

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Electronic Supplement to:

Effect of PCI on Quality of Life in Patients With Stable Coronary Disease

William S. Weintraub¹, John A. Spertus², Paul Kolm¹, David J. Maron³, Zefeng Zhang⁴, Claudine Jurkovitz¹, Wei Zhang¹, Pamela M. Hartigan⁵, Cheryl Lewis⁴, Emir Veledar⁴, Jim Bowen¹, Sandra B. Dunbar⁴, Christi Deaton⁶, Stanley Kaufman⁷, Robert A. O'Rourke⁸, Ron Goeree⁹, Paul G. Barnett¹⁰, Koon K. Teo⁹, William E. Boden¹¹, On behalf of the Department of Veterans Affairs Cooperative Studies Program No.424 (COURAGE Trial) Investigators and Study Coordinators*

1: Christiana Care Health System, Newark, DE

2: Mid America Heart Institute/University of Missouri – Kansas City, Kansas City, MO

3: Vanderbilt University Medical Center, Nashville, TN

4: Emory University, Atlanta, GA

5: Cooperative Studies Program Coordinating Center, VA Connecticut Healthcare System, West Haven, CT

6: Manchester University, Manchester, United Kingdom

7: The Epimetries Group, LLC, San Francisco, CA

8: McMaster University, Hamilton, Ontario, Canada

9: San Antonio Veterans Affairs Medical Center, San Antonio, TX

10: Veterans Affairs Health Economics Resource Center, Palo Alto, CA

11: Western New York Veterans Affairs Healthcare Network and Kaleida Health System, Buffalo, NY

*Members of the COURAGE Study Group are listed in reference 6.

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This document is an electronic supplement to the manuscript “Effect of PCI on Quality of Life in Patients With Stable Coronary Disease” (ref to be added). This document is best view simultaneously with the main manuscript.

Authors, COURAGE QOL Paper

The members of the COURAGE Trial were as follows: *Writing Committee*: W.E. Boden (study co-chair), R.A. O’Rourke (study co-chair) K.K. Teo (study co-chair), P.M. Hartigan, W. Weintraub, D. Maron, G.B.J. Mancini; *Executive Committee*: W.E. Weintraub (chair), W.E. Boden, R.A. O’Rourke, K.K. Teo, P.M. Hartigan, M.Knudtson, D.J. Maron, E.Bates, A.S. Blaustein, D.C. Booth, R.G. Carere, S.G. Ellis, G. Gosselin, G.Gau, A.K. Jacobs, S.B. King, III, W.J. Kostuk, C. Harris, J. Spertus; P. Peduzzi (ex officio); *Data and Safety Monitoring Board*: T. Ryan (chair), B. Turnbull, T. Feldman, R.O. Bonow, W.L. Haskell, P. Diehr, P. Lachenbruch, D.D. Waters, D.E. Johnstone; *Adjudication Committee*: L.S. Cohen (chair), B. Cantin, W.D. Hager, F.F. Samaha, J.L. Januzzi, J. Arrighi, B. Chaitman; *Economics Committee*: W.S. Weintraub (chair), P. Hartigan, R.A. O’Rourke, W.E. Boden, P. Barnett, J. Spertus, R. Goeree; *Modifiable Cardiovascular Risk Factors Committee*: D. Maron (chair), W.E. Boden, R.A. O’Rourke, K.K. Teo, W.W. Weintraub.

VA Cooperative Studies Program Coordinating Center, VA Connecticut Healthcare System, West Haven - P. Peduzzi (director); M. Antonelli, (associate director of operations); J. Smith (project manager); R. Kilstrom, B. Hunter, M. Edgington, E. Petrokaitis (coordinators); L. Durant (quality assurance officer); S. O’Neil (endpoints coordinator); T.M. Economou, J. Nabors (programmers); P. Collins, A. Kossack (data clerks); *VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, NM* - M. Sather (director), C. Harris (assistant director), W. Gagne (project manager), C. Fye (pharmacist); *VA Cooperative Studies Human Rights Committee, West Haven, CT* – R. Marottoli (chair), H.G. Allore, D.G. Beckwith, W. Farrell, R.C. Feldman, R. Mehta, J.C. Neiderman, E.B. Perry, S. Kasl, M. Zeman; *VA Office of Research and Development, Clinical Science R&D, Washington, DC* - T.J. O’Leary (acting director), G.D. Huang (deputy director, Cooperative Studies Program); *Study Chairs Offices – Western New York VA Healthcare Network and Buffalo General Hospital/SUNY, Buffalo, NY* - W.E. Boden (study co-chair), M.Dada, K. Potter (national coordinators); *South Texas Veterans HCS-Audie Murphy Campus, San Antonio, TX* - R.A. O’Rourke (study co-chair), P. Casperson (national coordinator), A. O’Shea, G. Jordan (Program Assistants); *McMaster University Medical Center, Hamilton, ON* - K.K. Teo (study co-chair), J.A. Piette, G. Woodcock (Coordinators); *Central Laboratories: Center for Outcomes Research: Christiana Care Health System, Newark, DE & Emory University, Atlanta, GA* - W.S. Weintraub; *Health Economics Research Center, Menlo Park, CA*: P. Barnett, S. Chen; *Program for Assessment of Technology in Health (PATH), Hamilton, ON* - R. Goeree, B. O’Brien, C. Henderson; *Angiographic Core Laboratory-Vancouver Hospital & HSC, Vancouver, B* -G.B. John Mancini, E. Yeoh; *Central Lipid Core Laboratory-Washington University in St. Louis, St. Louis, MO* - J. Ladenson, V.Thompson, D. Gibson, L. Mischle, V. Luzzi, T.G. Cole, J. McDowell; *EKG Core Laboratory-St. Louis University, St. Louis, MO* - B. Chaitman, T. Bertran, J.

Bussen, C. Moore; *Nuclear Core Laboratory-Cedars Sinai Medical Center, Los Angeles, CA* - D. Berman, G. Germano, J. Gerlach, R. Littman, R. Miranda-Peats, A. Hurayt; *Project PACE-San Diego State University, San Diego, CA* - K. Calfas, J. Sallis

Clinical study sites (listed by Health Systems); **VA:** *South Texas Veterans HCS-Audie Murphy Campus, TX:* G.L. Freeman, R.A. O'Rourke (site investigators), J. Bolton, P. Freeman, R. Mercado-Young, P. Baker (coordinators); *Houston VA Medical Center, TX:* A. Blaustein (site investigator), C. Rowe (coordinator); *Durham VA Medical Center, NC:* K.G. Morris (site investigator), S. Hoffman (coordinator); *VA New York Harbor HCS-Manhattan Campus, NY:* S.P. Sedlis (site investigator), M.K. Scott, E. Anteola (coordinators); *VA Ann Arbor HCS, MI:* C. Duvernoy, M. Starling (site investigators), C. Majors, K. Syzmanski (coordinators); *Lexington VA Medical Center, KY:* D.C. Booth (site investigator), M.L. Shockey (coordinator); *James A. Haley Veterans Hospital, FL:* R. Zoble (site investigator), I. Fernandez, K. Bell (coordinators); *VA Puget Sound HCS-Seattle Campus, WA:* K.G. Lehmann (site investigator), J. Dinkelspiel, M. Abel, A. Sorley (coordinators); *New Mexico VA HCS, NM:* M.W. Sheldon, M. Crawford (site investigators), K. Wagoner (coordinator); *Portland VA Medical Center, OR:* E. Murphy (site investigator), K. Avalos (coordinator); *Iowa City VA Medical Center, IA:* J.D. Rossen, D. Jagasia (site investigators), A. Ollinger, K. Schneider (coordinators); *Central Arkansas Veterans HCS- Little Rock Campus, AR:* B. Molavi, L. Garza, J. Saucedo (site investigators), P. Barton, R. Pacheco, S.S. Dodson, S. Kitchens (coordinators); *Atlanta VA Medical Center, GA:* K. Mavromatis, M. Leimbach (site investigators), Z. Forghani, D. House (coordinators), *Tennessee Valley HCS-Nashville Campus, TN,* : R.F. Smith (site investigator), C. Mitchell, P. Holzapfel, M.J. Brewer (coordinators); *Memphis VA Medical Center, TN:* K. Ramanathan (site investigator), T. Touchstone, Z. Qualls (coordinators).

CANADA: *London Health Sciences Centre-Univ. Campus, ON:* W.J. Kostuk (site investigator), S. Carr (coordinator); *London Health Sciences Centre-Victoria Campus, ON:* K. Sridhar (site investigator); *Sudbury Regional Hospital, ON:* S. Nawaz (site investigator), C. Dion, S. Musseau, R-A. Poirier, T. Sequin (coordinators); *Montreal Heart Institute, QU:* G. Gosselin (site investigator), M. Cuso, J. Theberge, M. Brouillette, P. Thibeault (coordinators); *Queen Elizabeth II HSC, NS:* L.M. Title (site investigators), P. Simon, L. Carroll, K. Courtney-Cox, N. Fitzgerald, C. Carter (coordinators); *Sunnybrook HSC, ON:* E.A. Cohen, (site investigator), E. Hsu, L. Balleza (site coordinators); *University Health Network-The Toronto Hospital, ON:* V. Dzavik, P. A. Barolet, McLaughlin, C. Lazzam (site investigators), J. Lan, A. Patel (coordinators); *Foothills Hospital, AB:* M. Knudtson, D. Goodhart (site investigators), D. Lundberg (coordinator); *Hamilton General Hospital/McMaster Clinic, ON:* M. Natarajan (site investigator), G. Cappelli, S. Savoy, C. Miller (coordinators); *St. Michael's Hospital, ON:* M. Kutryk, B. Strauss, M. Freeman (site investigators), A. DiMarco, K. Young, A. Fry, D.O'Donnell (coordinators); *Vancouver Hospital & HSC, BC:* A. Fung, C. Buller (site investigators), J. Chow (coordinator); *Saint John's Regional Hospital, NB:* D. Marr; R. Teskey (site investigators), F. Fitzgerald, E. Collings, C. Coyle, C. Ramsay, A. Williston (coordinators); *St. Paul's Hospital, BC:* R. Carere, C. Thompson (site investigators), T. Nacario, T. Williams (coordinators); *University of Alberta Hospital, AB:* W. Tymchak,

