

CORRELATION OF CARDIAC MARKERS VALUES IN ACUTE CORONARY SYNDROME WITH CORONARY DISEASE SEVERITY ASSESED BY EXERCISE STRESS TESTING AND INVASIVE EXAMINATION

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Summary. Strategy of combining predictive characteristics of troponin during the first 24 hours since admission to hospital and symptom limited test, done before discharge, proved to be an independent predictor of adverse events. The aim of the study: Correlation of cardiac markers values in acute coronary syndrome with severity of coronary disease estimated by exercise stress test and coronarography, as well as by impact of the markers on therapy choice. The study enrolled 333 patients. Laboratory analysis involved troponin T and I (TnT, TnI), myoglobin, CK-MB and CK-MB mass. Ergometric and invasive examinations were done at the end of hospitalisation. There is a significant relation in positive exercise stress tests in troponin positive patients, which is statistically significant. The analysis of exercise stress test showed a statistically significant increase of positive findings in troponin positive ones ($p < 0.05$). Out of 104 coronarographies in group with two diseased coronary vessels there were 46.4% Tn positive, compared to 29% troponin negative patients, what can also be seen in the group with ≥ 3 diseased coronary vessels (3.2 vs 14.8%). Out of 104 coronarographed patients, 29 (8.1%) underwent PTCA, and 25 (7%) ACBG. Statistical significance occurred in choosing patients for PTCA in comparison to Tn status ($p < 0.05$), while this was not the case with the group selected for ACBG. In our research a good diagnostic and prognostic troponin value was established and it was confirmed by statistically significant correlation of troponin values and exercise stress tests findings on discharge. They were a reliable indicator of degree and severity of coronarographic finding, as well as a guideline in choosing invasive strategy treatment.

Key words: Troponin, acute coronary syndrome, exercise stress test, coronary angiography

Introduction

Fast plaque progression has been described as a major characteristics of unstable angina. Angiography provides only a single view of the disease which is dynamic. The sooner angiography during acute phase is applied, the more serious lesions are found. So, there is a justification for a more aggressive approach and a much better effect in early invasive treatment in these patients. When troponin levels are elevated, more thrombotic material is present in coronary lesions, which explains a higher risk of new myocardial damage and better response to mechanical procedures, as well as to antithrombotic treatment. Also, the other risk indicators, such as age, diabetes, previous MI and previous angina, are connected with much more serious CAD, and thus with greater benefits from early invasive treatment (1).

An urgent strategy in early risk stratification in patients with medicament stabilised unstable angina is a combination of myocardial markers of necrosis and ECG indicators of residual myocardial ischemia. Another strategy is a combination of predictive characteristics of troponin in 24 hours since admission to hospital

and predischARGE symptom limited test. These measurements showed that they are independent predictors of death or nonfatal MI in 5 months. Moreover, combined approach allows better risk discrimination than single measurements (2).

ACC/AHA guidelines for treatment of unstable angina and NSTEMI recommended that low level exercise stress test can be done in low risk patients who were nonsymptomatic in 12 to 24 hours, while symptom limited tests can be done in patients without recruit ischemia in 7 to 10 days (3).

Elevated TnT levels in patients with unstable angina are predictors of adverse events. As there is no satisfactory therapeutic concept for such high risk patients, Heeschen (4) et al. studied cardiac risk before, during and after coronary revascularisation in patients with unstable angina, stratified according TnT status. In troponin positive patients clinical symptoms were much more refracted to medical treatment, coronarography was done much earlier, they had a higher incidence of cardiac events before revascularisation. Angiogram for troponin positive patients discovered a more serious coronary artery disease which demanded revascularisation. After coronary interventions there were more com-

plications. So, troponin testing is a reliable predictor in patients with unstable angina and such a high frequency has been observed earlier, especially when joined with coronary interventions (4).

