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Relationship of Genetic Markers for Atherosclerosis and Long-Term Outcome after Percutaneous Coronary Intervention with Stenting

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A B S T R A C T

The aim of the study was to describe the relationship of clinical outcome after percutaneous coronary intervention (PCI) with stenting and genetic polymorphisms (GP) which are known to relate to the incidence of in-stent restenosis and late thrombotic complications. The study included 190 patients with standardized clinical follow-up over 5 years, which were initially treated with PCI. We investigated clinical data, angiographic characteristics, 10 polymorphisms involved in neointimal hyperplasia and late thrombosis at 6 different levels and their relationship with the major adverse cardiac events (MACE). The long term clinical outcome was defined by MACE: death, target vessel revascularization (PCI or coronary bypass grafting, CABG) and myocardial infarction. Angiotensin receptor type I (AGTR A1166C) and angiotensinogen (AGT MET235THR) GPs correlated with repeat revascularization and total MACE. Carriers of G allele for NOS3 A922G GP were shown to have a significantly lower repeat revascularization rate in comparison with the AA genotype, as did the T allele carriers in the NOS3 C690T GP analysis when compared to the CC genotype. The Asp genome carriers with the NOS3 GLU298ASP GP were also shown to have significantly less re-PCI in contrast to the Glu/Glu genotype. The study could document the protective influence of the 4G/5G GP for plasminogen inhibitor activator-1, which carried the lowest rate of re-PCI and total MACE during the follow-up. GPs for β-1 G-protein subunit GNB3 C825T, fibrinogen FGB G455A and E-selectins Ser128Arg and Leu554Phe did not show statistical correlation with the clinical outcome. The results illustrate the potential use of genetic markers in defining patients with possibly worse clinical outcome after PCI, who may profit from more aggressive prevention of restenosis and late thrombotic complications.

***Key words**: genetic markers, percutaneous coronary intervention, stent, restenosis, late stent thrombosis, clinical outcome*

Introduction

PCI with stenting currently represents the dominant method for treating patients acute and symptomatic coronary artery disease. Two issues dominate the clinical course after stent placement: in-stent restenosis (ISR) and late stent thrombosis (LST). The latter has recently raised particular interest of the interventional cardiologic community, since it was questioned in relation with the safety of drug-eluting stent (DES) placement[1].

Restenosis, defined as »artery healing after injury cause by the transluminal coronary revascularization«[2] has been the main problem since the introduction of coronary angioplasty and stenting. The cause of ISR is intimal hyperplasia based on migration and proliferation of cells originating in the vessel intima. Evolution of restenosis is a complex and not completely understood process. Well known clinical (diabetes) and angiographic (stent length, vessel diameter, bifurcations, complex lesions, total occlusions) predictors do not account for all cases.

There is a vast amount of data on the pivotal role that genetic polymorphisms play in the pathogenesis of a variety of diseases[3–5]. Although numerous genetic markers have been implicated as risk factors for ISR, there are a significant proportion of those who are thought to have protective influence in these patients[6,7]. Several studies have dealt with the role of the renin-angiotensin-aldo-

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sterone system (RAAS) and possible beneficial influence of ACE inhibitors with respect to ISR[8-11]. G-protein polymorphisms have also been investigated in this context, since these molecules play an important role in signal transmission involved in vascular cell proliferation and platelet aggregation[12,13]. Nitric oxide synthase (eNOS) promotes production of nitric oxide (NO) in endothelial cells, which in turn acts as an atheroprotective molecule, due to inhibition of vascular smooth cell proliferation, control of extracellular matrix and regulation of thrombotic and inflammatory vessel wall reaction[14-17]. Furthermore, NO deficiency is related to thrombosis and restenosis at the site of vascular injury inflicted by percutaneous interventions[18]. Fibrinolysis, particularly the plasminogen activator inhibitor (PAI-1), is also linked to the ISR[19], as is shown by experimental and clinical data dealing with fibrinolysis disorders after PCI[20-25]. Increased level of fibrinogen is generally considered as a risk factor for cardiovascular events[26,27], but it was also demonstrated that is may be linked to increased incidence of ISR[28]. Mononuclear cell adhesion represents one of the earliest stages of atherosclerosis and selectins, such as E-selectin, play a prominent role in interaction between leucocytes, endothelial cells and platelets. Increased SES levels were noted in patients who developed restenosis after peripheral angioplasty and coronary stenting[29,30].

