New insights in mechanism, diagnosis and treatment of myocardial infarction

Bergheanu, S.C.

CHAPTER 9

THE 5352 A ALLELE OF THE PRO-INFLAMMATORY CASPASE-1 GENE PREDICTS LATE ACQUIRED STENT MALAPPOSITION IN STEMI PATIENTS TREATED WITH SIROLIMUS STENTS

ABSTRACT

Late acquired stent malapposition (LASM) is a common finding after sirolimus-eluting stent (SES) implantation and may be the cause for late stent thrombosis. Inflammation may play a pivotal role in LASM just as it plays in stent restenosis. We have therefore investigated 7 polymorphisms involved in inflammatory processes, related in previous reports to restenosis, on the risk of LASM in SES patients. Patients with ST-elevation myocardial infarction who underwent SES implantation and had intravascular ultrasonography (IVUS) data available for both immediate post-intervention and 9-month follow-up were included in the present study. In total, 104 patients from the MISSION! intervention study were genotyped for the caspase-1 5352 G/A, eotaxin 1382 A/G, CD14 260 A/G , colony stimulating factor 2 1943 C/T, IL10 -1117 C/T , IL10 4251 C/T and the tumor necrosis factor alpha 1211 C/T polymorphisms. LASM occurred in 26/104 (25%) of patients. We found a significantly higher risk for LASM in patients carrying the caspase-1 (CASP1) 5352 A allele (RR= 2.32; 95% CI 1.22-4.42). In addition, mean neointimal growth was significantly lower in patients carrying this LASM risk allele (1.6 vs 4.1%, p=0.014). The other 6 polymorphisms related to inflammation were not significantly related to the risk of LASM. In conclusion, carriers of the 5352 A allele in the caspase-1 gene are at increased risk of developing LASM after SES implantation. If this is confirmed in larger studies, screening for this polymorphism in patients undergoing percutaneous coronary interventions could eventually help cardiologists to better select between commercially available stents.

Keywords: inflammation, genes, stents, pathology

Sandrin C Bergheanu, MD[a,b,c]; Douwe Pons,MD[a,b]; Bas L van der Hoeven, MD, PhD[a]; Su-San Liem, MD[a]; Bob Siegerink, MsC[b]; Martin J Schalij, MD, PhD[a]; Johanna G van der Bom, MD, PhD[b,c] and J Wouter Jukema, MD, PhD[a,c,d]

[a]Department of Cardiology, [b]Department of Clinical Epidemiology, [c]Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden, and [d]Durrer Institute for Cardiogenetic Research, Amsterdam, The Netherlands.

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INTRODUCTION

Over the past years concerns were raised with regard to the long-term safety of coronary stents, mostly related to the fearful complication of late stent thrombosis. Several studies reported stent thrombosis to occur more frequently after drug-eluting stents (DES) than bare-metal stents (BMS) implantation[1-3] and to be associated with underlying stent malapposition.[4-6] Stent malapposition, as detected by intravascular ultrasonography (IVUS), represents a separation of the stent struts from the intimal surface of the arterial wall (in the absence of a side branch) with evidence of blood speckles behind the struts .[7] Stent malapposition may be acute (present immediately after implantation), persistent (present both immediately after implantation and at follow-up) or late acquired (present only at follow-up).

Intravascular ultrasonography (IVUS) studies have repeatedly identified positive vessel remodeling as the main mechanism of late acquired stent malapposition (LASM).[6,8-10] Positive remodeling is a complex process characterized by a regional increase in the vessel wall diameter.[7] A hypersensitivity reaction to the polymer coating of DES[9] and induction of apoptosis by sirolimus may lead to positive remodeling.[11,12]

In the GENDER study,[13] 7 polymorphisms located in the caspase-1,[14] eotaxin, CD14, colony stimulating factor 2 (CSF2),[15] interleukin 10 (IL10)[16] and tumor necrosis factor alpha (TNFα) genes,[17] were found significantly associated with clinical restenosis after a percutaneous coronary intervention (PCI) for stable angina pectoris. Besides its established role in restenosis, inflammation may also play an important role in LASM after DES implantation. On the long term, stent malapposition may be the consequence of chronic inflammation and delayed healing, resulting in tissue necrosis and erosion around the stent.[18]