(site investigator), L. Harris (coordinator); *Trillium Health Care, ON*: C. Lazzam (site investigator), Arlene Carter (coordinator); *Hopital du Sacre Coeur de Montreal, QU*: D. Palisaitis (site investigator). C. Mercure (coordinator). **US Non-VA**: *Mayo Clinic Rochester, MN*: M. Bell, P. G. Gau, P. Berger, T. Allison (site investigators), M.E. Peterson, T. Malibago (coordinators); *MIMA Century Research Associates, FL*: R. Vicari (site investigator), M. Carroll, N. Scallon, L. Parker, M. Howard; A. Snyman (coordinators); *University of Michigan Medical Center, MI*: E. Bates, S. Chetcuti (site investigator); A. Luciano; K. McNeely (coordinators); *Southern California Kaiser Permanente Medical Group, CA*: P. Mahrer (site investigator); S. Reyes, R. Browning, P. Scutella (coordinators); *University of Oklahoma HSC, OK*: J. Saucedo; S. Sadanandan; A. Kugelmass (site investigators), D.vanWieren, L. Feddersen, K. Husain, J. Wells (coordinators); *Mid America Heart Institute, MO*: J. O’Keefe, B. McAllister (site investigators), P. Kennedy, M. Rossen, A. Jacobs (coordinators); *Boston Medical Center, MA*: A. Jacobs. C. Berger (site investigators), S. Mayo, D. Fine, C. Zingariello, J. Hutchinson, D. Gannon (coordinators); *Emory University Hospital, GA*: J.I. Miller, III, S. Manoukian (site investigators), T. Arnold (coordinators); *Hartford Hospital*: F. Kiernan (site investigator), M. Dada, K. Potter, D. Murphy (coordinators); *Henry Ford Health System, MI*: A. Kugelmass (site investigator), R. Pangilinan (coordinator); *University of Rochester Medical Center, NY*: R. Schwartz (site investigator), L. Caufield (coordinator); *Vanderbilt University Hospital, TN*: R. Smith, D. Hansen (site investigators), C. Mitchell, P. Holzapfel, M.J. Brewer (coordinators); *SUNY Medical University Hospital, NY*: R. Carhart (site investigator), A. Pennella, M. Jones; *Cleveland Clinic, OH*: S.G. Ellis (site investigator), C. Stevenson (coordinator); *Barnes-Jewish Hospital, MO*: R.J. Krone (site investigator), J. Humphrey, K.M. Luepke (coordinators); *Mayo Clinic Scottsdale, AZ*: C. Appleton, M. Crawford (site investigators); J. Wisbey, L. Wood, B. Pyle (coordinators); *Christiana Care Health Systems, DE*: M.E. Stillabower (site investigator), A. DiSabatino (coordinator); *Rush-Presbyterian-St. Luke’s Medical Center, Chicago, IL*: M.Davidson, R. Hendel (site investigators), J. Mathien (coordinator).

Clinically Significant Increases from Baseline In SAQ Scores

Increases in SAQ scores from baseline were calculated for 1, 3, 6, 12, 24 and 36 months of follow-up. We defined “clinically significant” changes in each of the SAQ scales using criteria described by Wyrwich et al.¹ These criteria are based on evaluation of the questions for the specific domains. The measures are not continuous, but rather the scores vary discontinuously by movement from one level to the next, up or down. A clinically significant change should reflect a change in at least one but perhaps more than one of the questions making up a domain. Furthermore, the instrument being evaluated should otherwise be validated, including face validity, that it is well anchored, responsive, reliable and predictable.

The SAQ Physical Limitation (PL), Angina Stability (AS), Angina Frequency (AF), Treatment Satisfaction (TS) and Quality of Life (QoL) scales, are composed of 9, 1, 2, 4 and 3 questions with 5-6 responses each. Because the SAQ is transformed to a 0-100 point range, a ‘shift’ in a patient’s response of a single category would not result in the same change in score for each domain. Therefore, an intra-individual change within each scale requires a different threshold for each SAQ domain. Examination of the questions suggests that a single shift of only 1 response on 1 of the questions would not necessarily indicate a clinically significant change in a patient’s condition (except AS), while a change of more than 2 categories on any of the AF, TS or QoL questions (3 for PL) or a 1 category change on 2 or more questions (3 for PL) would be clinically significant. These magnitudes of change represent changes in score of 8.33, 25, 20, 12.5 and 16.66 points on the PL, AS, AF, TS and QoL scales, respectively.

Therefore, we defined clinical significance as ≥ 8 , ≥ 25 , ≥ 20 , ≥ 12 and ≥ 16 point differences on the physical limitation, angina stability, angina frequency, treatment satisfaction and quality of life scales respectively. Contingency table analysis (chi-square) was used to compare PCI + OMT and OMT differences. Multivariable logistic regression was used to adjust for age, gender, race, previous MI, diabetes, baseline CCS score, and previous CABG.

Table 2 in the manuscript presents the percentages of PCI + OMT and OMT patients with clinically significant increases in SAQ scores. There was a significantly greater percentage of PCI + OMT patients with greater increases in physical limitation and quality of life scores at 1, 3 and 6 months from baseline. Thereafter, there were no significant differences between PCI + OMT and OMT. Although the nonsignificant p values at 12 months and following could be attributed to decreasing sample sizes (and thus power), the observed differences in percentages between PCI and OMT became smaller with increasing follow-up. Differences in angina frequency favored PCI + OMT over all 36 months of follow-up. For angina stability, there was only a significant difference between PCI + OMT and OMT at 1 month. Differences in treatment satisfaction were virtually the same except at 24 months with OMT percentage greater than PCI + OMT.

Adjustment for age, gender, race, previous MI, diabetes, baseline CCS score, and previous CABG made little impact on differences between observed and predicted proportions of patients with clinically significant increases in scores, differing in only the second and third decimal places. Consequently, the magnitude of p values of PCI + OMT vs. OMT differences changed only slightly.

Strategy for Handling and Analyzing Missing Quality of Life Data in the COURAGE Trial

Missing data present a challenge for analysis, particularly when the data are missing not at random (MNAR), that is, the potential response is related to the missing mechanism or the reason for missingness. Data that are missing at random (MAR), that is, the response is not related to the reason for missingness (but may be related to other covariates), can be imputed, or analyzed by straightforward maximum likelihood methods. Quality of life and health status data that are missing are probably MNAR, in that patients in poorer health may be less likely to complete a questionnaire regarding their health.

SAQ and RAND-36 data in the COURAGE trial followed typical patterns of longitudinal assessment – smaller number of responses with increasing follow-up time. Our strategy for handling missing data involved three components: 1) assessment of the amount of missing data in each arm of the study at each follow-up time, 2) assessment of the patterns of missing data, and 3) multiple analyses making MAR and MNAR assumptions. Each analysis makes assumptions about missing data that cannot be verified. Thus, analyses of these data constitute sensitivity analyses to address a problem that exists in every study where there are missing data.

Missing data in PCI+OMT and OMT arms

The total number of patients with valid SAQ data at each follow-up time are given in Table 1 of the paper in parentheses following the mean and standard deviation. For example, there were 939 PCI+OMT, and 939 OMT only patients with baseline physical limitation scores. The proportion of patients missing a baseline score would be $1 - 939/1149$, or 18.2% for PCI+OMT, and $1 - 939/1138$, or 17.5% for OMT only. The last two columns of the table present the percent missing for each arm at each time point based on the total number of patients still being followed. In other words, patients lost to follow-up or who died were excluded from the denominator. The percent missing was very similar between the two groups at each time point. We concluded that the amount of missing data in each arm was similar, and would not need to be accounted for in the statistical models.

At 36 months, SAQ data were available for about 70% of COURAGE patients remaining in the trial. At 48 months the percentage fell to about 55% and we therefore limited the analyses to 36 months. The statement in the paper that 328 coronary intervention group and 303 medical therapy group patients had complete data for 36 months does not mean that only 631 had valid data at 36 months. The 631 (28% of the total 2,287 patients) were patients who had SAQ scores at each follow-up time from baseline to 36 months. There

would be other individuals who had scores at 36 months, but, for example, didn't have scores at 6 months or 24 months.

A table of means, standard deviations and valid N for the RAND-36 are presented in the supplement, but not in the manuscript. The percentage of missing RAND-36 scores was similar for PCI+OMT and OMT only patients at each follow-up time as it was for the SAQ.

Missing data patterns

Missing data patterns impact the type of analyses that can be done. Analyses for NMAR data generally assume a *monotone missing* pattern. That is, patients have complete data up to some given follow-up time and then drop out. Drop out is not assumed to be random and is referred to as nonignorable dropout. The following schematic represents the monotone drop out pattern for the SAQ from, left to right, baseline, 1, 3, 6, 12, 24 and 36 months. X represents a valid observation, and 0 a missing observation.

Monotone missing data pattern

X000000	Baseline only
XX00000	Baseline, 1 month
XXX0000	Baseline – 3 months
XXXX000	Baseline – 6 months
XXXXX00	Baseline – 12 months
XXXXXXX0	Baseline – 24 months
XXXXXXXX	Baseline – 36 months

Obviously not all patients fit one of these patterns and exhibit some *intermittent* missing pattern. Intermittent missing means that a patient may have, for example, a missing value at a given follow-up time, but then a valid observation at the next follow-up. The following schematic represents some of the intermittent patterns observed for the SAQ.