Occurrence of complications during long-term follow-up after PCI in a real-world setting is typically evaluated by investigating the rate of major adverse cardiac events (MACE). These include death, repeat revascularization of the target vessel (either by repeat PCI or by coronary bypass grafting, CABG) and myocardial infarction. Repeat revascularization is more likely to be related to the issue of ISR, whereas death and myocardial infarction raise the suspicion of LST.

Since very few published data addressed the mutual relationship of several polymorphisms in terms of their influence on ISR and LST, and the majority of published data did not include a long-term clinical follow-up, we explored these issues with the genetic data obtained in our PCI patients. This is of particular importance since the dominant strategies to manage and prevent these issues, including elective placement of drug-eluting stents (DES) and prolonged and/or intensified dual antiplatelet treatment (acetylsalicylic acid + clopidogrel) may be of limited availability and occasionally carry potential risks.

Subjects and Methods

Patients

A total of 205 consecutive patients admitted to »Magdalena« Hospital for Cardiovascular Surgery and Cardiology, Department of Cardiology, Krapinske Toplice, Croatia were included in this study. The PCI was performed in a standardized manner in all patients, as indicated by their clinical status (stable coronary disease, excluding patients with acute myocardial infarction). All patients received bare metal stents (BMS). Postprocedural therapy did not differ between patients and all had signed an informed consent for the procedure and the additional blood sampling related to genetic markers which were analyzed in this study. Clinical parameters were recorded for all patients, including age, sex, risk factors (diabetes according to WHO definition, arterial hypertension, smoking, hypercholesterolemia) and previous myocardial infarction.

PCI parameters

Periprocedural stenting data included number of vessels with significant stenosis (N), number of lesions (N), number of implanted stents (N), total length of stented segment (mm), average stent diameter (mm). Ejection fraction of the left ventricle (LVEF, %) and presence of chronic total occlusion (CTO) were also noted.

Clinical follow-up

There were two main procedures to obtain the follow-up data. For those patients who were readmitted to the hospital during the follow-up period, data were screened from their hospital charts. The follow-up data for patients who were not readmitted was obtained by means of a standardized transtelephonic contact. The follow-up data included time to occurrence of first major adverse cardiac event (in days), type of MACE (death, revascularization – re-PCI or CABG, and myocardial infarction). The follow-up period for all patients was greater than 5 years. Death was recorded if it was by certain or probable cardiac cause.

Determination of genetic markers

Peripheral blood was sampled after obtaining prior written informed consent. DNA was extracted and further processed by polymerase chain reaction (PCR). The methods for determining genetic polymorphisms were previously described elsewhere[31]. The results of the following genetic polymorphism analysis were used in this study: AGTR1 A1166C, GNB3 C825T, PAI1 5G/4G, NOS3 A(-922)G, NOS3 C(-690)T, NOS3 GLU298ASP, AGT MET235THR, SELE SER128ARG, SELELEU-554PHE, FGB G(-455)A. The clinical outcome variables (MACE, i.e. re-PCI, CABG, IM, death) were then analyzed with respect to specific genetic polymorphisms.

Statistical analysis

Discrete variables were expresses as whole numbers or percentage and compared using chi-square or Fisher exact test. Continuous variables were expressed as median value ± standard deviation and compared using two sample t-test or variance analyses for more than two groups. P value of less than 0.5 was considered statistically significant.