Material and Methods

This study enrolled patients who were treated in 2002-2004 at the Coronary Unit of Cardiology Clinic in the Clinical Center in Nis.

In the period of three years 2775 patients with all cardiac urgent states were admitted into Coronary Unit. Patients who were diagnosed ACS on admission, total of 1568 (56.50%), were excluded from that group.

Total follow-up period lasted 3 months. Health control check-ups were done in the first and third month since discharge from hospital and they involved clinical examination, ECG, determination of the course of the disease concerning recurrent angina, reinfarction, revascularisation or percutaneous interventions, as well as the results.

Using inclusive criteria, total of 333 patients were separated. Many patients could not join the examining group because this study is a multimarker one, so those patients who did not have the criteria for multimarker examination (at least two markers and at least two determinations) were excluded.

It was obvious that most of the examined patients belonged to group NSTEMI, that is 50%, what is significant regarding the aim of the study. The increase of this type of ACS was noticed in large studies, while there is a gradual decrease in STEMI at the same time (Graph 2).

Total number of male patients was 251 or 2/3, female patients 106 or 1/3. Mean age in male patients was 61.86 ± 11.02 and in female 64.19 ± 10.14 . Although women were older for about 2.3 years, that difference was not statistically important. There were 12.2% patients under age of 49, 31.3% patients between 50-59, 33.9% patients between the age of 60-69 and 22.6% patients over 70 years of age. The greatest number of patients was between 50 and 59, then between 60 and 69, while the other two age groups were present in a slightly lower percentage.

ECG was recorded during admission twice: in admission room and immediately after hospitalisation in Coronary Unit (within 10-15 minutes). All the patients were monitored for at least 24 hours. ECG analysis: ECG was recorded in 12-lead form at a paper speed of 25 mm/s with correct calibration of 1 mV. ST segment depression existed when J point was in depression for 1mm or more and was followed by horizontal or downsloping ST depression of at least 0.08 sec. in two adjacent precordial leads or two extremity leads. Q-wave or Q-wave equivalent was determined by Selvester QRS screening criterium. Finding was marked as Q-wave if it lasted ≥ 30 ms and aVF, ≥ 40 ms in leads I and aVL, ≥ 40 ms in more than two V4, V5 or V6 or any Q-wave in V2. Additionally, Q-wave equivalent is an accepted finding as R-wave ≥ 40 ms in V1, or R-wave ≤ 1 mm and ≤ 10 ms in V2.

Myocardial infarction is defined either as a new Q-wave (lasting ≥ 0.04 sec. or at least 1/4 of the R height in two or more adjacent leads) or as increase of markers of myocardial necrosis (troponin); new episodes of chest pain with combination of new troponin elevation are needed for making a diagnosis of myocardial infarction within 7 initial days.

Laboratory analysis was an aimed one, including cardiac necrosis biomarkers, firstly troponin T and troponin I, myoglobin, then classic enzyme markers of necrosis: CK-MB and CK-MB mass, and finally indicator of renal function-creatinine.

Troponin evaluation had two phases. In the first phase we used an immunoassay method for determining myoglobin and troponin T – bedside assay in the Coronary Unit at the Cardiology Clinic. ROCH Cardiac Reader was used. By this method 210 patients were examined in the beginning of the examination. After that, a new technology for determining troponin I was introduced in the central laboratory of the Clinical Center in Nis. By this method another 128 patients were examined. The second phase of examination was determining troponin I by method of Abbott Laboratories Diagnostic Division AX-SYM, Abbott Park, IL 60064 from the USA, used in central laboratory of the Clinical Center in Nis.

Quantitative immunological test for specific detection of myoglobin in blood, apparatus ROCH Cardiac Reader. Renal function was examined by creatinine values in blood. Borderline values of Central laboratory of the Clinical Center were accepted (creatinine 53-115 mmol/l).

Early exercise stress tests was done in the end of hospitalisation in 158 patients, but not in 91 patients, or 36.5%. The primary aim of this test was to confirm concord of troponin values results and positive exercise tests level.

