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Original Article

ONE-YEAR CARDIOVASCULAR OUTCOME IN PATIENTS ON CLOPIDOGREL ANTI-PLATELET THERAPY AFTER ACUTE MYOCARDIAL INFARCTION

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Abstract. *The aim of this study was to determine the risk factors in patients on clopidogrel anti-platelet therapy after acute myocardial infarction, for cardiovascular mortality, re-hospitalization and admission to emergency care unit. We followed 175 patients on dual antiplatelet therapy, with clopidogrel and acetylsalicylic acid, for 1 year after acute myocardial infarction, both STEMI and NSTEMI. Beside demographic and clinical characteristics, genetic ABCB1, CYP2C19 and CYP2C9 profile was analyzed using Cox-regression analysis. End-points used were: mortality, re-hospitalization and emergency care visits, all related to cardiovascular system. During the accrual and follow-up period, 8 patients (4.6%) died, mostly as a direct consequence of an acute myocardial infarction. Re-hospitalization was needed in 27 patients (15.4%), in nine patients (33.3%) with the diagnosis of re-infarction. Thirty-two patients (18.3%) were admitted to emergency care unit due to cardiovascular causes, up to 15 times during the follow-up. NSTEMI was an independent predictor of all three events registered (mortality OR=7.4, p<0.05; re-hospitalization OR=2.8, p<0.05); emergency care visit OR=2.4, p<0.05). Other significant predictors were related to kidney function (urea and creatinine level, creatinine clearance), co-morbidities such as arterial hypertension and decreased left ventricular ejection fraction, as well as clopidogrel dosing regimen. As a conclusion, it may be suggested that one of the most significant predictors of cardiovascular events (mortality, re-hospitalization and emergency care visits) is NSTEMI. Besides, clopidogrel administration according to up-to-date guidelines, with high loading doses and initial doubled maintenance doses, improves 1-year prognosis in patients with AMI.*

Key words: *clopidogrel, acute myocardial infarction, cardiovascular outcome*.

Introduction

Despite improvements in pharmacotherapy and management of patients with acute myocardial infarction, the mortality rate and the incidence of cardiovascular outcomes remain high. In Serbia, mortality is over 10%, partially due to low rate of primary PCI (22%), the most beneficial management option in these patients [1]. The rate of various cardiovascular events is the highest in the first month after the acute event, but remains significant even a year after [2]. Cardiovascular diseases are the most common cause of death in Serbia (53.3%), out of which 18.5% account for ischemic heart disease. More than a half of this mortality (54.0%) is caused my ACS. The highest number of newly diagnosed AMI is among patients older than 75 (34.1%), in both genders. Male and female gender ratio is 1:1.6. The overall incidence rate is 232.2 (or 107.7 when standardized to the world population). The Nis region is characterized with very low standardized incidence rate (below 105.0), but with moderate mortality rate (31.3), the same as the country's average [1]. The majority of the patients with AMI are treated according to the evidence-based guidelines. Nevertheless, pharmacogenetic factors may alter the medication efficacy and worsen the outcome in these patients. Besides, the risk of various cardiovascular events is associated with age and other patients' characteristics, medical history and revascularization

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method [2]. The rate of re-hospitalizations in a 30-day period goes up to 20% [3,4] in about a quarter due to cardiovascular causes [3]. After 3 months, the rate rises to 9.3%, and up to 20.2% after a year. Revascularization is needed in approximately 5% [5]. Known predictors are female sex, CABG surgery or PCI, prior ICD, vascular disease, chronic kidney disease, diabetes mellitus, rheumatic valvular disease, chronic pulmonary disease and anemia [5–7].

