Effect and significance of hyperlipoproteinemia on stent thrombosis in patients with implanted drug-eluting stents: The 5-year follow up study

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ABSTRACT

Background: Elevated blood lipid level, also known as hyperlipoproteinemia (HLP), is the most common metabolic disorder in the general population. According to US National Heart Institute data, about 36% of adults and 10% of children aged 9 to 12 have elevated cholesterol levels. The risk of ischemic heart disease increases by 2-3% with every 1% increase in total cholesterol levels. Therefore, men aged 55-65 with a 10% increase in total cholesterol have about 38% increased ischemic heart disease mortality. The study's main objective is to determine the occurrence of thrombotic complications in patients in whom first-generation drug-eluting stents are implanted and how these events are influenced by the presence of HLP.

Methods: The study is retrospective, clinical, and non-interventional with a five-year follow-up period for each patient. Initially, 800 patients undergoing index percutaneous coronary angioplasty with sirolimus-eluting and paclitaxel-eluting stent implantation were enrolled. Clinical data collected included cardiac disorders, the presence of diabetes mellitus, hyperlipoproteinemia, and smoking as a risk factor. In the examined group of patients, stent thrombosis was monitored according to Academic Research Consortium (ARC) criteria.

Results: The study included 800 patients who underwent percutaneous coronary angioplasty index. At the end of the follow-up period, 701 patients (87.6%) completed the clinical trial and were included in the statistical analysis. Stent thrombosis, determined according to ARC criteria, was reported as 'definitive stent thrombosis' in 22 patients (3.06%), 'probable stent thrombosis' in 1 patient (0.14%), and 'possible stent thrombosis' in 1 patient (0.14%). Of the 404 patients with HLP, 120 patients had a total cholesterol value >300 mg/dL. Twenty patients with definitive stent thrombosis had cholesterol >300 mg/dL. Patients with probable and possible stent thrombosis did not have HLP. A comparison of patients with stent thrombosis, with HLP and without HLP, revealed a statistically significant difference (16.67% vs. 1.35%, p <0.001). Comparing patients with unstable angina pectoris, with cholesterol value >300 mg/dL and without HLP, a statistically significant difference was observed (71.7% vs. 17.2%, p <0.001).

Conclusions: We report on the long-term follow up of patients with stent thrombosis after drug-eluting stent insertion with and without HLP. The results suggest that HLP influences the development of coronary disease, with a significant influence on complications following percutaneous coronary intervention.

Keywords: Stents; Hyperlipoproteinemia; Thrombosis; Coronary artery disease. **[Am J Med Sci 2022;364(6):758–765.]**

INTRODUCTION

Hyperlipoproteinemia (HLP) is defined as the increased content of individual lipoproteins in the blood. The importance of high lipid levels in serum, and especially elevated cholesterol as a risk factor for coronary artery disease, has been increasingly recognized. General consensus on the beneficial effects of cholesterol reduction has led to the establishment of national educational programs to address cholesterol and other lipids.[1] Percutaneous coronary intervention (PCI) has become a major therapeutic procedure for the treatment of coronary artery disease (CAD) in the past 30 years. However, several large-scale clinical trials have confirmed that even in the era of drug-eluting stents (DES), the rate of in-stent restenosis (ISR) after coronary artery stent implantation still ranges from 3% to 20%.[2] Factors affecting stent thrombosis can be divided into three groups:

clinical factors, factors related to lesions, and procedural factors. Clinical factors that have the greatest impact on the occurrence of stent thrombosis are age, diabetes mellitus, HLP, and unstable coronary heart disease.

