Antithrombotic therapy in coronary artery disease patients with atrial fibrillation

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Abstract

Background: Coronary artery disease (CAD) and atrial fibrillation (AF) frequently coexist in clinical practice, making it challenging for the treating physician to choose anticoagulation and antiplatelet therapies. The aim of this study was to investigate antithrombotic strategies and assess related adverse outcomes in stable coronary artery disease (SCAD) and acute coronary syndrome (ACS) patients with AF when the CHA2DS2-VASc score was ≥ 2.

Methods: We performed a retrospective study and collected data from a computer-based patient record management system in Zhengzhou University People’s Hospital in China. In total, 2978 patients with a hospital discharge diagnosis of CAD and concomitant AF who met the inclusion criteria were enrolled from January 1, 2012 to December 31, 2016, and data from 2050 patients were finally analysed. The χ² test was used to compare the incidences of clinical endpoints between the SCAD+AF group and the ACS + AF group. Multivariable Cox regression analysis was performed to identify independent predictive factors of adverse outcomes in both groups.

Results: Oral anticoagulant (OAC) monotherapy was the most common antithrombotic therapy in SCAD+AF patients (49.55%), while double antiplatelet therapy (DAPT) was the most common treatment in ACS + AF patients (54.19%) at discharge. OAC monotherapy significantly increased and the use of single antiplatelet therapy (SAPT) decreased during follow-up (34 ± 13 months) when compared to their use at discharge in the SCAD+AF group (all p < 0.001). In the ACS + AF group, the proportion of patients using DAPT decreased notably, while the proportions of patients using SAPT and dual therapy (DT) combining OAC with SAPT increased significantly during follow-up (all p < 0.001) compared to the proportions at discharge. According to multivariable Cox regression analysis, age, hypertension and prior stroke were independent risk factors for ischaemic stroke in the SCAD+AF group and ACS + AF group (all p < 0.05). Previous bleeding independently increased the risk of haemorrhage in both groups (all p < 0.01).

Conclusions: In this study, the proportion of anticoagulant-antiplatelet combined therapy was low in ACS + AF patients with high stroke risk. In clinical practice, the awareness of anticoagulation needs to be strengthened regarding patients with CAD and AF.

Keywords: Coronary artery disease, Acute coronary syndrome, Atrial fibrillation, Triple therapy, Oral anticoagulant, Double antiplatelet therapy, Dual therapy, Bleeding

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Background

Antithrombotic strategies include antiplatelet therapy (APT), which suppresses platelet function, and oral anticoagulant (OAC) therapy, which interferes with the signalling cascade of blood coagulation. APT is regarded as the cornerstone of the treatment of patients with stable coronary artery disease (SCAD) and of patients after acute coronary syndrome (ACS) [1]. OAC is closely associated with atrial fibrillation (AF), which exclusively promotes the development of thrombotic conditions in the left atrium and left atrial appendage and increases the risk of ischaemic stroke [2, 3]. Coronary artery disease (CAD) and AF are the primary heart diseases worldwide and are responsible for the high morbidity and mortality of cardiovascular and cerebrovascular diseases. By 2050, it is estimated that the number of AF patients in Asia will reach 72 million, which is more than double the combined numbers in Europe and the United States [4]. Thirty percent of AF patients have concomitant CAD, and up to 15% of patients with SCAD also have AF [5, 6]. The prevalence of AF in patients with ACS ranges from 10 to 21% and increases with severity of myocardial infarction (MI) and age [7]. Patients with CAD and AF have a high incidence of both ischaemic and haemorrhagic events, which frequently coexist in daily practice. The combination of AF and CAD is a general and complicated problem and makes it challenging for the treating physician to choose anticoagulation and antiplatelet therapies. In this setting, it is essential for the treating physician to determine the antithrombotic regimen with the desired benefit/risk ratio for specific patients. Current guidelines recommend short-term triple therapy (TT), consisting of OAC and double antiplatelet therapy (DAPT), although TT inevitably leads to a higher incidence of major bleeding [2, 3, 8, 9]. However, the management of many patients with CAD and AF in the real world has long relied on medical experience rather than guidelines and consensus.

A few factors affect the development of thromboembolic events among patients with AF, such as ischaemic stroke and systemic embolism, and these factors are integrated into the CHA2DS2-VASc score [10]. The CHA2DS2-VASc score is applied to assess the risk level of patients with AF and can subsequently provide guidance on the reasonable use of OAC. In this single-centre observational and retrospective study from Central China, we aimed to study antithrombotic therapies targeting patients with CHA2DS2-VASc scores ≥2 with SCAD and ACS concomitant with AF in clinical practice, to evaluate related adverse outcomes, and ultimately to provide evidence for the choice of antithrombotic strategy in the future.

Methods

Study design and population

This work was approved by the Ethics Committee of Zhengzhou University People’s Hospital [NO. 2016(40)] and was exempted from the requirement of informed consent. This was an observational retrospective study based on patients with a discharge diagnosis of CAD and concomitant AF. Data were collected from a computer-based patient record management system in Zhengzhou University People’s Hospital in Henan Province, China, from January 1, 2012 to December 31, 2016. The database covered the central region of China, spanning approximately 167,000 km² with a population of 0.96 billion inhabitants (2018 population statistics), representing 6.9% of the population of China. All information used for data analysis in this study was anonymized.

