"OVIDIUS" UNIVERSITY OF CONSTANȚA
DOCTORAL SCHOOL OF MEDICINE
ACADEMIC YEAR 2022-2023

DOCTORAL THESIS
-abstract-

Characteristics of cardiovascular involvement in persons living with human immunodeficiency virus

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CONSTANȚA

2023

CONTENT

INTRODUCTION

Cardiovascular involvement has become an important cause of morbidity and mortality in people living with HIV (PLWH). Although the incidence of HIV-related heart disease has decreased, PLWH have a 1.5-2 times grater risk of developing cardiac diseases (1). Incidence of coronary artery disease (CAD) in PLWH is continuously increasing in countries with wide antiretroviral access, becoming one of the most important etiologies of cardiac damage. They have a higher prevalence of traditional and particular risk factors, such as endothelial dysfunction, inflammation and antiretroviral therapy. Protease inhibitors may increase cardiovascular risk due to metabolic disturbance, especially by affecting the lipid profile. Certain Nucleoside Reverse Transcriptase Inhibitors (NRTIs) may increase the atherosclerosis process and lead to acute coronary syndrome through a direct effect on the endothelium, possibly exacerbating vascular smooth muscle cell injury. Abacavir can lead to intimal hyperplasia in patients treated by revascularization by percutaneous coronary intervention with drug eluting stent, thereby increasing the risk of coronary syndrome recurrence. Few and very different literature data related to the coronary artery disease extension and the outcome of PLWH with associated acute coronary syndrome are available.

The management of people living with human immunodeficiency virus with associated cardiovascular disease is complex, because of the pathophysiology of HIV infection as well as the comorbidities, requiring multidisciplinary approach.

THE CURRENT STATE OF KNOWLEDGE

In Chapter 1 “Epidemiological data” recent data on HIV infection in the world and in Romania are written.

In Chapter 2 “Traditional cardivoascular risk factors”, literature data are reviewed regarding the most common cardiovascular risk factors in PLWH such as: smoking, ilicit drugs consumption, obesity, dyslipidemia, diabetes mellitus, aterial hypertension, as well as general measures for the prevention of cardiovascular disease.

In Chapter 3 “Particular cardiovascular risk factors”, data regarding specific risk factors such as: endothelial dysfunction, inflammation, cellular activation or coagulation abnormalities have been described.

In Chapter 4 “Atherosclerotic involvment” data from literature were synthesized regarding the particularities of atherosclerotic vascular damage, prevalance of coronary artery disease and its impact on PLWH.

In Chapter 5 “Non-atherosclerotic myocardial damage”, some data related to the role of the HIV in direct myocardial damage and the effect of antiretroviral therapy on the heart were summarized.

In Chapter 6 “Other cardiac disorders” the various non-myocardial pathologies in PLWH such as: endocardial or pericardial damage, cardiac tumors, heart rhythm damage were highlighted.

In Chapter 7 “Evaluation of the cardiovascular system in people living with human immunodeficiency virus” we synthesized data on clinical examination and paraclinical evaluation methods (laboratory biomarkers, electrocardiography, echocardiography, coronary angiography, intravascular ultrasound) in PLWH.

PERSONAL CONTRIBUTION

1. General methodology

1.1 Hypothesis and general objectives:

Cardiovascular disease has become an important cause of morbidity and mortality in people living with human immunodeficiency virus (PLWH). Although the incidence of HIV-associated heart disease has decreased in recent years, PLWH have a 1.5-2 times greater risk of developing overt cardiac dysfunction (1). It is anticipated that by 2030, 78% of PLWH will suffer from cardiovascular diseases (2). Coronary involvement is more and more frequently reported in these patients. The etiology of coronary heart disease is multifactorial, including the increased prevalence of traditional cardiovascular risk factors and certain special risk factors. Different data on the degree of coronary involvement have been reported. There are studies reporting the same prevalence of lesions of the common left coronary trunk as in the general population (3,4), different frequency of mono, bi- or tri-vessels involvement (5–7), and other studies have shown that PLWH have more diffuse coronary lesions (8). Data in the literature on the prognosis of these patients after the development of acute coronary syndrome vary. The in-hospital risk of major cardiovascular events recurrence is the same, but in the medium and long term, PLWH have an increased risk of developing ACS recurrence and intrastent restenosis after acute coronary syndrome, being more frequently subjected to revascularization (9–11).

The main endpoint of the study is to analyze the characteristics of patients infected with the human immunodeficiency virus who developed acute coronary syndrome.

Secondary endpoints:

- Assessment of cardiovascular risk in PLWH
- Description of coronary damage particularities in PLWH compared to patients without documented HIV infection

- Determination of prognostic factors in patients with acute coronary syndrome and HIV infection compared to patients with acute coronary syndrome without documented HIV infection
- Establishment of correlations regarding the immune status of PLWH, their evolution and prognosis after acute coronary syndrome

1.2 Materials and Methods

This thesis includes two retrospective, longitudinal, observational, multicenter, case-control studies, including 50 patients infected with the human immunodeficiency virus and acute coronary syndrome.

First study is a retrospective, observational, longitudinal, multicentric study which compares characteristics related to acute coronary syndrome in people living with HIV and HIV negative patients. We identified 50 people living with HIV with ACS and we compared their characteristics with a control group consisting of 50 consecutive patients without HIV infection with ACS, matched for age and sex.

Second study is retrospective, observational, longitudinal, multicentric. The entire group of patients diagnosed with HIV infection and acute coronary syndrome consisted of 50 patients that were divided into two subgroups based on the nadir of CD4+ lymphocytes count.

We used medical databases accessing the main departments of cardiology and infectious diseases from Bucharest and Constanta, Romania, between October 2009 and October 2022. The diagnosis of acute coronary syndrome was established according to the European Society of Cardiology definition and included ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). We searched in databases the following International Classification of Disease codes for the HIV infection diagnostic: *B22, B23.0, B23.8, B24, R75, Z11.4, Z21* and

for acute coronary syndrome diagnostic *I25.11, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22.0, I22.1, I22.8, I22.9, I20.0, I20.1, I20.8, I20.9*. Adult patients (≥18 years) were eligible for enrollment in this study with ACS. Patients with endocarditis, pulmonary hypertension or new onset heart failure were excluded.

1.2.1 Statistical Analysis

The database was created in Microsoft Office Professional Plus 2016 (Microsoft Excel), then exported to Statistical Package for Social Sciences (SPSS) to be processed. The chi^2 test and student's *t-test* were used to evaluate statistical significance between categorical and continuous variables. The uniformity of both subgroups (A and B) was evaluated for basic characteristics at presentation and analysis was performed according to the characteristics of the variables followed. Data analysis was transposed as table, presenting absolute values for presence and *"p"* value for categorical variables. All the differences were considered significant at a two-tailed p-value <0.05. We used logistic regression to analyze the relationship between various independent predictors and major adverse cardiac and cerebrovascular events.

We used a multivariate logistic regression model to analyze the association between various independent variables and the MACCE binary endpoint. The endpoint was adjusted for Smoking, Diabetes mellitus, Culprit lesion, Type of ACS, Macrocytosis in its unit of measure. Odds ratios and corresponding 95% confidence intervals were calculated. The 95% confidence intervals have not been adjusted for multiple testing and should not be used to infer definitive effects.

