BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031180
Article Type:	Research
Date Submitted by the Author:	20-Apr-2019
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Keywords:	atrial fibrillation, acute coronary syndrome, oral anticoagulants

Oral Anticoagulant Treatment in Patients With Acute Coronary Syndrome and Atrial Fibrillation

Brief title: OAC Treatment in ACS patients with AF

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ABSTRACT

OBJECTIVE: Oral anticoagulant (OAC) treatment is globally underused in patients with atrial fibrillation (AF), especially in combination with antiplatelet therapy. This study aimed to examine the patterns of OAC therapy in managing acute coronary syndrome (ACS) patients with AF in South China undergoing percutaneous coronary intervention (PCI).

DESIGN: A retrospective cohort study.

SETTING: The study was conducted in the Shunde Hospital, Southern Medical University and the second hospital of Zhaoqing, China, from January 2013 to 31 December 2018.

PARTICIPANTS: Patients were aged ≥18 years, hospitalized for ACS and received PCI treatment.

OUTCOME MEASURES: AF was diagnosed based on an electrocardiogram recording or a Holter monitor. Prescription of OACs and antiplatelets were determined from the discharge medication list.

RESULTS: A total of 3612 ACS patients were included; 286 (7.9%) were diagnosed with AF, including 45 (1.2%) with paroxysmal AF and 241 (6.7%) with persistent/permanent AF. Although 95.5% of patients with AF were at high risk (CHA_2DS_2-VASc score ≥2) for stroke, only 21.7% were discharged on OACs; 10.5% received warfarin and 11.2% received non-vitamin K antagonist oral anticoagulants. Patients with a HAS-BLED score <3, with persistent/permanent AF were more likely to receive OAC treatment at discharge.

CONCLUSION: We found that approximately 8% of patients who underwent PCI during ACS hospitalization also demonstrated AF. Anticoagulant therapy was greatly underused. Patients with paroxysmal AF and an increased risk of bleeding were more unlikely to receive anticoagulant treatment. Further efforts should be made to increase the adherence to guideline recommendations for OACs.

Keywords: atrial fibrillation; acute coronary syndrome; oral anticoagulants

Strengths and limitations of this study

■ This study first documented the current real-world patterns of anticogulation therapy in managing ACS patients with AF in Southern China.

■All the patients were with documented AF and received drug eluting stent implantation.

■ The present study highlight further efforts should be made to increase adherence to guideline recommendations for OAC treatment among ACS patients with AF.

■ Data were obtained from two large hospitals in Southern China, and do not represent the current treatment status in other regions.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia worldwide.[1] It is associated with a four to five-fold increased risk of ischemic stroke.[2 3] Known or new-onset AF is a common comorbidity in patients with acute coronary syndrome (ACS). It has been reported that 2–21% of ACS patients have a history of AF.[4] Patients with ACS and AF have a poor prognostic outcome, including a higher risk of stroke.[5-7] Antithrombotic treatment with oral anticoagulants (OACs), such as warfarin or non-vitamin K antagonist oral anticoagulants (NOACs), is a cornerstone in the prevention of ischemic stroke in patients with AF.[8 9] However, for patients with AF presenting with acute myocardial infarction (AMI) or coronary artery disease, undergoing percutaneous coronary intervention (PCI) poses a great challenge with regard to the management of antithrombotic therapy.[10] These patients need dual antiplatelet therapy (DAPT) to reduce the risk of subsequent myocardial infarction and stent thrombosis, and OAC treatment to reduce the risk of stroke.[11]

Although academic guidelines recommend that a combination of OACs and DAPT should be initiated in these patients and then subsequently switched to monotherapy with OACs,[1 12 13] OACs have been largely underused in real-world clinical practice.[14-19] However, NOACs have not been applied in most reported studies.[14-19] Recently, there has been a significant price drop in NOACs and more evidence concerning the safety of these agents compared with warfarin. These factors may lead to greater use of NOACs instead of warfarin in patients at higher risk of bleeding, including those undergoing concomitant anti-platelet treatment. However,

the prevalence of antithrombotic therapy in Chinese patients with ACS and AF has not been explored after the introduction of NOACs. Therefore, the current study was undertaken to examine current real-world patterns of OAC therapy in managing ACS patients with AF in South China undergoing PCI.

Methods

Study population

This was a retrospective cohort study conducted in the Shunde Hospital, Southern Medical University and the second hospital of Zhaoqing, China, from January 2013 to 31 December 2018.

We reviewed the medical records of patients aged ≥18 years who were hospitalized for ACS and received PCI treatment. ACS was defined as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina (UA). STEMI was diagnosed based on elevated levels of biomarkers for myocardial necrosis (including troponin T, troponin I, or creatine kinase MB), with ST-segment elevation of 1 mm or more in at least two contiguous electrocardiogram (ECG) leads,[20] while NSTEMI was defined as ST-segment depression of ≥1 mm. Patients with typical ischemic symptoms and no elevation in biomarkers for myocardial necrosis, with or without ECG changes were classified as having UA.[21] AF was diagnosed using an ECG recording or a Holter monitor. Patients with AF lasting less than 7 d were classified as having paroxysmal AF,[1] and were otherwise classified as having persistent/permanent AF. All of the

patients received coronary angiography and PCI therapy. We excluded those without ECG recording data, death or were transferred out within 3 days of hospitalization, discharge medication list was not available and those had rheumatic heart disease or mechanical heart valves.

Risk stratification and anticoagulation treatment

Baseline characteristics were collected. We used the CHA_2DS_2-VASc score to evaluate the risk of stroke (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes mellitus, history of stroke/transient ischemic attack [doubled], vascular disease, age 65–75 years and female sex). The risk of bleeding was evaluated using the HAS-BLED score (hypertension, abnormal renal/liver function, history of stroke, history of bleeding, labile internationally normalized ratio, age >65 years, non-steroidal anti-inflammatory drugs or alcohol abuse).[1 12] Because data concerning the time in therapeutic range for warfarin was not available, we defined the labile internationally normalized ratio as 'none' and 0 points were given to all patients when calculating the HAS-BLED score.

Prescription of warfarin, NOACs, aspirin, and clopidogrel was determined from the discharge medication list. In the hospitals participating in the current study, rivaroxaban and dabigatran were the two types of NOAC available. Standard dosages of NOACs were defined as rivaroxaban 20 mg/day or dabigatran 150 mg twice daily for patients with creatinine clearance ≥50 mL/min, and rivaroxaban 15 mg/day or dabigatran 110 mg twice daily for creatinine clearance of 30–49 mL/min.[22 23] Any

daily dosages less than this range were defined as reduced dosages.

Statistical Analysis

AF patients were divided into two groups based on whether they received OAC treatment or not at discharge. Baseline characteristics, including CHA_2DS_2-VASc score, HAS-BLED scores, and antiplatelet therapy were examined. Continuous variables are presented as median (inter-quartile range) or mean (standard deviation), as appropriate. Categorical variables are expressed as number (percentages). Continuous variables were compared using the Wilcoxon rank-sum test or Student's *t*-test after testing for normality using the Kolmogorov–Smirnov test. Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate.

Multiple logistic regression models were used to examine the association between baseline characteristics and OAC treatment at discharge. Patients without OAC treatment were used as the reference. The variables adjusted in the multi-variable model were: sex, age (≥65 vs. <65 years), diabetes, hypertension, dyslipidemia, history of stroke, abnormal renal/liver function, non-steroidal anti-inflammatory drugs or alcohol abuse, history of bleeding, smoking status, type of ACS (UA or MI), cardiac function (Killip classification III–IV vs. I–II), and type of AF (paroxysmal or persistent/permanent). We further set the CHA_2DS_2-VASc score and HAS-BLED score as independent factors in the model, while their individual components (age, sex, cardiac function, diabetes, hypertension, history of stroke, history of bleeding) were not included to avoid over-adjustment. Adjusted odds ratios

(ORs) and corresponding 95% confidence intervals (CIs) are presented. All the statistical analysis was performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA). All comparisons are two-sided, with statistical significance defined as $P<0.05$.

Ethical clearance

The study complied with the Declaration of Helsinki and was approved by the institutional review board central committee at Shunde Hospital, Southern Medical University, China. As this was a retrospective analysis, patients' informed consent was waived by the institutional review board.

Results

Baseline characteristics

We reviewed 3813 electronic medical records of patients aged ≥18 years, who were hospitalized for ACS and received PCI treatment from January 2013 to November 2018. After excluding 121 patients who died or were transferred out during hospitalization, and 76 patients without a discharge medication list, 4 patients with mechanical heart valves, a total of 3612 patients were included in this study.

All of the patients received coronary angiography and drug eluting stent implantation, and 2219 of them (61.4%) were diagnosed with UA and referred for an elective procedure, while 1393 of them (38.6%) presented with AMI and received emergent PCI treatment.

Among all the included patients, 286 (7.9%) were diagnosed with AF; 45 of

these (1.2%) had paroxysmal AF and 241 (6.7%) had persistent/permanent AF. Compared with those without AF, ACS patients with AF were older and more likely to be female, with a higher prevalence of hypertension, diabetes and cardiac dysfunction, previous stroke/TIA, and higher mean CHA_2DS_2-VASc and HAS-BLED scores (all $P<0.01$, Table 1).