Patients who met all the following criteria were eligible for inclusion: 1) age above 18 years; 2) AF recorded on electrocardiogram (ECG) or Holter monitor during hospitalization; 3) coronary arteriography (CAG) or coronary computed tomography angiography (CTA) showing at least one stenosis of the great coronary artery ≥50% or typical electrocardiographic changes and elevated myocardium biochemical markers.

The exclusion criteria were as follows: 1) atrial flutter; 2) rheumatic valve disease; 3) any severe condition that would limit life expectancy to less than 1 year; 4) contra-indication to the use of OAC, aspirin, or P2Y12 platelet inhibitors (clopidogrel, prasugrel or ticagrelor); and 5) reversible AF (caused by surgery, mental stress, hyperthyroidism, alcohol and exhaustion).

Patients with a CHA2DS2-VASc score ≥2 in this study were finally divided into the SCAD+AF group and the ACS + AF group for further analysis.

Data collection

We gathered clinical characteristics such as age, history of hypertension and bleeding, types of AF, cardiovascular drugs at discharge, choice of operative procedures for cardiovascular events and risk scores for predicting cardiovascular complications, including the CHA2DS2-VASc score (congestive heart failure, hypertension, age > 75 years, diabetes mellitus, prior stroke with transient ischaemic attack or thromboembolism, vascular disease, age 65 to 74 years and sex) and the HAS-BLED score (hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio [INR], elderly status [age > 65 years], and drug or alcohol use).

Follow-up and outcomes

All patients were followed up for at least 1 year. Information concerning antithrombotic management strategy and clinical outcomes was obtained via phone calls to
patients with standardized questions and was recorded. Further information was obtained by reviewing hospital discharge reports relating to any other readmission during the follow-up period. All patients were followed up until death or the end of the study period (December 31, 2018). Outcomes included 1) ischaemic stroke, demonstrated by imaging; 2) bleeding, classified according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria [11, 12] as major bleeding, including intracranial haemorrhage or haemodynamic disorders or haemorrhage requiring intervention; moderate bleeding requiring blood transfusions but not resulting in haemodynamic disorders; and mild bleeding, not qualifying as major bleeding or moderate bleeding according to diagnostic standards; 3) MI, presenting the typical ECG changes and increased troponin or confirmed by CAG; 4) all-cause death, defined as death from any cause; and 5) thromboembolism, including ischaemic stroke, MI and systemic embolic events.

**Definitions**

ACS consists of unstable angina, ST-segment elevation myocardial infarction (STEMI), and non-ST-segment elevation myocardial infarction (NSTEMI) [12]. The assessment of SCAD referred to at least 12 months after the last coronary event with documented coronary stenosis by CAG or CTA [12, 13]. AF was diagnosed based on an ECG or Holter recording, and rheumatic valve AF and atrial flutter were excluded [14]. We defined the following antithrombotic regimens: single antiplatelet therapy (SAPT: aspirin or clopidogrel or ticagrelor), OAC (warfarin or rivaroxaban or dabigatran), DAPT (aspirin plus clopidogrel or ticagrelor), dual therapy (DT) referring to OAC plus SAPT, and TT referring to warfarin plus DAPT (aspirin plus clopidogrel).

**Statistical analysis**

Continuous variables and categorical variables are described as the mean ± standard deviation and percentages, respectively. Continuous variables were compared using t-tests, while categorical variables were compared using χ² tests. Multivariable Cox regression analysis was performed to identify independent predictive factors of adverse clinical events. A p-value < 0.05 was regarded as statistically significant. SPSS software (version 20.0) was used for performing calculations.

**Results**

**Baseline characteristics**

A total of 2978 patients with CAD and AF were enrolled from January 1, 2012 to December 31, 2016. A total of 198 patients were excluded, and 2780 patients were eligible. A total of 2177 patients had a CHA²DS²-VASc score ≥ 2, and 127 were lost to follow-up. Therefore, the final analysis included 2050 patients (Fig. 1). The characteristics of the study population at baseline are displayed in Table 1. There were 559 patients in the SCAD+AF group and 1491 patients in the ACS + AF group. Compared to the SCAD+AF group, the ACS + AF group showed a higher rate of percutaneous coronary intervention (PCI) (7.51% vs. 11.13%, p = 0.016). No significant difference was found in demographics, past medical history, cardiovascular drug therapies, types of AF, thromboembolism or bleeding risk scores between these two groups (all p>0.05). Statins were the most common medication prescribed and administered according to the patients’ records at discharge, both in the SCAD+AF group and ACS + AF group (88.55 and 86.38%, respectively). Hypertension was the most common complication in both groups (69.41 and 71.63%, respectively). Most patients who took warfarin for a long time exhibited INR controlled at 2–3 when they were discharged (Supplement Table 1).