In the present study we aimed at investigating these 7 inflammatory polymorphisms with regard to LASM and neointimal growth in a population of ST-elevation myocardial infarction patients treated by primary PCI with sirolimus-eluting stents (SES) in the prospective MISSION! Intervention Study.[19]

METHODS

IVUS measurements

Details about the MISSION! protocol and the MISSION! Intervention Study have been published elsewhere.[19,20] In brief, MISSION! Intervention Study was a single center, single blind, randomized prospective study to evaluate clinical, angiographic and IVUS results in documented acute STEMI patients treated with either BMS (Vision™, Guidant Corp. Indianapolis, Indiana, USA) or SES (Cypher™, Cordis Corp. Miami Lakes, Florida, USA). The study protocol was approved by the institutional ethical committee. Patients and operators performing the follow-up angiography were blinded to the treatment assignment. The study was conducted from February 2004

to October 2006. Patients had an IVUS examination immediately after the stent deployment and at nine-month follow-up. LASM at 9 months was common after SES implantation (26/104 patients, 25.0 %) but rare after BMS implantation (4/80 patients, 5.0%).[6] As a consequence, in the present study an analysis on LASM was conducted only for the SES group.

IVUS images were analyzed off-line, using quantitative IVUS analysis software (QCU-CMS 4.14, Medis, Leiden, The Netherlands).[21] After determining vessel, stent and lumen contours, their volumes were automatically calculated.

LASM was defined as stent malapposition present at 9-month follow-up IVUS examination but absent at immediate post-intervention IVUS examination. We have therefore examined first the follow-up IVUS images in order to identify cases of stent malapposition. After identification, IVUS images of follow-up and immediate post-intervention procedures were analyzed side-by-side in order to discriminate the late-acquired stent malapposition cases.

The neointima growth (%) at nine months was calculated with the formula: [stent volume(mm^3) – lumen volume(mm^3) in the stented region]/stent volume(mm^3) and represents the amount of new intimal tissue growth inside the stent as a fraction of the stent volume.

All patients gave informed consent before the procedure. An additional informed consent was obtained for follow-up angiography and IVUS at nine months. Patients were considered to have dislipidemia, hypertension and diabetes if they had been diagnosed such by a physician previous to the present myocardial infarction admission. IVUS imaging was performed with motorized pull-back (0.5mm/s) starting at least 10 mm distal to the stent and ending at the coronary ostium, using a 2.9F 20MHz catheter and a dedicated IVUS console (Eagle Eye, Volcano Corp. Rancho Cordova, California, USA).[22] Each angiogram and ultrasound sequence was preceded by 200-300μg of intracoronary nitroglycerin. After the initial procedure aspirin (100 mg/day) was prescribed indefinitely and clopidogrel (75 mg/day) for twelve months. During follow-up, patients were treated with beta-blockers, statins and ACE-inhibitors or ATII-blockers, according to current guidelines.[20]

Genotyping

Blood was collected in EDTA tubes upon admission to hospital and genomic DNA was extracted following standard procedures. A multiplex assay which included the caspase 1 (CASP1) 5352 A/G (rs580253), eotaxin (*CCL11*) -1382 A/G (rs4795895), CD14 -260 A/G (rs2569190), colony stimulating factor 2 (*CSF2*)1943 C/T (rs25882), IL10 -1117 C/T (rs1800896), IL10 4251 C/T (rs3024498) and the tumor necrosis factor alpha (*TNFα*) -1211 C/T (rs1799964) polymorphisms, was designed using Assay designer software (Sequenom). All PCR reactions had a final volume of 5 μl and contained standard reagents and 5 ng of genomic DNA. After PCR a primer extension reaction was performed to introduce mass-differences between alleles and, after removing salts by adding resin, approximately 15 nl of the product was

spotted onto a target chip with a 384 patches containing matrix. Mass differences were detected using an Autoflex (Bruker) matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF) and genotypes were assigned real-time using Typer 4.0 software (Sequenom). Cluster plots were made of the signals from the low and the high mass allele. Two independent researchers carried out the scoring. There were neither disagreements nor vaguely positioned dots produced by Genotyper 3.0 (Sequenom Inc.).

