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Efficacy and safety of new oral anticoagulants as part of triple antithrombotic therapy in patients with atrial fibrillation and acute coronary syndrome. Data from an observational study

Aim	To study efficacy and safety of a triple antithrombotic therapy with direct oral anticoagulants (DOAC) versus warfarin in patients with atrial fibrillation after acute coronary syndrome, for 12 months following discharge from the hospital.
Materials and methods	This single-site cohort, prospective, observational study performed at the Regional Vascular Center 2 of the N.A. Semashko Nizhniy Novgorod Regional Clinical Hospital included 402 patients. It was possible to maintain contacts with 206 patients for 12 months. These patients were divided into two groups, the DOAC treatment (n=105) and the warfarin treatment (n=101) as a part of triple antithrombotic therapy upon discharge. Clinical observation was performed at 1, 3, 6, and 12 months after the discharge by structured telephone interview. Predetermined efficacy endpoints included cardiovascular death, myocardial infarction, stent thrombosis, and ischemic stroke. Safety endpoints included bleeding defined as small, medium (clinically significant), and major in accordance with the TIMI classification.
Results	At 12 months of follow-up, 80 patients (76.19%) continued taking DOAC and 39 patients (38.61%, p<0.001) continued taking warfarin; in this process, only 25 patients (24.75%) monitored their INR on a regular basis. With a regular INR monitoring and TTR >70%, death rate did not differ in the warfarin and the DOAC treatment groups. However, there was a difference in reaching the composite efficacy endpoint (p=0.048): ischemic events occurred statistically significantly more frequently in the warfarin treatment group than in the DOAC treatment group.
Conclusions	In 12 months after discharge from the hospital, compliance with the DOAC treatment as a part of the antithrombotic therapy was significantly higher than compliance with the warfarin treatment. The triple antithrombotic therapy with DOAC was safer than the warfarin treatment by the number of hemorrhagic complications and more effective in prevention of ischemic events, primarily due to no need for monitoring of lab test values.

Keywords	Anticoagulants; DOAC; atrial fibrillation; triple antithrombotic therapy; acute coronary syndrome
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Introduction

Management of patients with atrial fibrillation (AF) who have experienced acute coronary syndrome (ACS) is one of the most talked-about issues in cardiology. The best-possible antiplatelet treatment of these patients is yet to be found. Different sources estimate the prevalence of AF in patients hospitalized for ACS as between 5% and 23% [1–4].

Atrial fibrillation is most common in elderly and senile patients exposed to various cardiovascular risk factors, such as hypertension, heart failure, coronary artery disease (CAD), diabetes mellitus, and chronic kidney disease [5]. Antiplatelet agents (acetylsalicylic acid, clopidogrel, ticagrelor, prasugrel) are often used to prevent atherothrombotic complications in such patients [6]. According to numerous sources,

dual antiplatelet therapy is essential after ACS and percutaneous coronary intervention (PCI) to reduce the risk of myocardial infarction and stent thrombosis [7]. Patients with AF also need long-term treatment with oral anticoagulants to prevent stroke or systemic embolism [5]. Therefore, triple therapy using an anticoagulant and two antiplatelets should be used for these patients for at least 1 month after ACS [5]. Such potent antiplatelet therapy is accompanied by an increased risk of bleeding [8]. Direct oral anticoagulants (DOACs) are a proper alternative to warfarin for the prevention of stroke in nonvalvular AF. Their clinical use is growing rapidly [9, 10].

The efficacy and safety of dabigatran in the prevention of ischemic stroke were studied in the RE-LY study in 18,113 patients with nonvalvular AF. Dabigatran was shown to be non-inferior to warfarin in the efficacy of thromboprophylaxis and safer in relationship to the development of bleeding [11]. The ROCKET AF study demonstrated that rivaroxaban 20 mg (15 mg) once a day is superior to warfarin in protecting patients with nonvalvular AF from stroke, and has a good safety profile and added patient convenience [12, 13]. In the ARISTOTLE study, apixaban, the direct XA inhibitor, reduced the incidence of strokes or systemic embolism, caused less bleeding than warfarin, and reduced mortality [14]. In the ENGAGEAF-TIMI 48 study, edoxaban 60 mg once a day was found to be not inferior to warfarin, and significantly decreased the likelihood of strokes and systemic embolism (by 21%), as well as that of extensive bleeding (by 20%), as compared to warfarin [5]. These four registry studies determined the use of DOACs as first-line drugs for the prevention of thromboembolism in patients with AF. However, the best-possible anticoagulant for patients with post-ACS AF is yet to be found, and the role of DOACs in triple antiplatelet therapy remains insufficiently studied.

The current guidelines highlight the need to administer any of the available anticoagulants: vitamin K antagonists, direct thrombin inhibitors (dabigatran), selective inhibitors of coagulation factor Xa (rivaroxaban, apixaban) [15]. The findings on dual antiplatelet therapy using DOACs are now available. In 2016, the PIONEER AF-PCI study of rivaroxaban was completed [7], and in September 2017, the results of the REDUAL PCI study of dabigatran were published [15, 16]. In March 2019, the AUGUSTUS study of apixaban [17] was completed, and in 2019, findings on edoxaban were obtained in the ENTRUST-AF-PCI study. Even before the completion of the above studies, an active study of the use of DOACs in triple antiplatelet therapy was begun in the Nizhny Novgorod Regional Hospital n.a. Semashko, when the 2014 guidelines were published [18] allowing the administration of DOACs as part of antiplatelet therapy.

