatin levels (visfatin >14.5 ng/ml) had higher 1-year rates of MACEs (26.50% vs 9.92%, P<0.001) and new-onset AF (10.24% vs 2.94%, P<0.001). Analysis with multivariate Cox hazard regression model revealed that the independent predictors for the occurrence of new-onset AF were plasma visfatin level (hazard ratio [HR] 1.51, 95% confidence interval [CI] 1.03 to 2.23, P=0.021) at 1 year. Conclusion: Plasma visfatin levels have a positive correlation with AF and MACEs in patients with acute STEMI treated with PPCI.

Keywords: Visfatin, atrial fibrillation, acute ST-elevation myocardial infarction, major adverse cardiovascular events

Introduction

The prevalence of ST-segment elevation myocardial infarction (STEMI) is increasingly worldwide and a leading cause of morbidity and mortality in the past decades [1]. Knowingly, the process that inflammation lead cause of atherosclerosis (AS) plays critical and continuous roles on the initiation and progression of STEMI [2], and increased serum level of inflammatory biomarker such as high sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6), which has been known as an important medium for initiation and progression of AS [3] and the pathogenesis of major adverse cardiovascular events (MACEs) [4, 5]. Previously, clinical epidemiological studies showed that hyperlipidemia is not the only cause of inflammation development in AS, and that a broader treatment approach tackling the initiation and progression of STEMI risk factors is required [6]. Recent work in hyperlipidemia research has revealed that adipocytokines contribute to AS, and when their production is not properly regulated, which can lead to STEMI [7]. In particular, the adipocyte-derived hormone adipocytokines increase with higher adiposity and adipose-tissue inflammation, has demonstrated inflammatory and cardiactoxicity properties in experimental studies [8-10].

A novel adipocytokine, visfatin, was found identical to pre-B cell colony-enhancing factor (PBEF) and mainly produced in visceral fat in mammal animal and humans [11]. In a hyperlipidemia and hyperglycemia patients, as compared to normal patients, visfatin induces macrophage accumulation and endothelial dysfunction, enlarge necrotic lipid-core volume and weaken fibrous cap of coronary atherosclerotic plaque [12-14]. Previously, a lot of studies showed that increased plasma level of visfatin was associated with increased risk of acute myocardial infarction such as STEMI [15]. In particular, heightened circulating visfatin levels have been positively correlated with the multiple inflammatory cytokine such as hs-CRP. Therefore, visfatin may be incorporate into cardiovascular diseases risk assessment algorithm. This raises the possibility that increased circulating levels of visfatin could help precipitate changes to circulating inflammatory the necessary for the development of AF and MACEs [16, 17]. Therefore, we investigated whether increased plasma level of visfatin is independently associated with the impact of new-onset AF with STEMI after PPCI, and our study may shed light on that visfatin could be used as a predictor for new-onset AF risk in the patients with STEMIs after PCI.

Patients and methods

Studied subjects and protocols

Studied subjects were enrolled from January of 2012 to April of 2015 after informed consent was obtained, and our current study was recruited from the First Affiliated Hospital of the University of South China and the Second Xiangya Hospital of the Central South University. Patients with STEMIs presenting within 12 hours of symptom onset were received both unfractionated and heparin aspirin plus either clopidogre or ticagrelor, and then immediate coronary angiography before primary PCI. Patients eligible for stenting were to receive TAXUS Express 2 paclitaxel-eluting stents (Boston Scientific Corporation, Natick, Massachusetts) or to an otherwise identical Express drug-metal stent (LEPU Medical Corporation, Beijing).

Clinical follow-up was performed at 30 days, 6 months, and 1 year after admission using a standardized protocol that included outpatient visits, telephone contacts and the recording of recurrent cardiac events. Use of warfarin or any long-term oral anticoagulation pills before this study and major contraindication to long-term anticoagulation drugs, cardiac functional insufficiency and had history of AF were major exclusion criteria to this study. AF was defined as the absence of P waves and atrial activity represented by fibrillatory waves and irregular RR intervals [18]. Patients were classified as having new-onset AF if they had no AF at presentation and no history of AF (including a history of paroxysmal AF or the treatment of AF) but had ≥1 episode of AF recorded on electrocardiography or telemetry during the index hospitalization after PPCI [18].