The lesion characteristics in stent thrombosis are also significant.[3] Types of stent thrombosis are considered ACUTE (24 hours from stent implantation), SUBACUTE (24 hours to 30 days after stent implantation), LATE (30 days to 1 year from stent implantation), and VERY LATE (more than one year after stenting). A new definition of stent thrombosis has been proposed by the Academic Research Consortium (ARC). Some authors believe that using ARC's definition of stent thrombosis provides the best estimate of the true frequency of this phenomenon. Stent thrombosis are classified as: Definitive (angiographic evidence of stent thrombosis with clinical signs of myocardial ischemia within 48 h), Probable (unexplained death within 30 days after stenting and myocardial infarction of the stent artery region), or Possible (an unspecified death after more than 30 days from stent implantation).[4]

Using the above classification system, our study's goal was to determine the thrombotic complications in patients in whom first-generation drug-eluting stents were implanted depending on the existence of HLP. Following this primary goal, other objectives included: 1) analysis of the incidence of acute, subacute, distant, and very distant thrombosis, depending on the existence of HLP in patients in whom first-generation drug-coated stents are implanted; and 2) analysis of the effect of HLP on the incidence of stent thrombosis. We hypothesized that stent thrombosis in patients with first-generation drug-eluting stents is more common in patients with HLP.

METHODS

Ethical concerns

The clinical study was approved by the Ethics Committee of the Institute for Cardiovascular Diseases on December 22, 2016, number 378/2017. All procedures are performed according to the Good Clinical Practice (GCP), Declaration of Helsinki (1964), and guidelines of ethics.

Protocol of study

The study was retrospective, clinical, non-interventional, with a five-year follow-up period for each patient. All consecutive patients at the Institute of Cardiovascular Disease "Dedinje" with sirolimus-eluting stent (Cypher®) or paclitaxel-eluting stent (Taxus®), were followed for five years.

Data collection

Initially, 800 patients undergoing index percutaneous coronary angioplasty with sirolimus-eluting and paclitaxel-eluting stent implantation were enrolled. Patients' clinical data collected included cardiac disorders such as or absence of angina, myocardial infarction, re-coronary angiography, re-surgery, and load test results. In addition, we noted outpatient visits and telephone contacts with the patient. Data also included demographic and angiographic data. Telephone interviews with patients were based on a questionnaire containing the contact details of the patient, presence of diabetes mellitus, HLP, smoking history, information on the occurrence of death, hospitalization for cardiac reasons, myocardial infarction, and percutaneous coronary re-intervention or surgical myocardial revascularization. Based on the questionnaire, if judged to have significant angina pectoris, the patients were invited to an outpatient examination for non-invasive testing. In case of ischemia, subjects were sent to coronary angiography and subsequent percutaneous myocardial revascularization or surgery or resumed therapy conservatively. In the examined group of patients, stent thrombosis was monitored according to ARC criteria.

Statistical analysis

For the presentation of data, descriptive statistical measures were used in addition to the description of the surveyed groups, namely: measures of central tendency (arithmetic mean and meridians), measures of variability (interval of variation and standard deviation) and relative numbers. Parametric and non-parametric methods of inferential statistics were used for data analysis, depending on the proven distribution of the data. Methods for examining the significance of differences were used for the mutual comparison of the study groups: one-factor numerical analysis of variance (ANOVA), Student's t-test, rank-sum test (Mann-Whitney U test) and Chi-square test. To determine the significance of the influence of individual factors on the occurrence of thrombosis after a certain period of intervention, methods were used to test the association; namely, univariate and multivariate logistic regression analysis (Cox analysis). Differences between groups were considered significant at $p<0.05$. Complete statistical analysis of the data was conducted with the statistical software package, SPSS Statistics 18 (Chicago, Illinois, USA).

RESULTS

The study included 800 patients from the Institute for Cardiovascular Diseases Dedinje who underwent index percutaneous coronary angioplasty with implantation of drug-eluting stents (sirolimus [Cypher®] and paclitaxel [Taxus®]). After the index procedure, 701 patients (87.6%) completed five years of clinical monitoring and their data were subjected to statistical analysis (Table 1). Of these patients, 584 (83.3%) were male. Twenty four

Table 1. Baseline clinical data.

