

Antithrombotic Strategies in Invasively Managed Patients with Non-ST Elevation Acute Coronary Syndromes and Non-Valvular Atrial Fibrillation in Romania

Alexandru George COTOBAN^{a, b}, Cristian Alexandru UDROIU^b, Radu VINA^c, Dragos VINERANU^{a, b}

^a“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

^bEmergency University Hospital Bucharest, Romania

^cViami Software, Viami Solution SRL, Bucharest, Romania

ABSTRACT

Introduction: Concomitant atrial fibrillation (AF) in non-ST segment elevation acute coronary syndrome (NSTEMI-ACS) patients complicates the decision-making process regarding short- and long-term antithrombotic strategies. Patient profiles and usage rates of different antithrombotic combinations in this patient subgroup in Romania are poorly described.

Premises and objectives: To describe the characteristics of invasively managed NSTEMI-ACS patients with AF (either known or newly diagnosed) compared to patients with no oral anticoagulation (OAC) indications, and analyze the rates and factors that influence the different antithrombotic regimens at discharge in AF patients.

Material and methods: The Romanian National NSTEMI-ACS Registry allows the enrollment of invasively managed NSTEMI-ACS patients admitted in 11 interventional centers. Patients with non-valvular AF and no other OAC indication were identified and compared with patients with no indication for OAC. The antithrombotic strategy at discharge was analyzed based on demographic, clinical, and invasive management characteristics.

Outcomes: A total of 1418 patients were enrolled between 2016 and 2019 out of which, 175 AF subjects and 1159 patients with no OAC indication were included in the analysis. Subjects with AF were older (70 ± 8.3 vs 62.9 ± 10.4 years, $p < 0.001$) and more likely to have a GRACE score >140 (aOR 2.28, 95% CI 1.58–3.31, $p < 0.001$), a history of heart failure (aOR 3.07, 95% CI 2.14–4.41, $p < 0.001$), dementia or Alzheimer disease (aOR 3.45, 95% CI 1.11–10.68, $p = 0.032$), and non-fatal major cardiovascular (CV) events during admission (aOR 6.71, 95% CI 1.61–27.94, $p = 0.009$). Globally, triple antithrombotic therapy (TAT) was used in 52.5% of AF patients. 69% of PCI patients received TAT. One in four patients with AF did not receive OAC at discharge. Prior treatment with OAC was the strongest predictor for OAC usage at discharge (aOR 12.34, 95% CI 3.21–47.61, $p < 0.001$).

Address for correspondence:

Prof. Dr. Dragos Vinereanu

Mailing address: Splaiul Independentei No.169, Emergency University Hospital, 10th Floor (Cardiology), Sector 5, Bucharest, Romania

Tel.: 021.318.05.19

Email: vinereanu@gmail.com

Article received on the 2nd of March 2021 and accepted for publication on the 15th of March 2021

Conclusion: More than one in 10 NSTEMI-ACS patients have a concomitant non-valvular AF diagnosis. These patients are significantly older and are more likely to have significant CV and non-CV disease. Triple antithrombotic therapy is the most used antithrombotic strategy, especially in the PCI subgroup. One in four NSTEMI-ACS AF patients do not receive OAC at discharge.

Keywords: non-ST elevation acute coronary syndromes, unstable angina, non-ST elevation myocardial infarction, atrial fibrillation, oral anticoagulants, antiplatelets, registry, Romania.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in patients presenting with acute coronary syndromes (ACS) (1). The combination of AF and non-ST elevation ACS (NSTEMI-ACS) complicates the decision-making process regarding short- and long-term antithrombotic strategies. In this high ischemic risk group, a combination between oral anticoagulants (OACs) and antiplatelets is usually recommended according to the type of revascularization and concomitant ischemic and bleeding risks. Recently, less potent antithrombotic strategies, combining P2Y₁₂ inhibitors (preferably clopidogrel) and non-vitamin K antagonist oral anticoagulants (NOACs), have been shown to be safe and effective (2) when compared to more complex regimens. The usage rates of specific antithrombotic strategies at discharge in invasively managed NSTEMI-ACS AF patients in Romania is poorly described. □

PREMISES AND OBJECTIVES

To describe the characteristics of invasively managed NSTEMI-ACS patients with AF (either known or newly diagnosed) compared to those with no OAC indications, and analyze the rates and factors that influence different antithrombotic combination choices at discharge in AF patients. □

MATERIALS AND METHODS

The Romanian National NSTEMI-ACS Registry allows the enrollment of invasively managed NSTEMI-ACS patients admitted in 11 interventional centers across the country. Those with non-valvular AF (as the single OAC indication) were identified and compared with patients who had no indication for OAC. Those with other indications for OAC or deceased were excluded. Antithrombotic strategies at discharge in AF

patients were analyzed based on demographic, clinical, and invasive management characteristics.

Statistical analysis

All analyses were performed using the IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY). Multiple imputation was used to complete missing variable values (<5% of all variables). No variables with >20% missing data were identified. Continuous variables were reported as mean ± standard deviation (SD). The independent-samples T test was used to compare continuous variables. Categorical variables were reported as counts and percentages. The Chi-square test was used for calculating crude odds ratios and 95% confidence intervals (CIs). After the univariate analysis, all variables with a p-value <0.1 were included in a backwards multivariate logistic regression model for identifying independent predictors and adjusting for confounding factors. Adjusted odds ratios, 95% CIs and p-values were reported. □

OUTCOMES

A total of 1418 patients were enrolled in the registry between May 2016 and November 2019. Of them, 181 (12.76%) were identified as having a non-valvular AF diagnosis (as the single OAC indication), whilst 1176 patients had no OAC indication. 175 AF and 1159 non-OAC patients were included in the analysis (Tables 1 and 2).

