EVALUATION OF PROGNOSIS IN PATIENTS WITH NON ST ELEVATION ACUTE CORONARY SYNDROMES WITH DIABETES MELLITUS OR METABOLIC SYNDROME IN CORRELATION WITH INFLAMMATORY AND OXIDATIVE STRESS

Conf.univ.dr. ***Elena Bobescu***[1,2], as.univ.dr. ***Horatiu Rus***[1,2], dr. ***Eduard Belu***[2], dr. ***Alexandru Covaciu***[1], șef lucr. ***Monica Marilena Tânțu***[3]
[1] Transilvania University of Brasov - Faculty of Medicine, [2] Clinic County Emergency Hospital - Department of Cardiology, Brasov, [1]University of Pitesti, Faculty of Sciences, Romania
Author correspondent: ***Elena Bobescu****, e-mail:* elena.bobescu@gmail.com

Abstract:

Aims: Evaluation of prognosis in patients with non ST elevation acute coronary syndromes (NSTE–ACS) and diabetes mellitus (DM) or metabolic syndrome (MS) in correlation with inflammatory and oxidative stress.

Methods: 172 patients (pts) with NSTE-ACS were included in a prospective study for a period of 3 years and divided in three groups in relation with DM or MS association.

Results: In NSTE-ACS patients with DM or MS it was observed a significant increased incidence of: lower than 40% ejection fraction ($p<0.05$); readmission for heart failure III-IV NYHA class and unstable angina ($p<0.05$); acute myocardial infarction and cardiac death ($p<0.05$) at 3 years of follow up in comparison with NSTE-ACS non MS non DM group. It was no significant differences between NSTE-ACS with diabetes mellitus and with metabolic syndrome groups at 3 years. In NSTE-ACS patients, presence of diabetes mellitus or metabolic syndrome were associated with significant higher incidence of inflammatory ($p<0.05$, $p<0.01$) and oxidative stress ($p<0.05$) at 6 months.

Conclusions: In non ST elevation acute coronary syndromes patients, the presence of diabetes mellitus or metabolic syndrome was associated with significant higher incidence of low ejection fraction, readmission for heart failure III-IV NYHA class and unstable angina, acute myocardial infarction and cardiac death at 3 years of follow up and with significantly increased inflammatory and oxidative stress at 6 months.

Key-words: *acute coronary syndrome, metabolic syndrome, diabetes mellitus, inflammatory and oxidative stress*

Background

The burden of cardiovascular disease (CVD) in Europe is responsible for over 2 mil cardiovascular deaths in EU -42% of total deaths- and represent the main cause of disease burden - 23% of total illness and death. [21, 24]. In patients with diabetes mellitus, 75% of deaths are represented by cardiovascular death; cardiovascular risk is 3-5 folds higher in diabetic's patients and 3 folds higher in patients with metabolic syndrome. Incidence of metabolic syndrome in patients with acute coronary syndrome is 29-46%, with increased incidence of heart failure, and a higher long-term mortality compared to those without metabolic syndrome. [1-5,12,19] The main causes of this burden of disease in diabetes mellitus and metabolic syndrome patients are high LDL cholesterol, low HDL cholesterol serum values, prothrombotic status - high plasminogen activator inhibitor-1 (PAI-1) and fibrinogen, endothelial dysfunction, high leucocytes adhesively to endothelium and mycroalbuminuria [25,35].

Aim

Evaluation of prognosis in patients with non ST elevation acute coronary syndromes (NSTE-ACS) and diabetes mellitus (DM) or metabolic syndrome (MS) in correlation with inflammatory and oxidative stress.

Methods

172 patients (pts) with NSTE-ACS were included in a prospective study for a period of 36 months and divided in three groups in relation with MS or DM association. Clinical, electrocardiographic, echocardiographic evaluations were performed initial and at 1, 6, 12, 24 and 36 months, biologic evaluations were performed initial at 1 and 6 months. C-reactive protein serum level (Immune- turbidimetry method) and fibrinogen plasma level (Turbidimetry method) were determinate as markers of inflammatory

syndrome. Anti ox-LDL antibody titers (ELISA technique INOVA kit manufacturer) and total antioxidant status (TAS) serum level (ABTS ® Method-RANDOX kits) were measured for oxidative stress evaluation. Left ventricular ejection fraction was measured by 2-D Echocardiography, volume/dimension Simpson's method. [5- 9, 11, 14, 16, 31-33]

Groups of study: NSTE-ACS non MS non DM - 37 patients with NSTE-ACS without metabolic syndrome and diabetes mellitus; ACS MS - 76 patients with an NSTE-ACS and metabolic syndrome; ACS DM – 59 patients with NSTE- ACS and diabetes mellitus (Figure 1).