General characteristics of the respondents	Patients: grouped by TC level (mg/dL)				*p* Value	*p* Value (A *vs.* B)	*p* Value (A *vs.* C)	*p* Value (B *vs.* C)
	[ALL] *N=701*	A: <200 mg/dL *N= 297*	B: 200-300 mg/dL *N=284*	C: >300 mg/dL *N=120*				
Gender:					0.992[a]	0.896[a]	0.967[a]	0.954[a]
Male	584 (83.3%)	248 (83.5%)	236 (83.1%)	100 (83.3%)				
Female	117 (16.7%)	49 (16.5%)	48 (16.9%)	20 (16.7%)				
Age, years (M ± SD)	51.98±6.28	51.42±6.59	52.50±5.91	52.10±6.28	0.116[b]	0.05[c]	0.316[c]	0.563[c]
Smoking Status:					0.01[a]	0.01[a]	0.01[a]	0.480[a]
Negative	444 (63.3%)	168 (56.6%)	191 (67.3%)	85 (70.8%)				
Positive	257 (36.7%)	129 (43.4%)	93 (32.7%)	35 (29.2%)				
Comorbidities:								
Diabetes mellitus	50 (7.1%)	18 (6.1%)	16 (5.6%)	16 (13.3%)	0.05[a]	0.827[a]	0.05[a]	0.01[a]
Hypertension arterial	232 (33.1%)	74 (24.9%)	80 (28.2%)	78 (65.0%)	< 0.001[a]	0.374[a]	< 0.001[a]	< 0.001[a]
Myocardial infarction	9 (1.3%)	3 (1.0%)	3 (1.1%)	3 (2.5%)	0.429[a]	0.956[a]	0.247[a]	0.273[a]
Renal disease	31 (4.4%)	9 (3.0%)	11 (3.9%)	11 (9.2%)	0.05[a]	0.577[a]	0.01[a]	0.05[a]
HDL (mg/dL):					<0.001[a]	<0.001[a]	<0.001[a]	<0.001[a]
35-55	283 (40.4%)	147 (49.5%)	111 (39.1%)	25 (20.8%)				
< 35	267 (38.1%)	15 (5.1%)	157 (55.3%)	95 (79.2%)				
> 55	151 (21.5%)	135 (45.5%)	16 (5.6%)	0 (0.0%)				
LDL (mg/dL):					<0.001[a]	<0.001[a]	<0.001[a]	<0.001[a]
< 100	157 (22.4%)	145 (48.8%)	12 (4.2%)	0 (0.0%)				
100-129	240 (34.2%)	140 (47.1%)	100 (35.2%)	0 (0.0%)				
130-190	213 (30.4%)	12 (4.0%)	172 (60.6%)	29 (24.2%)				
> 190	91 (13.0%)	0 (0.0%)	0 (0.0%)	91 (75.8%)				
Triglyceride (mg/dL):					<0.001[a]	<0.001[a]	<0.001[a]	<0.001[a]
< 150	95 (13.6%)	70 (23.6%)	17 (6.0%)	8 (6.7%)				
150-199	368 (52.5%)	188 (63.3%)	162 (57.0%)	18 (15.0%)				
200-499	231 (33.0%)	38 (12.8%)	102 (35.9%)	91 (75.8%)				
> 500	7 (1.0%)	1 (0.3%)	3 (1.1%)	3 (2.5%)				
STEMI	4 (0.6%)	1 (0.3%)	1 (0.4%)	2 (1.7%)	0.216[a]			
NSTEMI	5 (0.7%)	2 (0.7%)	2 (0.7%)	1 (0.8%)	0.984[a]			
Unstable AP	288 (41.1%)	51 (17.2%)	151 (53.2%)	86 (71.7%)	<0.001[a]	<0.001[a]	<0.001[a]	0.01[a]
Statin	677 (96.6%)	297 (100.0%)	280 (98.6%)	100 (83.3%)	<0.001[a]	0.05[a]	<0.001[a]	<0.001[a]
Dual antiplatelet Therapy	701 (100%.0)	297 (100%)	284 (100%)	120 (100%)	*NA*	*NA*	*NA*	*NA*
Re - PCI	103 (14.7%)	31 (10.4%)	35 (12.3%)	37 (30.8%)	<0.001[a]	0.474[a]	<0.001[a]	<0.001[a]
Surgical Revascularization	42 (6.0%)	12 (4.0%)	20 (7.0%)	10 (8.3%)	0.155[a]	0.113[a]	0.076[a]	0.651[a]