Data analysis

Allele frequencies were determined by gene counting. The Chi-squared test was used to test the consistency of the genotype frequencies at the SNP locus with Hardy-Weinberg equilibrium. Relative risks (RR) with 95% confidence intervals (CI) were calculated with the Chi-Square test. If less than 10 patients were homozygous for a particular allele, the homozygotes and heterozygotes were combined. Differences in neointima formation, as measured by IVUS, were calculated and compared using a Student's t-test. Differences in baseline characteristics between genotypes were assessed with Student's t-test (for continuous variables) and Chi-Square test (for categorical variables). Population attributable risk was calculated as [f(RR-1)]/[1+f(RR-1)], where f is the frequency of the genotype(s) of interest in the present SES population and RR is the relative risk for LASM. A p-value <0.05 was considered statistically significant.The SPSS software (version 15.0, SPSS Inc, Chicago, IL) was used for all statistical analyses.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

A total number of 104 SES patients with complete IVUS data were analyzed from our MISSION! Intervention Study database. The baseline characteristics are presented in Table 1.

Of all clinical and procedural factors analyzed, only the absence of diabetes seemed to predict LASM: none of the 10 diabetic patients and 26 of the 93 non-diabetic patients presented LASM. The 10 diabetic patients in our SES population also had more neointimal growth when compared to non-diabetics (8.9 vs. 2.7%, p=0.014).

The RR for LASM of all 7 polymorphisms are presented in table 2.

The CASP1 5352 G/A polymorphism was significantly associated with the risk for LASM: carriers of the CASP1 A allele were at clearly higher risk of developing LASM than homozygous wild type patients (41.9% vs 18.1, RR=2.3, 95%CI: 1.22-4.42). They also had less neointimal growth than patients not carrying the CASP1 A risk allele (1.6 vs. 4.1%, p=0.014). Only one patient was homozygous for the CASP1 A allele and was included in the heterozygous group in all analyses.

Table 1. Baseline clinical and angiographic characteristics. Adapted from van der Hoeven et al.[6]

Characteristic	Sirolimus-eluting stents (N=104)
Age (yrs)	58.6±11.5
Male sex – No.(%)	76 (73.1)
Diabetes mellitus – No.(%)	10 (9.6)
Current smoker – No.(%)	62 (59.6)
Hypercholesterolemia – No.(%)	22 (21.2)
Hypertension – No.(%)	36 (34.6)
Family history of CAD – No.(%)	45 (43.3)
Prior myocardial infarction – No.(%)	5 (4.8)
Prior PCI or CABG – No.(%)	2 (1.9)
Target vessel – No.(%)	
LAD	60 (57.7)
RCA	25 (24.0)
LCX	19 (18.3)
Multivessel disease – No.(%)	37 (35.6)
TIMI flow – No.(%)	
0-1	73 (70.2)
2-3	31 (29.8)
Vessel reference diameter (mm)	2.81±0.56
Minimal luminal diameter (mm)	0.23±0.36
Diameter stenosis (%)	92.0±12.4

Values are means (±SD) or numbers (percentages). CABG = coronary artery bypass graft; CAD = coronary artery disease; LAD = left anterior descending, LCX = left circumflex, PCI = percutaneous coronary artery, RCA = right coronary artery.

There were no significant differences in baseline characteristics in the GG vs. (AA+AG) genotypes of the CASP1 5352 G/A polymorphism (Table 3).

In the present sirolimus-eluting stent population the frequency of the AA+AG genotypes was (31/103) =30%. Population attributable risk (PAR) in sirolimus-eluting stent population was therefore [0.3*(2.3-1)]/[1+0.3*(2.3-1)]=28 %.

DISCUSSION

In this study we investigated the influence of 7 polymorphisms involved in inflammatory processes on LASM and neonitimal growth in SES patients. We found that of these polymorphisms, the caspase-1 5352 G/A polymorphism was a strong predictor of LASM. Moreover, there was a clear inverse relation between LASM risk and the

Table 2. Relative risk for late aquired stent malapposition in sirolimus-eluting stent patients.

