Published in final edited form as:

Am Heart J. 2012 March ; 163(3): 462–469. doi:10.1016/j.ahj.2012.01.005.

Relationship of Female Sex to Outcomes after Myocardial Infarction with Persistent Total Occlusion of the Infarct Artery: Analysis of the Occluded Artery Trial

Harmony R. Reynolds, MD¹, Sandra A. Forman, MA², Jacqueline E. Tamis-Holland, MD³, Philippe Gabriel Steg, MD⁴, Daniel B. Mark, MD⁵, Camille A. Pearte, MD¹, Antonio C. Carvalho, MD⁶, George Sopko, MD⁷, Li Liu, MS², Gervasio A. Lamas, MD⁸, Mariusz Kruk, MD⁹, Krystyna Loboz-Grudzien, MD, PhD¹⁰, Witold Ruzyllo, MD¹¹, and Judith S. Hochman, MD¹

¹Cardiovascular Clinical Research Center, New York University School of Medicine, New York, NY ²Clinical Trials and Surveys Corporation, Owings Mills, MD ³St. Luke's-Roosevelt Hospital Center and Columbia University College of Physicians and Surgeons, New York, NY ⁴INSERM U-698, Department of Cardiology, Hopital Bichat, AP-HP, and Université Paris 7, France ⁵Duke Clinical Research Institute, Duke University, Durham, NC ⁶Hospital São Paulo, UNIFESP - Sao Paulo, Brazil ⁷National Heart Lung and Blood Institute, Bethesda, MD ⁸Columbia University Division of Cardiology, Mount Sinai Medical Center, Miami Beach, FL ⁹National Institute of Cardiology, Warsaw, Poland ¹⁰Wroclaw Medical University, T. Marciniak Hospital, Wroclaw, Poland ¹¹National Institute of Cardiology, Warsaw, Poland

Abstract

Background—Long-term follow-up (up to 9 years) from the Occluded Artery Trial (OAT) allows for examination of sex differences in outcomes and the effect of PCI in a relatively homogeneous cohort of MI survivors.

Methods—OAT randomized 484 (22%) women and 1717 men to PCI of the occluded infarct-related artery vs. medical therapy alone >24 hours post-MI. There was no benefit of PCI on the composite of death, MI and class IV heart failure. We analyzed outcomes by sex and investigated for sex-based trial selection bias using a concurrent registry.

Results—Women were older and more likely to have LAD infarct-related artery, diabetes and hypertension, history of heart failure and rales at randomization, but less likely to smoke. The proportion and characteristics of women enrolled in the trial and the registry were similar, including LVEF and extent of disease. Women had higher rates of the primary composite [HR 1.48, $p=0.0002$], death [HR 1.50, $p=0.001$] and heart failure [HR 2.53, $p<0.0001$] but not reinfarction [HR 1.12, $p=0.57$]. Female sex was not independently associated with the primary endpoint or death on multivariate analysis. There was a trend toward independent association of female sex with heart failure [HR 1.66, $p=0.02$].

© 2012 Mosby, Inc. All rights reserved

Correspondence: Harmony R. Reynolds, MD, 530 First Avenue, Suite 9R, New York, NY 10016; tel: 212-263-6958; fax: 212-263-3988; harmony.reynolds@nyumc.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conclusion—Women in OAT had a higher primary endpoint event rate than men, mainly driven by heart failure. Female sex was not independently associated with death or MI in this well-defined cohort with comparable extent of coronary artery disease, similar medical therapy and equivalent LVEF by sex.

Background

There are differences in characteristics and outcomes of women and men across the spectrum of ACS. Women have poorer outcomes than men after myocardial infarction, particularly with ST elevation (STEMI),^{1–3} but such analyses are often confounded by differences in presentation, time to treatment, and treatment. Therefore, sex differences in mortality are not always apparent after multivariate analyses.⁴ In particular, women are known to present later in the course of MI⁵ and to receive reperfusion therapy less frequently than their male counterparts.⁶ These differences would be anticipated to result in a higher frequency of persistent total occlusion of the infarct artery among women than men.

We set out to investigate the effect of female sex on long-term outcomes within the Occluded Artery Trial (OAT), which enrolled patients (22% women) with total occlusion of the infarct artery. We also aimed to determine whether there was sex-related selection bias against inclusion in the trial by comparing women and men enrolled in OAT with patients of both sexes included in a concurrent registry and screening log.