Abbreviations: NA, not applicable; Re-PCI, repeated revascularization; TC, total cholesterol; unstable AP, unstable angina pectoris.
[a] Chi-square test,
[b] ANOVA test,
[c] Tukey Post Hoc Test.

patients had stent thrombosis, which were categorized according to ARC criteria; 22 patients (3.06%) had 'definitive stent thrombosis', of which 5 patients (0.7%) underwent surgical re-vascularization of the myocardium, and 17 patients (2.36%) had re-PCI, one patient (0.14%) had 'probable stent thrombosis' and 1 patient (0.14%) had 'possible stent thrombosis'.

Patients were divided into three groups based on total cholesterol (TC) value: group A TC <200 mg/dL (n=297), group B TC 200-300 mg/dL (n=284) and group C TC >300 mg/dL (n=120). Groups B and C represent patients with HLP.

Of the 404 patients with HLP, TC values >300 mg/dL were measured in 120 patients. Twenty two patients had stent thrombosis and HLP, all of which were classified as definitive stent thrombosis, 20 had TC >300 mg/dL.

The number of patients with myocardial infarction was similar in groups A (TC <200 mg/dL, 1.0%) and B (TC 200-300 mg/dL, 1.1%), while 2.5% of group C (TC >300 mg/dL) had myocardial infarction. There was a statistically significant difference between all three examined groups concerning the values of high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides.

Regarding the presence of diabetes mellitus, there was a statistically significant difference between group A (TC <200 mg/dL) and group C (TC >300 mg/dL) as well as between group B (TC 200-300 mg/dL) and group C (TC >300 mg/dL). In contrast, there was no statistically significant difference between groups A and B. Of note, there was a significant difference in smoking status between the three groups (A, B, C). Positive smoking status was more common in group A (TC <200 mg/dL, 43.4%) when compared to groups B (TC 200-300 mg/dL, 32.7%) and C (TC >300 mg/dL, 29.2%) (Table 1).

We then compared the number of diseased vessels, the number of vessels treated with angioplasty, which vessels received the stent, the incidence of complex angioplasty, and the incidence of major complications in groups A (TC <200 mg/dL), B (TC 200-300 mg/dL), and C (TC >300 mg/dL). Regarding the number of diseased vessels, there was a statistically significant difference between groups A (TC <200 mg/dL) and C (TC >300 mg/dL) and between groups B (TC 200-300 mg/dL) and C (TC >300 mg/dL). Regarding the number of vessels treated with angioplasty, there was also a statistically significant difference between groups A (TC <200 mg/dL) and C (TC >300 mg/dL) and groups B (TC 200-300 mg/dL) and C (TC >300 mg/dL). A statistically significant difference also existed only between groups A (TC <200 mg/dL) and B (TC 200-300 mg/dL) when evaluating vessels receiving stents (Table 2). The occurrence of stent thrombosis (definitive, probable, and possible) is shown in Table 3.

Survival analysis represents the time until the observed event occurs; in our study, the observed event was stent thrombosis. Specifically, we evaluated the time, in hours, until 50% of thrombosis events occured. When we look at the median, we observe that for group 2 it was 30 hours (Table 4 and Figure 1).

