

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

A complete versus inducible ischemia-guided revascularization after a culprit-only primary percutaneous coronary intervention in multivessel coronary artery disease – a pilot study

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SUMMARY

Introduction/Objective Revascularization in multivessel coronary artery disease (MVD) in patients with ST elevation myocardial infarction (STEMI) is a matter of debate. We sought to compare outcomes between revascularization strategies based on angiographic lesion severity or inducible ischemia.

Methods In prospective study, first ever STEMI patients with MVD, defined as > 70% stenosis in non-culprit vessel, treated with culprit only primary PCI were randomized to: A. Complete revascularization of all non-culprit significant lesions during initial hospitalization; B. Complete revascularization after 30 days, or C. Revascularization based on non-invasive testing for inducible ischemia. The study explored occurrence of major adverse cardio-cerebral events (MACCE) (cardiac death, repeated MI, cerebrovascular event).

Results The study enrolled 120 patients with door to balloon time within appropriate limits (A 51 ± 26 vs. B 47 ± 33 vs. C 44 ± 29 min, $p = 0.604$) The patients in group A underwent complete revascularization at 6 [4–7] days after primary PCI, while in the group B it was 35 [32–39] days. In group C, 16/43 (37.2%) patients underwent PCI at 82 [66–147] days after infarction ($p < 0.001$). The patients were followed for 2.7 ± 0.8 years. The events occurred less frequently in patients that underwent planned complete revascularization compared to those who underwent ischemia testing (7.8 vs. 20.9%, $p = 0.040$). Kaplan–Meier analysis favored complete delayed revascularization (MACCE A 8.8 vs. B 6.9 vs. C 20.9%, log rank $p = 0.041$).

Conclusions Planned, angiography guided, complete revascularization after initial event may be favorable strategy compared to single stress test for MVD in STEMI.

Keywords: coronary artery disease; myocardial infarction; stress echocardiography

INTRODUCTION

The multivessel coronary artery disease (MVD) is a common finding in patients presenting with ST elevation myocardial infarction (STEMI). It is estimated that around 40–50% of patients with STEMI present with MVD [1]. Previously, culprit only primary percutaneous coronary intervention (PCI) was indicated, but this was challenged by several studies suggesting benefits of immediate, complete revascularization at initial PCI or during initial hospitalization [2, 3, 4]. Although these studies enrolled relatively small number of participants with heterogeneous definition of MVD and composite end points, their results have caused important concern regarding the need for complete revascularization in patients with STEMI and MVD. Based on their results, guidelines for treatment of STEMI have been updated [5]. An observational, retrospective study has demonstrated benefit of staged PCI within 60 days of index intervention [6]. The strategy of dobutamine stress echocardiography testing after myocardial infarction seems feasible and safe and can predict serious adverse events during short term follow up [7].

We sought to investigate the appropriateness of staged, complete revascularization during hospitalization or after 30 days from initial PCI based on angiographic lesion severity compared to intervention based on outpatient non-invasive ischemia testing, aiming to reduce major adverse cardio-cerebral events (MACCE).

METHODS

This study was prospective, randomized, single center, open label study in patients with STEMI with MVD, initially treated with culprit only primary PCI. After successful culprit only primary PCI, patients were randomly assigned to one of three treatment arms: staged, complete revascularization of all non-culprit significant lesions in a single session during initial hospitalization; staged, complete revascularization of all non-culprit significant lesions in a single session after 30 days from initial hospitalization for STEMI and revascularization or deferral of revascularization of non-culprit coronary artery lesions based on ischemia testing using dobutamine stress echocardiography. The study was

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approved by the institutional committee on ethics and was done in accordance with the Helsinki declaration (Clinical trials identifier: NCT 02756000).