**Antithrombotic regimen in patients enrolled each year**

As shown in Fig. 2a, we assessed the antithrombotic regimen in patients with CAD and AF at discharge and annually thereafter. The most common drug prescribed was DAPT. Although the proportion of DAPT continuously decreased (47.93, 41.86, 40.53, 39.23 and 33.49%, respectively) and the use of DT (5.51, 10.85, 16.93, 21.19 and 21.48%, respectively) and TT (3.03, 3.88, 6.46, 8.37 and 8.80%, respectively) gradually increased over the years, the changes were not statistically significant (p = 0.055, p = 0.053 and p = 0.051 for trend, respectively). In the SCAD+AF group, the proportion of patients receiving SAPT clearly decreased over the study period (63.89, 52.78, 40.16, 36.17 and 25.20%, respectively, p = 0.048 for trend), and OAC monotherapy was the most common treatment beginning in 2014 (Fig. 2b). Figure 2c shows that the proportion of patients prescribed TT was small and steadily increased each (3.92, 5.02, 8.26, 9.88 and 11.76%, respectively, p = 0.048 for trend) in the ACS + AF group. In addition, the rate of DAPT use tended to decrease (67.45, 57.35, 54.74, 49.07 and 45.10%, respectively) and that of DT used showed an increasing tendency (7.06, 13.98, 22.94, 26.54 and 29.08%, respectively) from 2012 to 2016, but no significant difference was observed (p = 0.050 and p = 0.051 for trend, respectively).

**Antithrombotic strategy at discharge and during follow-up**

Figure 3a shows that OAC monotherapy and SAPT were the most common antithrombotic therapies, and the proportions of the two therapies were similar...
(49.55 and 43.11%, respectively) in the SCAD+AF group at discharge, while most patients in the ACS+AF group received DAPT and DT (54.19 and 20.59%, respectively). During follow-up, we recorded the change in antithrombotic treatments compared with previous treatments (Fig. 3b). In the SCAD+AF group, OAC monotherapy was still the most frequently used therapy, and the proportion of OAC monotherapy was higher than that of SAPT (64.67 and 27.25%, respectively). The proportion of OAC significantly increased (64.67% vs. 49.55%, \( p < 0.001 \)), while the proportion of SAPT significantly decreased (27.25% vs. 43.11%, \( p < 0.001 \)) during follow-up compared to the same parameters at discharge. In the ACS+AF group, SAPT and DT were the most common treatments among patients (35.74 and 28.48%, respectively), and the proportion of patients using DAPT significantly decreased (9.96% vs. 54.19%, \( p < 0.001 \)), while the proportions of patients using SAPT and DT significantly increased (35.74% vs. 11.80%, \( p < 0.001 \) and 28.48% vs. 20.59%, \( p < 0.001 \), respectively) during follow-up when compared to the same parameters at discharge.

**Clinical complications and the corresponding antithrombotic strategy during follow-up**

The incidence of adverse clinical outcomes in the SCAD+AF group and ACS+AF group during the follow-up of 34 ± 13 months is indicated in Table 2, including 23 patients (1.12%) with ischaemic stroke, 93 patients (4.54%) with bleeding, 19 patients (0.93%) with MI and 39 patients (1.90%) experiencing all-cause death events. The ACS+AF group had a higher incidence of bleeding and all-cause death events than the SCAD+AF group (5.37% vs. 2.33%, \( p = 0.003 \) and 2.28% vs. 0.89%, \( p = 0.041 \), respectively). The incidence of mild and moderate bleeding events was higher in the ACS+AF group than in the SCAD+AF group (3.35% vs. 1.61%, \( p = 0.035 \) and 1.74% vs. 0.54%, \( p = 0.039 \), respectively). There was no significant difference in major bleeding, ischaemic stroke or MI event rates between the 2 groups (0.27% vs. 0.18%, \( p = 1.000 \); 1.07% vs. 1.17%, \( p = 0.732 \) and 1.01% vs.
Table 1 Baseline characteristics of study population

| Characteristics                             | SCAD + AF (n = 559) | ACS + AF (n = 1491) | P-value |
|---------------------------------------------|---------------------|---------------------|---------|
| Female, n (%)                              | 256 (45.80)         | 672 (45.07)         | 0.064   |
| Age, (years)                               | 71.12 ± 0.86        | 72.34 ± 0.76        | 0.841   |
| Smoking, n (%)                             | 172 (30.77)         | 450 (30.18)         | 0.796   |
| Alcohol drinking history, n (%)            | 144 (25.76)         | 363 (24.35)         | 0.509   |
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| Heart failure, n (%)                       | 62 (11.09)          | 193 (12.94)         | 0.258   |
| Arterial hypertension, n (%)               | 388 (69.41)         | 1068 (71.63)        | 0.324   |
| Diabetes mellitus, n (%)                   | 99 (17.71)          | 318 (21.33)         | 0.070   |
| Hypercholesterolemia, n (%)                | 171 (30.59)         | 519 (34.81)         | 0.072   |
| Peptic ulcer, n (%)                        | 20 (3.58)           | 43 (2.88)           | 0.418   |
| Previous stroke, n (%)                     | 35 (6.26)           | 130 (8.72)          | 0.069   |
| Previous Bleeding, n (%)                   | 6 (1.07)            | 23 (1.54)           | 0.423   |
| Previous MI, n (%)                         | 9 (1.61)            | 27 (1.81)           | 0.758   |
| AF type                                     |                     |                     |         |
| Paroxysmal, n (%)                          | 275 (49.19)         | 710 (47.62)         | 0.525   |
| Persistent, n (%)                          | 183 (32.74)         | 455 (30.52)         | 0.334   |
| Permanent, n (%)                           | 101 (18.07)         | 326 (21.86)         | 0.059   |
| CHA2DS2-VASc score                         | 3.14 ± 1.03         | 3.65 ± 1.22         | 0.422   |
| HAS-BLED score                             | 2.19 ± 1.38         | 2.12 ± 1.11         | 0.696   |
| PCI, n (%)                                  | 42 (7.51)           | 166 (11.13)         | 0.016*  |
| CABG, n (%)                                 | 3 (0.54)            | 18 (1.21)           | 0.179   |
| ACEI/ARB, n (%)                             | 357 (63.80)         | 993 (66.60)         | 0.245   |
| β-blocker, n (%)                            | 374 (66.91)         | 1041 (69.82)        | 0.204   |
| Statins, n (%)                              | 495 (88.55)         | 1288 (86.38)        | 0.194   |
| Diuretics, n (%)                            | 81 (14.49)          | 207 (13.88)         | 0.725   |
| Digoxin, n (%)                              | 91 (16.28)          | 287 (19.25)         | 0.123   |
| CCB, n (%)                                  | 132 (23.61)         | 318 (21.33)         | 0.266   |
| Proton pump inhibitors, n (%)               | 315 (56.35)         | 863 (57.88)         | 0.533   |
| INR                                         | 2.16 ± 0.42         | 2.27 ± 0.38         | 0.236   |