Methods

Patient Population

A full description of the design and methods of the Occluded Artery Trial has been published.⁷ Subgroup analysis by sex was pre-specified. Patients were eligible at minimum > 24 hours (3–28 calendar days) from symptom onset if they had total occlusion of the infarct-related artery (IRA), met trial criteria for increased risk (ejection fraction [EF] <50% or proximal IRA occlusion) and remained in stable clinical condition. Major exclusion criteria included class III or IV heart failure, (HF), cardiogenic shock, serum creatinine ≥ 2.5 mg/dl (221 μ mol/L), left main or three-vessel coronary disease, rest angina, and severe ischemia on stress testing. A screening log recorded eligibility criteria and basic demographics for all patients with MI was at each site for one month at the time of site startup. A registry was kept of those patients fully eligible for the trial but not enrolled. Follow up was continued for up to 9 years.⁸ Mean follow up duration for this analysis was 6 years.

Enrolled patients (n=2201) were randomly allocated to PCI with optimal medical therapy (PCI) or optimal medical therapy (MED) alone.⁸ An angiography core laboratory reviewed qualifying angiogram and PCI images. Cardiac markers were measured in both groups 3 times during the first 48 hours after randomization and ≤ 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.

Study endpoints

The primary endpoint was the composite of all-cause mortality, reinfarction, or NYHA class IV heart failure (HF). All endpoints were adjudicated by an independent classification committee (MMCC), blinded to treatment assignment⁷ reinfarction events suspected by sites were reviewed and classified by type according to the universal definition of MI⁷ by a committee of 5 investigators who were blinded to treatment assignment.⁸ Secondary endpoints included the individual components of the primary endpoint, angina, revascularization, and quality of life measures, among others. Baseline HF was defined as

rales or S3 at randomization, prior history of HF, highest Killip class >I, or NYHA class II at randomization.

Statistical Analysis

Continuous variables are presented using mean and standard deviation and were compared using the t-test for parametric variables. Median values with the interquartile ranges were compared using the Wilcoxon nonparametric test for nonparametric variables. Categorical variables were compared using the chi-square test. The association of sex and study endpoints was analyzed using Cox regression models. Age adjustment was performed. Multivariate Cox models included all baseline clinical and angiographic characteristics including age, days from MI to randomization, prior history of diabetes, angina, cerebrovascular disease and peripheral vascular disease, current smoking, estimated glomerular filtration rate (eGFR), EF, and baseline HF. Hazard ratios for sex were adjusted for the baseline variables predictive of the primary outcome on multivariate analysis. All p-values are 2 sided. All analyses were by intention to treat. To control for type I error, study protocol pre-specified that $p \leq 0.01$ would be considered significant in the secondary analyses. eGFR was calculated using the 4-component Modified Diet and Renal Disease (MDRD) equation, and was entered into multivariate models based on CKD stages (eGFR <60, 60–89 or ≥ 90). Statistical Analysis Systems (SAS), version 9.2 (SAS Institute, Cary, NC) software was used for all analyses.

Results

Baseline characteristics by sex and treatment assignment

Women enrolled in OAT were older than men on average (63.5 ± 11.2 years vs. 57.2 ± 10.5 , $p < 0.0001$) and the age structure of the population was different between women and men (46.7% age >65 vs. 24.2%, $p < 0.0001$). Women were more likely to have history of diabetes, hypertension and HF, but less likely to have prior MI and to smoke. Women had lower eGFR. Women were more likely to have the LAD as the IRA but had similar rates of multivessel disease and angiographically visible collaterals. (Table 1) There were no important differences by treatment assignment (PCI vs. MED) for either sex (data not shown).

Comparison of patients enrolled with those registered and screened

Women comprised 22.0% of enrolled patients, 22.4% of registered patients ($n=335$ fully eligible, not enrolled), and 30.4% of 4,623 patients in the OAT screening log.⁷ Women in the registry were of similar age, race distribution and risk factor profile as women enrolled in the trial. The same was true of men. Reasons for non-enrollment, including patient or physician refusal, were similar for men and women. A similar proportion of both sexes had received thrombolytic therapy.

Among screened patients, men were more likely to have undergone thrombolytic therapy (24.6% vs. 19.0%, $p < 0.0001$), primary PCI (36.5% vs. 29.7%, $p < 0.0001$) and angiography (80.1% vs. 71.8%, $p < 0.0001$). Men were more likely to have ST elevation on the ECG (62.6% vs. 53.4%, $p < 0.0001$). Angiography, if performed, was done within the OAT qualifying time window for nearly all patients of both sexes who did not have primary PCI. Information on total IRA occlusion was not collected in the screening log.

Treatment

Women were more likely to receive long-acting nitrates, calcium channel blockers, and diabetic medications at index MI discharge. Use of other medications was similar (Table 2).