Patient population

All patients admitted with clinical and electrocardiographic signs of first ever STEMI (chest pain lasting less than 12 hours with persistent ST elevation of ≥ 1 mm in two contiguous leads on ECG recording) and MVD on initial coronary angiogram, defined as visually assessed stenosis of more than 70% of any of the non-culprit vessels, were treated with primary PCI of infarct related artery (IRA) only. Within 24 hours after completion of primary PCI, after obtaining a written informed consent, they were randomly assigned 1:1:1 to one of the treatment arms. The hemodynamically unstable patients, defined as presence of Killip class IV, need for mechanical circulatory support and/or ventilation prior, during and after primary PCI, presence of significant valvular disease or decision that patient needs to be treated with coronary artery bypass grafting (CABG) and/or valvular replacement or reconstruction surgery after initial culprit only PCI were not considered for the study. Patient were excluded from the study if myocardial infarction was caused by stent thrombosis or there was a chronic total occlusion of any of the coronary arteries on initial angiogram. Patients previously treated by CABG or having estimated life expectancy less than one year were also excluded from the study. Patients unsuitable for dobutamine stress echocardiography because of poor acoustic windows were also excluded from the study.

Randomization

Patients were randomized in a 1:1:1 fashion to one of the treatment arms according to computer generated algorithm (GraphPad Software, Inc., San Diego, California, US) after completion of primary PCI and signed informed consent form. Crossover between treatment arms was allowed only in case of persistent chest pain or patient's hemodynamic instability that requires immediate coronary angiography and/or intervention that was further acknowledged as study endpoint. Vascular access, PCI technique, use of guiding catheters, coronary guidewires, thrombus aspiration, predilatation and stent implantation were used according to operators' preference, both at primary PCI and at repeated intervention.

Medical treatment

After establishing diagnosis of STEMI, patients were pre-treated with loading dose of aspirin (300 mg) and ticagrelor (180 mg) or clopidogrel (600 mg), while heparin (80–100 IU/ kg iv.), was given before insertion of coronary guidewire. After PCI aspirin, 100 mg per day, was given indefinitely with ticagrelor 90mg twice a day or clopidogrel, 75 mg per day. Recommended duration of dual antiplatelet therapy was 12 months. Patients were treated with beta blocking agents, ACE inhibitors and statins according to the current guidelines for STEMI [5].

Patients were seen in an office visit one month after final PCI or Dobutamine stress echocardiography – vital and clinical status along with prescribed medications were assessed, ECG and arterial blood pressure measurement done. Angina status assessment was done according to the Canadian Cardiovascular Society (CCS) Classification of angina or Braunwald angina classification.

Vital and clinical status, presence of angina, medications, hospitalization for any reason, myocardial infarction, repeated PCI or CABG were assessed at one year after initial procedure or at the end of follow up (telephone interview or office visit).

Dobutamine stress echocardiography

Dobutamine stress echocardiography (DSE) was performed in all stable patients assigned to this study arm at least 30 days after the coronary event according to the guidelines. In patients with suboptimal parasternal echo windows, the test was considered valid for interpretation if all apical views are obtained and suitable for analysis. The test was considered positive for inducible ischemia in the presence of new or worsening wall motion abnormalities in two or more adjacent segments [8].

Definitions

A culprit artery was defined as an artery with an identifiable thrombus and/or significant lesion on angiogram corresponding to ischemic ECG changes. Significant lesion was defined as coronary artery stenosis with narrowing of the lumen of more than 70% assessed by quantitative coronary angiography (QCA) software (Leonardo multimodality workstation, Siemens, Erlangen, Germany).

A repeated revascularization was considered clinically indicated if angiography during follow-up showed a diameter stenosis greater than or equal to 50 percent at any point in the coronary artery previously treated and if one of the following occurred: 1) a positive history of recurrent angina pectoris, presumably related to the target vessel; 2) objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel; 3) abnormal results of any functional diagnostic test (e.g. stress echocardiography, fractional flow reserve); 4) a revascularization with a diameter stenosis greater than 70% even in the absence of the above-mentioned ischemic signs or symptoms.

Death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. Any death during the index hospitalization for STEMI was regarded as cardiac death. Sudden death was defined as unexplained death in previously stable patients. Myocardial infarction (MI) is defined according to the Fourth universal definition of myocardial infarction [9]. Procedure-related MI is regarded as present with creatinine kinase (CK) MB fraction ≥ 3 times upper limit of normal after PCI procedure or total CK ≥ 3 times upper limit of normal in the absence of CKMB measurement. Bleeding is defined according to the Bleeding Associated Research Consortium criteria [10].

Cerebrovascular accident was defined as sudden onset of vertigo, numbness, aphasia, or dysarthria due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm that persists > 24 hours.