Intermittent missing pattern

0XXXX00
X0XXXXX
X0XXXX0
XXXX0XX
XX0XXX0
XXX0XXX
XX0XXXX
XXXX0X0

For patients with intermittent missing patterns, we assumed that missing was random up to their last follow-up and imputed those values. For example, patients with pattern X0XXXX0 would have their 1 month value imputed, and then would have been considered a “drop out” at 36 months. Thus we created a data file of only monotone missing patterns, and then analyzed these data with a pattern mixture model assuming nonignorable dropout. References were provided in the manuscript for this strategy. The same strategy was followed for RAND-36 data

Multiple imputation

Multiple imputation of missing data typically involves generating 3-5 data files with complete data, analyzing each separately, and then combining the results such that the parameter estimates and standard errors of the models reflect the uncertainty of multiple imputation. With repeated measures data, the process becomes more complicated.

First, missing SAQ and RAND-36 baseline values were imputed using demographic and baseline clinical variables. We generated 5 such data files. Then we randomly selected one of these and imputed missing 1 month values using demographic and clinical variables, and the baseline value, whether observed or imputed, again generating 5 such data files. Randomly selecting one of these 5, we imputed missing 3 month values, using demographic and clinical variables, baseline and 1 month variables, generating 5 “filled in” files. We repeated this process for missing values up to 24 months and analyzed the data to 36 months, combining the results for 5 randomly selected “filled in” data files, all with monotone missing patterns. Observed scores of SAQ domains were used to impute missing values of other SAQ domains preceding and concurrent with the follow-up time of the missing value. The same procedure was followed for the RAND-36. Imputation and analysis was limited to 36 months because of the large amount of missing data beyond this time frame.

As described in the Methods section of the manuscript, multiple imputation by chained equations (MICE) as implemented in the Stata routine *ice* was used to impute missing data. A run-in of 100 cycles was used to assess stability of the imputed data. There were no observed patterns in the imputed data beyond 20 cycles. And there was no evidence of auto-regression between imputations; correlations were virtually identical among all imputations.

To summarize, the amount of missing SAQ and RAND-36 data increased with increasing follow-up from baseline, but the amount of missing data were very similar for PCI+OMT and OMT only arms at each follow-up time. We made the assumption that intermittent missing data patterns were MAR and imputed these data up to 24 months post-treatment. The imputed data were stable after a run-in of about 20 cycles and showed no evidence of auto-regression among imputations.

Analysis

Analyses of data with missing values can be considered sensitivity analyses because all analyses make assumptions and about missingness that cannot be verified. Our primary analyses involved 1) analysis of observed data at each follow-up time with separate unpaired t-tests, 2) longitudinal analysis of all data assuming that missingness was MAR using linear mixed effects models, and 3) multiple imputation of intermittent missing data, assuming it was MAR, and analysis using a pattern mixture model assuming nonignorable dropout. This analysis also used mixed effects models. In addition, we analyzed the 631 patients that had complete data out to 36 months post-treatment. The assumption was that the 631 were a representative sample of the total 2,287 patients.

The first analysis comparing PCI+OMT vs. OMT only means at each time point utilized unpaired t-tests. Unadjusted p values for each comparison were presented for SAQ means in Table 1. We debated whether to include some adjustment for multiple testing, such as a Bonferroni correction, but ended up including only the unadjusted p values. If a correction was made for testing 5 SAQ domains at each follow-up time, a p value of 0.005 would have been required for a statistically significant finding ($0.05/2/5$ for a two-sided test at the 0.05 alpha level). It turned out that for most of the SAQ domains, the unadjusted and adjusted p values would have given essentially the same results – significant differences at 3 and 6 months, and sometimes 12 and 24 months. In the main clinical paper, multiple testing was accounted for by using an alpha level of 0.01. This strategy would have led to the same conclusions in this analysis.

The analysis at each time point does not, of course, allow a statistical conclusion about changes in mean scores over time – only a descriptive inference can be made. To assess whether there were changes in mean scores over time, and differences between PCI + OMT and OMT with respect to change, longitudinal, or repeated measures, analyses were performed using mixed effects models. In these models, treatment and follow-up time were fixed effects and patients were random effects. These models included a treatment by time interaction term to assess whether the pattern of change over time, i.e., trends, were the same for PCI + OMT and OMT. A significant interaction would indicate that trends over time differed between the two arms. Inspection of the plots of mean scores (Figures 2 and 3 in the manuscript) indicated that changes in mean scores over time were not linear. Thus, quadratic and cubic polynomials of time (time squared and time cubed) were included in the mixed models to account for the nonlinear trends. The models included the linear, quadratic and cubic interactions with treatment type. These models utilized all available data with the assumption that missing data were MAR. Both PCI + OMT and OMT had significant increases in means scores up to 3-6 months post-treatment. Generally, the time by treatment type interaction (up to the cubic interaction) was significant for all SAQ and most RAND-36 domains. The significant time by treatment type interactions indicated that the increase in mean scores was significantly greater for PCI + OMT than the increase for OMT. Means scores tended to remain at about the same level for both arms after 6-12 months.

Pattern mixture models assume that dropout is nonignorable, but make no differentiation regarding the cause of dropout. Thus, COURAGE patients who died were not analyzed any differently than those who dropped out for unknown reasons. Pattern mixture models require a monotone missing pattern and so the intermittent missing data were imputed assuming MAR. The follow-up time at which a SAQ or RAND-36 score was missing, and there were no subsequent observations, was considered the dropout time. These models included quadratic and cubic, along with interaction terms, as in the mixed effects MAR models. Data were analyzed out to 36 months post-treatment. Differences between PCI and OMT arms were consistent with those found in the mixed effects models and the analyses of observed means. Generally, estimates of predicted mean scores from these models tended to be lower by as much as 5-6 points than the observed mean scores.

All of the analyses suggested an increase in SAQ and RAND-36 mean scores from baseline to about 6 months for both PCI and OMT arms. Increases to about 6 months were significantly greater for PCI+OMT than for OMT only. Thereafter, mean scores remained at about the same levels.

Table 1S shows the baseline characteristics of patients, and end points, by randomly assigned group, percutaneous coronary intervention (PCI) and optimal medical therapy (OMT) vs. OMT alone.

Table 1S: Baseline Characteristics and Endpoint Summary

Variable	PCI+OMT (n = 1149)	OMT (n = 1138)	P Value
Baseline			
Age (years)	62 ± 10	62 ± 10	0.54
Male gender (%)	85(979)	85(968)	0.95
Prior MI (%)	38(437)	39(439)	0.80
Diabetes (%)	32 (367)	35(399)	0.12
Hypertension (%)	66 (757)	67 (764)	0.53
CCS Angina Class (%)			0.24
Missing	3 (0)	2 (0)	
0	135 (12)	148 (13)	
I	340 (30)	341 (30)	
II	409 (36)	425 (37)	
III	261 (23)	221 (19)	
Median duration of angina - months‡	5 (1, 15)	5 (1, 15)	0.53
Median episodes per week with exertion or at rest, last month‡	3 (1,6)	3 (1,6)	0.83
Endpoints			
Death (%)	7.7 (85)	8.3 (95)	0.38
MI (%)	12.3 (143)	11.8 (128)	0.33
Death or MI (%)	19.0 (211)	18.5 (202)	0.62

PCI=percutaneous coronary intervention. OMT=optimal medical therapy. MI=myocardial infarction. CCS=Canadian Cardiovascular Society.

Table 2S shows risk factors and medications from the main clinical paper. Some improvement over time is noted, but the patients generally had good risk factor control at baseline. Whether this constituted “optimal medical therapy” is conjectural.

Table 2S: Risk Factors and Medication Usage Over Time*

Risk Factor	PCI+OMT (N=1149)				OMT (N=1138)			
	Baseline	1 Year	3 Years	5 Years	Baseline	1 Year	3 Years	5 Years
	<i>median ± SE</i>							
Sys BP	131±0.77	126±0.64	125±0.68	124±0.81	130±0.66	124±0.73	123±0.78	122±0.92
Dias BP	74±0.33	72±0.35	70±0.52	70±0.81	74±0.33	70±0.43	70±0.52	70±0.65
LDL Chol	100±1.17	84±0.97	76±0.85	71±1.33	102±1.22	81±0.86	74±0.92	72±1.21
Medication								
No. evaluated	114	104	837	428	113	102	838	417
	7	4			8	8		
ACE inhibitor	669 (58)	668 (64)	536 (64)	284 (66)	680 (60)	633 (62)	522 (62)	260 (62)
ARB	48 (4)	93 (9)	104 (12)	49 (11)	54 (5)	99 (10)	108 (13)	67 (16)
Statin	992 (86)	972 (93)	780 (93)	398 (93)	1014 (89)	972 (95)	769 (92)	386 (93)
Other anti-lipid	89 (8)	236 (23)	324 (39)	211 (49)	94 (8)	253 (25)	321 (38)	224 (54)
Aspirin	1097 (96)	995 (95)	792 (95)	408 (95)	1077 (95)	977 (95)	796 (95)	391 (94)
Beta blocker	975 (85)	887 (85)	705 (84)	363 (85)	1008 (89)	916 (89)	724 (86)	357 (86)
CCB	459 (40)	415 (40)	360 (43)	180 (42)	488 (43)	501 (49)	418 (50)	217 (52)
Nitrates§	714 (62)	553 (53)	396 (47)	173 (40)	825 (72)	690 (67)	511 (61)	237 (57)

*Plus-minus values are medians ± SE, with the SE calculated with the use of the interquartile range.
 PCI=percutaneous coronary intervention. OMT=optimal medical therapy. Sys=systolic.
 Dias=diastolic. LDL=low density lipoprotein. ACE=angiotensin converting enzyme.
 ARB=angiotensin-receptor blocker. CCB=calcium channel blocker.
 §PCI + OMT as compared with OMT is significant at all time points (P<0.001)

Figure 1S is a Kaplan-Meier curve indicating the frequency of OMT patients receiving coronary revascularization over time.