Demographic characteristics including BMI, age, gender, family history of cardiovascular disease (CVD), hypertension and diabetes mellitus were recorded by questionnaire and were double-checked by three experts of cardiology. Fasting venous blood at admission was drawn for the assessment of fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), hs-CRP and glycated hemoglobin (HbA1c). Plasma level of visfatin at admission was measured by enzyme-linking immune-absorbent assay (ELISA, Biosource International, USA) with a sensitivity of 602 pg/ml. All performances were conducted in accordance to manufacture's instruction and three independent experiments were performed in duplicate. The study was conducted in agreement with the guidelines approved by the Human Research Ethics Committee at both University of South China and Central South University, all patients gave informed consent to the study and was performed conform the Declaration of Helsinki.

Studied endpoint

The endpoints were the composite occurrence of MACEs, including death and nonfatal outcomes; i.e., recurrent myocardial infarction (re-MI) or clinically driven target lesion revascularization (TLR) (within the stent + 5 mm in both proximal and distal directions). Death was defined as all causes of death. Re-MI was defined by the presence of recurrent ischemic symptoms or electrocardiographic changes accompanied by a CK-MB concentration that was more than twice the upper limit of the nor-

Table 1. Clinical, angiographic, and procedural characteristics at baseline according to the presence or absence of new-onset atrial fibrillation after percutaneous coronary intervention

Variable	New-Onset AF		*P*-value
	Yes (n=42)	No (n=562)	
Age (years)	59.00 ± 13.52	60.90 ± 11.92	NS
Men	34/42 (80.95%)	477/562 (84.87%)	NS
Diabetes mellitus	14/42 (33.33%)	90/562 (16.01%)	<0.001
Hypertension*	28/42 (66.67%)	288/562 (51.24%)	<0.001
Hyperlipidemia&	21/42 (50.00%)	225/562 (40.04%)	<0.001
Clinical and Laboratory			
BMI	26.40 (24.22-29.84)	26.62 (24.53-30.01)	NS
FBG (mmol/L)	5.91 (5.02-8.32)	5.31 (3.68-7.59)	0.022
HbA1c (%)	6.72 ± 1.37	6.14 ± 1.29	0.019
Lp (a) (mmol/L)	176.97 (101.17-291.26)	176.23 (91.58-411.12)	NS
TC (mmol/L)	4.94 ± 1.19	4.45 ± 1.01	NS
TG (mmol/L)	1.96 ± 1.15	1.61 ± 0.96	NS
LDL-C (mmol/L)	3.12 ± 1.19	2.67 ± 1.12	NS
HDL-C (mmol/L)	0.76 ± 0.19	0.92 ± 0.22	NS
apoA (mmol/L)	0.99 ± 0.19	1.08 ± 0.22	NS
apoB (mmol/L)	0.85 ± 0.28	0.83 ± 0.18	NS
Hs-CRP (mmol/L)	1.76 (1.14-3.12)	1.38 (1.07-2.87)	0.019
Visfatin (ng/ml)	24.70 (11.91-33.82)	18.62 (9.81-27.62)	0.039
Previous myocardial infarction	4/42 (9.52%)	56/562 (9.96%)	NS
≥2-vessel coronary artery disease	17/42 (40.47%)	232/562 (41.28%)	NS
Chronic renal insufficiency	3/42 (7.14%)	29/562 (5.16%)	NS
Baseline TIMI flow grade 0/1	30/42 (71.42%)	400/562 (71.17%)	NS
Postprocedural TIMI grade 3 flow	40/42 (95.23%)	548/562 (97.50%)	NS
Postprocedural blush grade 3	35/42 (83.33%)	466/562 (82.91%)	NS
Index PCI vessel			
Left anterior descending coronary artery	16/42 (38.09%)	215/562 (38.25%)	NS
Left circumflex coronary artery	6/42 (14.28%)	90/562 (16.01%)	NS
Right coronary artery	19/42 (45.23%)	253/562 (45.01%)	NS
Left main coronary artery	1/42 (2.38%)	9/562 (1.60%)	NS
Drug			
Clopidogrel therapy	20/42 (47.61%)	285/562 (50.71%)	NS
Ticagrelor therapy	22/42 (52.38%)	277/562 (49.28%)	NS
Stents			
Boston stents	12/42 (28.57%)	163/562 (29.00%)	NS
LEPU stents	30/42 (71.43%)	399/562 (71.00%)	NS

