Clinical and Stent-related Risk Factors for Recurrent Angina After Successful Percutaneous Coronary Intervention

VIOLETA DINESCH[1]*, MIHAIL DINESCH[2], MIRCEA BURUIAN[3]

[1]University of Medicine and Pharmacy, Department of Internal Medicine M3, 38 Gheorghe Marinescu Str., 540139, Tirgu Mures, Romania

[2]Department of Cardiology, Institute for Cardiovascular Disease and Heart Transplant, 50 Gheorghe Marinescu Str., 540136, Tirgu Mures, Romania

[3] University of Medicine and Pharmacy, Department of Morphologic Sciences M,38 Gheorghe Marinescu Str., 540139, Tirgu Mures, Romania

We evaluated the clinical and stent-related risk factors for recurrent angina (RA) symptoms after percutaneous coronary intervention (PCI), as identifying and treating them could improve patient outcomes. We retrospectively analysed patients readmitted at our clinic after successful PCI; 147 (81.66%) patients were hospitalised for RA. Advanced age was associated with RA symptoms. Drug-eluting stents used at the index PCI, especially in small coronary arteries, seemed protective against RA symptoms. In-stent restenosis, which was associated with RA, was more frequent in bare-metal stents than in drug-eluting stents. Further studies are needed to identify other potential risk factors for RA and to determine how to positively influence the evolution of known risk factors.

Keywords: recurrent angina, percutaneous coronary intervention, drug-eluting stent, bare-metal stent

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality worldwide. Percutaneous coronary intervention (PCI) with stenting has markedly changed the treatment of CAD, becoming the most commonly used myocardial revascularisation method. The evolution in the design and composition of the stent platforms of bare-metal stents (BMS), and the development of drug-eluting stents (DES) coated with antiproliferative drugs to reduce the neointimal hyperplasia responsible for in-stent restenosis (ISR), were stages in the progress of interventional cardiology. Recurrent angina (RA) after a successful PCI raises questions about the prognosis of the patient. Our study aimed to evaluate the clinical and PCI-related risk factors for RA, as their identification and adequate treatment could influence patient outcomes.

Experimental part

We retrospectively included post-PCI patients readmitted at the Adult Cardiology Clinic at the Institute of Cardiovascular Diseases and Transplantation Tirgu Mures from January 2012 to December 2015. We compared the following parameters between the groups with (stable/unstable angina, ST/non-ST elevation myocardial infarction) and without (cardiological reassessment without symptomatology) RA: sociodemographic (age, sex), cardiovascular risk factors (hypertension, smoking, diabetes mellitus, obesity, hypercholesterol-aemia), results of coronarography performed pre-PCI and at readmission, details of the index PCI (type of stent used, localisation in the coronary artery), and type of medication used at the time of readmission (single or dual antiplatelet therapy, statin).

The acquired data were analysed using STATA (version 14.0, Stata Corporation, College Station, TX, USA) and R (version 3.3.3, R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as mean ± standard deviation and were compared using the t-test. Categorical variables are expressed as frequency and proportions and were compared using contingency tables, the chi-square test, and Fisher's exact test. $p<0.05$ was considered statistically significant. The study design was approved by the institutional ethics review board, and all patients provided informed consent.

Results and discussions

The study included 180 patients, of which, 147 (81.66%) were readmitted for RA. The mean duration of follow-up was 30.97 ± 31.84 months for the RA group and 24.33 ± 35.12 months for the Non-RA group (odds ratio [OR] 0.99, p = 0.298). The baseline demographics and clinical characteristics of the patients are shown in table 1.

Parameter	RA group	Non-RA group	p
Age, years	62.58 ± 10.04	58.87 ± 9.25	0.053
Male	109 (74.14)	27 (81.81)	0.354
Hypertension	139 (93.9)	29 (90.6)	0.237
Diabetes mellitus	34 (23.12)	6 (18.18)	0.537
Hypercholesterolaemia	75 (50.7)	12 (37.5)	0.128
Smoke	20 (13.5)	4 (12.5)	0.79
Obesity	41 (27.89)	10 (30.3)	0.781

Data are expressed as number (%) or as mean ± SD.

Table 1
BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS OF THE PATIENTS WITH AND WITHOUT RA

* email: doc_violeta@yahoo.com

Most patients in both groups benefited from BMS at the index PCI, with additional BMS in the RA group, but without statistical significance between the RA and Non-RA groups (table 2).

Table 2
STENT TYPE USED AT THE INDEX PCI

Parameter	BMS	BMS + DES	DES	p
RA group	104 (70.74)	12 (8.16)	31 (21.08)	0.14
Non-RA group	16 (48.48)	7 (21.21)	10 (20.3)	

Data are expressed as number (%).

An interesting, but not unexpected observation was noted in relation to stent localisation in the coronary artery at the index PCI. Although the left-anterior-descending-artery localisation of BMS was similarly predominant in both groups, the localisation of DES in the small coronary arteries was associated with the Non-RA group (table 3).

LMCA- left main coronary artery, LAD- left anterior descending artery, RCA- right coronary artery, LCX- left circumflex coronary artery

One-third of patients required revascularisation for ISR. Although the presence of ISR was statistically associated with RA and BMS-ISR was more common than DES-ISR (p = 0.009), ISR localisation at the DES or BMS level was not associated with any of the study groups (table 4).

By comparing the patients with DES-ISR and those with BMS-ISR, the presence of a greater number of lesions at a distance from the stent was significantly related to BMS-ISR (table 5).

Parameter		RA group	Non-RA group	p
BMS		116 (78.91)	23 (69.69)	0.25
BMS localisation	LMCA	2 (1.36)	0	0.5
	LAD	76 (51.7)	12 (36.36)	0.06
	RCA	36 (24.48)	8 (24.24)	0,13
	LCX	25 (17)	5 (15.15)	0.87
	Other coronary artery	18 (12.24)	5 (15.15)	0.76
DES		43 (29.25)	16 (48.48)	0.033
DES localisation	LMCA	5 (3.4)	1 (3.03)	0.91
	LAD	26 (17.68)	8 (24.24)	0.542
	RCA	12 (8.16)	5 (15.15)	0.07
	LCX	15 (10.2)	1 (3.03)	0.635
	Other coronary artery	4 (2.72)	5 (15.15)	0.004

Data are expressed as number (%)

Table 3
STENT LOCALISATION AT THE INDEX PCI

Parameter	RA group	Non-RA group	p
ISR alone	23 (15.65)	3 (9.09)	0.421
ISR + native coronary stenosis	25 (17.01)	2 (6.06)	0.175
ISR (accumulated)	48 (32.65)	5 (15.15)	0.046
DES-ISR	6 (40.81)	0	0.594
BMS-ISR	42 (28.57)	5 (15.15)	0.113
Native coronary stenosis alone	70 (47.62)	16 (48.48)	0.928
No native coronary stenosis	29 (19.73)	12 (36.36)	0.039

