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## Electrophysiological Effects of Late Percutaneous Coronary Intervention for Infarct-Related Coronary Artery Occlusion. The Occluded Artery Trial - Electrophysiological Mechanisms (OAT-EP)

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### Abstract

**Background**—OAT-EP tested the hypothesis that opening a persistently occluded infarct-related artery (IRA) by percutaneous coronary intervention and stenting (PCI) after the acute phase of myocardial infarction (MI) compared to optimal medical therapy alone (MED) reduces markers of vulnerability to ventricular arrhythmias.

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Electrophysiological Effects of Late Percutaneous Coronary Intervention for Infarct-Related Coronary Artery Occlusion. The Occluded Artery Trial - Electrophysiological Mechanisms (OAT-EP)

The “late open artery hypothesis” posits that clinical outcomes can be improved by late opening of persistently occluded infarct-related arteries (IRAs) during the subacute phase of myocardial infarction (MI), when myocardial salvage is not anticipated. Several mechanisms have been proposed for the putative benefit of late reperfusion, including stabilization of the electrophysiological substrate and downstream prevention of malignant ventricular arrhythmias. This ancillary study of the Occluded Artery Trial evaluated the effects of late opening and stenting of an occluded infarct artery on several noninvasive measures of electrophysiologic stability during the first year after MI. Heart rate variability (HRV), assessing the autonomic nervous system, was the primary measure. Major secondary measures evaluated repolarization (dynamic changes in T wave morphology, or T wave variability (TWV)) and delayed myocardial conduction (filtered QRS duration (fQRS) on the signal averaged ECG). Compared to medical therapy alone, late reperfusion and stenting of a persistently occluded IRA did not change HRV, fQRS, or TWV during the first year after MI. These results are consistent with the lack of clinical benefit, including no reduction in sudden death, with PCI for stable patients with persistently occluded IRAs after MI in the main Occluded Artery Trial.

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**Methods and Results**—Between April 2003 and December 2005, 300 patients with an occluded native IRA 3 to 28 days after MI (median 12 days) were randomized to PCI or MED. Ten minute digital Holter recordings were obtained prior to randomization, at 30 days, and at one year. The primary endpoint was the change in  $\alpha 1$ , a nonlinear heart rate variability parameter, between baseline and one year. Major secondary endpoints were the changes in the filtered QRS (fQRS) duration on the signal-averaged ECG (SAECG), and variability in T wave morphology (T wave variability, TWV) between baseline and one year. There were no significant differences in the changes in  $\alpha 1$  [-0.04 (-0.12, 0.04)], fQRS [3.0 ms (-4.8 ms, 10.7 ms)], or TWV [2.2  $\mu$ V (-1.4  $\mu$ V, 5.9  $\mu$ V)] between the PCI and MED groups (MED change - PCI change, 95% CI). Multivariable analysis revealed that the results were unchanged after adjustment for baseline clinical variables and medication treatments during the Holter recordings.

**Conclusions**—PCI with stenting of a persistently occluded IRA during the subacute phase after MI compared to medical therapy alone had no significant effect on changes in heart rate variability, the time-domain SAECG, or TWV during the first year after MI. These findings are consistent with the lack of clinical benefit, including no reduction in sudden death, with PCI for stable patients with persistently occluded IRAs after MI in the main Occluded Artery Trial.

### Keywords

myocardial infarction; arrhythmia; artery occlusion; stents; sudden death

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Early coronary reperfusion using either thrombolytics or primary percutaneous coronary intervention (PCI) reduces long-term mortality in patients who present with ST-segment elevation myocardial infarction (MI).<sup>1</sup> Early coronary reperfusion has been correlated with increased heart rate variability and a decreased incidence of late potentials, suggesting that at least part of the clinical benefit of early reperfusion is explained by a decreased vulnerability to ventricular arrhythmias.<sup>2,3</sup> However, up to one third of eligible patients do not receive effective early reperfusion due to such factors as late presentation or lack of efficacy of thrombolytics.<sup>3,4</sup>

The “late open artery hypothesis” posits that clinical outcomes can be improved by late opening of persistently occluded infarct-related arteries (IRAs) during the subacute phase of MI, when myocardial salvage is not anticipated.<sup>5</sup> Several mechanisms have been proposed to account for the putative benefit of late reperfusion, including stabilization of the electrophysiological substrate and downstream prevention of malignant ventricular arrhythmias. Although experimental studies have suggested that late reperfusion decreases arrhythmic events,<sup>6</sup> clinical studies that have examined this question have been limited by small sample size, lack of treatment randomization, and technical factors such as lack of stenting that limited sustained vessel patency after PCI.<sup>7,8</sup>

The Occluded Artery Trial (OAT) was an international randomized trial funded by the National Heart Lung and Blood Institute (NHLBI) that tested the hypothesis that PCI and stenting of occluded IRAs identified on days 3 to 28 after MI compared to medical therapy alone would reduce the combined incidence of death, recurrent MI, and New York Heart Association Class IV heart failure.<sup>9</sup> OAT-EP, also funded by the NHLBI, is a mechanistic ancillary study of OAT. The primary aim of OAT-EP was to test the hypothesis that PCI plus optimal medical therapy would result in a greater increase in heart rate variability (HRV) during the first year after MI than optimal medical therapy alone. Major secondary aims were to test the hypotheses that PCI would reduce dynamic changes in T wave morphology, or T wave variability (TWV) and filtered QRS duration (fQRS) on the signal averaged ECG (SAECG) at one year after MI.

## Methods

### Study Design

OAT-EP enrolled participants between April 2003 and December 2005 at 36 of 216 OAT sites with separate Institutional Review Board approval from OAT (see Appendix for the list of participating centers). OAT-EP patients were OAT participants who provided additional informed consent. Randomization to PCI and stenting plus optimal medical therapy (PCI) or optimal medical therapy alone (MED) was done using the same randomization process as for other OAT participants.