There were trends towards higher rates of PCI success in women (91.6% vs. 86.3%, $p=0.03$) and stenting attempts in women (92.4% vs. 87.0%, $p=0.02$).⁹

Primary and secondary outcomes by sex and treatment assignment (Table 3)

Women were more likely to experience the primary outcome (7-year life table event rate, 27.1 vs. 21.3, HR 1.48, $p=0.0002$) and had a higher risk of death during long term follow up (7-year mortality rates 18.2 vs. 14.5; HR 1.50; $p=0.001$). There was no difference in adjudicated reinfarction by sex (Table 3) but death or reinfarction was more common among women (HR 1.35, 99% CI 1.02–1.81, $p=0.006$). Women were more likely to develop class IV HF (HR 2.53, 99% CI 1.51–4.23; $p<0.001$). Among patients with no baseline HF factors and no history of HF ($n=1504$), women were still at higher risk of class IV HF (7-year life table event rate 6.4 vs. 2.4, HR 2.59, 99% CI 1.19–5.61, $p=0.002$).

In the larger male subgroup, there was a suggestion of higher rates of reinfarction and death or reinfarction for those assigned to PCI. There was no interaction between sex and treatment assignment on any outcome at the pre-specified significance level.

Age adjustment and multivariate analysis—After age adjustment, there was a trend for female sex to be associated with the primary endpoint (HR 1.26, 99% CI 0.95–1.68, $p=0.03$), but there was no such association for death (HR 1.10, 99% CI 0.78–1.54, $p=0.48$). There was no interaction between age and sex on the primary outcome. Female sex remained a significant predictor of class IV HF after age adjustment (HR 1.96, 99% CI 1.14–3.36, $p<0.001$).

On multivariate analysis, female sex was not independently associated with the primary outcome (HR 1.19, 99% CI 0.89–1.58, $p=0.12$) or death (HR 1.06, 99% CI 0.75–1.50, $p=0.67$) when eGFR was included in the model. There was a trend toward independent association of female sex with class IV HF on multivariate analysis (HR 1.66, 99% CI 0.95–2.90, $p=0.02$) which did not meet trial criteria for statistical significance. However, female sex was independently associated with the primary outcome and the secondary outcome of HF when creatinine was included in the multivariate model rather than eGFR (primary outcome HR 1.47, 99% CI 1.09–1.98, $p=0.001$; class IV HF HR 2.48, 99% CI 1.44–4.27, $p<0.0001$). In contrast, older age remained a significant predictor of the primary endpoint and death when eGFR was included in the model, with a trend toward independent association with class IV HF.¹⁰ Calculation of eGFR using the Cockcroft-Gault formula did not change results (data not shown).

Sex and type of reinfarction event—There was no difference by sex in the type of reinfarction classified based on the universal definition of MI (Table 4). As in the overall trial⁸, in men, there was a higher rate of type 4b (stent-related) reinfarction among those patients assigned to PCI. There was no difference by treatment assignment for the few type 4b events among women, and there was no interaction between treatment assignment and sex for any other MI type.

Angina, revascularization and IRA patency—Rose angina prevalence was similar in women and men at most time points in follow-up, with a higher prevalence among women at the 12 month visit only. On initial follow-up both women and men assigned to PCI were less likely to have angina. These differences disappeared in later follow-up (Table 5). There was no sex difference in non-protocol revascularization (HR 0.94 women vs. men, 99% CI 0.70–1.26, $p=0.58$). In the angiographic ancillary study¹¹ there were no differences in 1-year IRA patency rates by sex for either treatment group (PCI: 83.9% of women vs. 82.4% of men, $p=0.84$; MED: 32.1% vs. 23.7%, $p=0.35$). In the nuclear viability ancillary study, there

was a trend toward more preservation of viability in the infarct zone among women (at least moderately retained infarct zone viability 77% vs. 69%, $p=0.02$).¹²

Quality of Life—Dyspnea was more common among women at baseline and throughout follow up. Women had lower Duke Activity Status Index composite scores at baseline and through 24-month follow up, indicating poorer cardiac-specific functional status. (Table 6) There were no significant differences in quality of life measures by treatment group in either sex. Women were more likely to be unemployed and to stop working during follow up.