Ethical considerations

This study was approved in 2004 by the Ethics committee of the »J. J. Strossmayer« University, School of Medicine, and by the Ethics committee of the »Magdale-

na« Hospital for Cardiovascular Surgery and Cardiology, Department of Cardiology, Krapinske Toplice, Croatia

Results

190 out of 205 patients (92.7%) completed the follow-up and qualified for statistical analysis. MACE data for all patients were obtained 5 years after the initial PCI, so that all patients had a follow-up period of ≥1,825 days. The mean value of follow-up period for patients free of MACE was 1,917.4±214.1 days (range 1,825 to 2,187), whereas for the patients with one of the MACE it was 701.3±600.6 days (1,825 to 1,945). This difference was statistically significant.

Patient clinical and angiographic characteristics for the two groups, according to total MACE are listed in Table 1. Group 1 indicates patients who were free of MACE, whereas group 2 includes patients who experienced one of the MACE during the follow-up period. The incidence of any MACE was 26.3% (N=50 patients). The groups did not differ in clinical characteristics, except for diabetes and previous myocardial infarction (although the latter was not reflected in difference in LVEF). The incidence of MACE was higher in patients with more diseased vessels, more lesions and with smaller stent diameter; interestingly, patients with PCI of CTO had fewer events during the follow-up.

Table 2 shows the results genetic polymorphism analysis according to long-term clinical outcome. Follow-up data have been grouped in by most likely event mechanism. Repeat revascularization of the target vessel because of in-stent restenosis was related to re-PCI and CABG, whereas late thrombotic complications and/or disease progression were best described by death and myocardial infarction.

The genetic marker for angiotensinogen II receptor type I (AGTR A1166C) showed that C allele carriers have statistically significant higher risk for re-PCI and MI, in contrast to subjects without the C allele. With angiotensinogen polymorphism (AGT MET235THR), M allele carriers (MM and MT, TM) showed significant differences in comparison with the TT genotype, with the M allele carrier status conferring a higher risk for re-PCI, combined outcome of re-PCI and CABG, as well as total events during follow-up. Three genetic polymorphisms for nitric oxide synthase were investigated. NOS3 A922G marker showed significant difference between G allele carriers and AA genotype with respect to revascularization events (re-PCI, re-PCI + CABG). T allele carriers in the NOS3 C690T polymorphism analysis had significantly fewer major adverse cardiac events, in contrast to CC genotype. NOS3 GLU298ASP marker study showed a protective influence for in-stent restenosis in Asp carriers (they had significantly lower rate of re-PCI than Glu/Glu genotype). However, presence of Asp allele was an adverse factor for late thrombotic events or disease progression, since these subjects had significantly higher rate of the combined event of myocardial infarction and death during the follow-up.

TABLE 1
CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS OF PCI PATIENTS WITH STENT IMPLANTATION WITH RESPECT TO FOLLOW-UP OUTCOME.

Clinical characteristics	Group 1 (N=140)	Group 2 (N=50)
Age (years)	57.9±9.6 (20–82)	59.1±9.6 (40–80)
Gender		
Male (N)	111 (79.3%)	36 (72.0%)
Female (N)	29 (20.7%)	14 (28.0%)
Arterial hypertension (N)	75 (53.6%)	32 (64.0%)
Diabetes (N)	23 (16.4%)	10 (20.0%)*
Blood glucose (mmol/L)	6.6±2.4	6.9±2.9
Smoking (N)	17 (12.1%)	8 (16.0%)
Previous infarction (N)	77 (55.0%)	20 (40.0%)*
Total cholesterol (mmol/L)	6.1±1.4	5.7±1.9
HDL	1.0±0.3	1.0±0.3
LDL	4.2±1.3	3.9±1.8
Triglycerides (mmol/L)	2.2±1.1	2.1±0.8
Fibrinogen (mmol/L)	3.4±0.9	3.9±1.9

Results for the plasminogen activator inhibitor-1 marker (PAI1 5G/4G) showed significant difference for the 4G5G genotype and re-PCI, total MACE (lowest rate) and death (highest rate).

The genetic polymorphism analysis for the G-protein β-1 subunit (GNB3 C825T), fibrinogen (FGB G455A) and E-selectin (SELE Ser128Arg and SELE Leu554Phe) did not show any significant differences for the observed parameters.