2. First study – Coronary involvement features and prognostic factors in patients with acute coronary syndrome and human immunodeficiency virus infection

2.1 Introduction

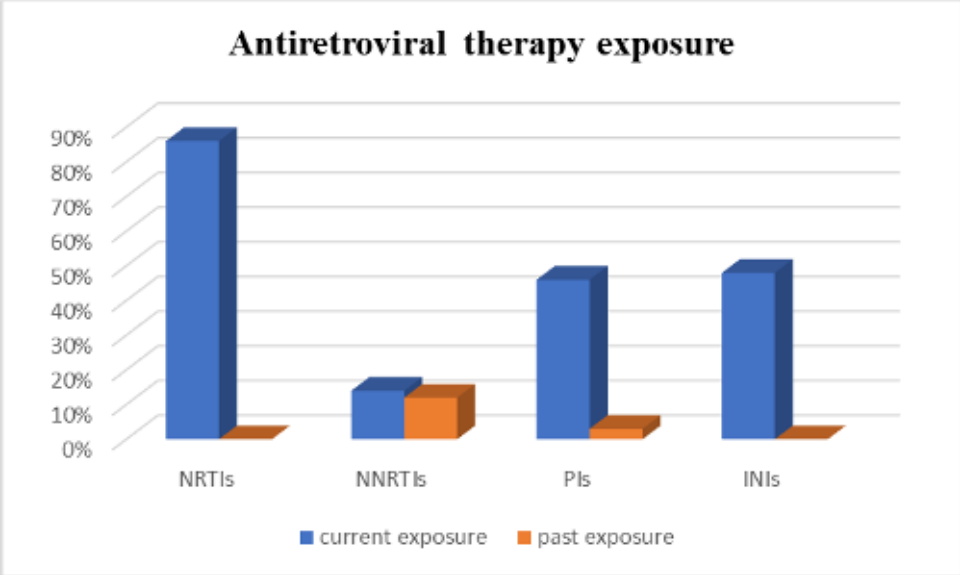
2.2 Hypothesis and objectives

2.3 Materials and Methods

We conducted a retrospective, longitudinal, observational, multicentric study to compare characteristics related to acute coronary syndrome in people living with HIV and HIV-negative patients. We used medical databases accessing the main departments of cardiology and infectious diseases from Bucharest and Constanta, Romania, between October 2009 and October 2022. We identified 50 people living with HIV with ACS (group A), and we compared their characteristics with a control group consisting of 50 consecutive patients without HIV infection with ACS (group B), matched for age and sex.

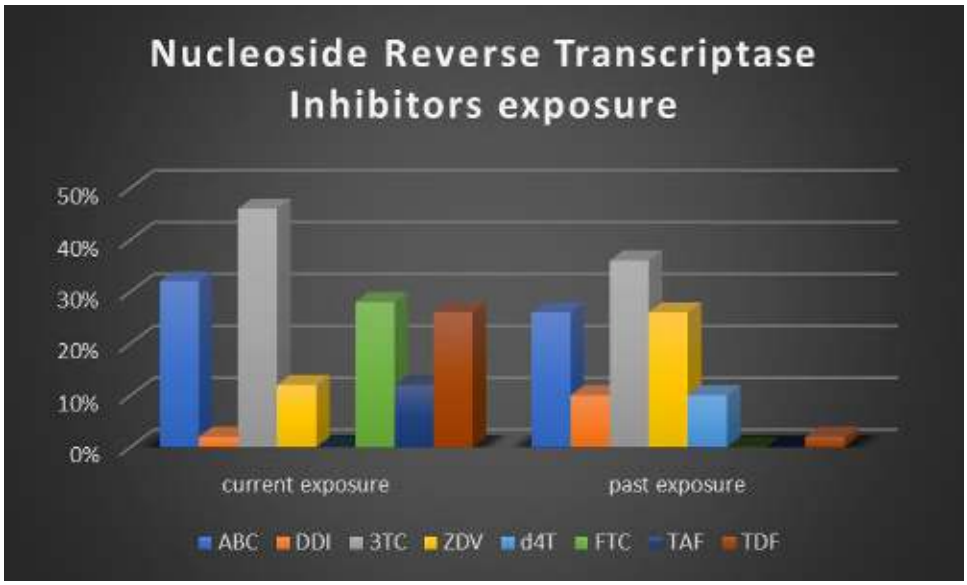
2.4 Results

The characteristics of HIV-infected patients with acute coronary syndrome



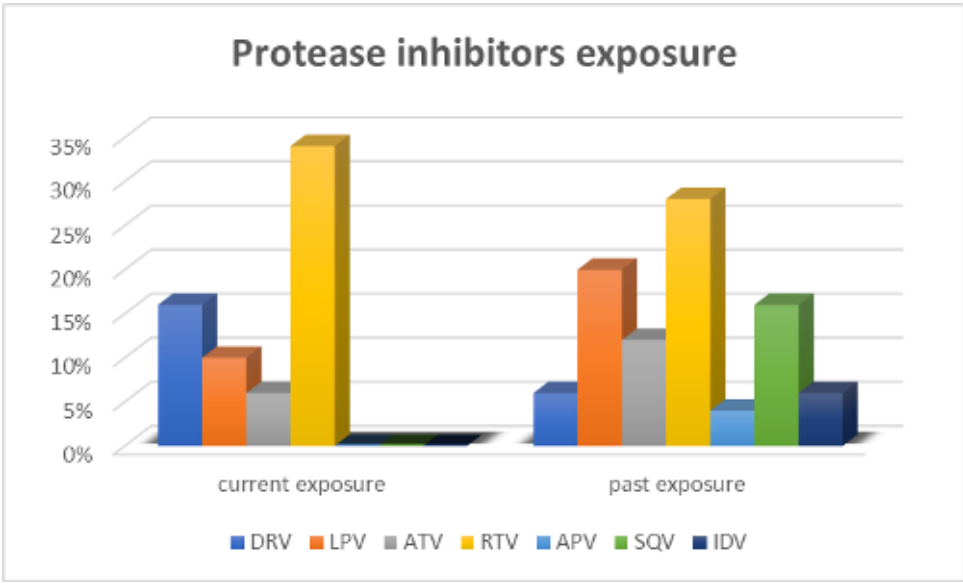
NRTIs - Nucleoside Reverse Transcriptase Inhibitors; NNRTIs - Non-Nucleoside Reverse Transcriptase Inhibitors; PIs - protease inhibitors; INIs - Integrase inhibitors.

Figure 34: Antiretroviral therapy exposure



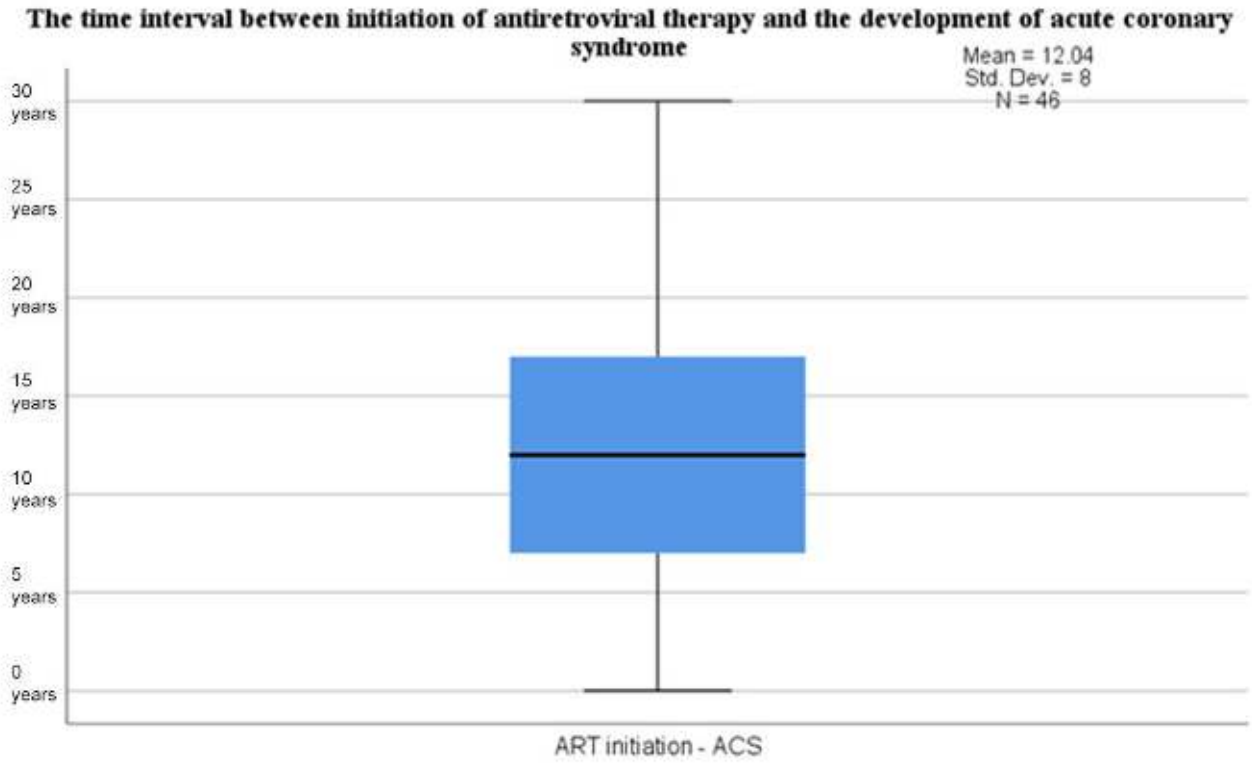
ABC – abacavir; DDI – diadozin; 3TC – lamivudine; ZDV – zidovudine; d4T – stavudine; FTC – emtricitabine; TAF – tenofovir alafenamide; TDF- tenofovir disoproxil fumarate.