Anti-thrombotic therapy

The in-hospital anti-thrombotic treatment regimens in ACS patients with and without AF are presented in Table 2. The rates of parenteral anticoagulant treatment, including low molecular weight heparin and fondaparinux, were higher in patients with AF compared with those without AF (35.7% vs. 21.0%, $P<0.01$). The in-hospital use of antiplatelet agents, including aspirin and clopidogrel, was high and similar in ACS patients with and without AF (all $P>0.05$). Prescription of OACs in AF patients was low (n = 85, 29.7%); 38 of them received warfarin (13.3%) and 47 of them received NOACs (16.4%). In patients undergoing NOAC treatment, 42 of them (89.3%) received reduced dosages.

At hospital discharge, the use of anti-platelet agents was similar as in-hospital usage, and nearly 99% of patients with and without AF received DAPT. However, only 21.7% of patients with AF (n = 62) were discharged on OACs, and 10.5% of them received warfarin and 11.2% received NOACs (Table 2). Similarly, in patients undergoing NOAC treatment, 90.6% of them received reduced dosages.

Determinants of OAC treatment at discharge

We examined the association between baseline characteristics and OAC treatment at discharge. In all the included AF patients, only 4.5% were at moderate risk (CHA_2DS_2-VASc score 1), and 95.5% were at high risk (CHA_2DS_2-VASc score ≥2) for stroke. In terms of bleeding, 31.8% of the patients had a HAS-BLED score ≥3, which was defined as a high risk of bleeding. As shown in Table 3, patients with a HAS-BLED score <3, with persistent/permanent AF were more likely to receive OAC treatment at discharge. However, neither a high risk of stroke nor other clinical characteristics were associated with OAC treatment.

Discussion

There are three main findings in this study. First, the overall incidence of AF was 7.9% in patients with ACS who received PCI during hospitalization. Second, although most patients with AF had a high risk of stroke, less than 30% received OAC treatment at discharge. Third, patients with a lower risk of bleeding and persistent/permanent AF were more likely to receive anticoagulation therapy.

DAPT was recommended in ACS patients who underwent PCI to decrease the risk of stent thrombosis.[21] However, antiplatelet treatments cannot prevent the activation of coagulation factors and are not as effective as OACs in preventing stroke in AF patients. For AF patients who undergo PCI, if the CHA2DS2-VASc score ≥2, initial treatment with DAPT plus OACs (triple therapy) for at least 4 weeks is recommended under the current guidelines.[12 24] However, such a "triple therapy"

strategy poses risks for bleeding and OACs are globally underused in clinical practice.[14-19 25] The China acute myocardial infarction (CAMI) registry found that from 2013–2014, only 5.1% of ACS patients with AF were treated using warfarin, and 1.7% were treated using both warfarin and DAPT.[25] No NOACs were prescribed in ACS+AF patients in the CAMI study. In the current study, we found that this situation had improved. Approximately 30% of ACS patients with AF who underwent PCI received anticoagulation therapy at discharge, and half were prescribed NOACs. This improvement may be caused by the accumulation of clinical research data, the availability of consensus guidelines for treatment, increased physician awareness of anticoagulation therapy and a price reduction in NOACs in China. However, it should be noted that OACs were still significantly underused in AF patients who received PCI, and further efforts should be made to increase adherence to guideline recommendations for OAC treatment among eligible ACS patients with AF.

Compared with warfarin, NOACs are more convenient for use, including advantages such as fixed dose regimens, no requirement for frequent blood monitoring, no food and drug restrictions and less risk of bleeding.[26 27] In the current study, we found that there was a substantially increased use of NOACs in Chinese patients during the past few years. This is consistent with data from the Danish nationwide administrative registries, which found that by 2016, the use of NOACs in any combination with antiplatelets was exceeding that of warfarin in combination with antiplatelets.[28] However, in the current cohort, most patients (approximately 90%) received a reduced dosage of NOACs, such as rivaroxaban 10 mg/day. This may be

driven primarily by the increased risk of bleeding caused by triple therapy. It has been reported that in AF patients with AMI and/or PCI, when in combination with DAPT, low-dose NOACs plus DAPT was associated with a lower rate of clinically significant bleeding than a vitamin K antagonist plus DAPT.[29 30]

In contrast with previous studies which showed that the use of OACs in patients with ACS and AF was not influenced by either stroke risk or bleeding risk,[18 19] the current study found that patients with a HAS-BLED score <3 were more likely to receive OAC treatment at discharge. These results suggest that physicians are still hesitant to prescribe "triple therapy" because of concerns about the risk of bleeding. It should be noted that many patients with a high risk of bleeding also have an increased risk of stroke and stent thrombosis. Current guidelines on the management of AF have proposed a clear algorithm for the management of these patients.[1 12] However, providing optimal treatment is still a great challenge in real-world practice.

The current study further found that patients with paroxysmal AF were less likely to receive OACs than those with persistent/permanent AF. This was not a surprise. Current guidelines recommend that for patients with paroxysmal AF, the need for anticoagulant therapy should be determined based on the risk of stroke, same with persistent AF.[1 12] However, studies have shown that the risk of stroke in patients with paroxysmal AF is lower than that those with persistent/permanent AF.[31 32] The benefit of anticoagulation in new-onset AF, occurring in the setting of an acute attack with ACS, acute pulmonary disease, or sepsis, is associated with a higher risk of bleeding, but not with a reduced risk of ischemic stroke.[33] Therefore, for paroxysmal

AF that occurs in the case of ACS, there is still much doubt about whether these patients need long-term anticoagulant therapy. Recently, a study showed that in patients with paroxysmal AF, a greater burden of AF is associated with a higher risk of ischemic stroke.[34] Therefore, follow-up studies should be conducted to observe the re-occurrence of AF in the future.

There are some limitations in the current study. First, we did not evaluate the link between anticoagulant therapy and adverse events during hospitalization and after discharge. Second, patient status was distinguished as paroxysmal AF or persistent/permanent AF based on medical records, and misclassifications cannot be totally avoided. Third, this study was a retrospective study. Data were obtained from two large hospitals in Guangdong Province, China, and do not represent the current treatment status of other regions. Finally, we also found that some patients without AF were prescribed OACs; however, the indications were unrecorded.

Conclusion

The current study found that nearly 8% of patients who underwent PCI during ACS hospitalization had AF. Although these patients were at an increased risk of stroke, anticoagulant therapy was greatly underused. Patients with paroxysmal AF and an increased risk of bleeding were more unlikely to receive anticoagulant treatment. The promotion of NOAC use could increase the proportion of these patients who receive anticoagulant therapy.

Contributors YH and LM conceptualised the study, designed the protocol. YH, YW, JL and LM analysed the data and drafted the manuscript. XL, HZ and GL collected the data. YH, HZ and YZ revised the manuscript.

Acknowledgements: The project was supported by Scientific Research Fund of Foshan, Guangdong, China (No: 2016AB003353), the National Natural Science Foundation of China (No: 81600239), the Science and Technology Innovation Project from Foshan, Guangdong (FS0AA-KJ218-1301-0006) and the Clinical Research Startup Program of Shunde Hospital, Southern Medical University (CRSP2019001). The funders had no role in the design and implementation of the study, in the collection, analysis, and interpretation of the data, and in the preparation, review, or approval of the manuscript.

Competing interests: None declared.

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Table 1. Baseline characteristics of ACS patients with and without AF

	With AF(n=286)	Without AF(n=3326)
Age (year)	68 (58, 76)*	61 (52,74)
Sex [Female (%)]	128 (44.8)#	1285 (38.6)
SBP (mmHg)	129.3±22.4#	125.4±23.9
DBP (mmHg)	78.5±18.4#	76.2±17.9
Hypertension [n(%)]	123 (43.0)#	1214 (36.5)
Fasting plasma glucose (mmol/L)	5.8±3.6#	5.4±3.2
Diabetes mellitus [n(%)]	65 (22.7)#	582 (17.5)
Serum creatinine (μmol/L)	96 (65,124)	92(63,136)
Current smoker	66 (23.1)	729 (21.9)
LDL-C (mmol/L)	3.2±1.9	3.0±1.8
HDL-C (mmol/L)	1.1±0.6	1.0±0.5
TC (mmol/L)	5.4±2.2	5.3±2.2
TG (mmol/L)	1.9±1.8	1.8±1.6
Dyslipidemia[n(%)]	103 (36.0)	1173 (35.3)
Previous stroke/TIA[n(%)]	17 (5.9)#	68 (2.0)
AMI[n(%)]	115 (40.2)	1278 (42.5)
UA[n(%)]	171 (59.8)	2048 (57.5)
Killip classification III-IV [n(%)]	84 (29.4)*	786 (23.6)
CHA_2DS_2-VASc score	3.5±2.0*	3.1±1.8*
HAS-BLED score	3.0±1.6*	2.8±1.7*

Continuous variables are presented as median (inter-quartile range) or mean (standard deviation). Categorical variables are expressed as number (percentages).

ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TIA, transient ischemic attack; UA, unstable angina

#P<0.05 vs. 'without AF' group. *P<0.01 vs. 'without AF' group.