Data are expressed as the mean ± standard deviation or number (%) of subjects. *Statically significant at p < 0.05. Abbreviations: SCAD: stable coronary artery disease; ACS: acute coronary syndrome; AF: atrial fibrillation; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium receptor antagonist; INR: international normalized ratio.

Fig. 2 Antithrombotic therapy in newly enrolled patients each year. The antithrombotic regimen trends in (a) the total population, (b) SCAD+AF patients and (c) ACS + AF patients included from 2012 to 2016. *Statically significant for trend at p < 0.05. Abbreviations: SCAD: stable coronary artery disease; ACS: acute coronary syndrome; AF: atrial fibrillation; OAC: oral anticoagulant; SAPT: single antiplatelet therapy; DAPT: double antiplatelet therapy; DT: dual therapy; TT: triple therapy.
0.72%, \( p = 0.725 \), respectively. Compared to warfarin monotherapy, the use of non-vitamin K antagonist (VKA) oral anticoagulant (NOAC) alone significantly decreased the incidences of thromboembolism and bleeding events in patients with CAD and AF (1.91% vs. 6.97%, \( p = 0.048 \) and 1.27% vs. 5.91%, \( p = 0.046 \), respectively, Supplement Table 2). In addition, NOAC was associated with a lower incidence of bleeding events than warfarin in patients prescribed OAC-SAPT combined therapy (2.68% vs. 9.62%, \( p = 0.039 \)).

**Independent predictive factors of adverse outcomes**

According to multivariate Cox regression analysis, age, hypertension and prior stroke were independently

| Table 2 The incidence of major adverse outcomes during follow-up |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | n (%)           | OAC             | SAPT            | DAPT            | DT              | TT              | \( P \)-value  |
| Ischemic stroke  |                 |                 |                 |                 |                 |                 |               |
| SCAD+AF          | 23 (1.12)       | 4 (0.20)        | 12 (0.59)       | 6 (0.29)        | 1 (0.05)        | 0 (0)           |               |
| ACS + AF         | 7 (1.25)        | 1 (0.18)        | 4 (0.72)        | 2 (0.36)        | 0 (0)           | 0 (0)           |               |
| ACS+AF           | 16 (1.07)       | 3 (0.20)        | 8 (0.54)        | 4 (0.27)        | 1 (0.07)        | 0 (0)           | 0.732         |
| Bleeding         |                 |                 |                 |                 |                 |                 |               |
| SCAD+AF          | 93 (4.54)       | 14 (0.68)       | 7 (0.34)        | 20 (1.05)       | 23 (1.12)       | 29 (1.41)       |               |
| ACS + AF         | 13 (2.33)       | 5 (0.89)        | 2 (0.36)        | 1 (0.18)        | 1 (0.18)        | 4 (0.72)        |               |
| ACS+AF           | 80 (5.37)       | 9 (0.60)        | 5 (0.34)        | 19 (1.27)       | 22 (1.48)       | 25 (1.68)       | 0.003*        |
| mild bleeding    |                 |                 |                 |                 |                 |                 |               |
| SCAD+AF          | 59 (2.88)       | 11 (0.54)       | 6 (0.29)        | 12 (0.59)       | 16 (0.78)       | 14 (0.68)       |               |
| ACS + AF         | 9 (1.61)        | 4 (0.72)        | 2 (0.36)        | 0 (0)           | 1 (0.18)        | 2 (0.36)        |               |
| ACS+AF           | 50 (3.35)       | 7 (0.47)        | 4 (0.27)        | 12 (0.80)       | 15 (1.01)       | 12 (0.80)       | 0.035*        |
| moderate bleeding|                 |                 |                 |                 |                 |                 |               |
| SCAD+AF          | 29 (1.41)       | 3 (0.15)        | 1 (0.05)        | 7 (0.34)        | 6 (0.29)        | 12 (0.59)       |               |
| ACS + AF         | 3 (0.54)        | 1 (0.18)        | 0 (0)           | 1 (0.18)        | 0 (0)           | 1 (0.18)        |               |
| ACS+AF           | 26 (1.74)       | 2 (0.13)        | 1 (0.07)        | 6 (0.40)        | 6 (0.40)        | 11 (0.74)       | 0.039*        |
| major bleeding   |                 |                 |                 |                 |                 |                 |               |
| SCAD+AF          | 5 (0.24)        | 0 (0)           | 0 (0)           | 1 (0.05)        | 1 (0.05)        | 3 (0.15)        |               |
| ACS + AF         | 1 (0.18)        | 0 (0)           | 0 (0)           | 1 (0.05)        | 0 (0)           | 1 (0.18)        |               |
| ACS+AF           | 4 (0.27)        | 0 (0)           | 0 (0)           | 1 (0.07)        | 1 (0.07)        | 2 (0.13)        | 1.000         |
| MI               |                 |                 |                 |                 |                 |                 |               |
| SCAD+AF          | 19 (0.93)       | 7 (0.34)        | 5 (0.24)        | 2 (0.10)        | 3 (0.15)        | 2 (0.10)        |               |
| ACS + AF         | 4 (0.72)        | 2 (0.36)        | 2 (0.36)        | 0 (0)           | 0 (0)           | 0 (0)           |               |
| ACS+AF           | 15 (1.01)       | 5 (0.34)        | 3 (0.20)        | 2 (0.13)        | 3 (0.20)        | 2 (0.13)        | 0.725         |
| All-cause death  |                 |                 |                 |                 |                 |                 |               |
| SCAD+AF          | 39 (1.90)       | 11 (0.54)       | 8 (0.39)        | 7 (0.34)        | 4 (0.20)        | 9 (0.44)        |               |
| ACS + AF         | 5 (0.28)        | 1 (0.18)        | 2 (0.36)        | 0 (0.00)        | 1 (0.18)        | 1 (0.18)        |               |
| ACS+AF           | 34 (2.28)       | 10 (0.67)       | 6 (0.40)        | 7 (0.47)        | 3 (0.20)        | 8 (0.54)        | 0.041*        |