Objective

To study the efficacy and safety of triple antiplatelet therapy using DOACs and warfarin in patients with post-ACS AF within 12 months after discharge from hospital.

Material and Methods

A single-center prospective cohort observational study was conducted at the Regional Vascular Center No. 2 of the Nizhny Novgorod Regional Hospital n.a. Semashko, consecutively registering all patients with AF hospitalized for ACS in 2014–2017; these included 402 patients. We were able to maintain contact with 206 patients for a 12-month follow-up. Patients were divided into two groups according to whether they received DOACs (n=105) or warfarin (n=101) as part of triple antiplatelet therapy at discharge. Structured telephone surveys were performed at 1, 3, 6, and 12 months after discharge. During the survey, patient compliance, adverse clinical events, and all-cause hospitalizations within the study period were assessed.

Cardiovascular mortality, myocardial infarction, stent thrombosis, and ischemic stroke within 12 months after discharge were used as predefined efficacy endpoints. All events that occurred during the follow-up period were registered. Bleeding (minor, moderate [clinically significant], major according to the TIMI [thrombolysis in myocardial infarction] classification) was used as the safety endpoints. All cases of bleeding that occurred within 12 months were registered. Compliance with long-term anticoagulant therapy was assessed using a structured survey. Daily use of an anticoagulant agent at the recommended dose at discharge was adopted as a criterion of compliance. The control of international normalized ratio (INR) at least once a month and time in therapeutic range (TTR) >70% were used as the criteria of compliance in patients treated with warfarin. If a patient discontinued anticoagulant therapy, he or she was asked a direct question about the reasons and time of termination. Patients were reminded of the importance of regular control of INR and maintaining it within the target range if they failed to (less than once a month or TTR<70%). They were

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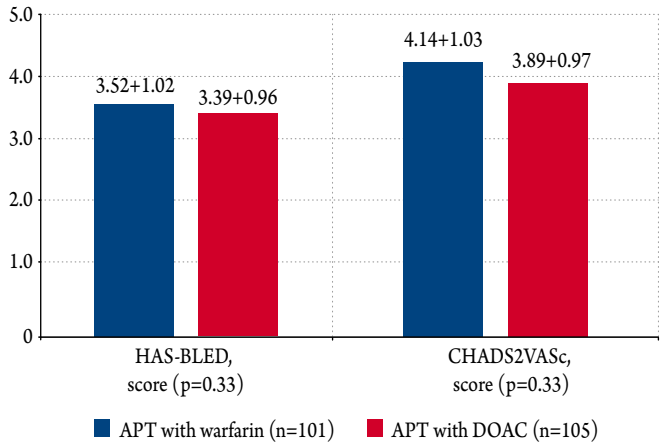
Figure 1. Assessment of the risk of thrombosis and bleeding



APT, antiplatelet therapy; DOACs, direct oral anticoagulants.

offered a switch from warfarin to DOAC if regular and effective INR control was not possible.

All patients were admitted urgently to the emergency cardiology department with a clinical picture of ACS. PCI was indicated according to the guidelines in force at the time of admission [19–21], which included ACS with and without ST elevation on electrocardiogram. All hospitalized patients underwent echocardiographic examination, Holter monitoring, total blood count, urinalysis, and biochemical profile. If necessary, abdominal and kidney ultrasound scans and fibrogastroduodenoscopy were also performed.

The study design was observational. The treatment regimen did not differ from the antiplatelet therapy of non-study patients and was administered according to the current clinical standard for patients with AF and ACS at the time of admission [5, 19–22]. The choice between warfarin or a DOAC was made based on the patient's wishes (financial ability to purchase the drug after the discharge, ability to control INR regularly, and the likelihood of maintaining the target INR according to the SAMe2 TT2R2 score). Patients previously treated with oral anticoagulants were asked to continue prior anticoagulant therapy.

As established in the clinical standards, all patients with ACS received a loading dose of acetylsalicylic acid (ASA) 150–300 mg and clopidogrel 300–600 mg; unfractionated heparin (UFH) 70–100 U/kg was bolus-injected. PCI was performed through a transfemoral or radial approach.

The efficacy and safety of antiplatelet therapy and patient compliance were assessed.

Long-term anticoagulant therapy was indicated for all patients due to the presence of permanent, paroxysmal, or persistent nonvalvular AF and the risk factors with the $CHADs^2VASc$ score ≥2 in male patients and ≥ 3 in female patients (Figure 1).

Statistical analysis of data was carried out using Excel spreadsheets and the R Studio software. The Shapiro–Wilk test was used to assess the distribution of quantitative variables. In the case of the normal distribution of the variable, the arithmetic mean (M) and standard deviation (SD) were calculated. Nonparametric methods of statistical analysis were used for the non-normal distribution of the variable, in which case the median (Me) and the quartiles (25th quartile; 75th quartile) were calculated. The inter-group comparison of quantitative variables was based on the Student's T-test and the Mann-Whitney U-test. Categorical variables were compared using the χ^2 test, the two-tailed Fisher's exact test, and the Yates' χ^2 test. A log-rank test was performed to construct the survival curve and the curve of efficacy endpoints. The differences were considered to be significant at two-tailed $p<0.05$.