### Patient Sample

Eligibility criteria for OAT-EP mirror those of OAT.<sup>9</sup> Patients had a documented MI and underwent cardiac catheterization within 3 to 28 days; day 1 was the date of symptom onset, hence the minimum interval between symptom onset and the qualifying cardiac catheterization study was 24 hours. Angiographic criteria included IRA occlusion judged suitable for stenting and at least one high risk criterion: proximal coronary occlusion subtending at least 25% of the left ventricle, or left ventricular ejection fraction < 50%. IRA occlusion was defined as 100% stenosis with Thrombolysis In Myocardial Infarction (TIMI) grade 0 or 1 antegrade flow. Patients with clinical instability, left main or 3-vessel disease, or severe inducible ischemia were excluded. OAT-EP patients were also required to be in sinus rhythm so that HRV and TWV could be measured,<sup>10,11</sup> and to have a QRS duration < 120 ms so that the time domain SAECG could be performed.<sup>12</sup>

### Study Procedures

OAT-EP participants gave informed consent for participation prior to OAT randomization to minimize selection bias for participation in the ancillary study. Patients assigned to PCI were to undergo the procedure within 24 hours of randomization whenever possible. Ten-minute digital Holter monitor recordings were performed prior to randomization, at 30 days, and at one year using a Burdick 92510 recorder (Spacelabs-Burdick, Deerfield, WI). The recordings were performed using Frank leads (X, Y, Z) at a sampling rate of 1000 Hz with the patient lying quietly in the supine position. The digital Holter data were stored on PC cards, which were shipped to the Holter Core Laboratory at the University of Maryland for downloading and analysis. The OAT-EP core lab personnel were blinded with respect to the OAT treatment randomization (PCI vs. MED). The Holter data were manually edited to eliminate ectopic beats and signal noise, then analyzed for the fractal scaling exponent ( $\alpha 1$ ), time and frequency domain HRV parameters, the time domain SAECG, and T wave variability (TWV) as previously described.<sup>10-15</sup> The SAECGs were acquired in accordance with the published recommendations for recording conditions, lead placement, sampling rate, and signal filtering.<sup>16</sup> The analysis of  $\alpha 1$  and TWV was conducted at the University of Rochester. Recordings were excluded from HRV analysis if the prevalence of ectopic beats or noisy segments exceeded 25%, from SAECG analysis if the noise level was > 1  $\mu$ V, and from TWV analysis if the heart rate was unstable or if excessive ectopy or noise was present.<sup>10-12</sup>

### Study Endpoints

The primary study endpoint was the change in  $\alpha 1$  at one year. Major secondary endpoints were the changes in fQRS and TWV at one year. These study endpoints were chosen to fully characterize the effects of PCI of occluded IRAs on the major determinants of arrhythmia vulnerability: the autonomic nervous system (HRV), impulse conduction (SAECG), and ventricular repolarization (TWV). The primary endpoint ( $\alpha 1$ ) was chosen because its prognostic value is superior to other HRV variables in post-myocardial infarction patient populations with clinical characteristics similar to those of OAT.<sup>13-15</sup> Similarly, fQRS was

chosen because it is prognostically the most important SAECG variable,<sup>12</sup> while TWV has prognostic value in high-risk patients with coronary artery disease.<sup>11</sup>

Other secondary variables included standard time domain (RR interval, SDNN, SDANN, rMSSD, pNN50) and frequency domain (total power, VLF, LF, HF, LF/HF ratio) HRV variables, and other time domain SAECG variables (LAS, RMS40).<sup>10,12</sup>

### Statistical Analysis

An intention-to-treat principle was used for the primary treatment-related analyses. The primary endpoint ( $\alpha 1$ ) was evaluated with  $\alpha=0.05$  for a 2-sided *t*-test comparing change in  $\alpha 1$  from baseline to one year between the 2 treatment groups. As in the main OAT trial, a *p* value of 0.01 for secondary analyses was considered strong evidence of association. Changes in  $\alpha 1$  were normally distributed and suitable for the *t*-test. Changes in TWV and fQRS were not normally distributed, and were winsorized then analyzed with the *t*-test. Winsorization is a method to control the variability introduced by extreme values. This method typically identifies the top and bottom 5% and reduces them to the next highest (or lowest) value. This method permits the use of procedures that require a normal distribution (i.e. multiple regression), while controlling the influence of these extreme values.<sup>17</sup>

The planned sample size of 300 subjects was chosen to provide 80% power to detect a clinically relevant difference of 0.1 in the change in  $\alpha 1$  from baseline to one year between the 2 treatment groups, based on data from prior studies that indicated that baseline levels of  $\alpha 1$  would be 1.0 with a common SD of 0.2.<sup>13-15</sup> Because this outcome is a measure of longitudinal change, the correlation between the measurements at baseline and one year must be taken into account. We assumed that the standard deviation in the change in  $\alpha 1$  would be between 0.28 (for a correlation ( $\rho$ ) of 0) and 0.169 (for  $\rho=0.65$ ) and that the standard deviation of  $\alpha 1$  would be the same at baseline and 1 year. Based on these assumptions, the study would have 80% power or more to detect a difference in  $\alpha 1$  of 0.14 units ( $\rho=0$ ) to 0.083 ( $\rho=0.65$ ) between the PCI and MED patients. This calculation assumed a crossover rate of 25% (PCI in MED patients within 30 days of randomization and no attempt at PCI or failed PCI, which are biological crossovers, in the PCI-assigned patients), and a 15% loss to follow-up.

The analyses were repeated for time domain and frequency domain HRV variables, and for other time domain signal averaged ECG variables. A secondary analysis was conducted using unpaired *t* tests to determine if the study results were affected by inclusion of additional patients who were excluded due to lack of complete baseline and follow-up information. Secondary analyses of the primary and major secondary endpoints were also performed after excluding crossovers (“as treated” analysis). Other secondary analyses assessed the changes in the primary and major secondary endpoints at 30 days. A sensitivity analysis was conducted because recurrent MI during the year between the Holter measurements could affect changes in arrhythmia marker values. For this analysis, patients with recurrent MI were excluded from the analysis of changes in  $\alpha 1$ , fQRS, and TWV between baseline and one year.

For multivariable models, we used stepwise linear regression with backward elimination, with a *p* value of 0.05 required for a variable to be retained in the model. Separate multivariable models were constructed for the change in each arrhythmia marker variable between baseline and one year. The pre-specified variables tested in each stepwise model were treatment group (PCI vs. MED), age, sex, race (white vs non-white), prior MI, interval between qualifying MI and the Holter recording, baseline values of the arrhythmia marker variable, hypertension, diabetes, multivessel disease, collateral arteries, baseline left ventricular ejection fraction, left anterior descending coronary artery culprit, thrombolytics, ST elevation or new Q waves on ECG, beta blocker use at baseline and one year, and angiotensin converting enzyme use at baseline and one year. Since the models of change in  $\alpha 1$ , fQRS, and TWV had normally

distributed residuals that exhibited homoscedasticity, these measures were suitable for analysis with linear regression.

