Long-Term Outcome of Acute Coronary Syndromes in Patients on Chronic Oral Anticoagulants: Data from the EPICOR Study

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. All authors have contributed equally to this work.

Short running title: Oral anticoagulants in ACS

ABSTRACT

Objective: To analyse characteristics, management and outcomes of patients with acute coronary syndromes (ACS) receiving chronic oral anticoagulant (OAC) therapy enrolled in the EPICOR (long-t**E**rm follow-u**P** of antithrombotic management patterns **I**n acute **COR**onary syndrome patients) prospective, international, observational study of antithrombotic management patterns in ACS survivors (NCT01171404).

Method: This *post-hoc* analysis evaluated the association between OAC use at baseline (OACb) and time from hospital admission to percutaneous coronary intervention (PCI) (tHA-PCI), pre-PCI thrombolysis in myocardial infarction (TIMI) 3 flow, stent type, length of hospitalisation, and clinical endpoints; death, non-fatal MI, and non-fatal stroke, a composite of these ± bleeding, over 2 years' follow-up.

Results: Of 10,568 ACS patients, 345 (3.3%) were on OACb (non-ST-segment elevation ACS [NSTE-ACS], n=268; ST-segment elevation MI [STEMI], n=77). OACb patients were older with more comorbidities. In NSTE-ACS OACb patients, tHA-PCI was longer (median 57.4 *vs* 27.8 h; p = .008), and TIMI 3 flow rarer (26.0 *vs* 33.5%; p=0.035). OACb patients had longer mean hospital stay (NSTE-ACS: 8.9 *vs* 7.6 days; p<0.001; STEMI: 9.5 *vs* 7.8 days; p =0.015), and higher rates of the composite endpoint (NSTE-ACS: 16.8 *vs* 8.8%; p<0.0001; STEMI: 23.4 *vs* 5.9%; p<0.0001). Bleeding events were more common with OACb (NSTE-ACS: 6.0 *vs* 3.3%; p=0.01; STEMI: 6.5 *vs* 2.8%; p=0.04).

Conclusion: At 2 years, OACb use was associated with increased risk of cardiovascular and bleeding events in STEMI and NSTE-ACS. NSTE-ACS patients on OACb experienced prolonged time to intervention, lower rates of TIMI 3 flow and longer hospitalization.

Word count: 250 [250 max]

Keywords: acute coronary syndrome, oral anticoagulant, EPICOR

1. INTRODUCTION

Approximately 5-8% of patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) have an indication for long-term oral anticoagulation, including atrial fibrillation (AF), mechanical heart valves or venous thromboembolism [1]. Current guidelines recommend that patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) and ST-segment elevation myocardial infarction (STEMI) undergoing PCI and with a requirement for oral anticoagulants (OAC) should receive triple therapy, with OAC given in conjunction with dual antiplatelet therapy (DAPT) (aspirin plus clopidogrel) for a period of 4 weeks to 6 months, depending on level of bleeding risk [2, 3]. After this time, it is recommended that dual therapy with OAC and either aspirin or clopidogrel is continued for up to 12 months, before moving on to OAC monotherapy [2, 3]. In NSTE-ACS patients with planned medical management or coronary artery bypass graft, dual therapy is recommended for 12 months, with no triple therapy given.

The prevalence of major bleeding with triple therapy is 2.6-4.6% at 30 days, increasing to 7.4-10.3% at 12 months [4]. The management of patients with indications for OAC who undergo stent implantation for an ACS therefore remains a challenge, requiring risks of ischemic stroke and stent thrombosis to be weighed against the increased bleeding risk in these patients [5, 6].

The aim of this study was to analyse the baseline characteristics, management strategies and clinical outcomes of patients with ACS receiving oral anticoagulants as chronic medication at baseline (OACb) using data from the EPICOR (long-t**E**rm follow-u**P** of antithrombotic management patterns **I**n acute **COR**onary syndrome patients) study.

2. MATERIALS AND METHODS

EPICOR was a prospective, international, observational study (NCT01171404), designed to describe the use of antithrombotic management strategies for the treatment of ACS survivors during the acute

phase and over a follow-up period of up to 2 years from the index event. The study was conducted in 555 hospitals in 20 countries from the following regions: North Western Europe, South Western Europe, Eastern Europe/Turkey and Latin America, between September 2010 and March 2011. Among 10,568 recruited patients with ACS who survived to hospital discharge, 5625 had NSTE-ACS and 4943 had STEMI. The EPICOR study design has been published, including details of site selection, patient enrolment, definitions and the variables analysed [7]. Written informed consent was obtained from all participants. Ethical approval was obtained from the review/health board for each site in each country participating in EPICOR as previously described [8].

