Combination of Oral Anticoagulant with Antiplatelet and All-cause Mortality in Elderly Patients with Atrial Fibrillation and Ischemic Heart Disease

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Authors' contributions

Article Information

ABSTRACT

Aim: Clinicians are often face the dilemma of choosing more appropriate antithrombotic regimen, since there is no evidence regarding the role of combination of Oral Anticoagulant (OAC) and antiplatelet which played in elderly patients with Atrial Fibrillation (AF) and Ischemic Heart Disease (IHD). We therefore aimed to investigate the effect of combination of OAC and antiplatelet on all-cause mortality in elderly patients with AF and IHD.
Study Design: This is a retrospective analytical study.
Place and Duration of the Study: The study was conducted in Chinese PLA General Hospital, Beijing, China. Selected patients' data available for the period between 2008 and 2014 were included in this study.
Methods: A total of 669 elderly patients with AF and IHD between 2008 and 2014 were included (mean age, 80.8 years; 67.5% men). The endpoint was all-cause mortality. Risk of all-cause death was examined with Kaplan-Meier analysis and adjusted Cox regression models.
Results: During a median follow-up of 1.3 years, the mortality rate was 74.3% for patients with

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antiplatelets, 58.6% for OAC and 42.9% for combination of both, respectively. OAC and /or antiplatelet use were associated with risk of mortality (chi-square=11.03, log rank p = 0.004) using unadjusted Kaplan-Meier analysis. In overall cohort, the adjusted hazard ratios for mortality for combination of OAC and antiplatelet was 0.41 (95% CI 0.19-0.87, p = 0.019) as compared to antiplatelet use, 0.80 (95% CI 0.39-1.64, p = 0.541) as compared to OAC use. In subgroup age ≥ 75 years, the adjusted hazard ratios for mortality were 0.40 (95% CI 0.16-1.02, p = 0.054) for combination of OAC and antiplatelet as compared to antiplatelet use, 0.79 (95% CI 0.31-1.96, p = 0.605) for combination of OAC and antiplatelet as compared to OAC use, and compared to antiplatelet use, the adjusted hazard ratio for mortality were 0.51 (95% CI 0.32-0.81, p = 0.005) for OAC use.

Conclusions: Combination of OAC with antiplatelet is associated with reduced all-cause mortality and OAC is better on outcome as compared to antiplatelet agents, but OAC plus antiplatelet is not superior to OAC in elderly patients with AF and IHD and in subgroup aged ≥ 75 years.

1. INTRODUCTION

Atrial Fibrillation (AF) and Ischemic Heart Disease (IHD) are prevalent with increasing age, particularly among those older than age 60 [1]. Previous evidence showed that Oral Anticoagulant (OAC) is superior to antiplatelets for stroke protection in AF [2], and OAC is more effective than antiplatelet drugs in reducing the risk of thromboembolic events associated with AF [3]. Antiplatelet agents are preferred in patients with IHD as well as those receiving percutaneous coronary intervention (PCI) [4-6]. However, clinicians are often face the dilemma of choosing more appropriate antithrombotic regimen for elderly patients with both AF and IHD. The PIONEER AF-PCI study is the first randomized comparison of VKA vs novel oral anticoagulant therapy in patients with NVAF receiving antiplatelet therapy after PCI to assess the relative risks of bleeding complications in patients at least 18 years of age who have AF and have undergone a PCI procedure [7]. There is no evidence regarding the role of combination of OAC and antiplatelet which played in elderly patients with AF and IHD. We therefore investigated the effect of combination of OAC and antiplatelet on all-cause mortality in elderly patients with AF and IHD.

2. PATIENTS AND METHODS

2.1 Study Design

This was a retrospective analytical study.

2.2 Setting

The study conducted in Chinese PLA General Hospital, Beijing, China.

2.3 Study Population

Selected patients' data available for the period between 2008 and 2014 were included in this study. A total of 699 older patients (≥ 60 years) with AF and IHD were eligible for this study. Diagnosis of AF is based on electrocardiography (ECG) (12-lead ECG), or 24-hour Holter ECG, and medical history at enrolment. IHD included myocardial infarction, unstable and stable angina, which was diagnosed according to recent cardiovascular guideline. Demographics, other medical diagnoses, OAC or antiplatelet agents, and laboratory data were also collected from the patients discharged. Exclusion criteria included any one of the following conditions: rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, mitral valve repair, and death in hospital. $CHADS_2$ score (cardiac failure or dysfunction, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack (doubled) was used for stroke risk stratification.