Table 2. Anti-thrombotic treatment in ACS patients with and without AF

	With AF(n=286)	Without AF(n=3326)
In-hospital		
Aspirin [n(%)]	280 (97.9)	3291 (98.9)
Clopidogrel [n(%)]	284 (99.3)	3318 (99.8)
Parenteral anticoagulants [#][n(%)]	102 (35.7)[*]	698 (21.0)
OACs[n(%)]	85 (29.7)[*]	8 (0.2)
Warfarin[n(%)]	38 (13.3)[*]	3 (0.1)
NOACs [n(%)]	47 (16.4)[*]	5 (0.2)
At discharge		
Aspirin [n(%)]	281 (98.3)	3289 (98.9)
Clopidogrel [n(%)]	282 (98.6)	3316 (99.7)
OACs [n(%)]	62 (21.7)	7 (0.2)
Warfarin [n(%)]	30 (10.5)	3 (0.1)
NOACs [n(%)]	32 (11.2)	4 (0.1)

Categorical variables are expressed as number (percentages).

ACS, acute coronary syndrome; AF, atrial fibrillation; NOACs, non-vitamin K antagonist oral anticoagulants; OACs, oral anticoagulants

[*]$P<0.01$ vs. 'without AF' group.

Table 3. Determinants of oral anticoagulant treatment at discharge

Determinants	OR	95% CI	P-value
Sex (male *vs* female)	0.98	0.65-1.48	0.92
Age (≥65 *vs* <65 years)	1.56	0.36-6.76	0.55
Smoking (yes *vs* no)	1.22	0.23-6.47	0.82
Diabetes mellitus (yes *vs* no)	1.65	0.89-3.06	0.11
Hypertension (yes *vs* no)	1.34	0.46-3.90	0.59
Dyslipidemia (yes *vs* no)	0.99	0.58-1.69	0.97
Abnormal renal/liver function (yes *vs* no)	1.18	0.61-2.28	0.62
Non-steroidal anti-inflammatory drugs/alcohol abuse (yes *vs* no)	1.04	0.47-2.30	0.92
Cardiac function (Killip classification III-IV *vs* I-II)	1.44	0.78-2.66	0.24
History of stroke (yes *vs* no)	2.88	0.96-8.64	0.06
History of bleeding (yes *vs* no)	0.87	0.55-1.37	0.55
Type of ACS (AMI *vs* UA)	0.93	0.64-1.35	0.70
Type of AF (persistent/permanent *vs* paroxysmal)	4.75	1.89-11.9	0.0009
CHA_2DS_2-VASc score (≥2 *vs* <2)	2.98	0.85-10.2	0.09
HAS-BLED score (<3 *vs* ≥3)	3.12	1.25-7.78	0.01

The variables adjusted in the multi-variable model were: sex, age (≥65 vs. <65 years), diabetes, hypertension, history of stroke, history of bleeding, smoking status, type of ACS (UA or MI), cardiac function (Killip classification III–IV vs. I–II), and type of AF (paroxysmal or persistent/permanent). When CHA_2DS_2-VASc score and HAS-BLED score were included as independent factors in the model, the individual components (age, sex, cardiac function, diabetes, hypertension, history of stroke, history of bleeding) were not included to avoid over-adjustment.

ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; UA, unstable angina

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031180.R1
Article Type:	Original research
Date Submitted by the Author:	01-Jul-2019
Complete List of Authors:	Mai, Linlin; Shunde Hospital, Southern Medical University (The first people's hospital of Shunde), Cardiology Luo, Jianjing; Shunde Hospital, Southern Medical University (The first people's hospital of Shunde), Cardiology; The Second Hospital of Zhaoqing, Guangdong, Cardiology Wu, Yu; Shunde Hospital, Southern Medical University (The first people's hospital of Shunde), Cardiology Liu, Xinyue; Shunde Hospital, Southern Medical University (The first people's hospital of Shunde), Cardiology Zhu, Hailan; Shunde Hospital, Southern Medical University (The first people's hospital of Shunde), Cardiology Zheng, Haoxiao; Shunde Hospital, Southern Medical University (The first people's hospital of Shunde), Cardiology Liang, Guoquan; The Second Hospital of Zhaoqing, Guangdong, Cardiology Zhang, Yan; Shunde Hospital, Southern Medical University (The first people's hospital of Shunde), Cardiology Huang, YUli; Shunde Hospital of Southern Medical University, Cardiology
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Evidence based practice
Keywords:	atrial fibrillation, acute coronary syndrome, oral anticoagulants

A Retrospective Cohort Study of Oral Anticoagulant Treatment in Patients With Acute Coronary Syndrome and Atrial Fibrillation

Brief title: OAC Treatment in ACS patients with AF

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ABSTRACT

OBJECTIVE: To examine the real-world patterns of oral anticoagulant (OAC) therapy in patients with acute coronary syndrome (ACS) and atrial fibrillation (AF) in South China undergoing percutaneous coronary intervention (PCI) and determine the clinical characteristics associated with OAC prescription.

DESIGN: A retrospective cohort study.

SETTING: The study was conducted in the Shunde Hospital, Southern Medical University and the second hospital of Zhaoqing, China, from January 2013 to 31 December 2018.

PARTICIPANTS: Patients were aged ≥18 years, hospitalized for ACS and received PCI treatment.

OUTCOME MEASURES: AF was diagnosed based on an electrocardiogram recording or a Holter monitor. Prescription of OACs and antiplatelets were determined from the discharge medication list.

RESULTS: A total of 3612 ACS patients were included; 286 (7.9%) were diagnosed with AF, including 45 (1.2%) with paroxysmal AF, 227 (6.3%) with persistent/permanent AF and 14 (0.4%) with unclassified AF. Although 95.5% of patients with AF were at high risk (CHA_2DS_2-VASc score ≥2) for stroke, only 21.7% were discharged on OACs; 10.5% received warfarin and 11.2% received non-vitamin K antagonist oral anticoagulants. Patients with pre-admission use of OAC, a HAS-BLED score <3, with persistent/permanent AF were more likely to receive OAC treatment at discharge.

CONCLUSION: We found that approximately 8% of patients who underwent PCI during ACS hospitalization also demonstrated AF. Anticoagulant therapy was greatly underused. Patients with paroxysmal AF and an increased risk of bleeding were less likely to receive anticoagulant treatment. Further efforts should be made to increase the adherence to guideline recommendations for OACs.

Keywords: atrial fibrillation; acute coronary syndrome; oral anticoagulants

Strengths and limitations of this study

■This is the first study to document the current real-world patterns of anticogulation therapy in managing ACS patients with AF in Southern China.

■All the patients were with documented AF and received drug eluting stent implantation.

■ The present study highlight further efforts should be made to increase adherence to guideline recommendations for OAC treatment among ACS patients with AF.

■ Data were obtained from two large hospitals in Southern China, and do not represent the current treatment status in other regions.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia worldwide.[1] It is associated with a four to five-fold increased risk of ischemic stroke.[2 3] Known or new-onset AF is a common comorbidity in patients with acute coronary syndrome (ACS). It has been reported that 2–21% of ACS patients have a history of AF.[4] Patients with ACS and AF have a poor prognostic outcome, including a higher risk of stroke.[5-7] Antithrombotic treatment with oral anticoagulants (OACs), such as warfarin or non-vitamin K antagonist oral anticoagulants (NOACs), is a cornerstone in the prevention of ischemic stroke in patients with AF.[8 9] However, for patients with AF presenting with acute myocardial infarction (AMI) or coronary artery disease, undergoing percutaneous coronary intervention (PCI) poses a great challenge with regard to the management of antithrombotic therapy.[10] These patients need dual antiplatelet therapy (DAPT) to reduce the risk of subsequent myocardial infarction and stent thrombosis, and OAC treatment to reduce the risk of stroke.[11]

Although academic guidelines recommend that a combination of OACs and DAPT should be initiated in these patients and then subsequently switched to single anti-platelet agent combined with OACs,[1 12 13] OACs have been largely underused in real-world clinical practice.[14-19] However, NOACs have not been applied in most reported studies.[14-19] Recently, there has been a significant price drop in NOACs and more evidence concerning the safety of these agents compared with warfarin. These factors may lead to greater use of NOACs instead of warfarin in patients at higher risk of bleeding, including those undergoing concomitant anti-platelet treatment. However,

the prevalence of antithrombotic therapy in Chinese patients with ACS and AF has not been explored after the introduction of NOACs. Therefore, the current study was undertaken to examine current real-world patterns of OAC therapy in managing ACS patients with AF in South China undergoing PCI.

Methods

Study population

This was a retrospective cohort study conducted in the Shunde Hospital, Southern Medical University and the second hospital of Zhaoqing, China, from January 2013 to 31 December 2018.

We reviewed the medical records of patients aged ≥18 years who were hospitalized for ACS and received PCI treatment. ACS was defined as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina (UA). STEMI was diagnosed based on elevated levels of biomarkers for myocardial necrosis (including troponin T, troponin I, or creatine kinase MB), with ST-segment elevation of 1 mm or more in at least two contiguous electrocardiogram (ECG) leads,[20] while NSTEMI was defined as ST-segment depression of ≥1 mm. Patients with typical ischemic symptoms and no elevation in biomarkers for myocardial necrosis, with or without ECG changes were classified as having UA.[21] AF was diagnosed using an ECG recording or a Holter monitor. For patients with length of hospital stay ≥7 days, those with AF lasting <7 d were classified as having paroxysmal AF,[1] and were otherwise classified as having

persistent/permanent AF. In patients with no prior history of AF and with length of hospital stay <7 days, those with AF were defined as unclassified. All of the patients received coronary angiography and PCI. We excluded those with rheumatic heart disease or mechanical heart valves, death during hospitalization or were transferred out within 3 days, or without discharge medication list available.