We describe the baseline characteristics of EPICOR patients with or without OACb and 2-year clinical outcomes. We defined 2 clinical endpoints including: (1) major adverse cardiovascular events (MACE): composite endpoint including death, non-fatal myocardial infarction [MI], and non-fatal stroke, and, (2) net adverse clinical events (NACE): composite endpoint including bleeding. In-hospital bleeding events were defined as gastrointestinal, genitourinary, intracranial, vascular access, other, or leading to haemodynamic compromise. Clinical variables related to the initial coronary event include time from onset of chest pain to first PCI, time from hospital admission to first PCI, pre-PCI thrombolysis in MI (TIMI) flow, stent type and length of hospital stay.

2.1 Statistical analysis

Patient characteristics, medical history and in-hospital findings were compared between subgroups of patients with and without OAC use by diagnosis of NSTE-ACS or STEMI. Categorical variables were compared between the subgroups using a Chi-squared test, and continuous variables were compared using 2-sample *t* tests and non-parametric tests.

Results from unadjusted and adjusted Cox proportional hazards model are also presented. The association between patient characteristics and 2-year clinical outcomes was evaluated by inspection of each hazard ratio (HR) and p-values obtained from fitting multivariate Cox proportional hazards models. The candidate variables included were: gender, current smoker, prior PCI, prior coronary

artery bypass graft and time from symptom onset to PCI (≤24 h/>24 h/no PCI). A final model for the composite clinical endpoint was derived, with OACb use forcibly included and other significant candidate variables retained, using a stepwise selection procedure, to analyse the association between OACb and outcomes. The stepwise selection algorithm used was a combination of a forward and backward process, with each forward selection step followed by one or more backward elimination steps, so that effects previously entered into the model did not necessarily remain. A $p<0.05$ was the criterion for including a variable in the final model. Comparison of times to event for patient groups by OAC use are presented based on the Kaplan-Meier unadjusted Cox proportional hazards model.

3. RESULTS

Of 10,568 patients with ACS who survived to hospital discharge in EPICOR, 345 (3.3%) were on known OACb (n = 268 with NSTE-ACS and n = 77 with STEMI) at baseline, predominantly (98.8%) with acenocoumarol or warfarin. Baseline characteristics of all patients are shown in Table 1. In both NSTE-ACS and STEMI groups, patients on OACb were older, with more comorbidities.

Table 1. Baseline characteristics of patients with or without oral anticoagulant at baseline (OACb) from the EPICOR study by non-ST-segment elevation acute coronary syndrome (NSTE-ACS) or ST-segment elevation myocardial infarction (STEMI) index event.

Parameter	NSTE-ACS			STEMI		
	Without OACb (n = 5357)	**With OACb (n = 268)**	**p**	**Without OACb (n = 4866)**	**With OACb (n = 77)**	**p**
Age, years; mean (SD)	63.5 (12.0)	71.4 (10.5)	<.0001	59.2 (12.0)	70.3 (10.4)	<.0001
Age group, years; n (%)						
<50	692 (12.9)	7 (2.6)		1051 (22.6)	1 (1.3)	
50–59	1357 (25.3)	30 (11.2)		1511 (31.1)	12 (15.6)	
60–69	1555 (29.0)	68 (25.4)		1270 (26.1)	20 (26.0)	
70–79	1217 (22.7)	100 (37.3)		761 (15.6)	27 (35.1)	
≥80	535 (10.0)	63 (23.5)		273 (5.6)	17 (22.1)	
Male, n (%)	3825 (71.4)	171 (63.8)	.008	3867 (79.5)	57 (74.0)	.241
Hypertension, n (%)	3500 (65.3)	209 (78.0)	<.0001	2353 (48.4)	56 (72.7)	<.0001
Hypercholesterolaemia, n (%)	2798 (52.2)	156 (58.2)	.056	1893 (38.9)	47 (61.0)	<.0001
Body mass index >30 kg/m^2, n (%)	1224 (22.8)	71 (26.5)	.167	953 (19.6)	12 (15.6)	.380
Type 2 diabetes mellitus, n (%)	1311 (24.5)	95 (35.4)	<.0001	806 (16.6)	19 (24.7)	.058
Current smoker, n (%)	1585 (29.6)	36 (13.4)	<.0001	2192 (45.0)	12 (15.6)	<.0001

