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Impact of the Polymorphism rs5751876 of the Purinergic Receptor ADORA2A on Periprocedural Myocardial Infarction in Patients Undergoing Percutaneous Coronary Intervention

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Aim: Periprocedural myocardial infarction (PMI), a severe complication of Percutaneous Coronary Intervention (PCI) procedures, has a negative prognostic effect, both at short and long-term follow-up. So far, adenosine's role in preventing PMI has shown contrasting results. A genetic variant of ADORA2A receptor, 1976 C>T, has been suggested as a potential determinant of the interindividual response to adenosine, thus conditioning its potential benefits on PMI. In our study, we investigated whether the ADORA2A 1976 C>T polymorphism is associated with PMI occurrence in patients undergoing coronary stenting.

Methods: The study included consecutive patients undergoing PCI at the Azienda Ospedaliera-Universitaria "Maggiore della Carità," Novara, Italy, between January 2010 and January 2016. Their genetic status was assessed using polymerase chain reaction (PCR) and restriction-fragment-length-polymorphism technique. Myonecrosis biomarkers were measured at intervals from 6 to 48 hours. PMI was defined as CKMB increased 3 times over the Upper Limit of Normal (ULN), or 50% of pre-PCI value; periprocedural myonecrosis was defined as troponin I increased 3 times over the ULN or by 50% of the baseline value.

Results: We included 1,104 patients undergoing PCI, 863 (78.2%) of whom carried the ADORA2A T-allele. No difference was found for the main demographic, clinical features, or biochemistry parameters. However, C-carriers had lower statin therapy use ($p=0.008$) and lower HDL-cholesterol levels ($p=0.01$). Homozygous C/C patients had more frequent multivessel disease ($p=0.03$), longer lesions ($p=0.01$) and Type C lesions ($p=0.01$), thus requiring more complex procedures. After correction for baseline confounding factors at multivariate analysis, there was no difference in myocardial necrosis according to the ADORA2A genotype ($p=0.40$). In contrast, PMI tended to increase in the homozygous C/C population ($p=0.06$), but this trend was attenuated at multivariate analysis after correction for baseline confounding factors (C/C: OR[95%CI]=1.52 [0.88–2.6], $p=0.14$).

Conclusions: Our study showed that the polymorphism rs5751876 of the ADORA2A receptor is associated with a higher prevalence of complex coronary lesions and multivessel disease. However, it does not significantly influence the occurrence of periprocedural MI or myonecrosis.

Key words: Polymorphism, Adenosine, Percutaneous coronary intervention, Myocardial infarction

In recent decades, technical improvements and new, more potent antiplatelet agents have significantly improved the outcomes for patients undergoing coronary angioplasty[1-3]. However, PMI has emerged as one of the most serious complications. It still occurs in 6–18 % of patients undergoing PCI, with negative effects on both short and long-term outcomes[4].

Distal embolization, no reflow, side branch loss, and silent microvascular thrombotic obstruction by neutrophil and platelet plugs have been claimed for these events, preventing adequate myocardial perfusion[4-6].

Several periprocedural MI prevention strategies have been evaluated, especially for pharmacological therapies such as antiplatelet agents, statins and beta-blockers, which have proven effective in reducing PMI. Furthermore, adenosine has been proposed to prevent periprocedural ischemic events because of its multiple antiplatelet and anti-inflammatory effects. It inhibits the adhesion of neutrophils, the release of cytokines from mononuclear cells, and the release of oxygen radicals. It either can limit cardiomyocyte apoptosis[7-8].

However, despite adenosine's potential benefits in reducing PMI, such a positive effect has never been confirmed in clinical studies. Indeed, the adenosine receptor A2A has been shown to display a great number of polymorphisms, which may interfere with the receptor activities. A common genetic variant, observed in over 50% of the population, is due to a single nucleotide polymorphism (SNP) that causes a C>T substitution in position 1976 of the ADORA2A gene. The SNP's carriage has different effects on the vasodilatation induced by adenosine in different studies[9-10], and C-carriers have also been associated with reducing Ticagrelor's effectiveness[11]. Therefore, our study aimed to investigate whether the ADORA2A 1976 C>T polymorphism is associated with PMI or myonecrosis in patients undergoing PCI.

