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Health Status and Quality of Life in Patients With Stable Coronary Artery Disease and Chronic Kidney Disease Treated With Optimal Medical Therapy or Percutaneous Coronary Intervention (Post Hoc Findings from the COURAGE Trial)

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Abstract

Chronic kidney disease (CKD) is an important clinical co-morbidity that increases the risk of death and myocardial infarction in patients with coronary artery disease (CAD) even when treated with guideline-directed therapies. It is unknown, however, whether CKD influences the effects of CAD treatments on patients' health status, their symptoms, function, and quality of life. We performed a post hoc analysis of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) study to compare health status in patients with stable

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Disclosures

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CAD with and without CKD defined as a glomerular filtration rate of <60 ml/min/1.73 m^2 randomized to either percutaneous coronary intervention (PCI) and optimal medical therapy (OMT) or OMT alone. Health status was measured at baseline, 1, 3, 6, 12, 24, and 36 months of follow-up with the Seattle Angina Questionnaire in 310 patients with CKD and 1,719 patients without CKD. Linear mixed-effects models were used to analyze Seattle Angina Questionnaire scores longitudinally. Mean scores for angina-related quality of life, angina frequency, and physical limitation domains improved from baseline values in both patients with and without CKD and plateaued. Early improvement (1 to 6 months) was more common in patients treated with PCI plus OMT than with OMT alone in both patients with and without CKD. Treatment satisfaction scores were high at baseline in all groups and did not change significantly over time. In conclusion, although CKD is an important determinant of event-free survival in patients with stable CAD, it neither precludes satisfactory treatment of angina with PCI plus OMT or OMT alone nor is it associated with an unsatisfactory quality of life.

Chronic kidney disease (CKD) is strongly associated with increased incidence of cardiovascular events in patients with stable coronary artery disease (CAD). Previous analyses from the COURAGE trial have shown that percutaneous coronary intervention (PCI) when added to optimal medical therapy (OMT) with a 14% crossover to revascularization does not reduce the risk of death or myocardial infarction in patients with CKD.[1] There is little information available, however, on the effects of treatments for CAD on health status in patients with CKD. CKD has been associated with reduced physical functioning scores on the Seattle Angina Questionnaire (SAQ) in patients with CAD enrolled in a large cross-sectional study, but the effects of therapy on longitudinal health status outcomes have not been analyzed in that cohort.[2] Coronary artery bypass grafting has been shown to improve physical functioning in patients with moderate (stage 3) CKD,[3] but the effects of PCI and OMT on health status in patients with CKD have not been previously reported. Accordingly, we performed a post hoc analysis of clinical outcomes in the COURAGE trial after stratifying patients by their baseline kidney function.[4]

Methods

As described previously, 287 patients from the United States and Canada were enrolled in a randomized trial designed to determine whether PCI plus OMT, when used as an initial management strategy, reduces the risk of all-cause mortality or nonfatal myocardial infarction in patients with stable CAD compared with OMT alone.[4,5] CKD was not an exclusion criterion to enrollment, and there was no upper creatinine cutoff value. Glomerular filtration rate was estimated by the abbreviated 4-variable Modification of Diet in Renal Disease equation.[6] CKD was defined as a glomerular filtration rate of <60 ml/min/1.73 m^2. Intensive guideline-directed therapy and lifestyle intervention were applied equally to all patients.

Angina-related health status was measured by SAQ,[7–9] which was obtained at baseline, 1, 3, 6, and 12 months, and annually thereafter. The SAQ is a self-administered 19-item questionnaire that can be completed in <5 minutes and quantifies disease-specific health status in 5 domains: (1) physical limitations due to angina (e.g., limiting activities to avoid

angina), (2) recent change in the severity of angina, (3) the frequency of angina, (4) satisfaction with treatment for angina, and (5) angina-related quality of life. Scores range from 0 to 100, with higher scores indicating better health status. For responder analyses, clinical significance of changes in each of the SAQ scales was determined by the criteria of Wyrwich et al,[10] in which a change of ≥8 points on the physical limitation domain, ≥25 on the angina stability domain, ≥20 on the angina frequency domain, ≥12 on the treatment satisfaction domain, and ≥16 on the quality of life domain were considered clinically significant.