Atrial fibrillation patients were on average eight years older, had higher ischemic and bleeding risk score values, lower left ventricle ejection fraction, and a longer hospital stay. Non-obstructive coronary artery disease (CAD) was 2.3 times more likely to be identified in AF patients, whilst the risk of non-fatal major adverse cardiovascular events during hospital stay was 6.7 times higher than in subjects with no OAC indication (Figure 1).

TABLE 1. AF and non-OAC patient characteristics (deceased patients or those with non-AF OAC indications were excluded) – continuous variables

Characteristic	Non-valvular AF mean \pm SD N=175	Non-OAC group mean \pm SD N=1159	Unadjusted p-value
Age	70.06 \pm 8.38	62.94 \pm 10.44	<0.001
Admission BP	133.95 \pm 24.60	138.22 \pm 21.93	0.031
Admission HR	88.61 \pm 26.44	76.16 \pm 15.25	<0.001
BMI	29.26 \pm 5.27	28.88 \pm 5.04	>0.1
Hemoglobin (g/dL)	13.49 \pm 1.78	13.78 \pm 1.70	0.035
Glycaemia (mg/dL)	145.21 \pm 71.80	135.62 \pm 62.91	0.070
eGFR (mL/min/1.73 m ²)	65.48 \pm 21.81	74.72 \pm 25.11	<0.001
In-hospital GRACE score	152.21 \pm 34.10	125.96 \pm 31.88	<0.001
CHA ₂ DS ₂ -VASc score	3.67 \pm 1.63		
CRUSADE score	33.70 \pm 13.99	24.48 \pm 14.46	<0.001
HAS-BLED score	2.55 \pm 1.08		
LVEF at discharge (%)	42.88 \pm 10.42	48.52 \pm 9.02	<0.001
Hospital stays (days)	7.03 \pm 4.82	5.56 \pm 3.52	<0.001
The independent T-test was used for between-group comparisons. AF=atrial fibrillation, OAC=oral anticoagulation, SD=standard deviation, BP=blood pressure, HR=heart rate, BMI=body mass index, eGFR=estimated glomerular filtration rate, GRACE=Global Registry of Acute Coronary Events, CRUSADE=Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA Guidelines, LVEF=left ventricle ejection fraction.			

TABLE 2. AF and non-OAC patient characteristics (deceased patients or those with non-AF OAC indications were excluded) – categorical variables

Characteristic	Non-valvular AF N=175; n (%)	Non-OAC group N=1159; n (%)	Unadjusted p-value
Demographics and CVD history			
Male gender	116 (66.3%)	821 (70.8%)	>0.1
Age above 65	129 (73.7%)	482 (41.6%)	<0.001
Hypertension	138 (78.8%)	899 (77.7%)	>0.1
Active smoking	21 (12.0%)	310 (26.7%)	<0.001
Former smoker	55 (31.4%)	309 (27.1%)	>0.1
Dyslipidemia	105 (60.0%)	717 (61.8%)	>0.1
Diabetes	69 (39.4%)	370 (33.4%)	>0.1
CVD family history	24 (13.7%)	205 (17.7%)	>0.1
Prior ischemic stroke or TIA	19 (10.8%)	66 (5.69%)	0.009
Known PAD	13 (7.4%)	78 (6.7%)	>0.1
Prior STEMI	31 (17.7%)	224 (19.3%)	>0.1
Prior NSTEMI	17 (9.7%)	106 (9.1%)	>0.1
Known CCS	39 (22.3%)	244 (21.1%)	>0.1
Prior UA	29 (16.6%)	221 (19.1%)	>0.1
Prior PCI	33 (18.9%)	279 (24.1%)	>0.1
Prior CABG	2 (1.1%)	32 (2.8%)	>0.1
Known HF or DCM	72 (41.1%)	187 (16.1%)	<0.001
Prior PM/ICD	9 (5.1%)	18 (1.6%)	0.002

Continued on next page

Continued from previous page

Comorbidities			
COPD	19 (10.9%)	60 (5.2%)	0.006
At least moderate CKD (eGFR<60 mL/min/1.73 m ²)	71 (40.6%)	103/1151 (27.4%)	<0.001
Dementia or Alzheimer disease	6 (3.4%)	10 (0.8%)	0.002
Prior GI bleeding	7 (4.0%)	20 (1.7%)	0.035
Chronic inflammatory disease	11 (6.3%)	38 (3.3%)	0.033
Diagnostic work-up and management			
Reported chest pain	146 (83.4%)	635 (81.5%)	>0.1
Reported shortness of breath	91 (52.0%)	471 (40.6%)	0.001
Acute HF or shock at presentation	33 (18.9%)	119 (10.3%)	0.001
Anterior NSTE-ACS	67 (38.3%)	372 (32.1%)	>0.1
NSTEMI (Tn assay)	120 (68.5%)	628 (64.1%)	>0.1
GRACE score >140	110 (62.8%)	328 (33.4%)	<0.001
Early invasive management (<24 h)	88 (50.3%)	596 (51.4%)	>0.1
CRUSADE score >40	50 (28.6%)	173 (14.9%)	<0.001
Radial approach	103 (58.8%)	722 (64.0%)	>0.1
Non-obstructive CAD	30 (17.1%)	111 (9.6%)	0.002
Multivascular CAD	96 (54.9%)	648 (55.9%)	>0.1
Underwent PCI	116 (66.3%)	902 (77.8%)	0.001
CABG indication	18 (10.3%)	113 (9.7%)	>0.1
LVEF <40% at discharge	48 (27.4%)	138 (11.9%)	<0.001
Non-fatal MACE	6 (3.4%)	10 (0.8%)	0.002
Non-fatal major bleeding	2 (1.1%)	8 (0.7%)	>0.1