Beside patients' characteristics and co-morbidities, primarily decreased, but increased clopidogrel efficacy, as well, may be the reason of poor clinical outcome. P-glycoprotein is a transporter involved in the absorption process of various drugs prescribed in patients with AMI. The presence of polymorphic T allele of *ABCB1* gene may alter their bioavailability, and their pharmacodynamics effects. The absorption of clopidogrel, used in combination with acetylsalicylic acid as dual anti-aggregation therapy, is impaired in *ABCB1 TT* homozygotes, which may account for more than 25% in Caucasians [8]. Besides, interactions with proton-pump-inhibitors prescribed for gastroprotection, carvedilol (and some other ACE-inhibitors), statins and calcium-channel blockers, via P-glycoprotein inhibition are possible [9]. Other polymorphisms of importance are on the genes encoding cytochrome P450 enzymes, particularly CYP2C19 and CYP2C9. Both of them are involved in the clopidogrel transformation into active metabolite. The induction or inhibition of these enzymes, as well as the other CYP involved in clopidogrel biotransformation, such as CYP3A4, may lay in the basis of significant drug interactions [10].

The aim of this study was to determine the risk factors in patients on clopidogrel anti-platelet therapy after acute myocardial infarction, for cardiovascular mortality, re-hospitalization and admission to emergency care unit.

Subjects and Methods

The study was approved by Ethics Committee of the University of Niš, Faculty of Medicine. All the subjects were treated in accordance with the Declaration of Helsinki. Before being recruited, each patient gave an informed consent. It was designed as a prospective cohort study.

Patients included in the study were treated at the Clinic of Cardiology, Clinical Center Niš, Serbia. They were recruited upon acute coronary syndrome with/without ST-elevation diagnosis with biochemical and electrocardiographical confirmation. We followed 175 patients, both with STEMI (75.2%) and NSTEMI (20.9%). Half of the patients (49.7%) were treated with primary PCI. Thirty-six patients (20.6%) were revascularized with fibrinolytics administration, alteplase (18.9%) or streptokinase (1.7%). Among alteplase patients, 7(4.0%) underwent rescue PCI. Conventional therapy was applied to the rest 29.7% patients.

Study group characteristics are shown in Table 1. There were 122 male (69.7%) and 53 female (30.3%) patients. Their age varied from 30 to 89 years (average 60.80±11.33 years).

Table 1 Baseline characteristics of the study patients group

	mean ± SD	
Age (years)	60.81 ±	11.29
Heart rate (1/min.)	79.60 ±	19.08
Systolic blood pressure (mmHg)	130.92 ±	26.81
Diastolic blood pressure (mmHg)	79.79 ±	16.02
Ejection fraction (%)	50.77 ±	11.70
End-systolic dimension (mm)	52.33 ±	6.55
End-diastolic dimension (mm)	37.35 ±	8.07
Right ventricular systolic pressure (mmHg)	34.82 ±	11.71
Left atrial size (mm)	39.76 ±	5.59
Body-mass index (kg/m^2)	26.99 ±	3.91
Cholesterol (mmol/l)	5.58 ±	1.37
LDL (mmol/l)	3.62 ±	1.19
HDL (mmol/l)	1.12 ±	0.58
Triglycerides (mmol/l)	2.01 ±	2.68
Hemoglobin (g/l)	138.91 ±	19.51
Hematocrit (l/l)	0.41 ±	0.06
Platelets (10^9/l)	253.03 ±	78.75
Leukocytes (10^9/l)	11.82 ±	10.91
Erythrocytes (10^{12}/l)	4.69 ±	0.65
AST (U/l)	138.52 ±	170.49
ALT (U/l)	45.25 ±	49.47
LDH (U/l)	934.33 ±	769.07
Glucose(mmol/l)	8.28 ±	4.56
Creatinine (μmol/l)	103.41 ±	44.72
Creatinine clearance (ml/min.)	79.28 ±	25.71
Urea (mmol/l)	6.76 ±	3.20
Sodium (mmol/l)	136.33 ±	10.31
Potassium (mmol/l)	4.33 ±	0.48
CRP (mg/l)	18.28 ±	32.55
Troponins (ng/l)	12.82 ±	28.47
Creatine kinase (U/l)	1052.74 ±	1403.40
CKMB (U/l)	100.86 ±	126.35
Fibrinogen (g/l)	4.63 ±	2.06
	N	(%)
Male	122	(69.7%)
STEMI	135	(77.1%)
Previous AMI	31	(17.7%)
Hypertension	110	(62.9%)
DM	49	(28.0%)
Atrial fibrillation	16	(9.1%)
Smoking	60	(34.3%)