Figure 35: Nucleoside Reverse Transcriptase Inhibitors exposure



DRV – darunavir; LPV – lopinavir; ATV – atazanavir; RTV – ritonavir; APV – amprenavir; SQV – saquinavir; IDV – indivir.

Figura 37: Protease inhibitors exposure



ART – Antiretroviral therapy; ACS – Acute coronary syndrome.

Figure 41: The time interval between initiation of antiretroviral therapy and the development of acute coronary syndrome

Comparative analysis of the two groups

Table 7 – Epidemiological data, cardiovascular risk factors in the two groups

	Group A	Group B	p
Epidemiological data			
Male, n (%)	47 (94%)	46 (92%)	
Age, mean (SD)	49 (9.03)	49.62 (11.43)	
Cardiovascular risk factors			

Smoking, n (%)	32 (64%)	43 (86%)	**0.011**
Hypertension, n (%)	30 (60%)	32 (64%)	0.775
Dyslipidemia, n (%)	37 (74%)	38 (76%)	0.955
Diabetes mellitus, n (%)	9 (18%)	12 (24%)	0.464
Personal history of CAD, n (%)	15 (30%)	12 (24%)	0.499
Obesity, n (%)	4 (8%)	17 (34%)	**0.003**
Atypical angina, n (%)	10 (20%)	1 (2%)	**0.003**
Comorbidities			
Peripheral artery disease, n (%)	13 (26%)	4 (8%)	**0.016**

Cardiovascular risk factors were balanced between the two groups (Table 7). However, PLWH had significant lower rate of smoking (64% vs. 86%, p=0.011) and obesity (8% vs. 34%, p=0.003). There were no significant differences between other cardiovascular risk factors. PLWH had atypical angina at ACS onset more frequently (20% vs. 2%, p=0.003).

Table 8 – Type of acute coronary syndrome, severity of acute myocardial infarction, angiographical features

	Group A	**Group B**	**P**
Type of ACS (global)			0.012
STEMI, n (%)	21 (42%)	37 (74%)	
NSTEMI, n (%)	12 (24%)	5 (10%)	
UA, n (%)	17 (34%)	8 (16%)	
Culprit lesion (global)			0.063
LAD, n (%)	20 (46.5%)	20 (40%)	

LCX, n (%)	7 (16.3%)	12 (24%)
RCA, n (%)	7 (16.3%)	16 (32%)
LM, n (%)	3 (7%)	1 (2%)
Unidentified culprit lesion, n (%)	6 (14%)	2 (4%)

There were some differences between culprit vessel in both groups, but without statistical significance (Table 8). The most common was the left anterior descending artery in both groups (46.5% in group A vs. 40% in group B). The culprit vessel was the left circumflex artery in 16.3% of the patients in group A, compared to 24% of the patients in group B, the right coronary artery for 16.3% of the patients in group A and 32% of the patients group B, the left main artery in 7% of the patients in group A and in 2% of the patients in group B (p=0.063).

Table 12: The analysis of statistic basic descriptive differences for continuous variables in the two subgroups

Variable	HIV-infection	Number	Mean	Std. Deviation	Std. Error Mean	P value
Hemoglobin (g/dl)	1	49	14.093	1.92222	.27460	0.141
	0	50	14.595	1.41074	.19951	
MCV (fl)	1	49	95.324	9.92211	1.41744	0.002
	0	50	89.190	9.33902	1.32074	
Creatinine clearance (CKD-EPI) (ml/min/m²)	1	49	85.510	33.7002	4.8143	0.014
	0	50	101.79	31.3078	4.4276	
Total cholesterol (mg/dl)	1	47	173.21	50.079	7.305	0.004
	0	50	207.50	62.166	8.792	
CK-MB max U/L	1	46	103.72	106.405	15.689	0.039

	0	50	157.06	139.778	19.768	
SYNTAX I Score (points)	1	37	13.459	11.8247	1.9440	0.022
	0	45	7.867	9.7825	1.4583	
Euro-Score II (%)	1	36	2.7613	4.06114	.6768581	0.004
	0	44	.90363	.665586	.1003409	
GRACE Score (points)	1	26	80.54	34.656	6.797	0.029
	0	15	55.33	33.848	8.739	
TIMI Risk Score for STEMI (%)	1	21	8.764	8.2994	1.7694	0.009
	0	37	4.224	4.5183	.7428	
12 months risk of TIMI major or minor Bleeding	1	38	1.2205	1.26834	.20575	0.041
	0	46	.7813	.61427	.09057	
12 months risk of TIMI Major Bleeding	1	38	.6476	.61875	.10037	0.051
	0	46	.4426	.30485	.04495	
In-hospital stay	1	50	8.12	11.078	1.567	0.279
	0	50	6.38	2.249	0.318	

In Table 12, various data related to biological profile, coronary artery disease extension scores, operative risk score, prognostic scores after acute coronary syndrome and scores that estimate the risk of bleeding are analyzed in continous variables.

Tabel 15: Multivariate logistic-regression analysis for MACCE at 360 days								
							95% C.I. for EXP(B)	
Parameter	**B**	**S.E.**	**Wald**	**df**	**Val. P**	**Exp(B)**	**Lower**	**Upper**
HIV-infection	0.952	572	2.773	1	0.096	2.591	0.845	7.947
Smoking	-0.080	0.618	0.017	1	0.897	0.923	0.275	3.098
Diabetes mellitus	1.368	0.560	5.966	1	0.015	3.927	1.310	11.772
Culprit lesion	-0.059	0.256	0.052	1	0.819	0.943	0.571	1.558
ACS type	-0.198	0.296	0.447	1	0.504	0.821	0.460	1.465
Macrocytosis	0.252	0.571	0.195	1	0.659	1.286	0.420	3.939
Constant	-1.333	0.863	2.385	1	0.122	0.264		

