Original Article

Current Use of Oral Anticoagulants and Prognostic Analysis in Patients with Atrial Fibrillation Undergoing Coronary Stenting

Heng-Bo Zhai[1,2], Jun Liu[1], Zhi-Chao Dong[1], Dong-Xia Wang[1], Bo Zhang[1]

[1]Department of Cardiology, The First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning 116011, China
[2]Department of Cardiology, The General Hospital of Shenyang Military, Shenyang, Liaoning 110016, China

Abstract

Background: It is currently believed that triple oral antithrombotic therapy in patients with atrial fibrillation (AF) after percutaneous coronary intervention (PCI) should be recommended if there are no contraindications. However, selecting triple therapy for AF patients undergoing PCI is still challenging when bleeding risk is considered. This study aimed to investigate the current use of oral anticoagulants (Vitamin K antagonists [VKA]) and perform prognostic analysis in real-world patients with AF undergoing coronary stenting.

Methods: A total of 276 consecutive coronary artery disease (CAD) patients with or without AF undergoing coronary stenting were retrospectively evaluated and analyzed. The univariate and multivariate analyses were conducted to explore the current use of VKA and prognosis of patients with AF undergoing coronary stenting. The primary end-point was composite of all-cause death, nonfatal recurrent myocardial infarction, stroke, serious bleeding events, unplanned repeat revascularization, and worsening heart failure at 12-month follow-up after coronary stenting.

Results: AF patients undergoing coronary stenting have more clinical concomitant diseases. Only 9.0% AF patients after coronary stenting received triple antithrombotic therapy (VKA, aspirin, and clopidogrel) at discharge. AF was independently associated with increased risk of the 12-month composite end-points (relative risk = 5.732, 95% confidence interval 1.786–18.396, $P = 0.003$).

Conclusions: In real-life AF patients undergoing coronary stenting, guideline-recommended VKA was less used. AF patients had adjusted worse prognosis during 12-month follow-up after discharge. It is of utmost importance to improve the current status of oral anticoagulants use.

Key words: Antithrombotic Therapy; Atrial Fibrillation; Coronary Artery Disease; Percutaneous Coronary Intervention; Prognosis

Introduction

Atrial fibrillation (AF) is a common finding in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) . The previous studies confirmed that 20–30% of patients with AF have coexisting CAD,[1] and about 5–15% of AF patients will require stenting at some point in their lives.[2] The use of dual antiplatelet therapy (DAPT) is of crucial importance in patients undergoing coronary stenting in preventing stent thrombosis. Patients with AF undergoing PCI are at a risk of stroke and require oral anticoagulants. Triple antithrombotic therapy, including Vitamin K antagonist (VKA), aspirin, and clopidogrel, is recommended for AF patients after coronary stenting if there are no contraindications, however, compared with DAPT, triple antithrombotic therapy increased the risk of bleeding by 3–4 times.[3] Therefore, it has become a realistic issue how to weigh the risk of thrombosis and hemorrhage in PCI patients with AF and CAD. Currently, controversy exists about whether AF was independently predictive of mortality or major adverse cardiovascular events after 1 year in acute coronary syndrome (ACS) versus

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Address for correspondence: Dr. Bo Zhang, Department of Cardiology, The First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning 116011, China
E-Mail: dalianzhangbo@yahoo.com

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stable CAD,[4-8] while the current studies confirmed that AF was associated with an increased risk of acute myocardial infarction, and the effective treatment was of important clinical significance.[9] Currently, PCI and stenting are frequently used in the treatment for patients with CAD in China, and triple antithrombotic therapy at hospital discharge should have been paid more and more attention after 2010 ESC guidelines on AF.[10] Therefore, it is particularly important to explore the "real world" of oral anticoagulants use and prognosis in patients with AF undergoing coronary stenting in clinical practice.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University . The requirement for written informed consent of the patients was waived by the Ethics Committee because of the retrospective nature of the study.