Discussion

Analysis of the Occluded Artery Trial (OAT) affords the opportunity to examine sex differences in outcomes and the effect of PCI in a relatively homogeneous subset of MI survivors. The low proportion of women enrolled in OAT is surprising because the trial selected patients with persistent total occlusion of the infarct-related artery, a finding that might have been expected to be more common among women. Women present later after MI onset¹³ and are less likely to receive reperfusion therapy.⁶ Comparison with the concurrent OAT registry and screening log demonstrated that a similarly low proportion of women screened were fully eligible for the trial and confirmed lower use of early reperfusion therapy in women screened for OAT. The proportion of female patients with MI who were entered into the screening log at OAT sites during the enrollment period was just 30%, lower than the proportion of patients with MI who are female in large United States registries, about 39%.^{14, 15} The rate of use of angiography in patients with MI at OAT sites was lower for women than men during the enrollment period and entry criteria for OAT did include angiographic parameters. It is likely that some women with total occlusion of the infarct artery were not identified because they did not undergo angiography. In addition, women less frequently have obstructive CAD at angiography after MI.⁴ Alternatively, it is possible that women were more likely to spontaneously recanalize the infarct artery by the time of coronary angiography, thus precluding enrollment into the trial. However, spontaneous recanalization was not more common among women in the angiographic ancillary study over the year after study enrollment.

While pre-trial care differed between men and women, in-trial care was similar by sex, and women enrolled in OAT had similar LVEF and angiographic extent of atherosclerosis as compared to men. PCI success rates were also similar in women and men and post-PCI in-trial care did not differ. Still, women were at higher risk of adverse outcomes including the primary composite, death and class IV HF. In the setting of high PCI success rates and very high utilization of evidence-based post-MI medications, female sex was not an independent predictor of death after adjustment for age. This differs from a prior analysis of a large French database,¹⁶ likely due to more uniform treatment of women and men in OAT and the highly selected nature of this clinical trial population. Our data support the results of the most recent studies demonstrating similar adjusted outcome for women and men with CAD.⁴

The outcome of HF is of particular interest because prior studies have shown excess risk of HF in women, including on multivariate analysis.^{1, 17, 18–20} Women enrolled in OAT were more likely to have class IV HF. Dyspnea was more common among women in the quality of life substudy at all time points. Unfortunately, the limited sample size in this substudy does not permit comparison of symptom reporting with outcomes. The high frequency of confirmation of class IV HF in women, even higher than that among men, would suggest that differences in symptom reporting were not the cause of excess HF events among women.

Female sex was an independent predictor of class IV HF when creatinine was included in the multivariate model but this relationship was blunted when estimated GFR was included and did not meet trial criteria for significance. Inclusion of eGFR in multivariate models did not change the relationship between age and outcomes, arguing against over-adjustment by inclusion of eGFR.¹¹ These findings underscore the importance of using eGFR as the indicator of renal function for multivariate analyses. A higher adjusted risk of HF for women after STEMI has been shown previously in several studies^{1,17-19} but notably not in the VALIANT study, which was the only one of these reports to include eGFR in the multivariate model.²⁰ This may suggest that higher risk of HF in women after MI is mediated largely by poorer renal function in women who develop MI as compared to men. Diastolic function is another possible link, particularly considering that >40% of patients who developed class IV HF in both sexes had post-MI LVEF >45%. Women may be at higher risk for HF due to a stronger relationship between increasing vascular load and slower myocardial relaxation velocities²¹ as well as smaller LV volumes.²²

Limitations

Our analysis is limited by the small proportion of women in OAT and the highly selected nature of this clinical trial population. However, women enrolled in OAT were representative of women eligible for the trial based on comparison with the registry. EF at the time of heart failure event was not recorded on study forms.

Conclusions

Women made up a smaller proportion of the OAT cohort than of patients with MI screened at OAT sites during the trial, likely related to selection of patients for angiography. Rates of use of evidence-based medical therapy within the trial were high, with no sex differences. In this context, there was no independent effect of sex on the primary endpoint, mortality or reinfarction with a trend toward an independent association between female sex and class IV HF. Higher mortality among women was due primarily to older age at presentation. Our findings confirm a higher rate of HF in women vs. men despite state-of-the-art management of established CAD which is not due to age alone and appears to be mediated largely by poorer renal function. Further research is needed to elucidate factors related to heart failure presentation in post-MI women.

Acknowledgments

Disclosures

Dr Hochman: grant support to her institution from Eli Lilly and Bristol Myers Squibb Medical Imaging and product donation from Millennium Pharmaceuticals, Schering-Plough, Guidant, and Merck for OAT. Consultation fees from Bristol Myers Squibb, honoraria for Steering Committee service from CV Therapeutics, Eli Lilly and Glaxo Smith Kline and honoraria for serving on the Data Safety Monitoring Board of a trial supported by Schering-Plough.

Dr. Mark: grant support from Medtronic, Inc. Modest ownership interest in GDS. Consultant for CVT and Astra-Zeneca.