Data are expressed as number (%)

Table 4
RESULTS OF CORONAROGRAPHY AT READMISSION

STEMI- ST-elevation myocardial infarction, LMCA- left main coronary artery, LAD- left anterior descending artery, RCA- right coronary artery, LCX- left circumflex coronary artery, DAPT- dual antiplatelet therapy

Recurrent angina after PCI is a frequent clinical outcome with a high economic burden [1]. Our study aimed to identify the impact of clinical and PCI-related factors on the development of post-PCI RA. Advanced age was a clinical risk factor for RA. DES utilisation, particularly in small coronary arteries, seemed to be protective against RA. ISR, which was associated with RA, occurred more frequently with BMS than with DES. Comparing DES-ISR and BMS-ISR, only the presence of a higher number of stenoses in the native coronary artery was associated with BMS-ISR.

Advanced age is a common predictor of the development of cardiovascular pathology because it is linked with a greater prevalence of cardiovascular risk factors and comorbidities. Go et al demonstrated a double prevalence of angina symptoms in the 60 to 79-years age group compared to the 40 to 59-years age group [2]. In post-PCI patients, Gaglia Jr. et al showed in a study, within 1-year post-PCI, that increasing age was associated with less post-PCI angina [3]. Contrarily, advanced age was a predictor of RA symptoms compared to the asymptomatic patients in our study.

Data from the literature support the hypothesis of a higher prevalence of adverse outcomes after PCI in the female sex [4-5]. However, in our study, there were no between-sex differences in post-PCI pathology. This is explicable from several points of view. First, there was no recorded

Table 5
DES-ISR vs. BMS-ISR

Parameter		DES-ISR 5 (11.3)	BMS-ISR 48 (88.7)	p
Age, years		67 ± 6.98	61.45 ± 0.75	0.224
Male		5 (83.33)	37 (78.72)	0.793
Hypertension		6 (100)	45 (95.74)	0.606
Diabetes mellitus		3 (50)	12 (25.53)	0.456
Smoke		1 (16.66)	5 (10.63)	0.276
Obesity		1(16.66)	9 (19.14)	0.865
Hypercholesterolaemia		2 (33.33)	23 (48.93)	0.471
Symptomatology	STEMI	0	5 (10.63)	1
	Unstable angina	3 (50)	12 (25.53)	0.334
	Stable angina	3 (50)	25 (53.19)	0.609
	Cardiological reassessment	0	5 (10.63)	1
Stents number/patient		1.17 ± 0.4	1.49 ± 0.77	0.325
Native coronary stenosis	LMCA	0	1 (2.12)	0.71
	LAD	0	10 (21.27)	0.21
	RCA	1 (16.6)	11 (23.4)	0.7
	LCX	0	6 (12.76)	0.353
	Other coronary artery	0	11 (23.4)	0.183
Number of native coronary stenosis/patient		0.17 ± 0.4	0.74 ± 0.82	0.017
Medication	Aspirin	3 (50)	16 (34.04)	0.443
	DAPT	2 (33.33)	29 (61.7)	0.184
	Statin	4 (66.66)	35	0.683

Data are expressed as number (%) or as mean ± SD.

post-PCI mortality, which is higher for women than for men. Second, the incidence of primary PCI, which has a greater potential for complications, was lower in the women. Third, the small proportion (24%) of female patients in this study may have been a limitation in our analysis.

Smoking is a known cardiovascular risk factor in those over 50 years of age, and the benefits of smoking cessation are recognised even in the DES era [6]. In a study involving 2765 patients, Jang et al demonstrated that post-PCI smokers continued to have a higher incidence of angina episodes and a poorer quality of life compared to non-smokers [7]. A small percentage (13.3%) of the patients in our study were active smokers at the time of post-PCI hospitalisation, but this did not significantly influence the post-PCI evolution of RA symptoms. However, our study did not investigate the differences in the smoking intensity of smokers/former smokers and the time since the cessation of smoking.

Although present in higher percentages in the RA group, none of the other cardiovascular risk factors attained statistical significance. Our findings may be the consequence of good control for these risk factors or due to the few number of patients, which may have hampered the ability to identify any important associations.

The incremental improvement in both DES and BMS technology was clearly demonstrated in the results of Norwegian Coronary Stent Trial (NORSTENT), where second-generation DESs were not superior to contemporary BMS regarding both major cardiovascular outcomes and post-PCI angina [8]. In our study, DES use at the index PCI was associated with a lower frequency of post-PCI anginal symptoms compared to BMS use. Nevertheless, it is also true that the data regarding the DES/BMS generation used at index PCI were not recorded, so a stratified analysis with stent generation was not possible. Moreover, in our study, DES localisation at the index PCI in small arteries was significantly associated with the Non-RA group. We did not find any data in the literature regarding the association between DES/BMS localisation in small arteries and RA. However, DES has significantly lower rates of repeat revascularisation and major adverse cardiovascular events compared to BMS in the treatment of small coronary arteries [9] and this, perhaps, explains our findings.

Several studies have demonstrated the superiority of DES over BMS regarding the need for target-lesion revascularisation [10-11]. In agreement with previous research, in our study, BMS-ISR was significantly more frequent than DES-ISR, but without significant between-study-group differences. Comparing the DES-ISR subgroup and the BMS-ISR subgroup, only a greater number of native coronary stenoses, suggesting a more massive atherosclerotic load, was associated with BMS-ISR.

Our study has several limitations. First, our study had a small sample size, as previously mentioned; therefore, the statistical power to detect other associations between risk factors for RA may have been reduced. Second, the study was retrospective and included patients from a single centre; thus, our results may not be generalisable.

Conclusions

Advanced age is a risk factor for RA. DES utilisation, especially in the small coronary arteries, appears to be protective against the RA. ISR was associated with RA and occurred more frequently in BMS than in DES. Further studies with a large sample size and longer-term follow-

up are needed to identify other potential risk factors for RA and to determine how to positively influence the evolution of known risk factors.

