

Timing of Coronary Angiography After Successful Fibrinolytic Therapy in ST-Segment Elevated Myocardial Infarction

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Abstract

Background: We aimed to compare outcomes of patients received successful fibrinolytic treatment (FT) for ST-segment elevated myocardial infarction (STEMI) and performed coronary angiography (CAG) within 24 - 72 h or after 72 h.

Methods: Between March 2013 and November 2014, 76 STEMI patients received successful FT and performed CAG > 24 h were included in the study. Patients were divided into two groups according to the time-interval from FT admission to CAG performing (Group-1, 24 - 72 h (n = 29), Group-2, > 72 h (n = 47)). The primary end point was major adverse cardiac events (MACE) defined as cardiovascular death, non-fatal myocardial infarction, and heart failure.

Results: The mean age of patients were 56 ± 11.4 years old (27.6% female). CAG was performed within mean 2.17 ± 0.38 days in the Group-1 and 2.9 ± 11.5 days in the Group 2 ($P < 0.001$). At short-term follow-up (6 months), MACE rate was higher in Group-2 (21.3%) than Group-1(13.8%), but it was not statistically significant ($P = 0.661$). The rate of MACE was 37.9% in Group-1 and 38.3% in Group-2 ($P = 0.974$) in the long-term follow-up (median: 57 months). Overall cardiac mortality rate was 7.9%, the re-infarction rate was 19.7% and heart failure was 17.1% in long-term follow-up, and there were no significant difference between groups.

Conclusions: Present study has shown that performance of CAG after 24 h of successful FT, within 24 - 74 h or > 72 h, did not shown any difference in term of MACE both in short and long-term follow-up.

Keywords: Fibrinolytic treatment; ST-segment elevated myocardial infarction; Coronary angiography

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Introduction

Early reperfusion in patients with ST-segment elevation myocardial infarction (STEMI) has been shown to improve clinical outcomes. Primary percutaneous coronary intervention (PCI) represents the gold standard reperfusion treatment of the occluded epicardial arteries [1, 2]. However, fibrinolytic treatment (FT) still remains the gold standard option, where primary PCI cannot be performed in the recommended time [1-3]. Relevant guidelines for the management of STEMI published recommend to perform coronary angiography (CAG) and if necessary PCI within 24 h after successful FT [1, 3]. Also, same guidelines recommend to do not perform CAG 2 or 3 h after successful FT. However, many patients do not perform PCI after successful FT in the recommended time interval since many different reasons. Although many previous studies determined the advantageous of early PCI strategy (< 24 h) after successful FT, few studies published concerning the results of exceeding 24 h from successful FT to CAG [4-6]. Also, long-term benefits of CAG after the recommend time interval are not clear. On this background, we aimed to compare the short and long-term outcomes of STEMI patients who received successful FT and did not perform CAG within 24 h and underwent CAG within 24 - 72 h or after 72 h.

Materials and Methods

Study design and definition of variables

Between March 2013 and November 2014, all consecutive patients with the diagnosis of STEMI who were submitted to FT as primary strategy of reperfusion and did not perform CAG within 24 h after successful FT were included in the study. ST-segment elevated myocardial infarction (STEMI) was defined as following criteria: ST-segment elevation ≥ 0.1 mV in two or more leads (0.2 mm for V1 - V3) or a new-onset left bundle branch block on an electrocardiogram, and typical ongoing ischemic chest pain for longer than 30 min [7]. The study was designed as prospective and observational. Patients who performed rescue PCI in the context of an unsuccessful TT (without reduction of ST-segment elevation, persistent chest pain for 90 min after initiation of thrombolysis or hemodynamic instability) were excluded. Moreover, patients who were < 18

years old or > 85 years old, or whose symptoms of myocardial infarction present for > 12 h, pregnancy, standard exclusion criteria for FT, and having history of heart failure were excluded from the study [1].