Results

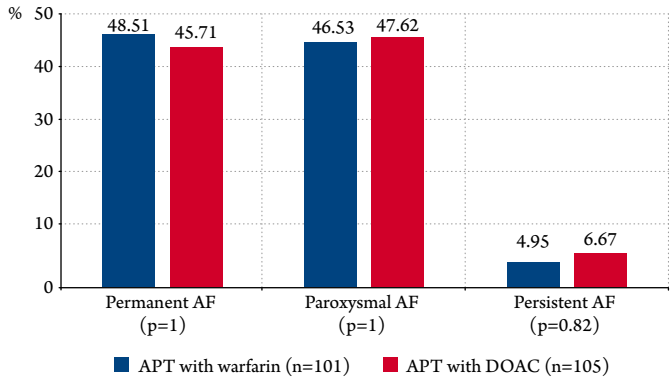
The prospective observational study included 206 patients with concomitant permanent (n=97, 47.0%) / paroxysmal (n=97, 47.0%) / persistent (n=12, 5.83%) AF and ACS who were available for follow-up for 12 months (Figure 2). Stenting was performed in 88 patients (42.72%) patients (Figure 3).

A total of 150 stents were implanted, and only 38 (25.33%) were drug-eluting stents. Stents were implanted mainly in one affected artery (Figure 4). Stenting of two or three coronary arteries was required less often. The mean number of stents per patient was 2 (±1). The target arteries for PCI are shown in Figure 5.

Patients (n=206) were divided into two groups, according to whether they received warfarin (n=101) or DOACs (n=105) as part of triple antiplatelet therapy. DOACs were recommended to use in combination antiplatelet therapy at a reduced dose [5]. Sixty-five patients administered rivaroxaban 15 mg once a day, 34 patients used dabigatran 110 mg twice a day, and 6 patients received apixaban 2.5 mg twice a day.

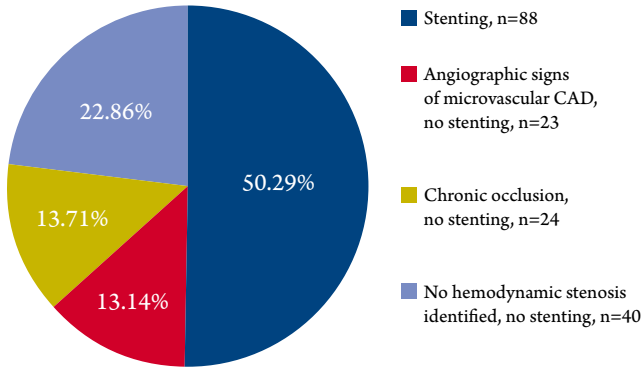
Clopidogrel 75 mg a day was prescribed to all patients for 12 months, as well as ASA 100 mg for 1 or 6 months, depending on the risk of bleeding according to HAS-BLED score. The groups were comparable in basic parameters (Table 1). All patients received ASA 100 mg a day, and most patients used ASA for 1 month after the onset of ACS (Figure 6).

Figure 2. Clinical forms of atrial fibrillation



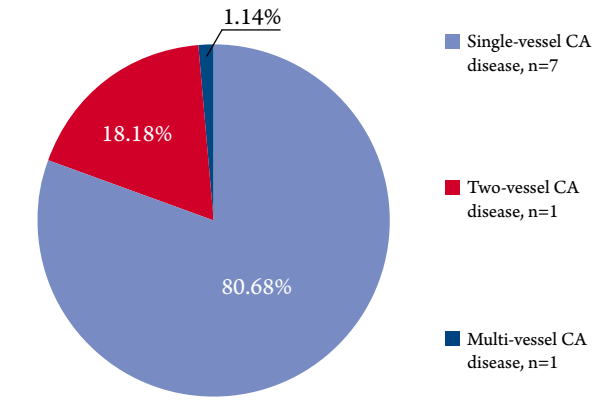
AF, atrial fibrillation; APT, antiplatelet therapy; DOACs, direct oral anticoagulants.

Figure 3. Results of selective coronary angiography (n=175*)



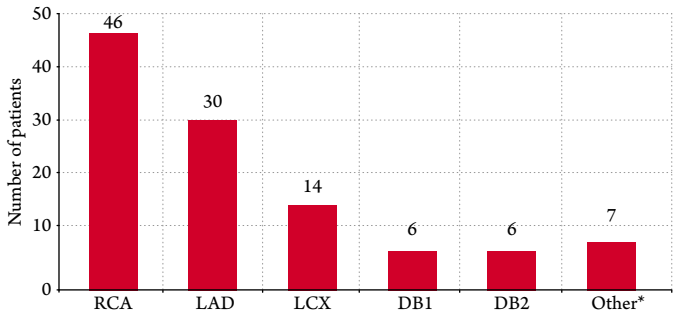
*, refusal of selective coronary angiography, n=31 (15.05%). CAD, coronary artery disease.

Figure 4. Number of affected coronary arteries



CA, coronary artery.