*Statically significant at \( p < 0.05 \). Abbreviations: SCAD stable coronary artery disease, ACS acute coronary syndrome, AF atrial fibrillation, MI myocardial infarction, OAC oral anticoagulant, SAPT single antiplatelet therapy, DAPT double antiplatelet therapy, DT dual therapy, TT triple therapy.
associated with an increased risk of ischaemic stroke in the SCAD+AF group (odds ratio [OR], 1.03, 95% confidence interval [CI], 1.01–1.06, \( p = 0.007 \); OR, 1.33, 95% CI, 1.04–1.72, \( p = 0.014 \) and OR, 1.39, 95% CI, 1.12–2.17, \( p = 0.009 \), respectively; Table 3) and the ACS + AF group (OR, 1.44, 95% CI, 1.06–1.98, \( p = 0.006 \); OR, 1.50, 95% CI, 1.22–1.83, \( p = 0.020 \) and OR, 1.25, 95% CI, 1.04–1.56, \( p = 0.031 \), respectively). OAC was independently associated with a decreased risk of ischaemic stroke in both groups (OR, 0.33, 95% CI, 0.25–0.46, \( p = 0.016 \) and OR, 0.54, 95% CI, 0.30–0.93, \( p = 0.005 \), respectively). Age and previous bleeding independently increased the risk of bleeding in the ACS + AF group (OR, 1.85, 95% CI, 1.28–2.66, \( p = 0.020 \) and OR, 1.78, 95% CI, 1.33–2.39, \( p = 0.006 \), respectively), while only a history of bleeding independently increased the risk of haemorrhage in the SCAD+AF group (OR, 1.85, 95% CI, 1.12–3.07, \( p = 0.001 \)). Multivariate Cox regression analysis also revealed that APT was an independent protective factor for MI in the SCAD+AF group (OR, 0.71, 95% CI, 0.58–0.86, \( p = 0.004 \)) and the ACS + AF group (OR, 0.66, 95% CI, 0.56–0.79, \( p < 0.001 \), and diabetes mellitus was an independent risk factor for MI in the ACS + AF group (OR, 2.23; 95% CI, 1.75–2.83, \( p = 0.001 \)). Age and heart failure were independently associated with an increased risk of all-cause death in the SCAD+AF group (OR, 1.67; 95% CI, 1.37–2.02, \( p = 0.005 \) and OR, 2.81; 95% CI, 1.82–4.34, \( p = 0.028 \), respectively) and the ACS + AF group (OR, 1.47; 95% CI, 1.21–1.79, \( p = 0.001 \) and OR, 3.02; 95% CI, 1.61–5.68, \( p = 0.003 \), respectively). OAC (OR, 0.32; 95% CI, 0.18–0.57, \( p < 0.001 \) and OR, 0.47; 95% CI, 0.28–0.77, \( p = 0.009 \), respectively) and APT (OR, 0.71; 95% CI, 0.54–0.95, \( p = 0.015 \) and OR, 0.57; 95% CI, 0.42–0.75, \( p < 0.001 \), respectively) were independently associated with a decreased risk of all-cause death in both groups.

Discussion

The major findings of the current study were as follows: (1) OAC was the most frequently implemented treatment prescribed at discharge in SCAD+AF patients, whereas DAPT was the most common treatment in ACS + AF patients; (2) During the follow-up, the proportions of patients using OAC and SAPT significantly increased and decreased, respectively, in the SCAD+AF group, and the use of DAPT significantly decreased while the proportions of patients using SAPT and DT significantly increased in the ACS + AF group when compared to the use of these treatments at discharge; (3) Compared to the SCAD+AF group, the incidence of bleeding and all-cause death events was significantly higher in the ACS + AF group; (4) Multivariate analysis showed that OAC was an independent protective factor for ischaemic stroke, and previous bleeding was independently associated with an increased risk of bleeding in both groups; and (5) NOAC was superior to warfarin in patients with CAD and AF.