Statistical analysis

Categorical variables were presented as numbers and percentages and were compared using chi square test. Continuous variables were expressed as mean \pm standard deviation (SD) or medians with interquartile ranges. Continuous variables were compared using the one-way ANOVA or Kruskal Wallis' test based on their distributions. Clinical outcomes were analyzed according to the intention-to-treat principle. Each endpoint was assessed by the Kaplan–Meier method and compared by log-rank test. Statistical analysis was done using IBM SPSS Statistics 20.0 software (IBM Corp. Armonk, New York, US). A *p* value of < 0.05 was regarded as statistically significant.

RESULTS

The study included 120 patients in Clinical Hospital Centre Zemun, high volume university PCI center from June 2016 to January 2019. The study was prematurely stopped due to slow enrollment and after interim analysis revealed a potential futility in the ischemia testing arm of the study. The 182 patients were evaluated for the study after meeting the inclusion criteria. Due to poor acoustic window 21 patients (11.5%) could not be randomized to stress echocardiography, 14 patients (7.7%) have not signed an informed consent form to participate in the study and surgical revascularization was recommended in 27 patients (14.8%).

The patients included in the study had high incidence of hypertension, dyslipidemia and smoking. There was borderline difference in body mass index (BMI) between the groups (Table 1). Three vessel disease was seen in over 40% patients in the group of patients randomized to complete revascularization during initial admission,

Table 1. Clinical characteristics of the patients in the study groups

Variable	In hospital (n = 34)	After 30 days (n = 43)	Ischemia testing (n = 43)	<i>p</i>
Age (years)	61 \pm 8	60 \pm 11	60 \pm 9	0.877
Male gender (%)	70.6	74.4	65.1	0.640
Heredity (%)	41.1	44.2	44.2	0.956
Smoking (%)	44.1	53.5	65.1	0.179
Hypertension (%)	79.4	72.1	83.7	0.418
Dyslipidemia (%)	52.9	55.8	69.7	0.255
Diabetes mellitus (%)	23.5	32.5	21	0.439
PAD (%)	0.0	4.6	2.3	0.429
CKD (%)	2.9	2.3	4.6	0.826
COPD (%)	8.8	7	7	0.942
BMI (kg/m ²)	29 \pm 4	27 \pm 4	27 \pm 4	0.047
LVEF (%)	43 \pm 7	43 \pm 8	45 \pm 7	0.963

BMI – body mass index; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; LVEF – left ventricular ejection fraction; PAD – peripheral arterial disease

which was higher incidence than in other groups, but the difference was insignificant. Thrombus aspiration was used as a first intervention in only 1/4 to 1/3 of patients while the balloon angioplasty was used in more than half of patients in all groups. The interventions were deemed successful in almost all patients with restoration of TIMI III flow (Table 2).

Table 2. Primary PCI characteristics in the study groups

Variable	In hospital (n = 34)	After 30 days (n = 43)	Ischemia testing (n = 43)	<i>p</i>
Prehospital time (min)	295 \pm 199	225 \pm 196	241 \pm 220	0.531
D2B time (min)	51 \pm 26	47 \pm 33	44 \pm 29	0.604
Radial access (%)	55.9	51.2	46.5	0.715
Triple vessel disease (%)	41.2	23.2	23.2	0.146
LAD culprit (%)	41.2	37.2	30.3	0.593
Cx culprit (%)	17.6	18.6	13.9	0.832
RCA culprit (%)	41.2	44.2	55.8	0.382
Thrombus aspiration (%)	35.3	25.6	25.6	0.568
Predilatation (%)	50	65.1	60.4	0.398
GP IIb/IIIa inhibitor (%)	20.6	18.6	20.9	0.959
Total contrast load (ml)	157 \pm 71	156 \pm 63	153 \pm 42	0.963
TIMI III flow (%)	100	97.7	97.7	0.669

Cx – circumflex artery; D2B – door to balloon time; GP – glycoprotein; LAD – left anterior descending; RCA – right coronary artery; TIMI – thrombolysis in myocardial infarction

Table 3. Incidence of MACCE events in the study groups

Variable	In hospital (n = 34)	After 30 days (n = 43)	Ischemia testing (n = 43)
Death, n (%)	0 (0)	0 (0)	2 (4.6)
Repeated MI, n (%)	1 (2.9)	1 (2.3)	2 (4.6)
Repeated PCI, n (%)	2 (5.9)	2 (4.6)	4 (9.2)
CVI, n (%)	0 (0)	0 (0)	1 (2.3)
MACCE, n (%)	3 (8.8)	3 (6.9)	9 (20.9)