In order to ensure that OAT-EP patients are representative of patients in the community with occluded IRAs post-MI, we compared the clinical characteristics of OAT-EP patients with three relevant patient populations: other randomized OAT patients who did not participate in OAT-EP, the OAT pre-trial Registry<sup>18</sup> and the concurrent OAT registry.<sup>19</sup> The variables for these comparisons were age, sex, left ventricular ejection fraction < 50%, and culprit IRA. We also compared long-term outcomes in OAT-EP and other OAT patients to ensure that lower risk patients were not inadvertently selected to participate in OAT-EP. These outcomes included the primary OAT endpoint (death, nonfatal reinfarction, and NYHA class IV heart failure) and its individual components. Kaplan-Meier life table analysis was used to calculate estimated event rates and the log-rank test was used for the comparison of outcomes.

The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

## Results

The target sample of 300 patients was successfully enrolled in OAT-EP, representing 14% of the OAT study population of 2201 patients. There were an additional 157 patients enrolled in OAT, but not OAT-EP, at participating sites; although the precise reasons for exclusion were not tracked, these patients were typically excluded because they did not meet the additional OAT-EP inclusion criteria, refused to consent for OAT-EP, were randomized before the baseline Holter data could be acquired, or were judged to be unlikely to return for the follow-up one year Holter due to distance from the enrolling site.

The observed crossovers were 14 failed PCI and 1 PCI not done in the PCI group (10%) and 4 PCI within 30 days in the MED group (2.6%). The loss to follow-up with reasons for patient attrition is shown in Figure 1. Complete baseline and follow-up data for the primary endpoint ( $\alpha 1$ ) was available at baseline and one year for 79% of the study cohort. Complete data for the major secondary endpoints (fQRS and TWV) was available at baseline and one year for 57% and 69% of patients, respectively. This sample size yielded 80% power to detect a change of 0.1 units in  $\alpha 1$ , 99% power to detect a 10ms change in fQRS, and 91% power to detect a 10  $\mu$ V change in TWV, each of which represents a clinically relevant change.<sup>11-15</sup> More patients were excluded from TWV and fQRS analyses because of excessive signal noise on some recordings, which prohibited performance of these analyses. Data were available at one year for  $\alpha 1$ , fQRS, and TWV for 86%, 76%, and 80% of patients, respectively.

### Baseline Characteristics

The baseline clinical and angiographic characteristics of the PCI and MED groups were similar in most respects, with the exception of a significant difference in the prevalence of diabetes (Tables 1 and 2). There was no significant difference in the time from the qualifying MI to the Holter recording when the PCI and MED groups were compared (13.3 $\pm$ 8.6 days vs. 13.0 $\pm$ 7.8 days respectively). OAT-EP patients were representative of the larger OAT study cohort with respect to most clinical and angiographic characteristics. However, OAT-EP patients had a lower incidence of prior MI, were more likely to be hypertensive, were less likely to have received thrombolytic therapy for the index MI, and had a greater prevalence of multivessel disease (Tables 1 and 2). The patients with and without complete data available for the primary endpoint at baseline and one year had similar baseline demographic characteristics, with the exception of median days between MI and randomization (14 days vs 7 days, respectively).



There were no significant differences between OAT-EP patients and patients in the OAT concurrent Registry with respect to age, sex, and identity of the IRA (data not shown). Patients in the OAT pre-trial Registry were slightly older than OAT-EP patients (62 vs. 57 years) and had fewer men (72% vs. 79%); however, there were no significant differences in the identity of the IRA and left ventricular ejection fraction (data not shown). There were no significant differences in the 3-year OAT primary endpoint event rate (death, nonfatal reinfarction, and NYHA class IV heart failure) or its individual components when OAT-EP and other OAT patients were compared (10.3% vs. 14.3% respectively,  $p=0.16$ ).

### Cardiovascular Medication Use

There were no significant differences between the study groups in cardiovascular medication use during the Holter recordings either at baseline or one year (Table 3). Thienopyridine use was significantly more common in the PCI group at baseline (92% vs 37%).

### Primary Endpoint

There was no significant difference between the MED and PCI groups in the change in  $\alpha 1$  (MED change - PCI change, 95% CI: -0.04 (-0.12, 0.04); Table 4, Figure 2a). On multivariable analysis of the change in  $\alpha 1$ , the treatment group assignment (PCI vs. MED) was still not a significant predictor ( $p=0.31$ ) after adjustment for baseline clinical variables and cardiovascular medication use during the Holter recordings. There was no significant change in  $\alpha 1$  at one year as compared with baseline within the MED or PCI groups (Table 4, Figure 2a).

### Secondary Endpoints

There were no significant differences between the MED and PCI groups in the changes in fQRS or TWV (MED change - PCI change, 95% CI: fQRS [3.0 ms (-4.8 ms, 10.7 ms)], TWV [2.2  $\mu$ V (-1.4  $\mu$ V, 5.9  $\mu$ V)]; Table 4, Figures 2b and 2c). Separate multivariable models were constructed for the change in fQRS and the change in TWV. Treatment group assignment (PCI vs. MED) was still not a significant predictor ( $p=0.14$  for fQRS and  $p=0.89$  for TWV) in either model after adjustment for baseline clinical variables and cardiovascular medication use during the Holter recordings.

There was a small, but significant increase in fQRS within the MED group (Table 4, Figure 2b). No significant changes in fQRS were observed within the PCI group. There was a small, but significant decrease in TWV in the overall study group and within the PCI group (Table 4, Figure 2c). No significant changes in TWV were observed within the MED group.