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RESEARCH ARTICLE

Risk Factors Associated with Acute Coronary Syndrome after Successful Percutaneous Coronary Intervention

Violeta Dinesch[1*], Mihail Dinesch[2], Ileana Voichita Sirbu[3], Cosmin Macarie[3], Mircea Buruian[4]

1. University of Medicine and Pharmacy Tîrgu Mures, Romania
2. Department of Cardiology, Institute for Cardiovascular Disease and Heart Transplant, Tîrgu Mures, Romania
3. Department of Internal Medicine M3, University of Medicine and Pharmacy, Tîrgu Mures, Romania
4. Department of Morphologic Sciences M1, University of Medicine and Pharmacy Tîrgu Mures, Romania

Objective: Admission for acute coronary syndrome after successful percutaneous coronary intervention is a delicate situation for the patient and doctor. Predictors of these cases are poorly described. **Methods**: We retrospectively analysed the files of post-percutaneous coronary intervention patients admitted to the Department of Cardiology of the Institute for Cardiovascular Disease and Heart Transplant in Tirgu Mures between January 2012 and December 2015. Analyses using the t-test, chi-square test, and Fisher test were performed to compare demographics, clinical and angiographic characteristics of patients with acute coronary syndrome, patients with stable angina, and those without symptoms. **Results**: One hundred eighty post-percutaneous coronary intervention patients were readmitted; 46 patients (25.55%) were readmitted for acute coronary syndrome. Histories of arterial hypertension and renal dysfunction at hospital admission were associated with acute coronary syndrome. Bare metal stent in-stent restenosis and localisation of bare metal stent in-stent restenosis of the left descendent coronary artery were angiographic predictors of acute coronary syndrome. **Conclusion**: Several clinical and angiographic factors identify patients at high risk for acute coronary syndrome after successful percutaneous coronary intervention. Recognition and treatment of these factors may prevent readmission for such a dangerous condition and may improve outcomes.

Keywords: acute coronary syndrome, percutaneous coronary intervention, in-stent restenosis

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Introduction

Coronary artery stents, both bare metal stents and drug-eluting stents, significantly reduce the incidence of events related to culprit lesion treated during the first (index) percutaneous coronary intervention; however, coronary artery disease is a continuous process. Reoccurrence of symptomatology, particularly acute coronary syndrome, is a challenging situation because acute coronary syndrome is still a major cause of death and has a high economic burden. Identification of factors that could predict the development of acute coronary syndrome, especially preventable factors, would be extremely useful for the clinical management of these patients.

Methods

This was a single-centre retrospective analysis of 180 readmitted post-percutaneous coronary intervention patients over a 4-year period (January 2012-December 2015). Patients were divided into three groups: acute coronary syndrome patients, patients with stable angina, and asymptomatic patients. Baseline characteristics, cardiac history, risk factors, comorbidities, results of coronarography at the index percutaneous coronary intervention and at readmission, stent type used at the index percutaneous coronary intervention, and medication after percutaneous coronary intervention were compared between the three subgroups.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and compared using t-tests. Categorical variables were presented as numbers and percentages and compared using chi-square or Fisher tests. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using STATA 14.0 (Stata Corporation, College Station, TX, USA).

Results

Forty-six (25.55%) patients with acute coronary syndrome, 101 (56.11%) patients with stable angina, and 33 (18.33) asymptomatic patients were readmitted after successful percutaneous coronary intervention (Table I).

Patients with acute coronary syndrome were older than asymptomatic patients (63.93 ± 10.69 vs. 58.87 ± 9.25 years; p=0.031) and more often had a history of myocardial infarcts than patients with stable angina (p=0.005).

Arterial chronic hypertension and impaired renal function (estimated glomerular filtration rate ≤60 ml/min) were more frequent in the acute coronary syndrome group than in the other two groups. There were no other differences

* Correspondence to: Violeta Dinesch
E-mail: doc_violeta@yahoo.com

Table I. Baseline characteristics, cardiovascular risk factors, and comorbidities

	Stable angina group		Asymptomatic group		ACS group
	101 (56.11%)	*p	33 (18.33%)	*p	46 (25.55%)
Age, years	61.97 ± 9.72	0.273	58.87 ± 9.25	0.031	63.93 ± 10.69
Male, n (%)	76 (75.25)	0.652	27 (81.82)	0.301	33 (71.74)
HTN, n (%)	93 (92.8)	0.057	29 (87.88)	0.027	46 (100)
Diabetes mellitus, n (%)	19 (18.81)	0.066	6 (18.18)	0.152	15 (32.61)
Obesity, n (%)	28 (27.72)	0.946	10 (30.3)	0.844	13 (28.26)
Dyslipidemia, n (%)	50 (49.5)	0.586	12 (36.36)	0.114	25 (54.25)
Smoker, n (%)	14 (13.86)	0.578	4 (12.12)	0.752	8 (17.39)
eGFR ≤60 ml/min, n (%)	20 (19.8)	0.006	4 (12.12)	0.006	19 (41.3)
Previous MI, n (%)	43 (42.57)	0.005	18 (54.55)	0.246	31 (67.39)
Previous CABG, n (%)	6 (5.94)	1	0	0.261	3 (6.52)

*p compared with ACS group.

ACS, acute coronary syndrome; HTN, hypertension; MI, myocardial infarction; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate.

in baseline characteristics, risk factors, and comorbidities between the three groups.

Right coronary artery disease was more frequent in the acute coronary syndrome group than in the other two groups; however, the numbers of diseased vessels between the three groups at the index procedure or readmission were not different. Drug-eluting stent utilisation at index percutaneous coronary intervention was more frequent in the asymptomatic group. Bare metal stent in-stent restenosis and localisation of in-stent restenosis to the left descending artery occurred more often in the acute coronary syndrome group than in the stable angina group or asymptomatic group (Table II).

Discussion

Arterial chronic hypertension is a classical and well-known cardiovascular risk factor for the development of atherosclerosis and coronary artery disease. A previous study revealed a 63.4% prevalence of hypertension among acute coronary syndrome patients [1]. The impact of hypertension on patients with acute coronary syndrome is related to the progression of coronary atherosclerosis and favours the