Coronarography was done in 104 patients and was indicated in another 89 patients, it was not done in 166 patients. The greatest number of coronarographies was done at the Department for Invasive Diagnostics at Cardiology Clinic and less coronarographies were done in other centers. The key interest of the coronarography study was to compare the coronarographic finding regarding the number of the involved blood vessels and troponin status.

Statistic analysis of data significance was done by percentage relation, t test and χ^2 test, Odds ratio (OR), Fisher test and Kappa measurement agreement.

Aim of the study

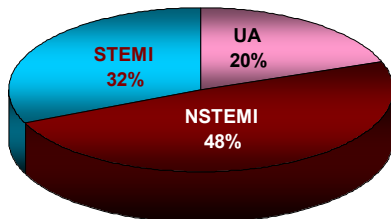
Correlation of cardiac markers values in acute coronary syndrome with severity of coronary disease estimated by exercise stress test and coronarography, as well as by marker influence on the choice of therapy.

Results

Applying inclusive criteria, 333 patients were included. Many patients could not be involved into the examined group because the study was a multimarker

one, so those patients who did not have the criteria for the multimarker examination (at least two markers and at least two determinations) were rejected.

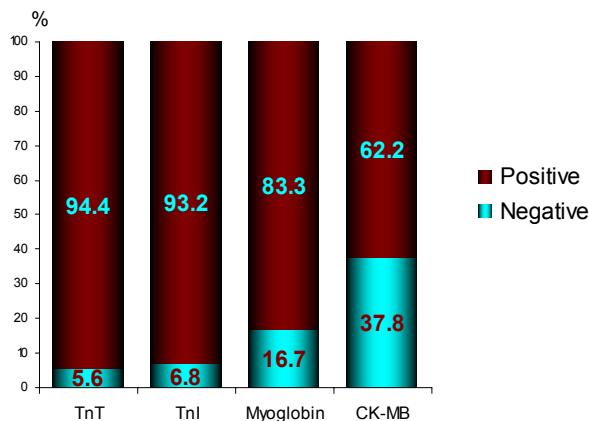
It was obvious that the most of the examined patients belong to NSTEMI group, about 50%, what is significant regarding the aim of the study



Graph 1. Different ACS forms percentage survey

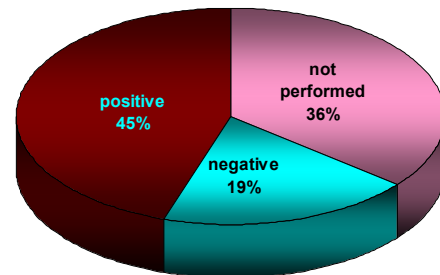
By including the aimed group NSTEMI on the basis of consensus document ESC/ACC, high TnT and TnI sensitivity was observed, as well as high myoglobin sensitivity and standard diagnostic possibilities CK-MB. The patients had, in statistically significant percentage, positive findings to TnT compared to myoglobin (94.4% to 83.3%; $\chi^2 = 4.29$; $p=0.039<0.05$) and compared to CK-MB (94.4% to 62.2%; $\chi^2 = 24.06$; $p=0.000<0.001$ OR=10.19; $3.27<OR<35.31$). Myoglobin was statistically significantly more often positive than CK-MB ($\chi^2 = 9.00$; $p=0.003<0.01$ OR=3.04; $1.37<OR<6.88$). From the obtained data it is clear that troponin T was a more sensitive necrosis marker compared to CK-MB for 32.2%. Myoglobin showed high sensitivity as an early marker with positive values in 83.3%, proving to be a sensitive marker for early diagnostics of myocardial necrosis.