Figure 5. Target artery for percutaneous coronary intervention



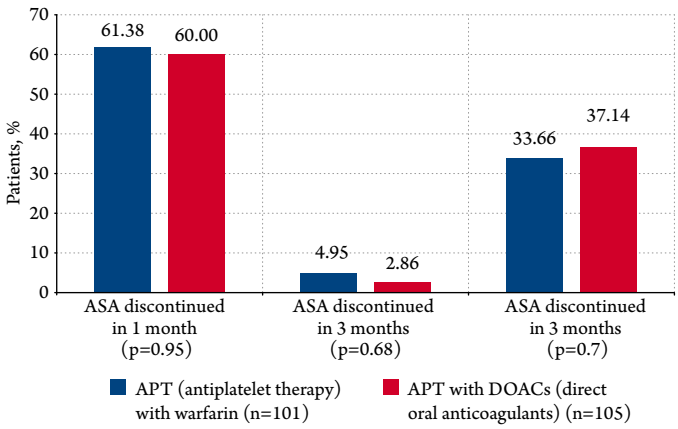
*, PLB, OM1, OM2, graft stenting. RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; DB1, first diagonal branch; DB2, second diagonal branch; PLB, posterior lateral branch; OM1, first obtuse marginal branch; OM2, second obtuse marginal branch.

Compliance with Long-term Anticoagulant Therapy

Of statistical significance, more patients continued to administer DOACs throughout the follow-up period. In 12 months after discharge, 80 (76.19%) patients continue taking DOACs and 39 (38.61%) patients receive warfarin ($p<0.001$). Only 25 (24.75%) patients regularly control their INR. The criterion for regular control of INR was the determination of INR at least once a month. The INR levels lying within the therapeutic range in more than 70% of examinations (TTR>70%) was adopted as an additional criterion (Figure 7).

Within 12 months of follow up, 28 (27.72%) lethal outcomes were registered in the warfarin group: 11 (10.89%) patients died after termination of anticoagulant therapy, 4 (3.96%) patients died during the administration of warfarin and regular control of INR with TTR >70%, and 13 (12.87%) patients died while on warfarin yet with ineffective control of

Figure 6. Duration of administration of acetylsalicylic acid (ASA)



ASA, acetylsalicylic acid; APT, antiplatelet therapy.

INR (control less than once a month or TTR<70%). Of 9 (8.57%) patients who died in the DOAC group, 6 (5.88%) patients continued using the drug, and 3 (2.86%) patients died after discontinuation of the

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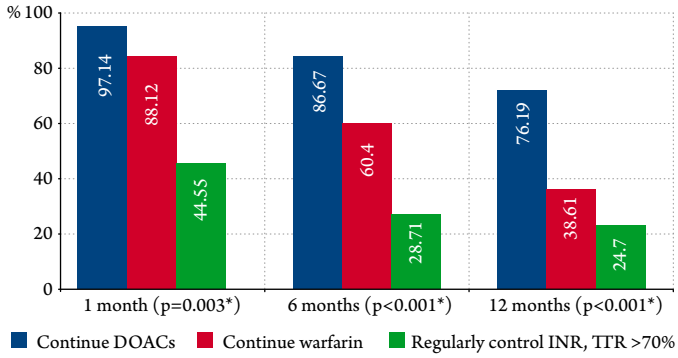
Table 1. Patient clinical characteristics

Sign	APT with warfarin (n=101)	APT with DOACs (n=105)	p value
Age, years	67.95 ± 9.41	68.09 ± 8.31	0.88
Male, n (%)	55 (54.46)	66 (62.86)	0.28
AHF, Killip I–II, n (%)	91 (90.1)	100 (95.2)	0.25
AHF, Killip III–IV, n (%)	10 (9.9)	5 (4.76)	0.25
LVEF, %	50 [41; 55]	53 [46; 55]	0.11
Unstable angina, n (%)	51 (50.49)	68 (64.76)	0.1
Non-ST-elevation MI, n (%)	17 (16.83)	9 (8.57)	0.26
ST-elevation MI, n (%)	33 (32.67)	28 (26.67)	0.43
Hypertensive heart disease, n (%)	100 (99.0)	104 (99.05)	1.0
Diabetes mellitus, n (%)	44 (43.56)	27 (25.71)	0.09
Insulin therapy, n (%)	17 (16.83)	10 (9.52)	0.59
Obesity, n (%)	35 (34.65)	33 (31.43)	0.26
BMI, kg/m^2	30 ± 5.33	29.05 ± 4.9	0.18
COPD, n (%)	14 (13.86)	15 (14.29)	0.93
Anemia, n (%)	16 (15.84)	10 (9.52)	0.35
History of MI, n (%)	36 (35.64)	32 (30.48)	0.52
Dyslipidemia, n (%)	71 (70.3)	74 (70.48)	0.35
Total cholesterol, mmol/L	6.25 ± 2.31	6.18 ± 2.68	0.82
Peripheral vascular disease, n (%)	16 (15.84)	14 (13.33)	0.9
Peptic ulcer, n (%)	2 (1.98)	4 (3.8)	0.71
CKD, n (%)	43 (42.57)	36 (34.2)	0.43
GFR, mL/min/1.72m^2	68.0 ± 18.49	70.06 ± 16.98	0.4
History of CABG, n (%)	1 (0.99)	2 (1.9)	1.0
History of PCI, n (%)	10 (9.9)	19 (18.1)	0.2
History of hemorrhagic stroke, n (%)	1 (0.99)	2 (1.9)	1.0
History of ischemic stroke, n (%)	8 (7.92)	14 (13.33)	0.19
Newly diagnosed AF, n (%)	26 (25.74)	29 (27.62)	0.76
Smoking, n (%)	48 (47.52)	40 (38.09)	0.21
History of RFA, n (%)	3 (2.97)	0	0.23
SSS, n (%)	15 (14.85)	15 (14.29)	1.0
Cardiac pacing, n (%)	7 (6.93)	11 (10.48)	0.51
Pre-hospital thrombolysis, n (%)	7 (6.93)	8 (7.62)	1.0
Concomitant treatment with amiodarone, n (%)	21 (20.79)	30 (28.57)	0.26
Concomitant treatment with IPP, n (%)	9 (8.91)	6 (5.71)	0.54
PCI and stenting, n (%)	50 (49.5)	38 (36.19)	0.13
Bare metal stent, n (%)	42 (41.58)	30 (28.57)	0.16
Drug-eluting stent, n (%)	12 (11.88)	12 (11.43)	0.39
HR, bpm/min	71.5 ± 18.99	73.09 ± 17.12	0.53
SBP at admission, mmHg	146.39 ± 23.93	148.55 ± 30.87	0.57
SBP at discharge, mmHg	127.08 ± 14.58	124.34 ± 12.59	0.15
Total cholesterol, mmol/L	6.25 ± 2.31	6.18 ± 2.68	0.82