Risk stratification and anticoagulation treatment

Baseline characteristics including age, sex, smoking, history of hypertension, diabetes, dyslipidemia, chronic kindey disease, previous stroke/TIA, history of AF and pre-admission use of OAC, ACS type, Killip classification were collected via the hospital medical record. Blood biochemical measurements, such as fasting plasma glucose, high-density lipoprotein cholesterol, total cholesterol, and triglyceride levels were measured using an automated biochemical analyzer. Estimated glomerular filtration rate was calculated using the modified Modification of Diet in Renal Disease equation adapted for Chinese.[22]

We used the CHA_2DS_2-VASc score to evaluate the risk of stroke (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes mellitus, history of stroke/transient ischemic attack [doubled], vascular disease, age 65–75 years and female sex). The risk of bleeding was evaluated using the HAS-BLED score (hypertension, abnormal renal/liver function, history of stroke, history of bleeding, labile internationally normalized ratio, age >65 years, non-steroidal anti-inflammatory drugs or alcohol abuse).[1 12] Because data concerning the time in therapeutic range for warfarin was not available, we defined the labile internationally normalized ratio as

'none' and 0 points were given to all patients when calculating the HAS-BLED score.

Prescription of warfarin, NOACs, aspirin, and clopidogrel was determined from the discharge medication list. In the hospitals participating in the current study, rivaroxaban and dabigatran were the two types of NOAC available. Standard dosages of NOACs were defined as rivaroxaban 20 mg/day or dabigatran 150 mg twice daily for patients with creatinine clearance ≥50 mL/min, and rivaroxaban 15 mg/day or dabigatran 110 mg twice daily for creatinine clearance of 30–49 mL/min.[23 24] Any daily dosages less than this range were defined as reduced dosages.

Statistical Analysis

AF patients were divided into two groups based on whether they received OAC treatment or not at discharge. Baseline characteristics, including CHA_2DS_2-VASc score, HAS-BLED scores, and antiplatelet therapy were examined. Continuous variables are presented as median (inter-quartile range) or mean (standard deviation), as appropriate. Categorical variables are expressed as number (percentages). Continuous variables were compared using the Wilcoxon rank-sum test or Student's *t*-test after testing for normality using the Kolmogorov–Smirnov test. Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate.

Multiple logistic regression models were used to examine the association between baseline characteristics and OAC treatment at discharge. Patients without OAC treatment were used as the reference. The variables adjusted in the multi-variable model were: sex, age (≥65 vs. <65 years), diabetes, hypertension, dyslipidemia, history of stroke, abnormal renal/liver function, non-steroidal

anti-inflammatory drugs or alcohol abuse, history of bleeding, smoking status, type of ACS (UA or MI), cardiac function (Killip classification III–IV vs. I–II), type of AF (paroxysmal or persistent/permanent) and pre-admission use of OAC. We further set the CHA_2DS_2-VASc score and HAS-BLED score as independent factors in the model, while their individual components (age, sex, cardiac function, diabetes, hypertension, history of stroke, history of bleeding) were not included to avoid over-adjustment. Adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) are presented. All the statistical analysis was performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA). All comparisons are two-sided, with statistical significance defined as $P<0.05$.

Ethical clearance

The study complied with the Declaration of Helsinki and was approved by the institutional review board central committee at Shunde Hospital, Southern Medical University, China. As this was a retrospective analysis, patients' informed consent was waived by the institutional review board.

Patient and public involvement

Patients and the general public were not involved in this study.

Results

Baseline characteristics

We reviewed 3813 electronic medical records of patients aged ≥18 years, who were hospitalized for ACS and received PCI treatment from January 2013 to

December 2018. After excluding 121 patients who died or were transferred out during hospitalization, and 76 patients without a discharge medication list, 4 patients with mechanical heart valves, a total of 3612 patients were included in this study.

All of the patients received coronary angiography and drug eluting stent implantation, 1393 of them (38.6%) presented with AMI and received emergent PCI treatment, 2219 of them (61.4%) were diagnosed with UA and received PCI during the index hospitalization after carefully non-invasive examination.

Among all the included patients, 286 (7.9%) were diagnosed with AF; 45 of these (1.2%) had paroxysmal AF, 227 (6.3%) had persistent/permanent AF and 14 (0.4%) with unclassified AF. According to the hospital medical record, 48 patients were with document history of AF and 26 (54.2%) of them were received OAC therapy prior to admission. Compared with those without AF, ACS patients with AF were older and more likely to be female, with a higher prevalence of hypertension, diabetes and cardiac dysfunction, previous stroke/TIA, and higher mean CHA_2DS_2-VASc and HAS-BLED scores (all $P<0.01$, Table 1).

Anti-thrombotic therapy

The in-hospital anti-thrombotic treatment regimens in ACS patients with and without AF are presented in Table 2. The rates of parenteral anticoagulant treatment, including low molecular weight heparin and fondaparinux, were higher in patients with AF compared with those without AF (35.7% vs. 21.0%, $P<0.01$). The in-hospital use of antiplatelet agents, including aspirin and clopidogrel, was high and similar in ACS patients with and without AF (all $P>0.05$). Prescription of OACs in AF patients

was low (n = 85, 29.7%); 38 of them received warfarin (13.3%) and 47 of them received NOACs (16.4%). In patients undergoing NOAC treatment, 42 of them (89.3%) received reduced dosages.

At hospital discharge, the use of anti-platelet agents was similar as in-hospital usage, and nearly 99% of patients with and without AF received DAPT. However, only 21.7% of patients with AF (n = 62) were discharged on OACs, and 10.5% of them received warfarin and 11.2% received NOACs (Table 2). Similarly, in patients undergoing NOAC treatment, 90.6% of them received reduced dosages.

Determinants of OAC treatment at discharge

We examined the association between baseline characteristics and OAC treatment at discharge. In all the included AF patients, only 4.5% were at moderate risk (CHA_2DS_2-VASc score 1), and 95.5% were at high risk (CHA_2DS_2-VASc score ≥2) for stroke. In terms of bleeding, 31.8% of the patients had a HAS-BLED score ≥3, which was defined as a high risk of bleeding. The baseline characteristics of the AF patients received OAC or not at discharge were presented on Table 3. As shown in Table 4, patients with pre-admission use of OAC, a HAS-BLED score <3, with persistent/permanent AF were more likely to receive OAC treatment at discharge. However, neither a high risk of stroke nor other clinical characteristics were associated with OAC treatment.

Discussion

There are three main findings in this study. First, the overall incidence of AF was

7.9% in patients with ACS who received PCI during hospitalization. Second, although most patients with AF had a high risk of stroke, less than 30% received OAC treatment at discharge. Third, patients with pre-admission use of OAC, a lower risk of bleeding and persistent/permanent AF were more likely to receive anticoagulation therapy after PCI.

DAPT was recommended in ACS patients who underwent PCI to decrease the risk of stent thrombosis.[21] However, antiplatelet treatments have no clinical benefit in the treatment of atrial fibrillation. For AF patients who undergo PCI, if the CHA2DS2-VASc score ≥2, initial treatment with DAPT plus OACs (triple therapy) for at least 4 weeks is recommended under the current guidelines.[1, 12] However, such a "triple therapy" strategy poses risks for bleeding and OACs are globally underused in clinical practice.[14-19] The China acute myocardial infarction (CAMI) registry found that from 2013–2014, only 5.1% of ACS patients with AF were treated using warfarin, and 1.7% were treated using both warfarin and DAPT.[25] No NOACs were prescribed in ACS+AF patients in the CAMI study. In the current study, we found that this situation had improved. Approximately 30% of ACS patients with AF who underwent PCI received anticoagulation therapy at discharge, and half were prescribed NOACs. This improvement may be caused by the accumulation of clinical research data, the availability of consensus guidelines for treatment, increased physician awareness of anticoagulation therapy and a price reduction in NOACs in China. However, it should be noted that OACs were still greatly underused.

Compared with warfarin, NOACs are more convenient for use, including

advantages such as fixed dose regimens, no requirement for frequent blood monitoring, no food and drug restrictions and less risk of bleeding.[26 27] In the current study, we found that there was a substantially increased use of NOACs in Chinese patients during the past few years. This is consistent with data from the Danish nationwide administrative registries, which found that by 2016, the use of NOACs in any combination with antiplatelets was exceeding that of warfarin in combination with antiplatelets.[28] However, in the current cohort, most patients (approximately 90%) received a reduced dosage of NOACs, such as rivaroxaban 10 mg/day. This may be driven primarily by the concern of increased risk of bleeding. It has been reported that in AF patients with AMI and/or PCI, when in combination with DAPT, low-dose NOACs plus DAPT was associated with a lower rate of clinically significant bleeding than a vitamin K antagonist plus DAPT.[29 30]

In contrast with previous studies which showed that the use of OACs in patients with ACS and AF was not influenced by either stroke risk or bleeding risk,[18 19] the current study found that patients with a HAS-BLED score <3 were more likely to receive OAC treatment at discharge. Furthermore, the number of patients treated with OAC at discharge (21.7%) was significant decreased than that during hospitalization (29.7%). These results suggest that physicians are still hesitant to prescribe “triple therapy” because of concerns about the risk of bleeding. Both the American College of Cardiology (ACC)/American Heart Association (AHA)/ Heart Rhythm (HRS) and the European Heart Rhythm Association (EHRA)/ European Society of Cardiology (ESC) guidelines for the management of patients with AF have proposed a clear

algorithm for the management of these patients.[1] [12] The most recently AHA/ACC/HRS guideline recommended that in patients with AF at increased risk of stroke who have undergone PCI with stenting for ACS, double therapy with P2Y12 inhibitors (clopidogrel) and low-dose rivaroxaban 15 mg daily or dabigatran 150 mg twice daily is reasonable to reduce the risk of bleeding as compared with triple therapy.[1] The EHRA/ESC guideline also proposed that dual therapy with OAC plus one clopidogrel may be considered in patients with excessive bleeding risk and have low thrombotic risk.[12] However, providing optimal treatment is still a great challenge in real-world practice. In our study, we found that patients with ACS after PCI and AF were almost all treated with DAPT (nearly 99% of patients). However, OAC is greatly underused. These results pointed out a very "awkward" situation, clinicians are concern about the risk of bleeding as well as stent thrombosis, so they choose to select DAPT but not double therapy with one P2Y12 inhibitor and OAC. These results showed that there are great gap between real clinical practice and recommendations from the academic guidelines. Further efforts should be made to increase adherence to guideline recommendations for OAC treatment among eligible ACS patients with AF.