Dr. Steg: research support from Sanofi-Aventis. Speaker for Boehringer-Ingelheim, BMS, GSK, Medtronic, Nycomed, Sanofi-Aventis and Servier. Advisory board for Astellas, AstraZeneca, Bayer, Boehringer-Ingelheim, BMS, Endotis, GSK, Medtronic, MSD, Nycomed, Sanofi-Aventis, Servier and The Medicines Company.

Funding Sources: OAT was supported by grants (U01 HL062509, U01 HL062511, U01 HL062257) from the NHLBI, National Institutes of Health.

References

1. Reynolds HR, Farkouh ME, Lincoff AM, et al. Impact of female sex on death and bleeding after fibrinolytic treatment of MI in GUSTO V. *Arch Intern Med.* 2007; 167:2054–2060. [PubMed: 17954798]
2. Maynard C, Litwin PE, Martin JS, et al. Gender differences in the treatment and outcome of acute myocardial infarction. Results from the MI Triage and Intervention Registry. *Arch Intern Med.* 1992; 152:972–976. [PubMed: 1580724]
3. Vaccarino V, Krumholz HM, Yarzebski J, et al. Sex differences in 2-year mortality after hospital discharge for MI. *Ann Intern Med.* 2001; 134:173–181. [PubMed: 11177329]
4. Berger JS, Elliott L, Gallup D, et al. Sex differences in mortality following acute coronary syndromes. *JAMA.* 2009; 302:874–882. [PubMed: 19706861]
5. Cohen M, Gensini GF, Maritz F, et al. The role of gender and other factors as predictors of not receiving reperfusion therapy and of outcome in ST-segment elevation MI. *J Thromb Thrombolysis.* 2005; 19:155–161. [PubMed: 16082602]
6. Nallamothu BK, Blaney ME, Morris SM, et al. Acute reperfusion therapy in ST-elevation MI from 1994–2003. *Am J Med.* 2007; 120:693–699. [PubMed: 17679128]
7. Hochman JS, Lamas GA, Knatterud GL, et al. Design and methodology of the Occluded Artery Trial (OAT). *Am Heart J.* 2005; 150:627–642. [PubMed: 16209957]
8. Hochman JS, Reynolds H, Džavík V, et al. Long term effects of percutaneous coronary intervention of the totally occluded infarct-related artery in the subacute phase after MI. *Circulation.* 2011; 124:2320–2328. [PubMed: 22025606]
9. Buller CE, Mancini G, Dzavik V, et al. PCI Failure in the Occluded Artery Trial (OAT): Frequency, Mechanisms, and Outcome. *Circulation.* 2007;II–416.
10. Skolnick, ADV.; Menon, V.; Liu, L., et al. *AJC.* 2011. Comparison of Late Results of Percutaneous Coronary Intervention Among Stable Patients ? 65 vs. >65 Years of Age With An Occluded Infarct Related Artery (From The Occluded Artery Trial). In Press
11. Dzavik V, Buller CE, Lamas GA, et al. Randomized trial of percutaneous coronary intervention for subacute infarct-related coronary artery occlusion to achieve long-term patency and improve ventricular function: the Total Occlusion Study of Canada (TOSCA)-2 trial. *Circulation.* 2006; 114:2449–2457. [PubMed: 17105848]
12. Udelson JEPC, Peart CA, Kimmelstiel CD, et al. The Occluded Artery Trial (OAT) Viability Ancillary Study (OAT-NUC): Influence of Infarct Zone Viability on Left Ventricular Remodeling After Percutaneous Coronary Intervention versus Medical Therapy Alone. *Am Heart J.* 2001; 161:611–621. [PubMed: 21392619]
13. Zijlstra F, Patel A, Jones M, et al. Clinical characteristics and outcome of patients with early (<2 h), intermediate (2–4 h) and late (>4 h) presentation treated by primary coronary angioplasty or thrombolytic therapy for acute MI. *Eur Heart J.* 2002; 23:550–557. [PubMed: 11922645]
14. French WJ. Trends in acute MI management: use of the national registry of MI in quality improvement. *Am J Cardiol.* 2000; 85:5–9.
15. Bertoni AG, Bonds DE, Lovato J, et al. Sex disparities in procedure use for acute MI in the United States, 1995 to 2001. *Am Heart J.* 2004; 147:1054–1060. [PubMed: 15199355]
16. Milcent C, Dormont B, Durand-Zaleski I, et al. Gender Differences in Hospital Mortality and Use of Percutaneous Coronary Intervention in Acute MI: Microsimulation Analysis of the 1999 Nationwide French Hospitals Database. *Circulation.* 2007; 115:833–839. [PubMed: 17309933]
17. Weaver WD, White HD, Wilcox RG, et al. Comparisons of characteristics and outcomes among women and men with acute MI treated with thrombolytic therapy. GUSTO-I investigators. *JAMA.* 1996; 275:777–782. [PubMed: 8598594]
18. Heer T, Schiele R, Schneider S, et al. Gender differences in acute MI in the era of reperfusion (the MITRA registry). *Am J Cardiol.* 2002; 89:511–517. [PubMed: 11867033]
19. Srichaiveth B, Ruengsakulrach P, Visudharom K, et al. Impact of gender on treatment and clinical outcomes in acute ST elevation MI patients in Thailand. *J Med Assoc Thai.* 2007; 90(Suppl 1):65–73. [PubMed: 18431888]