### Secondary analyses

The analysis of all available data at one year revealed no significant differences in  $\alpha 1$ , fQRS, or TWV ( $\alpha 1$ : 1.07 vs. 1.02,  $p=0.19$ ; fQRS: 113.1 vs. 114.3 ms,  $p=0.55$ ; TWV: 36.4 vs. 36.9  $\mu$ V,  $p=0.84$ ; for PCI and MED groups, respectively). Four patients in the PCI group and one patient in the MED group had recurrent MI before the one-year Holter measurements were performed. A sensitivity analysis revealed that excluding patients with recurrent MI did not alter the primary study results (Changes from baseline to one year in  $\alpha 1$ : 0.00 vs. -0.03,  $p=0.45$ ; fQRS: +1.6 vs. +3.7 ms,  $p=0.26$ ; TWV: -6.7 vs. -3.4  $\mu$ V,  $p=0.40$ ; for PCI and MED groups, respectively). The primary study results were unchanged when the data were analyzed after excluding crossovers within 30 days ("as treated" analysis, changes from baseline to one year in  $\alpha 1$ : 0.00 vs. -0.04,  $p=0.35$ ; fQRS: +2.0 vs. +3.8 ms,  $p=0.35$ ; TWV: -7.0 vs. -2.7  $\mu$ V,  $p=0.29$ ; for PCI and MED groups, respectively). There were no significant differences between the PCI and MED groups in the changes in the primary and major secondary endpoints at 30 days

( $\alpha 1$ : -0.03 vs. -0.05,  $p=0.63$ ; fQRS: -1.4 vs. +0.6 ms,  $p=0.17$ ; TWV: -1.7 vs. -1.0  $\mu\text{V}$ ,  $p=0.88$ ; for PCI and MED groups, respectively).

There were significant increases between baseline and one year in several time domain and frequency domain HRV variables (mean RR, SDNN, pNN50, rMSSD, total power, LF, HF; Table 4). However, there were no significant differences between the PCI and MED groups in the changes in time domain and frequency domain HRV variables, or changes in other time domain signal averaged ECG variables (Table 4).

## Discussion

The major findings of this study are that PCI with stenting of a persistently occluded IRA during the subacute phase after MI compared to medical therapy alone had no significant effect on changes in HRV, the time-domain SAECG, or TWV during the first year after MI. Although late IRA patency was achieved in 83% of OAT patients<sup>20</sup> and at least moderately retained viability was present at baseline in 69%,<sup>9</sup> PCI had no significant effect on changes in the major determinants of arrhythmia vulnerability: the autonomic nervous system (HRV), impulse conduction (SAECG), and ventricular repolarization (TWV).

Several mechanisms have been proposed to explain the presumed benefits of late opening of the IRA, including prevention of ventricular remodeling, improvement of left ventricular function by recovery of hibernating myocardium, and stabilization of the electrophysiological substrate.<sup>5</sup> In an animal model of experimental myocardial infarction, late reperfusion reduced the incidence of arrhythmic death as compared to permanent coronary artery occlusion despite identical infarct size in the two groups.<sup>6</sup> However, clinical studies that examined the effects of balloon angioplasty without adjunctive stenting on arrhythmia markers have yielded conflicting results.<sup>7,8</sup> These studies were limited by small sample sizes, lack of treatment randomization, the use of patients with failed angioplasty as controls, and likely poor long-term vessel patency since stents were not utilized.

The present study is the first large, adequately powered, randomized controlled trial to investigate whether PCI and stenting of occluded coronary arteries late after MI reduces markers of vulnerability to ventricular arrhythmias. We did not observe any significant effect of PCI on changes in HRV ( $\alpha 1$ ), myocardial impulse conduction (fQRS), or ventricular repolarization (TWV) at one year. There was a significant increase in fQRS within the MED group and a significant decrease in TWV within the PCI group. Although these within-group changes could be interpreted as a small benefit of PCI (improvement in TWV within the PCI group, worsening of fQRS within the MED group), these changes were not significantly different when the treatment groups (PCI vs. MED) were compared. Furthermore, the magnitude of these changes was far below the differences that we pre-specified as clinically relevant to detect based on prior outcome data when we calculated the required sample size for the study (10 ms change in fQRS, 10  $\mu\text{V}$  change in TWV).<sup>11,12</sup> The results of OAT-EP are concordant with the results of OAT, which did not suggest an effect of PCI on total mortality, cardiac death, death from arrhythmia, sudden unexplained death or development of sustained VT or need for implantable cardioverter-defibrillator placement.<sup>9</sup>

It is well recognized that traditional time and frequency domain HRV variables change to a greater extent than  $\alpha 1$  after MI.<sup>21</sup> We observed an identical pattern in our study, as  $\alpha 1$  was unchanged but several time and frequency domain HRV variables increased substantially between baseline and one year. Importantly, there were no significant differences between the PCI and MED groups in the changes in any of the study variables. Since we did observe improvement in most HRV variables as well as changes in fQRS and TWV, these data indicate that our study variables were sensitive enough to detect changes in critical electrophysiological

characteristics and that PCI had no effect on these variables. Furthermore, since prior studies indicate that HRV is maximally recovered by one year after MI,<sup>22</sup> it is unlikely that more extended follow-up would have changed our results.

### Study Limitations

Since many OAT-EP centers performed the OAT treatment randomization (PCI vs MED) immediately after the qualifying coronary angiogram, all baseline electrophysiological measures had to be acquired before the angiogram. Long-term Holter recordings and exercise T wave alternans assessment were not feasible since these additional requirements would have delayed the qualifying angiogram and limited enrollment, and because most centers did not have T wave alternans equipment. Although HRV increases with the length of the recording (10 minutes vs 24 hours),<sup>10</sup> the results of short-term recordings correlate well with 24-hour recordings and are suitable for measuring changes over time.<sup>22</sup> Furthermore, the prognostic value of short-term Holter recordings has been demonstrated for traditional HRV parameters and for  $\alpha 1$ .<sup>15,23,24</sup> There is less experience with TWV than T wave alternans, and the precise relation between the two techniques requires further study. However, since TWV was previously demonstrated to have prognostic value in high-risk patients with coronary artery disease in the landmark MADIT-2 trial,<sup>11</sup> it should provide an accurate assessment of ventricular repolarization in OAT-EP patients.

The use of follow-up Holter recordings is subject to bias due to deaths within the first year and difficulty in obtaining follow-up on sicker patients. However, we did not observe any important differences in the baseline clinical characteristics of patients with and without one year data available, which suggests that sicker patients were not excluded. Furthermore, the numbers of patients in the PCI and MED groups who did not have complete data at baseline and one year due to death and other reasons were similar.