CVI – cerebrovascular insult; MI – myocardial infarction; PCI – percutaneous coronary intervention; MACCE – major adverse cardio-cerebral event

The patients randomized to complete revascularization during initial hospitalization underwent the procedure at a median of 6 [4–7] days after primary PCI, while the median time to complete PCI was 35 [32–39] days in a group randomized to staged intervention. In ischemia testing group patients underwent dobutamine stress echocardiography at 36 [31–46] days after initial admission for STEMI. Of these patients 16/43 (37.2%) were treated with PCI based on positive test results at the median of 82 [66–147] days after infarction (*p* < 0.001). All patients with positive stress test result were treated with PCI of the non-culprit vessels, according to the study protocol.

The patients were followed for median of 1046 [734–1220] days and the adverse events occurred infrequently in all groups. The incidence of stable angina class CCS II and higher was similar in all study groups (group I 1/34, group II 3/43, group III 3/43, *p* = 0.137). Kaplan–Meier freedom from angina curves demonstrated relatively late onset of angina, similar in all study groups (log rank *p* = 0.309) (Figure 1). The MACCE events occurred more frequently in patients assigned to ischemia testing after initial culprit only primary PCI (table 3). Adverse cardiovascular events

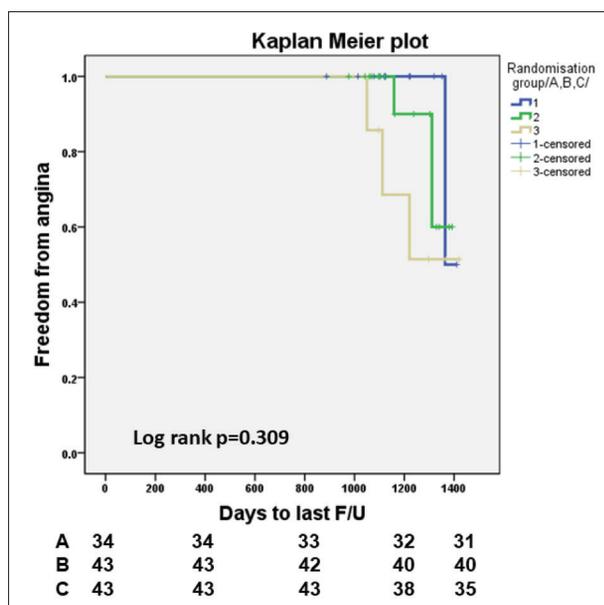


Figure 1. Kaplan–Meier plot representing freedom from angina CCS II during follow up in days after initial event (study groups A – immediate complete revascularization; B – delayed complete revascularization; C – revascularization based on stress-echocardiography)

occurred less frequently in patients that underwent planned revascularization either at the initial hospitalization or after 30 days from initial primary PCI, compared to those who underwent ischemia testing (7.8 vs. 20.9%, $p = 0.040$). Kaplan–Meier survival analysis favored complete delayed revascularization (log rank $p = 0.041$) (Figure 2).

DISCUSSION

This pilot randomized study, done in a single, high volume PCI university center, has demonstrated that strategy based on single dobutamine stress echocardiography test to detect ischemia in non-culprit vessels territory after culprit only primary PCI was associated with increased incidence of adverse cardiovascular events compared to complete staged, angiography guided revascularization after primary PCI for first ever STEMI in patients with MVD during long term follow up.

The decision when to do staged PCI after primary PCI can be affected by many factors. A prothrombotic and inflammatory milieu related to possible stent thrombosis, large myocardial territory at risk with multivessel PCI in STEMI along with the procedural risks (increased radiation and contrast load) can all lead to decreased benefit of immediate complete revascularization [11, 12]. In addition, an estimate of severity of the non-culprit lesions could be jeopardized by spasm of the entire coronary tree leading to unnecessary PCI procedures [13]. Older age, overt heart failure, decreased renal function and additional medical conditions requiring attention can be the reasons to avoid complete revascularization during initial hospitalization that could translate to increased incidence of adverse events [14, 15]. The staged PCI for STEMI can be beneficial compared to culprit only PCI as Cui and al. has showed in retrospective