20. Lewis EF, Velazquez EJ, Solomon SD, et al. Predictors of the first heart failure hospitalization in patients who are stable survivors of MI complicated by pulmonary congestion and/or left ventricular dysfunction: a VALIANT study. *Eur Heart J*. 2008; 29:748–756. [PubMed: 18308687]
21. Shim CY, Park S, Choi D, et al. Sex differences in central hemodynamics and their relationship to left ventricular diastolic function. *J Am Coll Cardiol*. 2011; 57:1226–1233. [PubMed: 21371640]
22. Chung AK, Das SR, Leonard D, et al. Women Have Higher Left Ventricular Ejection Fractions Than Men Independent of Differences in Left Ventricular Volume: The Dallas Heart Study. *Circulation*. 2006; 113:1597–1604. [PubMed: 16567580]

1a. Primary endpoint

1c. Reinfarction

Figure 1.
Kaplan-Meier analysis of the composite primary endpoint and its components, by sex.
(a) Primary endpoint
(b) Death
(c) Reinfarction
(d) Class IV heart failure

Table 1

Baseline Characteristics among Women and Men enrolled in the Occluded Artery Trial

Characteristics	Women N=484	Men N=1717	P Value
Age (years)	63.5±11.2	57.2±10.5	<0.0001
Age >65	226 (46.7)	415 (26.2)	
Non-white race	94/484 (19.4)	344/1717 (20.0)	0.77
History			
<i>Diabetes</i>	143/484 (29.5)	311/1717 (18.1)	< 0.0001
<i>Hypertension</i>	305/484 (63.0)	766/1717 (44.6)	< 0.0001
<i>Hypercholesterolemia</i>	268/484 (55.4)	874/1716 (50.9)	0.08
<i>Family History</i>	202/484 (41.7)	681/1717 (39.7)	0.41
<i>Current Smoker</i>	129/484 (26.7)	730/1717 (42.5)	< 0.0001
<i>Prior MI</i>	38/484 (7.9)	209/1717 (12.2)	0.008
<i>Prior Angina</i>	113/484 (23.3)	382/1717 (22.2)	0.61
<i>Prior PCI</i>	20/484 (4.1)	85/1717 (5.0)	0.46
<i>Prior Heart Failure</i>	20/483 (4.1)	32/1716 (1.9)	0.004
Days from MI to randomization – median (IQR)	8.5 (5.0,17.0)	8.0 (5.0,16.0)	0.90
NYHA class II–IV	131/483 (27.1)	328/1717 (19.1)	0.0001
ST segment elevation	320/467 (68.5)	1096/1669 (65.7)	0.25
New Q Waves	296/484 (61.2)	1179/1717 (68.7)	0.002
Rales	42/484 (8.7)	95/1713 (5.5)	0.01
HR (bpm)	73.7±11.8	71.2±11.9	< 0.0001
Systolic BP (mmHg)	122.7±19.5	120.3±17.5	0.01
Diastolic BP (mmHg)	70.9±12.3	72.7±11.0	0.001
BMI	28.9±6.0	28.4±4.6	0.03
LAD infarct artery	202/484 (41.7)	591/1717 (34.4)	0.003
Multivessel disease	72/484 (14.9)	307/1699 (18.1)	0.10
Collateral vessels present	430/480 (89.6)	1492/1693 (88.1)	0.38
EF	47.9±11.8	47.7±10.9	0.69
EF ≤50	223/483 (46.2%)	792/1702 (46.5%)	0.89
Estimated Glomerular Filtration Rate (ml/min)	73.0±22.0	82.8±20.9	<0.0001
Fasting Glucose (mg/dl)	127.8±48.2	117.6±39.8	<0.0001
Baseline HF factors	188/484 (38.8)	509/1717 (29.6)	0.0001

Values are mean±SD for continuous variables unless otherwise indicated, or n (%). BMI=Body Mass Index; BP=Blood Pressure, EF=ejection fraction, HF=heart failure; HR=Heart Rate IQR=Interquartile Range LAD=Left Anterior Descending coronary artery NYHA=New York Heart Association PCI=Percutaneous Coronary Intervention

Table 2

Medication use by sex at discharge.