The chi-square test was used for between-group comparisons. Non-fatal MACE was defined as any of: myocardial infarction, stent thrombosis, mechanical complications, life-threatening arrhythmias or ischemic stroke. Major bleeding was defined as any of: intracranial hemorrhage, major extracranial hemorrhage or requiring transfusion.

AF=atrial fibrillation, OAC=oral anticoagulation, N=total number, n=number of cases with characteristic, CVD=cardiovascular disease, TIA=transient ischemic attack, PAD=peripheral artery disease, STEMI=ST-elevation myocardial infarction, NSTEMI=non-ST elevation myocardial infarction, CCS=chronic coronary syndrome, UA=unstable angina, PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting, HF=heart failure, DCM=dilated cardiomyopathy, PM=pacemaker, ICD=implantable cardioverter-defibrillator, COPD=chronic obstructive pulmonary disease, CKD=chronic kidney disease, eGFR=estimated glomerular filtration rate, GI=gastrointestinal, NSTE-ACS=non-ST elevation acute coronary syndrome, Tn=troponin, GRACE=Global Registry of Acute Coronary Events, CRUSADE=Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA Guidelines, CAD=coronary artery disease, LVEF=left ventricle ejection fraction, MACE=major adverse cardiovascular events.

Among all patients, 97.1% (170/175) had an indication for OAC as per the European Society of Cardiology (ESC) AF management guideline recommendations (3). Specifically, 90.3% (158/175) had a class I indication (CHA₂DS₂-VASc score ≥2 for men and ≥3 for women) and 6.8% (12/175) a class IIa indication (score 1 for men and 2 for women). The mean CHA₂DS₂-VASc score was 3.67 ± 1.63.

Of all patients with a prior AF diagnosis, 43.4% (60/138) were on OAC at the moment of admission [28 on vitamin K antagonists (VKA) and 32 on NOAC], with 93.3% (56/60) of them receiving OAC at discharge. Two patients in each group did not receive OAC at discharge; 23% (6/26) of prior VKA patients were switched to NOAC at discharge, whereas 13.3% (4/30) were switched from NOAC to VKA. No differences were ob-

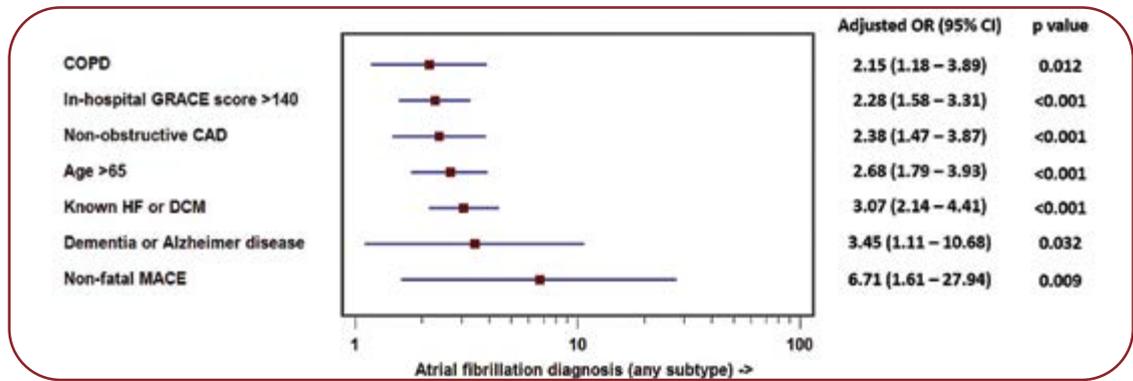


FIGURE 1. Factors independently associated with an AF diagnosis (any subtype) in NSTE-ACS patients. COPD=chronic obstructive pulmonary disease, GRACE=Global Registry of Acute Coronary Syndromes, CAD=coronary artery disease, HF=heart failure, DCM=dilated cardiomyopathy, MACE=major adverse cardiovascular events