Table II. Intervention features

		Stable angina group		Asymptomatic group		ACS group
		N (%)	p*	N (%)	p*	N (%)
Number of diseased vessels at index PCI	1	50 (49.5)	0.301	10 (30.3)	0.279	18 (39.13)
	2	32 (31.68)		15 (45.45)		16 (34.78)
	3	16 (15.84)		6 (18.18)		12 (26.09)
	>3	3 (2.97)		2 (6.06)		0
Lesion localisation at index PCI	LMCA	3 (2.97)	0.377	0	0.261	3 (6.52)
	LAD	70 (69.31)	0.569	24 (72.37)	0.906	34 (73.91)
	RCA	40 (39.6)	0.056	19 (57.58)	0.926	26 (56.52)
	LCX	35 (34.65)	0.808	10 (30.3)	0.828	15 (32.61)
	Other coronary artery	24 (23.76)	0.385	11 (33.33)	0.102	8 (17.39)
Time interval between index PCI and readmission (mean ± median), months		27.68 ± 29.66	0.07	24.33 ± 35.12	0.09	37.86 ± 35.52
Number of diseased vessel at readmission	0	45 (44.55)	0.087	15 (45.45)	0.142	11 (23.91)
	1	37 (36.63)		14 (42.42)		21 (45.65)
	2	14 (13.86)		3 (9.09)		10 (21.74)
	3	5 (4.95)		1 (3.03)		4 (8.7)
Lesion localisation at readmission	LMCA	2 (1.98)	0.589	0	0.507	2 (4.35)
	LAD	22 (21.78)	0.161	6 (18.18)	0.152	15 (32.61)
	RCA	22 (21.78)	0.028	6 (18.18)	0.046	18 (39.13)
	LCX	7 (6.93)	0.226	5 (15.15)	1	6 (13.04)
	Other coronary artery	21 (20.79)	0.476	6 (18.18)	0.409	12 (26.09)
Stent type at index PCI	DES	34 (33.66)	0.081	16 (48.48)	0.006	9 (19.57)
	BMS	77 (76.24)	0.239	23 (69.7)	0.108	39 (84.78)
DES ISR, n (%)		4 (3.96)	0.258	0	0.136	4 (8.7)
BMS ISR, n (%)		34 (33.66)	0.033	6 (18.18)	0.002	24 (52.17)
BMS ISR localisation	LMCA	10 (9.9)	0.052	1 (3.03)	0.021	10 (21.47)
	RCA	8 (7.92)	1	2 (6.06)	1	3 (6.52)
	LCX	6 (5.94)	1	1 (3.03)	0.636	3 (6.52)
	Other coronary artery	3 (2.97)	0.648	1 (3.03)	1	2 (4.35)

*p compared with ACS group.

LMCA, left main coronary artery; LAD, left descendent artery; RCA, right coronary artery; LCX, left circumflex coronary artery; DES, drug-eluting stent; BMS, bare metal stent; ISR, in-stent restenosis.

development of vulnerable atherosclerotic plaques through which rupture can occur during acute coronary syndrome. The prognoses of patients with known hypertension and acute coronary syndrome are also impaired. In the Kamir registry, a history of hypertension was related to higher in-hospital mortality [2]. In the GISSI-2 study, in-hospital and 6-month mortality rates were higher for hypertensive patients than for normotensive myocardial infarction patients [3].

Chronic kidney disease is associated with accelerated atherosclerosis and is a predictor of cardiovascular morbidity, mortality, and all-cause mortality for patients with acute coronary syndrome [4,5]. Mechanisms related to the adverse outcomes are more severe vessel disease on presentation with acute coronary syndrome [4], differences in coronary plaque morphology [6], less aggressive revascularization, and medical therapy.

The superiority of drug-eluting stents compared to bare metal stents regarding target lesion revascularisation has been investigated in many studies. In NORSTENT, the largest randomised study to compare contemporary drug-eluting stents and bare metal stents, target lesion revascularisation and definite stent thrombosis were significantly lower for drug-eluting stent patients than for bare metal stent patients [7]. Furthermore, in our study, bare metal stent in-stent restenosis was more frequent than drug-eluting stent in-stent restenosis in the acute coronary syndrome group. These findings raise the question of the utility of bare metal stents in the era of drug-eluting stents and bioabsorbable vascular stents. High haemorrhagic risk and inadequate dual antiplatelet therapy may be reasons why bare metal stents are preferred to drug-eluting stents.

The localisation of bare metal stent in-stent restenosis was not unusual because tortuosity and angulation of the left descending coronary artery can predispose patients to accelerated progression of atherosclerosis [8.9].

Right artery disease was more frequent in the acute coronary syndrome group than in the other two groups at readmission. This raised the hypothesis of incomplete revascularisation at index percutaneous coronary intervention or progression of atherosclerosis after index percutaneous coronary intervention.

Study limitations

Our study had several limitations. First, the data were retrospectively extracted by reviewing medical observation files and depended on the accuracy and completeness of them. Second, the study included only patients admitted to our clinic. Patients admitted to other hospitals or who died were not included in our study. Finally, the time interval between index percutaneous coronary intervention and readmission has not been standardized. However, the average time interval for each group was not statistically significant.

Conclusion

Hypertension and impaired renal function are clinical risk factors for acute coronary syndrome. Right coronary artery disease, bare metal stent in-stent restenosis, and left descending artery localisation of bare metal stent in-stent restenosis are angiographic risks associated with acute coronary syndrome. Recognition and treatment, particularly of preventable factors, may improve the outcomes and prognoses of coronary disease patients after successful percutaneous coronary intervention.

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Conflict of interest

None to declare.

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RESEARCH ARTICLE

Risk of Contrast-Induced Nephropathy after Repeated Contrast Medium Administration

Violeta Dinesch[1*], Mihail Dinesch[2], Cosmin Macarie[3], Ileana Voichita Sirbu[3], Mircea Buruian[4]

1. University of Medicine and Pharmacy Tirgu Mures, Romania
2. Department of Cardiology, Institute for Cardiovascular Disease and Heart Transplant, Tirgu Mures, Romania
3. Department of Internal Medicine M3, University of Medicine and Pharmacy, Department of Cardiology, Institute for Cardiovascular Disease and Heart Transplant, Tirgu Mures, Romania
4. Department of Morphologic Sciences M1, University of Medicine and Pharmacy, Tirgu Mures, Romania

Objective: Non-invasive coronary computed tomography angiography is frequently used to exclude coronary artery disease in patients with low-to-intermediate pre-test probability because of the high negative predictive value. The strategy of coronary computed tomography angiography and subsequent invasive coronary angiography in case of positive findings has risks owing to repeated contrast medium administration and the possibility of contrast-induced nephropathy. **Methods**: We retrospectively evaluated the changes in the serum creatinine level and estimated glomerular filtration rate (at baseline, 24 h, and 48 h after contrast administration) in patients with repeated contrast medium administration in order to evaluate contrast-induced nephropathy development. All patients were intravenously hydrated with 1000 ml sodium chloride (0.9%) per day during hospitalization. **Results**: The study included 17 patients. Of these patients, 7 (41.2%) had prior impaired renal function (estimated glomerular filtration rate <60 ml/min/1.73 m2). The mean coronary computed tomography angiography contrast medium (iopromide 769 mg/ml) volume was 114.11 ± 7.75 ml and the mean invasive coronary angiography contrast medium (iohexol 755 mg/ml) volume was 129.7 ± 19.24 ml. The serum creatinine level was significantly higher and the estimated glomerular filtration rate was significantly lower at 48 hours after the second contrast medium administration than at baseline (p = 0.05 and p = 0.03, respectively). None of the patients had contrast-induced nephropathy. **Conclusion**: Repeated contrast medium administration was not associated with contrast-induced nephropathy development at 48 hours after the second contrast medium administration, even in patients with prior impaired renal function.