	Women (n=484)	Men (n=1717)	P value
Aspirin	460 (95.0)	1645 (95.8)	0.47
Thienopyridine (Clopidogrel or ticlopidine)	294 (60.7)	1035 (60.3)	0.85
Warfarin	48 (9.9)	167 (9.7)	0.90
IV Gp IIb/IIIa antagonist	4 (0.8)	14(0.8)	0.98
Beta blocker	421(87.0)	1511 (88.0)	0.55
ACE-I or ARB	399 (82.4)	1372 (79.9)	0.22
Lipid lowering agent	385 (79.5)	1403 (81.7)	0.28
Long acting nitrate	138 (28.5)	360 (21.0)	0.0005
Calcium channel blocker	40 (8.3)	89 (5.2)	0.01
Diuretic	122 (25.2)	249 (14.5)	<0.0001
Spirolactone	32 (6.6)	92 (5.4)	0.29
Digoxin	18 (3.7)	43 (2.5)	0.15
Anti-arrhythmic	18 (3.7)	66 (3.8)	0.90
Insulin	47 (9.7)	90 (5.2)	0.0003
Oral Hypoglycemic	92 (19.0)	206 (12.0)	<0.0001
Thrombolytic	89 (18.4)	335 (19.5)	0.58

Medications differing by treatment assignment in each sex: Women: thienopyridines (93.0% PCI vs. 28.5% MED, $p<0.0001$), long acting nitrates (21.9% PCI vs. 35.1% MED, $p=0.001$) and lipid lowering agents (74.4% vs. 84.7%, $p=0.005$). Men: aspirin (97.3% PCI vs. 94.3% MED, $p=0.002$), thienopyridines (90.2% vs. 30.3%, $p<0.0001$), warfarin (7.1% vs. 12.4%, $p=0.002$) and long acting nitrates (18.2% vs. 23.8%, $p=0.004$).

Table 3

Seven-year life table event rates by sex and treatment assignment in OAT

	Primary	Death	MI	Death or MI	HF Class IV
Women (n=484)	27.1	18.2	7.7	23.6	9.3
Men (n=1717)	21.3	14.5	7.4	20.2	4.2
<i>P</i> (W vs. M)	<0.001	0.001	0.57	0.007	<0.001
W PCI (n=242)	25.5	16.4	6.6	21.5	9.2
W MED (n=242)	28.6	20.0	8.7	25.5	9.3
<i>P</i> (W PCI vs. W MED)	0.58	0.43	0.22	0.35	0.92
M PCI (n=859)	21.3	14.1	8.0	20.3	4.1
M MED (n=858)	21.3	14.9	6.7	20.2	4.3
<i>P</i> (M PCI vs. M MED)	0.26	0.79	0.05	0.15	0.79
Interaction p (trt*sex, adjusted)	0.29	0.44	0.05	0.13	0.81

Table 4

Rates of different types of reinfarction based on the universal definition of myocardial infarction, by sex and treatment assignment.

	Female (n=484)				Male (n=1717)				P (Male vs. Female)	Interaction p
	Total	PCI (n=242)	MED (n=242)	P (PCI vs. MED)	Total	PCI (n=859)	MED (n=858)	P (PCI vs. MED)		
Type 1 – Spontaneous	27 (5.6%)	7 (2.9%)	20 (8.3%)	0.01	79 (4.6%)	39 (4.5%)	40 (4.7%)	0.90	0.38	0.03
Type 2 – Secondary	2 (0.4%)	2 (0.8%)	0 (0%)	0.16	5 (0.3%)	4 (0.5%)	1 (0.1%)	0.18	0.67	0.49
Type 3 – Sudden death	2 (0.4%)	2 (0.8%)	0 (0%)	0.16	10 (0.6%)	5 (0.6%)	5 (0.6%)	1.00	0.66	0.19
Type 4 – PCI or Stent-related	9 (1.9%)	8 (3.3%)	1 (0.4)	0.20	34 (2.0%)	28 (3.3%)	6 (0.7%)	0.0001	0.87	0.64
Type 5 – CABG-related	1 (0.2%)	0 (0%)	1 (0.4%)	0.32	0 (0%)	0 (0%)	0 (0%)	null	0.06	n/a

27 additional reinfarction events met criteria for reinfarction using the universal definition of MI as compared to the OAT reinfarction definition²⁴, these are included in this table.

Table 5

Angina during follow up by sex and treatment assignment.