The patients had, in statistically significant higher percentage, positive findings to TnI compared to CKMB (93.2% to 62.2%; $\chi^2 = 14.86$; $p=0.000<0.001$ OR=8.31; $2.28<OR<35.8$). TnI and myoglobin were not statistically significantly different in positivism of the findings ($\chi^2 = 2.31$; $p=0.129$ n.s.). From the obtained data it can be seen that TnI was a more sensitive marker of myocardial necrosis compared to CK-MB for 31%



Graph 2. Positive markers frequency in patients with NSTEMI

Exercise stress testing was done in 148 patients, or 64.1%. There were 45.1% positive tests.



Graph 3. Tabular survey of performed Exercise Stress Tests

Exercise stress test was done in a significant number of patients, 148 or 64.1% with ACS. A considerable proportion of positive tests (45.1%) can be seen.

There is significant relation in positive exercise stress tests in patients who had positive TnT levels on admission. This difference is statistically significant ($\chi^2 = 5.20$; $p=0.023<0.05$)

Table 1. Exercise Stress Test and TnT status relation

Exercise Stress Test	TnT -		TnT +		Total
	n	%	n	%	
Negative	22	36.7	16	19.5	42
Positive	38	63.3	66	80.5	100
Total	60		82		142

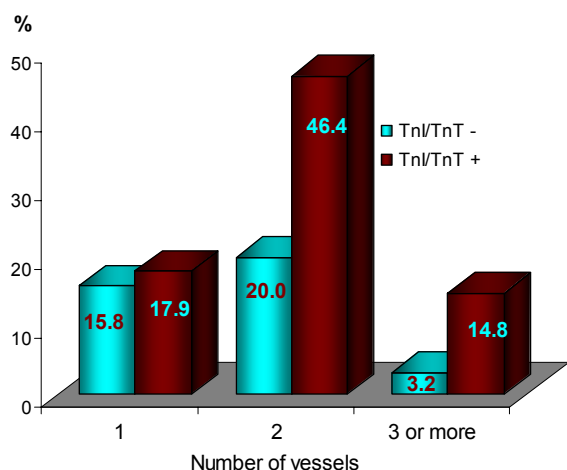
By analysing exercise stress tests results in united population TnT and TnI, it can be seen that the increase of positive tests is higher and statistically significant in the group with elevated troponin levels on admission ($\chi^2 = 5.10$; $p=0.024<0.05$ statistically significant)

Table 2. Exercise Stress Test and TnTnT/TnI status relation

Exercise Stress Test	Tn (T + I) -		Tn (T + I) +		Total
	n	%	n	%	
Negative	35	36.08	11	18.97	46
Positive	62	63.92	47	81.03	109
Total	97		58		155

A significant number of coronarographies was done (n=104) and in another 89 patients there were indications for coronarography because of recurrent angina or because of hemodynamic reasons. In the follow-up period of three months they were on the waiting list ($\chi^2 = 4.17$; $p=0.125>0.05$ n.s.).

In the group of patients with two diseased coronary vessels there were 46,4% troponin positive ones compared to 29% troponin negative patients. This increase can also be seen in the group with three or more diseased coronary vessels (3.2 vs 14.8%), but this difference is not statistically important.



Graph 4. Coronarography findings and troponin status ratio

Out of 104 patients with coronarography done, 29 (8.1%) were undergoing PTCA procedure and 25 (7%) bypass revascularisation. A statistic significance was present in choosing patients for PTCA procedure compared to troponin status (Fisher $p=0.018 < 0.05$).

Table 3. Troponin status and PTCA relation

PTCA	Tn (T + I) -		Tn (T + I) +		Total
	n	%	n	%	
PTCA -	97	97.0	207	89.2	304
PTCA +	3	3.0	25	10.8	28
Total	100		232		332

In patients selected for ACBG, troponin status was of no influence (Fisher $p=0.363 > 0.05$ N.S).