All patients received standard weight-adjusted dose fibrin specific thrombolytic agent within 10 min after the first medical contact in emergency service. Also, all patients received aspirin 300 mg orally, clopidogrel 300 mg on the first day, and enoxaparin 30 mg intravenously followed by a subcutaneous dose of 1 mg/kg repeated every 12 h up to hospital discharge or revascularization for a maximum of 7 days [3]. In addition, all patients received beta-blockers, statin and angiotensin-converting enzyme inhibitors unless contraindication. Also, all patients received clopidogrel 75 mg daily for 12 months at the discretion of the treating physician.

Patients who were newly diagnosed with diabetes mellitus (DM) or were already on anti-diabetic therapy, or whose fasting plasma glucose ≥ 126 mg/dL were identified as diabetic [8]. Hypertension was defined as blood pressure (BP) $\geq 140/90$ mm Hg or the use of antihypertensive medication. Smoking was defined as smoking ≥ 1 cigarettes a day for at least 1 year, without an attempt to quit. Dyslipidemia, defined as total cholesterol ≥ 174 mg/dL or on the treatment with lipid-lowering drugs. Heart failure was diagnosed based on relevant guidelines of European Society of Cardiology [9]. Routine echocardiography was performed before discharge (Vivid-7, GE Healthcare) in the line of American Echocardiography Society guideline [10]. All routine laboratory parameters were recorded in planned control from hospital digital system. The researchers adhered to the principles of Helsinki Declaration throughout the study and the protocol of the study was approved by the Ethical Committee of Ege University, Faculty of Medicine.

For the purpose of this study, 76 consecutive patients with successful FT were included. The population was divided into two groups according to the time interval from FT admission to CAG performing; Group-1, patients who underwent CAG within 24 - 72 h after FT; Group-2, patients who underwent coronary angiography after 72 h of FT.

Outcomes and follow-up

The primary end point was major adverse cardiac events (MACE) defined as cardiovascular death, non-fatal myocardial infarction, and heart failure. Secondary end points were the individual component of primary end point. To assess clinical status and adverse events, patients were seen at the outpatient clinic 6 months and 1 year after index event. At 2, 3, 4 and 5 years, clinical follow-up was performed through telephone contact. All patients were followed for a median 57 months (interquartile range 48 - 69 months).

Statistical analyses

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS 20.0) for Windows (SPSS Inc., Chicago, Illinois, USA). Continuous data were presented

as means and standard deviation. The Kolmogorov-Smirnov test was used to evaluate whether the continuous variables were normally distributed. Differences in continuous variables between the two groups were determined by Student's *t*-test or Mann-Whitney U-test. Categorical variables were summarized as percentages and were compared by the Chi-square test or Fisher's exact test. A survival analysis between the two groups was performed using the Kaplan-Meier method with a log-rank analysis. A *P* value < 0.05 was considered statistically significant.

Results

Totally 76 patients were included in the study, and all patients were followed for a median 57 months (interquartile range 48 - 69 months). The baseline clinical features of patients were summarized in Table 1. The mean age of patients were 56 ± 11.4 years old (27.6% female). There were no significant differences between groups in term of clinical characteristics and laboratory parameters except family history of coronary artery disease (Group-1: 37.9% vs. Group-2: 12.8%; *P* = 0.001), diabetes mellitus (Group-1: 31.0% vs. Group-2: 8.5%; *P* = 0.025), and left ventricular ejection fraction (Group-1: $53.4 \pm 8.7\%$ vs. Group-2: $46.0 \pm 9.2\%$; *P* = 0.003). Vast majority of patient received FT within 3 h of symptom onset (Table 2). All patients in both groups were referred to CAG; the procedure was delayed by a mean time of 2.17 ± 0.38 days in the Group-1 and 2.9 ± 11.5 days in the Group 2 (*P* < 0.001). The total number of PCI procedures was similar between groups (Table 2). At discharge, 100% of patients were prescribed aspirin, 100% clopidogrel, 98.7 % statins, 93.4% beta-blockers, and 89.5% angiotensin converter enzyme or angiotensin receptor blocker, with no difference between groups. At 6 months, medication was unchanged (Table 3).

