Dual antiplatelet therapy and antithrombotic treatment in patients with acute coronary syndrome – does everyday medical practice reflects current recommendations? A pilot study

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Abstract

Background: Dual antiplatelet therapy for 12 months is currently recommended for all patients with acute coronary syndrome (ACS), both for those treated pharmacologically or with percutaneous coronary interventions (PCI). Recently, the need for simultaneous administration of dual antiplatelet and oral anticoagulant therapy (triple therapy) has become more common. However, in addition to intensifying antiplatelet treatment, the risk of haemorrhagic complications is also significantly increased with triple therapy.

Aim: To assess the in-hospital use of triple therapy in patients with ACS, who have indications for long-term anticoagulation, and to define the reasons for not administering such a therapy.

Methods: The analysis included 298 patients diagnosed with ACS who were admitted to our department. Analysis of recommended treatment was conducted upon discharge from hospital after ACS and during hospitalisation. The reason for discontinuation or non-compliance with oral anticoagulant (OAC) therapy was also assessed.

Results: Out of 298 patients diagnosed with ACS, 53 (17.8%) had indications for long-term anticoagulation. The largest group consisted of patients with unstable angina who were treated pharmacologically (51.7%). The most common indication for chronic anticoagulation was paroxysmal atrial fibrillation (AF) (62%). At discharge from hospital, only 15.1% of patients received triple therapy. There was no significant association between the mode of treatment (triple therapy vs. lack of it) and indication for antiplatelet treatment ($p = 0.18$) or anticoagulation ($p = 0.27$). Among risk factors for bleeding, only prior episode of bleeding [$p = 0.0002$; odds ratio (OR) 4.17] and treatment with PCI ($p = 0.02$; OR impossible to assess because of too small group) were significantly associated with withdrawal of triple therapy.

Conclusions: The use of triple therapy in patients presenting with ACS and indications for long-term anticoagulation is insufficient. The reasons for not prescribing triple therapy are not clear. One explanation could be excessive concerns about haemorrhagic complications. There is a lack of equivocal guidelines and large randomised trials which would clearly define the optimal management strategy for patients presenting with ACS and indications for long-term anticoagulation therapy.

Key words: triple therapy, antiplatelet therapy, oral anticoagulants, acute coronary syndromes

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Introduction

Dual antiplatelet therapy for 12 months is currently recommended for all patients with acute coronary syndrome (ACS), both for those treated pharmacologically or with percutaneous coronary interventions (PCI) [1-3]. The goal of antiplatelet treatment in non-ST-elevation ACS (NSTE-ACS) is the liquefaction of thrombi rich in platelets, stabilisation of atherosclerotic plaques and prevention of total occlusion of the vessels. On the other hand, therapeutic management of ST-elevation myocardial infarction (STEMI) is focused on restoration of blood flow in an infarct-related artery. Antiplatelet agents are the basis for pharmacological treatment in interventional cardiology, particularly after implantation of drug-eluting stents (DES). However, the use of DES is associated with an increased risk of late stent thrombosis compared with bare metal stents (BMS) [4, 5].

The concomitant administration of dual antiplatelet and oral anticoagulant therapy (OAC) is becoming increasingly common. Diseases accompanying coronary

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heart disease such as hypertension, heart failure, left ventricular ejection fraction (LVEF) < 35%, diabetes, ischaemic stroke or age greater than 75 years are also risk factors for thromboembolic events. Their co-existence with atrial fibrillation (AF) makes the use of long-term anticoagulant treatment mandatory [6]. According to the current guidelines, prevention of thromboembolic events with oral anticoagulants is also necessary for patients with prosthetic heart valves [7, 8], valvular heart diseases if additional risk factors exist [9, 10], prior deep vein thrombosis or pulmonary embolism [11], and primary pulmonary hypertension [12].

The risk of haemorrhagic complications increases significantly with intensified antiplatelet treatment, and antiplatelet drugs are the second most common cause of complications (after ischaemic events) in patients with ACS. Independent prognostic factors that are related to the occurrence of serious bleeding, include advanced age, female gender, history of prior bleeding, treatment with percutaneous coronary intervention (PCI), renal failure and use of glycoprotein IIb/IIIa receptor antagonists [13, 14]. Increased bleeding risk with worsening renal function is associated with an increased risk of death in the GRACE registry. This means that caution should be taken when selecting aggressive invasive, antiplatelet or antithrombotic treatment in high-risk patients, and individual patient assessment should be conducted in each case [15].