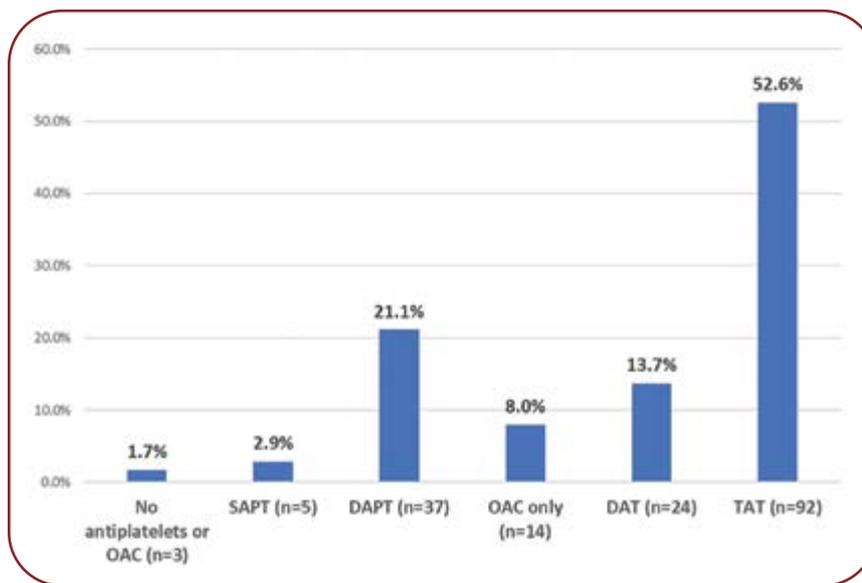


FIGURE 2. The rates of antithrombotic regimens at discharge in NSTE-ACS AF patients. OAC oral anticoagulation, SAPT=single antiplatelet therapy, DAPT=dual antiplatelet therapy, DAT=dual antithrombotic therapy, TAT=triple antithrombotic therapy, NSTE-ACS=non-ST elevation acute coronary syndrome, AF=atrial fibrillation

served between the VKA and NOAC usage rates in subjects with newly diagnosed AF ($p > 0.05$).

The global usage rate of OAC at discharge (either as monotherapy or in combination with at least one antiplatelet), including patients with newly diagnosed AF, was 74.3% (130/175). Among patients receiving OAC, NOAC usage was reported in 57.7% (75/130) of cases, and in 92% (69/75) of them factor Xa inhibitors were recommended.

The rates of antithrombotic regimens at discharge in NSTE-ACS AF patients are presented in Figure 2 and Table 3. Dual antiplatelet therapy (DAPT) was recommended in one out of five patients, dual antithrombotic therapy (DAT) in less than 15% of cases, whereas TAT was used in half of patients. Overall, 87.4% of patients were discharged on either DAPT, DAT or TAT. Clopidogrel was the P2Y12 receptor inhibitor of choice when used in combination with an OAC +/- aspirin.

Oral anticoagulants as monotherapy or in combination with a single antiplatelet was preferred in the optimal medical therapy (OMT) subgroup. Patients with an indication for coronary artery bypass grafting (CABG) had almost equal rates of DAPT, DAT and TAT at discharge, whereas TAT was the most used combination in those with percutaneous coronary interventions (PCI) (Figure 3).

Treatment with an OAC prior to admission was the strongest overall independent predictor for OAC use at discharge either as monotherapy or in combination with at least one antiplatelet (aOR 12.35, 95% CI 3.22 – 47.62, $p < 0.001$) (Figure 4). Globally, the usage rates of OAC or OAC subtype choice at discharge were not independently correlated with the values of GRACE, CHA₂DS₂-VASc, CRUSADE, HAS-BLED scores, NSTE-ACS subtype, presence and severity of obstructive CAD or type of myocardial revascularization.

TABLE 3. Antithrombotic regimens recommended at discharge in non-valvular AF NSTE-ACS patients

No antiplatelets or OAC	3	175	1.7%
SAPT	5	175	2.9%
Aspirin only	4	5	80%
Clopidogrel only	1	5	20%
DAPT	37	175	21.1%
Aspirin + Clopidogrel	23	37	62.2%
Aspirin + Ticagrelor	14	37	37.8%
OAC only	14	175	8%
VKA	3	14	21.4%
F Xa inhibitor	10	14	71.4%
F IIa inhibitor	1	14	7.1%
DAT (antiplatelet + OAC)	24	175	13.7%
Aspirin + OAC	11	24	45.8%
Aspirin + VKA	2	11	18.2%
Aspirin + F Xa inhibitor	9	11	81.8%
P2Y12 receptor inhibitor + OAC	13	24	54.2%
Clopidogrel + OAC	13	13	100%
Clopidogrel + VKA	5	13	38.5%
Clopidogrel + F Xa inhibitor	7	13	53.8%
Clopidogrel + F IIa inhibitor	1	13	7.7%
TAT (Aspirin + P2Y12 receptor inhibitor + OAC)	92	175	52.6%
Aspirin + Clopidogrel + OAC	88	92	95.7%
Aspirin + Clopidogrel + VKA	43	88	48.9%
Aspirin + Clopidogrel + F Xa inhibitor	41	88	46.6%
Aspirin + Clopidogrel + F IIa inhibitor	4	88	4.5%
Aspirin + Ticagrelor + OAC	4	92	4.3%
Aspirin + Ticagrelor + VKA	2	4	50%
Aspirin + Ticagrelor + F Xa inhibitor	2	4	50%
The usage rates of ticagrelor among SAPT or DAT were 0%.			
The global prasugrel usage was 0%.			
<i>AF=atrial fibrillation, NSTE-ACS=non-ST elevation acute coronary syndrome, OAC=oral anticoagulation, SAPT=single antiplatelet therapy, DAPT=dual antiplatelet therapy, VKA=vitamin K antagonist, F Xa=activated coagulation factor X, F IIa=activated coagulation factor II, DAT=dual antithrombotic therapy, TAT=triple antithrombotic therapy.</i>			

Non-vitamin K antagonist oral anticoagulants were more likely to be used at discharge in patients with prior NOAC treatment (aOR 0.18, 95% CI 0.05–0.67, p 0.010), whereas VKAs were more frequently used in patients who underwent PCI, had an anterior ACS, lower hemoglobin, or were on prior VKA treatment (all $p < 0.05$) (Figure 4). Although NOAC usage rates were numerically higher in patients receiving OAC only or DAT at discharge, and similarly to VKA rates in TAT patients, the rates of NOAC or VKA usage

were not independently associated with specific antithrombotic combinations at discharge.