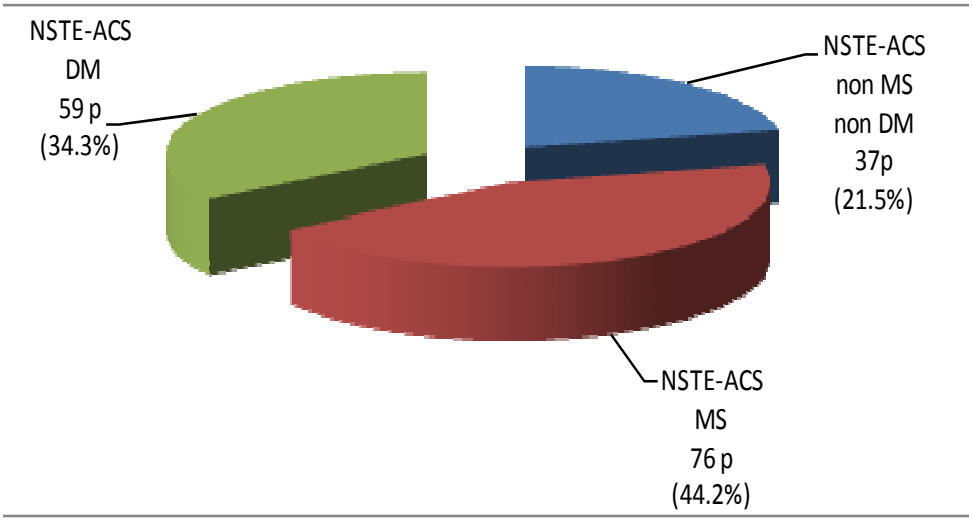

Figure 1: Groups of study

Statistical Analysis: Comparison between groups was performed using Chi-square test and multiple regression analysis. A value of $p<0.05$ was considered statistically significant.

Results and discussion: Baseline characteristics of patients were represented by additional markers, old and new factors with role in cardiovascular risk evaluation and optimal standard medical therapy in accordance with ACC/AHA guideline update for the management of patients non ST-segment elevation acute coronary syndrome. [3, 5-7, 10] It was no significant differences in baseline characteristics between study groups. (Table I)

	NSTE-ACS non MS non DM	**NSTE-ACS MS**		**NSTE-ACS DM**	
TOTAL (pts)	37	76		59	
ADDITIONAL MARKERS, OLD AND NEW FACTORS WITH ROLE IN CARDIOVASCULAR RISK					
Age > 65	18(48.6%)	36(47.4%)	ns	29(49.2%)	ns
Male	23(59.6%)	44(57.9%)	ns	35(59.3%)	ns
Smokers	13(35.1%)	28(36.8%)	ns	23(39%)	ns
Hypertension(>140/90mmHg)	25(67.6%)	50(65.8%)	ns	40(67.8%)	ns
Diabetes Mellitus	14(37.8%)	29(38.2%)	ns	22(37.3%)	ns
Body mass index >25 kg/m^2	29(78.5%)	57(75%)	ns	45(76.3%)	ns
Cholesterol>200mg/dl	26(70.5%)	54(71.1%)	ns	41(69.5%)	ns
LDL cholesterol>130mg/dl	23(62.2%)	68(63,2%)	ns	38(64.4%)	ns
HDL cholesterol<40mg/dl	19(51.4%)	39(51.3%)	ns	31(52.5%)	ns
Triglycerides>200mg/dl	15(40.5%)	30(39.5%)	ns	23(39%)	ns
Troponin T > 0,1ng/ml	35(94.6%)	70(92.1%)	ns	55(93.2%)	ns
CK-MB > 24U/l	30(81.1%)	58(76.3%)	ns	46(78%)	ns
Fibrinogen>400mg/dl	25(67.6%)	52(68.4%)	ns	41(69.5%)	ns