Methods

We selected patients who underwent elective coronary angiography after pharmacological stabilization between January 2010 and January 2016, for both elective indication or acute coronary syndrome (UA/NSTEMI). STEMI and hemodynamically unstable patients who required urgent angioplasty or patients who refused to provide written informed consent were excluded. The study was approved by our local Ethics Committee. Coronary angioplasty was performed with standard techniques. The operator determined the use of stents, types of stents and stent implantation techniques, as well as the use of directional or rotational atherectomy, IVUS, and glycoprotein IIb-IIIa inhibitors. All patients received, according to guidelines, a high-dose bolus of clopidogrel (600 mg) at the time of hospitalization or before angioplasty. Patients were clinically followed until hospital discharge. Dual antiplatelet therapy, with acetylsalicylic acid (100 mg) and a P2Y12 inhibitor (clopidogrel 75 mg or ticagrelor 180 mg or prasugrel 10 mg daily), was continued from the day after PCI for at least four weeks.

We considered periprocedural myonecrosis a demonstration of rise and fall of troponin I > 3x ULN or a 50% increase with respect to pre-procedural values. Myocardial infarction was considered both for CKMB > 3xULN or 1.5 x baseline value if already > 5 µg/l.

Biochemical Measurements

Blood samples were drawn upon admission for patients undergoing elective (following a fasting period of 12 h) or urgent coronary angiography. Glucose, creatinine, HbA1c, and lipid profiles were determined by standard methods. White blood cells count and formulas was measured in blood samples collected in tripotassium EDTA (7.2 mg) tubes. These blood samples were analyzed within 2 h from venipuncture by an automatic blood counter (A Sysmex XE-2100). Cardiac biomarkers (Troponin I and CK MB) were measured at baseline, before coronary revascularization, and later 6, 12, 24, and 48 h after PCI, as previously described[12-13].

Genetic Analysis

After all patients provided informed consent, we performed genetic analyses to define the presence of the C>T 1976 ADORA2A polymorphism. Genomic DNA was obtained from 200 µl of whole blood through a dedicated kit (GenElute™ Blood Genomic DNA, Sigma Aldrich).

The ADORA2A gene's target region was amplified by a PCR using following primers: forward 5'-TCC CCA CCA TGA GCG GAG GCC CAA TGG CGA-3', and reverse 5'-CAA GCC AAC CAG AAA GAT AAA G-3'. A negative control, containing no genomic DNA, was added for every PCR reaction to confirm there was no contamination. The PCR product of 235 base pairs was then digested by restriction enzyme HIN1I, producing two fragments of 180 and 55 base pairs when the allelic variant C was present. These digested fragments were then analyzed with agarose gel electrophoresis to separate the fragments based on their base pair lengths. A UV scan was performed to identify the genomic bands distribution that was evaluated independently by two investigators to define the genetic status (FN, MV).

In addition, we confirmed our results by repeated

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genotyping in a sample of consecutive patients and by repeating the analyses on a randomly selected sample encompassing 10% of the entire population. Results were confirmed in the overall cohort by repeated analyses.

Statistical Analysis

Statistical analysis was performed using SPSS 23.0 statistical package. Continuous data were expressed as mean ± SD and categorical data as percentage. The chi-square test was used for categorical data, including study endpoint evaluations; meanwhile, the ANOVA test was used for continuous data. Patients were grouped according to genotype results, considering separately T-allele carriers in homozygosis vs heterozygosis. Bonferroni's correction was applied for multiple comparisons in case of overall significant p value ($p<0.05$). Multiple logistic regression was used to define the relationship between the C>T 1976 polymorphism and periprocedural myocardial necrosis and infarction after correcting for baseline confounding factors (all variables significantly associated to the genetic status at univariate analysis) that were entered in a "in block" model. A p value <0.05 was considered statistically significant.