Means of observed scores for each SAQ domain at each time point were analyzed with unpaired *t* tests, comparing PCI plus OMT versus OMT alone for patients with or without CKD. Linear mixed-effects models were used to analyze SAQ scores longitudinally. These models included the main effects for treatment status, CKD status and time, as well as all 2-way interactions (treatment × time, CKD × time, and treatment × CKD) and the 3-way interaction (treatment × CKD × time). In addition, quadratic terms of time were included to account for nonlinear trends. In these analyses, missing data were considered missing at random. A second set of analyses treated intermittent missing data (e.g., valid values at 3 and 12 months, but a missing value at 6 months) as missing at random and were imputed using the method of multiple partial imputation.[5] The time point after the last available score for a given patient was considered the dropout point. Dropout was considered nonignorable, and the data were analyzed with a pattern mixture model l.[5] Finally, the aforementioned analyses were repeated including age, gender, race, diabetes, heart failure, and hypertension as covariates.

The proportion of patients with clinically significant increases in SAQ scores as defined previously were analyzed by chi-square tests for 2 by 2 tables comparing PCI plus OMT versus OMT alone with respect to change from baseline for participants with and without CKD. These analyses were performed at each time point. Longitudinal analyses were made by a generalized estimating equation for repeated measurements and were used to calculate adjusted percentage of patients with clinically significant improvement (yes or no) at each time point. These analyses included main effects for treatment status, CKD status and time, as well as all 2 interactions described previously. The same covariates included in the mixed models were also included in the general estimating exchange models.

All analyses were truncated at 36 months because data were not available for an increasingly large proportion of patients at later time points. A level of significance of $p < 0.01$ was used for all subgroup analyses and interactions.

The study was approved by institutional review committees at each participating site, and all patients gave informed consent.

Results

There were 2,029 patients with available glomerular filtration rate data from which CKD status could be calculated. Among patients treated with PCI plus OMT, 143 (14%) had CKD, whereas among patients treated with OMT alone, 167 (17%) had CKD. Table 1

compares demographic and clinical data for PCI plus OMT versus OMT alone, stratified by CKD status. There were no significant differences between PCI plus OMT and OMT alone for patients with and without CKD for any of the observed variables, including average Canadian Cardiovascular Society angina class score (1.8 ± 1.0 vs 1.7 ± 1.1, p = 0.552 respectively for patients with CKD and 1.7 ± 1.0 vs 1.6 ± 0.9, p = 0.246 for patients without CKD). However, patients with CKD, regardless of treatment, were older, more likely to be women and to have diabetes mellitus, hypertension, heart failure, and Canadian Cardiovascular Society angina class ≥3 (p <0.01 for all).

Table 2 lists PCI plus OMT versus OMT comparisons of observed domain means according to the CKD status. Mean scores for all but treatment satisfaction, which began high, increased substantially from baseline to 1 month for both PCI plus OMT and OMT alone, and then plateaued in both patients with and without CKD. The nonadjusted longitudinal analyses taking into account missing data showed similar results. For the physical limitation domain, there was a significant treatment status × CKD status interaction (p = 0.006), but this was due primarily to a difference in baseline scores. For treatment satisfaction, there was a significant effect of treatment status (p = 0.003). Patients treated with PCI plus OMT had better scores than patients treated with OMT alone whether they had CKD or not. The interaction treatment status × CKD status was not significant (p = 0.063) but was for the CKD status × time (p = 0.022), suggesting a different rate of improvement for those with and without CKD. Patients with CKD had lower treatment satisfaction scores at baseline than patients without CKD but increased at a greater rate and were similar to non-CKD scores from 12 months onward (Figure 1). CKD status was no significant factor influencing change in the quality of life or angina frequency domains. There was a significant treatment status × time interaction for the angina frequency (p = 0.003) domain. For angina frequency, scores of patients treated with PCI plus OMT were higher than in patients treated with OMT alone through 12 months of follow-up but were essentially at the same level by 36 months (Figure 1).

Addition of the covariates in the models did not change any of the associations between CKD, treatment status, and SAQ scores, except for the quality of life domain for which the interaction treatment status × time where p = 0.04 versus p = 0.057 in the nonadjusted model. Of the 987 patients treated with OMT alone, 227 (23.0%) had subsequent PCI (crossover) at any time during the study. The inclusion of crossover status as a covariate in the models did not result in any significant effect on the SAQ scores (p >0.15 for all analyses).

Figure 2 shows the percentage of patients with clinically significant increases in SAQ scores from baseline. For physical limitation, the percentage of patients with CKD with a clinically significant increase was greater among those treated with PCI plus OMT versus those treated with OMT alone at 1, 3, and 6 months. There were no significant differences between PCI plus OMT and OMT alone among the patients without CKD at any follow-up time (Figure 2). The results followed a similar pattern for quality of life (Figure 2) as for angina frequency; it is among those without CKD where the percentage of patients with a clinically significant increase was greater in the group treated with PCI plus OMT versus OMT alone (Figure 2). With 2 exceptions, there were no significant differences between PCI plus OMT

and OMT for either patients with or without CKD at any follow-up time for treatment satisfaction. For angina stability, which describes acute changes in angina, the 1-month angina stability score in patients with CKD showed a greater percentage of patients treated with PCI plus OMT with clinically significant improvement. At 36 months, for treatment satisfaction in the non-CKD group, there was a greater percentage of OMT patients with clinically significant improvement (Figure 2).