C-reactive protein > 0,5mg/dl	28(75.7%)	58(76.3%)	ns	45(76.3%)	ns
Anti ox-LDL antibody > 150 UI/l	25(67.6%)	50(65.8%)	ns	41(69.5%)	ns
Total antioxidant status <1.3mmol/l	35(94.6%)	70(92.1%)	ns	55(93.2%)	ns
Ejection fraction < 40%	9(22.5%)	18(23.7%)	ns	12(20.3%)	ns
OPTIMAL STANDARD MEDICAL THERAPY					
Aspirin	37(100%)	76(100%)	ns	59(100%)	ns
Enoxaparinum	37(100%)	76(100%)	ns	59(100%)	ns
Clopidogrelum	37(100%)	76(100%)	ns	59(100%)	ns
Ramiprilum/Zofenoprilum	33(89.2%)	68(89.5%)	ns	52(88.1%)	ns
Metoprololum/Nebivololum	34(91.9%)	70(92.1%)	ns	54(91.5%)	ns
Simvastatinum / Atorvastatinum	30(81.1%)	65(85.5%)	ns	50(84.7%)	ns
Nitroglicerinum iv	34(91.9%)	70(92.1%)	ns	55(93.2%)	ns
Diltiazemum	2(5.4%)	5(6.7%)	ns	4(9.2%)	ns
Isosorbidi mononitras	16(43.2%)	30(39.5%)	ns	15(25.4%)	ns

Table I. Baseline characteristics of patients represented by additional markers, old and new factors with role in cardiovascular risk and optimal standard medical therapy

Bidimensional echocardiography evaluation of ejection fraction is correlated with angiographic determination of left ventricle function, a low ejection fraction is associated with increase incidence of cardiovascular death. [18, 20, 24]

Incidence of left ventricular ejection fraction lower than 40% as a measure of global function was significantly increase ($p< 0.05$) at 3 years of follow up in non ST elevation acute coronary syndromes patients with metabolic syndrome or diabetes mellitus in comparison with ACS non MS non DM group. (Table I)

Major acute cardiovascular events were present with a significant higher incidence in patients with non ST acute coronary syndrome patients and metabolic syndrome or diabetes mellitus.

Number of readmissions for heart failure III-IV NYHA class and unstable angina was significantly higher ($p<0.05$) in groups with metabolic syndrome or diabetes mellitus. (Table II)

	NSTE-ACS non MS non DM	**NSTE-ACS MS**	**NSTE-ACS DM**
TOTAL (pts)	37	76	59
Left ventricular ejection fraction <40%	5 (13.5%)	23 (30.2%) ***p<0.05***	22 (37.3%) ***p<0.05***
Heart failure NYHA III-IV class with readmission	7(18.9%)	30 (39.5%) ***p<0.05***	27 (45.8%) ***p<0.025***
UA with readmission	9(24.3%)	39 (51.3%) ***p<0.025***	33 (55.9%) ***p<0.025***
AMI/reinfarctization	2 (5.4%)	18 (23.7%) ***p<0.05***	17 (28.8%) ***p<0.05***
Stroke	1 (2.7%)	4 (5.3%)***ns***	6 (10.2%)***ns***
Cardiac death	2 (5.4%)	14 (18.4%) ***p<0.05***	15 (25.4%) ***p<0.05***

Table II: Results at 3 years

NSTE-ACS - non ST elevation acute coronary syndromes, MS – metabolic syndrome; DM- diabetes mellitus; AMI-acute myocardial infarction; UA-unstable angina

Incidence of acute myocardial infarction and cardiac death at 3 years was significantly increased ($p<0.05$) in patients with non ST elevation acute coronary syndromes and

metabolic syndrome or diabetes mellitus in comparison with non MS non DM NSTE-ACS patients (Table II).

In patients with diabetes mellitus, 75% of deaths are represented by cardiovascular deaths and cardiovascular risk is 3-5 folds higher in diabetic's patients and 3 folds higher in metabolic syndrome. Incidence of metabolic syndrome in patients with acute coronary syndrome is 29-46%, with increased incidence of heart failure, and worse long-term mortality compared to those without metabolic syndrome. [4, 5, 12].

Incidence of major acute cardiovascular events and readmission for heart failure or unstable angina was higher in patients with non ST acute coronary syndrome and diabetes mellitus in comparison with patients with metabolic syndrome but not so high to reach statistic significant at 3 years of follow up.

In non ST elevation acute coronary syndromes patients, presence of metabolic syndrome or diabetes mellitus were associated with significant increased incidence of high serum level of C reactive protein ($p<0.05$ in NSTE-ACS MS, $p<0.01$ in NSTE-ACS DM) and low total antioxidant status serum level ($p<0.05$ in NSTE-ACS MS and DM) at 6 months of follow up. It was no significant differences between non ST elevation acute coronary syndromes with metabolic syndrome and with diabetes mellitus groups, both cardiovascular risk factors seems to have at 3 years of follow up an almost similar impact on prognosis, higher but not significant in diabetes mellitus patients. (Table III)