Cumulative Rate of OMT Crossover to Revascularization

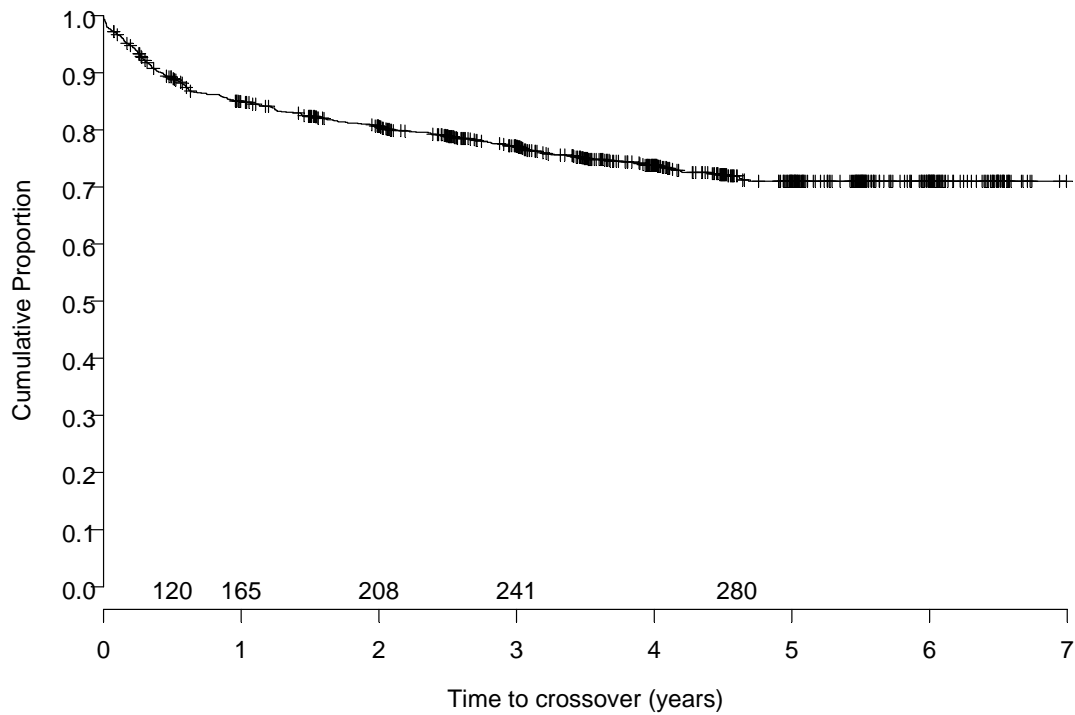


Figure 1S. Numbers on horizontal axis are OMT crossovers to revascularization at 6 months, 1, 2, 3 years. Last crossover at 4.6 years. | indicates censored observations, i.e., no crossover.

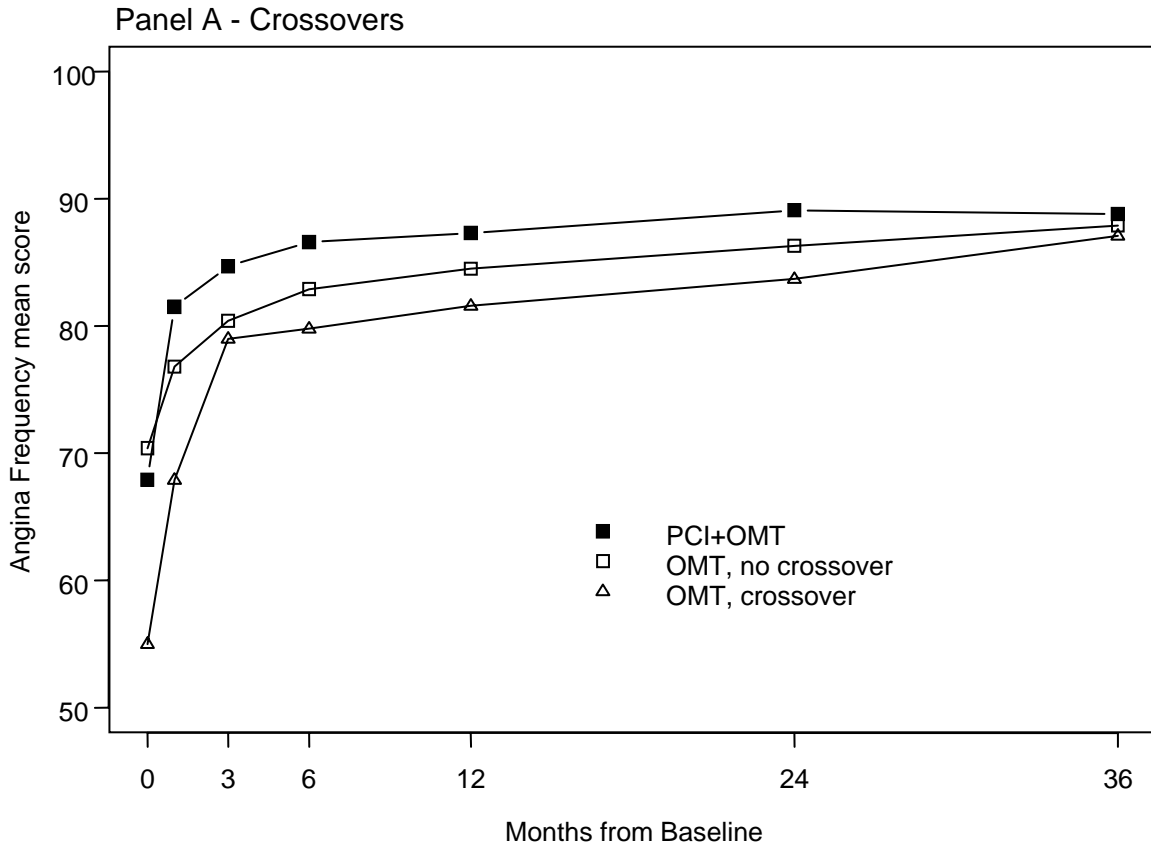


Figure 2S, Panel A

Figure 2S, panel A shows the angina frequency domain scores from baseline to 36 months in the coronary intervention group and the medical therapy group divided by patients who do and do not crossover to coronary revascularization within 3 months of randomization. The data for figure 2S is shown in table 3S. Abbr: OMT, Optimal medical therapy

Table 3S: Angina Frequency Means for Crossovers Within 3 Months

Follow-up	PCI+OMT	OMT		PCI vs OMT Non-crossover	P Values	
		Non-crossover	OMT Crossover in first 3 months (n=68)		PCI vs OMT Crossover	NC vs CO
Baseline	67.9 ± 26.4	70.4 ± 25.5	55.0 ± 28.5	0.	< 0.0001	< 0.0001
1 month	81.5 ± 22.6	76.8 ± 23.8	67.9 ± 28.6	< 0.0001	< 0.0001	0.0004
3 months	84.7 ± 21.8	80.4 ± 23.3	79.0 ± 25.6	0.0001	0.078	0.27
6 months	86.6 ± 19.8	82.9 ± 22.1	79.8 ± 22.7	0.0003	0.019	0.09
12 months	87.3 ± 19.4	84.5 ± 20.5	81.6 ± 24.1	0.0055	0.051	0.14
24 months	89.1 ± 17.7	86.3 ± 19.3	83.7 ± 21.0	0.0033	0.046	0.14
36 months	88.8 ± 18.3	87.9 ± 18.1	87.1 ± 17.7	0.40	0.59	0.69

NC=non-crossover CO=crossover.

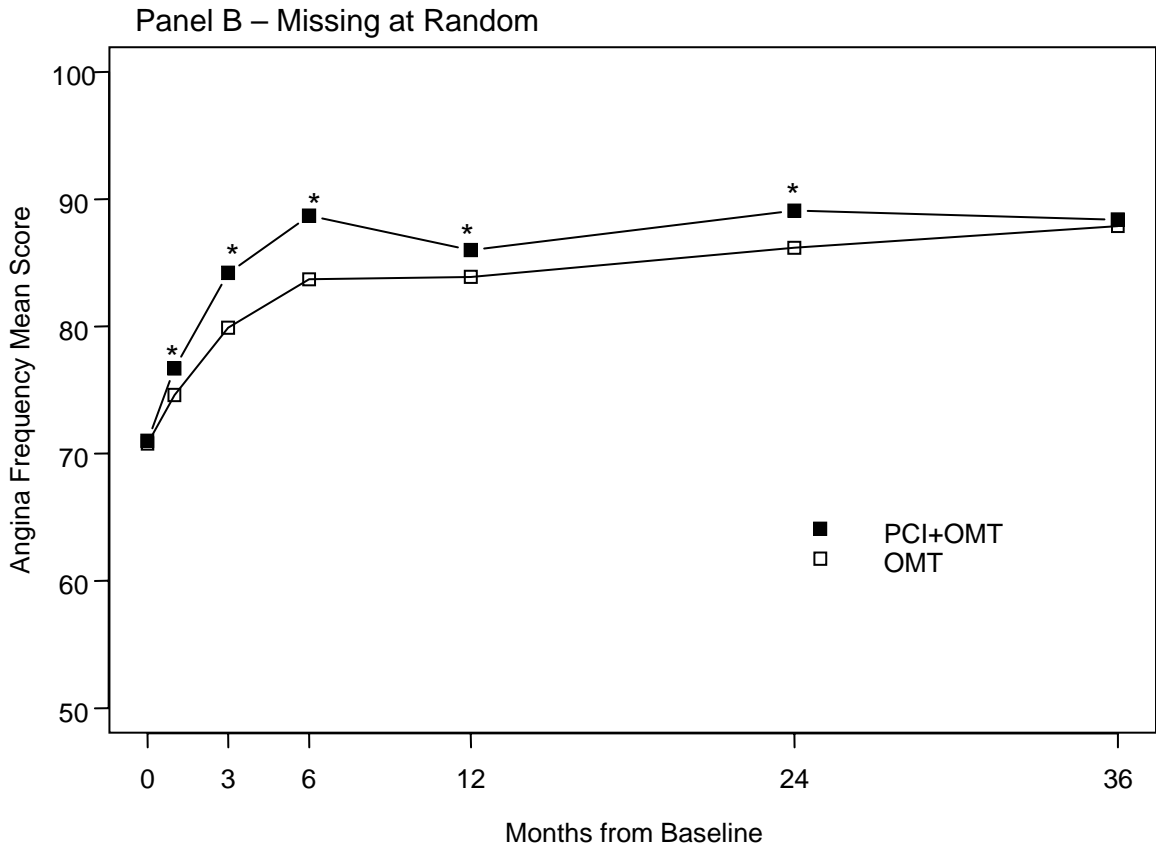


Figure 2S, Panel B

* = $p < 0.01$

Figure 2S, Panel B shows the angina frequency domain scores from baseline to 36 months in the coronary intervention group and the medical therapy group with missing data imputed assuming missing at random.