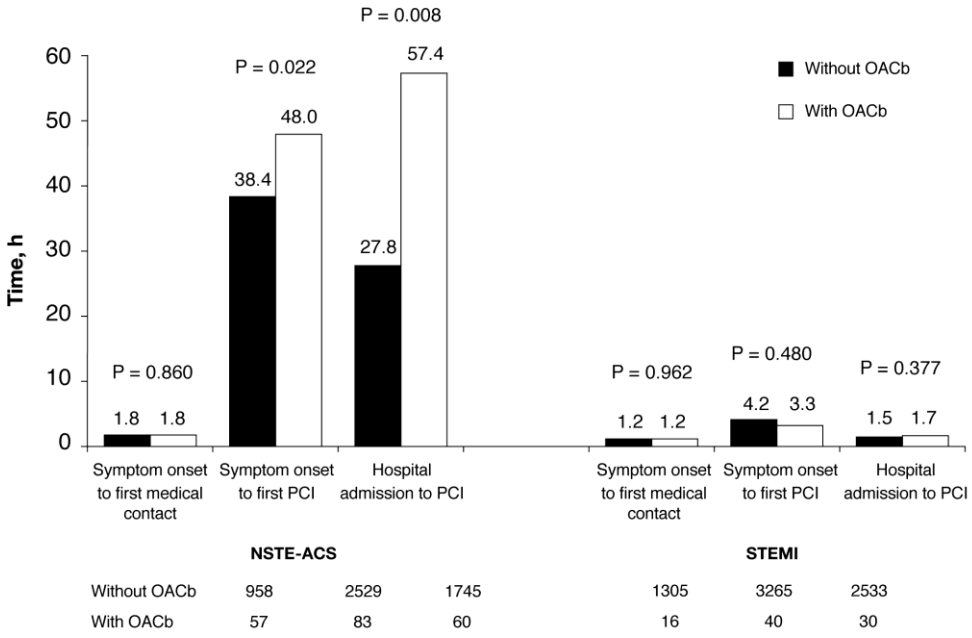
Family history of CAD, n (%)	1659 (31.0)	69 (25.7)	.071	1438 (29.6)	13 (16.9)	.015
History of myocardial infarction, n (%)	1338 (25.0)	124 (46.3)	<.0001	471 (9.7)	27 (35.1)	<.0001
History of TIA or stroke, n (%)	311 (5.8)	54 (20.1)	<.0001	138 (2.8)	12 (15.6)	<.0001
Atrial fibrillation, n (%)	208 (3.9)	160 (59.7)	<.0001	88 (1.8)	41 (53.2)	<.0001
Peripheral artery disease, n (%)	346 (6.5)	38 (14.2)	<.0001	135 (2.8)	10 (13.0)	<.0001

CAD, coronary artery disease; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack.

3.1 In-hospital findings

In patients on OACb, none with NSTE-ACS and 39 (50.6%) with STEMI underwent primary PCI; however, 56 (72.7%) and 116 (43.3%) of each group, respectively, underwent any PCI. In NSTE-ACS patients who underwent any PCI, time from hospital admission to first PCI was longer in those on OACb *vs* those not on OACb (median 57.4 *vs* 27.8 h; p=0.008). In contrast, there was no difference in time to first PCI between STEMI patients with and without OACb (Fig. 1).

Fig. 1. Median time lapse from symptom onset and hospital admission to first medical contact and percutaneous coronary intervention (PCI), in non-ST-segment elevation acute coronary syndrome (NSTE-ACS) and ST-segment elevation myocardial infarction (STEMI) patients from the EPICOR study.



Times from symptom onset to first PCI are for centres with an on-site catheterization laboratory.

OACb, oral anticoagulant at baseline.

Angiographic data are presented in Supporting Table SI. Similar percentages of patients with and without OACb had the total coronary occlusion of the culprit vessel in both ACS groups. In the

NSTE-ACS group, the proportion of patients with TIMI 3 flow prior to PCI was 26.0 *vs* 33.5% for with *vs* without OACb, respectively (p=0.035). The proportions were lower in the STEMI group, as may be expected (9.0 *vs* 15.1%, respectively (p= 0.176) with no significant difference between those on OACb and not on OACb.