2.4 Antithrombotic Treatment Regimens

We defined the following antithrombotic treatment regimens: single-antiplatelet therapy (aspirin and/or clopidogrel), single-anticoagulant therapy (warfarin, dabigatran or rivaroxaban), antiplatelet plus anticoagulant therapy (antiplatelet agents and anticoagulants). A dosing regimen was used for aspirin (100 mg/d), clopidogrel (75 mg/d), rivaroxaban (10 mg/d) and dabigatran (110 mg, 2/d). Warfarin dose was allowed to change on the basis of international ratio (INR) level.

2.5 Outcome Measure

The outcome measure was all-cause mortality. Survival status was ascertained on 31 December

2014 from an electronic clinical information system in our hospital.

2.6 Ethical Considerations

The registry and analysis of data were approved by ethics committee of our hospital. Individual patient consent was not required, but patients or his/her relatives were informed of entry into our study.

2.7 Statistical Analysis

For baseline characteristics, categorical variables are presented as frequencies with percentages and continuous variables as means with SDs. All continuous variables were first tested for normality and homogeneity of variance. The continuous variables with normal distribution were analysed using student's t-tests and Mann-Whitney U rank-sum tests were used for these continuous variables with non-normality. Pearson chi-square tests for categorical variables. We compared mortality outcomes with Kaplan-Meier analysis and log-rank tests. Furthermore, Cox proportional hazards models were used to calculate and test hazard ratios. Differences were considered statistically significant at $p < 0.05$. Statistical analyses were performed with IBM SPSS Statistic 21.0 (IBM Corporation, Armonk, NY, USA).

3. RESULTS

3.1 Patient Characteristics

A total of 699 patients were included in the present analysis. Among these patients, 31 patients had paroxysmal AF, 668 patients had persistent or permanent AF. 42.9% patients received aspirin, 48.1% patients prescribed OACs (warfarin or novel oral anticoagulants), 9.0% patients took antiplatelet and OACs. In patients aged ≥75 years, 46.5% patients received antiplatelets, 45.5% patients prescribed OACs, 8.0% patients took antiplatelets and OACs. The mean $CHADS_2$ scores were 3.84 in patients receiving antiplatelets, 3.88 in patients receiving OACs and 4.22 in patients receiving both antiplatelet and OAC, respectively. Baseline demographics of these patients are listed in Table 1. During a median follow-up of 1.3 years [interquartile range (IQR): 0.5-2.3 years], mortality rate gradually decreased in taking antiplatelets (74.3%), OACs (58.6%) and both combination (42.9%) patients (Table 1).

3.2 Outcomes in Relation to OAC and /or Antiplatelet Use

In the unadjusted analysis, OAC and /or antiplatelet use was associated with risk of mortality (chi-square=11.03, log rank p = 0.004), and OAC or combination of OAC and antiplatelets was associated with reduced mortality as compared with antipaltelet using Kaplan-Meier analysis (Fig. 1).

Compared to antiplatelet use, the adjusted hazard ratio for mortality were 0.51 (95% CI 0.32-0.81, p = 0.005) for OAC use, 0.41 (95% CI 0.19-0.87, p = 0.019) for combination of antiplatelet and OAC. Compared to OAC use, the adjusted hazard ratios for mortality were 1.96 (95% CI 1.23-3.11, p = 0.005) for antiplatelet use, 0.80 (95% CI 0.39-1.64, p = 0.541) for combination of OAC and antiplatelet (Table 2, Fig. 2).

In subgroup analysis, as compared to antiplatelet use, the adjusted hazard ratios for mortality were 0.51 (95% CI 0.30-0.86, p = 0.012) for OAC use, 0.40 (95% CI 0.16-1.02, p = 0.054) for combination of OACs and antiplatelets in subgroup age ≥ 75 years (Table 3). In addition, as compared to OAC use, the adjusted hazard ratios for mortality were 1.98 (95% CI 1.16-3.38, p = 0.012) for antiplatelet use, 0.79 (95% CI 0.31-1.96, p = 0.605) for combination of OAC and antiplatelet in subgroup age ≥ 75 years (Table 3).