Patients

From November 1, 2010 to November 1, 2014, a total of 110 consecutive AF patients undergoing coronary stenting with CAD were retrospectively evaluated in the Cardiology Department, The First Affiliated Hospital of Dalian Medical University; and from October 1, 2014 to November 1, 2014, a total of 166 consecutive patients undergoing coronary stenting without AF were also collected and evaluated as the control. The inclusion criteria of AF included a preexisting diagnosis of permanent, persistent, or paroxysmal AF and those who developed new-onset AF during their index admission. Patients with serious heart diseases (severe primary cardiomyopathy, valvular heart disease, and congenital heart disease) and those accompanied by severe liver dysfunction (liver cirrhosis), kidney dysfunction (serum creatinine ≥177 μmol/L), hematopathy, severe infection, and malignant tumor during their index admission were excluded from the study. Patient demographics, clinical characteristics, procedural variables, adverse events, and antithrombotic therapy prescribed with duration of therapy were recorded on standardized data collection forms.

Follow-up and primary end-points

The follow-up clinical reevaluation of patients was performed by telephone contact from December 1, 2015, to December 31, 2015, and the data including the use of antithrombotic therapy and adverse events were recorded and followed up for 12 months after coronary stenting. The primary end-point was composite of all-cause death, nonfatal recurrent myocardial infarction (MI), stroke, serious bleeding events, unplanned repeat revascularization, and worsening heart failure. Data quality was checked by the project director.

Definitions

Serious bleeding events were defined according to the Bleeding Academic Research Consortium (BARC) criteria as major (BARC 3a, 3b, 3c, and 5) bleeding events. The risk of stroke or systemic embolism in patients with AF was estimated by the CHA2DS2-VASc score and bleeding risk by the HAS-BLED score.[11] Recurrent MI was based on the recurrence of chest pain, new electrocardiogram changes indicative of ischemia, and an increase in creatine kinase (CK), CK-MB, or troponin I ≥50% higher than the previous value. Stroke was defined as the occurrence of persistent-specific neurological deficits with imaging evidence of stroke. Worsening heart failure was defined as the readmission worsening heart failure after coronary stenting.

Statistical analysis

Statistical analyses used SPSS 19.0 (SPSS Inc., Chicago, IL, USA). Continuous data were described with means ± standard deviation (SD) and categorical data with median (25^{th}–75^{th}). For comparison of means and median, the Student's *t*-test of two independent samples and nonparametric analysis (Mann-Whitney *U*-test) were performed, respectively. Chi-square test was use for the comparisons between two groups for categorical data. The data were censored with a closing date of 12 months after coronary stenting. The cumulative event rates were estimated by the Kaplan-Meier method, and differences were analyzed with a log-rank test. To predict the independent association between AF and the primary end-point, confounding effects were controlled by performing multivariate Cox regression analyses. The regression model was adjusted for all relevant clinical variables including the demographics, coronary risk factors, baseline factors, and procedural characteristics. We calculated hazard ratio and 95% confidence intervals (*CI*s) and considered $P < 0.05$ to represent statistical significance.

Results

Baseline characteristics

This analysis included 276 participants (110 AF patients; 166 without AF). Compared with those without AF, participants with AF were older, more likely to have the histories of previous heart failure, stroke, and hypertension. On admission, the AF patients were more likely to have high diastolic blood pressures, heart rates, serum creatinine, and worsening heart function (the enlargement of the left atrial and higher brain natriuretic peptide) and have low serum lipids (total cholesterol, low-density lipoprotein; $P < 0.05$). There were no differences in multivessel lesions and total stent length between the two groups [Table 1].

Current use of oral anticoagulants

Overall, 79.1% (87/110) patients with AF undergoing coronary stenting were high-risk cases who should have accepted triple antithrombotic therapy in accordance with the 2010 ECS guidelines (CHA2DS2-VASc score ≥2 points, without contraindications to anticoagulation) at discharge.[10] However, only 9.0% cases (7/87) received triple antithrombotic therapy after coronary stenting, and most AF patients (86.2%)

Table 1: Baseline characteristics for patients with AF versus non-AF undergoing coronary stenting

