Increased prevalence of cardiovascular risk factors in patients with acute coronary syndrome and indications for treatment with oral anticoagulation

Michał Owsiak¹, Agnieszka Pelc-Nowicka¹, Leszek Badacz², Jacek Dubiel³, Dariusz Dudek⁴, Grzegorz Gajos⁵, Janusz Grodecki⁶, Piotr Jankowski⁷, Kalina Kawecka-Jaszczyk⁷, Ewa Mirek-Bryniarska¹, Jadwiga Nessler⁵, Piotr Podolec⁸, Jerzy Sadowski⁹, Wiesława Traczyk⁸, Michał Zabojšek¹, Krzysztof Žmudka¹⁰, Leszek Bryniarski⁷

¹Department of Cardiology, Jozef Dietl Hospital; ²Department of Cardiology, L. Rydygier District Hospital; ³2nd Department of Cardiology, Jagiellonian University Medical College; ⁴Haemodynamic Department, Jagiellonian University Medical College; ⁵Department of Coronary Heart Disease, Jagiellonian University Medical College; ⁶Department of Cardiology, G. Narutowicz Memorial General Hospital; ⁷1st Department of Cardiology and Hypertension, Jagiellonian University Medical College; ⁸Department of Cardiac and Vascular Diseases, Jagiellonian University Medical College; ⁹Department of Cardiovascular Surgery and Transplantology, Jagiellonian University Medical College; ¹⁰Department of Interventional Treatment of Cardiovascular Diseases, Jagiellonian University Medical College, Krakow, Poland

Abstract

Background: Antiplatelet drugs currently constitute the basic treatment of coronary artery disease (acute coronary syndrome [ACS], stable angina and patients treated with percutaneous coronary interventions [PCI]). The number of patients with indication for dual antiplatelet therapy with comorbidities with high thrombo-embolic risk (such as atrial fibrillation [AF], venous thrombotic disease, valvular diseases) is increasing. That is why the need for simultaneous administration of dual antiplatelet and oral anticoagulant therapy (triple therapy) has become more common recently. The AF is the most common indication for chronic anticoagulation. Because of the lack of large randomised trials regarding triple therapy, characteristics of this group has not been well established.

Aim: To assess the presence of cardiovascular (CV) risk factors and concomitant diseases in patients with ACS requiring triple therapy.

Methods: Retrospective analysis included 2279 patients diagnosed with ACS who were admitted to the Departments of Cardiology in Cracow in 2008. In this group, 365 (16%) patients had indications for chronic anticoagulation. Demographic and clinical characteristics of these patients were compared with those of patients included in other published registries.

Results: Patients requiring triple therapy were aged 73.2 ± 9.5 years. Hypertension was diagnosed in 80%, hyperlipidaemia in 63%, smoking in 36%, prior myocardial infarction in 33%, prior stroke in 15%, previous treatment with PCI in 13%, coronary artery bypass grafting in 7%, diabetes in 36%, heart failure in 46%, anaemia in 33% and chronic ulcer disease or gastroesophageal reflux disease in 9%. The mean left ventricular ejection fraction was 46 ± 15%. Compared with other registries of patients without indications for triple therapy, our patients had significantly more frequently hypertension, diabetes and were older.

Conclusions: Patients after an ACS requiring triple therapy have more often a history of comorbidities and CV risk factors when compared with the group of patients with ACS without indication for triple therapy.

Key words: acute coronary syndrome, oral anticoagulant therapy, triple therapy, cardiovascular risk factors

Kardiol Pol 2011; 69, 9: 907–912

Address for correspondence:
Michał Owsiak, MD, Department of Cardiology, Jozef Dietl Hospital, ul. Skarbowa 1, 31–121 Kraków, Poland, e-mail: michaloo@op.pl
Received: 30.11.2010 Accepted: 02.02.2011
Copyright © Polskie Towarzystwo Kardiologiczne

www.kardiologiapolska.pl
INTRODUCTION

Antiplatelet drugs are the basis of the management of coronary artery disease (CAD), both in patients with acute coronary syndromes (ACS) and in patients undergoing percutaneous coronary interventions (PCI). Patients with a history of an ACS are still at risk of recurrent ischaemic episodes as a consequence of persistent platelet stimulation. Hence, the antiplatelet therapy is mandatory both during an acute episode and as a long-term maintenance therapy [1].