Discussion

In terms of clinical characteristics, the results of this study correspond with the well-known fact that diabetes is a definite risk factor for an increased incidence of MACE in patients after PCI with stenting. This could also be documented in our results after more than 5 years of follow-up. However, albeit significant, the difference observed in our patient series (total MACE 20.0% for diabetics *vs.* 16.4% for non-diabetics) was still less prominent than is usually found in the literature. This is explained by the revascularization indication policy, which consistently favored surgery for diabetic patients and this was particularly emphasized by the fact that the PCI patient were scheduled to receive bare-metal and not drug-eluting stents. Overall risk profile of study patients did not differ significantly from the profile found in Croatian coronary patients[32].

The analysis of angiographic findings with respect to the long-term outcome also showed the expected trend for excess in MACE with patients who had multivessel disease, more lesions and smaller stent diameter; however, this was not the case for total stent length and occurrence of CTO recanalization. The latter may be at-

TABLE 2
GENETIC POLYMORPHISMS OF PCI PATIENTS WITH STENT IMPLANTATION WITH RESPECT TO FOLLOW-UP OUTCOME

Genetic polymorphism		Patients	MACE		
		N	Re-PCI + CABG	MI + death	Total
Angiotensin II receptor– type I AGTR A1166C	AA	100 (52.6%)	13 (13.0%)*	10 (10.0%)	23 (23.0%)
	AC,CA + CC	90 (47.4%)	21 (23.3%)	6 (6.6%)	27 (29.9%)
Angiotensinogen AGT MET235THR	MM + MT,TM	145 (76.3%)	28 (19.2%)*	13 (9.0%)	41 (28.3%)*
	TT	45 (23.7%)	6 (13.3%)	3 (6.6%)	9 (19.9%)
G-protein β-1 subunit GNB3 C825T	CC	91 (47.8%)	17 (18.7%)	8 (8.8%)	25 (27.5%)
	CT,TC + TT	99 (52.2%)	17 (17.0%)	8 (8.0%)	25 (25.0%)
Nitric oxide synthase NOS3 A922G	AA	76 (40.0%)	16 (21.1%)	6 (7.8%)	22 (28.9%)
	AG, GA + GG	114 (60.0%)	18 (15.8%)*	10 (8.8%)	28 (24.6%)
NOS3 C690T	CC	144 (75.8%)	14 (9.8%)	6 (7.8%)	43 (29.9%)
	CT, TC + TT	46 (24.2%)	2 (4.4%)*	10 (8.8%)	7 (15.3%)*
NOS3 GLU298ASP	Glu/Glu	97 (51.1%)	25 (25.7%)	6 (6.2%)*	31 (31.9%)
	Glu/Asp+Asp/Asp	93 (48.9%)	9 (9.7%)*	11 (11.8%)*	20 (21.5%)*
Plasminogen inhibitor activator-1 PAI1 5G/4G	4G4G	42 (22.1%)	10 (23.8%)	4 (9.5%)	14 (33.3%)
	4G5G	101 (53.2%)	15 (14.9%)*	9 (8.9%)	24 (15.0%)*
	5G5G	47 (24.7%)	9 (19.1%)	3 (6.4%)	12 (25.5%)
Fibrinogen FGB G455A	GG	107 (56.3%)	18 (16.8%)	10 (9.4%)	28 (26.2%)
	GA, AG + AA	83 (43.7%)	16 (19.3%)	6 (7.2%)	22 (26.5%)
E-selectin SELE Ser128Arg	Ser/Ser	154 (81.1%)	30 (19.4%)	12 (7.7%)	42 (27.1%)
	Ser/Arg	35 (18.4%)	4 (11.4%)	4 (11.4%)	8 (22.8%)
	Arg/Arg	1 (0.5%)	–	–	–
SELE Leu554Phe	Leu/Leu	170 (89.5%)	31 (18.2%)	14 (8.2%)	45 (26.4%)
	Leu/Phe	20 (10.5%)	3 (15.0%)	2 (10.0%)	5 (25.0%)

MACE are grouped by most likely mechanism (re-PCI + CABG – ISR *vs.* MI + death – LST and/or disease progression); PCI = percutaneous coronary intervention; MACE = major adverse coronary events; re-PCI = repeat percutaneous coronary intervention; CABG = coronary artery bypass grafting; MI = myocardial infarction; LST = late stent thrombosis. *$p<0.05$.

tributed to the relatively small proportion of CTO patients, whereas the stenting tactics with consistent use of high pressure inflation and relative oversizing may in part explain the fact that the length of stented segment did not significantly affect the long-term success.