Of all patients, 66.3% (116/175) underwent PCI. In this subgroup, the cumulative usage rate of DAPT and DAT/TAT was 99.1% (115/116). No independent correlations were identified between the type of antithrombotic regimen and age, PCI procedure details (number, location, type, total length or mean stent diameter) or the risk score values suggesting high bleeding or ischemic risks (GRACE, CHA₂DS₂-VASC, CRUSADE, HAS-BLED, and clinical criteria for at least moderate ischemic

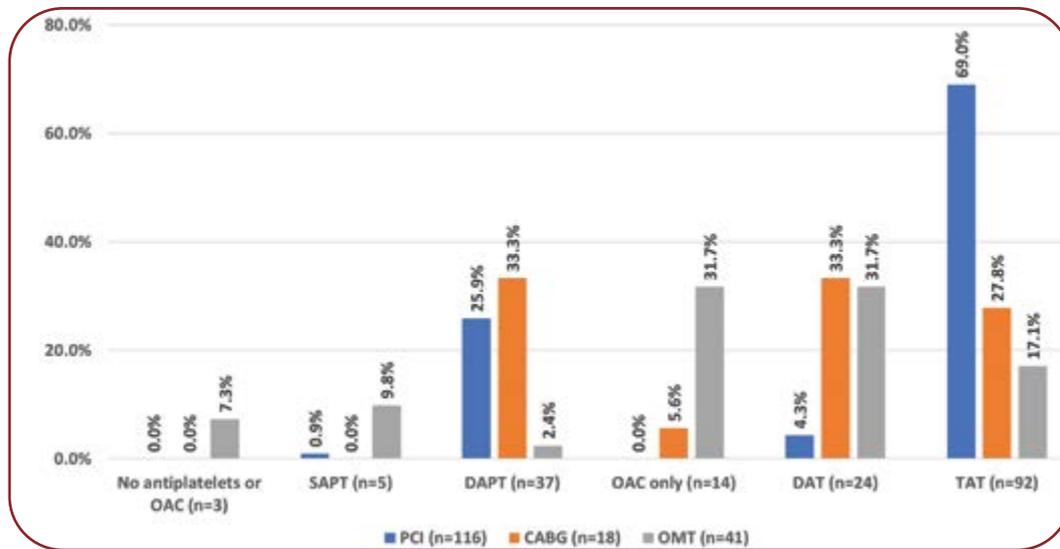


FIGURE 3. Antithrombotic strategies stratified by the type of myocardial revascularization. OAC=oral anticoagulation, SAPT=single antiplatelet therapy, DAPT=dual antiplatelet therapy, DAT=dual antithrombotic therapy, TAT=triple antithrombotic therapy, PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting, OMT=optimal medical therapy