Pharmacological therapy was carried out according to the guidelines. All the patients received antiplatelet and anticoagulant drugs. Antiaggregation therapy was achieved with ASA (98.3%) and clopidogrel (100.0%). The therapy of AMI consisted of ACE inhibitors (68.4%), beta-blockers (75.4%), diuretics (20.6%), spironolactone (17.7%), calcium channel blocker (11.4%), amiodarone (10.3%), digoxin (6.3%), long-lasting vasodilators (24.6%) and trimetazidine (10.3%), as well. Besides, they were given lipid-lowering statins (94.3%), pantoprazole for gastroprotection (90.3%) and anxiolytics (33.7%).

Table 2 Primers used for SNPs detection

ABCB1 C3435T	C (5'-GGTGTCACAGGAAGAGATC-3') T (5'-CAGCCGGGTATAGTCACAGGAAGATATT-3') Reverse (5'-GGCCAGAGAGGCTGCCACAT-3')
CYP2C19*2	Forward (5'-AATTACAACCAGAGCTTGGC-3') Reverse (5'-TATCACTTTCCATAAAAGCAAG-3')
CYP2C19*17	Forward (5'-GCCCTTAGCACCAAATTCTC-3') Reverse (5'-ATTTAACCCCCTAAAAAAACACG-3')
CYP2C9*2	Forward (5'-GTATTTTGGCCTGAAACCCATA-3') Reverse (5'-GGCCTTGGTTTTTCTCAACTC-3')

Thirty-one patients (17.7%) had previous AMI (re-infarction patients were excluded from the study). Among co-morbidities, 110 (62.9%) had HTA diagnosed for 11.29±8.61 years, while 49 (28.0%) suffered from diabetes mellitus type 2 for approximately 8.64±7.83 years, and 16 patients (9.1%) had atrial fibrillation. Anamnestic data showed that one third of the patients (34.3%) were current smokers (former smokers were considered non-smokers).

Accrual time was 1 year, while the follow-up time was 6 months. During that period patients were monitored for reporting to the emergency unit, re-hospitalizations and mortality. Non-related non-cardiovascular events were not included into analysis.

During the accrual and follow-up period, all the patients were genotyped for ABCB1 C34335T (rs1045642), CYP2C19*2 (rs4244285) and *17 (rs12248560), as well as CYP2C9*2 (rs1799853). From each collected whole blood sample, we have isolated genomic DNA manually. Using the PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) method and specific primers (Table 2), before-mentioned small nuclear polymorphisms (SNPs) were detected.

Statistical Package for Social Sciences (SPSS 16.0; Chicago, Ill., USA) was used for statistical data analysis. Baseline characteristics are presented as frequencies or means with SDs. Quantitative variables were compared between groups using Student's t-test, while for qualitative variables Fisher's exact test was performed. A p value <0.05 was considered to be a measure of statistical significance. Using Cox-regression, hazard ratios and 95% CIs were calculated, and therefore, potentiated the comparison of outcome occurrence between groups and the effect of each predictor.

Results

During the accrual and follow-up period, 8 patients (4.6%) died. In 6 cases it was the direct consequence of an acute myocardial infarction. The other two deaths both had cardiovascular cause: infective myocarditis and lower extremity thrombosis. They occurred between 7 and 297 days after the recruitment. Re-hospitalization was needed in 27 patients (15.4%). Most of them were re-hospitalized only once during the follow-up period, while the maximum number of re-hospitalizations was 7 in one case. Nine patients (33.3%) were re-hospitalized with the diagnosis of re-infarction. In one of the cases the re-infarction was caused by stent thrombosis. The symptoms of angina pectoris, stable (22.2%) or unstable (11.1%), were the reason for re-admission reported as well. Thirty-two patients (18.3%) were admitted to emergency care unit due to cardiovascular causes, up to 15 times during the follow-up.