Data for figure 2S, Panel B

Table 4S: Angina Frequency Means for MAR Assumption			
Follow-up	PCI+OMT	OMT	P Value
Baseline	71.0 ± 19.6	70.6 ± 19.7	0.71
1 month	76.8 ± 14.9	74.5 ± 15.8	0.001
3 months	84.6 ± 16.9	80.0 ± 17.0	< 0.0001
6 months	88.9 ± 18.0	83.8 ± 17.6	< 0.0001
12 months	86.3 ± 20.9	83.9 ± 20.8	0.019
24 months	89.3 ± 21.0	86.2 ± 21.0	0.004
36 months	88.8 ± 20.4	87.8 ± 20.5	0.43

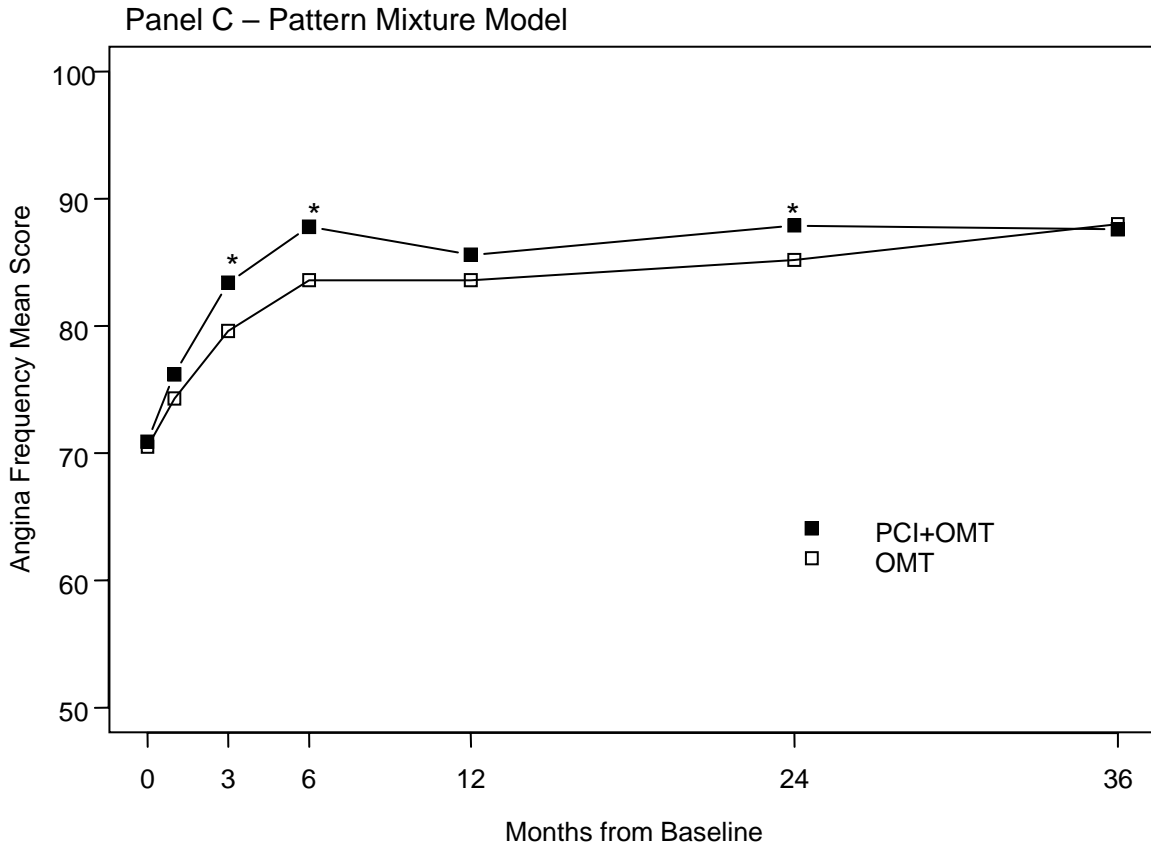


Figure 2S, Panel C

* = $p < 0.01$

Figure 2S, Panel C shows the angina frequency domain scores from baseline to 36 months in the coronary intervention group and the medical therapy group with missing data imputed using a pattern mixture model.

Data for Figure 2S, panel C

Table 5S: Angina Frequency Means for Partial Multiple Imputation

Follow-up	PCI+OMT	OMT	P Value
Baseline	70.9 ± 29.5	70.5 ± 27.0	0.74
1 month	76.3 ± 25.5	74.3 ± 23.0	0.056
3 months	83.5 ± 25.7	79.7 ± 23.2	0.0002
6 months	87.9 ± 25.6	83.7 ± 22.6	< 0.0001
12 months	85.7 ± 26.8	83.7 ± 24.4	0.086
24 months	88.9 ± 25.2	85.7 ± 22.6	0.006
36 months	88.4 ± 21.6	87.6 ± 21.4	0.48

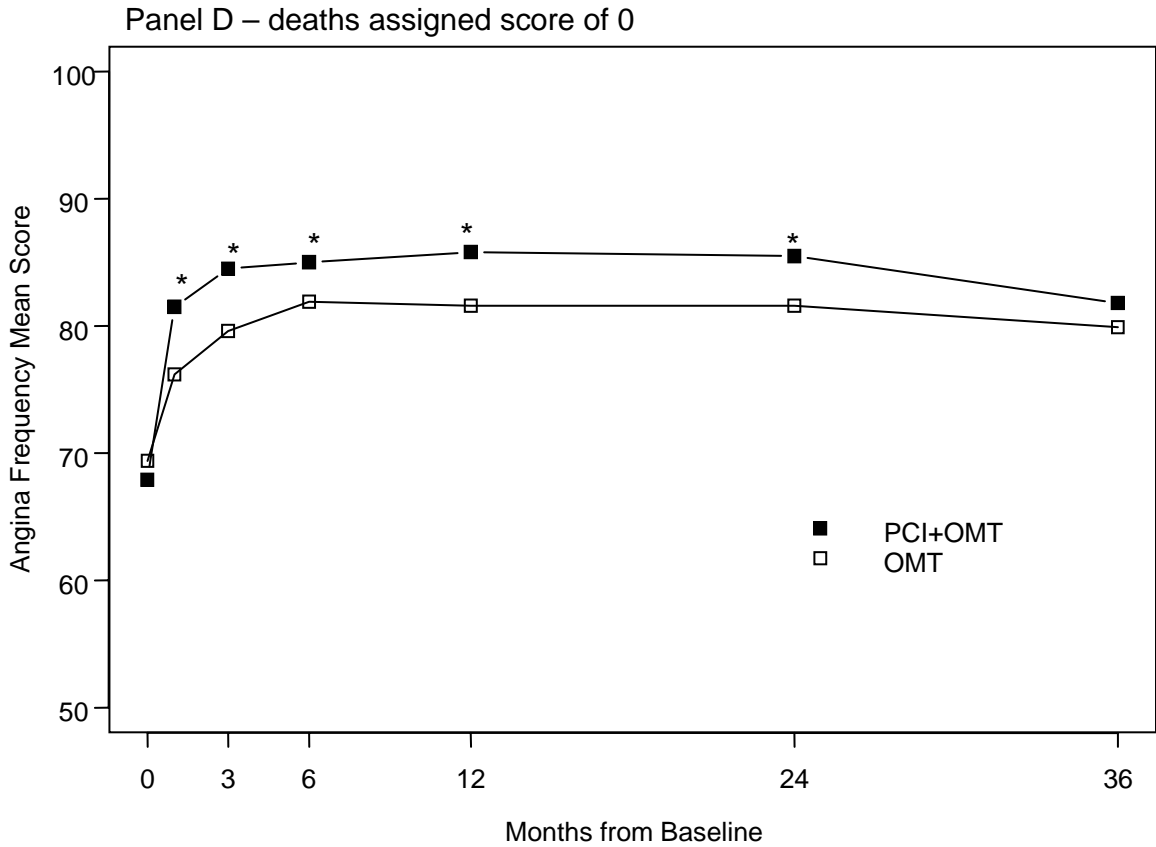


Figure 2S, Panel D

* = $p < 0.01$

Figure 2S, Panel D shows the angina frequency domain scores from baseline to 36 months in the coronary intervention group and the medical therapy group with scores for patients who have died assigned a value of zero from the time of death until 36 months.