With respect to the genetic markers involved in the action of the renin-angiotensin-aldosterone system (RAAS), there are reports that document that the polymorphism A1166C found in the 3'-non-coding region of the gene for angiotensin II type I receptor in subjects with CC genotype is linked to increased vasoconstriction through a not yet well-understood mechanism[33,34]. Our results support the fact that C allele carriers have an increased risk for re-PCI and myocardial infarction; possible influence of concomitant ACE inhibitor therapy was not subject of this investigation. The angiotensinogen polymorphism analysis (AGT MET235THR) is also consistent with prevalent data from the literature[35]. The study by Toyofuku et al.[36] showed that 235T homozygotes experience a significant beneficial effect of ACE inhibitor therapy with respect to ISR. Indeed, our results confirmed this observation, since they showed, irrespective of ACE inhibitor treatment, a protective influence of the TT genotype in context of restenosis. Conversely, the M allele represents a genetic risk factor and carries an increased incidence of re-PCI, combined outcome of re-PCI + CABG, and total number of MACE during the follow-up period.

Nitric oxide is a known factor in vascular tone control[37,38], free superoxide radicals scavenger and inhibitor of platelet aggregation, leukocyte adhesion and smooth muscle cell proliferation[39]. One previous study with another eNOS genetic marker[40] showed that the TT genome was related to increased risk of death or myocardial infarction, but not with clinical outcomes implying in-stent restenosis (i.e. re-PCI or CABG). Our study demonstrated similar results for the Asp genotype of the NOS3 GLU298ASP polymorphism, since we could show a protective effect on ISR in Asp carriers (they had significantly lower incidence of re-PCI than the Glu/Glu genotype). However, the presence of the Asp allele was shown to be adverse factor for late thrombotic events, since

these subjects had an excess of combined outcome of infarction and death in the long-term follow-up. Nevertheless, because of the prevalent share of re-PCI in total MACE, this was still linked with favorable outcome.

Our results indicate that the polymorphism of the 4G5G gene for plasminogen activator inhibitor-1 (PAI-1) is associated with reduced incidence of ISR. This data is consistent with previous observations[41], however, there are in sharp contrast with one earlier study, which found no association between outcome after stenting and genetic profile for PAI-1[42]. Nevertheless, pathophysiologic mechanism does provide a basis for the role of PAI-1 in development of ISR. PAI-1 is considered an important factor in thrombosis initiation and myocardial infarction; on the other hand, the pathophysiologic processes of healing are similar to those involved in ISR[43]. Data from our investigation suggest that PAI-1 may play a role in prediction of ISR, namely that the 4G5G polymorphism variant is associated with decreased incidence of re-PCI as clinical outcome.

In our series we found no correlation between genetic markers for G-protein β-1 subunit and fibrinogen[44], so we conclude that these polymorphisms are less likely to be used for possible detection of patients who will develop restenosis and/or late thrombotic event after PCI. In contrast, previous studies have shown that the 128Arg allele for E-selectin is related to premature atherosclerosis[45] and early onset of coronary artery disease[46]. In general, the relationship between E-selectin polymorphisms and de novo atherosclerotic lesions, as well as lesions that occur after interventional procedures, may be linked to the well known role of E-selectin on interactions of endothelial cells. The family of selectin adhesion molecules participates in leukocyte turnover and is essential for leukocyte adhesion at the site of inflammatory reaction. Selectins are considered fundamental for regulating the immunologic response of injured endothelial cells[47]. However, the results of this study do not support the relationship between investigated polymorphisms for E-selectin and clinical outcome, which stands in contrast to findings in the literature. With respect to conflicting results for genetic markers of atherosclerosis, this is not an uncommon finding in the literature[48]. Our results could be interpreted by distribution of genes in this specific population, although we may conclude that these genes may not be used as reliable markers for clinical outcome in this group of patients.