Results

Our population is represented by 1104 patients who underwent coronary angioplasty. Among them, 863 patients carried the ADORA2A -T allele, 237 in homozygosis. Therefore, the prevalence of the polymorphic allele (T) was 49.8%, whereas the prevalence of the wild-type allele (C) was 50.2%. This result goes against the expected Hardy-Weinberg equilibrium ($p<0.001$).

C-patients represented the majority of our study population, although relatively few non- Caucasian (Arab, Negroid and Asian) patients (<10%) were included.

Table 1 shows the patients' main demographic and clinical features, therapy on admission, and biochemistry parameters. No difference was found between the groups except for lower statin treatment ($p=0.008$) and lower HDL-c levels ($p=0.01$) in C/C patients.

As shown in **Table 2**, the angiographic and procedural features were similar according to genetic status, except for a higher prevalence of multivessel disease ($p=0.03$), type C lesions ($p=0.01$), and longer lesions ($p=0.01$), in homozygous C/C patients, thus requiring more frequent predilatation during PCI ($p=0.001$).

Periprocedural myonecrosis occurred in 1090 (61.5%) of the patients. **Fig. 1** shows that the myocardial necrosis rate was not different according to the ADORA2A genotype (61.2% C/C vs 58.2% C/T vs 57.2% T/T; $p=0.40$). The results were confirmed at multivariate analysis after correction for baseline confounding factors (C/T: adjusted OR [95%CI] = 1.062 [0.75–1.50], $p=0.73$; C/C: adjusted OR[95%CI] = 1.27 [0.84–1.91], $p=0.26$).

Periprocedural MI was observed in 287 (17.4%) of the patients. As shown in **Fig. 2**, C/C genotype carriers tended to have higher periprocedural MI (22.3% C/C vs 15.1% C/T vs 15.4%T/T; $p=0.06$); that trend disappeared at multivariate analysis after correction for baseline confounding factors (C/T: adjusted OR[95%CI] = 0.98 [0.59–1.61], $p=0.93$; C/C: adjusted OR[95%CI] = 1.52 [0.88–2.6], $p=0.14$).

In fact, independent predictors of periprocedural myonecrosis and PMI are displayed in **Supplementary Table 1**.

Discussion

The current study represents the first attempt to evaluate an association between the ADORA2A 1976 C>T polymorphism and periprocedural MI. Our main finding is that this genetic variant affects neither myocardial necrosis nor PMI occurrence.

Improved revascularization technologies, adjunctive pharmacological therapies, and early access to reperfusion strategies have significantly ameliorated the outcomes of patients with coronary artery disease[14-18]. However, PMI still represents a relatively common complication of PCI with negative consequences on the outcomes[19].

Procedural complications, such as distal macroembolization, flow-limiting dissections, and branch occlusions, are certainly main determinants of these events; however, myonecrosis has also been identified in apparently uncomplicated PCI. Clinical factors increasing the circulating pro-thrombotic mediators and platelet hyperreactivity, such as diabetes, advanced age, and inadequate response to antiplatelet agents, are potentially responsible, in these patients, for microvascular thrombosis, platelet plugging, vasoconstriction, and slow-flow or no-reflow phenomena, impairing myocardial perfusion[1-3].