Table 5 presents the values of the Chi square test and its statistical significance as part of pairwise comparisons and shows that by comparing all three groups, A to B, A to C and B to C, using Log-rank test for even comparisons that groups A and B were significantly different than group C at the probability level of p <0.001 (Table 5). Based on the results in Tables 4 and 5, it is concluded that patients with HLP >300 mg/dL were significantly more likely to experience stent thrombosis and most of these events occur within 48h.

DISCUSSION

In our study of 701 patients, 404 patients (57.5%) had HLP, highlighting the relationship between HLP and the occurrence of coronary artery disease. Of the 24 patients with stent thrombosis, 20 had HLP, which suggests that HLP contributes to the development of coronary artery disease. Also, the results of this study suggest that HLP influences stent thrombosis.

Stent thrombosis is an acute ischemic event angiographically documented as Thrombolysis in Myocardial Infarction (TIMI) flow 0 or 1, i.e., the existence of a thrombus that limits the flow in the stent segment.[5] Success after dilatation or recanalization of a blood vessel is assessed using the TIMI classification: TIMI I: occlusion with a description of a small part of the distal section of a blood vessel. TIMI II: describing a blood vessel distal to the stenosis with prolonged contrast agent flow unlike other blood vessels. TIMI III: normal inflow and contrast output.[6,7] A "clinically susceptible" stent thrombosis is a clinical manifestation that corresponds to an acute ischemic event in the presence of electrocardiographic changes corresponding to the stent segment (artery), which implies sudden death within 30 days of intervention, and a broader definition involves sudden unexplained death over a period longer than 30 days. Consistent with the results in our study, thrombosis usually occurs during the first 48 hours following percutaneous coronary intervention, and significantly less during the first week after insertion of the stent.[8,9] The incidence of coronary stent thrombosis as a complication of percutaneous coronary intervention is from 0.4% to 2.8% in patients with multiple stents.[10,11] Stent thrombosis presents a serious complication that almost always causes a fatal outcome or non-fatal myocardial infarction (MI), usually associated with elevation of the ST segment.

We observed that HLP was associated with the occurrence of stent thrombosis. This is important, as HLP is the most common metabolic disorder in the general population. According to the US National Heart Institute data, about 36% of adults and 10% of children aged 9 to 12 have elevated cholesterol levels. The risk of

Table 2. Angiographic and interventional studies.

	Patients: grouped by TC level				*p* Value	*p* Value (A *vs.* B)	*p* Value (A *vs.* C)	*p* Value (B *vs.* C)
	[ALL] *N=701*	A: <200 mg/dL *N=297*	B: 200-300 mg/dL *N=284*	C: >300 mg/dL *N=120*				
Number of diseased vessels:					<0.001	0.295	<0.001	<0.001
Single vessel	359 (51.2%)	185 (62.3%)	159 (56.0%)	15 (12.5%)				
Two vessels	299 (42.7%)	97 (32.7%)	107 (37.7%)	95 (79.2%)				
Three vessels	43 (6.1%)	15 (5.1%)	18 (6.3%)	10 (8.3%)				
Number of vessels treated with angioplasty:					<0.001	0.190	<0.001	<0.001
Single vessel	410 (58.5%)	195 (65.7%)	180 (63.4%)	35 (29.2%)				
Two vessels	269 (38.4%)	97 (32.7%)	92 (32.4%)	80 (66.7%)				
Three vessels	22 (3.1%)	5 (1.7%)	12 (4.2%)	5 (4.2%)				
Vessel receiving the stent					0.05	0.01	0.073	0.510
LAD	31 (4.4%)	11 (3.7%)	12 (4.2%)	8 (6.7%)				
Circumflex	564 (80.5%)	255 (85.9%)	217 (76.4%)	92 (76.7%)				
Right coronary artery	106 (15.1%)	31 (10.4%)	55 (19.4%)	20 (16.7%)				
Incidence of complex angioplasty								
Left main	1 (0.1%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0.479	0.306	*NA*	0.515
Multiple vessels	11 (1.6%)	1 (0.3%)	0 (0.0%)	10 (8.3%)	<0.001	0.328	<0.001	<0.001
Long lesions	16 (2.3%)	5 (1.7%)	0 (0.0%)	11 (9.2%)	<0.001	0.05	<0.001	<0.001
Small vessels	13 (1.9%)	4 (1.3%)	4 (1.4%)	5 (4.2%)	0.119	0.949	0.073	0.086
Incidence of major complication (arterial dissection)	3 (0.4%)	1 (0.3%)	0 (0.0%)	2 (1.7%)	0.061	0.328	0.146	0.05