Data for figure 2S, panel D

Follow-up	PCI+OMT	OMT	P Value
Baseline	67.9 ± 26.4	69.4 ± 25.9	0.20
1 month	81.5 ± 23.0	76.2 ± 24.1	< 0.0001
3 months	84.5 ± 21.9	79.6 ± 24.5	< 0.0001
6 months	85.0 ± 21.7	81.9 ± 22.7	0.003
12 months	85.8 ± 21.8	81.6 ± 24.4	0.0002
24 months	85.5 ± 24.6	81.6 ± 26.3	0.003
36 months	81.8 ± 29.5	79.9 ± 29.6	0.26

Interactions Between Treatment Group and Tertile of Baseline SAQ Domain Score

The coefficients of variation for the SAQ scores are large, generally about 0.40. This led to the assessment of domains by tertile. The next five tables plus table 3 in the main paper present the analyses of the Seattle Angina Questionnaire angina frequency, physical limitation and quality of life domains divided by tertile (or by thirds). When divided by tertiles, the change over time will be subject to regression to the mean. Thus the change from baseline as well as the change after accounting for regression to the mean are both presented.² The clinically significant changes for these three domains are also presented (tables 3 in the main paper, 10S and 11S). Clinically significant changes were defined using the approach of Wyrwich et al (see the section “Clinically Significant Increases from Baseline In SAQ Scores”, above).¹ The results suggest greater advantage of PCI for patients with more frequent, severe angina.

Table 7S: Angina Frequency Tertile Scores (Mean Interaction P=0.008)

Tertile	Follow-up	PCI+OMT			OMT			P Value	Change from Baseline		Change Adjusted for Regression to Mean	
		Mean	±	SD	Mean	±	SD		PCI+OMT	OMT	PCI+OMT	OMT
1st	Baseline	35	±	14	35	±	14	0.75				
	1 month	68	±	27	58	±	25	0.0001	33	23	16	11
	3 months	74	±	27	65	±	26	0.0004	39	30	20	15
	6 months	78	±	25	72	±	25	0.023	43	38	20	18
	12 months	79	±	25	75	±	23	0.090	44	40	26	23
	24 months	84	±	21	79	±	23	0.029	49	45	28	25
	36 months	83	±	21	82	±	22	0.94	48	48	28	28
2nd	Baseline	71	±	8	71	±	8	0.18				
	1 month	81	±	19	76	±	20	0.0015	9.5	5.3	4.5	2.5
	3 months	86	±	18	79	±	22	< 0.0001	15	8.8	7.5	4.4
	6 months	87	±	18	82	±	21	0.002	16	12	7.5	5.6
	12 months	88	±	17	85	±	20	0.023	17	14	9.7	8.1
	24 months	90	±	16	85	±	19	0.001	18	14	10	8.0
	36 months	89	±	18	87	±	17	0.28	17	16	10	9.4
3rd	Baseline	97	±	5	97	±	5	0.61				
	1 month	93	±	14	88	±	19	0.002	-4.4	-8.7	-2.1	-4.1
	3 months	91	±	18	90	±	16	0.67	-6.0	-6.7	-3.0	-3.4
	6 months	92	±	15	89	±	19	0.015	-4.9	-8.2	-2.3	-3.9
	12 months	93	±	14	90	±	18	0.022	-4.3	-7.3	-2.5	-4.3
	24 months	92	±	15	91	±	15	0.64	-5.0	-5.8	-2.8	-3.3
	36 months	94	±	14	93	±	14	0.31	-2.8	-4.4	-1.6	-2.6

Table 8S: SAQ Physical Limitation Tertile Interaction (Mean Interaction P <0.0001)

Tertile	Follow-up	PCI+OMT			OMT			P Value	Change from Baseline		Change Adjusted for Regression to Mean	
		Mean	±	SD	Mean	±	SD		PCI+OMT	OMT	PCI+OMT	OMT
1st	Baseline	37	±	12	37	±	12	0.63				
	1 month	56	±	24	50	±	22	0.007	19	13	12	8
	3 months	59	±	25	55	±	23	0.12	22	18	15	13
	6 months	61	±	25	54	±	23	0.0004	25	16	18	12
	12 months	61	±	27	59	±	26	0.41	24	22	18	16
	24 months	61	±	27	58	±	25	0.19	24	21	18	15
	36 months	62	±	27	63	±	25	0.57	25	26	19	20
2nd	Baseline	69	±	8	68	±	8	0.28				
	1 month	76	±	19	72	±	17	0.015	7.8	4.5	4.8	2.8
	3 months	78	±	19	74	±	19	0.035	9.3	6.5	6.5	4.5
	6 months	80	±	19	75	±	18	0.0008	11.6	6.7	8.6	5.0
	12 months	77	±	22	74	±	19	0.28	7.9	6.5	5.8	4.8
	24 months	76	±	21	72	±	21	0.067	7.4	4.4	5.5	3.3
	36 months	74	±	22	75	±	21	0.81	5.7	7.0	4.4	5.4
3rd	Baseline	94	±	6	93	±	6	0.68				
	1 month	89	±	14	87	±	16	0.24	-4.7	-6.1	-2.9	-3.8
	3 months	91	±	13	87	±	16	0.003	-2.4	-6.1	-1.7	-4.2
	6 months	89	±	16	87	±	17	0.14	-4.7	-6.7	-3.5	-5.0
	12 months	88	±	16	86	±	17	0.20	-5.6	-7.3	-4.1	-5.3
	24 months	85	±	19	84	±	19	0.61	-8.2	-8.9	-6.1	-6.6
	36 months	85.0	±	19	81	±	22	0.10	-8.5	-11.9	-6.6	-9.2

Table 9S: SAQ Quality of Life Tertile Interaction (Mean Interaction P <0.0001)

Tertile	Follow-up	PCI+OMT			OMT			P Value	Change from Baseline		Change Adjusted for Regression to Mean	
		Mean	±	SD	Mean	±	SD		PCI+OMT	OMT	PCI+OMT	OMT
1st	Baseline	23	±	9	23	±	9	0.95				
	1 month	55	±	24	44	±	21	< 0.0001	32	21	17	11
	3 months	64	±	24	55	±	23	0.0001	41	32	22	17
	6 months	66	±	24	56	±	24	< 0.0001	43	33	25	19
	12 months	68	±	24	63	±	23	0.015	45	39	28	25
	24 months	71	±	24	68	±	24	0.12	48	44	28	26
	36 months	72	±	22	71	±	22	0.63	49	47	28	27
2nd	Baseline	50	±	7	50	±	7	0.28				
	1 month	67	±	21	61	±	20	0.0012	16	11	8.8	6.0
	3 months	72	±	21	67	±	21	0.013	22	18	12	9.5
	6 months	74	±	20	70	±	20	0.019	24	20	14	12
	12 months	74	±	20	74	±	20	0.68	24	24	15	15
	24 months	77	±	21	76	±	20	0.72	27	27	15	15
	36 months	78	±	20	78	±	19	0.75	28	29	16	17
3rd	Baseline	80	±	12	80	±	12	0.71				
	1 month	81	±	17	78	±	18	0.028	0.6	-2.4	0.3	-1.3
	3 months	83	±	16	80	±	19	0.041	2.8	0.0	1.5	0.0
	6 months	83	±	17	81	±	19	0.24	3.0	1.5	1.7	0.9
	12 months	85	±	15	80	±	20	0.0058	4.3	0.2	2.7	0.2
	24 months	84	±	19	82	±	20	0.25	3.7	1.9	2.1	1.1
	36 months	84	±	16	82	±	19	0.38	3.8	2.4	2.2	1.4

**Table 10S: Clinically Significant Increase in Physical Limitation Domain
(≥ 8 Point Increase from Baseline, Interaction P Value < 0.0001)**

SAQ Domain	Tertile	Follow-up	PCI + OMT	OMT	Unadjusted P Value	
Physical Limitation	1st	Baseline	37.6 \pm 12.3	37.2 \pm 12.1	0.63	
		1 Month	65	55	0.014	
		3 Months	71	64	0.14	
		6 Months	74	62	0.006	
		12 Months	71	69	0.65	
		24 Months	72	70	0.69	
		36 Months	72	74	0.65	
		2nd	Baseline	68.6 \pm 7.9	67.9 \pm 7.8	0.28
			1 Month	54	46	0.072
	3 Months		57	50	0.12	
	6 Months		61	52	0.054	
	12 Months		56	52	0.42	
	24 Months		59	48	0.024	
	36 Months		52	56	0.46	
	3rd		Baseline	93.5 \pm 6.4	93.3 \pm 6.4	0.68
			1 Month	14	15	0.86
		3 Months	20	16	0.17	
		6 Months	19	17	0.56	
		12 Months	17	13	0.28	
		24 Months	17	17	0.81	
		36 Months	13	16	0.50	

Data at baseline are mean \pm 1 SD. Subsequent data are percentages of patients with clinical meaningful change of ≥ 8 points from baseline.

**Table 11S: Clinically Significant Increase in Quality of Life Domain
(≥16 Point Increase from Baseline, Interaction P Value <0.0001)**

SAQ Domain	Tertile	Follow-up	PCI+OMT	OMT	Unadjusted P Value	
Quality of Life	1st	Baseline	23.4 ± 9.5	23.4 ± 9.1	0.95	
		1 Month	76	65	0.0042	
		3 Months	86	78	0.028	
		6 Months	88	78	0.0029	
		12 Months	89	88	0.80	
		24 Months	88	90	0.50	
		36 Months	93	90	0.31	
		2nd	Baseline	50.2 ± 6.6	49.7 ± 6.6	0.28
			1 Month	57	47	0.019
	3 Months		69	59	0.025	
	6 Months		73	64	0.11	
	12 Months		72	71	0.79	
	24 Months		74	77	0.42	
	36 Months		78	81	0.51	
	3rd		Baseline	80.3 ± 11.7	80.0 ± 11.8	0.71
			1 Month	21	18	0.36
		3 Months	25	26	0.90	
		6 Months	30	30	0.96	
		12 Months	34	30	0.32	
		24 Months	33	31	0.65	
		36 Months	36	33	0.55	

Data at baseline are mean ± 1 SD. Subsequent data are percentages of patients with clinically meaningful change of ≥16 points from baseline.