Adenosine is a natural mediator with a short half-life in the bloodstream, displaying a broad spectrum of effects in several districts and tissues, mediated by the family of the four ADA receptors. In particular, the A2A receptor is responsible for antiplatelet effects, as well as vasodilatory effects[20-21], by improving endothelial function and vasomotion. Therefore, previous studies have raised the hypothesis that ade-

Table 1. Baseline demographic, clinical characteristics, and biochemistry

	ADORA2A C/C	ADORA2A C/T	ADORA2A T/T	*P* value
Baseline Demographical and Clinical Characteristics				
Age (mean ± SD)	68.56 ± 11.67	67.85 ± 11.08	66.95 ± 10.08	0.28
Male Sex (%)	76.3	74.6	78.5	0.59
Diabetes (%)	31.4	37.9	30	0.75
BMI (mean ± DS)	27.45 ± 4.51	27.01 ± 4.53	26.70 ± 4.14	0.18
Hypercholesterolemia (%)	59.2	54.8	55.9	0.47
Active smokers (%)	25.8	25.6	26.8	0.21
Hypertension (%)	75.0	71.7	71.1	0.34
Familiarity for CAD (%)	32.1	30.8	29.4	0.52
Renal failure (%)	18.8	25.1	21.9	0.40
History of MI(%)	22.5	24.0	24.7	0.58
Previous PCI (%)	19.2	18.5	24.7	0.14
Previous CABG (%)	10.8	13.5	10.6	0.96
Previous CVA (%)	8.0	8.7	7.8	0.93
Indication to angiography(%)				0.87
Elective (%)	42.2	40.1	41.5	
Acute coronary syndrome (%)	57.8	59.9	58.5	
Therapy at admission				
ACE inhibitors (%)	39.1	37.4	35.0	0.36
ARB (%)	23.0	24.9	25.3	0.60
Statins (%)	47.0	57.0	59.7	0.008
Nitrates (%)	37.4	44.8	41.5	0.38
Beta Blockers (%)	53.7	59.2	57.5	0.41
ASA (%)	65.6	67.3	67.6	0.66
Clopidogrel (%)	22.4	31.9	27.7	0.21
Calcium Antagonists (%)	25.6	27.8	24.2	0.78
Diuretics (%)	32.7	32.3	27.0	0.24
Main chemistry (mean ± DS)				
Fasting blood glucose (60-110 mg/dl)	127.67 ± 46.49	128.77 ± 49.66	130.38 ± 54.63	0.84
Creatinine (0.8-1.3 mg/dl)	1.10 ± 0.77	1.12 ± 0.76	1.12 ± 0.78	0.95
WBC (4.00-11.0 x10^9/l)	8.17 ± 2.38	9.60 ± 31.97	8.26 ± 3.24	0.64
Haemoglobin (13-16 g/dl)	13.45 ± 1.75	13.37 ± 1.75	13.44 ± 1.60	0.76
Glycosylated haemoglobin (4.8-5.9 %)	6.35 ± 1.27	6.35 ± 1.31	6.28 ± 1.22	0.75
Platelets count (150-400 x10^3/µl)	218.57 ± 60.276	218.65 ± 71.40	213.78 ± 53.55	0.60
C-reactive protein (< 8 mg/l)	1.19 ± 3.03	1.50 ± 3.11	1.22 ± 2.06	0.25
Triglyceride (< 150 mg/dl)	140.72 ± 69.09	142.10 ± 87.90	134.88 ± 93.63	0.55
Total cholesterol (< 200 mg/dl)	167.56 ± 41.64	161.22 ± 44.52	163.08 ± 40.25	0.15
LDL cholesterol (100-129 mg/dl)	100.05 ± 35.15	94.78 ± 37.23	96.83 ± 39.01	0.18
HDL cholesterol (> 60 mg/dl)	39.87 ± 11.76	38.28 ± 11.33	40.78 ± 12.51	0.01
Uric acid (2.5-8 mg/dl)	6.04 ± 1.76	6.06 ± 1.75	6.04 ± 1.68	0.98

nosine could, potentially, prevent heart muscle damage following reperfusion therapies for acute myocardial infarction[22-23], suggesting a similar effect for PMI occurrence. However, different studies have shown conflicting results.