Table 4. Troponin status and ACBG relation

ACBG	(TnT + TnI) -		(TnT + TnI) +		Total
	n	%	n	%	
ACBG -	95	95.0	213	91.8	304
ACBG +	5	5.0	19	8.2	28
Total	100		232		332

Discussion

This research is in fact an implementation of so far obtained knowledge about cardiac biomarkers, troponins, having an enormous contribution in fundamental knowledge of pathophysiological events in onset, duration and treatment of ACS. It is a about one of the key cardiological problems in diagnosing non Q infarction compared to unstable angina, to diagnostic of small myocardial necrosis which bear a considerable risk (5).

By analyzing gender and age of our examined group, it can be seen that males were two and a half times more present than females, while females were 2,3 years older than males. Women had less serious and less extensive coronary disease. According to large studies experience,

women are behind men in morbidity and mortality for 7 to 10 years. The number of sick women at the age of 75 is the same as the number of sick men at the age of 65. This is thought to be a consequence of the protective role of women sex hormones. Since women live longer, the total number of the sick is almost the same. (4,5)

By analysing the structure of patients on admission and on discharge, a significant difference in frequency of ACS forms, made by implementation of cardiac necrosis markers, can be seen. Thus, on admission, the most frequent form of ACS in our population was UAP with 182 patients, or 50.98%, and on discharge NSTEMI with 120 patients, or 33.4% (5).

Ilić et al in their analysis of patients with ACS treated at the Coronary Unit of the Institute in Niska Banja, found similar frequency in patients with or without ST segment elevation and more frequency in male patients. There was no significant difference considering the age (6).

Necrosis markers findings in the examined group of patients with NSTEMI are of significant interest. There is a high level of positive results in troponin analysis, TnT in 71 patients, or 94.4% and toponin TnI in 44 patients, or 93.2%. By correlation of troponin values, using the until recently valid golden rule for myocardial necrosis CK-MB (119 patients) or 62.2% positive, it can be seen that it was possible to verify more myocardial necrosis or infarctions by troponins, even for 32% for TnT and 31% for TnI. A finding of considerable number of positive results of myoglobin (66 patients or 83.3%) is worth of our attention, because it is the earliest marker of myocardial necrosis. Although myoglobin has been criticized for low specificity, high sensitivity is very useful for early selection of patients in the intensive care units. A high degree of correlation of TnT and TnI with CK-MB was found (5).

Exercise stress tests showed very good compatibility with positive troponin status, indicating that such patients should be send to invasive diagnostics.

Exercise stress testing has traditionally been used for detecting significant obstructive coronary diseases among patients with stabile form of chest pain, and as a stress test before coronary angiography. Among the patients with NSTEMI ACS, primary aims of exercise stress test were the confirmation of the diagnosis of coronary disease and prognosis prediction. Exercise stress tests were predictive for future cardiac events in cases of stabile coronary disease in patients (2).

Biochemical markers for myocardial impairment detection play the key role for assesment and treatment of patients with ACS. When clinicians have to perform basic triage, treatment and monitoring on time sensitive tests results, there are tests for fast and appropriate diagnostic option, complementary with central laboratory tests. This is particularly true when choice of effective therapy depends on cardiac biomarkers. Studies demonstrated connection between troponin results and effects of glycoprotein IIb/IIIa antagonist and LMWH, which was demonstrated. In this scenario troponins are surogat markers of active thrombotic process.

Biomarkers must not be understood as exclusive methods. Used along with information from history taking, physical examination and 12-lead electrocardiogram, cardiac markers help in establishing diagnosis of myocardial infarction, risk assesment of subsequent clinical events and in planning further evaluation and treatment. Moreover, biomarkers have a potential to ensure insight in specific pathophysiology of coronary ischemia for individual patients. Reaching each of these aims, cardiac troponins are highly specific and sensitive markers of myocardial impairment, functioning as a strong means for defining prognosis and conducting therapy for patients with ACS.