The clinical outcomes at short-term (6 months) and long-term (median 57 months) follow-up were listed in Table 4. At short-term follow-up, MACE rate was higher in Group-2 than Group-1 but it was not statistically significant (21.3% vs. 13.8%; *P* = 0.661, respectively). Also, overall cardiac mortality rate was 1.3%, the re-infarction was 9.2%, and heart failure was 14.5% at 6 months follow-up and similar between groups (Table 4). Overall, the rate of the MACE was 38.2% in long-term follow-up. The rate of MACE was 37.9% in Group-1 and 38.3% in Group-2 (*P* = 0.974). In addition, overall cardiac mortality rate was 7.9%, the re-infarction rate was 19.7% and heart failure was 17.1% in long-term follow-up; and there were no significant difference between groups (Table 4). The MACE-free survivals across the groups are shown in Figure 1. Predicting survival with a combination of cardiovascular death, non-fatal myocardial infarction, and heart failure showed no significant difference in survival between groups.

Discussion

The present study has shown that performing CAG after successful FT within 24 - 72 h or after 72 h did not cause differ-

Table 1. Baseline Characteristics of Study Population

Variable	All patients (n = 76)	Group-1 (n = 29)	Group-2 (n = 47)	P
Age (years), (mean ± SD)	56 ± 11.4	54.8 ± 11.2	57.4 ± 11.5	0.354
Female, n, (%)	21 (27.6)	6 (20.7)	15 (31.9)	0.424
Hospitalization time (days)	7.0 ± 4.0	7.3 ± 5.8	6.8 ± 2.4	0.661
Hypertension, n, (%)	27 (35.5)	12 (41.4)	15 (31.9)	0.402
Diabetes mellitus, n, (%)	13 (17.1)	9 (31.0)	4 (8.5)	0.025
Hyperlipidemia, n, (%)	14 (18.4)	4 (13.8)	10 (21.3)	0.414
Current smoker, n, (%)	66 (86.8)	24 (82.8)	42 (89.4)	0.408
History of CAD, n, (%)	9 (11.8)	2 (6.9)	7 (14.9)	0.469
Family history of CAD, n, (%)	17 (22.4)	11 (37.9)	6 (12.8)	0.001
Systolic BP (mm Hg)	137 ± 27	134 ± 17	140 ± 32	0.344
Diastolic BP (mm Hg)	80 ± 16	79 ± 11	82 ± 19	0.521
Heart rate (per minute)	76 ± 14	73 ± 14	78 ± 14	0.176
Hemoglobin (g/dL)	14 ± 1.6	14 ± 1.4	14 ± 1.7	0.51
Hematocrit (%)	41.3	41.4 ± 3.8	41.3 ± 4.7	0.87
Creatinine (mg/dL)	0.89 ± 0.23	0.91 ± 0.27	0.88 ± 0.2	0.67
Aspartate aminotransferase (U/L)	27.3 ± 20.9	51 ± 92	59 ± 78	0.95
Alanine aminotransferase (U/L)	50.3 ± 83	28 ± 20.3	27 ± 21	0.83
Total cholesterol (mg/dL)	191 ± 40	192 ± 42	191 ± 37	0.93
LDL-C (mg/dL)	121 ± 36	119 ± 34	122 ± 37	0.66
HDL-C (mg/dL)	38 ± 10	38 ± 11	39 ± 9	0.68
Triglyceride (mg/dL)	179 ± 95	194 ± 123	169 ± 74	0.27
LVEF (%)	48.6 ± 9.6	53.4 ± 8.7	46.0 ± 9.2	0.003

BP: blood pressure; CAD: coronary artery disease; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; LVEF: left ventricular ejection fraction.

ent MACE rate both in short and long-term follow-up. Also there were no significant different between groups in term of secondary end points, cardiovascular death, re-infarction, and heart failure.