An open study by Lee *et al.*[24], including 62 patients undergoing PCI and treated with intracoronary adenosine, showed that is use reduced the incidence of myonecrosis (13% vs 39%).

The larger PREVENT ICARUS trial[12], a single-center, double blind, randomized trial of 260 patients undergoing PCI, indicated opposite results. The trial showed that pre-procedural intracoronary administration of a single high-dose bolus of adenosine provided no benefit in terms of periprocedural myonecrosis in patients undergoing elective PCI.

Table 2. Angiographic and procedural characteristics

Procedural features	C/C (n = 253)	C/T (n = 630)	T/T (n = 257)	P value
Multivessel disease (%)*	64.0	58.9	53.6	0.03
Left main or three-vessels disease (%)*	29.1	27.3	28.9	0.95
Left main (%)*	8.1	8.1	6.7	0.59
Left Anterior Descending (%)*	70.3	64.5	63.2	0.12
Circumflex branch (%)*	49.3	55.4	54.5	0.27
Anterolateral branch (%)*	6.9	5.9	5.7	0.61
Right Coronary Artery (%)*	61.3	58.2	57.7	0.45
Type C lesions (%)	37.9	32.5	27.2	0.01
Lesion length (mm ± DS)	23.78 ± 15.40	21.69 ± 14.78	19.56 ± 11.5	0.01
Target vessel diameter (mm ± DS)	3.11 ± 0.57	3.07 ± 0.55	3.06 ± 0.54	0.61
% Stenosis (mean ± DS)	90.73 ± 8.98	90.21 ± 9.48	89.0 ± 9.48	0.12
Calcifications (%)	14.8	14.3	14.4	0.90
Bifurcations (%)	19.8	21.2	24.6	0.21
Spontaneous dissections (%)	0.4	1.0	0.9	0.57
Thrombus (%)	13.2	11.3	11.4	0.56
Chronical occlusion (%)	7.9	9.7	7.9	0.98
Instent restenosis (%)	3.3	5.2	7.4	0.97
TIMI flow (%)				0.05
3 (%)	71.2	75.3	79.0	
2 (%)	5.8	3.8	3.9	
1 (%)	2.5	3.6	3.5	
0 (%)	20.6	17.3	13.5	
Procedural features				
GpIIb/IIIa inhibitors	42.1	47.3	40.5	0.76
Multivessel PCI	20.7	20.8	25.2	0.24
Target vessel				0.12
Right Coronary Artery (%)	36.9	32.7	33.5	
Left Main (%)	1.3	3.7	0.9	
Left Anterior Descending (%)	28	31.7	34.7	
Circumflex branch (%)	19.7	18.5	19.8	
Saphenous venous graft (%)	1.3	2.2	3.4	
Anterolateral branch (%)	12.8	11.2	7.7	
Calcifications (%)	14.8	14.3	14.4	0.90
Thrombus (%)	13.2	11.3	11.4	0.56
TIMI pre-PCI < 3 (%)	28.9	24.7	20.9	0.05
Instent restenosis (%)	3.3	5.2	7.4	0.97
Chronical occlusion (%)	7.9	9.7	7.9	0.98
Bifurcations (%)	19.8	21.2	24.6	0.21
Predilatation(%)	74.0	65.0	58.8	0.001
Direct stenting (%)	30.5	36.0	45.7	0.001
Max inflation (atm ± SD)	21.59 ± 3.81	21.42 ± 3.65	20.95 ± 3.85	0.25
Kissing balloon (%)	15.6	11.0	13.4	0.97
Thrombectomy (%)	5.2	4.0	1.9	0.07
TIMI post PCI < 3 (%)	1.7	2.6	2.8	0.99
Coronary dissection (%)	0.4	1.0	0.9	0.57
Coronary perforation (%)	0.4	1.4	1.9	0.98
Distal embolization (%)	1.7	1.3	0.9	0.98
Additional stent required (%)	2.6	2.2	0.9	0.22
Side branch loss (%)	1.3	0.5	0.9	0.65
Slow flow-no reflow (%)	9.6	1.6	1.4	0.34