4. DISCUSSION

In this study, we report an association of combination of OAC and antiplatelet with all-cause mortality in elderly patients with AF and IHD. We show that combination of OAC and antiplatelet is associated with reduced all-cause mortality and OAC are better on outcome as compared to antiplatelet, but OAC plus antiplatelet is not superior to OAC in elderly patients with AF and IHD and in subgroup aged ≥ 75 years.

Clinicians often meet a dilemma for antithrombotic therapy, where risk of stroke or stent thrombosis must be balanced with bleeding risk in elderly patients with AF and IHD. As we known, the cornerstone of AF treatment should include OACs if 1 or more stroke risk factors (such as vascular disease) are present [8], whereas initial preventive treatment after myocardial infarction or PCI consists of drugs for platelet antiaggregation [9]. Both single- and

Table 1. Baseline characteristics based on OAC and /or antiplatelet use

	Single-antiplatelets (n=300)	Single-anticoagulants (n=336)	Both combination (n=63)	p value
Characteristics				
Age, years	83.51±6.30	79.33±6.35	77.78±6.68	< 0.001
Age ≥ 75 years,%	269(89.7)	263(78.3)	46(73.0)	< 0.001
Male sex,%	179(59.7)	247(73.5)	45(71.4)	0.001
BMI, kg/m^2	25.28±4.07	26.34±4.58	26.14±5.09	0.112
Smoker,%	164(54.8)	182(54.1)	33(52.1)	0.942
Heart rate, bpm	74.97±16.80	74.87±14.31	75.18±21.76	0.990
SBP, mmHg	128.32±22.15	124.75±19.32	125.37±21.83	0.092
DBP, mmHg	72.14±12.88	71.77±11.39	72.40±12.23	0.895
CHADS$_2$ score	3.84±1.32	3.88±1.37	4.22±1.34	0.012
Medical histories				
Hypertension,%	172(57.2)	179(53.4)	39(62.3)	0.362
Diabetes,%	87(29.1)	125(37.2)	24(38.1)	0.074
CHF,%	288(96.0)	331(98.5)	62(98.4)	0.119
Stroke,%	170(56.7)	206(61.3)	48(76.2)	0.015
Lung disease,%	49(16.3)	88(26.2)	9(14.8)	0.005
Value disease,%	67(22.4)	101(30.0)	10(16.4)	0.028
Pacemaker,%	24(8.1)	28(8.2)	7(11.1)	0.714
PCI or CABG,%	108(36.1)	165(49.2)	51(80.6)	< 0.001
Laboratory tests				
Creatinine, µmol/L	130.18±66.45	118.61±44.10	114.59±37.69	0.012
eGFR, ml/min	46.32±18.19	52.52±18.68	54.10±18.87	< 0.001
Haemoglobin, g/L	127.18±15.68	131.22±16.56	128.90±15.55	0.007
Medications				
ACEIs,%	49(16.4)	92(27.4)	12(19.7)	0.004
ARBs,%	161(53.8)	193(57.3)	46(73.0)	0.020
Beta-blockers,%	247(82.2)	293(87.2)	56(88.9)	0.149
Digoxin,%	76(25.3)	101(30.1)	17(27.0)	0.409
Statins,%	98(32.7)	174(51.8)	49(77.8)	< 0.001
Nitrates,%	125(41.7)	103(30.8)	20(32.3)	0.016
Endpoint event				
All-cause death,%	223(74.3)	197(58.6)	27(42.9)	< 0.001

Notes: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHF, cardiac heart failure; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CHADS$_2$, cardiac failure or dysfunction, hypertension, age ≥ 75 years, diabetes, stroke or transient ischemic attack [doubled].