The longitudinal analyses of clinically significant improvement indicated that CKD status was not related to change in percentage of clinically significant improvement over follow-up time for patients treated with either PCI plus OMT or OMT alone for any of the SAQ domains ($p > 0.08$ for all interactions treatment status × CKD status).

Discussion

The high-risk cohort of patients with CKD enrolled in the COURAGE trial had relief of angina after initiation of treatment and derived clinically significant benefits from pharmacologic antianginal therapies and PCI to a similar extent as did patients without CKD with respect to quality of life, angina frequency, and angina stability SAQ domains. All patients were highly satisfied with their treatment even at baseline with mean scores >85. For physical limitation, patients with CKD had consistently lower mean scores than patients without CKD throughout follow-up. However, when analyzed as the rate of change in the percentage of patients with clinically significant increase from baseline, there were no statistically significant differences associated with CKD status for any of the domains. The percentage of patients with CKD with significant short-term improvement was greater for the group randomized to PCI plus OMT for physical limitation and quality of life at 1, 3, and 6 months, but the rate of change from 1 to 36 months was greater for patients treated with OMT alone. This is probably related to the fact that a larger percentage of patients treated with PCI plus OMT have immediate clinical improvement as was seen in the overall COURAGE study, which was attenuated over time. Likewise, the rate of change from baseline to 36 months in the percentage of patients with a clinically significant improvement in treatment satisfaction was greater in those treated with OMT. Improvement within the first 6 months was more common in patients treated with PCI and OMT than with OMT alone. Thus, consistent with the overall findings of the COURAGE trial,[4,5] patients with and without CKD had early benefit from PCI compared with OMT for symptomatic improvement, but these differences were no longer evident at 3 years.

There are several potential limitations of this study. This is a post hoc subgroup analysis, and as in any subgroup analysis, the lack of adequate sample size may influence both data interpretation and conclusions. Clinicians may have been reluctant to enroll patients with CKD and poor health status in the COURAGE trial, resulting in minimal differences in baseline SAQ scores between patients with and without CKD. We had a very small number of patients with advanced kidney disease, including patients on dialysis, enrolled in the COURAGE trial.[1] Nevertheless, our study provides important information on health status in a widely acknowledged high-risk cohort of patients with stable ischemic heart disease in whom treatment bias has been eliminated by random allocation of revascularization therapy.

Our present findings should encourage clinicians to treat angina intensively in patients with CKD using all appropriate guideline-based therapies as their health status benefits from treatment are comparable with those without CKD. In addition, initiation and continuation of therapies with survival benefits including statins and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, as appropriate, is essential in patients with CKD. Further randomized trials comparing revascularization to OMT are needed in the extremely high-risk population of patients with CAD and severe CKD to determine optimal therapeutic strategies that provide both effective relief of angina and improved survival.

