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Late coronary intervention for totally occluded LADs in stable patients after myocardial infarction: Results from the Occluded Artery Trial (OAT)

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Abstract

Background—We analyzed a pre-specified hypothesis of the Occluded Artery Trial (OAT), that late percutaneous coronary intervention (PCI) of the infarct-related artery (IRA) would be most beneficial for patients with anterior MI.

Methods—2201 stable high-risk patients with total occlusion of the IRA (793 left anterior descending [LAD]) on days 3 to 28 (minimum 24 hrs) after MI were randomized to PCI and stenting with optimal medical therapy (1101 patients) or to optimal medical therapy alone (1100 patients). The primary end point was a composite of death, recurrent MI, or hospitalization for class IV heart failure.

Results—The 5-year cumulative primary end point rate was more frequent in the LAD group (19.5%) than in the non-LAD group (16.4%) (HR=1.34, 99%CI 1.00–1.81, p=.01). Within the LAD group the HR for the primary end point in the PCI group (22.7%) compared with the medical therapy group (16.4%) was 1.35 (99%CI 0.86–2.13, p=.09), whereas in the non-LAD group the HR for the primary end point in PCI (16.9%) compared with medical therapy (15.8%) was 1.03 (99%CI 0.70–1.52, p=.83) (interaction p=.24). The results were similar when the effect of PCI was assessed in patients with proximal LAD occlusion.

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Conclusions—In stable patients, persistent total occlusion of the LAD post MI is associated with a worse prognosis compared with occlusion of the other IRAs. A strategy of PCI of occluded LAD IRA more than 24 hours post MI in stable patients is not beneficial and may increase risk of adverse events in comparison to optimal medical treatment alone.

Introduction

Rapid restoration of blood flow in the infarct-related artery (IRA), a cornerstone of contemporary treatment of acute myocardial infarction (MI), prevents myocardial necrosis and its consequences [1]. However, due to late presentation or failed fibrinolytic therapy, up to one third of patients have persistently occluded IRA after MI [2].

Recently, the Occluded Artery Trial (OAT) demonstrated that percutaneous coronary intervention (PCI) with optimal medical therapy does not reduce the frequency of major adverse events during a 4-year follow-up period compared to optimal medical therapy alone when performed on days 3–28 post MI in stable patients [3].

One of the secondary hypotheses of OAT was that late coronary revascularization of the IRA would be most beneficial for patients with anterior wall infarction [4]. Acute myocardial infarction involving the left anterior descending (LAD) coronary artery, especially its proximal segments, has been associated with a worse prognosis compared to MI involving other coronary arteries [5–7]. The difference is believed to be primarily related to a larger area of myocardium at risk with LAD occlusion, resulting in a greater impairment of left ventricular (LV) function and remodeling. Most of the previous studies have shown that late reperfusion can reduce adverse left ventricular remodeling and preserve LV function [8–11]. This effect was hypothesized to have the greatest impact in patients with the largest area of myocardium at risk. Therefore, a high risk population of patients with post MI occlusion of the LAD, and in particular its proximal segments, would be expected to benefit most from late recanalization.

Consequently, we compared the effect of late opening of LAD and non LAD IRAs on outcomes in stable patients post MI enrolled in OAT [3].

Methods

The design and methods of OAT study have been reported previously [4]. Current analysis included 2201 patients (2166 from the main OAT trial randomized between February 2000 and December 2005 and additional 35 patients enrolled in the extension phase of the OAT-NUC ancillary study in 2006). Eligible patients had a total occlusion of the IRA on days 3–28 (minimum 24 hours) after MI and met at least one of the high risk criteria: ejection fraction (EF) <50% and/or proximal occlusion of the IRA. Exclusion criteria included New York Heart Association (NYHA) class III or IV heart failure (CHF), shock, a serum creatinine concentration ≥2.5 mg per deciliter (221 μmol per liter), angiographically significant left main or three-vessel coronary artery disease, angina at rest, or severe ischemia on stress testing (performed if ischemia was suspected and required in those without infarct zone akinesis or dyskinesis). Patients were randomized to PCI with stenting and optimal medical therapy (1101 patients) or optimal medical therapy alone (1100 patients). Medical management included daily aspirin, anticoagulation if indicated, β-blockers, angiotensin-converting enzyme (ACE) inhibitors and lipid-lowering therapy, unless contraindicated. Thienopyridine therapy was initially recommended for 2 to 4 weeks following bare metal stent (BMS) implantation and 3 to 6 months following drug-eluting stent (DES) deployment. After publication of data supporting longer-term therapy following acute coronary syndrome, clopidogrel was recommended for one year in both groups [12]. Patients randomized to PCI were to undergo the procedure within 24 hours after treatment allocation with stenting of the occluded segment

as well as high-grade stenoses in major proximal or distal segments whenever technically feasible. Use of glycoprotein IIb/IIIa was strongly recommended.