Keywords: contrast-induced nephropathy, contrast medium administration, renal function

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Introduction

The rapid evolution of cardiovascular imaging during the last few decades has resulted in an increase in the use of intra-venous/intra-arterial iodinated contrast agents. Conventional invasive coronary angiography (ICA) is the gold standard approach for the evaluation of coronary artery disease (CAD), and non-invasive coronary computed tomography angiography (CCTA) is frequently used to exclude CAD in patients with low-to-intermediate pre-test probability. However, the strategy of CCTA and subsequent ICA in the case of positive findings has some risks owing to repeated contrast exposure and the possibility of subsequent contrast-mediated renal injury. Contrast-induced nephropathy (CIN) was first described in the 1950s [1], and it remains one of the leading causes of hospital-acquired acute renal injury [2]. Several studies have mentioned the incidence of CIN after single administration of radiocontrast medium [3,4]. However, in real life, repeated contrast medium administration (CMA) is not infrequent. The present study aimed to assess the change in renal function after two consecutive imaging procedures involving intra-venous and intra-arterial CMA in order to evaluate CIN development. To our knowledge, the risk of CIN development after CCTA followed by ICA has not been investigated previously.

* Correspondence to: Violeta Dinesch
E-mail: doc_violeta@yahoo.com

Methods

We reviewed the records of patients admitted to our institution for CCTA followed by ICA between January and December 2015. All study participants provided informed consent, and the study design was approved by the appropriate ethics review board.

Renal function was evaluated according to changes in the serum creatinine (sCr) level and eGFR 24 hours after each CMA and 48 hours after the last CMA compared with baseline values (before CMA). The diagnostic criterion for CIN was a rise in the sCr level by 25% or more or an absolute increase in the sCr level by 0.5 mg/dl or more compared with the baseline value. The eGFR was calculated using the Cockroft–Gault formula (creatinine clearance [CrCl] = [140–age] × weight / sCr × 72; $CrCl_{female}$ = CrCl × 0.85 [female sex adjustment]). The results are expressed as mean ± standard deviation (SD), and the data were compared using one-way ANOVA for repeated measurements. All statistical analyses were performed using STATA 14.0 (Stata Corporation, College Station, TX, USA). A p-value ≤0.05 was considered significant.

Results

The study included 17 patients. Prior impaired renal function (eGFR <60 ml/min/1.73 m^2) was noted in 41.2% of the patients, and a history of ST-elevation myocardial infarction (STEMI) was noted in 41.2% of the patients.

The demographic and clinical characteristics of the study patients are presented in Table I.

Table I. Demographic and clinical characteristics of the patients

Parameter	Number (%)
Male	16 (94.1)
Age (mean ± SD), years	61.41 ± 9.007
Hypertension	15 (88.2)
Diabetes mellitus	4 (23.5)
Hypercholesterolemia	6 (35.2)
Smoking history	5 (29.4)
Obesity	4 (23.5)
Prior STEMI	7 (41.2)
Prior non-STEMI	2 (11.8)
eGFR < 60 ml/min/1.73 m^2	7 (41.2)

eGFR: estimated glomerular filtration rate; STEMI: ST-elevation myocardial infarction

The time interval between procedures was 24 hours. In patients with a prior eGFR <60 ml/min/1.73 m^2, ICA was performed after an additional 24-hour period. All patients were intravenously hydrated with 1000 ml sodium chloride (0.9%) per day during hospitalisation. Oral fluid intake was not assessed. Iopromide (769 mg/ml) was used for CCTA, and iohexol (755 mg/ml) was used for ICA.

The mean contrast volume received was 114.11 ± 7.75 ml for iopromide and 129.7 ± 19.24 ml for iohexol.

The sCr levels and eGFRs at baseline, 24 hours after the first CMA (CCTA), and 24 and 48 hours after the second CMA (ICA) are shown in Table II.

There were no significant differences in the mean sCr level and mean eGFR between baseline and 24 hours after ICA (sCr: 0.92 ± 0.28 vs. 0.92 ± 0.33 mg/dl, F(2.32) = 1.6, p = 0.21; eGFR: 95.43 ± 26.69 vs. 94.48 ± 23.3 ml/min/1.73 m^2, F(2.32) = 1.22, p = 0.29). The sCr level was significantly higher and the eGFR was significantly lower 48 hours after ICA than at baseline (sCr: 0.95 ± 0.08 vs. 0.92 ± 0.28 mg/dl, F(3.48) = 3.08, p = 0.05; eGFR: 91.82 ± 21.84 vs. 95.43 ± 26.69 ml/min/1.73 m^2, F(3.48) = 4.13, p = 0.03). None of the patients met the diagnostic criterion for CIN.

Discussion

CIN affects up to 50% of patients at high risk [3], and it is a clinical reality with high health and economic burdens [5]. In a previous large meta-analysis, James et al. found that the presence of CIN following coronary angiography was associated with increased patient mortality and major cardiovascular events [6].

The risk of CIN after a second contrast exposure has been investigated in a few studies. Trivedi et al. reported a CIN incidence of 14.3% after repeated CMA, even in patients with preserved renal function [7]. On the other hand, Winther et al. performed a study on the effect of repeated CMA in patients with end-stage kidney disease and found a low risk of post-contrast acute kidney injury and long-term complications [8].

In the present study, we investigated the impact of both intra-venous and intra-arterial CMA on renal function assessed according to the sCr level and eGFR. The important finding of our study was the complete absence of CIN, even in patients with prior impaired renal function. Only 1 patient showed a significant decrease in the eGFR, resulting in a change in the classification of kidney disease from 3a to 3b. However, this patient had other risk factors for kidney disease, such as hypertension and insulin-dependent diabetes mellitus. Interestingly, several patients showed better values of sCr and eGFR at 24 hours after the first CMA, supporting the hypothesis of the correction of pre-renal dysfunction after the initial procedure by intravenous administration of sodium chloride (0.9%). It is known that oral hydration can improve renal function after CMA [9,10]. However, data on the extent of oral fluid intake before and after CMA were not available.

Our findings appear to confirm previous results indicating the lack of kidney injury after CMA [11,12]. Sinert et al. compared contrast-exposed patients with contrast-unexposed patients and did not find significant kidney injury after CMA in patients with previously normal renal function. In fact, the incidence of acute kidney injury was greater among patients without CMA than among those with CMA (8.9% vs. 5.7%) [13]. Additionally, McDonald et al. did not find a greater risk of nephropathy development in contrast-exposed patients than in contrast-unexposed patients, irrespective of baseline renal function [14]. These findings question whether CMA or other pathological conditions actually cause degradation of renal function.