Despite wide use of aspirin, the rate of recurrent ischaemic episodes is still high. Moreover, the markers of thrombin production remain elevated for many months in patients with unstable angina (UA), which is a marker of constant platelet activation [2]. Hence, the current guidelines for the treatment of ACS recommend double antiplatelet therapy, i.e. aspirin and clopidogrel, for 12 months, irrespective of the type of therapy in the acute phase [2, 3]. The combination of aspirin and clopidogrel is also included in the guidelines concerning patients after elective PCI in whom endothelial injury and platelet activation also play a causative role [4]. The recommended period of double therapy spans from 4 weeks in patients receiving a bare metal stent (BMS) to at least 12 months in patients receiving a drug eluting stent (DES) (class I, level of evidence B) [5]. Double antiplatelet therapy is currently the best known prevention of both in-stent thrombosis and recurrence of ischaemic episodes.

With increasing life expectancy in the general population, the number of patients with indications for double antiplatelet therapy is also increasing, with additional comorbidities augmenting the thromboembolic risk and requiring long-term oral anticoagulation. Among these, atrial fibrillation (AF) is the most common indication for a long-term antithrombotic treatment. Oral anticoagulation is also a basis of prevention and treatment of venous thromboembolism [6]. Another group of patients in whom life-long oral anticoagulation is mandatory are patients with implanted prosthetic valves [7, 8]. The ESC and AHA experts also recommend oral anticoagulation in patients with mitral valve disease and additional thromboembolic risk factors or with a history of thromboembolic episodes. Oral anticoagulation is also currently recommended in primary pulmonary hypertension and included in the recommendations for the treatment of secondary pulmonary hypertension [9].

Triple therapy, including two antiplatelet drugs and an oral anticoagulant, seem to be a theoretically ideal solution for patients after ACS or elective PCI requiring long-term anticoagulant therapy. Aspirin and clopidogrel reduce the risk of recurrent myocardial ischaemia and in-stent thrombosis whereas an oral anticoagulant reduces the thromboembolic risk. However, the results of small and retrospective studies indicate that the risk of haemorrhagic complications in patients on triple therapy is increased [10].

At the time of our analysis, there were no uniform recommendations for the management of such patients, and that is the reason why various combinations of antiplatelet and anticoagulant drugs were used in everyday practice. Only in 2010, the ECS guidelines for antithrombotic treatment of AF in patients after ACS or elective PCI proposed management stratified according to haemorrhagic risk level in this patient group. In low and intermediate haemorrhagic risk patients who underwent elective PCI with BMS implantation, one month of triple therapy is recommended, followed by antithrombotic treatment with warfarin only. On the other hand, after DES implantation, triple therapy should be maintained for 3–6 months (depending on the type of the eluted drug), and warfarin with clopidogrel or with aspirin should be continued up to 12 months and warfarin only after 12 months. In ACS patients with low and intermediate risk of haemorrhagic complications, irrespective of the type of stent implanted, triple therapy is recommended for the first 6 months, followed by warfarin combined with clopidogrel or aspirin up to 12 months, and by warfarin only beyond this period.

In patients with a high risk of haemorrhagic complications, a more cautious management is recommended, including avoidance of DES implantation and, after elective PCI, triple therapy for only 2 to 4 weeks, followed by warfarin only. In this group, after PCI due to an ACS, triple therapy is recommended for 4 weeks, followed by warfarin and clopidogrel or aspirin for up to 12 months, and warfarin only after that [11]. In the majority of studies and analyses published to date, triple therapy has been associated with improved prognosis in comparison with any other combination of drugs. To date, studies including patients with indications for triple therapy are limited and characteristics of this patient group have not been completely elucidated. The aim of our study was to assess the prevalence of cardiovascular (CV) risk factors and comorbidities in patients with indications for triple therapy, treated in CV centres of Cracow in 2008.