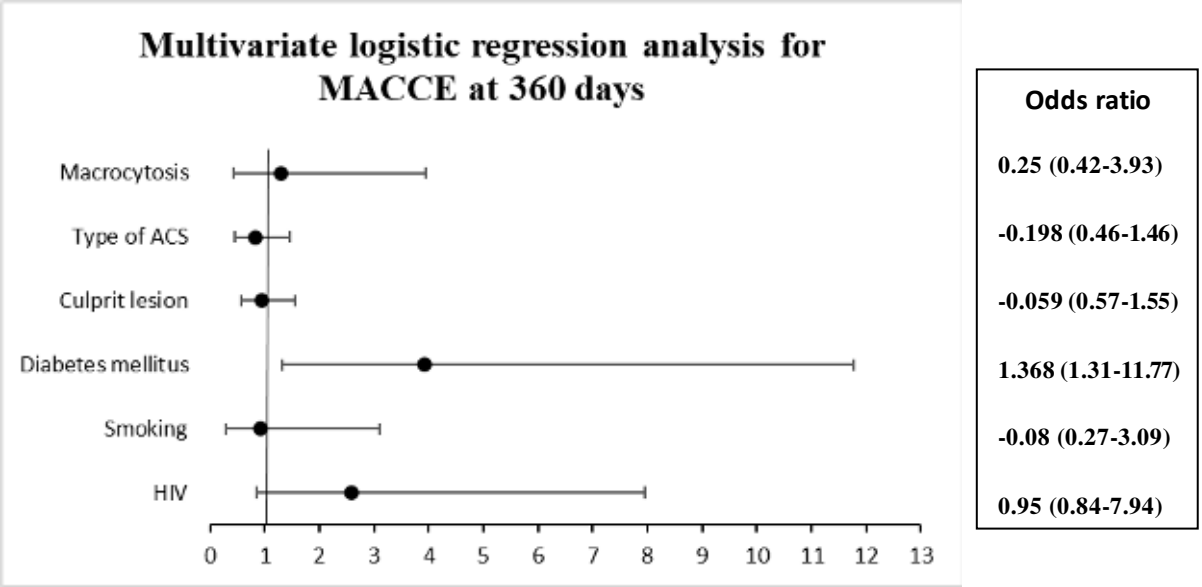


Figure 47: Multivariate logistic regression analysis for MACCE at 360 days

At multivariate regression analysis for 360-day MACCE, we didn't find significant changes for macrocytosis, type of acute coronary syndrome (STEMI, NSTEMI or UA) culprit lesion, smoking or HIV. Nevertheless, we noticed that patients with diabetes mellitus, OR 1.368 (95% CI 1.31-11.77, p=0.015) develop more frequently major adverse cardiac and cerebrovascular events at 360 days and HIV-infection patients had an increased tendency to develop 360-days MACCE (Figure 47).

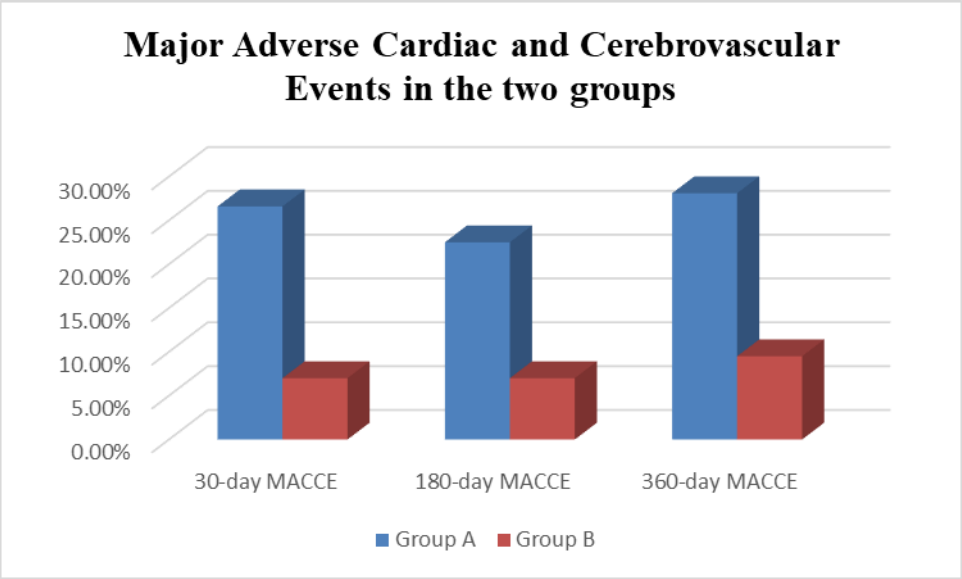


Figura 48: Major Adverse Cardiac and Cerebrovascular Events in the two groups

There were no significant differences between the two groups in ACS recurrence, hospitalization for heart failure, cardiovascular death or stroke at 30, 180 or 360-day follow-up. We observed significant higher prevalence of 30, 180, respective 360-day cumulative MACCE among group A compared to group B (26.66% vs. 7%, p=0.012), (22.5% vs. 7%, p=0.044), respective (25% vs. 6.9%, p=0.029).

2.5 Discussion

2.6 Conclusions

The present study has analyzed cardiovascular characteristics in patients with acute coronary syndrome and HIV infection. Patients in our study had a lower prevalence of traditional cardiovascular risk factors, acute coronary syndrome without persistent ST-segment elevation as the predominant diagnosis, more important coronary involvement, and higher in-hospital mortality. Major adverse cardiovascular events at 1 month, 6 months and 1 year were more common in PLWH compared to HIV-negative patients.

3. Second study – The immune status impact on outcome in people living with HIV and acute coronary syndrome

3.1 Introduction

3.2 Working hypothesis and specific endpoints

3.3 Materials and Methods

The entire study group of patients diagnosed with HIV infection and acute coronary syndrome consisted of 50 patients that were divided into two subgroups based on the nadir of CD4+ lymphocytes count. The hypothesis of the present study was the relationship between poor immune status, expressed by CD4 T cell count and the risk of cardiovascular adverse events and prognosis in HIV patients who developed an acute coronary syndrome. Also, we hypothesised that there may be a correlation between CD4 nadir and the severity of coronary lesions at angiography. We conducted an observational longitudinal, retrospective, case-control, multicentric study using medical databases from the main departments of cardiology and infectious disease from Bucharest and Constanta, Romania, over a period of 13 years, between October 2009 and October 2022.

We included people living with HIV diagnosed with acute coronary syndrome. Exclusion criteria were patient refusal and CD4+ nadir missing data. Four patients were excluded because of missing data regarding CD4 cell count, further analysis being done on the remaining 46 patients. Subgroup A consisted of 27 patients with CD4+ nadir $\leq$ 200 cells/mm^3 and subgroup B included 19 patients with CD4+ nadir > 200 cells/mm^3.

3.4 Results

Demographic data were similar between the two subgroups, with males being equally represented in both subgroups. Comparative analysis of cardiovascular risk factors found no significant differences between the two subgroups. Even without statistical significance, we observed that only hypertension was more prevalent, but non-significant, in subgroup of patients with compromised immune status (65.4% vs. 57.9%, p=0.608). All the other cardiovascular risk factors (smoking, dyslipidemia, diabetes, obesity or history of CAD - including angina, myocardial infarction, coronary angioplasty or coronary artery by-pass

graft revascularization) were less prevalent in these patients. It is to be underlined that atypical angina was more prevalent in immunocompromised patients. Although peripheral artery disease and chronic kidney disease were obviously more prevalent in absolute values in subgroup A (twice as much than in subgroup B), the data did not reach statistical significance (Table 16).

The following biomarkers were analyzed in the present study: serum hemoglobin, mean corpuscular volume, glomerular filtration rate (CKD-EPI), blood levels of sodium and potassium, myocardial necrosis markers (creatinkinase and creatinkinase-MB). Comparative analysis between the two subgroups showed no statistical difference, excepting hyperkalemia which was significantly more prevalent in subgroup A ($p = 0.021$). In our study, anemia (serum hemoglobin < 13 g/dl) was more prevalent in subgroup A, but macrocytosis was more frequently seen in patients from subgroup B (20% more comparative to subgroup B), both without statistical significance and there was no difference regarding myocardial necrosis markers (Table 16).