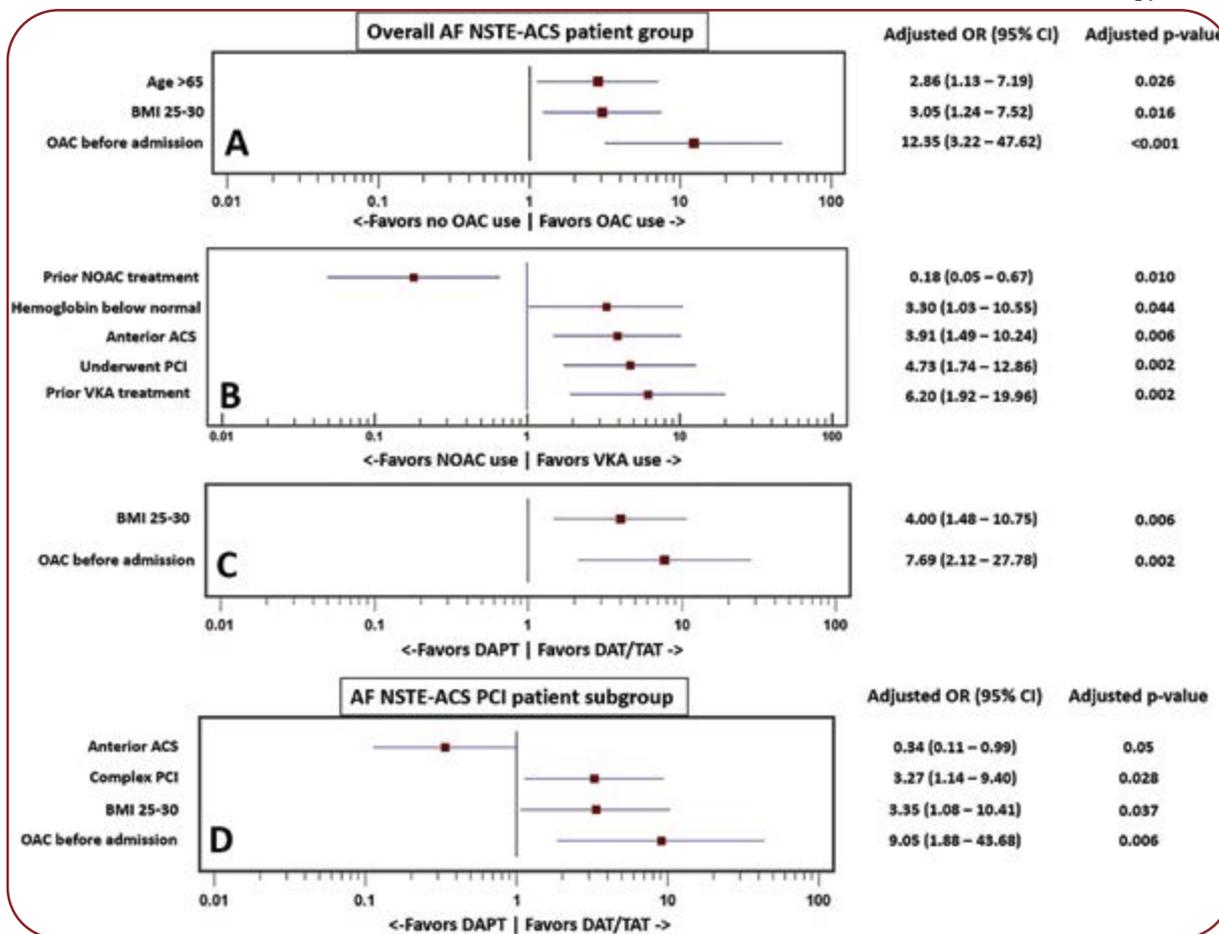


FIGURE 4 Independent factors associated with: (A) overall OAC use at discharge (monotherapy or in combination with at least one antiplatelet); (B) overall use of NOAC or VKA at discharge; (C) overall DAPT or DAT/TAT at discharge; (D) DAPT or DAT/TAT in the PCI subgroup. Lower level of normal for hemoglobin was defined as 13 g/dL for men and 12 g/dL for women. Complex PCI was defined according to the 2020 ESC NSTE-ACS management guidelines as any of: at least three stents implanted, at least three lesions treated, total stent length >60 mm, history of complex revascularization (left main, bifurcation with ≥ two stents implanted, chronic total occlusion) or history of stent thrombosis on antiplatelet treatment. No data regarding stenting of last patent vessel was available. AF=atrial fibrillation, NSTE-ACS=non-ST elevation acute coronary syndrome, OR=odds ratio, CI=confidence interval, BMI=body mass index, OAC=oral anticoagulation, NOAC=non-vitamin K antagonist oral anticoagulant, ACS=acute coronary syndrome, PCI=percutaneous coronary intervention, VKA=vitamin K antagonist, DAPT=dual antiplatelet therapy, DAT=dual antithrombotic therapy, TAT=triple antithrombotic therapy

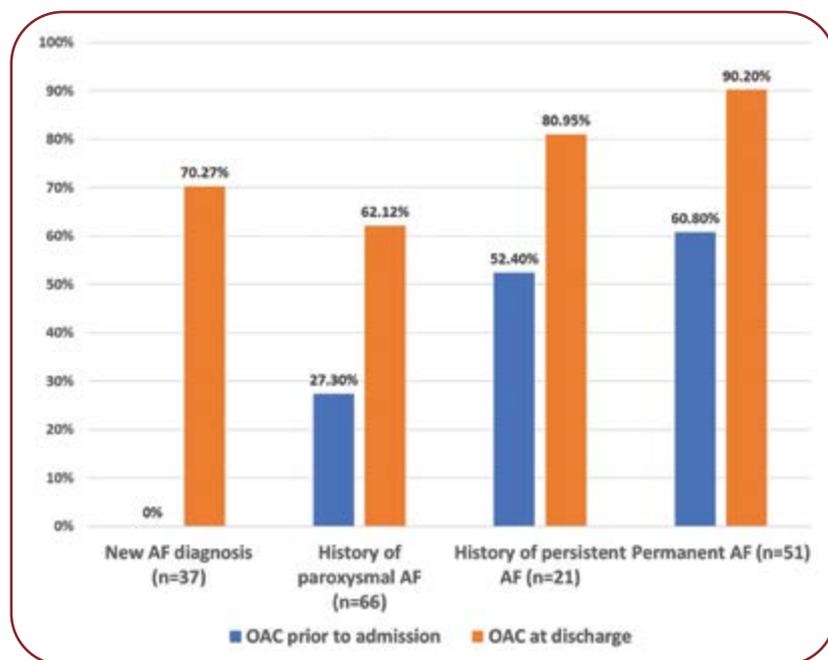


FIGURE 5. OAC usage rates (monotherapy or in combination with at least one antiplatelet) prior to admission and at discharge stratified by AF subtype. AF=atrial fibrillation, OAC=oral anticoagulation

risk as defined by the 2020 ESC NSTE-ACS management guidelines). Despite the small number of patients, a high degree of procedural complexity (as defined by the 2020 ESC NSTE-ACS management guidelines) was independently correlated with the use of DAT/TAT as opposed to DAPT (aOR 3.27, 95% CI 1.14–9.40, p 0.028) (Figure 4).