Images from the PCI were reviewed at the angiography core laboratory. Cardiac markers (preferably creatine kinase myocardial band or, if not available, troponin I or T or creatine kinase) were to be measured routinely in both groups three times during the first 48 hours after randomization and within 24 hours after PCI in patients assigned to PCI.

Institutional review boards at the participating centers approved the study protocol and all patients provided written informed consent. The project described was supported by Award Numbers U01 HL062509 and U01 HL062511 from the National Heart, Lung, And Blood Institute; Supplemental grant funds and product donations equivalent to <5% of total study cost from: Eli Lilly, Millenium Pharmaceuticals ans Schering Plough, Guidant, Cordis/Johnson and Johnson, Medtronic, Merck and Bristol Myers Squibb Medical Imaging. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final content, which does not necessarily represent the official views of the National Heart, Lung, And Blood Institute or the National Institutes of Health.

Study end points

The primary end point was defined as time to the first occurrence of MI, hospitalization or short-stay unit treatment of class IV CHF, or death from any cause. Secondary end points included the individual components of the primary end point, NYHA III CHF, stroke, nonprotocol revascularization and reported angina. Mean follow up was 3.2 years.

Statistical analysis

Baseline characteristics of study patients were summarized in terms of frequencies and percentages for categorical variables and by means and standard deviations (SD) for continuous variables with normal distribution. Categorical variables were compared by either Fisher exact or χ^2 test and continuous variables by student t-test. The primary analysis was intention-to-treat. The occurrence of the primary and secondary end points in the two treatment groups was compared by the log-rank test. Prespecified subgroup analyses of the primary or secondary outcome were carried out with Cox proportional hazards regression [4]. Additionally, a multivariable Cox proportional hazards model was developed to evaluate the relationship between the baseline characteristics, and occurrence of the primary end point and death alone. All baseline variables entered the multivariable stage, regardless of the significance of the association in the univariable analyses. In order to be sensitive to the likelihood of a Type 1 error after multiple analyses, statistical significance in all tests was set at $p<.01$. Results are reported with 99% confidence intervals (CI). Statistical testing was performed using the SAS System version 9.1.3 (SAS Institute, Cary, NC).

Results

Baseline characteristics

There were 793 patients (36%) with left anterior descending artery IRA and 1408 patients (64%) with non-LAD as the IRA (left circumflex artery [335, 15%] or right coronary artery [1073, 49%]). Baseline clinical and angiographic characteristics of patients with LAD IRA as compared with non-LAD are presented in Table 1. Patients with LAD IRA compared to non-LAD IRA were older and less frequently male or cigarette smokers with less common history of previous MI or PCI. Patients with LAD IRA were also more likely to have heart failure as demonstrated by higher Killip class during index MI, more frequent NYHA class II and lower LV ejection fraction at randomization. Patients with IRA-LAD had lower frequency of angiographically visible collateral vessels or TIMI flow<1 in IRA as compared with non-LAD.

There was no difference in median time between index MI and randomization in relation to LAD and non-LAD IRA. PCI success rates were similar for LAD and non-LAD IRAs. The elevation of cardiac markers within 48h after randomization was similar in both IRA groups.

Medications prescribed at discharge are shown in Table 2. Patients with LAD IRA were more likely prescribed medications to treat heart failure such as angiotensin-converting enzyme inhibitors, digoxin, spironolactone, and diuretic agents. They also were more likely to receive anti-arrhythmic drugs and warfarin. They were less likely to receive sublingual nitrates or lipid lowering-agents.