ABCB1 C3435T genotyping was 100.0% successful, while in 51 patients (29.1%) we could not determine CYP2C19 and CYP2C9 polymorphism. The observed genotype frequencies did not deviate significantly from those expected at Hardy-Weinberg equilibrium (Table 3).

Table 3 ABCB1 C3435T, CYP2C19 and CYP2C9 genotype frequencies

Gene	Genotype	N (f)	χ^2 (p)
ABCB1 C3435T	CC	41 (23.4%)	
	CT	81 (46.3%)	0.658 (0.720)
	TT	53 (30.3%)	
CYP2C19	PM	5 (4.0%)	
	IM	33 (26.6%)	4.649 (0.460)
	EM	46 (37.1%)	
	URM	40 (32.3%)	
CYP2C9	CC	115 (79.3%)	
	CT	28 (19.3%)	4.634 (0.099)
	TT	2 (1.4%)	

Table 4 Cardiovascular outcomes in relation to genotype

	Emergency care unit admission (HR (CI 95%), p)	Re-hospitalization (HR (CI 95%), p)	Cardiovascular death (HR (CI 95%), p)
ABCB1 genotype (CC-CT-TT)	1.2 (0.7-1.9), 0.526	1.4 (0.9-2.5), 0.170	0.5 (0.2-1.4), 0.221
ABCB1 TT genotype	0.9 (0.4-2.0), 0.866	1.3 (0.6-2.8), 0.556	0.3 (0.0-2.7), 0.298
ABCB1 any T allele	1.8 (0.7-4.8), 0.216	2.7 (0.8-9.1), 0.102	0.5 (0.1-2.1), 0.348
CYP2C19 phenotype (SM-IM-EM-URM)	0.8 (0.5-1.2), 0.245	0.9 (0.5-1.4), 0.528	0.8 (0.4-2.0), 0.694
CYP2C19 any *2 allele	1.5 (0.7-3.3), 0.309	1.4 (0.6-3.4), 0.442	1.8 (0.4-7.9), 0.460
CYP2C19 any *17 allele	0.8 (0.4-1.8), 0.612	1.0 (0.4-2.5), 0.885	0.5 (0.1-2.7). 0.448
CYP2C9 any *2 allele	0.4 (0.1-1.3), 0.128	0.7 (0.2-2.1), 0.553	0.6 (0.1-5.4), 0.686

As genetic predictors, we have analyzed the presence of various genotypes and phenotypes of ABCB1, CYP2C19 and CYP2C9 genes. For each of the three outcomes monitored, none of the predictors were shown to be statistically significant (Table 4).

We have tested the patients' characteristics, co-morbidities and social habits such as smoking as risk predictors of cardiovascular outcomes (Table 5–7). Even though univariate Cox-regression analysis have identified a number of statistically significant predictors of need for re-hospitalization (Table 5), after their inclusion into a multivariate model (χ^2=18.522, p<0.001), the only predictors that remained independently significant were the type of AMI, with or without ST-segment elevation, and clopidogrel dosing regimen. Patients after NSTEMI had 2.8 higher risk (p<0.05) of re-hospitalization due to cardiovascular indications. Patients with lower dose clopidogrel dosing regimens (lower or no loading dose) had 2.3 times higher risk of re-hospitalization (p<0.05).

Considering emergency care unit admission, due to cardiovascular symptoms and signs (Table 6), the majority of predictors identified by univariate Cox-regression modeling, remained independently significant in the multivariate model (χ^2=35.662, p<0.001). In comparison to STEMI, NSTEMI is associated with 2.4 times higher risk (p<0.05). High LDL (above 3mmol/l) leads to 2.5 times lower risk (p<0.05). Patients with decreased LVEF after AMI, below 45%, had 3 times (p<0.05) higher risk of need for emergence care. Increased creatinine concentration, for each 10μmol/l, increases the risk 1.1 times (p<0.001). Patients with HTA are at 3 times higher risk (p<0.05) of emergency care need. Among the drugs prescribed, therapy with calcium channel blockers increased the risk by 2.8 times (p<0.05).