Table 16 - The analysis of statistic basic descriptive differences for discrete variables in the two subgroups based on cardiovascular risk factors, clinical history, clinical and biological parameters

	CD4+ nadir ≤200 cells/mm^3	**CD4+ nadir >200 cells/mm^3**	**P value**
Males, n %	25 (92.6%)	18 (94.7%)	0.774
Smoking, n %	16 (61.5%)	12 (63.2%)	0.911
Hypertension, n %	17 (65.4%)	11 (57.9%)	0.608
Dyslipidemia, n %	20 (76.9%)	15 (78.9%)	0.871
Diabetes mellitus, n %	4 (15.4%)	5 (26.3%)	0.365
Obesity, n %	1 (3.8%)	3 (15.8%)	0.164
CAD history, n %	8 (29.6%)	6 (31.6%)	0.887

Atypical angina, n %	7 (28%)	3 (16.7%)	0.480
Macrocytosis, n %	9 (33.3%)	10 (52.6%)	0.233

Culprit coronary lesion was similar in both subgroups. We observed that the presence of left main (8.7% vs 0%) and right coronary artery (21.7% vs. 12.5%) lesions were more frequently found in subgroup A. In contrast, lesions of left anterior descending artery and left circumflex artery as culprit lesions were less frequent in subgroup A than in subgroup B (43.5% vs. 56.2%, respectively 13% vs. 25%).

Analysis of the extension of coronary disease revealed that patients in subgroup A had more frequently single vessel disease, but overall, the number of coronary lesions was similar in the two subgroups (p=0.704). The indication for coronary artery by-pass graft (CABG) and its achievement was similar in both subgroups as well as the rate of intrastent restenosis or the presence of venous graft stenosis (Table 17).

The complexity of the coronary artery disease was analysed using SYNTAX I score and significant differences were found between the subgroups, with 40% of patients in subgroup A having SYNTAX I score ≥ 23 points, while in subgroup B all patients had SYNTAX I score < 23 points (p=0.013) (Table 17).

Tabel 17: The analysis of statistic basic descriptive differences for discrete variables in the two subgroups in relation to acute coronary syndrome and coronary lesions

	CD4+ nadir ≤200 cells/mm³	**CD4+ nadir >200 cells/mm³**	**P value**
STEMI, n %	11 (40.7%)	8 (42.1%)	0.914
NSTEMI, n %	6 (22.3%)	5 (26.3%)	
Unstable angina, n %	10 (37%)	6 (31.6%)	
Culprit lesion **LAD**, n %	10 (43.5%)	9 (56.2%)	0.504
Culprit lesion **LCx**, n %	3 (13%)	4 (25%)	

Culprit lesion **RCA**, n %	5 (21.7%)	2 (12.5%)	
Culprit lesion **LM**, n %	2 (8.7%)	0 (0%)	
Non-culprit lesion present, n %	3 (13%)	1 (6.2%)	
Single vessel disease, n %	10 (45.45%)	5 (33.33%)	0.704
Two-vessel disease, n %	5 (27.73%)	5 (33.33%)	
Three-vessel disease, n %	7 (31.18%)	5 (33.33%)	
SYNTAX I ≥ 23p, n %	9 (40.9%)	0 (0%)	0.013

LAD – left anterior descending artery; LCx - left circumflex artery; RCA - right coronary artery; LM - left main coronary artery; SYNTAX I score - SYNergy between percutaneous coronary intervention with TAXus and coronary artery by-pass surgery score.

In general, antithrombotic treatment is mandatory for the first year after an acute coronary syndrome treated invasive or conservatory, but there are situations in which dual antiplatelet therapy needs to be extended. Therefore, the balance between thrombotic and bleeding risk should be carefully assessed in all patients. In our study group, an elevated DAPT (Dual Anti Platelet Therapy) score, over 2 points was present in both subgroups of patients, with no significant differences, but patients in subgroup A had an increased estimated risk of bleeding complications, with PRECISE-DAPT score compared with patients in subgroup B (30% vs 5.88%, p=0.061) (Table 18).

Table 18: The analysis of statistic basic descriptive differences for discrete variables in the two subgroups related to the risk of thrombotic and bleeding events.

	CD4+ nadir ≤200 cells/mm³	**CD4+ nadir >200 cells/mm³**	**P value**
High DAPT score (≥2 points), n %	5 (29.41%)	3 (20%)	0.539
PRECISE-DAPT score ≥ 25 points, n %	6 (30%)	1 (5.88%)	0.061

Major adverse cardiac and cerebrovascular events (MACCE) at 30 days and 360 days (acute coronary syndrome recurrence, heart failure requiring hospitalization, cardiovascular death and stroke) and cumulative MACCE did not differ between the two subgroups (Table 19). Cumulative MACCE at 180 days were more frequent in group A.

Table 19: The analysis of statistic basic descriptive differences for discrete variables in the two subgroups related to outcome and prognosis.			
	CD4+ nadir ≤200 cells/mm³	**CD4+ nadir >200 cells/mm³**	**P value**
Cumulative MACCE at 30 days, n %	6 (26.08%)	2 (11.11%)	0.229
Cumulative MACCE at 180 days, n %	1 (4.76%)	8 (42.1%)	0.004
Cumulative MACCE at 360 days, n %	4 (23.52%)	4 (26.66%)	0.837

Table 20: The analysis of statistic basic descriptive differences for continuous variables in the two subgroups						
Variable	**CD4+ nadir ≤ 200 cells/mm³**	**Number**	**Mean**	**Std. Deviation**	**Std. Error Mean**	**P value**
Age	1	27	50.00	12.676	2.440	.849
	0	19	49.32	10.822	2.483	
CD4+ lymphocyte (celule/mm³)	1	27	476.74	242.531	46.675	.001
	0	19	805.74	384.344	88.175	
Hemoglobin (g/dl)	1	27	13.9000	2.02123	.38899	.254
	0	18	14.5600	1.62463	.38293	
MCV (fl)	1	27	94.6481	11.25920	2.16683	.454
	0	18	97.0150	8.63796	2.03599	
Creatinine clearance (CKD-EPI) (ml/min/m²)	1	27	77.796	32.6624	6.2859	.059
	0	18	97.083	32.5647	7.6756	
SYNTAX I Score (points)	1	22	17.068	13.3865	2.8540	.022
	0	13	7.731	5.0275	1.3944	

SYNTAX II score PCI (puncte)	1	22	31.432	20.6306	4.3985	.046
	0	13	18.977	7.9748	2.2118	
PCI 4-year mortality (%)	1	22	18.618	25.0906	5.3493	.036
	0	13	3.254	2.0915	.5801	
Scor SYNTAX II CABG (puncte)	1	22	19.818	17.2018	3.6674	.194
	0	13	13.046	8.2357	2.2842	
CABG 4-year mortality (%)	1	22	8.032	16.4931	3.5163	.194
	0	13	2.015	1.3915	.3859	
Euro-Score II (%)	1	22	3.829545	4.90512606	1.0457763	.056
	0	13	1.100769	.784383638	.21754887	
GRACE Score (points)	1	15	84.67	36.203	9.348	.492
	0	9	74.22	34.003	11.334	
PRECISE-DPT	1	22	18.00	13.956	2.975	.037
	0	15	9.73	5.548	1.433	
TIMI Risk Score for STEMI (%)	1	22	1.6536	1.51422	.32283	.016
	0	15	.6467	.32264	.08330	
12 months risk of TIMI major or minor Bleeding	1	22	.8659	.73168	.15600	.013
	0	15	.3573	.17119	.04420	

At multivariate regression analysis for 360-day MACCE, we didn't find significant changes (Table 22). Nevertheless, we noticed that patients with diabetes, OR 2.070 (95% CI 0.888-70.661, p=0.064) and macrocytosis, OR 1.309 (0.787-17.407, p=0.098), have an increased tendency to develop major adverse cardiac and cerebrovascular events at 360 days (Figure 51).