Nowadays, performance of a routine early CAG within 24 h is recommended after successful FT, if there are no contraindications [1, 2]. In case of unsuccessful thrombolysis patients should undergo immediate CAG and rescue PCI [1, 2]. Many

previous studies have shown that an early routine CAG after successful FT reduced the rate of recurrent ischemia and re-infarction, compared with a watchful waiting strategy [5, 11-15]. Although these studies have variable time windows between FT and CAG, all of them were less than 24 h. In this context, the time window from FT to CAG is 2 - 24 h in recent guideline of European Society of Cardiology and 2 or 3 - 24 h in American Heart Association guideline with a IIa level of rec-

Table 2. Procedural Characteristics

Variable	All patients (n = 76)	Group-1 (n = 29)	Group-2 (n = 47)	P
Symptom onset to first medical contact				
< 1 h	47 (61.8)	19 (65.5)	28 (59.6)	0.873
1 - 3 h	23 (30.3)	8 (27.6)	15 (31.9)	
> 3 h	6 (7.9)	2 (6.9)	4 (8.5)	
Coronary angiography performed	70 (100)	29 (100)	47 (100)	NS
Time from FT to CAG	8.86 ± 10.4	2.17 ± 0.38	12.9 ± 11.5	< 0.001
PCI performed	69 (90.8)	26 (89.7)	43 (91.5)	0.788
Femoral access	70 (100)	29 (100)	47 (100)	NS

CAG: coronary angiography; FT: fibrinolytic treatment; PCI: percutaneous coronary intervention.

Table 3. Medication at Discharge and 6 Months Follow-Up

	All patients (n = 76)	Grup-1 (n = 29)	Grup-2 (n = 47)
Medication at discharge			
Aspirin, n, (%)	76 (100)	29 (100)	47 (100)
Clopidogrel, n, (%)	76 (100)	29 (100)	47 (100)
Statins, n, (%)	75 (98)	29 (100)	46 (98)
ACEI, n, (%)	68 (89)	26 (90)	42 (90)
Beta blockers, n, (%)	71 (93)	26 (90)	45 (96)
PPI, n, (%)	68 (89)	28 (96)	40 (85)
Medication at 6 months ^a			
Aspirin, n, (%)	75 (100)	29 (100)	46 (100)
Clopidogrel, n, (%)	73 (97)	29 (100)	44 (95)
Statins, n, (%)	75 (100)	29 (100)	46 (100)
ACEI, n, (%)	68 (90)	25 (86)	42 (93)
Beta blockers, n, (%)	72 (96)	27 (93)	45 (97)
PPI, n, (%)	68 (90)	25 (86)	43 (95)

^aOne patient in Group-2 died at the fourth month. ACEI: angiotensin converting enzyme inhibitor.

ommendation [1, 2]. Despite the recommendation of relevant guidelines, previous studies have shown that a high number of patients do not perform CAG within 24 h [4, 16]. In their study Costa et al has emphasized that two-thirds of the patients performed CAG > 24 h after successful FT [4]. Despite catheterization laboratories that performing PCI, 24 h a day and 7 days a week, seem to be increasing, in the same time the number of patients that referred to these hospitals increased. With the increasing number of patients in this center the stable patients might be schedule to the following days for performing CAG. Similarly, during the weekend, most of the catheterization laboratories just perform PCI for urgent patients and stable patients are frequently scheduled to the following working days, especially Monday. Many previous studies determined the advantageous of early PCI strategy (< 24 h) after successful FT, however there are few studies published concerning the results of exceeding 24 h time window from successful FT to CAG

[4]. In their study Costa et al [4] have shown that performing CAG outside of the 24 h time interval did not lead to higher in hospital mortality. In addition, the writing committee of American Heart Association guideline of management of STEMI believes that performing CAG beyond 24 h after successful FT likely will continue to benefit those patients with a patent but stenotic infarct artery. In stable patients who do not perform CAG within 24 h, CAG can be considered as part of a routine pharmacoinvasive or ischemia-guided approach > 24 h after administration of FT. However, the time-interval after > 24 h is not clear. Moreover, to our best knowledge, there is no clinical study that evaluated the both short and long-term results of CAG performing > 24 h after successful FT. In this context, to clarify the time intervals and evaluated the short and long-term results of CAG after > 24 h, we defined two time interval as early (24 - 72h) and late (> 72h). We have shown that there were no significant differences between two time-intervals in