Despite low mortality, we have identified (Table 7) two significant predictors in a multivariate Cox-regression model (χ^2=15.137, p<0.01). Acute myocardial infarction without ST-segment elevation was associated with 7.4 higher risk of cardiovascular mortality (p<0.05). The increase in urea concentration for each unit augments the risk 1.1 times (p<0.05).

Table 5 Predictors of re-hospitalization due to cardiovascular causes

Re-hospitalization (HR (CI 95%), p)	Univariate Cox-regression	Multivariate Cox-regression
Age (years)	1.041 (1.005-1.078), 0.024	
NSTEMI vs. STEMI	4.148 (1.948-8.829), 0.000	2.785 (1.102-7.038), 0.030
High LDL>3mmol/l	0.407 (0.176-0.942), 0.036	
Hemoglobin (g/l)	0.982 (0.965-1.000), 0.047	
Leukocytes (10^9/l)	0.817 (0.679-0.983), 0.032	
AST (U/L)	0.994 (0.988-0.999), 0.032	
Creatinine (μmol/l)	1.006 (1.000-1.011), 0.035	
Urea (mmol/l)	1.095 (1.019-1.178), 0.014	
CK(U/L)	0.999 (0.999-1.000), 0.049	
Previous AMI	4.102(1.919-8.771), 0.000	
HTA	5.069 (1.526-16.835), 0.008	
DM type 2	2.214 (1.036-4.732), 0.040	
Clopidogrel loading dose (mg)	0.996 (0.994-0.998), 0.000	
Clopidogrel loading dose/BMI (mg·m^2/kg)	0.905 (0.838-0.977), 0.011	
Clopidogrel dosing regimen (mg)	2.356 (1.227-4.522), 0.010	2.284 (1.136-4.593), 0.020
Carvedilol vs. Bisoprolol	3.060 (1.099-8.518), 0.032	
Diuretic	2.927 (1.358-6.308), 0.006	
Spironolactone	2.835 (1.298-6.192), 0.009	
Long lasting nitrates	2.557 (1.196-5.463), 0.015	

Table 6 Predictors of emergency care due to cardiovascular causes

Emergency care unit admission (HR (CI 95%), p)	Univariate Cox-regression	Multivariate Cox-regression
NSTEMI	3.071 (1.512-6.240), 0.007	2.379 (1.080-5.243), 0.031
High LDL>3mmol/l	0.431 (0.205-0.907) 0.027	0.399 (0.181-0.881), 0.023
EF<45%	2.395 (1.191-4.817), 0.014	3.044 (1.398-6.629), 0.005
Creatinine (μmol/l)	1.009 (1.004-1.014), 0.001	1.011 (1.004-1.017), 0.001
Urea (mmol/l)	1.152 (1.067-1.243), 0.000	
HTA	2.867 (1.179-6.969), 0.024	3.133 (1.200-8.180), 0.020
Diuretic	2.479 (1.212-5.072), 0.013	
Calcium channel blocker	2.664 (1.151-6.168), 0.022	2.782 (1.000-7.738), 0.050

Table 7 Predictors of cardiovascular mortality

Cardiovascular mortality (HR (CI 95%), p)	Univariate Cox-regression	Multivariate Cox-regression
NSTEMI	11.019 (2.223-54.615), 0.003	7.431 (1.371-40.267), 0.020
LDL (mmol/l)	0.514 (0.281-0.940), 0.031	
High LDL>3mmol/l	0.217 (0.049-0.970), 0.046	
Hemoglobin (g/l)	0.966 (0.938-0.995), 0.021	
Creatinine (μmol/l)	1.009 (1.003-1.015), 0.004	
Creatinine clearance (ml/min.)	0.933 (0.886-0.983), 0.009	
Urea (mmol/l)	1.162 (1.073-1.257), 0.000	1.094 (1.001-1.195), 0.046
Previous AMI	4.820 (1.205-19.277), 0.026	
Clopidogrel loading dose (mg)	0.994 (0.990-0.999), 0.016	
Clopidogrel dosing regimen (mg)	5.190 (1.166-23.107), 0.031	
Acetylsalicylic acid loading dose (mg)	0.993 (0.986-0.999), 0.034	
Calcium channel blocker	5.004 (1.195-20.946), 0.027	