The current study further found that patients with paroxysmal AF were less likely to receive OACs than those with persistent/permanent AF. This was not a surprise. The AHA/ACC/HRS guideline for the management of AF recommend that for patients with paroxysmal AF, the need for anticoagulant therapy should be determined based on the risk of stroke, same with persistent AF.[1] However, studies

have shown that the risk of stroke in patients with paroxysmal AF is lower than that those with persistent/permanent AF.[31 32] The benefit of anticoagulation in new-onset AF, occurring in the setting of an acute attack with ACS, acute pulmonary disease, or sepsis, is associated with a higher risk of bleeding, but not with a reduced risk of ischemic stroke.[33] Therefore, for paroxysmal AF that occurs in the case of ACS, there is still much doubt about whether these patients need long-term anticoagulant therapy. Recently, a study showed that in patients with paroxysmal AF, a greater burden of AF is associated with a higher risk of ischemic stroke.[34] Therefore, follow-up studies should be conducted to observe the re-occurrence of AF in the future.

There are some limitations in the current study. First, we did not evaluate the link between anticoagulant therapy and adverse events during hospitalization and after discharge. Second, patient status was distinguished as paroxysmal AF or persistent/permanent AF based on medical records, and misclassifications cannot be totally avoided. Third, this study was a retrospective study. Data were obtained from two large hospitals in Guangdong Province, China, and do not represent the current treatment status of other regions. Finally, we also found that some patients without AF were prescribed OACs; however, the indications were unrecorded.

Conclusion

The current study found that nearly 8% of patients who underwent PCI during ACS hospitalization had AF. Although these patients were at an increased risk of stroke, anticoagulant therapy was greatly underused. Patients with paroxysmal AF and

an increased risk of bleeding were less likely to receive anticoagulant treatment. The promotion of NOAC use could increase the proportion of these patients who receive anticoagulant therapy.

Contributors YH and LM conceptualised the study, designed the protocol. YH, YW, JL and LM analysed the data and drafted the manuscript. XL, HZ and GL collected the data. YH, HZ and YZ revised the manuscript.

Funding: The project was supported by Scientific Research Fund of Foshan, Guangdong, China (No: 2016AB003353), the National Natural Science Foundation of China (No: 81600239), the Science and Technology Innovation Project from Foshan, Guangdong (FS0AA-KJ218-1301-0006) and the Clinical Research Startup Program of Shunde Hospital, Southern Medical University (CRSP2019001). The funders had no role in the design and implementation of the study, in the collection, analysis, and interpretation of the data, and in the preparation, review, or approval of the manuscript.

Acknowledgement: We thank Conn Hastings, PhD, from Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac), for editing the English text during revision of this manuscript.

Data sharing statement: For access to data of this study, please contact Dr Yuli Huang. hyuli821@smu.edu.cn

Competing interests: None declared.

Patient consent for publication: Not required.

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Table 1. Baseline characteristics of ACS patients with and without AF

	With AF(n=286)	Without AF(n=3326)
Age (year)	68 (58, 76)*	61 (52,74)
Sex [Female (%)]	128 (44.8)#	1285 (38.6)
SBP (mmHg)	129.3±22.4#	125.4±23.9
DBP (mmHg)	78.5±18.4#	76.2±17.9
Hypertension [n(%)]	123 (43.0)#	1214 (36.5)
Fasting plasma glucose (mmol/L)	5.8±3.6#	5.4±3.2
Diabetes mellitus [n(%)]	65 (22.7)#	582 (17.5)
Serum creatinine (μmol/L)	96 (65,124)	92(63,136)
eGFR (ml/min/1.73m^2)	62.2±25.1#	70.3±26.0
Current smoker	66 (23.1)	729 (21.9)
LDL-C (mmol/L)	3.2±1.9	3.0±1.8
HDL-C (mmol/L)	1.1±0.6	1.0±0.5
TC (mmol/L)	5.4±2.2	5.3±2.2
TG (mmol/L)	1.9±1.8	1.8±1.6
Dyslipidemia[n(%)]	103 (36.0)	1173 (35.3)
Previous stroke/TIA[n(%)]	17 (5.9)#	68 (2.0)
Previous CKD	19 (6.6)#	75 (2.3)
Previous AF	48 (16.8)	--
AMI[n(%)]	115 (40.2)	1278 (42.5)
UA[n(%)]	171 (59.8)	2048 (57.5)
Killip classification III-IV [n(%)]	84 (29.4)*	786 (23.6)
CHA_2DS_2-VASc score	3.5±2.0*	3.1±1.8
HAS-BLED score	3.0±1.6*	2.8±1.7
Length of hospital stay	7.6±2.9*	7.1±2.6

Continuous variables are presented as median (inter-quartile range) or mean (standard deviation). Categorical variables are expressed as number (percentages).

ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial

infarction; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TIA, transient ischemic attack; UA, unstable angina

$^{\#}P<0.05$ vs. 'without AF' group. $^{*}P<0.01$ vs. 'without AF' group.

Table 2. Anti-thrombotic treatment in ACS patients with and without AF

	With AF(n=286)	Without AF(n=3326)
In-hospital		
Aspirin [n(%)]	280 (97.9)	3291 (98.9)
Clopidogrel [n(%)]	284 (99.3)	3318 (99.8)
Parenteral anticoagulants [#][n(%)]	102 (35.7)[*]	698 (21.0)
OACs[n(%)]	85 (29.7)[*]	8 (0.2)
Warfarin[n(%)]	38 (13.3)[*]	3 (0.1)
NOACs [n(%)]	47 (16.4)[*]	5 (0.2)
At discharge		
Aspirin [n(%)]	281 (98.3)	3289 (98.9)
Clopidogrel [n(%)]	282 (98.6)	3316 (99.7)
OACs [n(%)]	62 (21.7)	7 (0.2)
Warfarin [n(%)]	30 (10.5)	3 (0.1)
NOACs [n(%)]	32 (11.2)	4 (0.1)

Categorical variables are expressed as number (percentages).

ACS, acute coronary syndrome; AF, atrial fibrillation; NOACs, non-vitamin K antagonist oral anticoagulants; OACs, oral anticoagulants

[*]$P<0.01$ vs. 'without AF' group.

Table 3. Characteristics of the AF patients received OAC or not at discharge

	OAC Treatment (n=62)	Non-OAC Treatment (n=224)
Age (year)	69 (57, 77)	68 (59, 76)
Sex [Female (%)]	30 (48.4)	98 (43.8)
Smoking [n(%)]	16 (25.8)	50 (22.3)
Hypertension [n(%)]	32 (51.6)	91 (40.6)
Diabetes mellitus [n(%)]	19 (30.6)	46 (20.5)
Dyslipidemia[n(%)]	20 (32.3)	83 (37.1)
Abnormal renal [n(%)]	5 (8.1)	14 (6.3)
Abnormal liver function [n(%)]	1 (1.6)	4 (1.8)
Non-steroidal anti-inflammatory drugs/alcohol abuse [n(%)]	4 (6.5)	21 (9.4)
Killip classification III-IV [n(%)]	21 (33.9)	63 (28.1)
History of stroke [n(%)]	8 (12.9)#	9 (4.0)
History of bleeding [n(%)]	2 (3.2)	19 (8.5)
AMI [n(%)]	25 (40.3)	90 (40.2)
CHA_2DS_2-VASc score ≥2 [n(%)]	61 (98.4)	212 (94.6)
HAS-BLED score ≥3 [n(%)]	12 (19.4)*	79 (35.3)
Persistent/permanent AF [n(%)]	59 (95.2)*	168 (75)
Pre-admission use of OAC [n(%)]	19 (30.6)*	7 (3.1)

AF, atrial fibrillation; AMI, acute myocardial infarction; OAC, oral anticoagulant

#P<0.05 vs. 'non-OAC' group. *P<0.01 vs. 'non-OAC' group.