Characteristics	AF patients (n = 110)	Non-AF patients (n = 166)	Statistics	P
Age (years), mean ± SD	68.8 ± 9.5	63.8 ± 9.9	4.068*	<0.001
Gender (male), n (%)	89 (80.9)	121 (72.9)	2.337†	0.126
Clinical presentation, n (%)				
AMI	53 (48.2)	80 (48.2)	0.000†	0.999
Angina pectoris	57 (51.8)	86 (51.8)		
Hypertension, n (%)	78 (70.9)	97 (58.4)	4.438†	0.035
Diabetes, n (%)	38 (34.5)	48 (28.9)	0.978†	0.323
Smoking history, n (%)	51 (46.4)	63 (38.0)	1.931†	0.165
Previous CAD, n (%)	44 (40.0)	49 (29.5)	3.254†	0.071
Previous HF, n (%)	15 (13.6)	1 (0.6)	209.625†	<0.001
Previous stroke, n (%)	23 (20.9)	15 (9.0)	7.855†	0.005
Previous PCI, n (%)	14 (12.7)	22 (13.3)	0.016†	0.899
Previous CABG, n (%)	1 (0.9)	0 (0.0)	1.515†	0.399
SBP (mmHg), mean ± SD	138.63 ± 25.02	132.98 ± 22.74	1.942*	0.053
DBP (mmHg), mean ± SD	82.68 ± 15.07	78.67 ± 12.85	2.367*	0.019
Heart rate (beats/min), mean ± SD	80 (68–90)	70 (64–78)	4.285‡	<0.001
Peak cTnI (μg/L), median (25^{th}–75^{th})	1.85 (0.04–25.32)	1.07 (0.02–30.52)	−0.741‡	0.459
TC (mmol/L), mean ± SD	4.18 ± 1.08	4.54 ± 1.17	3.105*	0.013
TG (mmol/L), mean ± SD	1.55 ± 1.10	1.78 ± 1.08	1.569*	0.098
LDL-C (mmol/L), mean ± SD	2.41 ± 0.73	2.72 ± 0.83	3.065*	0.002
HDL-C (mmol/L), mean ± SD	1.07 ± 0.33	1.09 ± 0.27	0.396*	0.692
FBG (mmol/L), mean ± SD	6.82 ± 2.56	6.96 ± 3.23	0.505*	0.646
Serum K^+ (mmol/L), mean ± SD	4.01 ± 0.51	3.97 ± 0.44	0.713*	0.477
Scr (μmol/L), mean ± SD	80.94 ± 23.03	71.04 ± 22.21	3.083*	0.001
UA (μmol/L), mean ± SD	389.46 ± 119.34	342.75 ± 98.99	3.420*	0.001
hs-CRP (mg/L) , mean ± SD	9.33 ± 19.52	15.22 ± 38.44	0.804*	0.402
Fibrinogen (g/L), mean ± SD	3.03 ± 0.71	4.43 ± 13.75	1.002*	0.277
BNP (pg/ml), median (25^{th}–75^{th})	329.33 (145.75–669.37)	124.01 (42.56–307.43)	4.472‡	<0.001
LVEF (%), mean ± SD	51.43 ± 9.10	52.84 ± 8.36	0.915*	0.237
LVDd (mm), mean ± SD	49.73 ± 5.42	48.02 ± 6.36	2.141*	0.903
LAD (mm), mean ± SD	43.01 ± 5.10	37.17 ± 4.68	9.005*	<0.001
Multivessel lesions, n (%)	72 (66.1)	107 (64.5)	0.074†	0.786
Total stent length (mm), mean ± SD	39.15 ± 25.73	37.88 ± 23.71	0.579*	0.686
Discharge medication, n (%)				
ACEI or ARB	78 (70.9)	106 (63.9)	4.481†	0.224
Beta blocker	90 (81.8)	90 (81.8)	0.681†	0.409
Statins	109 (99.1)	164 (98.8)	0.054†	0.817
Aspirin	107 (97.3)	164 (98.8)	0.862†	0.353
Clopidogrel	107 (97.3)	164 (98.8)	0.862†	0.353
Warfarin	10 (9.1)	1 (0.6)	12.458†	0.001

*t values; †χ^2 values; ‡Z values. 1 mmHg = 0.133 kPa. AF: Atrial fibrillation; AMI: Acute myocardial infarction; CAD: Coronary artery disease; HF: Heart failure; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; cTnI: Cardiac troponin I; TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; FBG: Fasting blood-glucose; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; Scr: Serum creatinine; UA: Uric acid; hs-CRP: High-sensitivity C-reactive protein; BNP: Brain natriuretic peptide; LVEF: Left ventricular ejection fraction; LVDd: Left ventricular end-diastolic diameter; LAD: Left atrial diameter; ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blocker; SD: Standard deviation.