The AF subtype was not independently associated with different OAC usage rates. Numerically, the highest OAC use was observed in patients with permanent AF, but OAC rates increased at discharge in all AF subtypes (Figure 5).

However, one out of four patients with a guideline indication for OAC did not receive OAC at discharge. Compared to OAC patients, these patients were significantly younger (mean age 66.91 ± 10.45 vs 71.15 ± 7.26 , p 0.015), but had a similar mean CHA₂DS₂-VASc score (3.47 ± 1.68 vs 3.75 ± 1.62 , p >0.1). □

DISCUSSION

Atrial fibrillation is the most common arrhythmia found in ACS patients, with more than one in 10 of patients in our group having an AF diagnosis. Similarly to our results, previous reports found that these patients were generally older and had significantly more prior cardiac events and comorbidities (4).

In the context of ACS, AF is associated with lower rates of invasive management, worse complications and a higher short-term mortality (1).

An AF episode during admission for an NSTE-ACS is associated with an increase of up to 4.4-fold in-hospital mortality (5). Several factors have been associated with AF development during hospitalization, such as older age, particularly above 70, increased body mass index, enlarged left atrium diameter, presence of mitral regurgitation and increased B-type natriuretic peptide levels (6). Also, AF seems to play an important role in long-term prognostic, as new onset AF with a duration of more than six hours or a history of AF in NSTE-ACS patients are associated with poorer long-term outcomes (7, 8).

On the other hand, the management of ACS patients with AF has significantly improved during the last two decades, similarly to that of non-AF patients, with comparable beneficial effects in terms of outcomes (4). Compared to conservatively managed AF NSTE-ACS patients, myocardial revascularization has improved in-hospital survival in these patients by up to 44% (9).

The use of OAC prior to admission was the strongest predictor for OAC usage across all anti-thrombotic combinations at discharge, irrespective of AF subtype. Thus, some grade of therapeutic inertia might be present in prescribing OACs by physicians in real-life clinical settings. This observation was also valid when analyzing the specific OAC subtypes, the majority of patients with prior VKA treatment being discharged on VKAs, whereas most of those on prior NOACs were dis-

charged on NOACs. However, financial considerations may have influenced this result during the enrollment period, as NOACs are significantly more expensive compared to VKAs, which may have deterred certain patients from committing to long-term NOAC treatment. However, future NOAC usage rates are expected to increase, especially after the initiation of partial reimbursement of factor Xa inhibitors (apixaban and rivaroxaban) by the Romanian Healthcare System since June 2020.

Although OAC usage rates increased at discharge irrespective of AF subtype, about one in four patients did not receive OAC. Quality improvement educational interventions for physicians have been shown to significantly increase the proportion of patients treated with OACs and improve stroke prevention in AF patients (10). Reported reasons for withholding OAC include previous bleeding, frailty and age, and an overall high bleeding risk (11). Frailty was not assessed in our cohort, and validated risk scores indicating high ischemic or bleeding risks were not independently associated with withholding OACs or using a certain OAC subtype at discharge. However, overall OAC usage was significantly higher in patients aged above 65 (either as monotherapy or in combination with at least one antiplatelet). On the other hand, age was not independently associated with the choice between DAPT or DAT/TAT in the overall patients' group or in the PCI subgroup.

Several individual factors associated with higher ischemic (PCI, anterior ACS) or bleeding risk (anemia) were independently associated with higher VKA use. As no clear data was available at the time, the 2015 ESC NSTE-ACS guidelines (12) did not specifically recommend a certain OAC subtype (either VKA or NOAC) to be used within DAT or TAT in NSTE-ACS patients, in contrast to the current recommendations strongly favoring NOACs over VKAs.

Moreover, TAT at discharge was previously recommended as standard therapy at discharge and up to 1-6 months mainly in PCI patients (12.) A real-life survey in 2018 found that 70.3% of cardiologists would prescribe TAT at discharge for NSTEMI patients with AF and PCI (13), similarly to the 69% rate observed in the AF PCI NSTE-ACS patient subgroup of our data. Thus, our findings were largely in line with the guideline recommendations in effect, as the analyzed enrollment inter-

val in our group was between 2016 and 2019. As expected, the lack of revascularization by PCI, in both the OMT and CABG subgroups, lead to the more frequent use of lower potency antithrombotic combinations.

Published data from the WOEST, PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS and ENTRUST AF-PCI trials consistently reported lower bleeding rates and similar ischemic outcomes for DAT usage compared to TAT (14-18). The latest 2020 ESC NSTE-ACS management guidelines recommend DAT (preferably clopidogrel + NOAC) as the default antithrombotic strategy up to 12 months after PCI in NSTE-ACS patients with AF, following a short period (up to one week) of TAT (2). In the real world, this short TAT period would probably be superimposed on the hospitalization period, as suggested by the mean length of hospital stay of seven days observed in our AF NSTE-ACS patient group. As enrollment in the registry continues into 2021, real-world data regarding the implementation of these recommendations in NSTE-ACS AF patients in Romania will be available in the future.