SAQ and RAND-36 Treatment Group Interactions with Demographic and Baseline Clinical Variables

Additional analyses were performed to assess whether there were any interactions between treatment group and demographic and baseline clinical variables.

The results of these analyses are presented in Table 12S for the SAQ and Table 15S for the RAND-36. The tables present the p values for 1) the main effects of the treatment group, 2) follow-up time, 3) the specific covariate and 4) the interaction effects of treatment group by covariate and treatment group by covariate by follow-up time. Using a p value ~ 0.01 , there were few indications of an interaction of treatment group with demographic and baseline clinical variables for either the SAQ or the RAND-36. There was a treatment group by gender by follow-up time interaction for angina stability ($p = 0.004$) (figure 3S). Female and male mean angina stability scores were similar from baseline to 12 months, but at 24 and 36 months, females in the PCI+OMT group had significantly greater mean scores than females in the OMT group, whereas PCI+OMT and OMT male means were more similar. While statistically significant, there is no pathophysiologic explanation for this interaction, and it may be spurious. A borderline treatment group by prior CABG by follow-up time interaction for angina frequency ($p = 0.011$) (figure 4S) was explained by a lower baseline mean of PCI+OMT patients with a prior CABG compared with OMT patients with a prior CABG and patients without a prior CABG in both PCI+OMT and OMT groups.

Table 12S: Treatment Group Interactions for the SAQ

SAQ Domain	Model Effect	Covariate =						
		Age	Gender	Race	Diabetes	Prior MI	Prior CABG	CCS
Physical Limitation	Treatment group (TG)	0.0420	0.0443	0.0432	0.0641	0.0696	0.0378	0.0400
	Follow-up	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	Covariate	< 0.0001	0.0050	< 0.0001	< 0.0001	0.0001	< 0.0001	< 0.0001
	TG x Covariate x Follow-up	0.3925	0.4460	0.4217	0.4538	0.5510	0.2463	0.5377
Angina Stability	Treatment group (TG)	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	Follow-up	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	Covariate	0.0485	0.7652	0.2229	0.0149	0.1365	< 0.0001	< 0.0001
	TG x Covariate x Follow-up	0.1096	0.0041	0.2330	0.1185	0.1306	0.4557	0.1287
Angina Frequency	Treatment group (TG)	0.0004	0.0004	0.0004	0.0005	0.0005	0.0004	0.0002
	Follow-up	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	Covariate	0.0165	0.0828	0.5858	0.0432	0.0206	< 0.0001	< 0.0001
	TG x Covariate x Follow-up	0.4975	0.1347	0.7826	0.2090	0.3254	0.0113	0.1799
Treatment Satisfaction	Treatment group (TG)	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	Follow-up	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	Covariate	0.0223	0.0637	< 0.0001	0.0184	0.4339	0.0637	< 0.0001
	TG x Covariate x Follow-up	0.9717	0.9026	0.1279	0.5882	0.5218	0.6445	0.6422
Quality of Life	Treatment group (TG)	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	< 0.0001
	Follow-up	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	Covariate	< 0.0001	0.7229	< 0.0001	0.0002	0.0057	< 0.0001	< 0.0001
	TG x Covariate x Follow-up	0.3398	0.2030	0.6692	0.1838	0.8331	0.0270	0.2093

P values for interactions for the Seattle Angina Questionnaire are noted in table 7S. Highlighted interactions are significant or borderline significant.

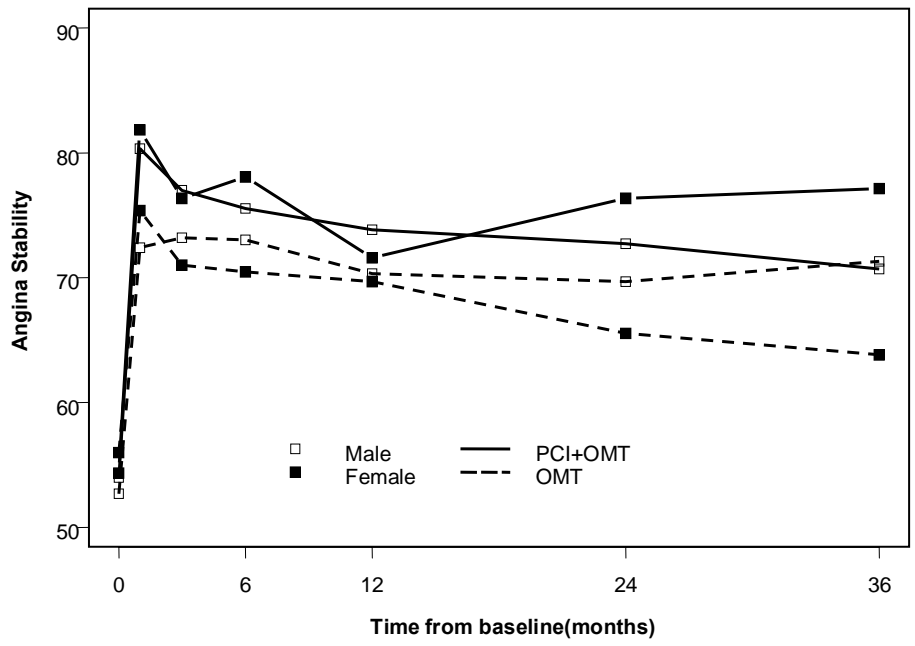


FIGURE 3S. Angina Stability. Treatment Group by Gender by Follow-up Time.

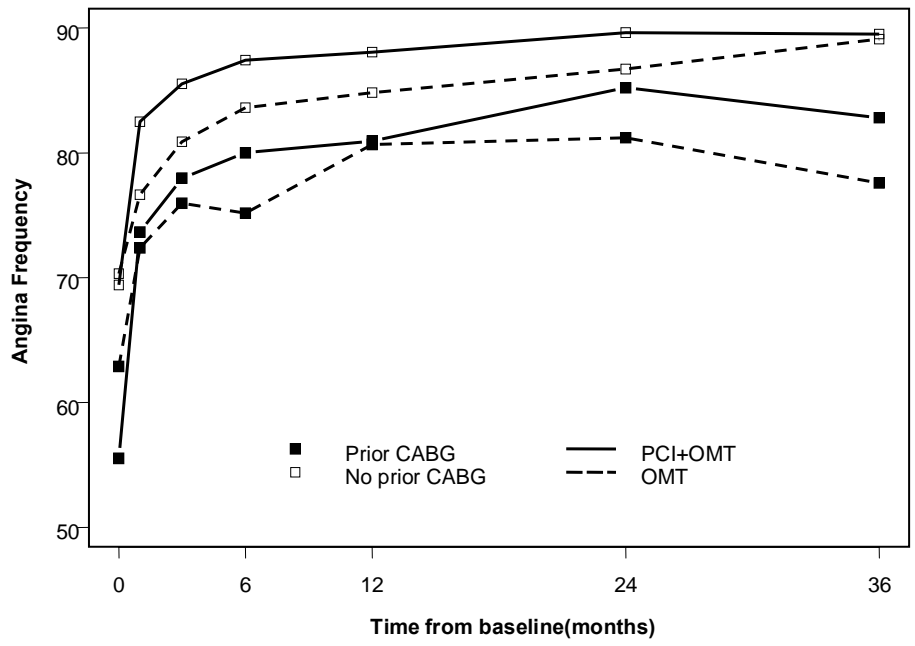


FIGURE 4S. Angina Frequency. Treatment Group by Prior CABG by Follow-up Time.

RAND-36 Data

There is an extensive experience with the RAND-36 as a general measure of health status. A review of this literature is beyond the scope of this text. The interested reader is referred to key references.^{3,4} Norms are available from the study by Hays et al.³

Table 13S: RAND-36 Scores From Baseline to 36 Months

RAND-36 Domain	Follow-up	PCI+OMT	OMT	Unadjusted P Value	% missing data*	
		Mean \pm SD	Mean \pm SD		PCI+OMT	OMT
Physical Functioning	Baseline	58 \pm 27 (987)	59 \pm 27 (973)	0.39	14	15
	1 Month	65 \pm 27 (896)	61 \pm 27 (894)	0.0003	22	21
	3 Months	69 \pm 27 (861)	65 \pm 26 (867)	0.001	23	23
	6 Months	68 \pm 27 (899)	66 \pm 26 (844)	0.035	19	23
	12 Months	69 \pm 27 (857)	66 \pm 28 (847)	0.018	21	20
	24 Months	66 \pm 28 (766)	65 \pm 27 (759)	0.61	24	24
	36 Months	66 \pm 29 (596)	64 \pm 28 (595)	0.22	30	31
Role Limitation- Physical	Baseline	38 \pm 41 (987)	37 \pm 42 (971)	0.51	14	15
	1 Month	47 \pm 42 (892)	46 \pm 43 (893)	0.72	22	21
	3 Months	61 \pm 42 (862)	52 \pm 43 (866)	0.0001	23	23
	6 Months	62 \pm 42 (897)	57 \pm 43 (844)	0.024	19	23
	12 Months	64 \pm 42 (856)	61 \pm 42 (845)	0.11	21	21
	24 Months	62 \pm 42 (765)	61 \pm 42 (759)	0.66	24	24
	36 Months	66 \pm 42 (595)	60 \pm 42 (595)	0.03	30	31
Role Limitation- Emotional	Baseline	56 \pm 43 (987)	57 \pm 43 (968)	0.76	14	15
	1 Month	62 \pm 42 (892)	62 \pm 42 (888)	0.87	22	22
	3 Months	69 \pm 41 (857)	65 \pm 42 (863)	0.045	23	23
	6 Months	70 \pm 41 (894)	68 \pm 41 (843)	0.46	19	23
	12 Months	73 \pm 38 (857)	70 \pm 40 (845)	0.10	21	21
	24 Months	69 \pm 41 (761)	70 \pm 40 (758)	0.73	24	24
	36 Months	71 \pm 40 (592)	68 \pm 42 (590)	0.21	31	31
Energy / Fatigue	Baseline	47 \pm 24 (986)	47 \pm 23 (974)	0.91	14	14
	1 Month	53 \pm 23 (894)	48 \pm 24 (893)	0.0001	22	21
	3 Months	56 \pm 23 (861)	52 \pm 23 (866)	< 0.0001	23	23
	6 Months	56 \pm 23 (898)	53 \pm 23 (844)	0.008	19	23
	12 Months	56 \pm 23 (858)	54 \pm 24 (846)	0.028	21	20
	24 Months	55 \pm 24 (766)	52 \pm 24 (756)	0.026	24	24
	36 Months	56 \pm 23 (596)	52 \pm 24 (594)	0.014	30	31
Emotional Well-being	Baseline	71 \pm 20 (986)	71 \pm 20 (974)	0.82	14	14
	1 Month	74 \pm 19 (894)	73 \pm 19 (893)	0.23	22	21
	3 Months	76 \pm 19 (861)	74 \pm 19 (866)	0.039	23	23
	6 Months	75 \pm 19 (898)	75 \pm 19 (844)	0.56	19	23
	12 Months	75 \pm 19 (858)	75 \pm 20 (846)	0.63	21	20
	24 Months	75 \pm 20 (766)	76 \pm 19 (756)	0.21	24	24