Table 4. Determinants of oral anticoagulant treatment at discharge

Determinants	OR	95% CI	P-value
Sex (male *vs* female)	0.90	0.44-1.84	0.77
Age (≥65 *vs* <65 years)	1.38	0.31-6.14	0.67
Smoking (yes *vs* no)	1.07	0.26-4.40	0.93
Diabetes mellitus (yes *vs* no)	1.48	0.80-2.74	0.21
Hypertension (yes *vs* no)	1.35	0.43-4.24	0.61
Dyslipidemia (yes *vs* no)	0.73	0.21-2.54	0.62
Abnormal renal (yes *vs* no)	1.25	0.55-2.84	0.59
Abnormal liver function (yes *vs* no)			
Non-steroidal anti-inflammatory drugs/alcohol abuse (yes *vs* no)	1.02	0.23-4.52	0.97
Cardiac function (Killip classification III-IV *vs* I-II)	1.40	0.65-3.02	0.39
History of stroke (yes *vs* no)	2.76	0.94-8.10	0.06
History of bleeding (yes *vs* no)	0.80	0.23-2.78	0.73
Type of ACS (AMI *vs* UA)	0.95	0.19-4.75	0.95
Type of AF (persistent/permanent *vs* paroxysmal)	4.32	1.25-14.9	0.02
CHA_2DS_2-VASc score (≥2 *vs* <2)	2.65	0.93-7.55	0.07
HAS-BLED score (<3 *vs* ≥3)	3.10	1.18-8.14	0.02
Pre-admission use of OAC (yes *vs* no)	8.92	2.69-29.6	0.0003

The variables adjusted in the multi-variable model were: sex, age (≥65 vs. <65 years), diabetes, hypertension, history of stroke, history of bleeding, smoking status, type of ACS (UA or MI), cardiac function (Killip classification III–IV vs. I–II), and type of AF (paroxysmal or persistent/permanent).

Abnormal renal function was defined as chronic dialysis, renal transplant, serum creatinine ≥ 2.3 mg/dL (200 μmol/L);

Abnormal liver function was definced as chronic hepatic disease (eg, cirrhosis) or bilirubin >2 × upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 × upper limit normal.

When CHA_2DS_2-VASc score and HAS-BLED score were included as independent factors in the model, the individual components (age, sex, cardiac function, diabetes, hypertension, history of stroke, history of bleeding) were not included to avoid over-adjustment.

ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; UA, unstable angina

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-11 NA NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

A Retrospective Cohort Study of Oral Anticoagulant Treatment in Patients With Acute Coronary Syndrome and Atrial Fibrillation

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031180.R2
Article Type:	Original research
Date Submitted by the Author:	25-Aug-2019
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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Evidence based practice
Keywords:	atrial fibrillation, acute coronary syndrome, oral anticoagulants

A Retrospective Cohort Study of Oral Anticoagulant Treatment in Patients With Acute Coronary Syndrome and Atrial Fibrillation

Brief title: OAC Treatment in ACS patients with AF

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ABSTRACT

OBJECTIVE: To examine the real-world patterns of oral anticoagulant (OAC) therapy in patients with acute coronary syndrome (ACS) and atrial fibrillation (AF) in Southern China undergoing percutaneous coronary intervention (PCI) and determine the clinical characteristics associated with OAC prescription.

DESIGN: A retrospective cohort study.

SETTING: This study was conducted in the Shunde Hospital, Southern Medical University and the second hospital of Zhaoqing, China, from January 2013 to 31 December 2018.

PARTICIPANTS: Patients were aged ≥18 years, hospitalized for ACS and received PCI treatment.

OUTCOME MEASURES: AF was diagnosed based on an electrocardiogram recording or a Holter monitor. Prescription of OACs and antiplatelets were determined from the discharge medication list.

RESULTS: A total of 3612 ACS patients were included; 286 (7.9%) were diagnosed with AF, including 45 (1.2%) with paroxysmal AF, 227 (6.3%) with persistent/permanent AF and 14 (0.4%) with unclassified AF. Although 95.5% of patients with AF were at high risk (CHA_2DS_2-VASc score ≥2) of stroke, only 21.7% of them were discharged on OACs(10.5% received warfarin and 11.2% received non-vitamin K antagonist oral anticoagulants). Patients with pre-admission use of OAC, a HAS-BLED score <3, with persistent/permanent AF were more likely to receive OAC treatment at discharge.

CONCLUSION: We found that approximately 8% of patients who underwent PCI during ACS hospitalization also demonstrated AF. Anticoagulant therapy was greatly underused. Patients with paroxysmal AF and an increased risk of bleeding were less likely to receive anticoagulant treatment. Further efforts should be made to increase the adherence to guideline recommendations for OACs.

Keywords: atrial fibrillation; acute coronary syndrome; oral anticoagulants

Strengths and limitations of this study

■This is the first study to document the current real-world patterns of anticogulation therapy in managing ACS patients with AF in Southern China.

■All the patients were with documented AF and received drug eluting stent implantation.

■ The present study highlight further efforts should be made to improve theadherence to guideline recommendations for OAC treatment among ACS patients with AF.

■ Data were obtained from two large hospitals in Southern China, and do not represent the current treatment status in other regions.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia worldwide.[1] It is associated with a four to five-fold increased risk of ischemic stroke.[2 3] Known or new-onset AF is a common comorbidity in patients with acute coronary syndrome (ACS). It has been reported that 2–21% of ACS patients have a history of AF.[4] Patients with ACS and AF have a poor prognostic outcome, including a higher risk of stroke.[5-7] Antithrombotic treatment with oral anticoagulants (OACs), such as warfarin or non-vitamin K antagonist oral anticoagulants (NOACs), is a cornerstone in the prevention of ischemic stroke in patients with AF.[8 9] However, for patients with AF presenting with acute myocardial infarction (AMI) or coronary artery disease, undergoing percutaneous coronary intervention (PCI), it poses a great challenge with regard to the management of antithrombotic therapy.[10] These patients need dual antiplatelet therapy (DAPT) to reduce the risk of subsequent myocardial infarction and stent thrombosis, and OACs treatment to prevent the risk of stroke.[11]

Although academic guidelines recommend that a combination of OACs and DAPT should be initiated in these patients and then subsequently switched to single anti-platelet agent combined with OACs,[1 12 13] OACs have been largely underused in real-world clinical practice.[14-19] However, NOACs have not been applied in most reported studies.[14-19] Recently, there has been a significant price drop in NOACs and more evidence concerning the safety of these agents compared with warfarin. These factors may lead to greater use of NOACs instead of warfarin in patients at higher risk of bleeding, including those undergoing concomitant anti-platelet treatment. However,

the prevalence of antithrombotic therapy in Chinese patients with ACS and AF has not been explored after the introduction of NOACs. Therefore, the current study was undertaken to examine current real-world patterns of OAC therapy in managing ACS patients with AF in Southern China undergoing PCI.

Methods

Study population

This was a retrospective cohort study conducted in the Shunde Hospital, Southern Medical University and the second hospital of Zhaoqing, China, from January 2013 to 31 December 2018.

We reviewed the medical records of patients aged ≥18 years who were hospitalized for ACS and received PCI treatment. ACS was defined as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina (UA). STEMI was diagnosed based on elevated levels of biomarkers for myocardial necrosis (including troponin T, troponin I, or creatine kinase MB), with ST-segment elevation of 1 mm or more in at least two contiguous electrocardiogram (ECG) leads,[20] while NSTEMI was defined as ST-segment depression of ≥1 mm. Patients with typical ischemic symptoms and no elevation in biomarkers for myocardial necrosis, with or without ECG changes were classified as having UA.[21] AF was diagnosed using an ECG recording or a Holter monitor. For patients with length of hospital stay ≥7 days, those with AF lasting <7 d were classified as having paroxysmal AF,[1] and were otherwise classified as having

persistent/permanent AF. In patients with no prior history of AF and with length of hospital stay <7 days, those with AF were defined as unclassified. All of the patients received coronary angiography and PCI. We excluded those with rheumatic heart disease or mechanical heart valves, death during hospitalization or were transferred out within 3 days, or without discharge medication list available.

Risk stratification and anticoagulation treatment

Baseline characteristics including age, sex, smoking, history of hypertension, diabetes, dyslipidemia, chronic kindey disease, previous stroke/TIA, history of AF and pre-admission use of OAC, ACS type, Killip classification were collected via the hospital medical record. Blood biochemical measurements, such as fasting plasma glucose, high-density lipoprotein cholesterol, total cholesterol, and triglyceride levels were measured using an automated biochemical analyzer. Estimated glomerular filtration rate was calculated using the modified Modification of Diet in Renal Disease equation adapted for Chinese.[22]

We used the CHA_2DS_2-VASc score to evaluate the risk of stroke (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes mellitus, history of stroke/transient ischemic attack [doubled], vascular disease, age 65–75 years and female sex). The risk of bleeding was evaluated using the HAS-BLED score (hypertension, abnormal renal/liver function, history of stroke, history of bleeding, labile internationally normalized ratio, age >65 years, non-steroidal anti-inflammatory drugs or alcohol abuse).[1 12] Because data concerning the time in therapeutic range for warfarin was not available, we defined the labile internationally normalized ratio as

'none' and 0 points were given to all patients when calculating the HAS-BLED score.

Prescription of warfarin, NOACs, aspirin, and clopidogrel was determined from the discharge medication list. In the hospitals participating in the current study, rivaroxaban and dabigatran were the two types of NOAC available. Standard dosages of NOACs were defined as rivaroxaban 20 mg/day or dabigatran 150 mg twice daily for patients with creatinine clearance ≥50 mL/min, and rivaroxaban 15 mg/day or dabigatran 110 mg twice daily for creatinine clearance of 30–49 mL/min.[23 24] Any daily dosages less than this range were defined as reduced dosages.

