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Six month results of randomized clinical trial: Multivessel stenting versus staged revascularization for ST-elevation myocardial infarction patients with second generation drug eluting stents

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Abstract: Background: There are no randomized trials described outcomes of multivessel percutaneous coronary interventions (PCI) (in primary and staged revascularization) with second generation drug eluting stents (DES) in patients with ST-elevation myocardial infarction (STEMI). We are presenting preliminary results of randomized trial (NCT01781715). Methods: Six-month outcomes of 89 consecutive patients with STEMI and multivessel coronary artery disease (CAD) (SYNTAX 18.6±7.9 points) undergoing primary PCI with zotarolimus-eluting stents (Resolute Integrity; Medtronic) were studied. We used two strategies of multivessel stenting: in primary PCI (MS primary, n=46) (the IRA was opened followed by dilatation of other significantly narrowed arteries during the same procedure) and multivessel stenting in staged revascularisation (MS staged, n=43) (the IRA only was treated during the primary intervention while the complete revascularization was planned in a second procedure (8.5±4.2 days)) in our prospective randomized study. Results: During follow-up of 6 months there was no cardiac death in overall group. We observed 1 (2.3%) non-cardiac death in MS staged group vs 0 in MS primary (p=0.9), 0 non-fatal myocardial infarction (MI) in MS staged group vs 3 (6.5%) in MS primary (p=0.3) due to definite stent thromboses (ST) (2.5% on the number of stents). There was no target vessel revascularization (TVR) in MS staged group, but it was performed in 2 cases (4.3%) in MS primary group (p=0.5). Major adverse cardiac event (MACE) (cardiac death, MI, TVR) was diagnosed in 2.3% and 6.5% in MS staged and MS primary group (p=0.7). Conclusions: second generation DES in STEMI patients with multivessel CAD are satisfactory safely and effectively as part of the strategy of multivessel stenting in primary PCI and multivessel staged PCI (8.5±4.2 days). Multivessel stenting in primary PCI was associated with higher risk of stent thrombosis (ST) compared with multivessel staged PCI in six month follow-up period.

Keywords: ST-Elevation Myocardial Infarction, Primary Percutaneous Coronary Intervention, Multivessel Coronary Artery Disease, Second Generation Drug-Eluting Stents

1. Introduction

Primary percutaneous coronary intervention (PCI) is the most effective strategy of treatment in patients with acute ST-segment elevation myocardial infarction (STEMI). STEMI patients in 40-70% of cases have multiple significant coronary lesions, which confer a substantially increased risk of cardiovascular morbidity and mortality [1-3].

Contemporary guidelines recommend PCI for only the infarct-related artery (IRA) during the urgent procedure, leaving the other stenosed vessels untreated (culprit-only

revascularisation) or to dilate during a second elective procedure (staged revascularisation). Simultaneous treatment of IRA and non-IRA is recommended only in patients with cardiogenic shock [4-5]. However, these guidelines are based on the results of earlier studies. With advancing technology and newer drug eluting stents (DES), outcomes have improved even in patients undergoing multivessel and higher-risk elective procedures [6-7]. Therefore, the optimal management of patients with multivessel disease in this setting remains still unclear.

The aim of this study was to evaluate 6-month outcomes of multivessel revascularization (in primary and staged PCI) with second generation DES in STEMI patients. It is important because both strategy (multivessel stenting in primary PCI and staged PCI with limited time between procedures) are not in guidelines.

2. Methods

2.1. Study Population

The purpose of this open label safety/efficacy randomized clinical trial (NCT01781715) is to determine outcomes of 89 consecutive patients with STEMI and multiple coronary artery disease (CAD) undergoing multivessel stenting in primary PCI or staged PCI with second generation DES. Primary endpoints of this study was: (1) All death (cardiac and non cardiac), (2) Any MI (STEMI and non-STEMI), (3) TVR. Secondary: (1) Composite rate of all death, any MI and TVR, (2) Stent thrombosis (ST).