dual-antiplatelet therapy are valuable after an MI and after a PCI procedure [10,11]. Benefit of long-term OAC therapy in selected patients with AF is also demonstrated by a randomized trial [2]. Use of clopiogrel without aspirin was associated with a significant reduction in bleeding complications and no increase in the rate of thrombotic events in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention [12]. The WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) study showed that a composite secondary end point of death, myocardial infarction and stent thrombosis was significantly lower in the dual-therapy group compared with the triple-therapy group [12]. Oral anticoagulant plus aspirin were associated with a significant increased risk of all-cause death, and OAC and clopidogrel was equal or better on both benefit and safety outcomes compared to triple therapy in AF patients after myocardial infarction and PCI [13]. Addition of antiplatelet to OAC is not associated with a reduction in risk of recurrent coronary events or thromboembolism, whereas risk of bleeding is increased significantly in atrial fibrillation patients with stable coronary artery disease [14]. However, the evidence for an

optimal long-term antithrombotic treatment strategy in elderly patients with AF coexisting IHD is little. As we known, only one study demonstrated that among older patients aged ≥ 65years with AF and IHD, antithrombotic strategy was not associated with improved 1-year adjusted outcomes [15]. Therefore, further investigation into optimizing antithrombotic strategies in this population is warranted. In our study, only 9.0% patients received the combination of antiplatelet and OAC, and the mean CHADS$_2$ scores were 4.22 in patients with both antiplatelet and OAC. We showed that combination of OAC and antiplatelet was associated with reduced all-cause mortality as compared with antiplatelets, however the antithrombotic combination was not superior to OAC in elderly patients with AF and IHD, and

OAC use was better on outcome as compared with antiplatelets.

Prior findings of an annual stroke risk of 23.5% in patients with AF 80 to 89 years old [16], however, bleeding with warfarin is more common in the first year of treatment in very old patients with [17], and older patients are at higher risk for bleeding after falls, physicians may favour platelet inhibitors over oral anticoagulation in older patients due to a perceived lower bleeding risk [18], although data from clinical trials show similar bleeding rates for aspirin plus clopidogrel versus warfarin alone [19]. Our study showed that among older patients with AF and IHD, OAC use was low, and only 8.0% patients took antiplatelet plus OAC in subgroup aged ≥ 75 years. Moreover, the optimal antithrombotic

Table 2. Cox regression analyses for the association of OAC and/or antiplatelet use with mortality in elderly patients with AF and IHD

	Univariable hazard ratio [95% CI]	p value	Multivariable hazard ratio [95% CI]	p value
OAC and /or antiplatelet therapy		0.004		0.007
Single-antiplatelets	Reference	—	Reference	—
Single-OACs	0.79(0.65-0.96)	0.017	0.51(0.32-0.81)	0.005
Both combination	0.57(0.38-0.84)	0.005	0.41(0.19-0.87)	0.019
Single-antiplatelets	1.27(1.04-1.53)	0.017	1.96(1.23-3.11)	0.005
Single-OACs	Reference	—	Reference	—
Both combination	0.72(0.48-1.07)	0.100	0.80(0.39-1.64)	0.541

Adjusting for age, gender, BMI, smoker, heart rate, SBP, DBP, CHADS$_2$, lung disease, valve disease, pace maker, PCI or CABG, eGFR, hemoglobin, ACEIs, ARBs, beta-blockers, digoxin, statins, nitrates.

Table 3. Cox regression analyses for the association of OAC and/or antiplatelet therapy with mortality in subgroups aged ≥75 and < 75 years

	Univariable hazard ratio [95% CI]	p value	Multivariable hazard ratio [95% CI]	p value
In patients aged < 75 years				
OAC and /or antiplatelet therapy		0.041		0.007
Single-antiplatelets	Reference	—	Reference	—
Single-OAC	0.45(0.44-0.92)	0.030	0.25(0.09-0.37)	0.002
Both combination	0.30(0.12-0.76)	0.001	0.38(0.11-0.63)	0.021
Single-antiplatelets	1.32(1.04-1.66)	0.030	2.08(1.68-2.59)	0.002
Single-OACs	Reference	—	Reference	—
Both combination	0.40(0.16-0.97)	0.042	1.43(0.20-2.36)	0.725
In patients aged ≥75 years				
OAC and /or antiplatelet therapy		0.085		0.022
Single-antiplatelets	Reference	—	Reference	—
Single-OACs	0.83(0.67-1.02)	0.079	0.51(0.30-0.86)	0.012
Both combination	0.67(0.42-1.07)	0.093	0.40(0.16-1.02)	0.054
Single-antiplatelets	1.21(0.98-1.49)	0.079	1.98(1.16-3.38)	0.012
Single-OACs	Reference	—	Reference	—
Both combination	0.81(0.50-1.30)	0.373	0.79(0.31-1.96)	0.605

Adjusting for age, gender, BMI, smoker, heart rate, SBP, DBP, CHADS$_2$, lung disease, valve disease, pace maker, PCI or CABG, eGFR, hemoglobin, ACEIs, ARBs, beta-blockers, digoxin, statins, nitrates.