Abbreviations: LAD, left anterior descending artery; NA, not applicable, TC, total cholesterol.
Chi-square test was performed.

Table 3. Patient outcomes and follow up.

	Patients: grouped by TC level				p
	[ALL]	A: <200 mg/dL	B: 200-300 mg/dL	C: >300 mg/dL	
Total patients with stent thrombosis	24 / 701 (3.42%)	4 / 297 (1.35%)	0 / 284 (0.0%)	20 / 120 (16.67%)	< 0.001
Category of stent thrombosis:					0.01
Definitive (in the first 48h)	22 / 701 (3.14%)	2 / 297 (0.67%)	0 / 284 (0.0%)	20 / 120 (16.67%)	
Probable (in the first 30 days)	1 / 701 (0.14%)	1 / 297 (0.34%)	0 / 284 (0.0%)	0 /120 (0.0%)	
Possible (after 30 days)	1 / 701 (0.14%)	1 / 297 (0.34%)	0 / 284 (0.0%)	0 /120 (0.0%)	
Outcomes - death	0 / 701 (0.0%)	0 / 297 (0.0%)	0 / 284 (0.0%)	0 /120 (0.0%)	

Abbreviation: TC, total cholesterol.
Chi-square test was performed; number of patients/total patients (%) are shown in table.

Table 4. Means and medians for survival time.

HLP: grouped by TC level	Mean[a] (hours)				Median (hours)			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
A: <200 mg/dL	1545	8	1528	1561	.	.	.	.
B: 200-300 mg/dL	1517	12	1492	1542	.	.	.	.
C: >300 mg/dL	137	104	,000	342	30	5	19	40
Overall	1510	10	1490	1530	.	.	.	.

Abbreviations: HLP, hyperlipoproteinemia; TC, total cholesterol.
[a] Estimation is limited to the largest survival time if it is censored.

ischemic heart diseases increases by 2-3% with every 1% increase in TC levels. Therefore, men aged 55-65 with a 10% increase in TC have about 38% increased risk of ischemic heart disease mortality. According to the Framingham studies, men with TC greater than 300 mg/dL and women with greater than 250 mg/dL are 3-5 times more likely to develop ischemic heart disease over the next five years.[12] Numerous studies have shown