Of particular concern in CAD management has been the use of APT in patients with AF receiving OAC for stroke prevention when their CHA2DS2-VASc score is \( \geq 2 \). Aspirin is still the gold standard for secondary prevention in SCAD patients, with clopidogrel being an alternative treatment, and aspirin has been indicated to decrease major cardiovascular events by approximately 20 to 25% [15, 16]. Therefore, patients with SCAD and AF may, in theory, need treatment with DT to avoid thromboembolic and recurrent cardiovascular events [17]. Consistent with our findings that a higher incidence of bleeding events occurred in patients using DT or TT than in those using SAPT or OAC monotherapy in the SACD+AF group, registry studies showed that the risk of haemorrhage increased 2-fold when APT and warfarin were used simultaneously [18]. The same result was also found among patients taking a combination of NOAC and APT [19, 20]. Contemporary guidelines and expert consensus built on observational data [5, 6, 21] suggested using OAC alone as the default strategy to reduce haemorrhage events in such patients [3, 22]. In our study, the most common treatment beginning in 2014 was OAC monotherapy in the SCAD+AF patients newly enrolled each year, and prescription of OAC alone was the most commonly used treatment in SCAD patients with AF at discharge and during follow-up. The proportions of patients prescribed OAC monotherapy and SAPT significantly increased and decreased, respectively, in the follow-up period when compared to the proportions at discharge in the SCAD+AF group, which supported the above viewpoint. A multicentre, open-label trial carried out in Japan also showed that rivaroxaban (a NOAC) monotherapy was not inferior to the combined treatment (rivaroxaban plus a single antiplatelet agent) in regard to efficacy and was superior in regard to safety in patients with SCAD and AF [9]. The rate of DT use was also low in patients in the SCAD+AF group. Indeed, most observational studies indicated that DT was linked with a higher risk of haemorrhage without exerting obvious positive effects on thromboembolic outcomes [5, 6, 21]. Nevertheless, concomitant antiplatelet therapy was essential for patients with SCAD and AF in the case of coronary revascularization, after which DAPT should be recommended for 6 to 12 months in most patients except those at a high risk of bleeding, for whom 1–3 months of DAPT may be more acceptable [8, 23, 24]. A small number of SCAD+AF patients were found to choose DAPT and anticoagulant-antiplatelet combined therapy in this study, which may be due to PCI. Moreover, as the 2018 European Heart Rhythm Association recommended, changing from DAPT to NOAC alone
| Table 3 | Independent predictors of major adverse outcomes by multivariable Cox regression analysis in SCAD+AF group and ACS+AF group |
|---------|------------------------------------------------------------------------------------------------------------------|
|         | SCAD + AF                                                                                                           | ACS + AF                                                                                                           |
|         | OR (95% CI)                                                                                                         | OR (95% CI)                                                                                                         |
|         | P-value                                                               | P-value                                                               |
| Ischemic stroke |                                                                              |                                                                              |
| Age ≥ 65 | 1.03 (1.01–1.06)                                                      | 1.44 (1.06–1.98)                                                      | 0.006*                                                               |
| Female | 1.35 (0.85–1.99)                                                      | 1.21 (0.93–1.60)                                                      | 0.117                                                               |
| Hypertension | 1.33 (1.04–1.72)                                                   | 1.50 (1.22–1.83)                                                      | 0.020*                                                               |
| Heart failure | 0.99 (0.94–1.03)                                                   | 1.26 (0.89–1.78)                                                      | 0.193                                                               |
| Diabetes mellitus | 0.62 (0.27–1.46)                                                   | 0.92 (0.36–2.27)                                                      | 0.890                                                               |
| Previous stroke | 1.39 (1.12–2.17)                                                   | 1.25 (1.04–1.56)                                                      | 0.031*                                                               |
| Previous bleeding | 1.68 (0.77–3.68)                                                   | 1.16 (0.57–2.42)                                                      | 0.713                                                               |
| Coronary stent | 0.81 (0.31–2.26)                                                   | 0.78 (0.37–1.53)                                                      | 0.440                                                               |
| OAC | 0.33 (0.25–0.46)                                                      | 0.54 (0.30–0.93)                                                      | 0.005*                                                               |
| APT | 0.72 (0.42–1.10)                                                      | 0.88 (0.44–1.65)                                                      | 0.637                                                               |
| Bleeding |                                                                              |                                                                              |
| Age ≥ 65 | 1.29 (0.51–3.35)                                                      | 1.85 (1.28–2.66)                                                      | 0.020*                                                               |
| Female | 1.30 (0.57–2.93)                                                      | 0.90 (0.76–1.10)                                                      | 0.162                                                               |
| Hypertension | 1.10 (0.74–1.63)                                                   | 1.14 (0.95–1.33)                                                      | 0.148                                                               |
| Heart failure | 1.04 (0.75–1.45)                                                   | 0.67 (0.39–1.13)                                                      | 0.134                                                               |
| Diabetes mellitus | 0.95 (0.77–1.16)                                                   | 1.05 (0.87–1.23)                                                      | 0.960                                                               |
| Previous stroke | 1.17 (0.42–3.27)                                                   | 1.55 (0.70–3.45)                                                      | 0.172                                                               |
| Previous bleeding | 1.85 (1.12–3.07)                                                   | 1.78 (1.33–2.39)                                                      | 0.006*                                                               |
| Coronary stent | 0.67 (0.41–1.11)                                                   | 1.34 (0.67–2.70)                                                      | 0.316                                                               |
| OAC | 1.17 (0.56–2.25)                                                      | 2.28 (0.58–3.91)                                                      | 0.243                                                               |
| APT | 1.32 (0.86–2.01)                                                      | 2.18 (0.71–6.73)                                                      | 0.171                                                               |
| MI |                                                                              |                                                                              |
| Age ≥ 65 | 1.65 (0.73–3.74)                                                      | 1.16 (0.56–2.13)                                                      | 0.723                                                               |
| Female | 1.55 (0.83–2.91)                                                      | 0.93 (0.59–1.46)                                                      | 0.738                                                               |
| Hypertension | 1.34 (0.82–2.17)                                                   | 2.29 (0.71–7.40)                                                      | 0.166                                                               |
| Heart failure | 0.79 (0.40–1.62)                                                   | 0.99 (0.91–2.08)                                                      | 0.787                                                               |
| Diabetes mellitus | 1.26 (0.60–3.31)                                                   | 2.23 (1.75–2.83)                                                      | 0.001*                                                               |
| Previous stroke | 1.42 (0.82–2.60)                                                   | 1.71 (0.69–4.27)                                                      | 0.248                                                               |
| Previous bleeding | 1.28 (0.70–2.64)                                                   | 1.51 (0.96–2.37)                                                      | 0.308                                                               |
| Coronary stent | 1.03 (0.89–1.17)                                                   | 0.95 (0.81–1.10)                                                      | 0.558                                                               |
| OAC | 0.90 (0.57–1.38)                                                      | 1.30 (0.65–2.58)                                                      | 0.639                                                               |
| APT | 0.71 (0.58–0.86)                                                      | 0.66 (0.56–0.79)                                                      | <0.001*                                                               |
| All-cause death |                                                                              |                                                                              |
| Age ≥ 65 | 1.67 (1.37–2.02)                                                      | 1.47 (1.21–1.79)                                                      | 0.001*                                                               |
| Female | 0.85 (0.57–1.28)                                                      | 0.93 (0.66–1.37)                                                      | 0.750                                                               |
| Hypertension | 1.01 (0.96–1.04)                                                   | 1.12 (0.93–1.31)                                                      | 0.087                                                               |
| Heart failure | 2.81 (1.82–4.34)                                                   | 3.02 (1.61–5.68)                                                      | 0.003*                                                               |
| Diabetes mellitus | 0.84 (0.52–1.19)                                                   | 0.96 (0.67–1.38)                                                      | 0.839                                                               |
| Previous stroke | 1.11 (0.87–1.38)                                                   | 1.40 (0.55–3.23)                                                      | 0.560                                                               |
| Previous bleeding | 2.07 (0.72–5.71)                                                   | 1.28 (0.85–1.91)                                                      | 0.215                                                               |
| Coronary stent | 0.76 (0.54–1.09)                                                   | 0.70 (0.42–1.17)                                                      | 0.148                                                               |
| OAC | 0.32 (0.18–0.57)                                                      | <0.001*                                                              | 0.009*                                                               |
| APT | 0.71 (0.54–0.95)                                                      | 0.57 (0.42–0.75)                                                      | <0.001*                                                               |