SNP	N	LASM N (%)	RR (95%CI) for LASM
CASP1 5352 G/A	103	26	
GG	72	13(18.1)	1.0 (ref)
GA	30	13(43.3)	2.4 (1.27-4.55)
AA	1	0(0)	NA
GA+AA*	31	13(41.9)	2.32 (1.22-4.42)
CCL11-1382 A/G	104	26	
AA	78	21(26.9)	1.0 (ref)
AG	25	5(20)	0.74 (0.31-1.67)
GG	1	0(0)	NA
AG+GG*	26	5(19.2)	0.71 (0.3-1.7)
CD14 -260 A/G	104	26	
AA	32	12(37.5)	1.0 (ref)
AG	50	7(14.0)	0.37 (0.16-0.85)
GG	22	7(31.8)	0.85 (0.4-1.8)
CSF2 1943 C/T	104	26	
CC	60	13(21.7)	1.0 (ref)
CT	35	10(28.6)	1.32 (0.65-2.69)
TT	9	3(33.3)	1.54 (0.54-4.36)
CT+TT*	44	13(29.5)	1.36 (0.7-2.65)
IL10 -1117 C/T	104	26	
CC	29	9(31.0)	1.0 (ref)
CT	49	11(22.4)	0.72 (0.34-1.53)
TT	26	6(23.1)	0.74 (0.3-1.8)
IL10 4251 C/T	104	26	
CC	59	18(30.5)	1.0 (ref)
CT	36	7(19.4)	0.64 (0.3-1.37)
TT	9	1(11.1)	0.36 (0.06-2.4)
CT+TT*	45	8(17.8)	0.58 (0.28-1.22)
TNF -1211 C/T	103	26	
CC	65	19(29.2)	1.0 (ref)
CT	31	5(16.1)	0.55 (0.23-1.34)
TT	7	2(28.6)	0.98 (0.29-3.35)
CT+TT*	38	7(18.4)	0.63 (0.29-1.36)

*A dominant model was used. LASM = late-acquired stent malapposition. NA = not applicable. RR = relative risk. SNP= single nucleotide polymorphism.

amount of neointimal growth. This polymorphism has previously been identified to play a role in clinical restenosis after PCI.[14]

The caspase family of cysteine proteases is a key component in signal transduction cascades leading to inflammatory responses.[23] Caspase-1 (CASP1 or

Table 3. Baseline characteristics by CASP1 5352 G/A genotype

Characteristic	GG (%)	GA+AA (%)	p-value
Male sex	73.6	71	0.78
Caucasians	83.3	90.3	0.63
Age (yrs)	57.4±11.7	60.7±10.7	0.18
BMI (Kg/m²)	26.9±3.6	28.6±5.6	0.11
Diabetes	9.7	9.7	0.99
Current smokers	61.1	58.1	0.77
Hyperlipidemia	18.1	29	0.21
Hypertension	31.9	38.7	0.51
Family history of CAD	44.4	41.9	0.81
Previous MI	4.2	6.5	0.62
Previous PCI	1.4	0	0.51
Previous CABG	0	3.2	0.13

Values are percentages or means (±SD). BMI = body mass index (kg/m²), CAD = coronary artery disease, CABG = coronary artery bypass graft, MI = myocardial infarction, PCI = percutaneous coronary intervention

interleukin-1β-converting enzyme, ICE) transforms immature IL-1β to the mature form which can then be secreted by monocytes and macrophages.[23] CASP1 is also required for the production of IL-1α and activation of IL-18.[23] The other members of the caspase family, namely caspases 2, 3, 6-10 are mainly involved in apoptosis. Because caspases share similarities in structure and substrate specificity,[23] CASP1 was initially thought to have a pronounced apoptotic effect. Initial studies showed that overexpression of CASP1 could promote apoptosis in rat fibroblasts.[24] However, other studies showed that CASP1 null mice exhibit defects in IL-1 and IL-18 production but did not clearly present defects in the regulation of apoptosis.[25,26]

One previous study[14] found the 5352 AA genotype of CASP1 to be associated with the higher risk for target vessel revascularization (TVR) and angiographic restenosis in patients undergoing percutaneous transluminal coronary intervention (PTCA) and BMS deployment.

In the present study we found that patients carrying the 5352 A allele had a significantly higher risk for LASM. Furthermore, with IVUS analysis we found the 5352 A allele to be associated with significantly less neointimal growth at 9-month follow-up.