Five-year outcomes within IRA classification and treatment allocation

The five-year primary end point was more frequent in LAD (19.5%) than in non-LAD IRA (16.4%) (HR=1.34, 99%CI 1.00–1.81, p=.01) (Table 3, Figure 1). Analysis of secondary outcomes revealed excess of deaths (14.1% vs. 10.4%, HR=1.54, 99%CI 1.05–2.26, p=.003) and hospitalizations for class IV heart failure (6.4% vs. 3.6%, HR=1.93, 99%CI 1.11–3.34, p=.002), but no significant difference in recurrent MIs (5.2% vs. 6.5%, HR=0.91, 99%CI 0.54–1.55, p=.66) in the LAD group compared to the non LAD IRA group. Multivariable Cox analysis revealed that the LAD IRA was not independently associated with the primary end point or death. Factors independently associated with the primary end point were history of heart failure, peripheral vascular disease, diabetes, rales during randomization, decreased EF, time elapsed from MI and lower glomerular filtration rate (GFR). Independent predictors of death were: Killip class>1, history of cerebrovascular disease, angina, history of heart failure, decreased EF, days from MI and low GFR.

The HR for PCI vs. medical therapy alone for the primary end point was 1.35 (99%CI 0.86–2.13, p=.09) in the LAD group and 1.03 (99%CI 0.70–1.52, p=.83) in the non-LAD group (Table 4, Figure 2) (interaction p=.24). When secondary end points were analyzed, there were no significant differences in all cause deaths, fatal and non-fatal myocardial infarctions and hospitalizations for heart failure or strokes according to treatment allocation in both the LAD and non-LAD. The benefit of PCI on angina and revascularization over 5 year follow-up was more readily apparent in the larger non-LAD group (Table 4).

The results were similar for the primary outcome when the effect of PCI was assessed in patients with proximal LAD occlusion before the first septal branch (proximal LAD, n=271; PCI vs. medical therapy, HR=1.51, 99%CI 0.72–3.14, p=.15) as well as in patients with occlusion up to second septal branch (modified proximal LAD, n=765; PCI vs. medical therapy, HR=1.35, 99%CI 0.85–2.13, p=.09).

Discussion

Our results confirm that the LAD IRA is a risk indicator among stable patients with persistent total occlusion of the infarct artery over a time horizon of several years post MI. The main reason for the unfavorable outcome in this group of patients compared to other infarct locations was an association with larger index infarctions, as demonstrated by lower EF and higher Killip and NYHA classes. Multivariable modeling for the primary end point and death suggested that higher risk associated with the LAD IRA was mediated by lower ejection fraction and more frequent history of heart failure in those patients.

Contrary to the hypothesis, there was no suggestion that patients with LAD infarction benefited from late opening of the artery in the OAT time window.

Few studies on the role of PCI in the late reperfusion after MI performed have concentrated specifically on patients with anterior infarctions. All of them included a relatively small number

of patients in comparison to OAT, which enrolled 793 patients with LAD occlusion and 2201 patients overall. Pizzetti and colleagues showed that coronary angioplasty performed after a mean of 15 days in 67 patients with anterior MI improved LV ejection fraction and reduced a degree of LV dilation at 6 months in comparison to conservative treatment [8]. In another study by Horie et al. 83 patients with anterior MI were randomized to PCI or medical therapy after >24 hours from the onset of symptoms [9]. The trial showed that late PCI leads to smaller end-diastolic and end-systolic volumes at 6 months as well as fewer deaths, recurrent MI, and congestive heart failure at 50 months. Both of those studies however were performed over a decade ago, when patients less frequently received beta-blockers, angiotensin converting enzyme inhibitors or statins in comparison to contemporary standards. The less rigorous medical therapy may have increased the apparent positive effects of the interventional strategy, as all of those drugs have a potential to increase survival [13]. More recently a study by Silva et al. with high use of ACE inhibitors failed to demonstrate that PCI improves LV volumes or decreases infarct size, but did show an increase in LV ejection fraction and a change in the circumferential shortening of the remote segments in the PCI group compared to no-PCI group. The study, which enrolled 36 patients, was not powered to analyze clinical end-points [10].

Only one small trial – The Open Artery Trial (TOAT) performed more recently enrolled 66 patients with clinical characteristics similar to the OAT subgroup in this report (occluded LAD, ejection fraction <50%, mostly one-vessel disease and no ischemia on symptom-limited exercise treadmill test, over 80% of patients receiving beta-blockers and 100% ACE inhibitors) and utilized stents in all PCI patients [14]. Of note, contrary to TOAT, OAT allowed mild or moderate ischemia at randomization. Although not powered for clinical events, TOAT reported an apparent excess of events, including death, MI, stroke, congestive heart failure as well as revascularization at 12 months in patients randomized to PCI. In the same trial the end-systolic and end-diastolic volumes unexpectedly increased more in patients undergoing PCI than in patients treated conservatively.