*n = per patient

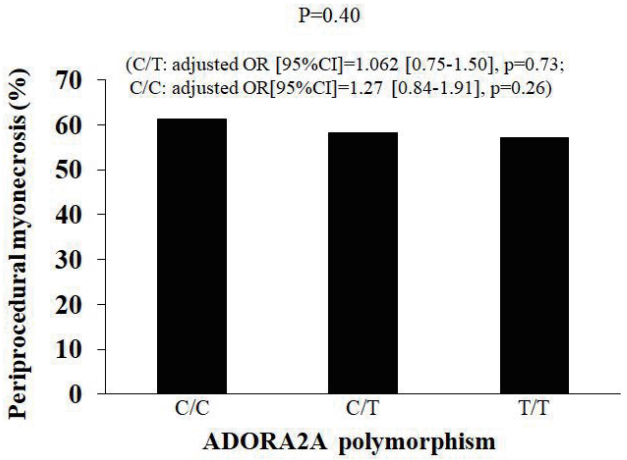

Fig. 1. Bar graph showing the prevalence of periprocedural myonecrosis, according to ADORA2A 1976 C>T polymorphism

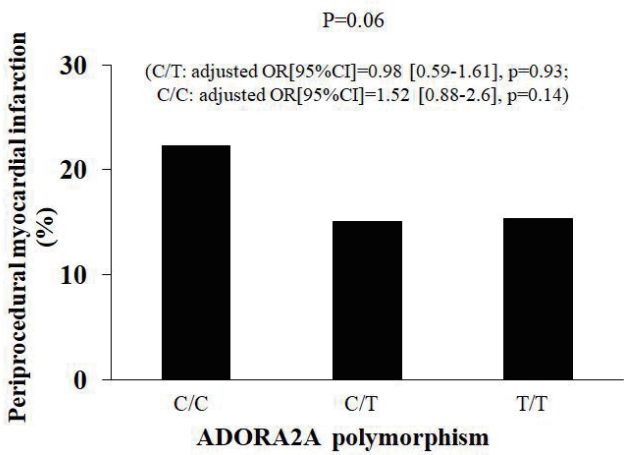

Fig. 2. Bar graph showing the prevalence of periprocedural myocardial infarction, according to ADORA2A 1976 C>T polymorphism

Despite the lack of data from larger randomized trials, and the heterogeneity in adenosine dosing used in available studies, other factors could play a relevant role in conditioning adenosine's effects. In fact, an interindividual variability in the response to adenosine has been suggested, potentially as a consequence of A2A receptor polymorphisms, which might interfere with its activity.

Polymorphism 1976 C/T is responsible for an ADORA2A gene mutation, encoding for A2A purinergic receptor. Although it does not affect the aminoacidic sequence, it is a synonymous mutation, causing an exonic exchange Tyr 361 Tyr, and has been associated with different disorders. In particular, the genotype T/T has been associated with panic attacks as well as caffeine or amphetamine - induced anxiety[25-29].

As for the genetic variant's cardiovascular effects, one study, by Riksen *et al.*[30], demonstrated that this polymorphism does not affect the vasodilator response to adenosine and caffeine in humans among 10 subjects with the T/T genotype and 10 C/C controls. On the contrary, in another study by Andreassi *et al.*, 80 patients with nonischemic-dilated cardiomyopathy (DCM) were enrolled, together with 162 healthy volunteers, undergoing Doppler-derived flow (CFR) evaluation of distal left anterior descending artery. Patients with the 1976- T/T genotype had significantly lower CFR than the C/C patients (2.3 ± 0.7 vs 2.0 ± 0.5 vs 1.9 ± 0.4, $P<0.05$ for CC, CT, and TT genotypes, respectively), thus demonstrating an association between T-allele and a reduced vasodilator response to adenosine in patients with non ischemic-dilated cardiomyopathy[10].