	NSTE-ACS non MS non DM	**NSTE-ACS MS**	**NSTE-ACS DM**
TOTAL (pts)	37	76	59
C-reactive protein>0,5mg/dl	6 (16.2%)	27 (35.5%) ***p<0.05***	25 (42.4%) ***p<0.01***
Fibrinogen> 400mg/dl	9(24.3%)	25 (32.9%) *ns*	18 (32.5%) *ns*
Total antioxidant status <1.3 mmol/l	4 (10.8%)	21 (27.6%) ***p<0.05***	19 (32.2%) ***p<0.05***
Anti ox-LDL antibody titers >150 mU/ml	6(16.2%)	19(25.3%) *ns*	18(28.8%) *ns*

Table III: Inflammatory and oxidative stress results at 6 months

C-reactive protein is an important inflammatory marker with high predictive value in subgroups of patients with non ST acute coronary syndrome patients: women, older, smokers, diabetics, patients with metabolic syndrome. Presence of high serum values of C reactive protein is associated with 3-4 fold higher incidences of cardiovascular events. [1, 3, 5]

Antioxidant defence has many components. Deficiency of any of this components produces the reduction of total antioxidant status. Metods of total antioxidant capacity determination are useful in myocardial ischemia when a depletion of total antioxidant status is demonstrated to be produced. [16-18, 22]

Conclusions

Incidence of left ventricular ejection fraction, unstable angina and heart failure III-IV NYHA class with readmission, acute myocardial infarction and cardiac death at 3 years of follow up was significantly increased in patients with non ST elevation acute coronary syndromes associated with metabolic syndrome and diabetes mellitus.

It was no significant differences between non ST elevation acute coronary syndromes with metabolic syndrome and with diabetes mellitus groups, both cardiovascular risk factors seems to have at 3 years of follow up an almost similar impact on prognosis, higher but not significant in diabetes mellitus patients.

In non ST elevation acute coronary syndromes, presence of metabolic syndrome or diabetes mellitus was associated with significant higher incidence of inflammatory and oxidative stress at 6 months of follow up.

References

[1] Alberts, Beyal. Molecular Biology of the Cell, 3rd edn. Garland Publishing, New York, 1996.

[2] Anderson HV, Cannon CP. Stone PH, et al: One-year results of the Thrombolysis In Myocardial Infarction (TIMI) IIIB clinical trial: A randomized comparison of tissue-type plasminogen activator versus placebo and early invasive versus early conservative strategies in unstable angina and non-Q-wave myocardial infarction. J Am Coll Cardiol 26: 1643-1650,1995.

[3] Bobescu E. Modalităti terapeutice de inhibare a funcţiilor placetare în bolile cardiovasculare. Ed University Press Targu Mures, 2009

[4] Bobescu E. Stresul oxidativ in sindroamele coronariene acute. Ed University Press Targu Mures, 2007

[5] Braunwald E, Antman EM, Beasley JW et al. ACC AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation, myocardial infarction-2002: summary article: a report of the American College of Cardiology, American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). Circulation 2002; 106: 1893-1900.

[6] Braunwald E. Antman EM. Beasley JW et al: ACC/ AHA guidelines for the management of patients with unstable angina/non-ST segment elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Unstable Angina and Non-ST Segment Elevation Myocardial Infarction). J Am CoIl Cardiol 36:970-1062, 2000.

[7] Braunwald E. Application of current guidelines to the management of unstable angina and non-ST-elevation myocardial infarction. Circulation 2003; 108:28111-28137.

[8] Buja LM, Willerson JT. Role of inflammation in coronary plaque disruption. Circulation. 1994; 89: 503-505.

[9] Cheitlin MD, Alpert JS, Amstrong WF, et al: ACC/AHA guidelines for the clinical aplication of Echocardiography: Executive sumary. A report of the American College of Cardiology/ American Heart Association Task Force on practice guidelines (Committee on Clinical Application of Echocardiography); Developed in collaboration with the American Society of Echocardiography. J Am CoIl Cardiol 29:862-879, 1997.

[10] Ernst E, Resch KL: Fibrinogen as a cardiovascular risk factor: A metanalysis and review of the literature. Ann Intern Med 118:956-963, 1993.

[11] Fisman EZ, Tenenbaum A. Cardiovascular Diabetology: Clinical, Metabolic and Inflammatory Facets. Adv Cardiol. Basel, Karger, 2008, vol 45,pp 114-126;

[12] Fragasso G, Perseghin G, De Cobelli F, et al. Effects of metabolic modulation by trimetazidine on left ventricular function and phosphocreatine/adenosine triphosphate ratio in patients with heart failure. European Heart Journal (2006) 27, 942–948

[13] Fuster V, Badimon L, Badimon JJ, et al. The pathogenesis of coronary artery disease and the acute coronary syndromes. N EngI J Med. 1992;326:242-250,310-318.