We examined patients with STEMI and multivessel CAD undergoing primary PCI. Between October 2011 and January 2013 in our 24 h catheterization laboratory we performed 205 primary PCI, among which we randomized 89 patients (43.4%) with multivessel CAD (defined as ≥70% diameter stenosis of two or more epicardial coronary arteries or their major branches by visual estimation with diameter ≥2.5mm). Inclusion criteria was: (1) Subject must be at least 18 years of age; (2) Subject is able to verbally confirm understandings of risks, benefits of treatment of either multivessel stenting or staged PCI using the zotarolimus-eluting stent (Resolute Integrity™ Stent, Medtronic) and he or she or his or her legally authorized representative provides written informed consent prior to any study related procedure; (3) Subject must have significant stenoses (≥ 70%) of two or more than two of coronary arteries and requiring primary PCI for acute ST elevation myocardial infarction (STEMI) within 12hrs; (4) Target lesions must be located in a native coronary artery with visually estimated diameter of less than 2.5 mm and more than 4.0 mm; (5) Target lesion(s) must be amenable for percutaneous coronary intervention.

Exclusion criteria were as follows: (1) Single lesions; (2) Acute heart failure Killip III-IV; (3) ≥ 50% left main stenosis; (4) Small vessels diameter (<2.5mm); (5) The patient has a known hypersensitivity or contraindication to any of the following medications: Heparin Aspirin Both Clopidogrel and Ticlopidine, Zotarolimus.

Included were patients with the presence of prolonged (more than 30 minutes) chest pain, started less than 12 h before hospital arrival and ST elevation of at least 1 mm in two or more contiguous limb electrocardiographic leads or 2 mm in precordial leads.

Procedure success was defined as the achievement of an angiographic residual stenosis of less than 20% and a thrombolysis in myocardial infarction (TIMI) flow grade 3 after treatment of the lesions. Before the procedure patients were treated with loading doses of aspirin, clopidogrel, unfractioned heparin. Post-PCI medical oral treatment included aspirin, statins and clopidogrel, which was recommended for 12 months in all cases after second generation zotarolimus-eluting stents implantation. Signed informed consent for primary PCI and for the study was obtained from all patients before the procedure.

Soon after every diagnostic angiography, the eligible patients were randomly allocated to two different strategies:

1. Multivessel stenting in primary PCI (MS primary): the IRA was opened followed by dilatation of other significantly narrowed arteries during the same procedure.
2. Multivessel stenting in staged revascularisation (MS staged): the IRA only was treated during the primary intervention while the complete revascularization was planned in a second procedure (8.5±4.2 days).

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institution's human research committee.

2.2. Definitions and Endpoints

Clinical and procedural data were collected by reviewing hospital records and angiographic runs stored in DICOM CDs.

The primary endpoint of the study was the incidence of major adverse cardiac events (MACE) defined as cardiac or non-cardiac death, re-infarction and repeat coronary revascularisation. For repeat revascularisation we included all PCI or CABG occurring after the baseline procedure and justified by recurrent symptoms, re-infarction or objective evidence of significant ischaemia on provocative testing [8]. Among repeat PCI we excluded staged procedures already scheduled. In the staged group we classified as repeat revascularisation only unplanned procedures. Follow up was obtained by outpatient visits or phone interviews.

We estimated clinical and angiographic criteria of ST. The incidence of ST was assessed throughout the follow-up period, according to the conventional ARC (Academic Research Consortium) classification [18]. Clinical criteria consisted of the acute onset of chest pain persisting for >15 min and/or accompanied by ST segment elevation or depression of at least 1 mm in two contiguous leads in the distribution of the target vessel. All patients with the clinical suspicion of ST underwent immediate coronary

angiography to confirm the diagnosis followed by PCI. Angiographic criteria of stent thrombosis consisted of partial or complete occlusion within the previously implanted stent with evidence of fresh thrombus.

Within the first 18 hours after index MI, recurrent MI required recurrent symptoms of myocardial ischemia associated with recurrent ST-segment elevation or depression of at least 1 mm in two contiguous limb electrocardiographic leads or 2 mm in precordial leads lasting at least 30 minutes. After 18 hours, recurrent MI was defined as appearance of new Q waves, new left bundle-branch block, and/or enzyme evidence (level of creatine kinase MB fraction and/or troponin) of MI.

2.3. Statistical Analysis

Continuous variables are presented as mean ± SD, categorical variables as percentages. For the endpoint «death» patients were censored at death or 27 June 2013 if alive. For MACE patients were censored at the date of first MACE or at the end of follow-up. Follow-up was 100% complete. We used Chi Squared and Mann Whitney 'U' test for statistical analysis to compare clinical, demographic, angiographic, PCI characteristics and outcomes in groups. All analyses were performed using Statistica for Windows 6.0 (StatSoft Inc., USA).