According to findings of our examination, there is a very good correlation of troponin status and coronarographic finding, which can be seen from data that the highest troponin level and the most frequent occurrence of positive troponins are found in double or triple vessel disease, with characteristics of complex changes. It was able to make a conclusion that troponin status is a reliable predictor of severity of coronary disease and angiographic finding and a safe parameter in indicating urgent coronographies and interventional procedures.

Despite the risk in all the interventional procedures, FRISC II showed a persistant reduction in mortality in invasive group during the study period. So, in spite of the high increase of early periprocedural myocardial infarction, there was no early mortality in invasive group. The results of coronary artery bypass surgery in unstable CAD were the best when surgery was done after a few days of stabilisation on intensive antithrombotic and antiischemic therapy (7).

TnT elevation in patients with unstable angina is predictable for negative events. As there is no appropriate therapeutic concept for such high risk patients, Heeschen and Hamm (4) studied cardiac risk before, during and after coronary revascularisation in patients with unstable angina stratified according to TnT status.

According to these authors' findings, troponon positive patients had much more serious coronary artery disease which demanded revascularisation (69% vs 59%). Also, after coronary intervention there were more complications (dying or MI 15.3% vs 4.8%). During 30 day follow-up, cardiac risk remained elevated in troponin positive patients. So, TnT fast testing reliably identifies high-risk patients with unstable angina. High frequency of the events was observed earlier, especially joined with coronary intervention. Early risk stratification plays a key role in selecting patients who will most benefit from the therapy. The above mentioned authors studied coronary intervention results according to TnT status. Meanwhile, eight patients developed acute infarction before angiography. In 108 TnT positive patients angiogram showed significant changes in at least one vessel. After considering all troponin positive patients, revascularisation was done by PTCA in 50% and ACBG in 11%. On the contrary, in troponin negative patients there were much less significant stenosis, so 46% of patient underwent revascularisation. It is inter-

esting that in troponin positive patients after coronary intervention there were more recurrent anginas pectoris, in relation 4.8% vs 2.2%. Contrary to other studies, in this one TnT status was taken for diagnostic and therapeutic decision making during hospitalization. Angiographic studies indicated that thrombus, in patients with unstable angina, is thrombocytes rich, in contrast to fibrin thrombus observed in patients suffering from AMI (3).

Ambroze et al investigated relation between troponin status and angiographic finding in patients with UA or NSTEMI. Complex lesions were found in 72% troponin positive patients and 41% in troponin negative ones. Presented data from the study supported the hypothesis that troponin elevation was joined with presence of complex lesions (plaque disruption and/or thrombosis). Supporting previous observations that microinfarction, possible secondary, because of embolisation of distal vascular bed, is a pathophysiological mechanism for positive troponin in patients with unstable angina and NSTEMI. Another mechanism for troponin positivity with the presence of thromb involves temporary total occlusion, vasospasam or occlusion of small lateral branches at lesion site. Sensitivity and specificity of elevated troponin for the presence of lesion complex was moderate with positive predictable values of 72%. Compared to angiostopy, angiography is relatively non-sensitive in discovering intracoronary thromb, although highly specific for their presence. It is probable that many troponin positive patients have intracoronary thromb which can be detected angiographically. The authors also presented a claim that the presence of complex lesions was not always joined with troponin positivity (8).

Numeruou clinical studies showed that interventions, especially revascularisations, can be performed by following troponin values. In that case very low borderline values are used for cTnT 0,01 µg/l (9,10,11,12).

In our investigation out of 104 patients with coronarography done, 29 patients (8,1%) underwent PTCA procedure, a 25 patients (7%) bypass revascularisation. Statistic significance occured while choosing patients for PTCA procedure in relation to troponin status, while in patients selected for ACBG troponin status was of no influence (5).