*Statistically significant at p < 0.05. Abbreviations: OR odds ratio, CI confidence interval, SCAD stable coronary artery disease, ACS acute coronary syndrome, AF atrial fibrillation, MI myocardial infarction, OAC oral anticoagulant, APT antiplatelet therapy
early (e.g., at 6 months) could be an alternative for SCA-
D+AF patients at low ischaemic and high haemorrhagic
risks after PCI [9].

Patients with ACS and AF need to be treated with
OAC for protection against ischaemic stroke and with
DAPT for the prevention of ischaemic events such as
stent thrombosis and MI. In the European Society of
Cardiology (ESC) guidelines for ACS patients with AF,
TT was still recommended as the default strategy [3].
Although our data showed a steadily increasing propor-
tion of TT use in ACS + AF patients from 2012 to 2016,
DAPT was the most frequently prescribed treatment ra-
ther than TT at discharge, and this relatively conserva-
tive choice may be due to the higher risk of bleeding
events associated with TT [18, 19, 25]. In this study, we
also demonstrated that NOAC alone significantly de-
creased the incidences of thromboembolism and bleed-
ing events in patients with CAD and AF compared to
the effects of warfarin monotherapy. Two methods that
are available for reducing this high bleeding risk are dis-
continuing aspirin and using NOAC instead of VKAs
due to their better safety profile [26]. Three trials, in-
cluding WOEST (n = 573,25% with ACS) [11], PIONEER
AF-PCI (n = 2124, 52% with ACS) [27] and RE-DUAL
PCI (n = 2725,51% with ACS) [28], have investigated the
concept of discontinuing aspirin after PCI and thus
using DT to treat these patients. Compared to the TT
group, major bleeding significantly decreased in the DT
groups (NOAC plus P2Y12 inhibition alone) of all three
trials. We also found that the proportion of ACS pa-
tients with AF being treated with DAPT and DT in the
follow-up period exhibited a decreasing and increasing
trend, respectively, when compared to the proportions at
discharge. In addition, among the newly included popu-
lation with ACS and AF each year, the number of people
using DT at discharge showed an increasing tendency
despite the fact that no significant difference was ob-
erved. Our study suggested that a relatively low number
of ACS + AF patients received PCI because over 70% of
patients were diagnosed with unstable angina, and the
majority of these patients had serious coronary artery le-
sions (<70%). Patients preferred to choose short-term
drug treatment if it could alleviate the symptoms of the
disease. Nevertheless, the ACS + AF group had a higher
incidence of bleeding than the SCAD+AF group, which
may be because more patients underwent PCI and were
treated with DAPT, DT and TT [29].