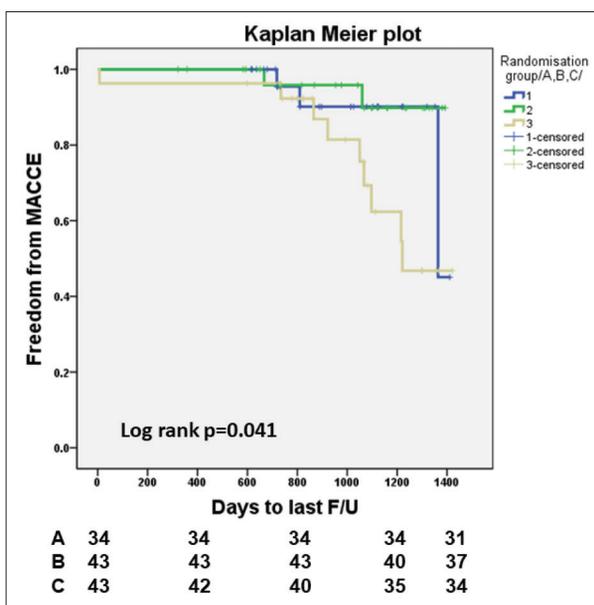


Figure 2. Kaplan–Meier plot representing freedom from major adverse cardio-cerebral events (MACCE) during follow up in days (study groups A – immediate complete revascularization; B – delayed complete revascularization; C – revascularization based on stress-echocardiography result)

analysis of more than 1000 patients. The staged procedure was done within 30 days of primary PCI and after propensity matching of patients, had lower incidence of MACCE. However, the same study failed to demonstrate the benefit of this strategy for diabetic patients [16]. The registry by Hannan et al. [6] has demonstrated a benefit in terms of reduced mortality at 12 months for staged PCI within 60 days after initial primary PCI compared to culprit only PCI within the initial hospitalization. The study also demonstrated increased in-hospital mortality for multivessel PCI at the initial procedure [6]. Recently published large trial that included more than 4000 patients has demonstrated consistent benefit of complete revascularization in MVD patients with STEMI compared to culprit only primary PCI during long term follow up. The complete revascularization was done either during initial hospitalization or within 45 days from initial event [17]. A large Korean registry data also supported the strategy of delayed complete revascularization during initial hospitalization in MVD [18]. The findings in our study support complete revascularization at initial hospitalization or after 30 days based on lesion severity assessed at initial coronary angiogram, showing reduced incidence of MACCE.

The strategy based on non-invasive ischemia testing, in our study, was associated with increased incidence of MACCE. Kaplan–Meier curves separate late in the follow up, when there was higher incidence of events in the ischemia testing group. The reason for this could be the progression of atherosclerotic disease that was not detected as significant ischemia burden on the early dobutamine stress echocardiographic study. Atherosclerosis is a progressive disease and it has been demonstrated that patients that suffered an event would have high incidence of repeated events despite the revascularization and medical treatment [19]. Also, stress testing after revascularization usually yields very few

repeated revascularization procedures irrespective of the test results [20]. However, positive test results in terms of inducible ischemia usually are related to increased incidence of adverse events. In the meta-analysis by Harb et al. [21], that analyzed the studies where stress echocardiography was used to detect ischemia after revascularization, it has been demonstrated that inducible ischemia was associated with increased incidence of adverse cardiovascular events. This study pointed out that older age and time interval between initial revascularization and the positive stress test were predictors of worse outcomes, meaning that longer the time interval between the revascularization and the test, more adverse events occurred. The authors stressed that the impact of time interval was caused by progression of coronary artery disease and more events occurring during longer follow up period [21]. The study by Sicari et al. [7], has pointed out that early stress test after MI could be helpful in predicting adverse events during short term follow up, up to one year, but thereafter progression of atherosclerotic disease in a non-culprit vessels may provoke new ischemic events, as shown in large Swedish registry of patients with MI undergoing culprit only primary PCI [8, 22]. Patients in our study underwent stress echocardiography early after initial event and additional tests were not planned, so the higher incidence of events was probably due to further progression of atherosclerosis and/or restenosis of previously treated lesions. Late onset of angina as a sign of progressing atherosclerosis, long after the test was done, further supports the idea that the higher rate of MACCE events in the ischemia-testing group was due to progression of atherosclerotic lesions that, albeit present, did not provoke myocardial ischemia at the time of the test. Also, stress tests in asymptomatic patients yield few repeated revascularization procedures, a fact that had to be accounted for [23]. On the other hand, in other two groups we might have treated with PCI some intermediate lesions that were not physiologically significant or causing ischemia, despite perceived as significant on coronary

angiogram. Due to small cohort of patients the benefits of such treatment probably exceeded the potential “costs” in terms of complications and restenosis [24, 25].