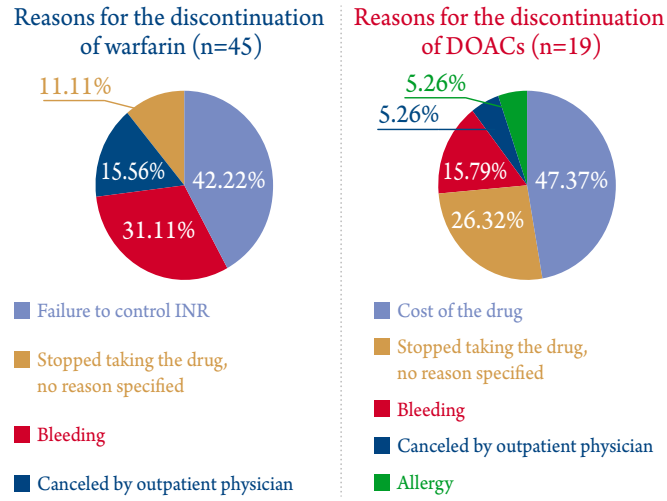
APT, antiplatelet therapy; AHF, acute heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction;
BMI, body mass index; COPD, chronic obstructive pulmonary disease; PICS, post-infarction cardiosclerosis;
CKD, chronic kidney disease; GFR, glomerular filtration rate; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention;
RFA, radiofrequency ablation; SSS, sick sinus syndrome; PPI, proton pump inhibitor, HR, heart rate; SBP, systolic blood pressure.

Figure 7. Compliance with anticoagulant therapy within 12 months after discharge from hospital



*, the significance of differences between the group that continues DOACs and the group that continues warfarin; DOACs, direct orgal anticogulants; INR, international normalized ratio; TTR, time in therapeutic range.

Figure 8. Reasons for the discontinuation of anticoagulants



anticoagulant. No lethal outcomes were reported in those patients who switched between the groups (replacement of warfarin with DOACs or vice versa).

The reasons for drug withdrawal varied between the two groups: warfarin was most often discontinued due to difficulties in control of INR (41.3%) and bleeding (30.43%). The most common reason for the withdrawal of DOACs was their cost (47.37%). The reasons for the withdrawal of anticoagulants are detailed in Figure 8.

Comparison of Safety of Triple Antiplatelet Therapy Using DOACs and Warfarin

All episodes of bleeding, including those that caused withdrawal of the drug, were considered in the analysis of the safety of antiplatelet therapy in terms of preventing bleeding. A sample of patients who continued anticoagulant therapy at least until bleeding developed was formed to assess treatment safety. It included 93 patients on DOACs and 77 patients receiving warfarin, including 38 patients who controlled INR at least once a month and had TTR>70%, and 39 patients with ineffective control of INR (less than once a month or TTR<70%). All episodes of bleeding that occurred during 12-month anticoagulant therapy were assessed. During the first month after discharge, the number of patients who had bleeding was significantly higher than later in the follow-up period. The differences were statistically significant (p<0.001). In the first month, hemorrhagic complications were reported in 42 (20.39%) of 206 patients. Subsequently, the number of patients with hemorrhagic complications decreased significantly (Figure 9), including due to discontinuation of the anticoagulant after bleeding

Figure 9. Hemorrhagic complications within 12 months after discharge from hospital