Statistical Analysis

AF patients were divided into two groups based on whether they received OAC treatment or not, at discharge. Baseline characteristics, including CHA_2DS_2-VASc score, HAS-BLED scores, and antiplatelet therapy were examined. Continuous variables are presented as median (inter-quartile range) or mean (standard deviation), as appropriate. Categorical variables are expressed as number (percentages). Continuous variables were compared using the Wilcoxon rank-sum test or Student's *t*-test after testing for normality using the Kolmogorov–Smirnov test. Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate.

Multiple logistic regression models were used to examine the association between baseline characteristics and OAC treatment at discharge. Patients without OAC treatment were used as the reference. The variables adjusted in the multi-variable model were: sex, age (≥65 *vs.* <65 years), diabetes, hypertension, dyslipidemia, history of stroke, abnormal renal/liver function, non-steroidal

anti-inflammatory drugs or alcohol abuse, history of bleeding, smoking status, type of ACS (UA or MI), cardiac function (Killip classification III–IV *vs.* I–II), type of AF (paroxysmal or persistent/permanent) and pre-admission use of OAC. We further set the CHA_2DS_2-VASc score and HAS-BLED score as independent factors in the model, while their individual components (age, sex, cardiac function, diabetes, hypertension, history of stroke, history of bleeding) were not included to avoid over-adjustment. Adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) are presented. All the statistical analysis was performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA). All comparisons are two-sided, with statistical significance defined as $P<0.05$.

Ethical clearance

The study complied with the Declaration of Helsinki and was approved by the institutional review board central committee at Shunde Hospital, Southern Medical University, China. As this was a retrospective analysis, patients' informed consent was waived by the institutional review board.

Patient and public involvement

Patients and the general public were not involved in this study.

Results

Baseline characteristics

We reviewed 3813 electronic medical records of patients aged ≥18 years, who were hospitalized for ACS and received PCI treatment from January 2013 to

December 2018. After excluding 121 patients who died or were transferred out during hospitalization, and 76 patients without a discharge medication list, 4 patients with mechanical heart valves, a total of 3612 patients were included in this study.

All of the patients received coronary angiography and drug eluting stent implantation, 1393 of them (38.6%) presented with AMI and received emergent PCI treatment, 2219 of them (61.4%) were diagnosed with UA and received PCI during the index hospitalization after carefully non-invasive examination.

Among all the included patients, 286 (7.9%) were diagnosed with AF; 45 of these (1.2%) had paroxysmal AF, 227 (6.3%) had persistent/permanent AF and 14 (0.4%) with unclassified AF. According to the hospital medical record, 48 patients were with document history of AF and 26 (54.2%) of them were received OAC therapy prior to admission. Compared with those without AF, ACS patients with AF were older and more likely to be female, with a higher prevalence of hypertension, diabetes and cardiac dysfunction, previous stroke/TIA, and higher mean CHA_2DS_2-VASc and HAS-BLED scores (all P <0.01, Table 1).

Anti-thrombotic therapy

The anti-thrombotic treatment regimens in ACS patients with and without AF are presented in Table 2. During the hospital stay, the ratio of parenteral anticoagulant treatmentwas higher in patients with AF compared with those without AF (35.7% *vs.* 21.0%, P <0.01). The in-hospital use of antiplatelet agents, including aspirin and clopidogrel, were similar in ACS patients with and without AF (both P >0.05). Prescription of OACs in AF patients was low (n = 85, 29.7%); 38 of them received

warfarin (13.3%) and 47 of them received NOACs (16.4%). In patients with NOACs treatment, 42 of them (89.3%) received reduced dosages.

At hospital discharge, the use of anti-platelet agents was similar as in-hospital usage, and nearly 99% of patients with or without AF received DAPT. However, only 21.7% of patients with AF (n = 62) were discharged on OACs, and 10.5% of them received warfarin and 11.2% received NOACs (Table 2). Similarly, in patients with NOACs treatment, 90.6% of them received reduced dosages.

Determinants of OACs treatment at discharge

We examined the association between baseline characteristics and OAC treatment at discharge. In all the included AF patients, only 4.5% were at moderate risk (CHA_2DS_2-VASc score 1), and 95.5% were at high risk (CHA_2DS_2-VASc score ≥2) of stroke. In terms of bleeding, 31.8% of the patients had a HAS-BLED score ≥3, which was defined as a high risk of bleeding. The baseline characteristics of the AF patients received OACs or not at discharge were presented on Table 3. As shown in Table 4, patients with pre-admission use of OACs, a HAS-BLED score <3, with persistent/permanent AF were more likely to receive OACs treatment at discharge. However, neither a high risk of stroke nor other clinical characteristics were associated with OACs treatment.

Discussion

There are three main findings in this study. First, the overall incidence of AF was 7.9% in patients with ACS and received PCI during hospitalization. Second, although

most patients with AF had a high risk of stroke, less than 30% received OACs treatment at discharge. Third, patients with pre-admission use of OACs, a lower risk of bleeding and persistent/permanent AF were more likely to receive anticoagulation therapy after PCI.

DAPT was recommended in ACS patients who underwent PCI to reduce the risk of stent thrombosis.[21] However, antiplatelet treatments have no clinical benefit in the treatment of AF. For AF patients who undergo PCI, if the CHA2DS2-VASc score ≥2, initial treatment with DAPT plus OACs (triple therapy) for at least 4 weeks is recommended under the current guidelines.[1, 12] However, such a "triple therapy" strategy poses risks for bleeding and OACs are globally underused in clinical practice.[14-19] The China acute myocardial infarction (CAMI) registry found that from 2013–2014, only 5.1% of ACS patients with AF were treated using warfarin, and 1.7% were treated using both warfarin and DAPT.[25] No NOACs were prescribed in ACS patients with AF in the CAMI study. In the current study, we found that this situation was improved. Approximately 30% of ACS patients with AF who underwent PCI received anticoagulation therapy at discharge, and half of them were prescribed with NOACs. This improvement may be caused by the accumulation of clinical research data, the availability of consensus guidelines for treatment, increased physician awareness of anticoagulation therapy and a price reduction in NOACs in China. However, it should be noted that OACs were still greatly underused.

Compared with warfarin, NOACs are more convenient to use, including advantages such as fixed dose regimens, no requirement for frequent blood

monitoring, no food and drug restrictions and less risk of bleeding.[26 27] In the current study, we found that there was a substantially increased use of NOACs in Chinese patients during the past few years. This is consistent with data from the Danish nationwide administrative registries, which found that by 2016, the use of NOACs in any combination with antiplatelets was exceeding that of warfarin in combination with antiplatelets.[28] However, in the current cohort, most patients (approximately 90%) received a reduced dosage of NOACs, such as rivaroxaban 10 mg/day. This may be driven primarily by the concern for increased risk of bleeding. It has been reported that in AF patients with AMI and/or PCI, when in combination with DAPT, low-dose NOACs plus DAPT was associated with a lower rate of bleeding than a vitamin K antagonist plus DAPT.[29 30]

In contrast with previous studies which showed that the use of OACs in patients with ACS and AF was influenced by neither stroke risk nor bleeding risk,[18 19] our study found that patients with a HAS-BLED score <3 were more likely to receive OACs treatment at discharge. Furthermore, the number of patients treated with OACs at discharge (21.7%) was significant decreased than that during hospitalization (29.7%). These results suggest that physicians are still hesitant to prescribe "triple therapy" because of concerns about the risk of bleeding. Both the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm (HRS) and the European Heart Rhythm Association (EHRA)/European Society of Cardiology (ESC) guidelines for the management of patients with AF have proposed a clear algorithm for the management of these patients.[1 12] The most recently

AHA/ACC/HRS guideline recommended that in ACS patients with AF at increased risk of stroke, double therapy with P2Y12 inhibitors (clopidogrel) and low-dose rivaroxaban 15 mg daily or dabigatran 150 mg twice daily is reasonable to reduce the risk of bleeding, as compared with triple therapy.[1] The EHRA/ESC guideline also proposed that dual therapy with OACs plus clopidogrel may be considered in patients with excessive bleeding risk and low thrombotic risk.[12] However, providing optimal treatment is still a great challenge in real-world practice. In this study, we found that patients with ACS after PCI and AF were almost all treated with DAPT (nearly 99% of patients). However, OACs is greatly underused. These results pointed out a very "awkward" situation, clinicians are concern about the risk of bleeding as well as stent thrombosis, so they choose to select DAPT but not double therapy with one P2Y12 inhibitor and OACs. These results showed that there are great gap between real clinical practice and recommendations from the academic guidelines. Further efforts should be made to improve the adherence to guideline recommendations for OACs treatment among ACS patients with AF.

The current study further found that patients with paroxysmal AF were less likely to receive OACs than those with persistent/permanent AF. This was not a surprise. The AHA/ACC/HRS guideline for the management of AF recommended that for patients with paroxysmal AF, the need for anticoagulant therapy should be determined based on the risk of stroke, same with persistent AF.[1] However, studies have shown that the risk of stroke in patients with paroxysmal AF is lower than that those with persistent/permanent AF.[31 32] The benefit of anticoagulation in new-onset

AF, occurring in the setting of an acute attack with ACS, acute pulmonary disease, or sepsis, is associated with a higher risk of bleeding, but not with a reduced risk of ischemic stroke.[33] Therefore, for paroxysmal AF that occurs in the case of ACS, there is still much doubt about whether these patients need long-term anticoagulant therapy. Recently, a study showed that in patients with paroxysmal AF, a greater burden of AF is associated with a higher risk of ischemic stroke.[34] Therefore, follow-up studies should be conducted to observe the re-occurrence of AF in the future.