The present study had several limitations. First, this study had a small sample size. Second, this retrospective study had a possible selection bias (oral hydration status and other prophylactic treatments to prevent CIN). Third, the sCr level and eGFR at 72 hours or more after the second CMA were not assessed. Renal function might decline late after CMA. Thus, further studies with a large sample size and long assessment period are needed.

In conclusion, although the sCr level was high and eGFR was low 48 hours after the second CMA, repeated CMA was not associated with CIN development at this point, even in patients with impaired renal function prior to CMA. Intravenous administration of sodium chloride (0.9%) might help improve renal function before and after CMA.

Table II. Evolution of serum creatinine (sCr) level and estimated glomerular filtration rate (eGFR)

Parameter	Baseline	24 hours after CCTA	24 hours after ICA	48 hours after ICA
sCr (mean ± SD), mg/dl	0.92 ± 0.28	0.89 ± 0.25	0.92 ± 0.33	0.95 ± 0.08
eGFR (mean ± SD), ml/min/1.73 m2	95.43 ± 26.69	97.68 ± 23.95	94.48 ± 23.3	91.82 ± 21.84

CCTA: coronary computed tomography angiography; ICA: invasive coronary angiography

Author's contribution

VD - Conceptualization, data curation, formal analysis, methodology, supervision, validation, visualization, writing original draft, writing review and editing
MD - Data curation, investigation, methodology, validation, writing review and editing
CM - Conceptualization, formal analysis, methodology, validation, writing original draft
IVS - Data curation, formal analysis, methodology, supervision, writing review and editing
MB - Conceptualization, formal analysis, methodology;, supervision, validation, writing review and editing

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Conflict of interest

None to declare.

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RESEARCH ARTICLE

Predictors of Progression of Coronary Atherosclerosis after Percutaneous Coronary Intervention

Violeta Dinesch[1*], Mihail Dinesch[2], Ileana Voichita Sirbu[3], Cosmin Macarie[3], Bogdan Vasile Halatiu[4], Mircea Buruian[5]

1. University of Medicine and Pharmacy Tirgu Mures, Romania
2. Department of Cardiology, Institute for Cardiovascular Disease and Heart Transplant, Tirgu Mures, Romania
3. Department of Internal Medicine M3, University of Medicine and Pharmacy, Department of Cardiology, Institute for Cardiovascular Disease and Heart Transplant, Tirgu Mures, Romania
4. Department of Physiology, University of Medicine and Pharmacy, Tirgu Mures, Romania
5. Department of Morphologic Sciences M1, University of Medicine and Pharmacy, Tirgu Mures, Romania

Objective: This study investigated predictors of progression of coronary atherosclerosis after percutaneous coronary intervention. Their identification may be useful in clinical practice. **Methods**: We retrospectively reviewed the database of the Cardiology Department of the Cardiovascular Disease and Heart Transplant Institute in Tirgu Mures from January 2012 to December 2015 and identified 180 patients readmitted after successful percutaneous coronary intervention. The t-test, chi-square test, Fisher's exact test, and mono- and multivariate analyses were used to evaluate associations between the patients' clinical and angiographic characteristics and the progression of coronary atherosclerosis. **Results**: The pre-percutaneous coronary intervention atherosclerotic burden was associated with a higher number of new coronary lesions at readmission. Hypertension and the placement of more than one bare-metal stent in the right coronary artery were associated with increased odds of the progression of coronary atherosclerosis. The use of drug-eluting stents at the index percutaneous coronary intervention and a greater number of drug-eluting stents in the left anterior descending artery were associated with a decreased chance of the progression of coronary atherosclerosis. **Conclusions**: A massive atherosclerotic load at index percutaneous coronary intervention and hypertension were predictors of the progression of coronary artery atherosclerosis. The number, type, and localisation of the stent at the index percutaneous intervention could influence the progression of coronary atherosclerosis. Further research is needed to identify other potential predictors and to determine how to optimize the treatment of known predictors.

Keywords: progression of coronary atherosclerosis, percutaneous coronary intervention, drug-eluting stents, bare-metal stent

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Introduction

The impressive progress in coronary stents has been accompanied by a considerable decrease in the need for revascularisation related to the target vessel treated at baseline [1]. Preventing the progression of coronary atherosclerosis by involving new vascular territories after successful percutaneous coronary intervention (PCI) is considered an attractive target. The present study aimed to assess the factors associated with the progression of coronary atherosclerosis after PCI. Their identification and treatment could influence the post-PCI prognosis of patients.

Methods

In order to identify predictors of the progression of coronary atherosclerosis, we reviewed the files of patients hospitalised in the Cardiology Department of the Cardiovascular Disease and Heart Transplant Institute in Tirgu Mures after successful PCI from January 2012 to December 2015. Only patients with coronary angiography upon readmission were included in the study.

The progression of coronary atherosclerosis was defined as follows:

- a reduction of ≥ 10% in the diameter of a pre-existing stenosis ≥ 50%
- 30% reduction in the diameter of a pre-existing stenosis < 50%
- the progression of stenosis to occlusion

The risk factors for cardiovascular disease, comorbidities, details related to the stent used at index PCI (type, number, localisation), and medication after the index PCI were used to compare patients in the group who experienced the progression of coronary atherosclerosis (group B) to those in whom it did not occur (group A).

The data were analysed using the STATA program (version 14.0, Stata Corporation, College Station, TX, USA). Continuous variables were expressed as mean ± standard deviation and were compared using the statistical significance t-tests and linear regression. The categorical variables were expressed as frequency and proportions. Comparisons were made using contingency tables, the chi-square test, and Fisher's exact test. In order to determine the meaning, significance, and strength of the relationships between the variables, logistic regression was used, with the result of

* Correspondence to: Violeta Dinesch
E-mail: doc_violeta@yahoo.com

the mono- and multivariate analyses being described as an odds ratio (OR) associated with a confidence interval of 95%. A p value of 0.05 was considered statistically significant.

The study design was approved by the institutional ethics review board, and all patients provided informed consent.

Results

In 137 patients (76.11%), at least one of the conditions for the progression of coronary atherosclerosis was met, while lesion regression was not found in any patients. Forty-three patients (23.88%) showed stable coronary lesions.

The massive atherosclerotic load found on the index PCI was associated with a higher number of new post-PCI lesions at readmission (p = 0.0002, rho = 0.278), suggesting the progression of coronary lesions (Table I).