The results of this study indicated the current status of
low anticoagulant therapy in patients with CAD and AF. This finding was consistent with the China Registry
of Atrial Fibrillation (CRAF), in which 25.6% of patients
with nonvalvar atrial fibrillation (NVAF) and a
CHA2DS2VASc score ≥2 received oral anticoagulant
monotherapy or anticoagulant-antiplatelet combined
therapy [30]. The clinical characteristics of NVAF pa-
tients in China and the higher risk of intracranial haem-
orrhage with anticoagulant treatment in Chinese
patients than in patients of other racial groups may
affect the utilization of anticoagulation therapy in clin-
ical practice [31]. The results also indicated that NOAC
was superior to warfarin in patients with CAD and AF.
The multivariable Cox regression model showed that
OAC was an independent protective factor against is-
chaemic stroke in both groups. These results indirectly
reminded us of the urgent need to improve the guide-
lines on antithrombotic drug selection and management
and to support the application of NOAC, especially for
patients who undergo coronary revascularization and are
at high risk of haemorrhage. Thus, when physicians con-
sider TT as antithrombotic therapy in patients with ACS
and AF, NOAC combined with P2Y12 platelet inhibitor
may be a better choice. However, the related research is
not conclusive. The multivariable Cox regression ana-
lysis also suggested that heart failure was significantly as-
associated with all-cause death, and it had been reported
that the progression of heart failure after ACS led to an
especially poor overall prognosis [32, 33], which may ex-
plain the higher mortality in the ACS + AF group in this
study.

Conclusions
This study suggested that the prescription rate of
anticoagulant-antiplatelet combined therapy was low in
ACS + AF patients with a high risk of stroke. In clinical
practice, the awareness of anticoagulation needs to be
strengthened in regard to patients with CAD and AF.
The optimal antithrombotic regimen in patients with
CAD and AF remains unclear when the CHA2DS2-VASc
score is ≥2. Further adequately powered randomized
controlled trials (RCTs) are needed to guide clinical
decisions.

Limitations
Our study has several limitations. First, the study has a
small sample size. Second, this study is a single-centre,
observational retrospective study and may not ade-
quately represent the current status of antithrombotic
therapy in the whole area. Third, because the follow-up
was carried out over the telephone, it is difficult for us
to assess the INR of patients in a timely manner when
patients adjust medications or when adverse events
occur, which led to a possible risk of bias. Fourth, there
are insufficient data about the exact dose of antiplatelet
and anticoagulant drugs, which may affect the analysis
of adverse outcomes [34]. In addition, we did not com-
pare the effects of the same type of antithrombotic drugs
on patients [16, 35]. Finally, NOAC did not enter the
market until 2013 in China, and these drugs cannot be
reimbursed by medical insurance. Therefore, the number of patients prescribed NOAC in this study was low. However, this analysis provides information on the current situation and time trends in the antithrombotic strategy, and the relationship between these incomplete data and clinical endpoints deserves to be further analysed.

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s12872-020-01609-8.

Additional file 1: Supplement Table 1. Warfarin duration and Levels of INR in patients at discharge.

Additional file 2: Supplement Table 2. The incidences of thromboembolism and bleeding events in patients prescribed warfarin or NOAC during follow-up.

Abbreviations
APT: Antiplatelet therapy; OAC: Oral anticoagulant; SCAD: Stable coronary heart disease; ACS: Acute coronary syndromes; AF: Atrial fibrillation; CAD: Coronary artery disease; MI: Myocardial infarction; TT: Triple therapy; DAPT: Double antiplatelet therapy; ECG: Electrocardiogram; CAG: Coronary arteriography; CTA: Computed tomography angiography; INR: International normalized ratio; STEMl: ST-segment elevation myocardial infarction; NSTE:MI: Non-ST-segment elevation myocardial infarction; SAPT: Single antiplatelet therapy; DT: Dual therapy; PCI: Percutaneous coronary intervention; OR: Odds ratio; CI: Confidence interval; NOAC: Non-VKA oral anticoagulant; ESC: European society of cardiology; GUSTO: Global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries; CRAFT: China registry of atrial fibrillation; NVAF: Nonvalvular atrial fibrillation

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Authors’ contributions
LLW, EYS and CYG conceived and designed the study. WLL, WLX, DTQ, QCC and XYL contributed to the acquisition of the data. YZ and SW performed the statistical analyses. LLW and EYS wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets that support the findings of this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
This work was approved by the Ethics Committee of Zhengzhou University People’s Hospital (NO.2016040) and was exempted from the requirement for informed consent. All information used for data analysis in this study was anonymized.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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