[14] Goldberg RJ, Currie K, White K, et al. Six-month outcomes in a multinational registry of patients hospitalized with an acute coronary syndrome (The Global Registry of Acute Coronary Events [GRACE]). Am J Cardiol 2004; 93: 288-293.

[15] Granger CB, Goldberg RJ, Dabbous 0, et al. The Global Registry of Acute Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med 2003; 163:2345-2353.

[16] Halliwell, B (1995) Antioxidant character-rization. Methodology and mechanism. Biochem. Pharmacol.49, 1341.

[17] Hasdai D, Behar S, Wallentin L, et al. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin. The Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). Eur Heart J 2002; 23: 1190-1201.

[18] Hochman JS, Tamis JE, Thompson TD, et al. Sex, clinical presentation. and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. N Engl J Med 341:226-232, 1999.

[19] Hyde TA, French JK, Wong CK, Straznicky, et al. Four-year survival of patients with acute coronary syndromes without ST-segment elevation and prognostic significance of 0.5-mm ST-segment

depression. Am J Cardiol 1999; 84: 379-85.

[20] International Task Force for Prevention of Coronary Heart Disease. Summary of the Expert Panel Meeting: Cholesterol-lowering with statins- are they all the same? New Orleans March 7 2004

[21] Iskesen I, Saribulbul O, Cerrahoglu M, et al. Trimetazidine Reduces Oxidative Stress in Cardiac Surgery Circ J 2006; 70: 1169–1173

[22] Kim JS, Kim CH, Chun KJ et al. Effects of trimetazidine in patients with acute myocardial infarction: data from the Korean Acute Myocardial Infarction Registry Clin Res Cardiol (2013) 102:915–922

[23] Koenig W, Sund M, Froelich M, et al: C-reactive protein, a sensitive marker of inflamation, predicts future risk of coronary heart disease in initially healthy middle-aged men: Results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsberg Cohort Study, 1984 to 1992. Circulation 99:237-242, 1999.

[24] Lakka HM, Laaksonen DE, Timo A, et al: The Metabolic Syndrome and Total and Cardiovascular Disease Mortality in Middle-aged Men JAMA. 2002;288:2709-2716.

[25] Manson IE, Coldjtz GA, Stampfer MI, et al: A prospective study of obesity and risk of coronary heart disease in women. N Engl J Med 322: 882-889, 1990.

[26] Morrow DA. Rifai N, Antman EM. et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI II A sub-study. Thrombolysis In Myocardial Infarction. J Am CoIl Cardiol 1998; 31: 1460-5.

[27] Ridker PM, Buring IE, Shih I, et al: Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. Circulation 98:731-733, 1998.

[28] Ridker PM, Hennekens CH, Buring lE, et al: C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl I Med 342:836-843, 2000.

[29] Ridker PM; Rifai N, Clearfield M, et al. The Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med. 2001;344:1959-1965.

[30] Roivairien M, Viik-Kajander M, Palosuo T, et al: Infections, inflammation, and the risk of coronary heart disease. Circulation 101:252-257, 2000.

[31] Rosengren A, Wedel H, Wilhelmsen L: Body weight and weight gain during adult life in men in relation to coronary heart disease and mortality. A prospective population study. Eur Heart J 20:269-271 1999.

[32] Schemper M, Heinze G. Revisited for prognostic factor studies. Stat Med 1997; 16:73-80.

[33] D, et al: Prediction of coronary heart disease using risk factors categories. Circulation 97:1837-1847, 1998.

[34] Wu AH, Apple FS, Gib!er WB, et al. National Academy of Clinical Biochemistry Standards of Laboratory Practice recommendations for the use of cardiac markers in coronary artery diseases. Clin Chem 1999;45:1104-21.

[35] Wu Q, Qin B, Liu Y, et al. Mechanisms underlying protective effects of trimetazidine on endothelial progenitor cells biological functions against H2O2 -induced injury: Involvement of antioxidation and Akt/eNOS signaling pathways. European Journal of Pharmacology 2013;

[36] Xu X, Zhang W, Zhou Y, et al. Effect of Trimetazidine on Recurrent Angina Pectoris and Left Ventricular Structure in Elderly Multivessel Coronary Heart Disease Patients with Diabetes Mellitus After Drug-Eluting Stent Implantation: A Single-Centre, Prospective, Randomized, Double-Blind Study at 2-Year Follow-Up Clin Drug Investig (2014) 34:251–258

[37] Zaninotto M, Altinier S, Lachin M, et al. Strategies for the early diagnosis of acute myocardial infarction using biochemical markers. Am J Clin Pathol 1999; 111 :399-405.