3. Results

3.1. Baseline Characteristics

Among the 205 patients with STEMI, we excluded 116 for the following reasons: 15 presented in Killip III-IV; 15 had left main coronary disease or small vessels; 42 had onset of symptoms > 12 hours; 44 had one-vessel coronary lesion. We thus included in the follow-up 89 patients with STEMI and multivessel CAD meeting the inclusion criteria. In general population the mean age was 58.3±10.6 years, 57 (64%) were men. The incidence of diabetes mellitus in study cohort was 23.6%. The MS primary group included 43 (48.3%) patients, the MS staged group 46 (51.7%) patients. The elective procedure in the MS staged group was performed on average 8.5±4.2 days after the primary PCI. We evaluated the results in two study groups (MS primary vs. MS staged).

Table 1 shows the baseline clinical and demographic characteristics in study groups. Patients of MS primary and MS staged group were comparable for all clinical and demographic characteristics. The majority of patients in both groups were male, had hypertension and acute heart failure Killip 1. Table 2 shows the baseline lesions and angiographic characteristics. Mean SYNTAX SCORE in the groups was not exceed 18 points, which corresponds to an intermediate severity of coronary lesions. About half patients in each group had 3-vessels CAD. There was no statistically significant differences between angiographic characteristics in the groups. Table 3 shows the special features of PCI. Radial access was used in about half patients in each group. PCI were successfully in more than 97% patients. Total mean stent length in each group exceeded 55 mm.

3.2. Events

Follow-up was completed in 100% of patients. After a follow-up of six months there was only 1 (2.3%) non cardiac death in MS staged group (colon cancer). At the same time, fatality outcomes in the MS primary group was not obtained. Throughout the follow-up, 1 (2.3%) patient in MS staged group and 3 (6.5%) in MS primary group experienced at least one MACE. Three patients in MS primary group received non-fatal MI due to ST. Two of these underwent TVR. One more patient had ST and MI without TVR. Two of three cases with ST were due to unauthorized discontinuation of clopidogrel taken. In all these cases we observed ST of just one of three implanted in primary PCI stents. Cases of ST and MI in MS staged group have not been reported. Total incidents of ST in study groups (on the number of stents) was 2.5% (3/120) in MS primary and 0 (0/112) in MS staged cohort (table 4). Survival free of MI and re-PCI was 43 (93.5%) patients in MS primary group and 42 (97.7%) in MS staged group p>0.05).

Table 1. *Patient clinical and demographic characteristics*

Variables	MS primary (n=46)		MS staged (n=43)		P
	n	%	n	%	
Age, years	58,6±11		58.9±10.4		0.8
Male	32	69.6	25	58.1	0.4
LVEF, %		51±9	52.2±7.4		0.5
Hypertension	44	95.6	37	86	0.2
Diabetes mellitus	12	26.1	9	20.9	0.7
Peripheral artery disease	12	26.1	11	25.6	0.8
Previous MI	5	10.8	2	4.6	0.5
Previous stroke	0	0	0	0	-
Acute heart failure (Killip II)	6	13	4	9.2	0.8

Table 2. *Baseline lesions and angiographic characteristics*

Variables	MS primary (n=46)		MS staged (n=43)		P
	n	%	n	%	
3-vessel disease	20	43.5	20	46.5	0.9
SYNTAX Score	18.6±8		18.2±7.6		0.9
Mean time between PCI, days	-		8.5±4.2		-
LAD IRA	21	45.6	13	30.2	0.2
Cx IRA	8	17.4	5	11.6	0.6
RCA IRA	17	36.9	25	58.1	0.07

Table 3. *The special features of procedures*

Variables	MS primary (n=46)		MS staged (n=43)		P
	n	%	n	%	
Femoral access	25/46	54.3	39/86	45.3	0.4
Radial access	20/46	43.5	46/86	53.5	0.4
Brachial access	1/46	2.2	1/86	1.2	0.8
Successfully PCI	45/46	97.8	42/43	97.7	0.5
Contrast medium, ml	313.8±101.5		353.6±167.6		0.4
Mean number of stents	2.6±0.8		2.6±0.9		0.8
Total mean stent length, mm	55.3±13.5		59.1±16.3		0.7
Mean stent diameter, mm	3.3±0.45		3.4±0.5		0.6