Tabel 22: Multivariate logistic regression analysis for MACCE at 360 days.								
							95% C.I. for EXP(B)	
Parameter	**B**	**S.E.**	**Wald**	**df**	**Val. P**	**Exp(B)**	**Lower**	**Upper**
Smoking	-0.358	0.864	0.173	1	0.678	0.699	0.129	3.790
Diabetes mellitus	2.070	1.117	3.435	1	0.064	7.921	0.888	70.661
Culprit lesion	0.113	0.378	0.089	1	0.765	1.119	0.534	2.347
Type of ACS	-0.627	0.414	2.296	1	0.130	0.534	0.238	1.202
Macrocytosis	1.309	0.790	2.744	1	0.098	3.701	0.787	17.407

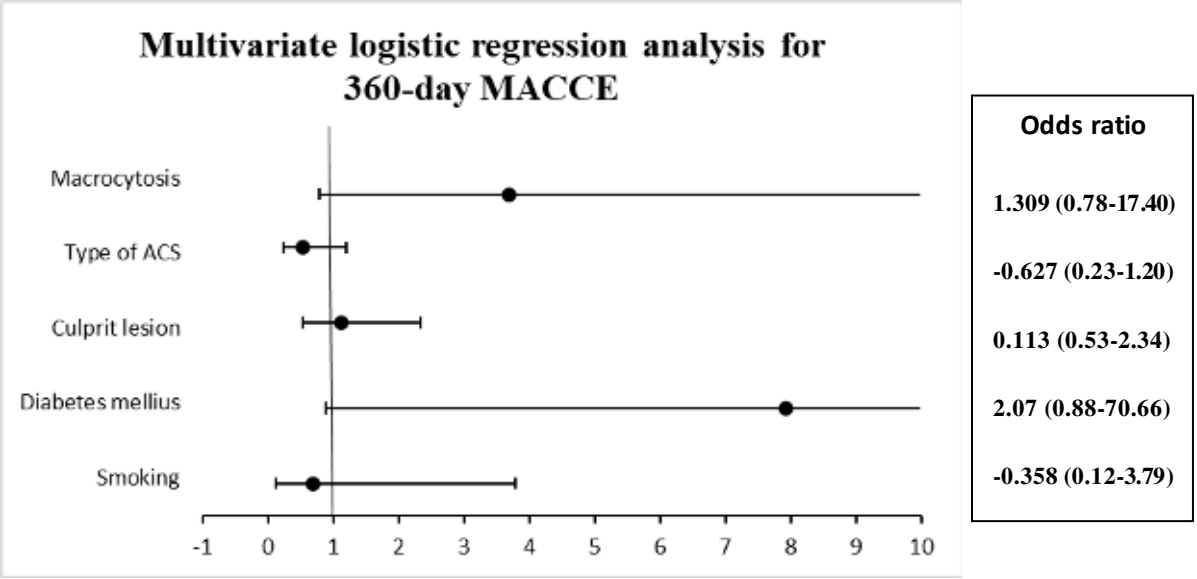


Figura 51: Multivariate logistic regression analysis for 360-day MACCE.

3.5 Discussion

3.6 Conclusions

People living with the human immunodeficiency virus with affected immune status (nadir CD4+ ≤ 200 cells/mm^3) have more complex coronary artery disease assessed by SYNTAX scores, increased operative risk and a higher risk of major and minor bleeding at

one year. In-hospital mortality rates are higher for PLWH with nadir CD4+ ≤ 200 cells/mm^3, but 30-day and 1-year follow-up showed a similar prognosis.

5. General discussion

We conducted two retrospective, longitudinal, observational, case-control studies. Fifty people living with human immunodeficiency virus (PLWH) who developed acute coronary syndrome (ACS) were analyzed. In the first study we compared their characteristics with a control group consisting of 50 consecutive patients without HIV infection with ACS, matched for age and sex. In the second study we analyzed the relationship between poor immune status, expressed by nadir CD4+ T cell count and the risk of cardiovascular adverse events and outcome in HIV patients who developed an acute coronary syndrome.

Data from studies report that traditional cardiovascular risk factors are present with high prevalence in people living with HIV. In PLWH who have already developed manifest coronary artery disease, the rate of cardiovascular risk factors does not seem to differ significantly compared to controls. In our first study, PLWH had lower rate of cardiovascular risk factor such as smoking (64% vs. 86%), arterial hypertension (60% vs. 64%), dyslipidemia (74% vs. 76%,), diabetes mellitus (18% vs. 24%) and obesity (8% vs. 34%), but significant differences were only observed in smoking (p=0.011) and obesity (p=0.003). The CUORE trial (12), reported a significantly lower prevalence of arterial hypertension, dyslipidemia and diabetes mellitus in PLWH with ACS. According to our study results and compared to the literature data, PLWH and ACS have a lower prevalence of some traditional risk factors (dyslipidemia, arterial hypertension, obesity) compared to the HIV-negative patients with ACS. The association of particular cardiovascular risk factors such as inflammation, endothelial dysfunction, coagulation abnormalities, exposure to certain antiretroviral drugs lead to a significant increase in the risk of coronary syndrome. Analyzing the relationship between immune status and traditional cardiovascular risk factors, no statistically significant differences were found between patients with nadir CD4+ $\leq$ 200 cells/mm^3 and those with nadir CD4 > 200 cells/mm^3 (smoking 61.5% vs. 63.2%, arterial hypertension 65.4% vs. 57.9%, dyslipidemia 76.8% vs 78.9%, diabetes mellitus 15.4% vs. 26.3%, obesity 3.8% vs. 15.8%).

The symptomatology of an ACS in a HIV-infected patients can often be nonspecific, similar to patients with chronic diseases such as diabetes mellitus or chronic kidney disease

(13,14). The first study showed that atypical angina (or angina equivalent) is 10 times more common in PLWH than in controls. It is possible that immune status has a contribution, according to the second study results which reported that PLWH with nadir CD4+ ≤ 200 cells/mm^3 have atypical presentations for ACS (28% vs. 16.7 %) more often, although the differences were not statistically significant.

Analysis of the biological profile (hemoglobin, mean erythrocyte volume, creatinine values and creatinine clearance, electrolytes, lipid profile, myocardial necrosis enzymes) in patients from the first study, showed signigicant differences in the analysis of continuous variables of mean erythrocyte volume, creatinine clearance, total cholesterol and peak serum values of total creatine kinase and MB-creatine kinase. It is well known that macrocytosis in more common among PLWH and zidovudine or stavudine exposure can lead to it (15). In the first study, MCV values wre significantly higher among PLWH compared to controls (95.32 fl [SD 9.92] vs. 89.19 fl [SD 9.33]). No data regarding the impact of macrocytosis in PLWH with ACS were found. In the second study, the biological profile of the patients in both subgroups were similar, except for the number of CD4+ cells, which was significantly lower in patients with nadir CD4+ ≤ 200 cells/mm^3 (474.74 cells/mm^3 [SD 242.53] vs. 805.74 cells/mm^3 [SD 384.35], p=0.001).

In the first study, we found that people living with HIV were less likely to present with ST elevation myocardial infarction than controls (42% vs. 74%, p=0.012). Regarding coronary acute syndrome type, the literature showed different data. ST elevation myocardial infarction was the most frequent type in a 44 HIV infected patients cohort studied by Perello et al. (59% vs. 24%) (14), but other studies reported lower prevalence of ST elevation myocardial infarction (49% vs. 56% (5) and 54% vs. 62.5% (16)). In the second study, no significant differences were found regarding the type of acute coronary syndrome between the two groups.