Data are expressed as median (interquartile range) or frequency (percentage). *History of and/or current hypertension (high arterial blood pressure) diagnosed per local standard criteria. &History of and/or current hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) diagnosed per local standard criteria.

mal range or more than 50% higher than the previous value measured during hospitalization. Stroke was defined as brain ischemia injury and disease bleeding symptoms as the main clinical manifestations. Advanced stroke requiring readmission was diagnosed on the basis of clinical signs, symptoms and cerebral CT or MRI findings.

The endpoints were the occurrence of AF. Case identification was based on: (i) interpretation of follow-up ECGs by the two cardiovascular specialist; (ii) the presence of diagnostic codes for AF on hospital discharges from two cardiovascular physician claims, except when these accompanied hospitalization for coronary bypass or valve replacement surgery; and (iii) diagnosis

Table 2. One-year clinical outcomes in patients with and without new-onset atrial fibrillation after percutaneous coronary intervention

Variable	New-Onset AF		HR (95% CI)	*P*-value
	Yes (n=42)	No (n=562)		
MACEs	13/42 (30.95%)	102/562 (18.15%)	2.16 (1.01-4.67)	0.039
Recurrent myocardial infarction	8/42 (19.04%)	50/562 (8.89%)	3.52 (1.22-10.2)	0.020
Death	6/42 (14.28%)	31/562 (5.51%)	4.32 (1.20-15.52)	0.026
Stroke	5/42 (11.90%)	29/562 (5.16%)	5.17 (1.38-19.39)	0.044