As demonstrated above previously published clinical trials on late reperfusion in patients with LAD occlusion after MI, except TOAT, reported improvement of LV function measured with LV ejection fraction or volumes. The TOSCA-2 study, an ancillary study of OAT also demonstrated that assignment to PCI is related to smaller increase of LV volume in a subgroup of patients with LV measurements, although this analysis did not compare different IRAs. The current analysis shows that surrogate benefits of late reopening of the IRA are not related to better prognosis in the subset of patients with LAD occlusion treated with PCI, those previously hypothesized to benefit most from the improvement of left ventricular function or prevention of its remodeling.

There was also no difference in outcomes in relation to the location of LAD occlusion [5,6]. An explanation for that finding may be that there were only a relatively small number of patients with mid or distal LAD occlusion, because OAT entry criteria included a requirement for proximal coronary occlusion (up to second septal branch in the case of the LAD) and/or depressed LVEF.

The percentage of patients with LAD occlusion in OAT (36% of all IRAs) was modestly lower then in primary PCI trials [15]. This difference is most likely because OAT focused on stable patients after MI, while LAD occlusion more often then occlusion of other IRAs leads to haemodynamic instability in the acute phase of MI. Therefore patients with LAD occlusion were less likely to qualify for OAT. This is also supported by the evidence of higher prevalence of collateral vessels in patients with LAD as IRA in OAT in comparison to patients from primary PCI trials. In patients with acute MI, the presence of angiographically detectable collateral vessels reduces the likelihood of hemodynamic instability, especially when LAD is involved in the infarct [7,15–17].

The analysis has several limitations. Conclusions drawn about the effects of PCI of the LAD in the context of MI pertain only to patients who would qualify for OAT, that is, stable patients with not more than moderate ischemia (mostly none or mild ischemia) who do not have three-vessel CAD. Although the number of patients with LAD occlusion is far greater than all prior studies of late recanalization of the IRA, the power of this subset analysis is lower then 94% observed in the main OAT report [3]. Nevertheless, there was no suggestion of any benefit of PCI for patients with LAD occlusion.

Conclusions

Persistent total occlusion of the LAD is associated with a worse prognosis compared with occlusion of other IRAs. A strategy of PCI of the occluded LAD more than 24 hours post MI in stable patients is not beneficial and may increase risk of adverse events in comparison to optimal medical treatment alone.

The great value of strategies aimed to avoid late presentation of patients with acute MI and a stronger involvement in regional programs of acute MI interventions to achieve rapid restoration of blood flow through IRA either in urban or rural areas should be therefore emphasized.

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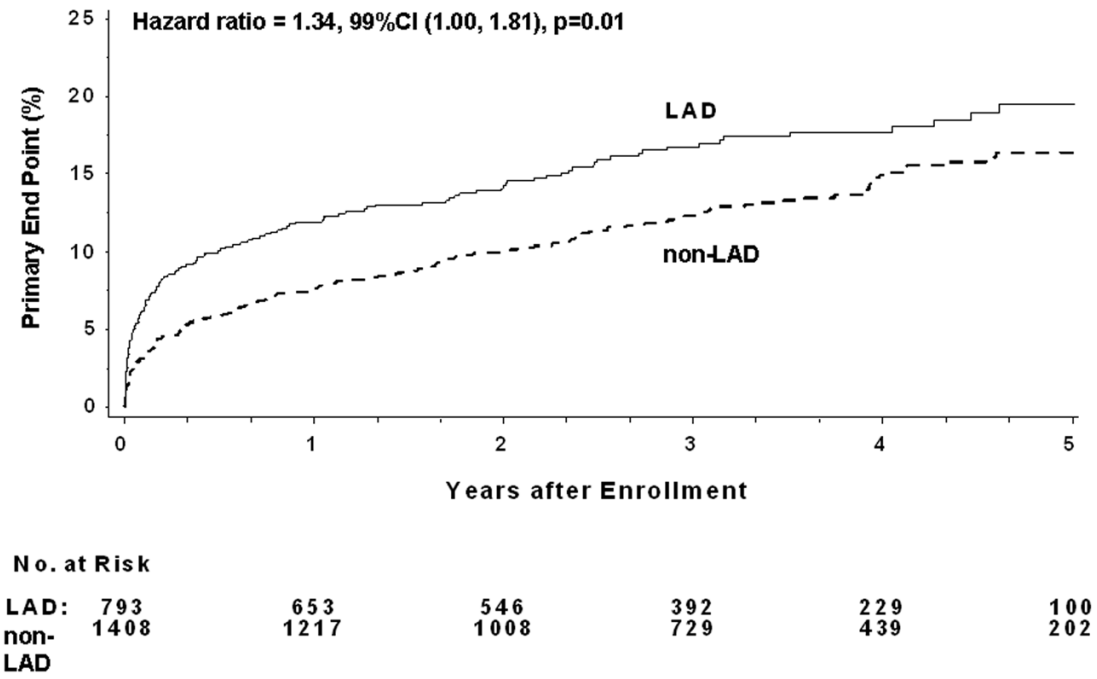