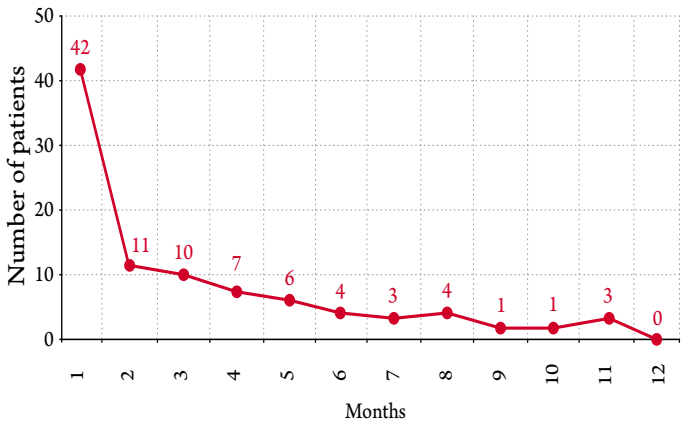
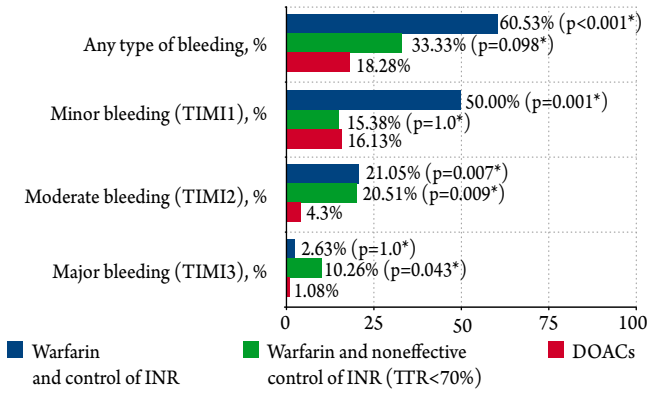


Figure 10. Bleeding during antiplatelet therapy within 12 months after discharge from hospital



*, the significance of differences versus the DOAC group. DOACs, direct oral anticoagulants; TIMI, thrombolysis in myocardial infarction; INR, international normalized ratio; TTR, time in therapeutic range.

and cancellation of ASA in the majority of patients, as was prescribed (61.38% of all patients in the warfarin group and 60.0% of all patients in the DOAC group received ASA for 1 month).

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Bleeding was reported in more patients who received controlled INR and had TTR >70% than in those who used DOACs: 23 of 38 (60.53%) versus 17 of 93 (18.28%) (p<0.001). In the warfarin group, a total of 13 (33.33%) of 39 patients who had ineffective control of INR suffered bleeding, which was comparable to the number of bleeding episodes in the DOAC group (p=0.098).

The differences between the patients on warfarin who controlled INR and those on DOACs are due to minor and moderate bleeding (TIMI). Minor bleeding was reported in 19 (50.0%) of 38 patients in the warfarin/INR-control group and 15 (16.13%) of 93 patients in the DOAC group (p=0.0001). Moderate bleeding was reported in 8 (21.05%) patients on warfarin with control of INR and 4 (4.3%) patients on DOAC (p=0.007). No differences were found in the number of major bleeding episodes, as only a few episodes were reported (one major bleeding episode in each group).

An interesting result was identified in the analysis of bleeding in the warfarin group without the control of INR versus the DOAC group. Although the groups did not differ in the total number of bleeding episodes (p=0.098), the severity of bleeding was different. In the non-INR-control warfarin group, there were more patients with moderate (8 [20.51%] patients, p=0.009) and major (4 [10.26%] patients, p=0.043) bleeding. The number of minor bleeding episodes in the non-INR-control warfarin and DOAC groups was comparable: 6 (15.38%) and 15 (16.13%) patients, respectively (p=1) (Figure 10).

Comparison of Efficacy of Triple Antiplatelet Therapy Using DOACs and Warfarin

To assess the efficacy of antiplatelet therapy, all ischemic events that occurred during the use of anticoagulants were considered. A sample of patients who continued antiplatelet therapy throughout the follow-up period or at least until the onset of the efficacy endpoint or death was formed to construct the survival curve and the curve of efficacy endpoints. The warfarin group included 56 such patients (39 patients continued treatment throughout the follow-up period and 17 patients died during treatment), and the DOAC group included 86 patients (80 patients continued treatment throughout follow-up and 6 patients died during the treatment period). Some patients stopped taking anticoagulants after bleeding. Therefore, patients who discontinued anticoagulants before the onset of the efficacy endpoint or switched the treatment group were excluded from the analysis. During the study, 16 (15.84%) patients in the warfarin group replaced warfarin with a DOAC, and 2 patients in the DOAC group (1.9%) replaced the DOAC with warfarin, as the latter is less expensive. No lethal outcomes were reported in those patients who switched between the groups (replacement of warfarin with DOACs or vice versa). Anticoagulant therapy and lethal outcomes in 12 months after the discharge are summarized in Figure 11.

No lethal outcomes were reported in those patients who switched between the groups (replacement of warfarin with DOACs or vice versa).

To assess the efficacy of antiplatelet therapy using warfarin and DOACs in terms of the prevention of ischemic events, a log-rank test was performed, and the survival curve and the curve of efficacy endpoints were constructed for both the DOAC (n=86) and warfarin (n=56) groups. Patients in the warfarin group were divided into two subgroups, according to whether they controlled INR (n=29) or did not (n=27).