3.2 Medications at discharge

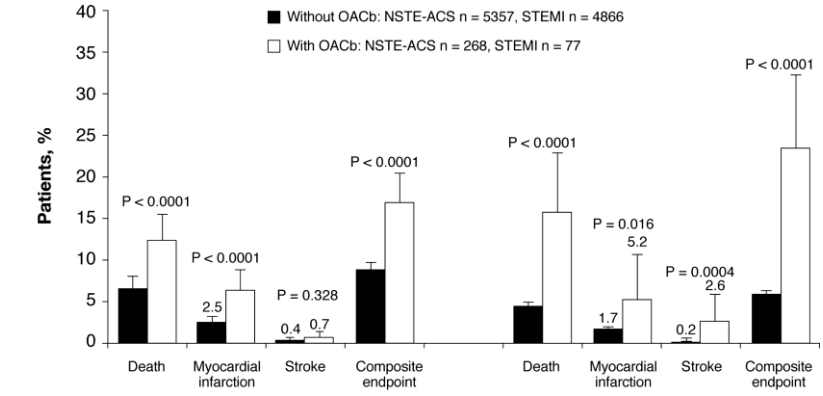
Significantly fewer patients receiving OACb were prescribed antiplatelet medications at discharge, *vs* those not on OACb: aspirin was prescribed for 80.2 *vs* 96.1% of patients with NSTE-ACS on OACb and not on OACb, respectively (p<0.0001), and for 87.0 *vs* 98.0% of STEMI patients (p<0.0001) (Supporting Table SII). $P2Y_{12}$ inhibitors were prescribed for 67.2 *vs* 86.4% of patients with NSTE-ACS on OACb and not on OACb, respectively (p<0.0001), and likewise for 85.7 *vs* 95.7% of STEMI patients (p<0.0001). Only 33.2% of NSTE-ACS patients on OACb and 39.0% of STEMI patients on OACb were receiving triple therapy. No significant differences were found for other cardiovascular (CV) therapies at discharge (Supporting Table SII).

3.3 Outcomes during follow-up

Patients receiving OACb in both the NSTE-ACS and STEMI groups had significantly higher rates of death in the 2-year follow-up period than those not on OACb (NSTE-ACS: 12.3 *vs* 6.5%; p<0.0001, and STEMI: 15.6 *vs* 4.4%; p<0.0001), and similarly for MI (NSTE-ACS: 6.3 *vs* 2.5%; p<0.0001 and STEMI: 5.2 *vs* 1.7%; p=0.016) (Fig. 2a). In the STEMI group, the incidence of stroke was also significantly higher on OACb (2.6 *vs* 0.2%; p<0.001) (Fig. 2a). Patients receiving OACb in both NSTE-ACS and STEMI groups had a significantly higher occurrence of the 2-year composite clinical endpoint of death, non-fatal MI and non-fatal stroke, *vs* those not on OACb (NSTE-ACS: 16.8 *vs* 8.8%; p<0.0001, and STEMI: 23.4 *vs* 5.9%; p<0.0001) (Fig. 2a). A Kaplan-Meier plot of time to the composite endpoint by ACS type and OACb use is presented in Fig. 3.

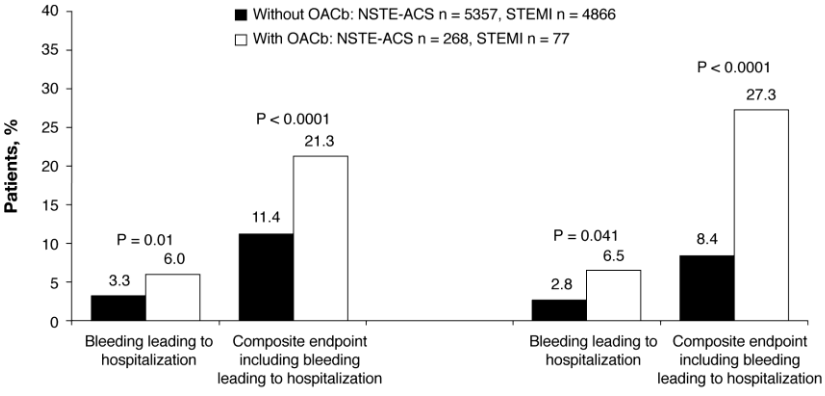
Fig. 2. EPICOR study, A) clinical outcomes at up to 2 years' follow-up* in non-ST-segment elevation acute coronary syndrome (NSTE-ACS) and ST-segment elevation myocardial infarction (STEMI) patients, and, B) bleeding events leading to hospitalization and composite endpoint (death, non-fatal myocardial infarction, non-fatal stroke, ± bleeding) leading to hospitalization at up to 2 years follow-up*.