Discussion

After a 1-year follow-up of patients after AMI, 4.6% died, 15.4% were re-hospitalized and 33.3% visited emergency unit, all associated with cardiovascular events. These rates are slightly lower than those reported in previous studies (1,3–5). One of the risk factors for poor clinical outcome, regarding all three events registered is NSTEMI. Compared to STEMI patients, NSTEMI patients are associated with 2.4 times higher risk of emergency care needed, 2.8 times higher risk of re-hospitalization, and even 7.4 times higher risk of cardiovascular death. It is suggested that STEMI patients are favored by rapid revascularization and more aggressive pharmacotherapy, resulting in lower rate of mortality and re-hospitalizations in 1-year period after AMI [11].

Elevated creatinine concentration was found to be and independent predictor of re-hospitalizations, while elevated urea concentration was associated with increased risk of cardiovascular mortality. Patients with chronic kidney disease, especially those with more severe stages, are less likely to be revascularized and prescribed evidence-based therapy. On the other hand, they presented more often with bleeding complications. When summed up, this results in higher mortality rate, particularly in STEMI patients [12].

Higher clopidogrel dosing regimen was found to be associated with lower risk of re-hospitalizations. When higher clopidogrel doses are administered, the production of clopidogrel active metabolite is multiplied, despite some saturation of the pharmacokinetic processes involved [13]. In the elderly, no loading dose is recommended, while lower loading dose is prescribed in patients administered fibrinolytics [14]. High loading dose gives the greatest benefit in the first days after AMI, but increased maintenance dose, recommended in the first week, significantly decreases the risk of major adverse cardiovascular events [15].

Hyperlipidemia is a known risk factor for ACS and for the worse prognosis after AMI [16]. Our results have shown that high LDL favored good prognosis, as found in similar studies [17]. This may be due to the therapy with statins. Beside lowering LDL, these drugs have a number of pleiotropic effects in atherosclerotic diseases. Statins may have antithrombotic effect, directly diminishing the possibility of various cardiovascular events, due to inhibited platelet and activation and procoagulant protein tissue factor expression [18]. Besides, there are significant changes in atherosclerotic plaque characteristics in patients receiving statin therapy, concerning calcium and fibrous deposition, as well as its elastic membrane, thus stabilizing the plaque [19].

After suffering AMI, in a large number of patients there is a decrease in left ventricular EF. This worsening of the cardiac contractile function is one of the prognostic factors for bad prognosis. The risk increases at least 3 times [17,20], as found in our results. Mild and severe left ventricular dysfunctions are associated with higher risk in patients with AMI, especially in combination with co-morbidities [21].

We have found patients with HTA to be at more than 3 times higher risk of suffering from cardiovascular symptoms during the follow-up period after AMI. In the previous studies, somewhat lower hazard risk ratio was found for these patients to experience major adverse cardiovascular events [22,23], but it may rise to 5 times higher risk in patients with unspecified chest pain [24]. Therefore, patients on antihypertensive drugs, such as calcium channel blockers, were associated with worse prognosis, as well.

Although there are numerous studies suggesting the association between genetic profile, including cytochrome P450 enzymes and P-glycoprotein, and outcome in patients after AMI [25–27], we have not obtained statistically significant results. This may be explained by insufficient number of events for such genetic analysis. Except for ABCB1 polymorphisms for P-glycoproteins, low-function genotypes are rare in the Caucasian population.

Conclusion

As a conclusion, we may imply that one of the most significant predictor of cardiovascular events (mortality, re-hospitalization and emergency care visits) is NSTEMI. Besides, clopidogrel administration according to up-to-date guidelines, with high loading doses and initial doubled maintenance doses, improves 1-year prognosis in patients with AMI.

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