The mean duration of follow-up was 29 ± 32 months for group A and 31 ± 32 months for group B (OR 1.001, p = 0.958). The progression of coronary atherosclerosis occurred in the coronary stents in 32 patients (23.35%), in the native coronary arteries in 64 patients (46.71%), and both in the stents and in the native coronary arteries in 41 patients (29.92%).

The demographic and clinical characteristics of the patients are shown in Table II.

A lack of anginal symptoms was a good predictor for group A (OR 0.36, p = 0.018), while acute coronary syn-

Table I. Results of the pre-PCI and readmission coronarography

Parameter		Pre-PCI coronarography	Readmission coronarography
Number of coronary lesions	Monovascular	78 (43.33)	72 (40)
	Bivascular	63 (35)	27 (15)
	Trivascular	34 (18.89)	10 (5.56)
	> 3	5 (2.78)	0
	Without lesions	0	71 (39.44)
Coronary lesion localisation	Left main coronary artery	6 (1.8)	4 (2.22)
	LAD	128 (39.38)	43 (23.88)
	RCA	85 (26.15)	46 (25.55)
	Left circumflex coronary artery	60 (18.46)	18 (10)
	Other coronary artery	43 (14.15)	43 (23.88)

Data are expressed as number (%).
LAD: Left anterior descending artery; PCI: percutaneous coronary intervention; RCA: right coronary artery

Table II. Demographic and clinical characteristics: group A vs group B

Parameter		Group A 43 (23.88)	Group B 137 (76.11)	p
Age, years		61.17 ± 8.34	62.25 ± 10.38	0.595*
Male sex		32 (74.41)	99 (72.26)	0.745**
Cardiovascular risk factors	Hypertension	34 (79.06)	126 (91.19)	0.004**
	Diabetes mellitus	7 (16.27)	30 (21.89)	0.428**
	Obesity	15 (34.83)	35 (25.54)	0.225**
	Smoking	4 (9.3)	19 (13.86)	0.738**
	Hypercholesterolaemia	20 (46.51)	64 (46.71)	0.993**
Comorbidities	Prior myocardial infarction	18 (41.86)	72 (52.55)	0.216**
	Prior aortocoronary bypass	2 (4.65)	7 (5.1)	1**
	eGFR ≤ 60 ml/min/1.73 m^2	8 (18.6)	35 (25.54)	0.352**
	Ejection fraction < 50%	8 (18.6)	32 (23.35)	0.516**
Type of readmission	Chronic	37 (86.36)	86 (67.15)	0.016**
	Emergency	6 (9.3)	45 (32.8)	
Diagnostic at readmission	Stable angina	26 (60.46)	72 (52.55)	0.34**
	Unstable angina	3 (6.97)	33 (24.08)	0.015***
	Acute myocardial infarction	0	9 (6.56)	0.117***
	Cardiological reassessment	12 (27.9)	17 (12.4)	0.015***
Number of stents/patient		1.62 ± 0.92	1.54 ± 0.96	0.313***
Type of stent	DES	18 (41.86)	35 (25.54)	0.038**
	BMS	28 (65.11)	107 (78.1)	0.069**
DES localisation at index PCI	Left main coronary artery	1 (2.32)	3 (2.18)	1***
	LAD	11 (25.58)	22 (16.05)	0.154***
	RCA	6 (13.95)	11 (8.02)	0.243***
	Left circumflex coronary artery	3 (6.97)	6 (4.37)	0.446***
	Other coronary artery	3 (6.97)	5 (3.64)	0.398***
BMS localisation at index PCI	Left main coronary artery	1 (2.32)	1 (0.72)	0.421***
	LAD	19 (44.18)	56 (40.87)	0.686***
	RCA	4 (9.3)	40 (29.19)	0.007***
	Left circumflex coronary artery	8 (18.6)	22 (16.05)	0.689**
	Other coronary artery	4 (9.3)	18 (13.13)	0.602**
Medical therapy	Aspirin	16 (37.2)	57 (41.6)	0.612**
	Dual platelet anti-aggregation	24 (55.81)	68 (49.6)	0.458**
	Angiotensin-converting enzyme inhibitor	21 (48.83)	90 (66.35)	0.041**
	Statin	34 (79.06)	94 (68.61)	0.153**

Data are expressed as number (%) or mean ± standard deviation.
*t-test; **Fisher exact test; ***chi-square test
BMS: bare-metal stents; DES: drug-eluting stents LAD: Left anterior descending artery; PCI: percutaneous coronary intervention; RCA: right coronary artery

drome statistically correlated with group B (OR 5.98, p = 0.004). Stable angina symptomatology did not indicate a significant association with either of the groups (OR 0.7, p = 0.341).

The use of drug-eluting stents at the index PCI and a greater number of drug-eluting stents at the left anterior descending artery (LAD) level decreased the chances for the patient to have progression of coronary atherosclerosis (OR 0.466, p = 0.04, and OR 0.52, p = 0.05) (Table III).

The use of bare-metal stents at the index PCI doubled the chances of the patient being in group B (OR 2), but the statistical significance was poor (p = 0.072). Instead, the placement of more than one bare-metal stent in the right coronary artery almost tripled the chances of being in group B (OR 2.81, p = 0.022) (Table III).

The progression of coronary atherosclerosis in the native coronary artery occurred most frequently in the LAD and the right coronary artery (OR 20.66, p = 0.004 and OR 10.52, p = 0.002) (Figure 1). Of the cardiovascular risk factors, only hypertension was statistically associated with the progression of atherosclerotic lesions (p = 0.004). We found a statistically significant association between the use of angiotensin-converting-enzyme inhibitors (ACEI) and the progression of coronary atherosclerosis (p = 0.041).

Discussion

In our study population, the predictors for the progression of coronary atherosclerosis after successful PCI were a greater pre-PCI atherosclerotic burden, in particular hypertension, and the placement of more than one bare-metal stent in the right coronary artery. The use of drug-eluting stents and a greater number of drug-eluting stents in the LAD were associated with a lack of progression of coronary atherosclerosis. In the native coronary artery, progression of atherosclerosis occurred more frequently in the LAD and in the right coronary artery territory.

Pre-PCI multi-vascular coronary lesions are commonly associated with the development of new post-PCI coronary lesions [2,3]. In agreement with previous research, a positive correlation was found in our study between the massive atherosclerotic load found on pre-PCI coronarography and multi-vascular coronary heart disease upon re-admission, suggesting the progression of existing coronary lesions or the occurrence of new lesions. The progression of coronary atherosclerosis was found in two-thirds of our patients, but regression was not found in any patients.