This study investigated the relation of clinical outcome to a total of 10 genetic polymorphisms which represent pathophysiologic mechanisms on 6 different levels included in processes of in-stent restenosis and late thrombotic events. Re-PCI and CABG were primarily clinical events linked with ISR, whereas death and myocardial infarction are manifestations of late thrombotic events or progression of underlying coronary disease.

In conclusion, genetic polymorphisms may be assigned in two groups with respect to their clinical outcome after PCI:

Positive influence	Negative influence
AA genotype of AGTR A1166C polymorphism	M allele carriers in AGT MET235THR
G allele carriers of NOS3 A922G polymorphism	
Carriers of T allele in NOS3 C690T polymorphism analysis	
Carriers of Asp genome in NOS3 GLU298ASP polymorphism	
4G/5G polymorphism for plasminogen inhibitor activator-1	

Interactive effects of multiple genetic factors and environmental influence on final phenotype of the complex pathological entity of coronary artery disease treated interventionally with stents reflect the general complexity of processes in cardiovascular medicine, so that surely further studies with more patients will be needed in order to confirm the findings of this study as relevant for clinical practice. The final result of such investigations could certainly mean identification of those genetic predictors which will reliably determine the clinical outcome after PCI.

REFERENCES

1. PFISTERER M, BRUNNER-LA ROCCA HP, BUSER PT, RICKENBACHER P, HUNZIKER P, MUELLER C, JEGER R, BADER F, OSSWALD S, KAISER CJ, Am Coll Cardiol, 48 (2006) 2584. — 2. SCHWARTZ RS, Animal models of human coronary restenosis. In: TOPOL EJ (Ed) Textbook of Interventional Cardiology (W.B. Saunders, 1994). — 3. BAŠIĆ BARONICA K, MLINAC K, OZRETIĆ D, VLADIĆ A, KALANJ BOGNAR S, Coll Antropol, 35 (2011) 11. — 4. NEDIĆ G, BOROVEČKI F, KLEPAC N, MUBRIN Z, HAJNŠEK S, NIKOLAC M, MUCK-SELER D, PIVAC N, Coll Antropol, 35 (2011) 79. — 5. LOZIĆ B, PRIMORAC D, GLAVINIĆ R, KUZMANIĆ ŠAMIJA R, ZEMUNIK T, Coll Antropol, 35 (2011) 385. — 6. KASTRATI A, DIRSCHINGER J, SCHOMIG A, Herz, 25 (2000) 34. — 7. KASTRATI A, KOCH W, BERGER PB, MEHILLI J, STEPHENSON K, NEUMANN FJ, VON BECKERATH N, BÖTTIGER C, DUFF GW, SCHÖMIG A, J Am Coll Cardiol, 36 (2000) 2168. — 8. POWELL JS, CLOZEL JP, MULLER RKM, Am J Pathol, 139 (1991) 1291. — 9. DESMET W, VROLIX M, DE SCHEERDER I, VAN LIERDE J, WILLIAMS JL, PIESSENS J, Circulation, 89 (1994) 385. — 10. MERCATOR STUDY GROUP, Circulation, 86 (1992) 100. — 11. FAXON DP, J Am Coll Cardiol, 25 (1995) 362. — 12. VON BECKERATH N, SCHUSTERSCHITZ Y, KOCH W, GRIESSER K, MEHILLI J, GORCHAKOVA O, SCHÖMIG A, KASTRATI A, Atherosclerosis, 167 (2003) 135. — 13. FREY UH, ARAL N, MULLER N, SIFFERT W, Thromb Res, 109 (2003) 279. — 14. NATHAN C, XIE Q, Cell, 78 (1994) 915. — 15. LLOYD-JONES DM, BLOCH KD, Annu Rev Med, 47 (1996) 365. — 16. WEVER RM, LÜSCHER TF, COSENTINO F, RABELINK TJ, Circulation, 97 (1998) 108. — 17. IGNARRO LJ, Annu Rev Pharmacol Toxicol, 30 (1990) 535. — 18. MONCADA S, PALMER RM, HIGGS EA, Pharmacol Rev, 43 (1991) 109. — 19. KOHLER HP, GRANT PJ, N Engl J Med, 342 (2000) 1792. — 20. HUBER K, JÖRG M, PROBST P, SCHUSTER E, LANG I, KAINDL F, BINDER BR, Thromb Haemost, 67 (1992) 209. — 21. SAKATA K, MIURA F, SUGINO H, SHINOBE M, SHIROTANI M, YOSHIDA H, MORI N, HOSHINO T, TAKADA A, Am Heart J, 131 (1996) 1. — 22. ISHIWATA S, TUKADA T, NAKANISHI S, NISHIYAMA S, SEKI A, Am Heart J, 133 (1997) 387. — 23. STRAUSS BH, LAU HK, BOWMAN KA,