A



Without OACb	349	136	21	469	214	83	9	286
With OACb	33	17	2	45	12	4	2	18

B



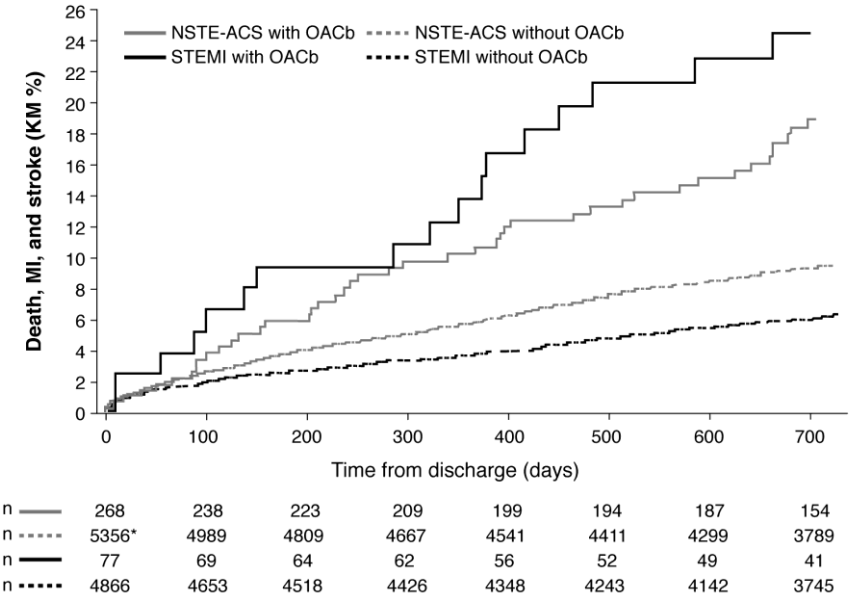
Without OACb	175	613	138	410
With OACb	16	57	5	21

Error bars are 95% CI.

*Not all patients were followed up for 2 years.

CI, confidence interval; OACb, oral anticoagulant at baseline.

Fig. 3. Time to death, myocardial infarction (MI), and stroke by final diagnosis and oral anticoagulant at baseline (OACb) use in non-ST-segment elevation acute coronary syndrome (NSTE-ACS) and ST-segment elevation myocardial infarction (STEMI) patients from the EPICOR study.



*One subject not discharged from the index hospitalization.

NSTE-ACS: with OACb 45/268 (16.8%) *vs* without OACb 469/5357 (8.8%), p<0.0001.

STEMI: with OACb 18/77 (23.4%) *vs* without OACb 286/4866 (5.9%), p<0.0001.

p-values obtained by unadjusted Cox proportional hazards model.

KM, Kaplan-Meier (time to composite endpoint of death, non-fatal MI and non-fatal stroke).

Bleeding events leading to hospitalization within 2 years were more frequent in patients receiving OACb in both groups (NSTE-ACS: 6.0 *vs* 3.3%; p=0.01, STEMI: 6.5 *vs* 2.8%; p=0.04) (Fig. 2b). Occurrence of the composite endpoint, including bleeding, was more frequent in both groups on OACb (p<0.0001) (Fig. 2b).

On multivariate analysis in NSTE-ACS patients, the higher risk of the composite of death, non-fatal MI, and non-fatal stroke up to 2 years was positively associated with age, diabetes mellitus, prior MI, AF, prior transient ischemic attack (TIA) or stroke, total days in hospital, lower LVEF, and stent implantation, but not with OACb treatment. In a parallel analysis in STEMI patients only, OACb

treatment, among several other parameters, was positively associated with death, MI or stroke (Table 2).

Table 2. Multivariate analysis for variables associated with composite of death, non-fatal myocardial infarction (MI), or non-fatal stroke at 2 years in non-ST-segment elevation acute coronary syndrome (NSTE-ACS) and ST-segment elevation myocardial infarction (STEMI) patients from the EPICOR study.

Parameter	**NSTE-ACS[a]**		**STEMI**	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
LVEF (<30% *vs* ≥40%)	3.88 (2.83–5.31)	<.001	3.72 (2.46–5.63)	<.001
LVEF (30-39% *vs* ≥40%)	2.42 (1.88–3.12)	<.001	1.50 (1.08–2.08)	.016
OACb as chronic medication	1.00 (0.70–1.43)	.982	2.40 (1.47–3.93)	<.001
Prior myocardial infarction	1.42 (1.15–1.75)	.001	1.91 (1.44–2.54)	<.001
Type 2 diabetes mellitus (*vs* no/unknown)	1.35 (1.12–1.63)	.001	1.46 (1.13–1.90)	.004
Transient ischaemic attack/stroke	1.44 (1.11–1.88)	.006	N/A	N/A
Atrial fibrillation	1.37 (1.01–1.85)	.040	N/A	N/A
Age (years)	1.04 (1.03–1.05)	<.001	1.03 (1.02–1.04)	<.001
Total days in hospital	1.02 (1.00–1.03)	.012	1.02 (1.00–1.03)	.007
Stent implantation (*vs* no procedure)	0.45 (0.37–0.56)	<.001	N/A	N/A

[a]Model also adjusted for current smoker (p=0.03), prior PCI (p=0.04) and procedure without stent (p<0.01).

CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; N/A, not applicable; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; OACb, oral anticoagulant at baseline; STEMI, ST-segment elevation myocardial infarction.

Analysis based on multivariate Cox proportional hazards model.