Table 4. Hazard ratios for all-cause death associated with OAC and/or antiplatelet use for subgroup according to CHADS$_2$ score

	Univariable hazard ratio [95% CI]	p value	Multivariable hazard ratio [95% CI]	p value
In CHADS$_2$ score ≤ 3				
OAC and /or antiplatelet therapy		0.460		0.675
Single-antiplatelets	Reference	—	Reference	—
Single-OACs	1.04(0.81-1.35)	0.748	0.78(0.33-1.86)	0.575
Both combination	0.73(0.42-1.28)	0.273	0.56(0.15-2.04)	0.376
Single-antiplatelets	0.96(0.74-1.24)	0.748	1.28(0.54-3.05)	0.575
Single-OACs	Reference	—	Reference	—
Both combination	0.70(0.40-1.23)	0.213	0.71(0.25-2.05)	0.529
In CHADS$_2$ score ≥ 4				
OAC and /or antiplatelet therapy		< 0.001		0.007
Single-antiplatelets	Reference	—	Reference	—
Single-OACs	0.54(0.40-0.73)	< 0.001	0.37(0.19-0.72)	0.003
Both combination	0.42(0.23-0.74)	0.003	0.31(0.09-1.05)	0.061
Single-antiplatelet	1.86(1.38-2.51)	< 0.001	2.69(1.39-5.19)	0.003
Single-OACs	Reference	—	Reference	—
Both combination	0.78(0.43-1.40)	0.402	0.83(0.24-2.88)	0.771

Adjusting for age, gender, BMI, smoker, heart rate, SBP, DBP, lung disease, valve disease, pace maker, PCI or CABG, eGFR, hemoglobin, ACEIs, ARBs, beta-blockers, digoxin, statins, nitrates.
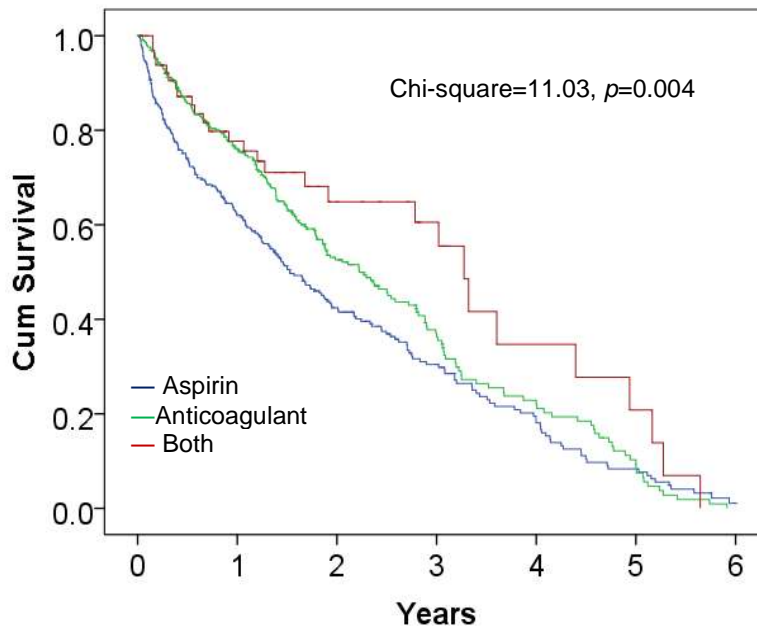