METHODS

A total of 2279 patients hospitalised for an ACS in 8 CV centres of Cracow were included in the study. In this group, the following CV risk factors were assessed: lipid disorders, defined as total cholesterol concentration of ≥ 5.0 mmol/L, LDL cholesterol concentration of ≥ 3.0 mmol/L or triglyceride concentration of ≥ 1.7 mmol/L; arterial hypertension, smoking, history of stroke, left ventricular ejection fraction (LVEF; calculated by the Simpson’s rule during transthoracic echocardiography), history of myocardial infarction (MI), history of PCI or coronary artery bypass grafting (CABG). Analysed comorbidities included diabetes, heart failure (HF), anaemia (defined as haemoglobin concentration of < 13.5 g/dL in men and < 12.0 g/dL in women), gastric or duodenal ulcerative
disease, gastroesophageal reflux disease based on the previous discharge reports. Hospital authorities clearance for medical record queries was obtained in each case, and the Bioethical Committee of the Jagiellonian University approved the study design (KBET/128/B/2009).

Statistical analysis
In the assessment of between-group differences, \( \chi^2 \) Pearson test was used for categorical variables and Student t test for unpaired data was applied for continuous variables that followed normal distribution. For the remaining variables, Mann-Whitney U test was used. A p value < 0.05 was significant.

RESULTS
In the study population, 365 (16%) patients (193 women, mean age 73.2 \( \pm \) 9.5 years) had indications for long-term oral anticoagulation according to the guidelines for the management of the following conditions: AF [12], history of deep venous thrombosis or pulmonary embolism [6], valvular prosthesis [7, 8], mitral valve insufficiency or stenosis [13, 14], and primary pulmonary hypertension [9].

The indications for chronic oral anticoagulation were as follows: paroxysmal AF — 218 (60%) patients, permanent AF — 78 (21%) patients, valvular disease with increased risk of thromboembolic episodes — 28 (8%) patients, persistent AF — 23 (6%) patients, prosthetic valve — 21 (6%) patients, venous thrombo-embolism — 14 (4%) patients, and pulmonary hypertension — 6 (2%) patients. Twenty three (6%) patients had more than one indication for long-term oral anticoagulation.

Indications for dual antiplatelet treatment in the study population were as follows: medically managed UA — in 112 (31%) patients, interventionally treated ST elevation MI (STEMI) with BMS implantation — in 76 (21%) patients, medically managed non ST elevation MI (NSTEMI) — in 69 (19%) patients, medically managed STEMI — in 31 (9%) patients, and interventionally treated NSTEMI with BMS implantation — in 27 (7%) patients.

In the study population, the most frequent CV risk factors and comorbidities were as follows: arterial hypertension (80%), lipid disorders (63%) and HF (46%). Diabetes was found in 36% patients, history of smoking in 36%, history of MI in 33%, anaemia in 33% patients, history of stroke in 15%, history of PCI in 13%, history of CABG in 7% and gastrointestinal ulcers or gastro-oesophageal reflux disease in 9%. The mean LVEF in the study group was 46 \( \pm \) 15%.

DISCUSSION
In the published mainly observational and rather small studies, usually only the bleeding risk was assessed. Hence, data concerning characteristics of patients requiring triple therapy are lacking. Cardiovascular risk factors and comorbidities in a retrospective study by Rogacka et al. [15] which included 127 patients undergoing coronary angioplasty, both in the course of an ACS and stable CAD and discharged with recommended triple therapy were as follows: 24% patients had diabetes; 46% — hyperlipidaemia; 67% — arterial hypertension; 74% — multi-vessel coronary disease; 36% — family history of CAD; 54% — history of MI; 38% — history of PCI; 31% — history of CAGB; 6% were smokers. Mean age of the studied population was 69.9 years, and the mean LVEF was 45 \( \pm \) 13%. On the other hand, Lip et al. [16], in a similar retrospective observational study, analysed 1234 patients undergoing PCI, either elective or in the course of ACS in the years 2000–2005. In 35 patients, AF requiring triple therapy was found. Mean age of the studied patients was 71 years and 22 (63%) patients had a history of CAD, 12 (34%) had diabetes, and 23 (66%) — arterial hypertension. The AF prior to admission was found in 19 patients.

The prospective, multicenter GRACE Registry included data from 800 ACS patients requiring triple therapy. Men represented 70.1% of the study group. Diabetes was found in 179 (22%) patients, arterial hypertension in 460 (58%), hyperlipidaemia in 401 (50%), MI in 117 (15%), and HF in 89 (11%). In 489 (61%) patients a STEMI was diagnosed, in 184 (23%) — NSTEMI, and in 127 (16%) — UA. The most frequent indication for chronic oral anticoagulation in this group was AF and atrial flutter [17].