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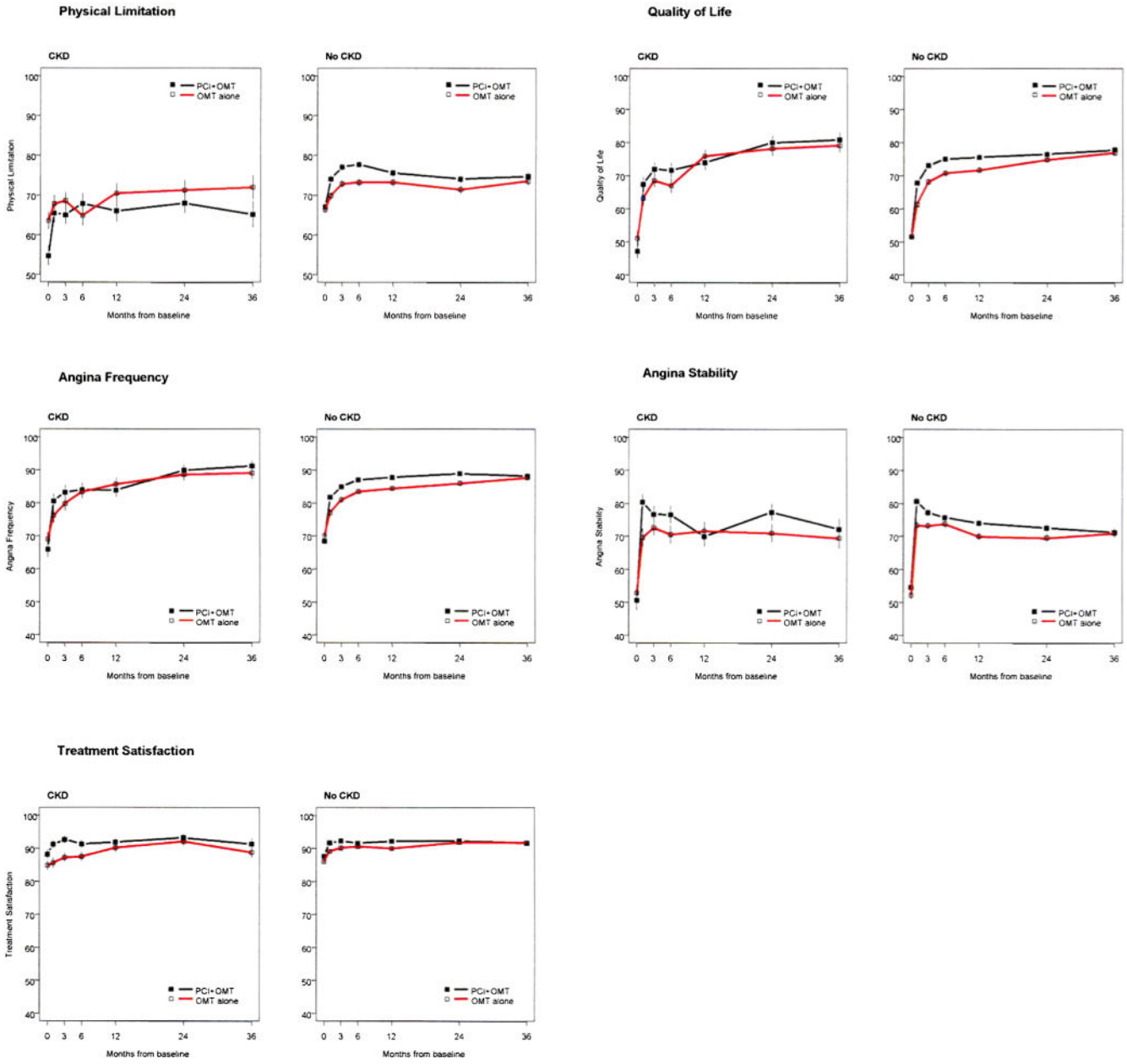

Figure 1.
Observed SAQ domain mean scores by CKD status, treatment arm, and follow-up.