How to treat MVD patient after primary PCI in STEMI remains an open question. Complete revascularization based on angiographic estimate of stenosis severity has proven benefits but comes with a risk of unnecessary interventions producing more restenosis and stent thrombosis. A strategy of repeated noninvasive ischemia testing after initial revascularization may discern between the patients deemed for revascularization and the ones who should be treated medically avoiding the risks of inappropriate invasive procedures. The timing and the interval between repeated test need to be investigated further.

Study limitation

The study included small number of selected patients (first ever myocardial infarction in native coronary artery, no CTO, preserved LVEF, good echocardiographic windows) with MVD and STEMI, therefore its conclusions may not be applicable to general population. In the study we used dobutamine stress echocardiography to assess ischemia. This test with its inherent limitations in detecting ischemia may influence decisions to perform further revascularization.

CONCLUSION

The ischemia-guided strategy based on early single dobutamine stress echocardiography test may be inferior to complete revascularization based on angiographic estimate of stenosis severity in multivessel disease patient within thirty days after primary PCI for first ever STEMI. The repeated testing may improve detection of atherosclerosis progression and allow institution of appropriate treatment.

Conflict of interests: None declared.

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Комплетна у односу на исхемијом вођену реваскуларизацију после примарне перкутане коронарне интервенције артерије одговорне за инфаркт у вишесудовној коронарној болести – пилот студија

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САЖЕТАК

Увод/Циљ Реваскуларизација у вишесудовној коронарној болести код болесника са инфарктом миокарда са *ST* елевацијом (*STEMI*) представља изазов. Упоредили смо клиничке исходе између различитих стратегија реваскуларизације руковођене ангиографски процењеним степеном сужења или на основу теста оптерећења срца.

Метод У проспективном истраживању, болесници са првим *STEMI*-јем и вишесудовном коронарном болешћу (више од 70% сужења артерије која није одговорна за инфаркт) рандомизовани су после примарне перкутане коронарне интервенције на болеснике са: А. комплетном перкутаном реваскуларизацијом свих лезија током иницијалне хоспитализације; Б. комплетном реваскуларизацијом после 30 дана; В. реваскуларизацијом на основу провокабилне исхемије. Студија је бележила настанак нежељених кардиоваскуларних догађаја – срчане смрти, поновљеног инфаркта миокарда, цереброваскуларног догађаја.

Резултати Укључено је 120 болесника код којих је време до реперфузије било у границама препоручених вредности (А 51 ± 26 vs. Б 47 ± 33 vs. В 44 ± 29 минута, $p = 0,604$). Бо-

лесници у групи А су подвргнути комплетној реваскуларизацији 6 (4–7) дана после примарне перкутане коронарне интервенције, док су у групи Б реваскуларизовани после 35 (32–39) дана. У групи В, 16/43 (37,2%) болесника је подвргнуто перкутаном коронарној интервенцији после 82 [66–147] дана од инфаркта ($p < 0,001$). Болесници су праћени током 2,7 ± 0,8 година. Нежељених догађаја је било мање код болесника који су подвргнути комплетној реваскуларизацији у односу на тестиране на исхемију (7,8 vs. 20,9%, $p = 0,040$). Каплан–Мејеровом анализом показана је предност комплетне реваскуларизације у току иницијалне хоспитализације (нежељени кардиоваскуларни догађаји А 8,8 vs. Б 6,9 vs. В 20,9%, $\log rank p = 0,041$).

Закључак Планирана, ангиографијом вођена комплетна реваскуларизација, после примарне перкутане коронарне интервенције, може бити боља стратегија у односу на појединачно тестирање на исхемију код вишесудовне коронарне болести.

Кључне речи: коронарна болест; инфаркт миокарда; тест оптерећења срца