Chi-square=11.03, p=0.004

Fig. 1. Kaplan-Meier analysis of mortality outcome in OAC and /or antiplatelet therapy

strategy in patients with AF and IHD remains unresolved. Some evidence demonstrated that the absolute benefit of warfarin in thromboembolic protection also increased with age [20,21]. Octogenarian AF patients undergoing PCI/stenting have a high mortality rate and major adverse cardiac events (death, acute myocardial infarction and/or revascularisation of target lesion), which can be reduced by OAC therapy [22]. Our study showed that OAC plus antiplatelet wasn't superior to OAC or aspirin for outcome in subgroup aged ≥ 75 years; but OAC was better on outcome as compared to antiplatelets. The results suggested that OACs should be the optimal antithrombotic strategy for long-term outcome in elderly patients aged ≥ 75 years with AF and IHD.
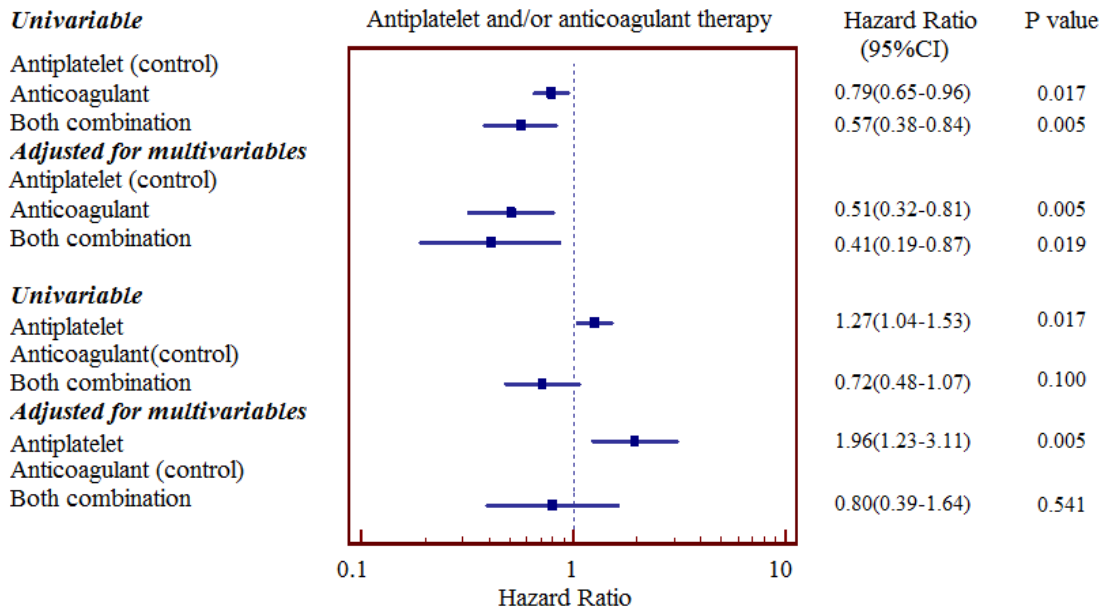
Fig. 2. Forest plots of hazard ratios (95% CIs) for mortality in antiplatelet and/or anticoagulant therapy

Notes: multivariables included age, gender, BMI, smoker, heart rate, SBP, DBP, CHADS$_2$, lung disease, valve disease, pace maker, PCI or CABG, eGFR, hemoglobin, ACEIs, ARBs, beta-blockers, digoxin, statins, nitrates.

Our study has some limitations. In elderly patients with AF and IHD, we investigated the relationships between anticoagulant and/or antiplatelet and all-cause mortality; however we didn't further observed the prognostic significance of triple antithrombotic therapy (OAC plus dual antiplatelet therapy). Patients without medication records were excluded, and a proxy for discharge medications was used. We also lacked data regarding both bleeding events, which precluded a net clinical benefit analysis, and AF and treatment duration; medication changes could have confounded our results. There were significantly statistical differences of some variables such as statin usage, eGFR, etc. among the three groups, so multivariate Cox regression was used to balance the effects of the confounders on outcome. Finally, the time point when AF was defined at enrollment, so we were unable to differentiate between persistent and permanent AF.

5. CONCLUSIONS

Combination of OAC with antiplatelet is associated with reduced all-cause mortality and OAC is better on outcome as compared to antiplatelets, but OAC plus antiplatelet is not superior to OAC in elderly patients with AF and IHD and in subgroup aged ≥ 75 years.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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    [PubMed PMID: 22983982].

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The peer review history for this paper can be accessed here:
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