SPARKES J, CHISHOLM RJ, GARVEY MB, FENKELL LL, NATARAJAN MK, SINGH I, TEITEL JM, Circulation, 100 (1999) 1616. — 24. FORNITZ GG, NIELSEN P, AMTORP O, KASSIS E, ABILDGÅRD U, SLOTH C, WINTHER K, ØRSKOV H, DALSGÅRD J, HUSTED S, Eur J Clin Invest, 31 (2001) 586. — 25. PRISCO D, FEDI S, ANTONUCCI E, CAPANNI M, CHIARUGI L, CHIOCCIOLI M, FALAI M, GIGLIOLI C, ABBATE R, GENSINI GF, Thromb Res, 104 (2001) 181. — 26. WILHELMSEN LSK, KORSAN-BENGTSEN K, LARSSON B, WELIN L, TIBBLIN G, N Engl J Med, 311 (1984) 501. — 27. YARNELL JW, BAKER IA, SWEETNAM PM, BAINTON D, O'BRIEN JR, WHITEHEAD PJ, ELWOOD PC, Circulation, 83 (1991) 836. — 28. OTSUKA M, HAYASHI Y, UEDA H, IMAZU M, KOHNO N, Atherosclerosis, 164 (2002) 371. — 29. BELCH JJ, SHAW JW, KIRK G, MCLAREN M, ROBB R, MAPLE C, MORSE P, Circulation, 95 (1997) 2027. — 30. RAUCHHAUS M, GROSS M, SCHULZ S, FRANCIS DP, GREISER P, NORWIG A, WEIDHASE L, COATS AJ, DIETZ R, ANKER SD, GLÄSER C, Intern J Cardiol, 83 (2002) 249. — 31. FERENČAK G, PAŠALIĆ D, GRŠKOVIĆ B, CHENG S, FIJAL B, ŠESTO M, SKODLAR J, RUKAVINA AS, Clin Chem Lab Med, 41 (2003) 541. — 32. PEĆIN I, MILIČIĆ D, JURIN H, REINER Ž, Coll Antropol, 36 (2012) 369. — 33. DANSER AHJ, SCHUNKERT H, Eur J Phamacol, 410 (2000) 303. — 34. MARKOVIĆ BB, BERGOVEC M, REINER Z, SERTIĆ J, VINCELJ J, MARKOVIĆ M, Coll Antropol, 31 (2007) 179. — 35. RAKUGI H, KIM DK, KRIEGER JE, WANG DS, DZAU VJ, PRATT RE, J Clin Invest, 93 (1994) 339. — 36. TOYOFUKU M, IMAZU M, SUMII K, YAMAMOTO H, HAYASHI Y, HIYAMA K, KOHNO N, Atherosclerosis, 160 (2002) 339. — 37. MONCADA S, PALMER RMJ, HIGGS EA, Pharmacol Rev, 43 (1991) 109. — 38. LOSCALZO J, WELCH G, Prog Cardiovasc Dis, 38 (1995) 87. — 39. LEFER AM, Circulation, 95 (1997) 553. — 40. GORCHAKOVA O, KOCH W, VON BECKERATH N, MEHILLI J, SCHÖMIG A, KASTRATI A, Eur Heart J, 24 (2003) 820. — 41. ORTLEPP JR, HOFFMANN R, KILLIAN A, LAUSCHER J, MERKELBACH-BRESE S, HANRATH P, Clin Cardiol, 24 (2001) 585. — 42. BÖTTIGER C, KOCH W, LAHN C, MEHILLI J, VON BECKERATH N, SCHÖMIG A, KASTRATI A, Am Heart J, 146 (2003) 855. — 43. VIRMANI R, FARB A, Curr Opin Lipidol, 10 (1999) 499. — 44. PULANIĆ D, RUDAN I, Coll Antropol, 29 (2005) 341. — 45. WENZEL K, FELIX S, KLEBER FX, BRACHOLD R, MENKE T, SCHATTKE S, SCHULTE KL, GLÄSER C, ROHDE K, BAUMANN G, Hum Mol Genet, 3 (1994) 1935. — 46. YE SQ, USHER D, VIRGIL D, ZHANG LQ, YOCHIM SE, GUPTA R, J Biomed Sci, 6 (1999) 18. — 47. HALLER H, Drugs, 53 (1997) 1. — 48. ŠMALCELJ A, SERTIĆ J, GOLUBIĆ K, JURCIĆ L, BANFIĆ L, BRIDA M, Coll Antropol, 33 (2009) 933.