In a retrospective observational study RICO, patients after STEMI requiring oral anticoagulants were assessed. In this group, compared with a control group not requiring oral anticoagulants, mean age was higher, arterial hypertension and diabetes were more prevalent, LVEF was lower and Killip class higher. In the study group, more patients had a history of MI, stroke or peripheral artery disease. The prevalence of ventricular arrhythmia, cardiogenic shock, and stroke was comparable in both groups [18]. In comparison to the aforementioned studies, our population was older and lipid disorders and hypertension were more prevalent (Fig. 1).

In PL-ACS Registry of ACS patients, arterial hypertension was found in 61–80% of patients, diabetes in 19–28%, hypercholesterolaemia in 41–53%, HF in 6–12%, history of stroke in 3–5%, smoking in 15–36%, history of MI in 13–29%, history of PCI in 7–23%, and history of CAGB in 1–6%. Mean age of patients in the PL-ACS Registry was 64–67 years, depending on the type of ACS [19, 20]. In a prospective observational Euroaspire study, which included non-selected population of patients with CAD after CAGB, PCI or ACS, the rate of CV risk factors and comorbidities was as follows: arterial hypertension — 48%, diabetes — 15%, and hypercholesterolaemia — 64% [21].

In the GRACE Registry, in the general population of patients with ACS, CV risk factors and comorbidities, depending on the type of ACS, were found as follows: arterial hypertension in 52–66%, diabetes in 21–28%, hypercholesterolaemia in 38–54%, smoking in 55–62%, history of MI in 20–41%, history of PCI in 8–25% and history of CAGB in...
Mean age of patients in the GRACE Registry was 65–68 years, depending on the type of ACS [17, 22].

In the Cracow Programme of Coronary Artery Disease Secondary Prevention held in the years 1996–1997, patients ≤ 70 were included, hospitalised for their first or subsequent MI, first or subsequent episode of UA, first PCI or patients that were referred for CABG. In this study of 536 patients (men 74%, women 26%, mean age 57 years), CV risk factors and comorbidities were found as follows: smoking — 37%, hypercholesterolaemia — 80%, obesity — 20%, arterial hypertension — 56%, and diabetes — 15.5% patients (Table 1) [23, 24].

In our study group patients with indications for triple therapy, compared with patients of the aforementioned registries, more frequently had arterial hypertension and diabetes and were older than patients without indications for triple therapy. The rates of the remaining risk factors varied between the populations. Lipid disorders were more frequent in our study group than in PL-ACS and GRACE Registries, less frequent than in the Cracow Secondary Prevention Programme and were of similar prevalence as in the Euroaspire Registry.

On the other hand, smoking was less frequent in our group in comparison with GRACE Registry and significantly more frequent in PL-ACS and Euroaspire. The rates of history of MI, PCI or CABG in the population described in our study was not significantly different compared to these registries (Table 1). In our study group, the mean LVEF was 46 ± 15%, and due to the lack of relevant data in the studies and Registries mentioned above, the rate of HF can not be compared.

CONCLUSIONS

Patients after ACS who have indications to triple therapy have also high or prevalence of some CV risk factors and comorbidities compared with CAD patients without indications for triple therapy.
Cardiovascular risk factors in CAD patients treated with triple therapy

Conflict of interest: none declared

References

Częstość występowania czynników ryzyka sercowo-naczyniowego jest zwiększona u chorych z ostrym zespołem wieńcowym ze wskazaniami do leczenia doustnym antykoagulantem

Michał Owsiak1, Agnieszka Pelc-Nowicka1, Leszek Badacz2, Jacek Dubiel3, Dariusz Dudek4, Grzegorz Gajos5, Janusz Grodecki6, Piotr Jankowski7, Kalina Kawecka-Jaszcz7, Ewa Mirek-Bryniarska1, Jadwiga Nessler5, Piotr Podolec8, Jerzy Sadowski9, Wiesława Tracz8, Michał Zabojszcz1, Krzysztof Żmudka10, Leszek Bryniarski7