No. at Risk

LAD:	793	653	546	392	229	100
non-LAD	1408	1217	1008	729	439	202

Figure 1.
Kaplan-Meier for the primary 5-year endpoint for combined PCI and medical therapy in LAD and non-LAD IRA (log rank test used for comparison between groups).

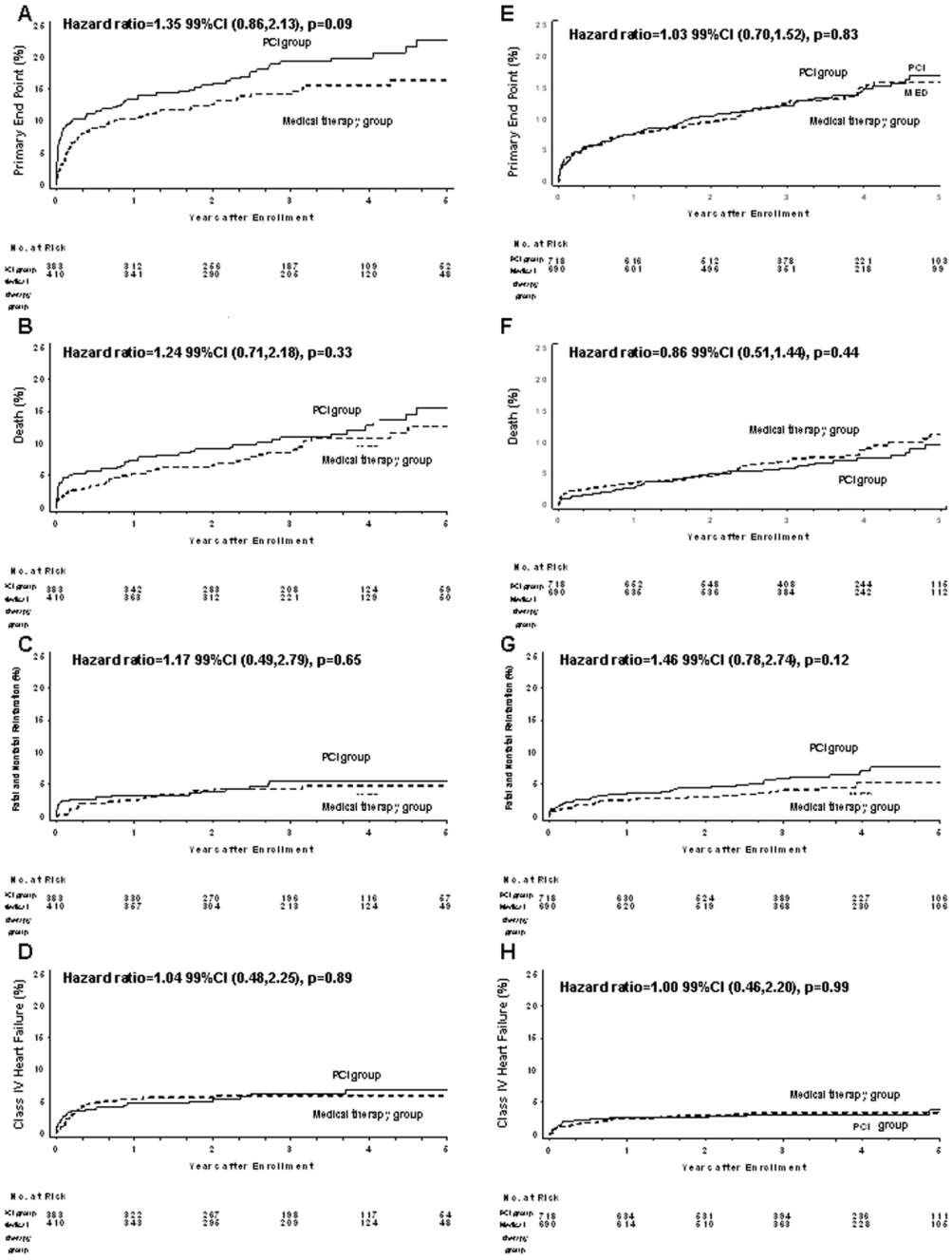

Figure 2.

Kaplan-Meier for the primary and secondary 5-year end points, according to treatment assignment (PCI vs. medical therapy) and the intention-to-treat analysis within study groups (LAD, non-LAD) (log-rank test used for comparisons between groups). **A–D** LAD: **A** – primary end point, **B** – death, **C** – fatal and nonfatal reinfarction, **D** – class IV heart failure requiring hospitalization or a stay in a short-stay unit; **E–H** non-LAD: **E** –primary end point, **F** – death, **G** – fatal and nonfatal reinfarction, **H** – class IV heart failure requiring hospitalization or a stay in a short-stay unit.

Table 1

Baseline clinical, angiographic and post-randomization core laboratory characteristics by infarct related artery

Characteristic	LAD* N=793	non-LAD* N=1408	P
Clinical			
Age – yr (SD)	59.5±11.2	58.1±10.8	.005