Despite the small number of patients, complex PCI was independently associated with a more potent antithrombotic therapy recommendation, mainly TAT. Although the additional benefit of using TAT over DAPT for preventing PCI related complications is probably minimal, the risk of embolic events is substantially higher when OAC is withheld in AF patients. Thus, a more adequate approach would be to reserve TAT at discharge for complex PCI cases or in those with other high ischemic risk criteria and manage most NSTE-ACS AF patients with DAT, as per current guideline recommendations.

The usage of OAC was also independently associated with a BMI between 25 and 30 in both overall patient group and PCI subgroup. No clear explanation for this result was found, but generally, BMI should not influence the decision of recommending OAC in AF patients, given the similar efficacy and safety of NOACs across all BMI categories, even at high weight values (19). However, physicians should take into account body weight when dosing VKAs (20).

Study limitations

Several limitations of our study can be identified. Given its observational nature, residual confoun-

ding factors and patient selection bias cannot be excluded. All patients were invasively managed during the index hospitalization and no data were available regarding conservatively managed NSTE-ACS patients with AF. The total reported number of patients was small, but enrollment in the registry is ongoing and may further clarify the management patterns of NSTE-ACS patients in Romania. □

CONCLUSION

More than one in ten NSTE-ACS patients in Romania have concomitant non-valvular AF. These patients are significantly older and are more likely to have significant CV and non-CV disease. Prior treatment with an OAC is the strongest

independent factor associated with OAC use at discharge. Global OAC usage rates increase at discharge irrespective of AF subtype, with NOACs – mostly factor Xa inhibitors – being used in over half of cases. Triple antithrombotic therapy at discharge is the most used antithrombotic strategy in AF NSTE-ACS patients, especially in the PCI subgroup. One in four NSTE-ACS AF patients do not receive OAC in spite of clear guideline recommendations. □

Conflicts of interest: none declared.

Financial support: none declared.

Acknowledgement: The authors were supported by the Romanian Academy of Medical Sciences and European Regional Development Fund: Funding Contract 2/Axa 1/31.07.2017/SMIS 107124.

REFERENCES

- Mohamed MO, Kirchhof P, Vidovich M, et al. Effect of Concomitant Atrial Fibrillation on In-Hospital Outcomes of Non-ST-Elevation-Acute Coronary Syndrome-Related Hospitalizations in the United States. *Am J Cardiol* 2019;4:465-475.
- Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2020;ehaa575.
- Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021;5:373-498.
- De Luca L, Casella G, Rubboli A, et al. Recent trends in management and outcome of patients with acute coronary syndromes and atrial fibrillation. *Int J Cardiol* 2017;248:369-375.
- González-Pacheco H, Márquez MF, Arias-Mendoza A, et al. Clinical features and in-hospital mortality associated with different types of atrial fibrillation in patients with acute coronary syndrome with and without ST elevation. *J Cardiol* 2015;2:148-154.
- Vukmirović M, Bošković A, Tomašević Vukmirović I, et al. Predictions and outcomes of atrial fibrillation in the patients with acute myocardial infarction. *Open Med* 2017;1:115-124.
- Giglioli C, Minelli M, Chiostrì M, et al. Prognostic impact of atrial fibrillation occurrence in patients with non-ST-elevation acute coronary syndromes: Is dysrhythmia duration a parameter to focus on? *Intern Emerg Med* 2014;5:521-528.
- Lau DH, Huynh LT, Chew DP, et al. Prognostic Impact of Types of Atrial Fibrillation in Acute Coronary Syndromes. *Am J Cardiol* 2009;10:1317-1323.
- Ogunbayo GO, Messerli AW, Ha LD, et al. Trends in the Incidence and In-Hospital Outcomes of Patients With Atrial Fibrillation Complicated by Non-ST-Segment Elevation Myocardial Infarction. *Angiology* 2019;4:317-324.
- Vinereanu D, Lopes RD, Bahit MC, et al. A multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation (IMPACT-AF): an international, cluster-randomised trial. *Lancet* 2017;10104:1737-1746.
- Seelig J, Pisters R, Hemels ME, et al. When to withhold oral anticoagulation in atrial fibrillation – an overview of frequent clinical discussion topics. *Vasc Health Risk Manag* 2019;15:399-408.
- Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;3:267-315.
- de Veer AJWM, Bennaghmouch N, Dewilde WJM, Ten Berg JM. How cardiologists manage antithrombotic treatment of patients with atrial fibrillation undergoing percutaneous coronary stenting: the WOEST survey 2018. *Neth Heart J* 2021;3:135-141.
- Dewilde WJM, Oirbans T, Verheugt FWA, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: An open-label, randomised, controlled trial. *Lancet* 2013;9872:1107-1115.
- Gibson CM, Mehran R, Bode C, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. *N Engl J Med* 2016;25:2423-2434.
- Cannon CP, Bhatt DL, Oldgren J, et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. *N Engl J Med* 2017;16:1513-1524.
- Lopes RD, Heizer G, Aronson R, et al. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. *N Engl J Med* 2019;16:1509-1524.
- Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet* 2019;10206:1335-1343.
- Kaplan RM, Tanaka Y, Passman RS, et al. Efficacy and Safety of Direct Oral Anticoagulants for Atrial Fibrillation Across Body Mass Index Categories. *J Am Heart Assoc* 2020;24:e017383.
- Self TH, Wallace JL, Sakaan S, Sands CW. Effect of body weight on dose of Vitamin K antagonists. *South Med J* 2015;10:637-643.