Table 4. Clinical Outcomes of Short and Long-Term Follow-Up

Variable	All patients (n = 76)	Group-1 (n = 29)	Group-2 (n = 47)	P
Short-term follow-up (6 months)				
Death, n, (%)	1 (1.3)	0	1 (2.1)	NS
Re-infarction, n, (%)	7 (9.2)	2 (6.9)	7 (10.6)	0.295
Heart failure, n, (%)	11 (14.5)	3 (10.3)	8 (17)	0.422
MACE, n, (%)	14 (18.4)	4 (13.8)	10 (21.3)	0.661
Long-term follow-up (median 57 months)				
Death, n, (%)	6 (7.9)	1 (3.4)	5 (10.6)	0.398
Re-infarction, n, (%)	15 (19.7)	5 (17.2)	10 (21.3)	0.668
Heart failure, n, (%)	13 (17.1)	7 (24.1)	6 (12.8)	0.201
MACE, n, (%)	29 (38.2)	11 (37.9)	18 (38.3)	0.974

NS: non-significant; MACE: major adverse cardiac events.

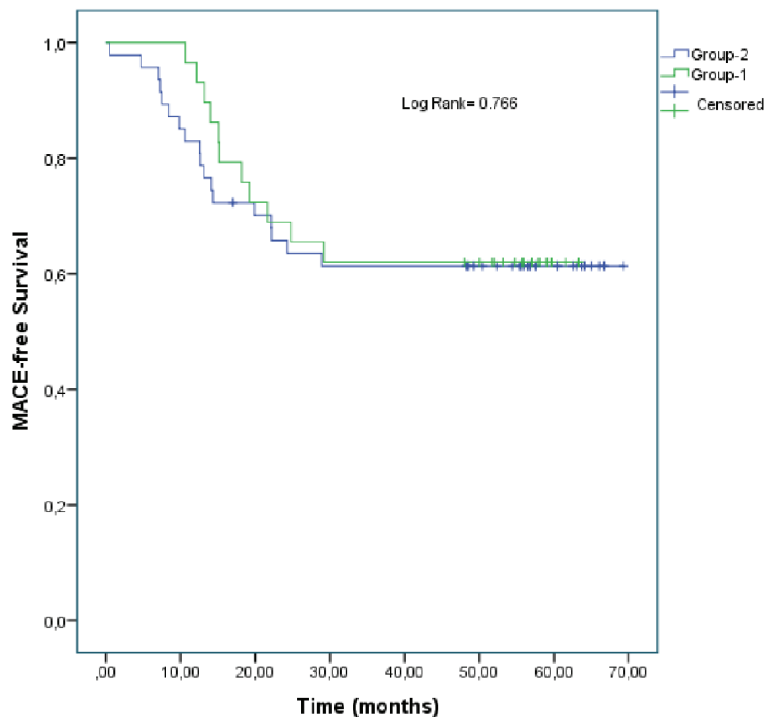


Figure 1. Kaplan-Meier analysis freedom from MACE.

term of MACE both in short and long-term follow-up. Similarly, there were no significant differences between groups in secondary end points; cardiovascular death, re-infarction, and heart failure and event-free survival.

Limitations

The presents study has several limitations that should be acknowledged: 1) It is a single center study and the number of patients are small; 2) The evaluation of the ideal time for CAG was not performed and just two groups were compared according to time interval; 3) The patients performed CAG < 24 h were not included the study.

Conclusions

In present study, it was shown that performance of coronary angiography in patients with STEMI after 24 h of successful FT, within 24 - 74 h or > 72 h, did not show any significant difference in term of MACE both in short and long-term follow-up.

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