Male sex – no. (%)	591 (74.5)	1126 (80.0)	.003
White race – no. (%)	630 (79.4)	1133 (80.5)	ns
History – no. (%)			
Angina	188 (23.7)	307 (21.8)	ns
Myocardial infarction	69 (8.7)	178 (12.6)	.005
PCI	19 (2.4)	86 (6.1)	<.0001
CABG	0 (0.0)	9 (0.6)	ns
Stroke	21 (2.6)	42 (3.0)	ns
Peripheral-vessel disease	24 (3.0)	59 (4.2)	ns
Heart failure	18 (2.3)	34 (2.4)	ns
Diabetes	185 (23.3)	269 (19.1)	ns
Hypertension	393 (49.6)	678 (48.2)	ns
Hypercholesterolemia	407 (51.3)	735 (52.2)	ns
Renal insufficiency	12 (1.5)	18 (1.3)	ns
Family history	310 (39.1)	573 (40.7)	ns
Current cigarette smoker – no. (%)	260 (32.8)	599 (42.5)	<.0001
Highest Killip class II–IV during index MI – no.(%)	189/788 (24.0)	228/1404 (16.2)	<.0001
NYHA at randomization class II – no. (%)	165/791 (20.9)	202/1406 (14.4)	.001
New Q waves – no.(%)	592 (74.7)	883 (62.7)	<.0001
ST-segment elevation – no.(%)	631/766 (82.4)	779/1360 (57.3)	<.0001
ST-segment elevation or Q-wave or R-wave loss – no. (%)	749 (94.5)	1156 (82.1)	<.0001
Thrombolytic therapy during first 24hr after onset of index MI – no. (%)	174 (21.9)	250 (17.8)	ns
Interval between MI and randomization – days			
Median	9	8	ns
25^{th}, 75^{th}	5,17	5,16	