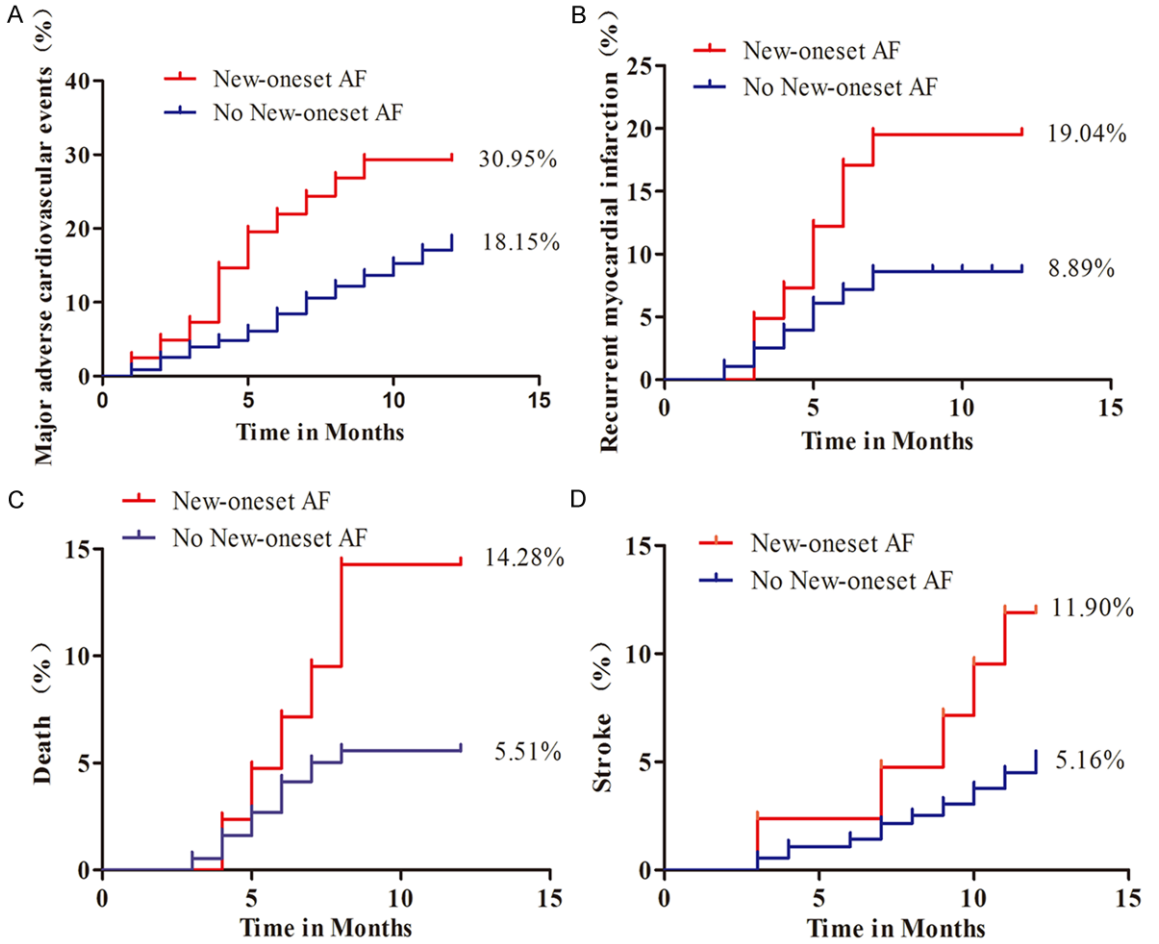

Figure 1. Kaplan-Meier curves showing cumulative event rates of ischemic and bleeding outcomes through 3 years according to the presence or absence of new-onset AF: (A) MACEs, (B) Recurrent myocardial infarction (C) Death, (D) Strokes.

of AF from two outpatient visits or physician carrier claims from Medicare data.

Statistical analyses

Continuous data was presented as mean ± SD or median (inter-quartile range) appropriately, and compared by the Student's t-test when data was normally distributed, otherwise compared by the Wilcoxon rank-sum test. Categorical data was presented as percentage and compared by χ^2 test. Univariate and multivariate regression analyses were performed to evaluate the relationship between visfatin and new-onset AF risk in patients with STEMIs. Follow-up analysis was performed using time-to-event data, to estimate the prognosis using the Kaplan-Meier method and the log-rank test.

Table 3. Major adverse cardiovascular events and according to plasma visfatin level

Variable	High (Visfatin >14.5 ng/ml)	Low (Visfatin ≤14.5 ng/ml)	*P*-value
	332	272	
Composite MACEs	88/332 (26.50%)	27/272 (9.92%)	<0.001
Definite/probable ST	11/332 (3.31%)	5/272 (1.83%)	NS
New-onset AF	34/332 (10.24%)	8/272 (2.94%)	<0.001
Recurrent myocardial infarction	42/332 (12.65%)	16/272 (5.88%)	0.021
Death	32/332 (9.63%)	5/272 (1.83%)	<0.001
Stroke	29/332 (8.73%)	5/272 (1.83%)	<0.001

Data are expressed as median (interquartile range) or frequency (percentage).

Table 4. Cox regression analysis for predictors of new-onset AF

Candidates Variable	Adjusted HR (95% CI)	*P*-value
Predictors of New-onset AF		
Visfatin	1.51 (1.03-2.23)	0.021
Hypertension	1.07 (1.00-1.07)	0.044
Diabetes mellitus	1.47 (1.04-2.07)	0.042
Hs-CRP	1.71 (1.17-2.49)	0.049

HR: hazard ratio, CI confidence interval.

Statistical analyses were performed by using SPSS software version 18.0 (SPSS, Inc., Chicago, Illinois). A value of $P<0.05$ was considered significant.

Results

Participants

A total of 604 STEMIs after PPCI were recruited from the First Affiliated Hospital of the University of South China and the Second Xiangya Hospital of the Central South University (see **Table 1**).

Baseline characteristics and outcomes

42 (6.95%) of 604 patients developed post-PPCI new-onset AF. Compared with patients without AF after PPCI, patients with new-onset AF had higher hs-CRP, FBG and visfatin levels, and had history of diabetes mellitus, hypertension and hyperlipidemia at baseline (**Table 1**). There were no differences in the rate of post-procedural TIMI grade 3, flow achieved, and index PCI vessel between the 2 groups at the end of the post-PCI. There were also no difference in the both clopidogrel and ticagrelor drugs, and both Boston and LEPU stents treated between the 2 groups at the end of the PPCI.