Unstable coronary artery disease increases TnT level and occurrence of ST segment depression results in poor prognosis. In FRISC II study it was evaluated if TnT level alone and combined with ST depression identifies much more serious coronary artery disease or more efficient invasive strategy. Invasive strategy reduces death/MI to 12 months with both ST depression and TnT level ≥ 0.03 µg/l from 22.1 to 13.2%. Patients with unstable coronary artery disease with combination of TnT level ≥ 0.03 µg/l and ST depression have poorer prognosis and in half of the cases triple vessel or left main disease. In these patients early invasive strategy will significantly decrease death/MI (7).

In unstable coronary artery disease, elevation of troponin level is associated with poorer prognosis. Also,

patients with ST segment depression have a greater risk of future cardiac events. FRISC II study randomized patients with unstable coronary artery disease to early invasive vs noninvasive strategy. Invasive strategy led to significant reduction of both death and MI. In this substudy of FRISC II study, authors investigated if TnT level alone, or in combination with occurrence of ST segment depression, can indicate angiographic severity of coronary artery disease and identify group of patients with different benefits from early invasive strategy (7, 13, 14).

Coronary angiography remains an essential device in examination and risk stratification in patients with ACS. Serious coronary lesions are more frequent in patients

with ischemic signs, that is, with segment depression or with troponin elevation (15).

Conclusion

In our investigation both diagnostic and prognostic troponin values were established, confirmed by statistically significant correlation of troponin values and exercise stress tests findings on discharge.

Cardiac troponin levels in patients with acute coronary syndrome were reliable factors for the degree and severity of coronarographic finding, as well as a guideline in choosing invasive treatment strategy.

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KORELACIJA VREDNOSTI SRČANIH MARKERA U AKUTNOM KORONARNOM SINDROMU SA TEŽINOM KORONARNE BOLESTI PROCENJENO TESTOM FIZIČKIM OPTEREĆENJEM I INVAZIVNIM ISPITIVANJEM

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Kratak sadržaj: Strategija kombinovanja prediktivnih svojstava troponina tokom prvih 24 časa od prijema i predotpusni simptom ograničeni test izveden na biciklu. su pokazala da su nezavisan prediktor nepovoljnih događaja. Cilj rada je da se

utvrdi korelacija vrednosti srčanih markera u akutnom koronarnom sindromu sa težinom koronarne bolesti procenjenom testom fizičkim opterećenjem i koronarografijom kao i uticajem markera na izbor terapije. Ispitivana populacija činilo je 333 bolesnika. Laboratorijsko ispitivanje je obuhvatilo troponin T i I (TnT, TnI), mioglobin, CK-MB i CK-MB mass. Spovedeno je ergometrijsko ispitivanje na kraju bolničkog lečenja i invazivno ispitivanje. Uočava se značajan odnos pozitivnih testova fizičkim opterećenjem kod troponin pozitivnih bolesnika što je statistički značajno ($p < 0.05$). Analizom ERGO testova pokazuje statistički signifikantan porast pozitivnih nalaza u troponin pozitivnih ($p < 0.05$) Od 104 urađenih koronarografija u grupi sa 2 obolela krvna suda bilo 46,4% Tn pozitivnih u odnosu na 29% troponin negativne bolesnika, što se uočava i u grupi sa ≥ 3 obolelih krvnih sudova (3,2 vs 14,8%). Od 104 koronarografisanih bolesnika 29 (8,1%) bilo je podvrgnuto PTCA, a 25 (7%) ACBG. Statistička značajnost se pojavila kod izbora bolesnika za PTCA u odnosu na Tn status ($p < 0.05$) dok to nije slučaj u grupi koji je selekcionirana za ACBG. U ispitivanju je utvrđena je dobra dijagnostička i prognostička vrednost troponina koja je potvrđena kroz statistički značajnu korelaciju vrednosti troponina sa nalazima testova fizičkim opterećenjem na otpustu i bili su pouzdan indikator stepena i težine koronarografskog nalaza, kao i vodič u izboru invazivne strategije lečenja..

Ključne reči: Troponin, akutni koronarni sindrom, test fizičkim opterećenjem, koronarna angiografija