Characteristic	LAD* N=793	non-LAD* N=1408	P
Stress test perfomed – no. (%)	168 (21.2)	430 (30.5)	<.0001
Ischemia in infarct-related artery territory – no. (%)			
Severe	0 (0)	1 (0.2)	ns
Moderate	16 (9.5)	43 (10.0)	
Mild	46 (27.4)	134 (31.2)	
None	106 (63.1)	252 (58.6)	
Angiographic			
TIMI flow grade in IRA prior to randomization- no. (%)	N=784	N=1187	
0	618 (78.8)	1187 (85.0)	.0002
1	159 (20.3)	207 (14.8)	
2	6 (0.8)	1 (0.1)	
3	1 (0.1)	1 (0.1)	
Collateral vessel present – no. (%)	656/780 (84.1)	1266/1393 (90.9)	<.0001
Multivessel disease – no. (%)	134/784 (17.1)	245/1399 (17.5)	ns
Ejection fraction			
Mean	42.3±11.5	50.7±9.3	<.0001
<50% – no. (%)	583/787 (74.1)	587/1398 (42.0)	<.0001
<40% – no. (%)	300/787 (38.1)	149/1398 (10.7)	<.0001
Post-randomization			
PCI successful – no. (%)	341/383 (89.0)	612/718 (85.2)	ns
Elevation of cardiac marker within 48h after randomization.	45/709 (6.35)	86/1255 (6.85)	ns

CABG – coronary artery bypass grafting, LAD – left anterior descending artery, MI –myocardial infarction, NYHA – New York Heart Association, PCI – percutaneous coronary intervention, TIMI – Thrombolysis in Myocardial Infarction

* There was no between group difference in baseline characteristics between those assigned to PCI and medical therapy only for LAD and non-LAD patients (except for a 2 mm Hg higher diastolic blood pressure for the medical therapy only LAD patients, 1.5 mmHg higher diastolic blood pressure for PCI non-LAD patients and 5.1% greater prevalence of diabetes for medical therapy only non-LAD patients).

Table 2

Medication use by infarct realted artery

Medication	LAD N=793	non-LAD N=1408	P
In-hospital			
Gp IIb/IIIa in first 24 hours	58 (7.3)	124 (8.8)	ns
Gp IIb/IIIa inhibitors	268 (33.8)	512 (36.4)	ns
On discharge			
Aspirin – no. (%)	753 (95.0)	1352 (96.0)	ns
Clopidogrel – no. (%)	363 (45.8)	712 (50.6)	ns
Ticlopidine – no. (%)	98 (12.4)	161 (11.4)	ns
Thienopyridine (clopidogrel or ticlopidine) – no. (%)*	457 (57.6)	872 (61.9)	ns
Warfarin – no. (%)	187 (23.6)	28 (2.0)	<.0001
Aspirin and thienopyridine and warfarin – no. (%)	70 (8.8)	8 (0.6)	<.0001
Beta blocker – no. (%)	723 (91.2)	1209 (85.9)	.0003
Calcium-channel blocker – no. (%)	34 (4.3)	95 (6.7)	ns
Sublingual nitrate – no. (%)	205 (25.9)	447 (31.7)	.004
Long acting nitrate – no. (%)	189 (23.8)	309 (21.9)	ns
ACE inhibitor or ARB – no. (%)	700 (88.3)	1071 (76.1)	<.0001
Diuretic agent – no. (%)	188 (23.7)	183 (13.0)	<.0001
Digoxin – no. (%)	42 (5.3)	19 (1.3)	<.0001
Spironolactone – no. (%)	72 (9.1)	52 (3.7)	<.0001
Insulin – no. (%)	66 (8.3)	71 (5.0)	.002
Oral hypoglycemic agent – no. (%)	117 (14.8)	181 (12.9)	ns
Lipid-lowering agent – no. (%)	622 (78.4)	1166 (82.8)	.01
Antiarrhythmic (other than beta-blocker) – no. (%)	46 (5.8)	38 (2.7)	.0003

ACE – angiotensin converting enzyme, ARB – angiotensin receptor blocker, GP –glycoprotein, LAD – left anterior descending artery

*A thienopyridine was prescribed for more then 99% of patients in the PCI group in whom PCI with stenting was successful. A thienopyridine was prescribed for 29% of patients assigned to medical therapy only.