Therefore, use of dual antiplatelet therapy in patients with ACS who have also indications for OAC seems reasonable, although the consensus statements from cardiology societies are not uniform. There is still a lack of large randomised trials to identify the optimal therapeutic management in patients undergoing dual antiplatelet therapy who have indications for long-term OAC.

The goal of the present study was to assess the in-hospital use of triple therapy in patients with ACS, who have indications for long-term OAC, and to define the reasons for not administering such therapy.

Methods

Patients

We conducted a retrospective analysis based on a search of our computerised database of patients diagnosed with ACS [STEMI, non-ST-elevation myocardial infarction (NSTEMI), unstable angina] who had also indications for OAC hospitalised in 2008 in the Department of Cardiology. Data were collected in 2008 because the European Society of Cardiology (ESC) Guidelines for Management of NSTE-ACS [2], which recommend the use of dual antiplatelet therapy for 12 months after an ischaemic event, were published in 2007. The American Heart Association/American College of Cardiology (AHA/ACC) guidelines related to STEMI [1] also recommend long-term concomitant treatment with acetylsalicylic acid (ASA) and thienopyridine. This indication was included in 2008 in the ESC Guidelines for Management of STEMI, which recommend obligatory use of dual antiplatelet therapy for 12 months after MI independent of the treatment approach [3].

Indications for long-term anticoagulation

Indications for long-term OAC were assumed to be: AF [6], prior deep vein thrombosis or pulmonary embolism [11], prosthetic heart valve [7, 8], mitral regurgitation or stenosis [9, 10], and primary pulmonary hypertension [12]. According to the ESC and ACC/AHA guidelines, the presence of one major or two moderate thromboembolic risk factors was considered as an indication for OAC in patients with AF. Major factors included history of previous stroke, transient ischaemic attack (TIA), cerebral embolism, mitral stenosis or prosthetic heart valve. Moderate factors included age > 75 years, hypertension, heart failure, LVEF < 35%, and diabetes. Patients with venous thrombotic disease (VTD) had clear indications for anticoagulant treatment if they had suffered two previous VTD episodes or one previous episode of VTD but had antiphospholipid antibodies, malignant disease or ≥ 2 congenital defects causing thrombophilia, such as lack of antithrombin, protein C or S, factor V Leiden, mutation G20210A of the prothrombin gene, hyperhomocysteinaemia, and activity of factor VIII > 150% [11]. According to the ESC and ACC/AHA guidelines, patients required OAC if they had mitral stenosis in sinus rhythm, a history of a prior embolic event or left atrial thrombus, dense spontaneous contrast or left atrial dimension ≥ 50 mm in echocardiography. In patients with mitral regurgitation, OAC should have been administered to patients with AF or those with a history of systemic embolism or evidence of atrial thrombus, and during the first 3 months following mitral valve repair [9, 10].

Risk factors for bleeding

Risk factors for bleeding were defined according to the GRACE registry, in which independent prognostic factors for serious bleeding were: age > 75 years, female gender, history of bleeding, treatment with PCI, renal failure and use of glycoprotein IIb/IIIa receptor antagonists [14]. Glomerular filtration rate (GFR), as indicated by the MDRD formula, was used as an indicator of renal dysfunction. A marked increase in bleeding risk has previously been shown to be associated with GFR levels < 60 ml/min [16].

Analysis of recommended treatment

Analysis of recommended treatment was conducted upon discharge from hospital after ACS and during hospitalisation, considering the presence of possible contraindications or complications during treatment. Data included the type of prescribed treatment (pharmaco-

logical, invasive or surgery), type and dose of antiplatelet drug (ASA and clopidogrel), type and dose of anticoagulant [low-molecular-weight heparin (LMWH), unfractionated heparin, fondaparinux, acenocoumarol or warfarin], intensity of anticoagulation if OAC was used (INR value, assessed at discharge) and the duration of antiplatelet therapy. Reasons for discontinuing or not administering anticoagulant therapy were also assessed (e.g., lack of patient compliance, contraindications for the drug, complications during treatment or planned angiography).