Moreover, we previously documented that the C/C genotype is associated with a blunted antiplatelet effect of ticagrelor[11].

The current study showed this genetic variant had no effect on myocardial necrosis. We observed a non-significant higher PMI occurrence in C/C homozygous patients ($p=0.06$). This weak association disappeared at multivariate analysis after correction for baseline confounding factors. These data may be explained by the observed larger prevalence of multivessel disease, longer lesions, and, therefore, more complex PCI procedures in patients with the C/C genotype, which may have increased the PMI risk.

Indeed, it can be postulated that the greater vasodilator response to adenosine in C/C homozygous patients allowed a higher compensation of coronary reserve, thus leading to later presentation and more advanced disease in these patients. Moreover C/C patients in our study had less frequent treatment with statins, which have been demonstrated to stabilize coronary plaques and reduce PMI incidence[31].

However, despite the differences in the rates of statin use, the LDL-C levels were similar among the three groups. Thus, it might be argued that the T-allele carriers could have displayed a worse lipid profile at baseline (pre-treatment), potentially conditioning the plaque composition and, thus, periprocedural complications. The relevance of this influence should certainly be evaluated in future studies. In fact, further larger studies, specifically dedicated to different ethnicities or special higher risk patient subsets, are certainly warranted to confirm our findings.

Limitations

Undoubtedly our work has some limitations due to the study design. In fact, including a non-randomized patient cohort from a single center has led to a higher prevalence of heterozygotes, not respecting the Hardy-Weinberg equilibrium. This may have occurred because of a founder effect, possibly because of the single center recruitment for our study. Another possible explanation could be only including patients who underwent PCI and are at higher cardiovascular risk. The observed association of C-allele with more complex lesions could explain the higher prevalence of heterozygotes in our population.

Additional limitation may be the clinical and angiographic differences among the groups, which may have influenced our findings. In fact, multiple comparisons among several baseline clinical and angiographic characteristics were required to detect potential confounders, potentially leading to false positive results. Nevertheless, our results were confirmed in a multivariable model after accounting for these baseline differences.

In addition, several additional genetic variants, located on different genes, could have been addressed for implementing our study since previous studies indicated a potential association with CAD severity, such as those involving the glyoxalase I (GLO1) enzyme[32]. However, without studies linking this polymorphism to PMI, and accounting for the present study's explorative nature, we preferred to perform a more focused study and address one polymorphism at time.

Finally, it may be argued that our population was not large enough to identify a prognostic role of the investigated polymorphism in PMI. However, based on an expected average risk of 15% in PMI in CC or CT patients, according to a population distribution 3:1, an anticipated two-sided test for differences in independent binomial proportions at the 5% significance level, considering clinically significant a 66% increase in relative risk of the expected occurrence of PMI (from 15% to 25%), our population would have had a statistical power of 93.5% to detect such a difference.

Conclusions

Our study showed that the polymorphism rs5751876 of ADORA2A receptor, despite being associated with a higher prevalence of complex coronary lesions and multivessel disease, does not significantly influence the occurrence of periprocedural MI or myonecrosis.

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Supplementary Table 1. Independent predictors of periprocedural myocardial infarction (PMI) and periprocedural

Periprocedural myocardial infarction			
Variable	Odds Ratio	[95% CI]	*P* value
Statins use	0.55	[0.39-0.79]	0.001
Lesion length	1.02	[1.009-1.031]	<0.001
Multivessel disease	1.66	[1.13-2.45]	0.010

Periprocedural myonecrosis			
Variable	Odds Ratio	[95% CI]	*P* value
Hypertension	1.57	[1.19-2.07]	0.001
Lesion length	1.01	[1.004-1.02]	0.006
Male gender	1.4	[1.05-1.87]	0.02