New-onset AF and rate of MACEs

One-year clinical follow-up outcomes in patients with and without new-onset AF post-PPCI are listed in **Table 2** and shown in **Figure 1**. Patients with new-onset AF had significantly higher 1-year rates of MACEs (30.95% vs 18.15%, P< 0.05), re-MI (19.04% vs 8.89%, P<0.05), death (14.28% vs 5.51%, P<0.05), stroke (11.28% vs 5.51%, P<0.05).

Visfatin levels and risk of AF or rate of MACEs

Based on Wei-Chin Hung et al [7] previous report that when plasma visfatin level >14.5 ng/ml is used for diagnosis of STEMIs, the sensitivity was 70.2%, and the specificity was 53.9%. Therefore, we use 14.5 ng/ml visfatin level as the criteria to distinguish between high visfatin and low visfatin groups, and the patients were divided into two groups. These 604 Patients were divided into high visfatin (>14.5 ng/ml) and low visfatin (≤14.5 ng/ml) post-PCI listing in **Table 3**. Patients with high visfatin had significantly higher MACEs (26.50% vs 9.92%, P<0.001), recurrent myocardial infarction (12.65% vs 5.88%, P<0.05), new-onset AF (10.24% vs 2.94%, P<0.001), death (9.63% vs 1.83%, P<0.001), and stroke (8.73% vs 1.83%, P<0.001).

The identifiable predictors of occurrence of new-onset AF post-PCI were visfatin (hazard ratio [HR] 1.51, 95% confidence interval [CI] 1.00 to 2.23, P<0.05), hypertension (HR 1.07, 95% CI 1.00 to 1.17, P<0.05), diabetes mellitus (HR 1.47, 95% CI 1.04 to 2.07, P<0.05), and hs-CRP (HR 1.71, 95% CI 1.17 to 2.49, P<0.05) at 1 year (**Table 4**).

Discussion

During the past decades, a lot of research focused on the potential role of adipocytokines in the development of atherosclerotic CVD [6]. Visfatin has been recognized as a novel adipo-

kine and biomarker of different-grade inflammation and cardiovascular diseases, and evidence from epidemiology and basic research also showed that down-regulated visfatin could retard AS progression and reduce cardiovascular events [15, 19, 20]. Therefore, the present study, drawn from a cohort of 604 patients, was designed to evaluate the incidence, predictors, and impact of new-onset AF in patients who undergo PPCI for STEMI with different-grade visfatin. The major results of the present analysis can be summarized as follows: (1) new-onset AF after PPCI was associated with higher rates of MACEs, recurrent myocardial infarction, death and stroke events at 1-year follow-up, and (2) high levels of visfatin after PPCI was a strong independent predictor of new-onset AF and MACEs at 1 year post-PPCI.

Several studies have reported a morbidity of new-onset AF with acute coronary syndromes (ACS) patients ranging from 2.3% to 21% [21, 22], and the most incidence of new-onset AF in ACS have been performed in patients with STEMIs [22], compared with 6.95% in our cohort. Moreover, in our studies visfatin, hs-CRP, and history of hypertension and diabetes mellitus were the identifiable independent predictors of the development of AF after PPCI. Other previously reported factors associated with the development of new-onset AF, such as right coronary artery and/or left anterior descending coronary artery infarct, and chronic renal insufficiency, and different glycoprotein IIb/IIIa inhibitors drugs, and different drug-coated stent were not replicated in our study. Our study inconsistency, combined with Garvey et al reports [18], may suggest that various inflammatory factors may contribute to the occurrence of new-onset AF after STEMI revascularization, but how to extent to successfully and without delay revascularization would to prevent or reverse these seriously handicap in a STEMI is still setting remains unknown.

Importantly, the present study was followed up for one year to track the adverse effect of new-onset AF after STEMI. Not only did patients with new-onset AF have much higher 1-year rates of major MACEs, but also they had significantly higher rates of re-MI, death and stroke. These results suggest that an incidental of new-onset AF at the time of admission has adverse influence in patients with STEMI. Unfortunately, we did not have data regarding the CHADS2-VASc and HAS-BLED scores in the group with new-onset AF. These data may be helpful in clarifying the susceptibility of patients in this group to stroke events.