Statistical analysis

Statistical analysis was performed using the STATISTICA 8 PL software (StatSoft Inc., United States). Patient characteristics are presented as percentages (categorical variables) or as mean values and standard deviations (continuous variables). The chi-square test was used for comparisons of categorical variables between study groups and allowed the relationship between analysed data to be assessed. Pearson's coefficient analysis was used to evaluate the strength of the relationship between the variables. Fisher's exact test was used for comparison involving small numbers of observations. A p value < 0.05 was considered significant. To assess the effects of risk factors on the type of applied treatment, a logistic regression model was used.

Results

Out of 298 patients diagnosed with ACS and hospitalised in 2008, 53 (17.8%) had clear indications for long-term OAC therapy. Clinical and demographic characteristics of patients, indications for antiplatelet and OAC therapy as well as risk factors for bleeding are listed in Table I.

Treatments prescribed at discharge from hospital are presented in Table II. Only one quarter of patients with clear indications received triple therapy, mainly double antiplatelet treatment together with OAC and, less frequently, triple therapy with ASA, clopidogrel and LMWH. No significant association between mode of treatment and indication for antiplatelet therapy as well as for OAC was observed. Similarly, there were no differences in the coexistence of other diseases (except hypertension: p = 0.02), cardiovascular risk factors and risk factors for bleeding between patients receiving and not receiving triple therapy (Table III).

Out of 8 patients who received double antiplatelet treatment together with acenocoumarol, 50% had an INR level greater than 3 at discharge, 37.5% had an INR less than 2, and only 12.5% presented with an INR within the therapeutic range of 2-3. There was no defined duration of applied treatment in most of these patients; only two were told to take ASA and clopidogrel for 12 months.

Based on a review of patients' records and information from discharge summaries, we tried to

Table I. Clinical and demographic characteristics of the study population

	n = 53
Age [years]	76.6 ± 8.9
Medical history, n (%)	
diabetes	22 (41.5)
chronic peptic ulcer disease	9 (17)
anemia	16 (30.2)
Risk factors for bleeding, n (%)	
female gender	38 (71.7)
age > 75 years	31 (58.5)
bleeding in the past	2 (3.8)
treatment with PCI	1 (1.9)
renal failure	26 (49.1)
Reo-Pro usage	0
Indications for antiplatelet therapy, n (%)	
STEMI treated pharmacologically	6 (11.3)
NSTEMI treated pharmacologically	10 (18.9)
NSTEMI treated surgically	2 (3.8)
UA treated pharmacologically	30 (56.6)
MI undefined treated pharmacologically	5 (9.4)
Indications for anticoagulation*, n (%)	
AF paroxysmal	36 (67.9)
AF permanent	6 (11.3)
AF persistent	6 (11.3)
VTD	3 (5.7)
prosthetic heart valve	6 (11.3)
heart valve disease	1 (1.9)
pulmonary hypertension	1 (1.9)

Abbreviations: PCI – percutaneous coronary intervention, STEMI – ST-elevation myocardial infarction, NSTEMI – non-ST-elevation myocardial infarction, UA – unstable angina, MI – myocardial infarction, AF – atrial fibrillation, VTD – venous thrombotic disease
** sum is over 100%, because in 4 patients two indications were present, and in 1 patient – three indications were present.*

Table II. Pharmacotherapy prescribed at discharge

	n = 53
Antiplatelet therapy, n (%)	
ASA	51 (96.2)
clopidogrel	26 (49.1)
Anticoagulation therapy, n (%)	
acenocoumarol	31 (58.5)
LMWH	4 (7.5)
Combined therapy, n (%)	
ASA + acenocoumarol	22 (41.5)
ASA + clopidogrel	14 (26.4)
ASA + clopidogrel + acenocoumarol	8 (15.1)
ASA + clopidogrel + LMWH	4 (7.5)
ASA alone	3 (5.7)
acenocoumarol alone	1 (1.9)
none	1 (1.9)
Other drugs, n (%)	
PPI or H2-blocker	46 (86.8)
ACE-I or ARB	45 (84.9)
beta-blocker	43 (81.1)
statin	51 (96.2)
nitrate	29 (54.7)

Abbreviations: ASA – acetylsalicylic acid, LMWH – low-molecular-weight heparin, PPI – proton pump inhibitor, ACE-I – angiotensin-converting enzyme inhibitor, ARB – angiotensin II receptor blocker