Patient survival (Figure 12) was comparable in the DOAC group and the INR-control warfarin group (p=0.39). The mortality rate was significantly higher (p<0.001) in the non-INR-control warfarin subgroup and reached 48.14% versus 13.79% in the INR-control subgroup and 6.98% in the DOAC group.

Within the entire follow-up period, 37 patients achieved the composite endpoint of efficacy (Figure 13): 11 (12.79%) outcomes in the DOAC group, 26 (46.43%) outcomes in the warfarin group, including 8 (27.59%) outcomes in the INR-control subgroup and 14 (51.85%) outcomes in the non-INR-control subgroup. The differences between the DOAC group and the non-INR-control warfarin group were significant (p<0.001). The log-rank analysis of the 12-month findings also detected more ischemic events in the INR-control warfarin group than in the DOAC group (p=0.048).

Discussion

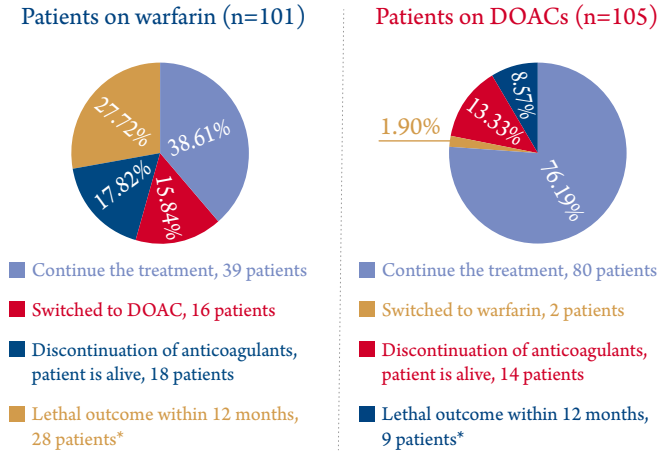
Several large trials have been completed to date that investigated antiplatelet therapy using DOACs and warfarin in patients with AF who had suffered ACS. However, the matter of duration of triple antiplatelet therapy in patients with concomitant AF and ACS remains open. Its efficacy and safety have not been sufficiently studied. The guidelines on the management of this patient group are based on one large randomized clinical trial studying dual antiplatelet therapy (recommendation class IIA, level B) [5].

In the WOEST trial, dual and triple therapy using warfarin was compared. It included 573 patients, some of whom received warfarin with clopidogrel; the others were administered warfarin with clopidogrel and ASA. One year later, hemorrhagic events were reported in 19.4% of patients in the dual antiplatelet therapy group versus in 44.4% of patients in the triple antiplatelet therapy group (odds ratio [OR] 0.36; 95% confidence interval [CI] 0.26–0.50; p<0.0001). In the dual antiplatelet therapy group, hemotransfusion was used significantly less frequently (3.9 vs. 9.5%; p<0.0001). A decrease in the rate of bleeding was mainly due to minor bleeding episodes [23]. It should be borne in mind that the study did not have sufficient statistical power to assess the differences in mortality between groups. Therefore, the results should be treated with caution. Moreover, the WOEST trial included too few patients, and only 70% of them had atrial fibrillation [24].

In the PIONEER AF-PCI trial, rivaroxaban-based antiplatelet regimens were shown to significantly decrease the rate of bleeding versus warfarin in combination with dual antiplatelet therapy [15]. In the RE-DUAL PCI trial, dual therapy using dabigatran was not inferior to triple therapy using warfarin in terms of the risk of thromboembolic complications and was safer given the number of hemorrhagic complications [15]. In the AUGUSTUS trial (which finished in 2019), the primary endpoint, which was the rate of major and minor clinically significant bleeding, was achieved in 10.5% of patients treated with apixaban and 14.7% of patients treated with warfarin (OR 0.69; 95% CI 0.58–0.81; p<0.001). The rate of ischemic events (cardiovascular death, myocardial infarction, ischemic stroke, confirmed stent thrombosis, emergency repeat revascularization) was comparable in the apixaban and warfarin groups. The incidence of strokes in the patients treated with apixaban was one-half that in those treated with warfarin (which could be due to a relatively small amount of time in the therapeutic range of INR in patients treated with warfarin) [17, 25]. The AUGUSTUS trial thus showed that apixaban in combination with clopidogrel was associated in patients with AF and formal indications for dual antiplatelet therapy with a significant decrease in the rate of major and clinically significant bleeding and a decrease in the rate of admissions to hospital, versus the patients treated with antiplatelet therapy using warfarin [25].

In the ENTRUST-AF PCI trial, it was determined that post-coronary stenting dual antiplatelet therapy using edoxaban was not inferior to triple combination therapy using warfarin in terms of the effect on the primary safety endpoint «major and minor clinically significant bleeding.» At the same time, a lower risk of major and clinically significant bleeding was demonstrated during dual antiplatelet therapy using

Figure 11. Anticoagulant therapy and lethal outcomes in 12 months after discharge from hospital



*, of the 28 lethal outcomes in the warfarin group, 11 patients died after discontinuation of an anticoagulant, 4 patients died during treatment with warfarin and regular control of INR, and 13 patients died during treatment with warfarin and no control of INR. **, of the 9 patients who died in the DOAC group, 6 patients continued the drug, and 3 patients died after discontinuation of the anticoagulant. DOACs, direct oral anticoagulants; INR, international normalized ratio.