just received DAPT after coronary stenting. For patients requiring triple antithrombotic therapy (n = 87), 67 cases were at high bleeding risk (HAS-BLED ≥3) and twenty cases were at low-moderate bleeding risk (HAS-BLED <3); 86.6% (58/67) and 85.0% (17/20) cases received DAPT at discharge, respectively. Overall, 9.1% (10/110) of patients with AF received VKA (warfarin) at discharge. At 12 months, only 5.5% (6/110) still used VKA (warfarin) [Figure 1a–1f].

Clinical outcome at 12-month follow-up

The 100% follow-up rate was implemented. At 12-month follow-up, Kaplan-Meier analysis showed there were higher rates of the composite end-points in AF group than the non-AF group (P = 0.002; Table 2 and Figure 2). The rates of stroke and readmission for worsening heart failure were higher in AF group (6.4% vs. 0.6%, and 20.4% vs. 7.8%, respectively, P < 0.05 for both). The two groups were comparable for the rates of all-cause death, nonfatal MI, serious bleeding

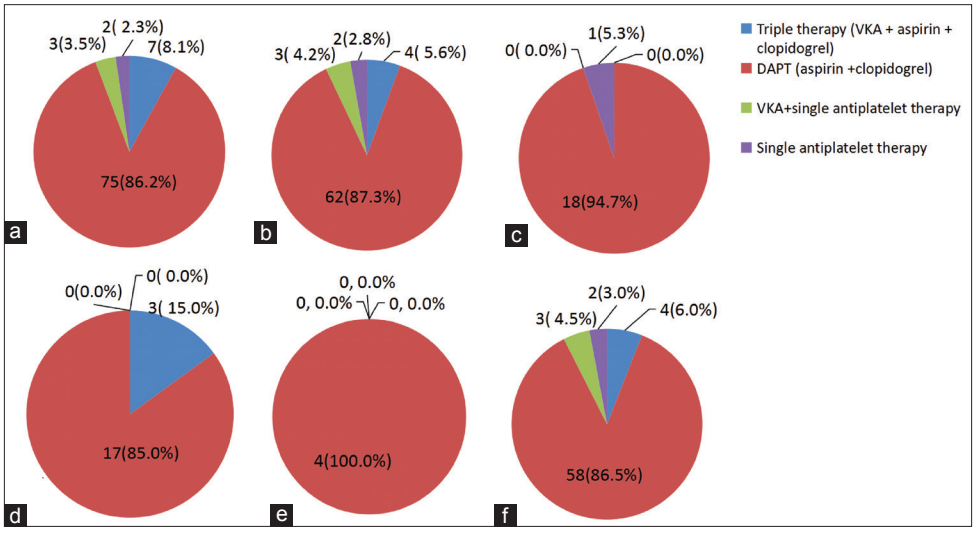

Figure 1: Proportion of patients receiving different antithrombotic therapies according to the CHA2DS2-VASc score and HAS-BLED score: (a) CHA2DS2-VASc ≥2 (*n* = 87); (b) HAS-BLED score ≥3 (*n* = 71); (c) stroke risk: Moderate (CHA2DS2-VASc <2) and bleeding risk (HAS-BLED score <3): Low/moderate (*n* = 19); (d) stroke risk: High (CHA2DS2-VASc ≥2) and bleeding risk (HAS-BLED score <3): Low/moderate (*n* = 20); (e) stroke risk: Moderate (CHA2DS2-VASc <2) and bleeding risk (HAS-BLED score ≥3): High (*n* = 4); (f) stroke risk: High (CHA2DS2-VASc ≥2) and bleeding risk (HAS-BLED score ≥3): High (*n* = 67). VKA: Vitamin K antagonists; DAPT: Dual antiplatelet therapy.