Table III. Coexistence of other diseases, cardiovascular factors and bleeding risk factors in patients receiving and not receiving triple therapy

	Triple therapy n = 12	No triple therapy n = 41	p
Age [years]	74.3	77.3	NS
Chronic peptic ulcer, n (%)	4 (33.3)	5 (12.2)	NS
Anemia, n (%)	4 (33.3)	12 (29.3)	NS
Heart failure, n (%)	7 (58.3)	14 (34.1)	NS
Hyperlipidemia, n (%)	6 (50.0)	29 (70.7)	NS
Diabetes, n (%)	5 (41.7)	17 (41.5)	NS
Hypertension, n (%)	38 (92.7)	8 (66.7)	0.02
Prior stroke, n (%)	2 (16.7)	6 (14.6)	NS
Prior myocardial infarction, n (%)	4 (33.3)	16 (39.0)	NS
Age > 75 years, n (%)	7 (58.3)	23 (56.1)	NS
Female gender, n (%)	8 (66.7)	30 (73.2)	NS
Bleeding in the past, n (%)	0 (0)	2 (4.9)	NS
Treatment with PCI, n (%)	1 (8,3)	0 (0)	NS
Renal failure, n (%)	7 (58.3)	19 (46.3)	NS
Reo-Pro usage, n (%)	0 (0)	0 (0)	NS

Table IV. Reasons for not prescribing triple therapy

	n = 41
Contraindications to oral anticoagulation therapy, n (%)	1 (2.4)
Anticipated poor compliance, n (%)	6 (14.6)
Planned angiography, n (%)	3 (7.3)
No clear reason, n (%)	31 (75.6)

determine reasons for not prescribing OAC (Table IV), but in most cases it was impossible.

Among risk factors for bleeding, only prior episode of bleeding (p = 0.0002; OR 4.17) and treatment with PCI (p = 0.02; OR impossible to assess because of too small group) had significant effects on withdrawal of dual antiplatelet therapy combined with OAC therapy. There was no significant association (p = 0.38) between the use of a proton pump inhibitor (PPI) for bleeding prophylaxis and coexistence of chronic peptic ulcer disease.

Discussion

The present analysis suggests that there is a substantial need for triple therapy. The number of patients with ACS increases with increasing mean life expectancy; one can also observe an increasing frequency of coexisting diseases that increase the risk of thromboembolic complications. The scale of the problem seems to be large, as the results of our analysis show that almost 20% of patients with ACS had indications for the use of concomitant antiplatelet and anticoagulant treatment. Data from the PL-ACS Registry regarding the epidemiology of ACS in Poland show that about 140 000 patients are hospitalised in Poland with ACS, which is a rate of about 4000 individuals per million population [17]. Extrapolating the results of our study, it can be assumed that the number of patients requiring dual antiplatelet therapy in combination with OAC therapy is about 2 800 per year in Poland.

Despite many discrepancies and doubts concerning the use of triple therapy in patients with ACS and concomitant indications for chronic OAC, it seems reasonable to prescribe it to such patients. Stenestrand et al. based on the data from the RIKS-HIA Registry have shown that OAC therapy in patients after MI, who had AF, resulted in a significant reduction in 1-year mortality, which was caused primarily by a lower rate of ischaemic heart death and fatal stroke [18]. This is in agreement with the results of the ACTIVE W study, which clearly demonstrated that OAC is superior to clopidogrel plus aspirin for prevention of vascular events in patients with AF at high risk of stroke, especially in those already taking OAC [19]. In a trial by Ruiz-Nodar et al. conducted in patients with AF undergoing PCI with stenting, a significant reduction of mortality and significant improvement in prognosis in terms of reduced incidence of death, MI or revascularisation were observed in patients receiving triple therapy [20]. Also Karjalainen et al. in their study confirmed that dual antiplatelet treatment combined with OAC is currently the best option for the majority of these patients [21].