Table 3

5-year outcomes by study groups

	LAD N=793		non-LAD N=1408		Cox P-value
	No of outcomes	Estimated 5-yr cumulative event rate (%)	No. of outcomes	Estimated 5-yr cumulative event rate (%)	
Centrally adjudicated					
Primary end point	131	19.5	180	16.4	.01
Death from all causes	84	14.1	100	10.4	.003
Fatal and nonfatal reinfarction	35	5.2	70	6.5	.66
Procedure-related	4		3		
Not procedure-related	31		67		
Nonfatal reinfarction	33	4.9	66	6.2	.67
NYHA class IV heart failure	45	6.4	43	3.6	.002
Cardiovascular death	63	10.2	57	5.6	<.001
Death or nonfatal reinfarction	109	17.1	158	15.4	.06
NYHA class III or IV heart failure	61	8.5	58	4.5	<.001
Death, reinfarction, or NYHA class III or IV heart failure	142	20.8	194	17.4	.006
Stroke	17	2.3	18	1.5	.11
Site-determined					
Nonprotocol revascularization	138	19.8	247	21.1	.81
Reported angina*	276	41.9	488	40.4	.76

LAD – left anterior descending artery, NYHA – New York Heart Association

*For the reported angina, which required at least one follow-up visit the following denominators were used: LAD – 750, non-LAD – 1364.

Table 4

5-year outcomes by treatment assignment

LAD	PCI (n=383)		Medical therapy (n=410)		P*	HR* (99%CI)	Inter action P
	No of outcomes	Estimated 5-yr cumulative event rate (%)	No. of outcomes	Estimated 5-yr cumulative event rate (%)			
Centrally adjudicated							
Primary end point	72	22.7	59	16.4	.09	1.35 (0.86–2.13)	.24
Death from all causes	45	15.6	39	12.7	.33	1.24 (0.71–2.18)	.22
Fatal and nonfatal reinfarction	18	5.6	17	4.8	.65	1.17 (0.49–2.79)	.58
Procedure- Related	4		0				
Not procedure- related	14		17				
Nonfatal reinfarction	18	5.6	15	4.3	.42	1.32 (0.54–3.25)	.76
NYHA class IV heart failure	22	6.9	23	6.0	.89	1.04 (0.48–2.25)	.93
Death or nonfatal reinfarction	60	19.2	49	15.1	.13	1.34 (0.82–2.21)	.39
NYHA class III or IV heart failure	32	9.6	29	7.5	.47	1.2 (0.62–2.33)	.24
Death, reinfarction, or NYHA class III or IV heart failure	80	24.6	62	17.1	.03	1.43 (0.92–2.21)	.08
Stroke	11	1.6	6	3.0	.30	0.59 (0.16–2.18)	.3
Site-determined							
Nonprotocol revascularization	65	20.1	73	19.5	.71	0.94 (0.60–1.46)	.26
Reported angina*	126	39.2	150	44.6	.25	0.87 (0.64–1.19)	.22
Non-LAD	PCI (n=718)		Medical therapy (n=690)				
Centrally adjudicated							
Primary end point	93	16.9	87	15.8	.83	1.03 (0.7–1.52)	
Death from all causes	47	9.6	53	11.2	.44	0.86 (0.51–1.44)	
Fatal and nonfatal reinfarction	42	7.7	28	5.2	.12	1.46 (0.78–2.74)	
Procedure-Related	2		1				
Not procedure-related	40		27				
Nonfatal reinfarction	40	7.4	26	5.0	.11	1.50 (0.78–2.87)	
NYHA class IV heart failure	22	3.8	21	3.4	.99	1.00 (0.46–2.2)	
Death or nonfatal reinfarction	83	16.0	75	14.8	.62	1.08 (0.72–1.63)	

LAD	PCI (n=383)		Medical therapy (n=410)		P*	HR* (99%CI)	Inter action P
	No of outcomes	Estimated 5-yr cumulative event rate (%)	No. of outcomes	Estimated 5-yr cumulative event rate (%)			
NYHA class III or IV heart failure	26	3.9	32	5.2	.34	0.78 (0.39–1.54)	
Death, reinfarction, or NYHA class III or IV heart failure	97	17.4	97	17.3	.81	0.97 (0.67–1.4)	
Stroke	10	1.6	8	1.3	.69	1.21 (0.36–4.1)	
Site-determined							
Nonprotocol revascularization	109	18.9	138	23.4	.02	0.74 (0.53–1.02)	
Reported angina**	220	36.3	268	44.7	.0003	0.72 (0.57–0.91)	

LAD – left anterior descending artery, NYHA – New York Heart Association

*Covariate adjustment of treatment effect (for diabetes and diastolic blood pressure) demonstrated minimal change in the hazard ratios.

**For the reported angina, which required at least one follow-up visit the following denominators were used: in the LAD group (PCI – 358, medical therapy – 392) and in the non-LAD (PCI – 694, medical therapy – 670).