Time	Female (n=484)			Male (n=1717)		
	PCI (n=242)	MED (n=242)	p value	PCI (n=859)	MED (n=858)	p value
4months	37/225 (16.4)	63/234 (26.9)	0.007	155/805 (19.3)	198/808 (24.5)	0.01
1year	38/222 (17.1)	56/223 (25.1)	0.04	127/788 (16.1)	163/783 (20.8)	0.02
2years	38/204 (18.6)	33/199 (16.6)	0.59	94/748 (12.6)	132/749 (17.6)	0.006
3years	23/188 (12.2)	27/180 (15.0)	0.44	65/677 (9.6)	90/697 (12.9)	0.05
4years	25/165 (15.2)	24/162 (14.8)	0.93	73/603 (12.1)	82/628 (13.1)	0.62
5 years	12/132 (9.1)	18/131 (13.7)	0.24	61/539 (11.3)	79/531 (14.9)	0.08
6 years	10/79 (12.7)	8/87 (9.2)	0.47	33/352 (9.4)	50/350 (14.3)	0.04
7 years	3/53 (5.7)	3/46 (6.5)	0.86	23/224 (10.3)	26/207 (12.6)	0.45
8 years	3/27 (11.1)	0/23 (0)	0.10	13/126 (10.3)	10/109 (9.2)	0.77

Table 6

Rose angina, Rose dyspnea and selected quality of life measurements by sex in the quality of life substudy.

Variable	Time	FEMALE (n=206)	MALE (n=745)	P value
		Mean $\pm$ SD Or %	Mean $\pm$ SD Or %	
Working Status:				
unemployed	Baseline (n=951)	72.3%	42.5%	<.0001
	4 months (n=940)	79.6%	48.3%	<.0001
	1 year(n=910)	79.1%	47.9%	<.0001
	2 years (n=885)	80.6%	49.3%	<.0001
	5 years (n=765)	81.3%	54.1%	<.0001
Working status:				
unemployed, among those employed at baseline				
	4 months (n=940)	28.8%	16.0%	<.0001
	1 year(n=910)	34.5%	18.8%	<.0001
	2 years (n=885)	37.0%	19.6%	<.0001
	5 years (n=765)	35.2%	19.3%	<.0001
SF-Mental health Normal bases	Baseline (n=951)	48.7 $\pm$ 10.9	49.2 $\pm$ 10.8	0.52
	4 months (n=940)	75.7 $\pm$ 17.3	76.7 $\pm$ 19	0.19
	1 year (n=910)	74.3 $\pm$ 18	78.0 $\pm$ 18.8	0.004
	2 years (n=885)	76.6 $\pm$ 17.6	78.1 $\pm$ 17.6	0.20
	5 years (n=765)	76.3 $\pm$ 18.2	77.6 $\pm$ 18.2	0.40
Scale:State of Health in the Past Month	Baseline (n=951)	70.0 $\pm$ 22.5	74.3 $\pm$ 20.1	0.03
	4 months (n=940)	75.5 $\pm$ 17.9	76.8 $\pm$ 18.9	0.22
	1 year (n=910)	76.0 $\pm$ 18.6	78.6 $\pm$ 17.5	0.14
	2 years (n=885)	74.2 $\pm$ 20.8	78.7 $\pm$ 17.2	0.04
	5 years (n=765)	76.0 $\pm$ 16.7	77.9 $\pm$ 18.0	0.13
DASI Composite Score	Baseline (n=951)	28.2 $\pm$ 19.6	39.0 $\pm$ 19.0	<.0001
	4 months (n=940)	26.6 $\pm$ 18.5	37.3 $\pm$ 18.9	<.0001
	1 year(n=910)	27.6 $\pm$ 19.7	38.8 $\pm$ 19.5	<.0001
	2 years (n=885)	28.4 $\pm$ 19.8	38.2 $\pm$ 19.4	<.0001
	5 years (n=765)	27.0 $\pm$ 19.8	38.1 $\pm$ 19.0	<.0001
Rose angina during last month	Baseline (n=951)	30.6%	25.5%	0.17
	4 months (n=940)	13.8%	13.4%	0.88
	1 year (n=910)	17.4%	9.9%	0.007
	2 years (n=885)	9.6%	9.5%	0.96
	5 years (n=765)	3.5%	7.6%	0.12
Rose Dyspnea	Baseline (n=951)	61.1%	43.6%	<.0001

Variable	Time	FEMALE (n=206)	MALE (n=745)	P value
		Mean $\pm$ SD Or %	Mean $\pm$ SD Or %	
	4 months (n=940)	48.8%	32.5%	<.0001
	1 year (n=910)	55.3%	30.2%	<.0001
	2 years (n=885)	49.7%	27.3%	<.0001
	5 years (n=765)	37.3%	25.4%	0.01