The results of our study show wide variability in the treatment regimens administered to patients with ACS and indications for OAC; the results are in agreement with those of previous studies and trials. Only 22.6% of patients requiring triple therapy received it. The most common indication for OAC was paroxysmal AF. In most cases, the doctors stopped clopidogrel, prescribing concomitant treatment of ASA and acenocoumarol. Rubolli et al. reported that triple therapy is recommended in 39% of patients with indications for OAC [22]. Lip et al. performed a retrospective analysis of 1234 patients who had undergone PCI, 35 of whom presented with AF; of these, 6 patients received triple therapy (17.1%) at discharge, 10 patients were administered clopidogrel for 1 year together with lifelong aspirin, 4 patients were treated with life-long aspirin and clopidogrel and 8 patients were told to stop one of their antiplatelet drugs and replace it with warfarin. The use of triple therapy was relatively low owing to concerns of life-threatening bleeding. There were no bleeding complications requiring hospitalisation at 30-day follow-up [23]. Analysis of 239 patients after PCI with indications for long-term OAC (such as AF, prosthetic heart valve, prior VTD) showed that 48.4% of patients received triple therapy after coronary stenting. Duration

of clopidogrel therapy was significantly shorter in the triple therapy group (about 4.14 months) and longer in patients receiving DES (5.88 months) compared with patients receiving BMS (4.09 months). Persistent AF was the most common indication for OAC (70%) [21]. In a prospective analysis that included 70 patients who had undergone coronary stenting and were receiving long-term OAC, 64.2% of patients received triple therapy on discharge from hospital. The overall percentage of patients who received triple therapy was 55.4% in the first month, 32.8% at 6 months and 16.9% at 1 year after PCI [24]. On the other hand, the RIKS-HIA analysis, which included a large group of patients (6 182 patients) showed that only 30% of patients with indications for OAC receive triple therapy in routine clinical practice. The patients who received OAC therapy were younger, had no history of chronic pulmonary disease and no dementia, but were more likely to have a history of stroke or coronary revascularisation [18].

The district, in which our hospital is located, is inhabited predominantly by the elderly, with chronic diseases such as diabetes, anaemia, hypertension, heart failure, prior MI or stroke, which undoubtedly was a cause for not using triple therapy due to a fear of a possible increased risk of hemorrhagic complications. Of note, almost all patients with ACS in our study were treated pharmacologically owing to the type of department and lack of direct access to a haemodynamic specialist unit. All patients with indications for urgent or early invasive strategy were transferred to hospitals with PCI availability and only a minority of these patients were transferred back to our department after revascularisation.

The lack of correlation between mode of treatment and indication for antiplatelet therapy and for anticoagulation, and the lack of differences between patients receiving and not receiving triple therapy in regards to coexistence of other diseases, cardiovascular risk factors and risk factors for bleeding, are probably due to the small number of patients in the observed group. We only observed a trend towards a higher age of patients not receiving triple therapy compared with those who received this treatment.

Using the GRACE scale, which is commonly used to assess the risk of bleeding, in our study only prior bleeding and treatment with PCI were factors significantly associated with no administering triple therapy. No such association was observed for advanced age, possibly due to the small number of patients in our group.

In the RICO Survey, the use of thrombolysis, heparin and antiplatelet drugs, and the usage of coronary angiography were much lower in patients receiving OAC therapy compared with those not receiving OAC. The use of OAC therapy, even when associated with antiplatelet drugs or heparin, did not significantly increase the risk of serious bleeding [25]. The common fear among doctors of increased bleeding complications with triple therapy does not seem to be justified. Out of 53 patients in our study, only 1 presented with minor gastrointestinal bleeding during hospitalisation, which was not associated with treatment but rather with a co-existing disease.

Another problem is identification of an appropriate intensity of OAC that is both efficacious and has a good safety profile in terms of haemorrhagic complications. In our study in patients receiving triple therapy only a minority had an INR within the therapeutic range of 2.0-3.0. This result can be only partially explained by the fact that the dose of OAC was fixed during hospitalisation in 75% of the patients and all patients received guidance of strict INR monitoring and adjustment of OAC dose after discharge. The RICO Survey showed that, in patients with STEMI who received dual antiplatelet therapy plus OAC therapy, only 44% had an INR between 2.0 and 3.0 [25]. On the other hand, a study conducted by Rossini et al. involving patients who had undergone PCI and were receiving triple therapy, showed that maintenance of INR at a lower therapeutic level (between 2.0 and 2.5) was not associated with an increased risk of bleeding (at 1- and 18-month observation points), MI, stroke or death compared with the group receiving dual antiplatelet therapy. Of note, patients with a prosthetic heart valve requiring maintenance of INR at a higher therapeutic level were excluded from the trial [26].