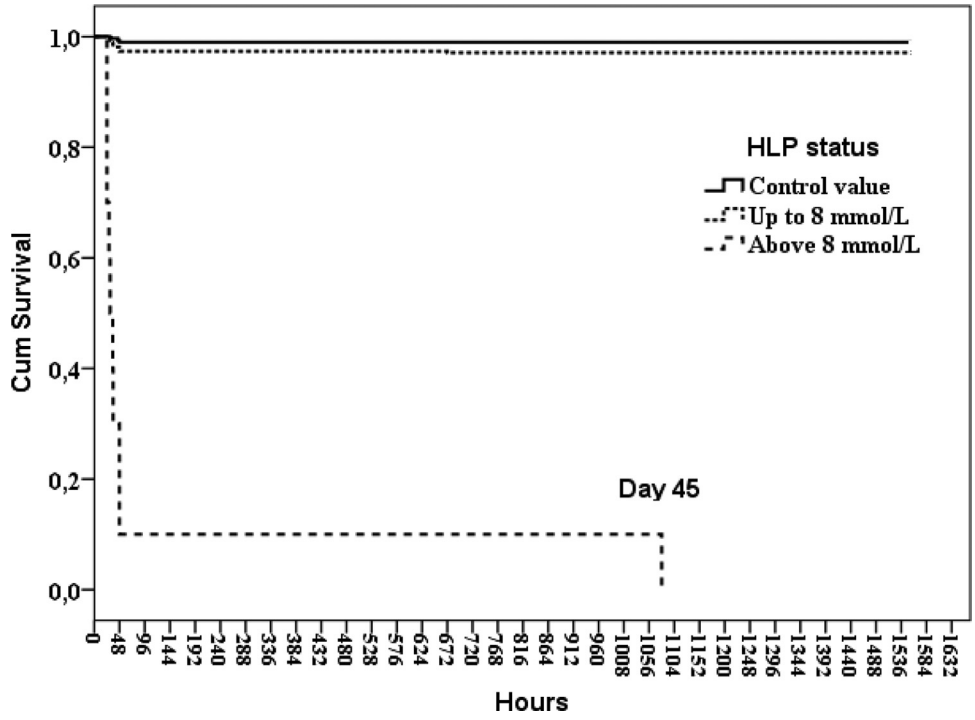

FIGURE 1. Survival analysis after thrombosis depending on the HLP status of patients.

Table 5. Log Rank test for pairwise comparisons.

HLP: grouped by TC level		A: <200 mg/dL		B: 200-300 mg/dL		C: >300 mg/dL	
		Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
Log Rank (Mantel-Cox)	**A: <200 mg/dL**			3,169	,075	437,362	,000
	B: 200-300 mg/dL	3,169	,075			341,480	,000
	C: >300 mg/dL	437,362	,000	341,480	,000		

Abbreviations: HLP, hyperlipoproteinemia; TC, total cholesterol.

that reducing LDL cholesterol alone can reduce the morbidity and mortality of ischemic heart disease by about 40%. This indicates the importance of detecting and treating lipid levels to prevent cardiovascular disease.[13,14]

Drug-eluting stents (DES) have become an important component of the toolbox for the treatment of coronary artery disease. However, the success of DES is highly dependent on each component of the complex and the interaction between the elements of the complex itself.[15] Distinct DES have different potential to inhibit neointimal proliferation. Since experiments on animal models cannot be directly translated into the human population, the results of clinical studies are used.[16] Sirolimus- and paclitaxel-eluting stents are a safe and effective agent in percutaneous coronary interventions conducted to treat atherosclerotic coronary artery disease.

The limitations of this study include its retrospective nature and the lack of information on other factors that might contribute to the outcomes studied. However, overall, our results are in line with previous scientific studies that show the influence of risk factors such as HLP and diabetes mellitus on the occurrence of coronary heart disease. In 2020, Farshid et al showed a significant impact of HLP and diabetes mellitus ($p = 0.008$ and 0.037 for females and males, respectively) on the development of coronary heart disease. In this study, the statistical significance was more pronounced in the female population.[17] In 2017, Reinhard et al observed a significant decline in the mean annual rate of major cardiac adverse events after a five-year follow-up of 154 patients after lipoprotein apheresis.[18]

In summary, our study, performed in a large cohort of subjects followed for a significant period, adds to the current literature pointing to HLP as an important contributor to stent thrombosis in the setting of coronary artery disease.

CONCLUSIONS

We can conclude that HLP affects the development of coronary disease, with a significant influence on the occurrence of complications after percutaneous coronary intervention.

AUTHOR CONTRIBUTIONS

MS designed the study, collected data, and wrote the paper. VIC analyzed data and performed the statistical analysis. All authors approved the final version of the manuscript.

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None.

CONFLICTS OF INTEREST

The authors declare that there is no potential conflict of interest regarding the publication of this article.

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