While it is possible that OAT-EP patients are not fully representative of patients in the community that meet OAT eligibility criteria, we view this as unlikely given that OAT-EP patients were comparable to patients in the main OAT trial, the OAT pre-trial Registry and the concurrent OAT Registry with respect to most important baseline clinical characteristics. Importantly, long-term outcomes were similar in OAT-EP and other patients in the main OAT trial, suggesting that lower-risk patients were not inadvertently selected to participate in OAT-EP.

### Conclusions

PCI with stenting of a persistently occluded IRA during the subacute phase after MI compared to medical therapy alone had no significant effect on changes in HRV, the time-domain SAECG, or TWV during the first year after MI. Given the absence of clinical benefit in OAT,<sup>9</sup> routine PCI is not recommended for persistent IRA occlusion in stable patients during the subacute phase after MI.

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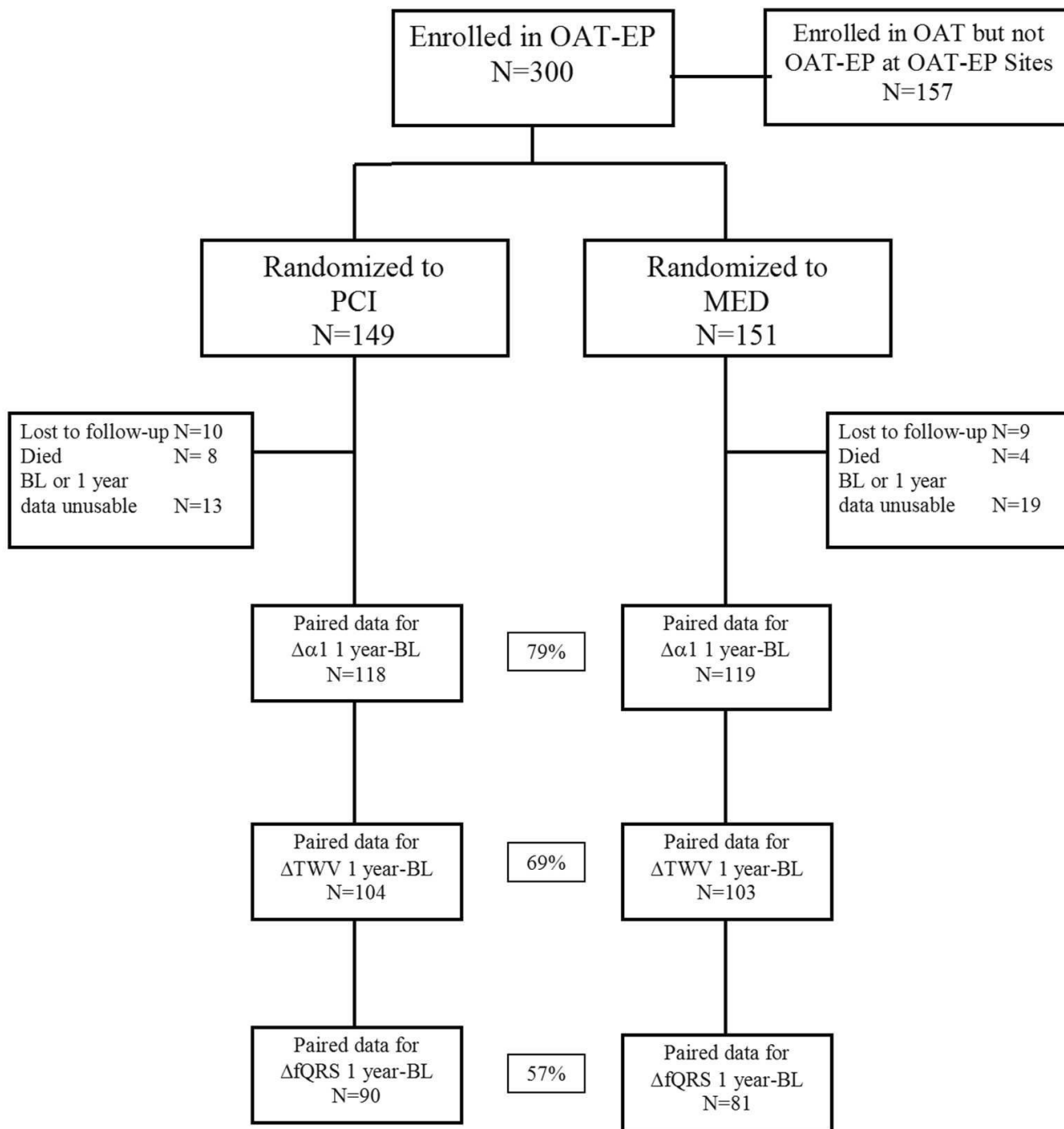
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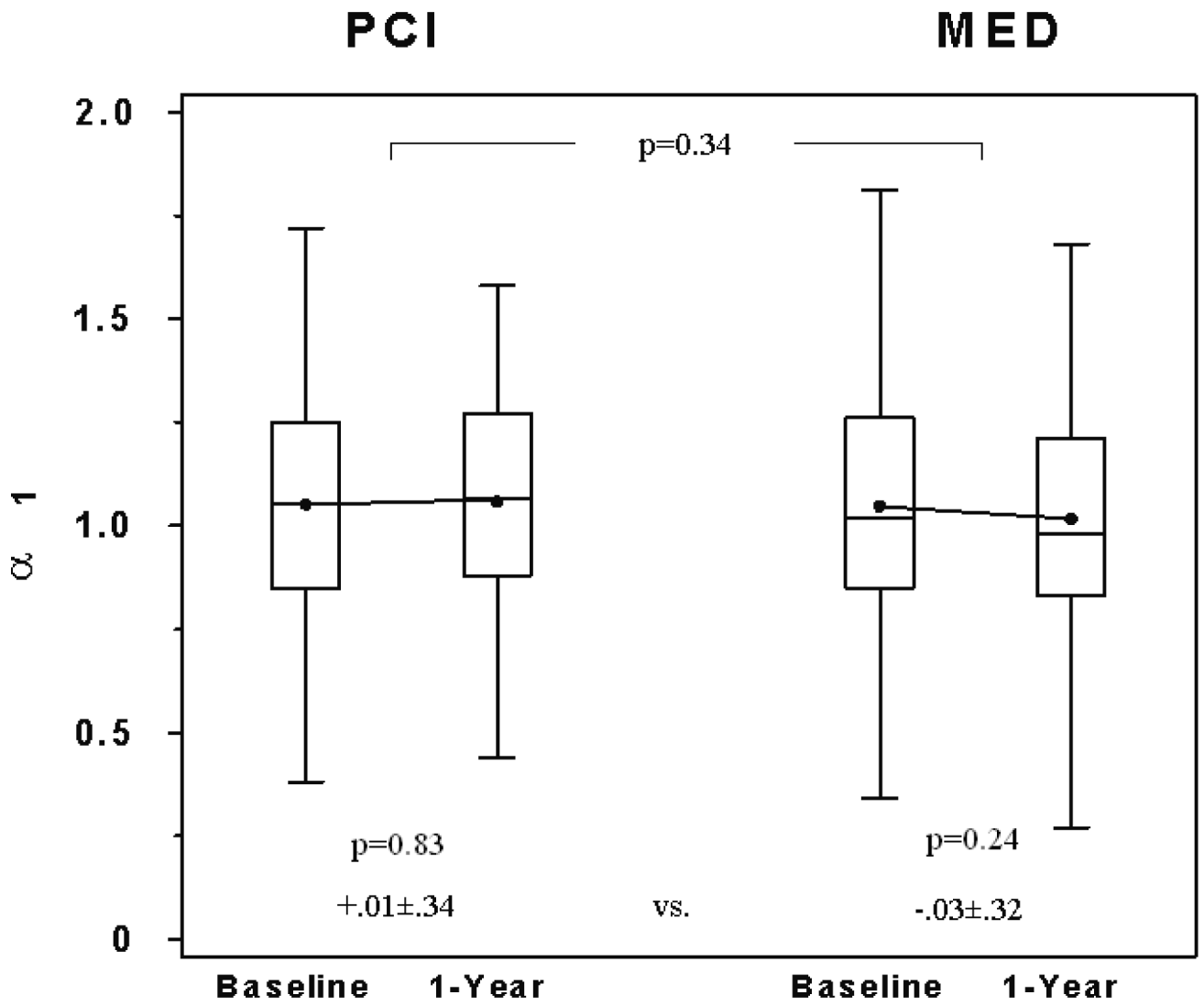
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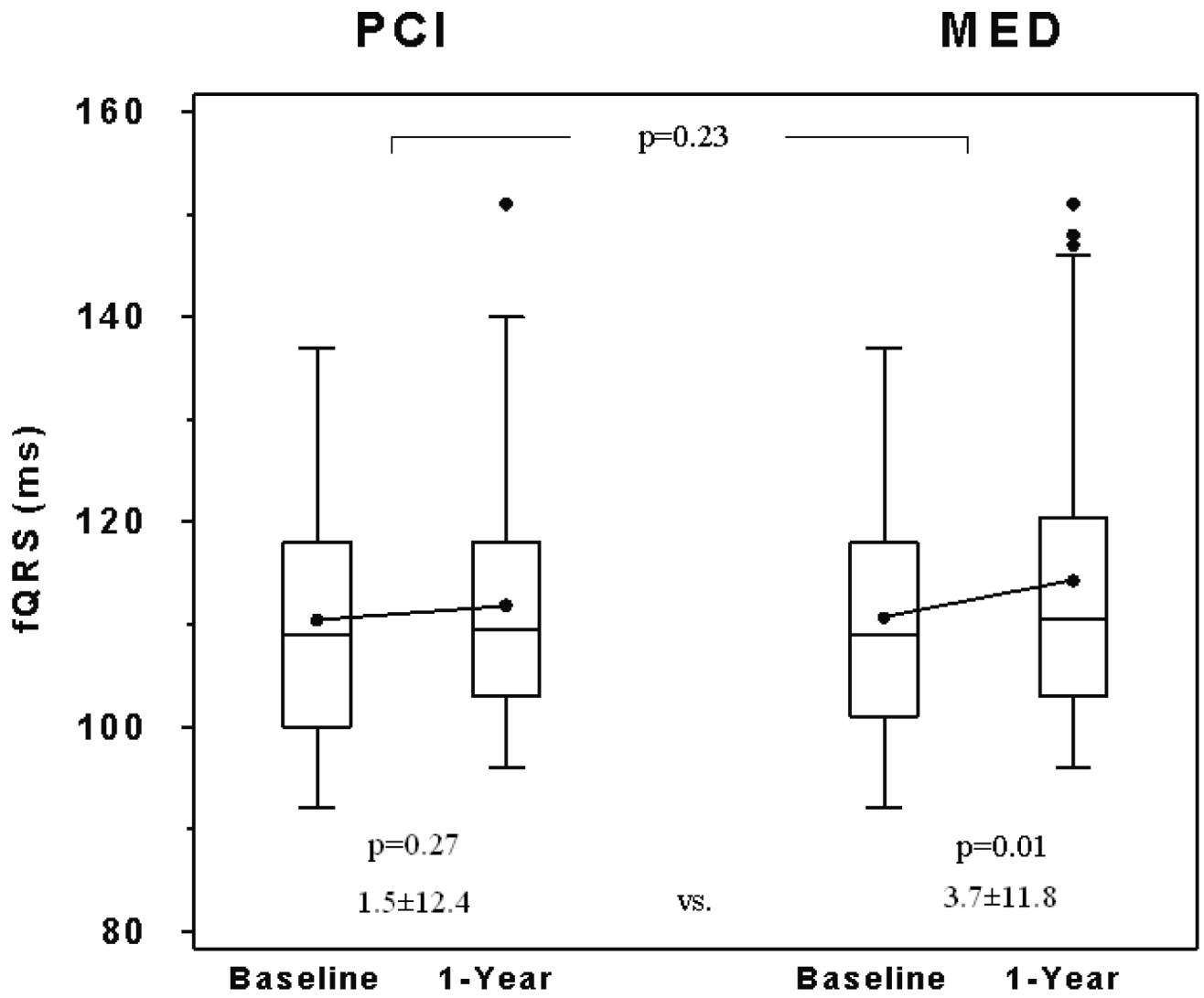
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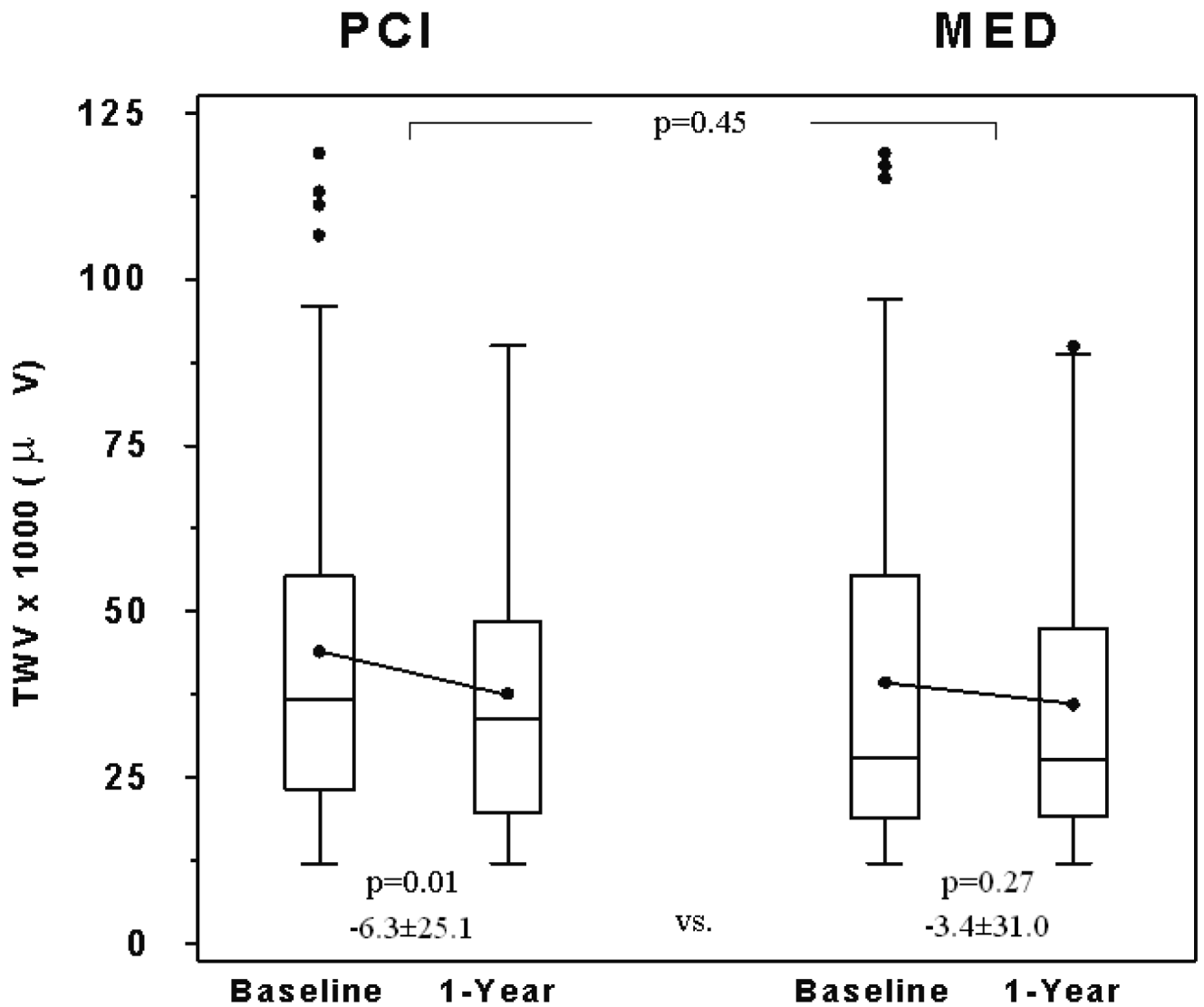