Table 4. *6-months outcomes*

Variables	MS primary (n=46)		MS staged (n=43)		P
	n	%	n	%	
Death	0	0	1	2.3	0.9
MI	3	6.5	0	0	0.3
TVR	2	4.3	0	0	0.5
Combined endpoint (cardiac death + MI + TVR)	3	6.5	1	2.3	0.7
Stent thrombosis (on the number of stents)	3/120	2.5	0/112	0	0.3

4. Discussion

The main finding of the present randomized study is that after a follow-up of 6 months, in STEMI patients with multiple coronary lesions (SYNTAX 18.6±7.9 points) treated with multivessel PCI (primary and staged) with second generation DES (Resolute Integrity), revascularization had satisfactory outcomes in two different strategies of PCI. Both MS primary and MS staged (8.5±4.2 days) approach resulted in a low risk of MACE in spite of high incidence of diabetes mellitus in study group (23.6%). Despite the fact that the strategy of MS primary was associated with a higher risk of reinfarction and TVR due to ST, significant differences between the groups in adverse outcomes were not obtained. Moreover, two of the three cases with ST associated with the unauthorized cancellation of dual antiplatelet therapy. Probably the main cause of adverse outcomes of revascularization in the MS primary group was not the PCI strategy itself, but low patient compliance to therapy.

According to current guidelines, PCI should be performed only in IRA, at least in patients without cardiogenic shock [9]. This recommendation is based on the hypothesis that single-vessel PCI has a more favourable benefit-to-risk ratio and better financial implications. Some studies suggest that the more conservative strategy of treating only the IRA could avoid the complications arising from longer procedures, such as the larger use of contrast medium with a potentially increased risk of contrast induced nephropathy, the increased administration or radiation, as well as the danger of ischaemia in non-infarcted myocardial regions [10-11].

There is no randomized data to definitely answer the issues about the specific scientific merits of any of approaches (multivessel stenting in primary PCI or staged PCI) [12]. And there is no evidence base for second generation DES in STEMI patients with multivessel CAD, but in recent years, with the development of new advanced devices the outcome of multivessel PCI has markedly improved [13-14].

To the best of our knowledge the present study is the first that estimates throughout a follow-up the multivessel stenting during primary PCI and multivessel staged (8.5±4.2 days) PCI with second generation DES in STEMI patients with multivessel disease. We found that aggressive approach (multivessel stenting) in STEMI patients (SYNTAX 18.6±8 points) with Resolute Integrity stents is associated with low risk of MACE in six-months follow-up period. It is clear when compare with published data. Six-months incidence of MACE in STEMI patients with multivessel disease in general cohort (BMS and DES) is 23.9-28%, re-MI 1.6-8.8%, death 3.3-6.3%, ST 1.8-4.3% [11, 15, 16]. In our study we observed six-months MACE, re-MI, death and ST in 4.5%, 3.4%, 1.1% and 1.3% of patients, respectively.

A possible explanation for the high effect of multivessel PCI (primary and staged) with second generation DES is good device characteristics that allows to perform a more complete treatment of multivessel disease in high risk STEMI patients. Indeed, the inflammatory reaction arising during acute coronary syndromes and responsible for plaque instability is not limited to the culprit lesion, but involves the entire coronary tree [17].

Our results suggest that the multivessel approach (primary and staged) with second generation DES is safe and possibly less expensive than an incomplete approach by reducing the probability of further unplanned procedures. We suppose that multivessel revascularisation could decrease the risks and discomfort for patients associated with new unscheduled procedures.

It is clear that further research in this area should be directed to the search criteria according to which it would be possible to choose a strategy of revascularization for PCI differentiated. There is no doubt the fact that the results of revascularization in STEMI patients with multivessel CAD may be improved by using the latest generation of DES.

5. Conclusions

In a cohort of patients with STEMI and multivessel CAD treated with second generation DES, Resolute Integrity stents are equally safely and effectively in multivessel primary PCI and staged approach (8.5±4.2 days). Probably, results of PCI with second generation DES in STEMI patients and multivessel CAD will allow review current guidelines. Novel finding of our study should promote further research in order to provide strong enough evidence

that may eventually update the current recommendations for patients with multivessel CAD and STEMI.

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