To assess the extent of coronary artery disease, we calculated the SYNTAX score, in continuous as well as in discrete variables (cut-off ≥23 puncte). Considering the results of the first study show significantly higher values of the SYNTAX I score in PLWH (24.3% vs. 4.4%, p=0.019 and 13.45 [SD 11.82] points vs. 7.86 [SD 9.78] points, p=0.022) and the results of the second study that PLWH with nadir CD4+ ≤ 200 cells/mm^3 have significantly

higher values of the same score (40.9% vs. 0%, p=0.013 and 17.06 [SD 13.38] points vs. 7.73 [SD 5.02] points, p=0.022), we can state that coronary artery disease is more severe in PLWH and ACS compared to patients without HIV-infection, but especially in PLWH with nadir CD4+ $\leq$ 200 cells/mm^3.

Both studies analyze specific prognostic scores after an acute coronary syndrome as well as thrombotic and hemorrhagic risk scores. In the first study the GRACE prognostic score values were significantly higher in HIV-infected patients compared to the HIV-negative patients (80.54 points [SD 34.65] vs. 55.33 points [SD 33.84], p=0.029). Comparing with the literature data, two similar studies have shown the opposite, that PLWH have lower GRACE score values than controls (5,10). In both studies, the DAPT risk score, which guides the extension of dual antiplatelet therapy more than one year after the ACS, was now different in the two groups. The hemorrhagic risk calculated by the PRECISE-DAPT score was higher in PLWH and SCA compared to controls in the first study, both in discrete variables (18.4% vs. 4.35%, p=0.037), as well as in continuous variable analysis of TIMI score derived from PRECISE-DAPT, which predicts the risk of major and minor bleeding at 12 months (1.22% [SD 1.26] vs. 0.78% [SD 0.61], p=0.041). In the second study, differences approaching statistical significance were revealed in the analysis of the discrete variables of PRECISE-DAPT (30% vs. 5.88%, p=0.061). Continuous variable analysis of PRECISE-DAPT score (18 points [SD 13.95] vs. 9.73 points [SD 5.54], p=0.037) and TIMI score showed statistically significant differences in major and minor bleeding at 12 months (1.65% [SD 1.51] vs. 0.64% [SD 0.32], p=0.016). No comparative studies that analyzed these risk scores in the type of patients included in our studies were found.

In both studies, we assessed the patients prognosis as the main endpoint. In-hospital mortality and major adverse cardiac and cerebrovascular events (MACCE) at 30,180 and 360 days were recorded and we also analyzed indepdendent variables (HIV, smoking, diabetes mellitus, ACS type, culprit lesion, macrocytosis) for these events. In the first study, in-hospital mortality reached a rate of 10% compared to 0% in controls (p=0.056) (17). PLWH with ACS had significantly more cumulative MACCE than control group: at 30 days (26.6% vs. 7%, p=0.021), at 180 days (22.5% vs. 7%, p=0.044) and at 360 days (25% vs. 6.9%, p=0.029). The literature data showed different results from this point of view, with some

studies reporting that in-hospital risk of MACCE in PLWH is similar to HIV negative patients, but the risk of recurrent ischemic events and the rate of readmissions for heart failure after an episode of acute coronary syndrome is higher in PLWH (10). Other studies have shown no differences between PLWH with ACS and controls in term of the occurrence of postinfarction angina (14), 30-day mortality (14), 12-month MACCE (5) or 20-month survival (18). Among the potential independent predictors analyzed for 30- and 360-day MACCE, there was a statistically significant effect of diabetes on MACCE at 360 days (OR 3.927, 95% CI 1.310-11.772, p=0.015). The second study showed a higher in-hospital mortality rate in patients with nadir CD4+ $\leq$ 200 cells/mm^3 compared to controls (14.81% vs. 5.26%), a statistically insignificant difference. Although after 30 days of discharge there were more cumulative MACCE (26.08% vs. 11.11%), higher ACS recurrence rates (8.69% vs. 5.55%), heart failure requiring hospitalization (8.69% vs. 5.55%), cardiovascular deaths (4.34% vs. 0%), these differences are not statistical significant. MACCE analysis at 180 days showed surprising results: fewer ACS recurrences in patients with nadir CD4+ $\leq$ 200 cells/mm^3 (4.8% vs. 21.1%), fewer admissions for heart failure (0% vs. 15.8%), fewer cardiovascular deaths (0% vs. 4.8%). Cumulative 180-day MACCE were significantly more frequent in patients with nadir CD4+ > 200 cells/mm^3 (4.76% vs. 42.1%, p=0.004). We could not find an argument for this fact. Cumulative 360-day MACCE were approximately equal in the two subgroups. Among the analyzed potential adverse predictors in logistic regression for MACCE at 30 and 360 days, none of smoking, diabetes mellitus, culprit lesion, type of ACS or macrocytosis had a statistically significant effect. Nevertheless, it is to be mentioned that for MACCE at 360 days, diabetes mellitus and macrocytosis nearly approached statistical significance. The current literature data shows that the only independent predictor for coronary syndrome recurrence is HIV infection and no other analyzed parameters such as nadir CD4+, viral load, CD4/CD8 ratio or duration of infection (10,19).

6. General conclusions

1. Forty years after its appearance, HIV and AIDS infection still represents a permanent challenge for all medical specialties.
2. Cardiac damage represents a very important chapter of the pathology associated with people living with the human immunodeficiency virus, which is why we conducted this research, proving that the cardiologist must be a member of the multidisciplinary team, which ensures the optimal assistance of these patients.
3. The first study highlighted the fact that PLWH who developed acute coronary syndrome have a lower prevalence of traditional cardiovascular risk factors such as smoking, hypertension, dyslipidemia, diabetes and obesity, compared to the control group
4. These patients have atypical clinical presentations for acute coronary syndrome more frequently, and the predominant diagnosis in PLWH is acute coronary syndrome without persistent ST-segment elevation.
5. Compared to the control group, PLWH have more extensive coronary artery disease as assessed by the SYNTAX score. Acute coronary syndrome specific risk and prognosis scores, GRACE and TIMI, were significantly higher in PLWH.
6. In-hospital mortality after acute coronary syndrome was higher in PLWH, who had significantly more major adverse cardiovascular events at 30, 180, and 360 days.
7. The analysis of the correlation between the patients' immune status and the cardiovascular risk profile (the second study), showed that the nadir of CD4+ lymphocytes does not influence the cardiovascular risk profile nor the usual biological parameters in PLWH who developed acute coronary syndrome.

8. PLWH with impaired immune status have more complex coronary artery disease, higher operative risk, and higher risk of major and minor bleeding at one year.
9. The in-hospital mortality rate is higher in PLWH with nadir CD4+ ≤ 200 cells/mm3, in the medium term the prognosis seems to be more severe in those with nadir CD4+ > 200 cells/mm3, and in the long term the number of major adverse cardiovascular events seems to be similar in the two groups.
10. The two studies reveal the necessity for the cardiologist to participate from the initial assessment of PLWH, establishing the potential risks and the patients' management.

7. The originality of the PhD thesis

Considering that coronary heart disease is becoming the most important cardiovascular disease in PLWH in developed countries (20) and that the international medical literature provides little data with varied results regarding the characteristics of PLWH who develop acute coronary syndrome, we chose the intersection of HIV infection and acute coronary syndrome as the main target of the research

A multicenter cohort, case-control, retrospective, observational, longitudinal study was conducted, from which two studies were derived that analyzed the clinical, biological, imaging characteristics, risk scores, short-, medium-, and long-term prognosis and the influence of some independent variables in patients with acute coronary syndrome and HIV infection. Moreover, in the second study, we also analyzed the impact of the immune status on the evolution and prognosis of these patients. One of the strengths of this study was the quantification of coronary lesions by specific scores (SYNTAX), showing that PLWH with ACS have more extensive coronary involvement than patients with ACS without documented HIV infection. Immune status assessed by lymphocyte nadir CD4+ has a special contribution in the development of coronary lesions. The results of this study open new ways in PLWH risk assessment, cardiovascular screening, primary prevention, highlighting subclinical cardiac dysfunction to determine the appropriateness of administering cardioprotective medication.