4. DISCUSSION

The results of this analysis of 2-year follow-up data from the EPICOR study showed that OACb treatment was associated with increased risk of adverse clinical outcomes, including the composite endpoint of death, non-fatal MI and non-fatal stroke, with or without bleeding, in both NSTE-ACS and STEMI patients. Patients on OACb also experienced prolonged time to intervention, lower occurrence of TIMI 3 flow, less use of DES, and longer hospital stay, compared with those not on OACb.

In general, in the setting of ACS, triple therapy with OAC, aspirin and clopidogrel is associated with at least a doubling of the risk of major bleeding [9, 10]. However, a recent joint European consensus statement recommends that triple therapy be given as the initial treatment to AF patients with ACS and/or undergoing PCI/stenting, with the duration of treatment dependent on the individual risk of ischaemic and bleeding events, acute *vs* elective procedures, and type of stent [11]. In this analysis from EPICOR, only about a third of patients on OACb were on a triple therapy regimen at discharge from hospital. A number of large-scale studies and meta-analyses have investigated the efficacy and safety of possible combinations of dual therapy with an OAC and single antiplatelet *vs* triple therapy in patients on OAC who undergo PCI [10, 12, 13]. A meta-analysis by D'Ascenzo et al. looking at randomized controlled trials and adjusted observational results in patients undergoing PCI showed no differences in major adverse cardiac events (MACE) with clopidogrel plus OAC compared with triple therapy [12]. In contrast, data from the prospective randomized WOEST (What is the Optimal antiplatElet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary StenTing) study showed superior safety as well as efficacy of dual therapy (clopidogrel plus warfarin) over triple therapy [10].

In the EPICOR study, anticoagulant therapy consisted mainly of vitamin K antagonists. The newer, non-vitamin K oral anticoagulants (NOACs) appear to have a more favourable risk profile [14], but European Heart Rhythm Association survey data indicate a level of uncertainty about the

best combination of NOACs and antiplatelet agents in ACS patients with AF [15].

Our analysis showed that patients receiving OACb were older and had more comorbidities than those without OACb. The majority of patients on OACb had a history of AF, which is associated with an increased risk for stroke [2, 4], and was the main indication for anticoagulation in our study population. Despite guideline recommendations [2, 11, 16-18], only 50.6% of patients with STEMI on OACb in the EPICOR study underwent primary PCI. However, recent insights from EPICOR indicate that real-world management of ACS patients is often not in accordance with current advice [19]. In the present analysis, median times from hospital admission to PCI were significantly longer in NSTE-ACS patients on OACb than those not on OACb, but they remained under 60 h, and therefore within the guideline-specified 72-h time window [3]. In contrast, OACb use did not have an impact on time to procedure in STEMI patients in this study.

According to the recent joint European consensus statement [11], AF patients with ACS and/or undergoing PCI/stenting should receive triple therapy for at least 1 month. It is recommended that patients with a lower haemorrhagic risk compared with stroke risk receive triple therapy for 6 months. In the EPICOR study, patients with ACS and AF receiving OAC at admission had the same indication for OAC at discharge. In the present analysis, patients receiving OACb in both the NSTE-ACS and STEMI groups had a significantly higher occurrence of the 2-year composite clinical endpoint of death, non-fatal MI and non-fatal stroke, versus those not on OACb. Furthermore, bleeding events leading to hospitalization were more common in patients receiving OACb in both groups, as may be expected. In the WAR-STENT registry, absolute 12-month rates of major bleeding with triple therapy, dual therapy and DAPT were 4%, 5%, and 2%, respectively [20]. Major bleeding events occurred in 44% and 50% of cases, with ongoing triple and dual therapy, respectively, and in 6% with ongoing DAPT. The results of the WOEST study in patients on OAC further reinforce the concept that triple therapy may give rise to more minor bleeding compared with dual therapy: Dewilde *et al*. demonstrated that use of OAC and clopidogrel without aspirin was associated with a

significant reduction in bleeding complications and no increase in the rate of thrombotic events, compared with triple therapy [10].