Adipokines have gained regard as risk markers for CVD and, potentially, AF [23]. Higher adipokines levels have been associated with worse cardiovascular outcomes, including coronary heart disease [24, 25], heart failure [26, 27] and all-cause mortality [28]. Visfatin as a novel adipokines and was originally cloned as a cytosolic enzyme leading to the synthesis of cytokine-like growth factor and nicotinamide adenine dinucleotide (NAD^+), which have been suggested an essential coenzyme in inflammatory states and multiple cellular redox reactions [29]. Furthermore, visfatin has been shown to be produced by immune cells such as macrophages usually participated in the pathophysiology of ACS events, and is found to contribute in promoting inflammation by induce pro-inflammatory molecules expressions such as TNF-α, IL1-β and IL-6 in macrophages [30]. In the last years, visfatin has been considered frequently involved in destabilization and rupture of atherosclerotic plaques, an initial and crucial step in the progression of the STEMIs [7, 31]. STEMI can lead to renin angiotensin aldosterone system (RAAS) activation, which has been suggested an incidental of new-onset AF by production of angiotensin II. Surprisingly, clinical date and basic research find a positive correlation between visfatin levels and RAAS activation [32, 33], suggesting that visfatin is a downstream target of RAAS activation. Moreover, Takebayashi et al [34]. shows a negative correlation between visfatin and artery flow-mediated dilatation, suggesting that visfatin is related to impaired endothelial function (ED). AF subjects have significantly impaired ED, which can be reversed through high levels of hs-CRP [35]. From these results we speculate that the level of visfatin is positively correlated with the occurrence of AF. In our cohort high level of visfatin, the incidence rate of atrial fibrillation high level of visfatin was 10.4%, compared with 2.94% in low level of visfatin. Not only did patients with high level of visfatin have much higher rates of MACEs, but also they had significantly higher rates of re-MI study in agreement with the findings of previous reports [7] that high plasma visfatin levels have much

higher rates of MACEs, and we also gives a newer point of view on the potential role of visfatin in the occurrence of new-onset AF.

AF has been associated with worse cardiovascular outcomes. There are many factors that can predict AF including hypertension [36], diabetes mellitus [37] and plasma hs-CRP levels [38]. In our study, cox regression analysis are consistent with the findings of previous reports about that hypertension [36], diabetes mellitus [37] and plasma hs-CRP levels were the identifiable independent predictors of the occurrence of new-onset AF after PPCI in STEMI patients. The previous studies have reported the elevated circulating levels of visfatin positively correlated with different clinical conditions, such as hypertension, diabetes mellitus and circulating hs-CRP levels which represent independent risk factors for inflammation-related CVD [39-41]. Therefore, we hypothesized that visfatin and new-onset AF have positive correlation, and our experimental results support the inference.

This study highlights the detrimental effects of new-onset AF after PPCI and has no significant correlation with the site of coronary artery lesion and successful revascularization. Patients with advanced high level of visfatin have a higher rate of new-onset AF occurrence, and both of them can play a synergistic role with the adverse effect of AF in causing worse outcomes at 1 year post-PPCI. Due to discuss the need to better distinguish and monitor patients who are at high levels of visfatin for developing AF after PPCI for STEMI, and point to the necessity of intensive treatment for this group of patients, therefore our findings are of far-reaching significance. Because the high mortality and disability rate for patients with concomitant AF who undergo PPCI remains a matter of consensus expert opinion, effective treatment to reduce the incidence of AF after PPCI for STEMI plays a decisive role to reduce the incidence of cardiovascular events.

Several limitations of the present study should be acknowledged. No information was available regarding the exact timing and duration of AF during the hospitalization and/or after discharge. Thus, we were unable to classify AF into paroxysmal or persistent, and we cannot comment on their respective effects. There were no data available on the strategy of AF management (rate control vs rhythm control) during the hospitalization and at follow-up. Although we had data regarding long-term compliance with antiplatelet therapy, we did not have data regarding long-term compliance or effectiveness with oral anticoagulation. Finally, AF and atrial flutter were collected as a single variable, limiting our capacity to analyze their effects separately.

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Disclosure of conflict of interest

None.

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