Conclusions

Dual antiplatelet therapy is obligatory in all patients presenting with ACS. Many of these patients have concomitant indications for long-term OAC (triple therapy). The use of recommended therapies in this subset of patients is insufficient. The reasons for not prescribing triple therapy are not clear. One explanation could be excessive concerns for haemorrhagic complications. There is a lack of firm recommendations and large randomised trials which would clearly define the optimal management strategy for patients presenting with ACS who have also indications for long-term OAC.

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Podwójna terapia przeciwpłytkowa i leczenie przeciwzakrzepowe – w jakim stopniu zalecenia ekspertów znajdują odzwierciedlenie w codziennej praktyce lekarskiej? Badanie pilotażowe

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Streszczenie

Wstęp: Stosowanie podwójnej terapii przeciwpłytkowej przez okres 12 miesięcy zalecane jest obecnie u wszystkich pacjentów z ostrym zespołem wieńcowym (OZW), niezależnie od tego, czy są leczeni zachowawczo czy inwazyjnie. W praktyce lekarskiej coraz częściej stajemy przed koniecznością równoczesnego stosowania podwójnej terapii przeciwpłytkowej i doustnego leczenia przeciwzakrzepowego (potrójna terapia). Wraz z intensyfikacją leczenia przeciwpłytkowego znamiennie wzrasta jednak ryzyko powikłań krwotocznych.

Cel: Ocena częstości stosowania potrójnej terapii u pacjentów z OZW wymagających równocześnie stosowania przewlekłego leczenia przeciwzakrzepowego w codziennej praktyce klinicznej oraz identyfikacja powodów niestosowania tego leczenia.

Metody: Analiza objęła 298 pacjentów z OZW hospitalizowanych w 2008 r. na Oddziale Kardiologii Szpitala Specjalistycznego im. J. Dietla w Krakowie. W trakcie hospitalizacji oraz przy wypisie ze szpitala przeprowadzano analizę zalecanego leczenia pod kątem występowania ewentualnych przeciwwskazań lub powikłań podczas leczenia OZW. W przypadku odstawienia lub niezastosowania leku przeciwzakrzepowego określano powód takiego postępowania.

Wyniki: Spośród 298 osób z OZW 53 (17,8%) miały wskazania do przewlekłej antykoagulacji. Najliczniejszą grupę stanowili pacjenci z niestabilną dusznicą bolesną leczeni zachowawczo (51,7%). Najczęstsze wskazanie do przewlekłej antykoagulacji stanowiło napadowe migotanie przedsionków (62%). Przy wypisie ze szpitala jedynie 15,1% osób spośród 53 ze wskazaniami otrzymało zalecenie stosowania potrójnej terapii. Nie wykazano istotnej zależności pomiędzy zastosowanym modelem leczenia (potrójna terapia przeciwzakrzepowa *vs* jej brak) a wskazaniem do leczenia przeciwpłytkowego ($p = 0,18$) ani przeciwzakrzepowego ($p = 0,27$). Wśród 8 pacjentów z zaleceniem stosowania potrójnej terapii, u których ją zastosowano, tylko 1 (12,5%) osoba miała terapeutyczny poziom INR. Spośród czynników ryzyka wystąpienia krwawienia jedynie wywiad w kierunku przebytego krwawienia ($p = 0,0002$; OR 4,17) oraz leczenia przezskórną angioplastyką wieńcową okazał się istotnym czynnikiem wpływającym na odstąpienie od zastosowania podwójnej terapii przeciwpłytkowej w skojarzeniu z doustnym antykoagulantem.

Wnioski: Częstość stosowania podwójnej terapii przeciwpłytkowej i doustnego leczenia przeciwzakrzepowego (potrójna terapia) u pacjentów z OZW oraz wskazaniami do przewlekłej antykoagulacji jest niewystarczająca. Powody niestosowania leczenia nie są jasne. Jednym z wyjaśnień może być przesadna obawa przed powikłaniami krwotocznymi. Nadal nie ma jednoznacznych rekomendacji oraz dużych badań klinicznych z randomizacją, które określiłyby optymalną strategię postępowania u chorych z OZW wymagających równocześnie stosowania przewlekłego leczenia przeciwzakrzepowego.

Słowa kluczowe: potrójna terapia, terapia przeciwpłytkowa, doustne antykoagulanty, ostre zespoły wieńcowe

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