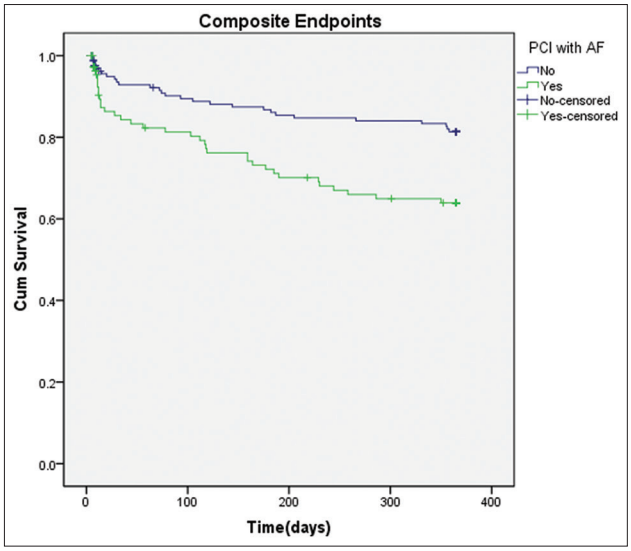

Figure 2: Unadjusted Kaplan-Meier analysis for the composite end-points in AF and non-AF groups (*P* = 0.002). AF: Atrial fibrillation; PCI: Percutaneous coronary intervention.

events, and repeat unplanned revascularization (*P* > 0.05 for all; Table 2). Multivariate Cox regression analysis showed that AF was one of the independent risk factors for 12-month follow-up after undergoing coronary stenting for CAD (relative risk [*RR*] = 5.732, 95% *CI* 1.786–18.396, *P* = 0.003).

Discussion

Our main finding was that VKA usage rate in the AF patients with PCI was extremely low. Oral anticoagulants did not get adequate attention for the AF patients after coronary stenting. This result was different from the finding from other studies that revealed a striking increase in the use of triple antithrombotic therapy at discharge after the 2010 ESC guidelines on AF.[7,10,12-14] The present study revealed that the AF patients undergoing coronary stenting were less likely to receive guideline-recommended triple antithrombotic therapy, especially for patients with a high HAS-BLED score and even for high thromboembolic risk patients at low bleeding risk.

In accordance with the known highest prevalence of triple antithrombotic therapy use among patients with AF of CHADS2 score ≥2,[11] 79.1% (87/110) patients with AF undergoing coronary stenting were at high risk of stroke and therefore should have initiated triple therapy at discharge whereas the actual use was only 8.9% (7/87 cases) as indicated by our data at discharge.

The use of oral anticoagulants is pivotal in high-risk CAD patients with AF as it has been shown to be superior to DAPT with clopidogrel and aspirin in ischemic stroke prevention.[15] Most patients with a high CHA2DS2-CASc score benefit from oral anticoagulants despite a high HAS-BLED score and the net clinical benefit balancing ischemic stroke against serious bleeding would favor oral anticoagulants for most patients.[16] It has been observed recently that most patients with AF undergoing PCI have a high HAS-BLED score (≥3), it is thus important to note that an HAS-BLED score of 3 or higher alone should not be used as the only reason to withhold oral anticoagulants.[15] In our study, the use of triple antithrombotic therapy was significantly lower than other studies,[12-14] especially in patients with a high HAS-BLED score and even in high thromboembolic risk patients at low bleeding risk.

Oral anticoagulants is often withheld for the AF patients undergoing coronary stenting, this may be due to concerns of excess bleeding related to the combination of DAPT

Table 2: Comparison of outcomes during 12-month follow-up in patients with AF versus non-AF undergoing coronary stenting, *n* (%)

Variables	AF patients (n = 110)	Non-AF patients (n = 166)	χ^2	P
All-cause death	2 (1.8)	5 (3.0)	0.381	0.706
Nonfatal MI	6 (5.5)	4 (2.4)	1.757	0.185
Stroke	7 (6.4)	1 (0.6)	7.802	0.005
Serious bleeding events	2 (1.8)	1 (0.6)	0.910	0.340
Repeat unplanned revascularization	4 (3.6)	10 (6.0)	0.783	0.376
Readmission worsening heart failure	23 (20.4)	13 (7.8)	9.976	0.002
Composite end-points	36 (32.7)	28 (16.9)	9.343	0.002

AF: Atrial fibrillation; MI: Myocardial infarction.

and VKA. The main side effect of VKA is severe bleeding, especially the combination of DAPT and VKA has been associated with an increased risk of bleeding.[17,18] Hence, this concern does seem to influence the clinical practice of those physicians with patients on anticoagulant therapy. Our data further showed Chinese AF patients following coronary stenting received less anticoagulant therapy than patients in the Western countries.[19] In our study, major bleeding at discharge was rare and comparable between the two groups, which may be also related to the fact that VKA usage rate was relatively low and experienced clinician paid more attention to the follow-up of these high-risk patients with triple antithrombotic therapy at discharge.