**Figure 1.**  
OAT-EP study flow. BL=baseline.









**Figure 2.** Comparison of baseline and 1-year A)  $\alpha 1$ , B) fQRS, and C) TWV between the 2 study groups. Box-and-whisker plots indicate medians (lines), means (dots), and interquartile ranges (box). Probability values indicate baseline to 1-year comparisons within each group and between groups as indicated.

**Table 1**

Baseline Clinical Characteristics for OAT-EP and other OAT patients

	OAT-EP PCI Group (N=149)	OAT-EP MED Group (N=151)	OAT-EP Both Groups (N=300)	Other OAT Patients (N=1901)
Age, years, mean±SD	57.2±10.5	57.6±10.5	57.4±10.5	58.8±11.0
Male, n(%)	111(74.5)	127(84.1)	238(79.3)	1479(77.8)
Race, n(%)				
White	115(77.2)	117(77.5)	232(77.3)	1531(80.5)
Black	3(2.0)	4(2.6)	7(2.3)	62(3.3)
Hispanic	26(17.4)	21(13.9)	47(15.7)	230(12.1)
Other	5(3.4)	9(6.0)	14(4.7)	78(4.1)
No.(%) with history of:				
Angina	28(18.8)	30(19.9)	58(19.3)	437(23.0)
Prior MI	10(6.7)	10(6.6)	20(6.7)	227(11.9)
Cerebrovascular disease	4(2.7)	6(4.0)	10(3.3)	72(3.8)
Peripheral vascular disease	5(3.4)	6(4.0)	11(3.7)	72(3.8)
Congestive heart failure	5(3.4)	3(2.0)	8(2.7)	44(2.3)
Prior PCI	5(3.4)	10(6.6)	15(5.0)	90(4.7)
Diabetes	22(14.8)	40(26.5)	62(20.7)	392(20.6)
Hypertension	81(54.4)	94(62.3)	175(58.3)	896(47.1)
Current smoker, n(%)	55(36.9)	64(42.4)	119(39.7)	740(38.9)
NYHA class at randomization, n(%)				
NYHA class I	126(84.6)	122(80.8)	248(82.7)	1582(83.4)
NYHA class II	23(15.4)	29(19.2)	52(17.3)	315(16.6)
NYHA class III or IV	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Glomerular filtration rate, ml/min, mean±SD	83.5±23.6	83.5±23.5	83.5±23.5	80.2±21.2