Figure 12. 12-month survival

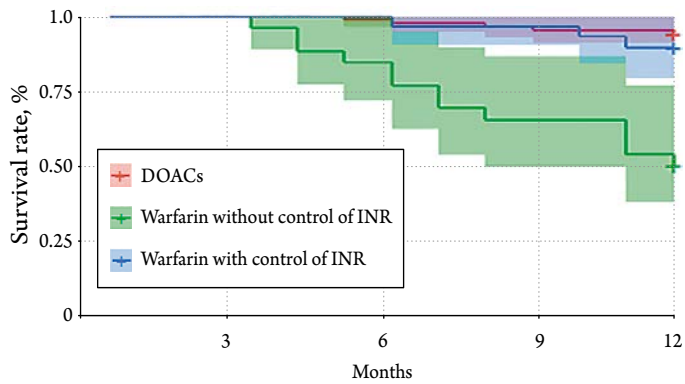
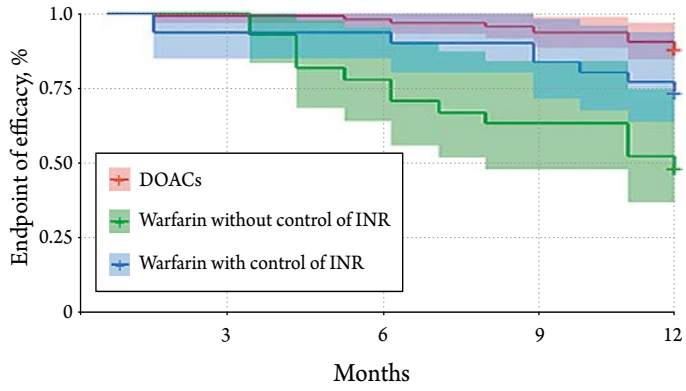


Figure 13. Endpoint of efficacy



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edoxaban versus the combination therapy using warfarin [26].

According to the published data, all of the above randomized trials lacked sufficient statistical power to estimate the efficacy of thromboembolic prevention [27]. However, the findings of these studies and the meta-analysis were used to specify the duration and the drugs used in triple and dual antiplatelet therapy in the new guidelines: the ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease (2017) and the ESC Guidelines on Myocardial Revascularization (2018) compared to the ESC Guidelines on AF (2016) [28- – 30].

The findings of our study of triple antiplatelet therapy suggest that DOACs in triple antiplatelet therapy are safer than warfarin and more effective in terms of preventing ischemic events.

The study of efficacy and safety of antiplatelet therapy in patients with post-ACS AF in real-world clinical practice showed that the majority of patients on warfarin found it difficult to control INR and often discontinued anticoagulant therapy. Insufficient anticoagulant therapy, according to numerous literature data, is associated with a higher risk of adverse outcomes. The meta-analysis of 21 studies [30] determined that low INR (less than 2) during the use of warfarin in patients with AF was accompanied by a 5.07-fold increase in the risk of ischemic outcomes versus that in the target INR ≥2.0, and the probability of bleeding was 3.21-fold in patients with INR >3.0 [30]. Similar data are provided by other authors [31].

In our study, only 24.75% of patients continue treatment and maintain INR within the target range in 12 months after discharge, which is obviously disappointing. The patient survey found the cost of the drug to be the main reason for discontinuation of DOACs. However, dabigatran, rivaroxaban, and apixaban have already been listed as life-saving and essential drugs and are free by medical prescription. Thus, the cost should not be a factor preventing a physician from prescribing an effective and safe treatment, since modern anticoagulants can be accessible for patients. However, we should not diminish the benefits of vitamin K antagonists. Despite some limitations, they are the drugs of choice in some situations (e.g., if a patient has prosthetic heart valves). In this case, patients should use only warfarin [5, 32].

The number of hemorrhagic complications was higher in patients who used warfarin and controlled INR due to minor and moderate bleeding, which often caused the withdrawal of the drug. Patients on warfarin who failed to control INR were in a state of false well-being: they experienced less minor bleeding, which was probably due to the level of INR <2 in most patients of this group. At the same time, the uncontrolled use of warfarin causes moderate and major bleeding significantly more often. Significantly more ischemic events were also reported in the non-INR-control subgroup.

There is no doubt that talking to patients about the importance of INR control and administration of the prescribed drugs is important, which has been confirmed once again in our study.

Conclusion

There were significantly more patients with AF who suffered ACS and continued takings DOACs as part of antiplatelet therapy in real-world clinical practice than those who continued with warfarin therapy. Triple antiplatelet therapy with DOACs appeared to be safer than warfarin in terms of the number of hemorrhagic complications and more effective in preventing ischemic events, mainly due to the lack of sufficient control of INR by patients on warfarin.

In regular control of INR and TTR>70%, the mortality rate did not differ between the warfarin and DOAC groups. However, the composite endpoint of efficacy, including ischemic stroke, stent thrombosis, myocardial infarction, and cardiovascular mortality within 12 months, was achieved more often in the warfarin group even in effective control of INR.

Ethical Aspects

Our study complied with the Declaration of Helsinki and was approved by the local ethics committee. All patients signed informed consent to participate in the study.

Limitations

The study design was observational.

No conflict of interest is reported.

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