Overall, the incidence of stroke events was higher in AF patients compared with controls during 12-month follow-up (6.4% vs. 0.6%, P = 0.005), which further illustrate the necessity of antithrombotic therapy in high thromboembolic risk patients with coronary stenting. To minimize bleeding risk in AF patients following coronary stenting, the right agent should be prescribed to the right patient at the right dose.[17] Triple antithrombotic therapy management regimens might be replaced by oral anticoagulants and clopidogrel without any additional risk of recurrent thrombotic events and a lower risk of bleeding.[20] PIONEER AF-PCI study suggested novel oral anticoagulants such as rivaroxaban plus antiplatelet therapy after PCI may be superior to common triple oral antithrombotic therapy in decreasing the *RR*s of bleeding complications.[21] Ongoing trials need to be further investigated to reduce bleeding without increasing thromboembolic events. Currently, clinician should pay more attention to the rational usage of VKA in AF patients undergoing PCI.

Another important finding was that we further demonstrated a significantly increased adjusted risk of the composite end-points for AF patients undergoing coronary stenting as compared to controls without AF. Besides stroke, the rate of readmission for worsening heart failure was higher in AF group (20.4% vs. 7.8%, P = 0.002). The two groups were comparable at the rates of all-cause death, nonfatal MI, and repeat unplanned revascularization (P > 0.05 for all). As expected, patients with AF undergoing coronary stenting had significantly worse outcomes, as compared to patients without AF, which is in accordance with most recent studies,[7,8,22] although in earlier study, AF was not independently predictive of mortality or major adverse cardiovascular events after 1 year except cerebrovascular events, bleeds, and vascular complications.[23] Our results differed from those previous studies[7,8,14] in that no significant difference regarding the incidence of all-cause mortality at 12-month follow-up was found between AF and non-AF patients undergoing coronary stenting. That could be explained by several factors including patterns of enrolled CAD patients, sample sizes, treatment methods including stent type and so on.

There are several potential pathological mechanisms for increased risk of the composite end-points in patients with AF undergoing coronary stenting. In our study, AF patients usually had more cardiovascular risk factors and comorbidities including older age, prior heart failure, hypertension, and worse renal function which were at high risk of poor outcomes. Moreover, AF may lead to adverse hemodynamic effects through rapid ventricular rates and serious arrhythmia. Low rate of VKA use should be another important factor that results in increased risk of stroke and long-term mortality because the use of antithrombotic treatment with VKA to prevent stroke reduces 26% mortality.[7] It has recently been reported that AF is associated with an increased risk of MI.[9,24] AF potentiates thrombogenic risk through systemic platelet activation, endothelial dysfunction, and inflammation which highlight the potential importance of other therapeutic modalities that strengthen antithrombotic therapy, improve endothelial function, and blunt the inflammatory response.[9]

Several limitations existed in this study. This was a retrospective, single-center study. Our included cases were consecutive patients; however, the periods of the patients undergoing coronary stenting without AF did not exactly match those of AF patients, because there were fewer AF patients with PCI in the same period, compared with non-AF patients with coronary stenting. Although we think there were no obvious changes in the treatment strategies and methods from 2010 to 2014, this might still pose a selection bias. The heterogeneity of the different AF categories could not be avoided due to the small sample size. In addition, controversy exists whether AF carries a different mortality risk in ACS versus stable CAD. Multicenter studies with

larger sample size are needed in real-world patients with AF undergoing coronary stenting.

Despite these limitations, our study revealed the current use of oral anticoagulants and further provides evidence for increased risk of the composite end-points in patients with AF undergoing coronary stenting. In real-life AF patients undergoing coronary stenting, guideline-recommended VKA was less used. AF patients had adjusted worse prognosis during 12-month follow-up at discharge. It is of utmost importance to improve the current grim status of oral anticoagulants use.

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Conflicts of interest

There are no conflicts of interest.

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