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POVEZANOST GENSKIH BILJEGA ATEROSKLEROZE I DUGOROČNOG ISHODA NAKON PERKUTANE KORONARNE INTERVENCIJE SA STENTOM

S A Ž E T A K

Cilj ovog ispitivanja bio je opisati povezanost kliničkog ishoda nakon perkutane koronarne intervencije (PCI) sa stentom i genskih polimorfizama (GP) za koje je poznato da su u odnosu s incidencijom in-stent restenoze i kasnih trombotskih komplikacija. Ispitivanje je uključilo 190 bolesnika sa standardiziranom kliničkim praćenjem tijekom više od 5 godina, koji su inicijalno liječeni s PCI. Ispitivali smo kliničke podatke, angiografske značajke, 10 polimorfizama koji su povezani s neointimalnom hiperplazijom i kasnom trombozom na 6 različitih razina te njihov odnos s glavnim neželjenim kardijalnim događajima (MACE). Dugoročni klinički ishod bio je definiran pomoću MACE: smrt, revaskularizacija ciljne žile (PCI ili koronarne premosnice, CABG) i infarkt miokarda. GP-i za angiotenzinski receptor tipa I (AGTR A1166C) i angiotenzinogen (AGT MET235THR) bili su povezani s ponovno revaskularizacijom i ukupnim MACE. Dokazano je da nositelji G alela za NOS3 A922G GP imaju značajno nižu stopu ponovne revaskularizacije u usporedbi s AA genotipom, što je bio slučaj i s nositeljima T alela u analizi NOS3 C690T GP-a, u usporedbi s CC genotipom. Također je dokazano da nositelji Asp genoma u NOS3 GLU298ASP GP-u imaju značajno manje re-PCI, za razliku od Glu/Glu genotipa. Ispitivanje je dokumentiralo i zaštitni utjecaj 4G/5G GP-a za inhibitor aktivatora plazminogena-1, koji je bio povezan s najnižom stopom re-PCI i ukupnih MACE tijekom praćenja. GP-i za β-1 G-protein podjedinicu GNB3 C825T, fibrinogen FGB G455A i E-selektine Ser128Arg i Leu554Phe nisu pokazali statističku korelaciju s kliničkim ishodom. Rezultati opisuju moguću primjenu genskih biljega u određivanju bolesnika s vjerojatnim lošijom ishodom nakon PCI, koji bi mogli imati koristi od agresivnije prevencije restenoze i kasnih trombotskih komplikacija.