**Table 2**

Index MI and Angiographic Characteristics for OAT-EP and other OAT Patients

	OAT-EP PCI Group (N=149)	OAT-EP MED Group (N=151)	OAT-EP Both Groups (N=300)	Other OAT Patients (N=1901)
ST-segment elevation or new Q-waves or loss of R-waves, n(%)	132(88.6)	135(89.4)	267(89.0)	1638(86.2)
Thrombolytic therapy within first 24 hours of Index MI, n(%)	20(13.4)	22(14.6)	42(14.0)	382(20.1)
Interval from MI to randomization, d, Median, (25 <sup>th</sup> percentile, 75 <sup>th</sup> percentile)	12(6,21)	11(6,20)	12(6,21)	8(5,15)
Stress test performed, n(%)	42(28.2)	39(25.8)	81(27.0)	517(27.2)
Ischemia in IRA territory, n(%)				
Severe	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Moderate	2(4.8)	1(2.6)	3(3.7)	56(10.8)
Mild	13(30.9)	10(25.6)	23(28.4)	157(30.4)
None	27(64.3)	28(71.8)	55(67.9)	303(58.6)
IRA, n(%)				
Left anterior descending	52(34.9)	51(33.8)	103(34.3)	690(36.3)
Left circumflex	19(12.8)	23(15.2)	42(14.0)	293(15.4)
Right coronary artery	78(52.3)	77(51.0)	155(51.7)	918(48.3)
IRA TIMI flow grade, n(%)				
Grade 0	112(75.2)	120(79.5)	232(77.3)	1573(83.7)
Grade 1	37(24.8)	31(20.5)	68(22.7)	298(15.8)
Grade 2	0(0.0)	0(0.0)	0(0.0)	7(0.4)
Grade 3	0(0.0)	0(0.0)	0(0.0)	2(0.1)
Collateral vessels present, n(%)	131(87.9)	132(87.4)	263(87.7)	1659(88.6)
Multivessel disease, n(%)	27(18.1)	43(28.5)	70(23.3)	309(16.4)
Left ventricular ejection fraction, mean±SD	47.7±10.9	47.9±10.3	47.8±10.6	47.7±11.2
Left ventricular ejection fraction<50%, n(%)	79(53.0)	74(49.0)	153(51.0)	1017(54.0)

**Table 3**

## Medical Therapy During Holter Recording

	Baseline PCI (N=149)	Baseline MED (N=149)	1 Year PCI (N=131)	1 Year MED (N=138)
ACE inhibitor, n(%)	120(80.5)	121(81.2)	97(74.0)	109(79.0)
Angiotensin receptor blocker, n(%)	5(3.4)	3(2.0)	9(6.9)	10(7.2)
Beta-blocker, n(%)	133(89.3)	138(92.6)	116(88.5)	128(92.8)
Calcium channel blocker, n(%)	8(5.4)	11(7.4)	7(5.3)	15(10.9)
Digoxin, n(%)	1(0.7)	3(2.0)	0(0.0)	2(1.4)
Diuretic, n(%)	24(16.1)	30(20.1)	25(19.1)	35(25.4)
Spirolactone, n(%)	6(4.0)	10(6.7)	8(6.1)	10(7.2)
Class I or III anti-arrhythmic, n(%)	2(1.3)	4(2.7)	4(3.1)	2(1.4)

Table 4

Changes in arrhythmia marker values between baseline and one year

	N	PCI Group		N	Baseline	Change	MED Group	One Year	Change	Difference	MED Change - PCI Change	
		Baseline	One Year								Lower	Upper
QT	118	1.05±0.30	1.06±0.27	119	1.05±0.29	.01±0.34	1.02±0.29	36.1±21.3	-0.03±0.32	-0.04	-0.12	0.04
TWV(μV)	104	44.0±28.4	37.7±21.5 *	103	39.5±27.5	-6.3±25.1	36.1±21.3		-3.4±31.0	3.0	-4.8	10.7
Time domain SAECG												
fQRS (ms)	90	110.4±12.4	111.9±13.2	81	110.6±12.2	1.5±12.4	114.3±14.9 *		3.7±11.8	2.2	-1.4	5.9
LAS	94	36.5±11.6	34.2±11.9	84	37.6±12.7	-2.2±11.6	36.7±13.3		-0.9±12.1	1.3	-2.1	4.8
RMS	95	27.3±18.1	30.4±21.3	84	25.8±16.2	3.1±19.4	27.1±18.7		1.3±15.1	-1.8	-7.0	3.4
Time domain HRV												
Mean RR interval (ms)	128	927.9±162.1	980.1±150.9 *	122	924.4±174.5	52.2±191.1	998.2±184.4 *		73.8±209.0	21.6	-28.2	71.5
SDNN (ms)	128	31.5±14.8	38.9±16.4 *	122	32.2±14.7	7.5±18.1	39.7±17.2 *		7.5±17.7	0.01	-4.5	4.5
SDANN (ms)	119	7.5±6.1	9.1±6.9	109	8.1±6.3	1.6±8.6	8.6±7.1		0.6±9.5	-1.0	-3.3	1.4
rMSSD (ms)	128	21.2±11.9	27.2±14.7 *	122	21.1±10.7	5.9±15.7	28.1±14.5 *		7.0±14.6	1.1	-2.7	4.9
pNN50 (%)	75	6.5±8.9	9.3±10.5	78	5.4±7.1	2.8±11.5	10.6±10.7 *		5.2±10.2	2.4	-1.1	5.9
Frequency Domain HRV												
Total power	95	689.5±685.6	947.3±825.8 *	81	790.4±776.3	257.8±897.6	1154.1±1134.3 *		363.6±1095.7	105.8	-190.8	402.4
VLF	95	282.5±223.4	338.2±250.2	81	340.5±326.2	55.7±347.2	344.5±286.7		4.0±428.4	-51.6	-167.0	63.8
LF	95	213.3±240.2	297.3±303.8	81	217.7±257.1	83.9±346.6	346.4±370.9 *		128.7±334.6	44.8	-57.1	146.6
HF	95	111.5±140.7	166.4±175.0 *	81	116.2±147.8	54.9±175.3	200.0±214.8 *		83.8±208.9	28.9	-28.3	86.0
LF/HF ratio	95	3.4±3.1	2.7±2.2	81	3.2±3.2	-0.7±3.3	2.7±2.4		-0.5±3.5	0.13	-0.89	1.15

There were no significant differences between the PCI and MED groups in the change of any of the listed variables (p &gt; 0.2 for all comparisons).

\* p&lt;0.01 for the change between baseline and one year within the group indicated.