	36 Months	75 ± 19 (596)	74 ± 20 (594)	0.17	30	31
Social Functioning	Baseline	71 ± 27 (988)	70 ± 27 (974)	0.95	14	14
	1 Month	75 ± 25 (894)	75 ± 26 (893)	0.95	22	21
	3 Months	81 ± 24 (861)	79 ± 25 (866)	0.022	23	23
	6 Months	81 ± 24 (898)	79 ± 26 (845)	0.03	19	23
	12 Months	81 ± 25 (857)	80 ± 25 (846)	0.69	21	20
	24 Months	79 ± 26 (766)	81 ± 24 (758)	0.31	24	24
	36 Months	80 ± 26 (596)	79 ± 26 (594)	0.59	30	31
Pain	Baseline	61 ± 26 (986)	62 ± 26 (974)	0.73	14	14
	1 Month	68 ± 26 (893)	66 ± 25 (893)	0.052	22	21
	3 Months	72 ± 25 (861)	68 ± 26 (866)	0.006	23	23
	6 Months	71 ± 26 (897)	70 ± 26 (844)	0.29	19	23
	12 Months	72 ± 25 (857)	70 ± 27 (845)	0.10	21	21
	24 Months	70 ± 26 (765)	69 ± 26 (758)	0.55	24	24
	36 Months	70 ± 27 (596)	68 ± 27 (594)	0.36	30	31
General Health	Baseline	57 ± 20 (987)	55 ± 20 (974)	0.044	14	14
	1 Month	61 ± 20 (896)	55 ± 20 (894)	< 0.0001	22	21
	3 Months	62 ± 21 (862)	57 ± 21 (867)	< 0.0001	23	23
	6 Months	61 ± 21 (898)	58 ± 21 (845)	0.0009	19	23
	12 Months	61 ± 21 (858)	58 ± 21 (847)	0.010	21	20
	24 Months	60 ± 22 (766)	58 ± 22 (759)	0.044	24	24
	36 Months	60 ± 22 (596)	57 ± 22 (595)	0.033	30	31

* Percent missing is based on denominator of total patients in follow-up at each time, i.e., patients no longer being followed (censored) or who died were excluded.

Clinically Significant Increases from Baseline in RAND-36 Scores

For the RAND-36, clinically significant differences were defined as 10 point increases for all domains. There were significant differences favoring PCI+OMT for Physical Functioning, Energy/Fatigue, Emotional Well-being and General Health at 1 and 3 months. The difference extended to 6 months for Physical Functioning.

Table 14S: Percentage of Patients With 10 Point or Greater Improvement in RAND-36 Scores From Baseline

Rand-36 Domain	Follow-up	PCI+OMT	OMT	P Value
Physical Functioning	1 Month	41	33	0.0010
	3 Months	48	40	0.0024
	6 Months	50	43	0.0113
	12 Months	47	43	0.2063
	24 Months	42	42	0.8913
	36 Months	42	39	0.2736
	Role Limitation-Physical	1 Month	34	34
3 Months		45	40	0.0463
6 Months		48	43	0.0443
12 Months		47	47	0.9511
24 Months		45	45	0.9587
36 Months		44	46	0.5883
Role Limitation-Emotional		1 Month	28	27
	3 Months	33	32	0.7286
	6 Months	37	33	0.0909
	12 Months	34	34	0.9031
	24 Months	33	33	0.8226
	36 Months	33	32	0.9257
	Energy/Fatigue	1 Month	41	33
3 Months		49	40	0.0005
6 Months		47	45	0.5180
12 Months		47	45	0.2705
24 Months		46	33	< 0.0001
36 Months		44	42	0.3608
Emotional Well-being		1 Month	29	23
	3 Months	32	27	0.0405
	6 Months	32	28	0.0826
	12 Months	29	29	0.9607
	24 Months	32	30	0.5118
	36 Months	31	27	0.0859
	Social Functioning	1 Month	40	41
3 Months		46	44	0.4424
6 Months		48	45	0.2425

	12 Months	45	47	0.5016
	24 Months	46	46	0.9894
	36 Months	41	43	0.4722
Pain	1 Month	48	43	0.0260
	3 Months	52	50	0.3356
	6 Months	52	49	0.1743
	12 Months	51	49	0.5545
	24 Months	48	46	0.5916
	36 Months	44	47	0.2862
General Health	1 Month	37	25	< 0.0001
	3 Months	39	30	0.0004
	6 Months	39	35	0.1262
	12 Months	37	36	0.6931
	24 Months	34	35	0.8858
	36 Months	37	34	0.3714

SAQ Treatment Group Interactions with Demographic and Baseline Clinical Variables

For the RAND-36, there were no significant treatment group by covariate by follow-up time interactions.

Table 15S: Treatment Group Interactions for the RAND-36

RAND-36 Domain	Model Effect	Covariate =						
		Age	Gender	Race	Diabetes	Prior MI	Prior CABG	CCS
Physical Functioning	Treatment group (TG)	0.0465	0.0494	0.0508	0.0789	0.1121	0.0478	0.0537
	Follow-up	0.0336	0.0532	0.0514	0.0428	0.0960	0.0485	0.0378
	Covariate	< 0.0001	< 0.0001	0.0007	< 0.0001	0.0004	< 0.0001	< 0.0001
	TG x Follow-up x Covariate	0.5509	0.0764	0.4773	0.0460	0.8521	0.0832	0.8576
Role Limitation-Physical	Treatment group (TG)	0.0352	0.0352	0.0354	0.0737	0.0645	0.0336	0.0306
	Follow-up	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	Covariate	0.0260	0.0125	0.1189	< 0.0001	0.0004	< 0.0001	< 0.0001
	TG x Follow-up x Covariate	0.9421	0.2866	0.6665	0.7051	0.4496	0.8633	0.2538
Role Limitation-Emotional	Treatment group (TG)	0.4916	0.4912	0.4891	0.6495	0.6930	0.4893	0.5058
	Follow-up	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	Covariate	0.0834	0.0754	0.0001	< 0.0001	0.0038	< 0.0001	< 0.0001
	TG x Follow-up x Covariate	0.2020	0.3927	0.3473	0.0604	0.1220	0.1924	0.1286
Energy/Fatigue	Treatment group (TG)	0.0047	0.0047	0.0048	0.0044	0.0140	0.0046	0.0043
	Follow-up	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	Covariate	< 0.0001	< 0.0001	0.0779	< 0.0001	0.1511	< 0.0001	< 0.0001
	TG x Follow-up x Covariate	0.3134	0.5000	0.7707	0.4064	0.6459	0.4180	0.9006
Emotional Well-being	Treatment group (TG)	0.7727	0.7804	0.7806	0.7932	0.9380	0.7811	0.8107
	Follow-up	0.0005	0.0007	0.0007	0.0007	0.0006	0.0007	0.0006
	Covariate	< 0.0001	0.0037	0.0181	0.0042	0.1650	0.7058	< 0.0001
	TG x Follow-up x Covariate	0.5305	0.9437	0.6793	0.2388	0.7380	0.5807	0.6283
Social Functioning	Treatment group (TG)	0.7351	0.7395	0.7384	0.7370	0.9728	0.7356	0.7957
	Follow-up	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	Covariate	< 0.0001	0.1000	0.0007	< 0.0001	0.0003	< 0.0001	< 0.0001
	TG x Follow-up x Covariate	0.4124	0.7294	0.4803	0.2195	0.8619	0.2092	0.6906
Pain	Treatment group (TG)	0.1297	0.1283	0.1294	0.1041	0.2037	0.1258	0.1415
	Follow-up	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	Covariate	0.1964	0.0006	0.0110	< 0.0001	0.0474	< 0.0001	< 0.0001
	TG x Follow-up x Covariate	0.1258	0.5057	0.7140	0.1066	0.9701	0.1546	0.7967
General Health	Treatment group (TG)	0.0002	0.0002	0.0002	0.0002	0.0006	0.0002	0.0002
	Follow-up	0.5320	0.5143	0.5030	0.5658	0.4977	0.5156	0.5591
	Covariate	< 0.0001	0.9038	0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	TG x Follow-up x Covariate	0.4315	0.2242	0.7896	0.6095	0.4568	0.5892	0.7812

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