Hypertension is a well-known atherogenic risk factor [4]. In our study, hypertension was the only cardiovascular risk factor associated with progression of coronary

Table III. Correlation between the progression of coronary atherosclerosis and the stents type, their number, and localisation in coronary artery

Stent type	Localisation at index PCI	Stents number			p	OR	SE	95% CI
		1	2	3				
DES	Left main coronary artery	4 (9.3)	0	0	0.956	0.94	1.095	0.0948567-9.265621
	LAD	27 (62.79)	6 (13.95)	0	0.045	0.52	0.16	0.2737484-0.9865113
	RCA	16 (37.2)	1 (2.3)	0	0.352	0.626	0.21	0.2338576-1.676849
	Left circumflex coronary artery	8 (18.6)	1 (2.3)	0	0.277	0.515	0.315	0.1553879-1.706088
	Other coronary artery	7 (16.27)	1 (2.3)	0	0.542	0.67	0.44	0.1864483-2.415322
BMS	Left main coronary artery	2 (1.45)	0	0	0.408	0.3	0.44	0.0188164-5.031484
	LAD	64 (46.71)	10 (7.29)	1 (0.72)	0.524	0.84	0.23	0.4886101-1.439753
	RCA	32 (23.35)	9 (6.56)	3 (2.15)	0.022	2.81	1.26	1.164559-6.802204
	Left circumflex coronary artery	29 (21.16)	1 (0.72)	0	0.784	0.89	0.388	0.3758553-2.093628
	Other coronary artery	21 (15.32)	1 (0.72)	0	0.461	1.51	0.85	0.5033165-4.55136

Data are expressed as number (%)
BMS: bare-metal stents; DES: drug-eluting stent; LAD: left anterior descending artery; OR: odds ration; PCI: percutaneous coronary intervention; RCA: right coronary artery; SE: standard error; CI: confidence interval

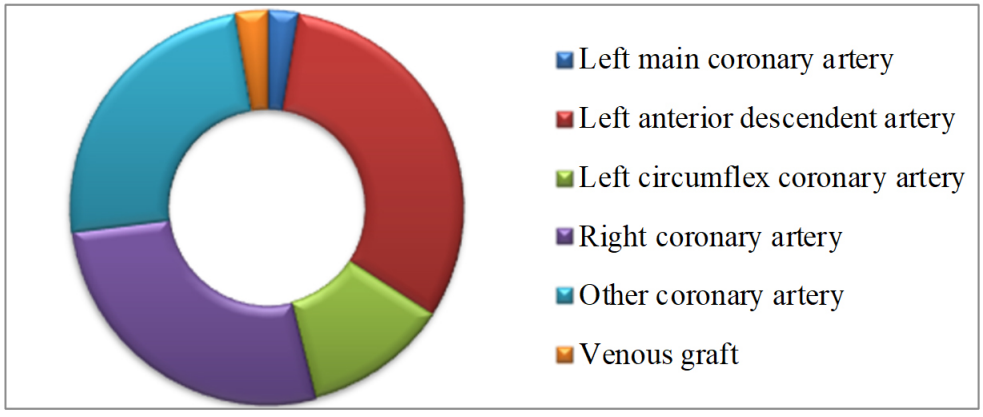

Fig. 1. Progression of atherosclerosis in the native coronary artery by location

atherosclerosis. Similar to our study, Borges et al. found that hypertension, along with male sex, is a predictive factor for the progression of coronary atherosclerosis [5]. The importance of aggressive treatment of all risk factors for cardiovascular disease is highlighted in the COURAGE trial, where patients with optimal medical therapy (intensive pharmacologic therapy and lifestyle intervention) had fewer cardiovascular events than PCI-treated patients [6].

The superiority of using drug-eluting stents compared to bare-metal stents in order to reduce the need for revascularisation related to the initially treated target vessel has been demonstrated in several trials [7,8]. However, in a study involving 428 patients randomised to PCI with drug-eluting stents or bare-metal stents, Zelwegger et al. concluded that the progression of coronary atherosclerosis was similar between the two groups regardless of the type of stent used in the index PCI [9]. In our study, the use of drug-eluting stents at the index PCI was a predictor for the absence of the progression of coronary atherosclerosis.

The progression of coronary atherosclerosis in the native coronary arteries has shown conflicting data. In the CASS trial, in patients treated with CABG, the progression of coronary atherosclerosis was more aggressive in LAD territory [10]. Additionally, Borges et al. found that PCI-treated patients had more progression of coronary atherosclerosis in LAD territory [5]. On the contrary, in the INTACT trial, the progression of coronary atherosclerosis occurred more frequently in the right coronary artery territory [11]. In our study, first the LAD and then the right coronary artery territory was associated with the progression of coronary atherosclerosis. Interestingly, in our study, a greater number of drug-eluting stents in the LAD was associated with a lack of progression of coronary atherosclerosis, while the placement of more than one bare-metal stent in the right coronary artery was a predictor for the progression of coronary atherosclerosis. We did not find any data in the literature about the association between placement, the number of drug-eluting stents/bare-metal stents at index PCI, and the progression of coronary atherosclerosis.

Numerous studies have demonstrated the beneficial effects of ACEI in patients with ischemic coronary artery disease, not only in reducing blood pressure but also in stabilising the atheromatous plaque and inducing the regression of uncalcified coronary stenoses [12,13]. In contrast, our study found a statistically significant association between the presence of ACEI and the progression of coronary atherosclerosis. This can be explained from at least from two points of view. First, hypertension, whose first line of treatment is ACEI, was statistically associated with the same group. Secondly, the study did not investigate the type and intensity of treatment with ACEI, and the effect of ACEI is not equal for all components of the class.

Our study has a few limitations. The present study was a single centre, retrospective study, and thus, our conclusions are not generalisable. Second, the small sample size reduced the statistical power to detect association with other predictive factors for the progression of coronary atherosclerosis.

Conclusion

A massive pre-PCI atherosclerotic load and hypertension were predictors of the progression of coronary artery atherosclerosis. The number, type, and localisation of the stent at the index percutaneous intervention could influence the progression of coronary atherosclerosis. Further research is needed in order to identify other potential predictors and to determine how to optimize the treatment of known predictors.

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Conflict of interest

None to declare.

Author's contribution

VD - Conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, visualization, writing original draft, writing review and editing
MD - Conceptualization, data curation, formal analysis, investigation, supervision, writing review and editing
IVS - Conceptualization, formal analysis, methodology, validation, writing review and editing
CM - Data curation, formal analysis, methodology, visualization, writing review and editing
BVH - Conceptualization, data curation, formal analysis, visualization, writing review and editing
MB - Conceptualization, formal analysis, methodology;, supervision, validation, visualization, writing review and editing

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