1Oddział Kardiologii, Szpital Specjalistyczny im. J. Dietla, Kraków; 2Oddział Kardiologii, Szpital Specjalistyczny im. L. Rydygiera, Kraków; 3II Klinika Kardiologii, Collegium Medicum Uniwersytetu Jagiellońskiego, Kraków; 4Klinika Hemodynamiki, Collegium Medicum Uniwersytetu Jagiellońskiego, Kraków; 5Klinika Choroby Wieńcowej, Collegium Medicum Uniwersytetu Jagiellońskiego, Kraków; 6Klinika Kardiologii, Szpital im. G. Narutowicza, Kraków; 7I Klinika Kardiologii i Nadciśnienia Tętniczego, Collegium Medicum Uniwersytetu Jagiellońskiego, Kraków; 8Klinika Chorób Serca i Naczyń, Collegium Medicum Uniwersytetu Jagiellońskiego, Kraków; 9Oddział Kliniczny Chirurgii Serca, Naczyń i Transplantologii, Collegium Medicum Uniwersytetu Jagiellońskiego, Kraków; 10Centrum Interwencyjnego Leczenia Chorób Serca i Naczyń z Pododdziałem Kardiologii Interwencyjnej, Collegium Medicum Uniwersytetu Jagiellońskiego, Kraków

Streszczenie

Wstęp: Leki przeciwpłytkowe są obecnie podstawą terapii choroby niedokrwiennej serca w ostrych zespołach wieńcowych (OZW), w stabilnej chorobie wieńcowej i u chorych poddanych przezskórnym interwencjom wieńcowym. Wciąż wzrasta liczba pacjentów ze wskazaniami do podwójnej terapii przeciwpłytkowej, dodatkowo obciążonych chorobami współistniejącymi, zwiększającymi ryzyko zatorowo-zakrzepowe (jak migotanie przedsionków, żylna choroba zakrzepowo-zatorowa, choroby zastawkowe serca). Dlatego też coraz bardziej powszechna staje się potrzeba długotrwałego leczenia 2 lekami przeciwpłytkowymi w połączeniu z doustnym lekiem przeciwzakrzepowym (terapia potrójna). Migotanie przedsionków jest najczęstszym wskazaniem do przewlekłego leczenia przeciwzakrzepowego. Ze względu na brak dużych, randomizowanych badań dotyczących chorych wymagających potrójnej terapii charakterystyka tej populacji nie jest dostatecznie poznana.

Cel: Celem pracy była ocena częstości występowania czynników ryzyka sercowo-naczyniowego i chorób towarzyszących u pacjentów po przebyciu OZW, ze wskazaniami do potrójnej terapii.

Metody: Retrospektywną analizą objęto 2279 pacjentów z rozpoznaniem OZW, hospitalizowanych w 2008 r. w krakowskich ośrodkach kardiologicznych. W tej grupie 365 (16%) pacjentów miało wskazania do przewlekłej antykoagulacji.

Wyniki: W grupie osób wymagających potrójnej terapii średnia wieku wyniosła 73,2 ± 9,5 roku. Częstość występowania czynników ryzyka sercowo-naczyniowego i chorób współistniejących przedstawiała się następująco: nadciśnienie tętnicze (80%), zaburzenia lipidowe (63%), palenie tytoniu (36%), zawał serca w wywiadzie (33%), udar mózgu w wywiadzie (15%), zabieg przezskórnej interwencji wieńcowej w wywiadzie (13%), zabieg pomostowania aortalno-wieńcowego w wywiadzie (7%), cukrzyca (36%), niewydolność serca (46%), niedokrwistość (33%) i choroba wrzodowa żołądka/dwunastnicy lub refluk-sowa przełyku (9%). Frakcja wyrzutowa lewej komory w badanej grupie wynosiła średnio 46 ± 15%.

Wnioski: Pacjenci po przebyciu OZW mający wskazania do potrójnej terapii są bardziej obciążeni czynnikami ryzyka sercowo-naczyniowego i chorobami współistniejącymi w porównaniu z osobami po przebyciu OZW bez wskazań do przewlekłej terapii doustnym antykoagulantem.

Słowa kluczowe: ostre zespoły wieńcowe, doustne leki przeciwzakrzepowe, potrójna terapia, czynniki ryzyka sercowo-naczyniowego

Kardiol Pol 2011; 69, 9: 907–912