There are some limitations in the current study. First, we did not evaluate the link between anticoagulant therapy and adverse events during hospitalization and after discharge. Second, patient status was distinguished as paroxysmal AF or persistent/permanent AF based on medical records, so misclassifications cannot be totally avoided. Third, as a retrospective study, data were obtained from two large hospitals in Guangdong Province, China, and do not represent the current treatment status of other regions. Finally, we also found that some patients without AF were prescribed with OACs, however, the indications were unrecorded.

Conclusion

This study found that nearly 8% of patients who underwent PCI during ACS hospitalization had AF. Although these patients were at an increased risk of stroke, anticoagulant therapy was greatly underused. Patients with paroxysmal AF and an increased risk of bleeding were less likely to receive anticoagulant treatment. The promotion of NOACs use can increase the treatment of anticoagulation in these

patients.

Contributors YH and LM conceptualised the study, designed the protocol. YH, YW, JL and LM analysed the data and drafted the manuscript. XL, HZ and GL collected the data. YH, HZ and YZ revised the manuscript.

Funding: The project was supported by Scientific Research Fund of Foshan, Guangdong, China (No: 2016AB003353), the National Natural Science Foundation of China (No: 81600239), the Science and Technology Innovation Project from Foshan, Guangdong (FS0AA-KJ218-1301-0006) and the Clinical Research Startup Program of Shunde Hospital, Southern Medical University (CRSP2019001). The funders had no role in the design and implementation of the study, in the collection, analysis, and interpretation of the data, and in the preparation, review, or approval of the manuscript.

Acknowledgement: We thank Conn Hastings, PhD, from Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac), for editing the English text during revision of this manuscript.

Data sharing statement: For access to data of this study, please contact Dr Yuli Huang. hyuli821@smu.edu.cn

Competing interests: None declared.

Patient consent for publication: Not required.

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Table 1. Baseline characteristics of ACS patients with and without AF

	With AF(n=286)	Without AF(n=3326)
Age (year)	68 (58, 76)*	61 (52,74)
Sex [Female (%)]	128 (44.8)#	1285 (38.6)
SBP (mmHg)	129.3±22.4#	125.4±23.9
DBP (mmHg)	78.5±18.4#	76.2±17.9
Hypertension [n(%)]	123 (43.0)#	1214 (36.5)
Fasting plasma glucose (mmol/L)	5.8±3.6#	5.4±3.2
Diabetes mellitus [n(%)]	65 (22.7)#	582 (17.5)
Serum creatinine (μmol/L)	96 (65,124)	92(63,136)
eGFR (ml/min/1.73m^2)	62.2±25.1#	70.3±26.0
Current smoker	66 (23.1)	729 (21.9)
LDL-C (mmol/L)	3.2±1.9	3.0±1.8
HDL-C (mmol/L)	1.1±0.6	1.0±0.5
TC (mmol/L)	5.4±2.2	5.3±2.2
TG (mmol/L)	1.9±1.8	1.8±1.6
Dyslipidemia[n(%)]	103 (36.0)	1173 (35.3)
Previous stroke/TIA[n(%)]	17 (5.9)#	68 (2.0)
Previous CKD	19 (6.6)#	75 (2.3)
Previous AF	48 (16.8)	--
AMI[n(%)]	115 (40.2)	1278 (42.5)
UA[n(%)]	171 (59.8)	2048 (57.5)
Killip classification III-IV [n(%)]	84 (29.4)*	786 (23.6)
CHA_2DS_2-VASc score	3.5±2.0*	3.1±1.8
HAS-BLED score	3.0±1.6*	2.8±1.7
Length of hospital stay	7.6±2.9*	7.1±2.6

Continuous variables are presented as median (inter-quartile range) or mean (standard deviation). Categorical variables are expressed as number (percentages).

ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial

infarction; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TIA, transient ischemic attack; UA, unstable angina

$^{\#}P<0.05$ vs. 'without AF' group. $^{*}P<0.01$ vs. 'without AF' group.

Table 2. Anti-thrombotic treatment in ACS patients with and without AF

	With AF(n=286)	Without AF(n=3326)
In-hospital		
Aspirin [n(%)]	280 (97.9)	3291 (98.9)
Clopidogrel [n(%)]	284 (99.3)	3318 (99.8)
Parenteral anticoagulants [#][n(%)]	102 (35.7)[*]	698 (21.0)
OACs[n(%)]	85 (29.7)[*]	8 (0.2)
Warfarin[n(%)]	38 (13.3)[*]	3 (0.1)
NOACs [n(%)]	47 (16.4)[*]	5 (0.2)
At discharge		
Aspirin [n(%)]	281 (98.3)	3289 (98.9)
Clopidogrel [n(%)]	282 (98.6)	3316 (99.7)
OACs [n(%)]	62 (21.7)	7 (0.2)
Warfarin [n(%)]	30 (10.5)	3 (0.1)
NOACs [n(%)]	32 (11.2)	4 (0.1)

Categorical variables are expressed as number (percentages).

ACS, acute coronary syndrome; AF, atrial fibrillation; NOACs, non-vitamin K antagonist oral anticoagulants; OACs, oral anticoagulants

[*]$P<0.01$ vs. 'without AF' group.

Table 3. Characteristics of the AF patients received OAC or not at discharge

	OAC Treatment (n=62)	Non-OAC Treatment (n=224)
Age (year)	69 (57, 77)	68 (59, 76)
Sex [Female (%)]	30 (48.4)	98 (43.8)
Smoking [n(%)]	16 (25.8)	50 (22.3)
Hypertension [n(%)]	32 (51.6)	91 (40.6)
Diabetes mellitus [n(%)]	19 (30.6)	46 (20.5)
Dyslipidemia[n(%)]	20 (32.3)	83 (37.1)
Abnormal renal [n(%)]	5 (8.1)	14 (6.3)
Abnormal liver function [n(%)]	1 (1.6)	4 (1.8)
Non-steroidal anti-inflammatory drugs/alcohol abuse [n(%)]	4 (6.5)	21 (9.4)
Killip classification III-IV [n(%)]	21 (33.9)	63 (28.1)
History of stroke [n(%)]	8 (12.9)#	9 (4.0)
History of bleeding [n(%)]	2 (3.2)	19 (8.5)
AMI [n(%)]	25 (40.3)	90 (40.2)
CHA_2DS_2-VASc score ≥2 [n(%)]	61 (98.4)	212 (94.6)
HAS-BLED score ≥3 [n(%)]	12 (19.4)*	79 (35.3)
Persistent/permanent AF [n(%)]	59 (95.2)*	168 (75)
Pre-admission use of OAC [n(%)]	19 (30.6)*	7 (3.1)

AF, atrial fibrillation; AMI, acute myocardial infarction; OAC, oral anticoagulant

#P<0.05 vs. 'non-OAC' group. *P<0.01 vs. 'non-OAC' group.

Table 4. Determinants of oral anticoagulant treatment at discharge

Determinants	OR	95% CI	P-value
Sex (male *vs* female)	0.90	0.44-1.84	0.77
Age (≥65 *vs* <65 years)	1.38	0.31-6.14	0.67
Smoking (yes *vs* no)	1.07	0.26-4.40	0.93
Diabetes mellitus (yes *vs* no)	1.48	0.80-2.74	0.21
Hypertension (yes *vs* no)	1.35	0.43-4.24	0.61
Dyslipidemia (yes *vs* no)	0.73	0.21-2.54	0.62
Abnormal renal (yes *vs* no)	1.25	0.55-2.84	0.59
Abnormal liver function (yes *vs* no)			
Non-steroidal anti-inflammatory drugs/alcohol abuse (yes *vs* no)	1.02	0.23-4.52	0.97
Cardiac function (Killip classification III-IV *vs* I-II)	1.40	0.65-3.02	0.39
History of stroke (yes *vs* no)	2.76	0.94-8.10	0.06
History of bleeding (yes *vs* no)	0.80	0.23-2.78	0.73
Type of ACS (AMI *vs* UA)	0.95	0.19-4.75	0.95
Type of AF (persistent/permanent *vs* paroxysmal)	4.32	1.25-14.9	0.02
CHA_2DS_2-VASc score (≥2 *vs* <2)	2.65	0.93-7.55	0.07
HAS-BLED score (<3 *vs* ≥3)	3.10	1.18-8.14	0.02
Pre-admission use of OAC (yes *vs* no)	8.92	2.69-29.6	0.0003

The variables adjusted in the multi-variable model were: sex, age (≥65 vs. <65 years), diabetes, hypertension, history of stroke, history of bleeding, smoking status, type of ACS (UA or MI), cardiac function (Killip classification III–IV vs. I–II), and type of AF (paroxysmal or persistent/permanent).

Abnormal renal function was defined as chronic dialysis, renal transplant, serum creatinine ≥ 2.3 mg/dL (200 μmol/L);

Abnormal liver function was definced as chronic hepatic disease (eg, cirrhosis) or bilirubin >2 × upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 × upper limit normal.

When CHA_2DS_2-VASc score and HAS-BLED score were included as independent factors in the model, the individual components (age, sex, cardiac function, diabetes, hypertension, history of stroke, history of bleeding) were not included to avoid over-adjustment.

ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; UA, unstable angina

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-11 NA NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.