Occurrence of the composite endpoint of death, non-fatal MI, and non-fatal stroke at 2 years was also more common in patients on OAC in both groups. All-cause mortality was significantly lower with dual *vs* triple therapy (2.6 *vs* 6.4%, p=0.027, HR 0.39), and dual therapy also reduced the secondary composite endpoint of death, non-fatal MI, and non-fatal stroke, target vessel revascularization and stent thrombosis, *vs* triple therapy [10]. On the other hand, Caballero *et al*. showed that octogenarian patients with AF who underwent PCI and were discharged on OAC had lower rates of MACE (28.9 *vs* 58.3%, p<0.01) and lower all-cause mortality rate at a median of 17 months follow-up (22.2 *vs* 44.4%, p=0.005), compared with those patients not on OAC at discharge [21]. In a meta-analysis by Gao *et al*. of 16 eligible trials including 9185 patients on OAC after coronary stenting, the risks of MACE (odds ratio [OR]: 1.06, 95% confidence interval [CI]: 0.82-1.39, p=0.65), all-cause mortality (OR: 0.98, 95% CI: 0.76-1.27, p=0.89), MI (OR: 1.01, 95% CI: 0.77-1.31, p=0.97), and stent thrombosis (OR: 0.91, 95% CI: 0.49-1.69, p=0.75) were similar with triple and dual therapy [13]. Compared with dual therapy, triple therapy was associated with a reduced risk of ischaemic stroke (OR: 0.57, 95% CI: 0.35-0.94, p=0.03), but a higher risk of major bleeding (OR: 1.52, 95% CI: 1.11-2.10, p=0.01) and minor bleeding (OR: 1.59, 95% CI: 1.05-2.42, p=0.03) [13]. In the recent PIONEER AF- PCI clinical trials, patients with AF undergoing PCI with placement of stents who were administered either low-dose rivaroxaban plus $P2Y_{12}$ inhibitor or very-low dose rivaroxaban plus DAPT, for 12 months, showed a lower rate of clinically-significant bleeding compared with standard therapy with a vitamin K antagonist plus DAPT for 1, 6 or 12 months [22]. Similar findings were reported in the RE-DUAL PCI trial; in patients with AF who had undergone PCI, risk of bleeding was lower among those who received dual therapy with dabigatran and a $P2Y_{12}$ inhibitor compared with triple therapy with warfarin, a $P2Y_{12}$ inhibitor, and aspirin [23].

In view of differences in baseline characteristics, such as age and presence of comorbidities,

in the patient groups with and without OACb in EPICOR, it was considered important to perform a multivariate analysis. In patients with NSTE-ACS, the results showed an association between risk of death, MI or stroke within 2 years and age, diabetes mellitus, prior MI, AF, prior TIA or stroke, total length of hospital stay and lower LVEF, but not with OACb treatment. In STEMI patients, however, use of OACb was found to confer a higher risk of adverse outcomes, along with several other factors, including age and a number of comorbidities. The reasons for this disparity are unclear, although patients with NSTE-ACS appeared to have a higher comorbidity rate compared with STEMI patients.

4.1 Limitations

A limitation of this study was the relatively small number of STEMI patients on OACb. Additional limitations included being a *post-hoc* analysis of a registry, and the observed loss to follow-up and the time lapse from enrolment into the registry in 2010-2011 to the present analysis as it is likely that patterns of antithrombotic and antiplatelet drug usage had undergone changes during this period. In addition, the interval and changes in OAC therapy since the completion of the EPICOR Asia study should be noted; NOACs are used in around half of patients but vitamin K antagonists are also still prescribed.

To conclude: (1) patients with NSTE-ACS or STEMI on OAC therapy are at high risk of adverse clinical outcomes, (2) OACb use is independently associated with death, MI, and the composite endpoint of death, non-fatal MI and non-fatal stroke during the first 2 years post-discharge in patients with STEMI, but not in NSTE-ACS, (3) In patients on OACb, higher rates of bleeding were observed during the 2-year follow-up period, (4) In NSTE-ACS patients on OAC at baseline, time to intervention was prolonged, and there were fewer DES placements and reduced likelihood of TIMI 3 flow, compared with patients not on OACb, and, (5) Both NSTE-ACS and STEMI patients on OACb had a longer hospital stay than those without.

DISCLOSURES

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SUPPORTIVE/SUPPLEMENTARY MATERIAL

SI Table. Angiographic data of patients with or without oral anticoagulant at baseline (OACb) from the EPICOR study by non-ST-segment elevation acute coronary syndrome (NSTE-ACS) or ST-segment elevation myocardial infarction (STEMI) index event.

SII Table. Cardiovascular medications at discharge of patients with or without oral anticoagulant at baseline (OACb) from the EPICOR study by non-ST-segment elevation acute coronary syndrome (NSTE-ACS) or ST-segment elevation myocardial infarction (STEMI) index event.

Supporting Information

Table S1. Angiographic data of patients with or without oral anticoagulant at baseline (OACb) from the EPICOR study by non-ST-segment elevation acute coronary syndrome (NSTE-ACS) or ST-segment elevation myocardial infarction (STEMI) index event.