In the above mentioned study,[14] authors investigated the role of the CASP1 5352 G/A polymorphism in patients treated by PTCA, in the majority followed by BMS implantation. In our study all patients received SES. Sirolimus (rapamycin) was initially described as a cytostatic anti-tumoral and immunosuppressant agent.[27] Experiments on various cell lines showed that in some cases they may develop resistance and

continue to grow while in others sirolimus may even induce apoptosis.[27-29] In current practice, SES perform better than BMS (and some other DES[30]) in respect to restenosis but are frequently associated with LASM.[6,31] Conversely, LASM is mostly absent after BMS implantation.[6,32] It is not clear to date whether sirolimus-induced apoptosis is the main mechanism for LASM or local inflammation plays the major role. Ozer et al.[33] showed that systemic inflammatory markers display different patterns according to the type of implanted stent: SES associate with a lower plasma increase in high-sensitivity C-reactive protein (hsCRP) when compared with BMS, but with a slightly higher interleukin 6 (IL-6) increase; tumor necrosis factor alpha (TNF-α) showed a similar trend in DES and BMS. Although the precise mechanism remains to be revealed, we speculate that sirolimus is responsible for the differential effect of the CASP 1 5352 G/A polymorphism in the BMS and SES population.

In our sirolimus-eluting stent population with a frequency of approximately 30% for 5352 AA/AG we calculated a population attributable risk for LASM of 28% In other words if the 5352 AA/AG genotypes could hypothetically be eliminated, then this would reduce LASM risk with 28% in the sirolimus-stented patients.

According to existing data, in case of the patients with one or two A allele of the CASP1 5352 G/A polymorphism, cardiologists might need to chose between a greater risk of LASM potentially triggering stent thrombosis (in SES) or a greater risk of stent restenosis (in BMS). Therefore, cardiologists may need to carefully assess risks and benefits related to patient's condition, previous coronary interventions and associated pathology before making this choice. In future, a better tailored dual-antiplatelet therapy as well as the new generation of stents may drastically decrease the risks associated with DES implantation.. At the same time, further research is needed to optimize the approach of patients with documented stent thrombosis[34].

In our study, none of the 10 diabetic patients and 26 of the 93 non-diabetic presented LASM. Diabetes is a predictor of restenosis after PCI in general[35] and higher glucose levels have been associated with diminished efficacy of sirolimus on smooth muscle cell proliferation in particular[36]. This may explain a lower incidence of LASM in diabetic compared to non-diabetic SES patients. In the larger DIABETES trial[37], IVUS analysis with a 40 MHz catheter identified at 9 month LASM in 11 out of the 75 (14.7%) SES treated lesions in diabetes patients.

The present study investigated inflammatory polymorphisms in STEMI patients. Although late (acquired) stent malapposition incidence is higher in STEMI versus non-STEMI patients, inconclusive data are available about the incidence of late (acquired) stent malapposition in STEMI patients receiving SES. Results from previous studies[38-41] vary according to the DES type, the length of the follow-up and the use of either IVUS or of the much higher resolution optical coherence tomography (OCT) for assessment. It is therefore unclear to what extent the present findings may be extrapolated to the wide category of non-STEMI patients, including those who receive SES during elective procedures or to patients receiving a different type of DES. To date there is no relation known between unstable plaque and CASP1. Moreover, there are yet no

arguments for a differential effect of CASP1 in SES versus non-SES which may limit the outcome of this study.

Our findings do not prove a causal relationship between CASP1 polymorphism and stent malapposition. The relation between 5352 G/A polymorphism and cytokine expression needs further investigation. In a subset of 69 patients, Monraats et al.[14] examined the functional role of the 5352 G/A polymorphism by measuring mature IL-1β levels. IL-1β levels were found numerically higher in individuals with the 5352 AA genotype compared with 5352 GA and 5352 GG genotypes but the difference did not reach statistical significance. In our analysis, a policy of not making adjustments for multiple comparisons was preferred since, in our view leads to fewer errors of data interpretation[42].

CONCLUSIONS

Our findings sustain the important role of inflammation (and possibly apoptosis) in the mechanism of LASM. The A allele of the 5352 G/A polymorphism is associated with higher risk of LASM in SES. If this is confirmed in larger studies, genotyping for CASP1 5352 G/A polymorphism may help cardiologists to make a better decision between SES and BMS implantation and may guide the (duration of) anti-platelet therapy in the future.

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