To our knowledge, the present paper is the only one from Romania that addresses this topic, internationally there are studies of this kind on small cohorts of patients.

LIST OF PUBLICATIONS

Articles published in extenso as a result of doctoral research

1. **Bajdechi M,** Gurghean A, Bataila V, Scafa-Udriste A, Radoi R, Oprea AC, Marinescu A, Ion S, Chioncel V, Nicula A, Anastasiou A, Bajdechi GE, Savulescu-Fiedler I, Dumitru IM, Rugina S. Cardiovascular Risk Factors, Angiographical Features and Short-Term Prognosis of Acute Coronary Syndrome in People Living with Human Immunodeficiency Virus: Results of a Retrospective Observational Multicentric Romanian Study. Diagnostics (Basel). 2023 Apr 24;13(9):1526. Doi: 10.3390/diagnostics13091526. PMID: 37174918: PMCID: PMC10177561 (Web Of Science, **IF 3.992**).

2. **Bajdechi M**, Scafa-Udriste A, Ploscaru V, Calmac L, Bajeu T, Gurghean A, Rugina S. Porcelain Aorta in a Young Person Living with HIV Who Presented With Angina. Diagnostics (Basel). 2022 Dec 13;12(12):3147. Doi: 10.3390/diagnostics12123147. PMID: 33553155; PMCID: PMC9776980 (Web Of Science, **IF 3.992**).

3. **Bajdechi M,** Mihai C, Scafa-Udriste A, Cherry A, Zamfir D, Dumitru I, Cernat R, Rugina S. Severe Coronary Artery Disease in a Person Living with HIV. Medicina (Kaunas). 2021 Jun 10;57(6):595. doi: 10.3390/medicina57060595. PMID: 34200527; PMCID: PMC8229972 (Web Of Science, **IF 2.948**).

4. **Bajdechi M,** Gurghean A, Mateescu I, Zekra L, Rugina S. Coronary Artery Disease in People Living With Human Immunodeficiency Virus. Internal Medicine, 2022, 19 (2), 71-75 (BDI, Index Copernicus)

5. **Bajdechi M,** Micu CE, Rugina S, Stoian GE, Gurghean A. Metabolic Syndrome and Myocardial Involvement in HIV-Infected Patients. Internal Medicine, 2019, 16.3: 37-45 (BDI, Index Copernicus).

6. Zekra L, Dumitru ID, **Bajdechi M**, Rugina S. Cardiovascular Risk Assessment in HIV-Infected Patients. ARS Medica Tommitana, 26.1: 5-9 (BDI, Index Copernicus).

7. **Bajdechi M,** Dumitru IM, Gurghean A, Zekra L, Rugina S. Sindromul coronarian acut la persoanele care trăiesc cu virusul imunodeficienței umane. PATOLOGIA INFECȚIOASĂ ÎN PANDEMIE, BOLI INFECȚIOASE, VIAȚA MEDICALĂ, Ed. MEDICHUB MEDIA, București, 2022.

BIBLIOGRAPHY

1. Feinstein MJ, Hsue PY, Benjamin LA, Bloomfield GS, Currier JS, Freiberg MS, et al. Characteristics, Prevention, and Management of Cardiovascular Disease in People Living with HIV: A Scientific Statement from the American Heart Association. Circulation. 2019;
2. Smit M, Brinkman K, Geerlings S, Smit C, Thyagarajan K, van Sighem A V., et al. Future challenges for clinical care of an ageing population infected with HIV: A modelling study. Lancet Infect Dis. 2015;
3. Escaut L, Monsuez JJ, Chironi G, Merad M, Teicher E, Smadja D, et al. Coronary artery disease in HIV infected patients. Intensive Care Med. 2003;
4. Mehta NJ, Khan IA. HIV-associated coronary artery disease. Angiology. 2003;
5. Boccara F, Mary-Krause M, Teiger E, Lang S, Lim P, Wahbi K, et al. Acute coronary syndrome in human immunodeficiency virus-infected patients: Characteristics and 1 year prognosis. Eur Heart J. 2011;
6. R.K. M. Cardiac Emergencies in Patients with HIV. Emergency Medicine Clinics of North America. 2010.
7. Hsue PY, Giri K, Erickson S, MacGregor JS, Younes N, Shergill A, et al. Clinical Features of Acute Coronary Syndromes in Patients with Human Immunodeficiency Virus Infection. Circulation. 2004;
8. Raphael Robert, Yves Cottin, Valerie Potard, Murielle Mary-Krause, Silvie Lang, Emmanuel Tieger FB. Coronary Angiographic Features and Major Adverse Cardiac or Cerebrovascular Events in People Living With Human Immunodeficiency Virus Presenting With Acute Coronary Syndrome. 2022;(June):1–3.
9. Boccara F, Cohen A, Angelantonio E, Meuleman C, Ederhy S, Dufaitre G, et al. Coronary Artery Bypass Graft in HIV-Infected Patients: A Multicenter Case Control Study. Curr HIV Res. 2008;
10. Boccara F, Mary-Krause M, Potard V, Teiger E, Lang S, Hammoudi N, et al. Hiv infection and long-term residual cardiovascular risk after acute coronary syndrome. J Am Heart Assoc. 2020;
11. Shah ASV, Stelzle D, Lee KK, Beck EJ, Alam S, Clifford S, et al. Global Burden of Atherosclerotic Cardiovascular Disease in People Living With HIV. Circulation. 2018;
12. Peyracchia M, De Lio G, Montrucchio C, Omedè P, d'Ettore G, Calcagno A, et al. Evaluation of coronary features of HIV patients presenting with ACS: The CUORE, a multicenter study. Atherosclerosis. 2018;
13. Seecheran VK, Giddings SL, Seecheran NA. Acute coronary syndromes in patients with HIV. Coronary Artery Disease. 2017.
14. Perelló R, Calvo M, Miró O, Castañeda M, Saubí N, Camón S, et al. Clinical presentation of acute coronary syndrome in HIV infected adults: A retrospective analysis of a prospectively collected cohort. Eur J Intern Med. 2011;
15. Genn É D, Sudre P, Anwar D, Saa Ï C, Hirschel B. Causes of macrocytosis in HIV-infected patients not treated with zidovudine. J Infect. 2000;
16. Uccello G, Mollace R, Stelitano M, Tavernese A, Muscoli S, Di Luozzo M, et al.

Clinical and angiographical features of first episode of acute coronary syndrome in patients with human immunodeficiency virus infection. HIV Res Clin Pract. 2021;

17. D'Ascenzo F, Cerrato E, Biondi-Zoccai G, Moretti C, Omedè P, Sciuto F, et al. Acute coronary syndromes in human immunodeficiency virus patients: A meta-analysis investigating adverse event rates and the role of antiretroviral therapy. Eur Heart J. 2012;
18. Boccara F, Teiger E, Cohen A, Ederhy S, Janower S, Odi G, et al. Percutaneous coronary intervention in HIV infected patients: Immediate results and long term prognosis. Heart. 2006;
19. Marcus JL, Hurley LB, Prasad A, Zaroff J, Klein DB, Horberg MA, et al. Recurrence after hospitalization for acute coronary syndrome among HIV-infected and HIV-uninfected individuals. HIV Med. 2019;
20. Boccara F, Lang S, Meuleman C, Ederhy S, Mary-Krause M, Costagliola D, et al. HIV and coronary heart disease: Time for a better understanding. Journal of the American College of Cardiology. 2013.