Parameter	NSTE-ACS			STEMI		
	Without OACb (n = 5357)	With OACb (n = 268)	p	Without OACb (n = 4866)	With OACb (n = 77)	p
Culprit artery, n	4216	181		4189	67	
Left main, n (%)	107 (2.5)	6 (3.3)	0.783	31 (0.7)	1 (1.5)	0.473
Left anterior descending, n (%)	1640 (38.9)	63 (34.8)	0.014	1861 (44.4)	27 (40.3)	0.569
Left circumflex, n (%)	880 (20.9)	27 (14.9)	0.006	557 (13.3)	12 (17.9)	0.259
Right coronary, n (%)	990 (23.5)	42 (23.2)	0.246	1595 (38.1)	19 (28.4)	0.133
Vein bypass graft, n (%)	89 (2.1)	13 (7.2)	0.0001	16 (0.4)	3 (4.5)	<0.0001
Arterial bypass graft, n (%)	13 (0.3)	1 (0.6)	0.676	1 (0.0)	2 (3.0)	<0.0001
Unknown, n (%)	497 (11.8)	29 (16.0)		128 (3.1)	3 (4.5)	
Culprit artery TIMI flow, n[a] (%)	4216 (78.7)	181 (67.5)		4189 (86.1)	67 (87.0)	
Occluded (TIMI flow 0 /1), n (%)	911 (21.6)	36 (19.9)	0.127	2326 (55.5)	36 (53.7)	0.855

Slow (TIMI 2), n (%)	813 (19.3)	43 (23.8)	0.699	598 (14.3)	11 (16.4)	0.597
Normal (TIMI 3), n (%)	1412 (33.5)	47 (26.0)	0.035	633 (15.1)	6 (9.0)	0.176
Unknown, n (%)	1080 (25.6)	55 (30.4)		632 (15.1)	14 (20.9)	
Any stent, n (%):	2968 (55.4)	116 (43.3)	<0.0001	3758 (77.2)	56 (72.7)	0.350
DES, n (% of any stent)	1571 (52.9)	45 (38.8)	0.003	1481 (39.4)	18 (32.1)	0.181
Non-DES, n (% of any stent)	1366 (46.0)	70 (60.3)	0.820	2255 (60.0)	38 (67.9)	0.599
Unknown, n (% of any stent)	58 (2.0)	2 (1.7)		89 (2.4)	0	

[a]Patients who underwent PCI.

DES, drug-eluting stent PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction.

Table S2. Cardiovascular medications at discharge of patients with or without oral anticoagulant at baseline (OACb) from the EPICOR study by non-ST-segment elevation acute coronary syndrome (NSTE-ACS) or ST-segment elevation myocardial infarction (STEMI) index event.

Parameter, n (%)	NSTE-ACS			STEMI		
	Without OACb (n = 5357)	With OACb (n = 268)	p	Without OACb (n = 4866)	With OACb (n = 77)	p
Antiplatelets						
Aspirin	5147 (96.1)	215 (80.2)	<0.0001	4770 (98.0)	67 (87.0)	<0.0001
$P2Y_{12}$ inhibitors	4631 (86.4)	180 (67.2)	<0.0001	4656 (95.7)	66 (85.7)	<0.0001
Clopidogrel	4382 (81.8)	177 (66.0)		4113 (84.5)	61 (79.2)	
Prasugrel	233 (4.3)	3 (1.1)		518 (10.6)	5 (6.5)	
Ticlopidine	19 (0.4)	0		25 (0.5)	0	
Other	12 (0.2)	0		14 (0.3)	0	
Any anticoagulant	151 (2.8)	195 (72.8)	<0.0001	171 (3.5)	44 (57.1)	<0.0001
Antithrombotic management patterns			<0.0001			<0.0001
No antiplatelet therapy	70 (1.3)	25 (9.3)		14 (0.3)	3 (3.9)	
Single antiplatelet therapy	765 (14.3)	91 (34.0)		264 (5.4)	15 (19.5)	
Dual antiplatelet therapy[a]	4498 (84.0)	151 (56.3)		4568 (93.9)	59 (76.6)	

Anticoagulant alone (no antiplatelet therapy)	27 (0.5)	25 (9.3)		10 (0.2)	2 (2.6)	
Anticoagulant + single antiplatelet therapy	58 (1.1)	80 (29.9)		44 (0.9)	12 (15.6)	
Anticoagulant + aspirin	46 (0.9)	54 (20.1)		30 (0.6)	5 (6.5)	
Anticoagulant + dual antiplatelet therapy	66 (1.2)	89 (33.2)		117 (2.4)	30 (39.0)	
Other CV therapies						
Beta-blockers	4547 (84.9)	226 (84.3)	0.806	4316 (88.7)	67 (87.0)	0.644
ACE inhibitors/ARB	3969 (74.1)	202 (75.4)	0.640	3928 (80.7)	61 (79.2)	0.740
Statins	4895 (91.4)	236 (88.1)	0.061	4591 (94.3)	71 (92.2)	0.421

[a]Aspirin plus clopidogrel, ticlopidine or prasugrel.

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker, CV, cardiovascular.