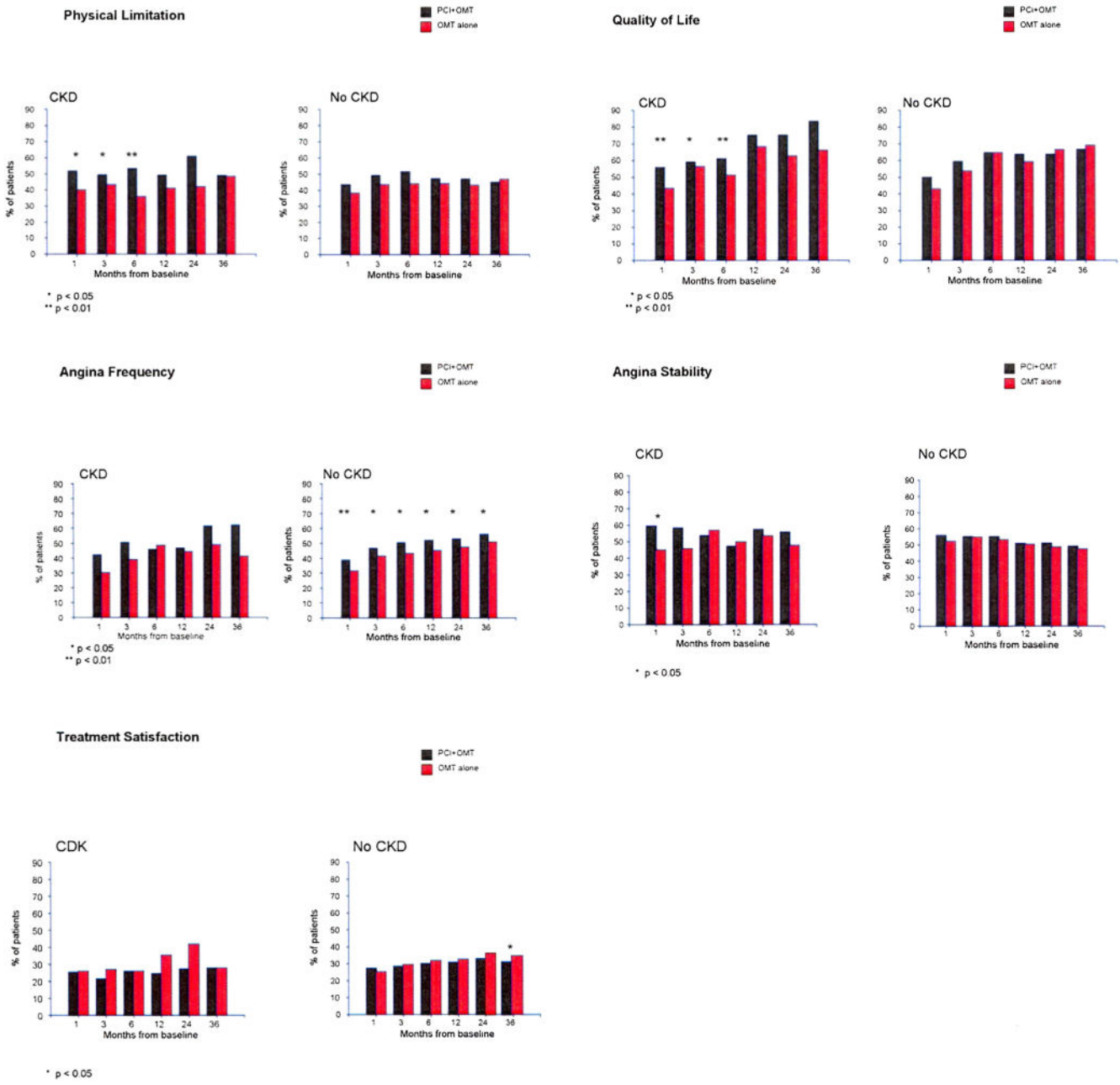

Figure 2.

Percentage of patients with clinically significant increases in SAQ domain scores by CKD status, treatment arm, and follow-up. Chi-square tests are used to compare the percentage of patients with clinically significant improvement between the 2 treatment arms.

Table 1

Demographic and clinical characteristics by chronic kidney disease (CKD) status and treatment

Variable	CKD Status	PCI Plus OMT, n = 1,042 (%)	OMT Alone, n = 987 (%)	p
Age (yrs)	CKD	68 ± 9	68 ± 10	0.983
	No CKD	61 ± 10	61 ± 9	0.952
Women	CKD	23 (33/143)	22 (37/167)	0.892
	No CKD	12 (109/899)	12 (96/820)	0.823
Caucasian	CKD	87 (124/143)	82 (137/167)	0.278
	No CKD	86 (776/899)	86 (707/820)	1.000
Diabetes mellitus	CKD	37 (53/143)	48 (79/165)	0.065
	No CKD	33 (287/877)	34 (273/801)	0.569
Canadian	CKD			0.795
Cardiovascular				
Society class				
0		13 (19/143)	17 (29/166)	
1		25 (36/143)	24 (40/166)	
2		32 (46/143)	31 (51/166)	
3–4		29 (42/143)	28 (46/166)	
	No CKD			0.441
0		11 (102/898)	12 (97/819)	
1		31 (278/898)	32 (260/819)	
2		36 (323/898)	38 (310/819)	
3–4		22 (195/898)	19 (152/819)	
Heart failure	CKD	12 (17/142)	13 (22/167)	0.864
	No CKD	3 (27/892)	3 (27/813)	0.783
Hypertension	CKD	86 (121/141)	78 (131/167)	0.104
	No CKD	85 (574/889)	68 (549/811)	0.183

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Table 2

Seattle Angina Questionnaire means, SDs, and sample size by chronic kidney disease (CKD) status, treatment, and follow-up

Domain	Visit	CKD					No CKD				
		PCI Plus OMT		OMT Alone		p	PCI Plus OMT		OMT Alone		p
		n	Mean ± SD	n	Mean ± SD		n	Mean ± SD	n	Mean ± SD	
Physical limitations	Baseline	109	54.7 ± 25.6	142	63.6 ± 26.2	0.008	765	67.1 ± 24.5	692	66.4 ± 25.0	0.60
	1 month	104	65.5 ± 24.6	120	67.8 ± 23.7	0.47	689	74.1 ± 23.5	635	69.8 ± 24.3	0.003
	3 month	108	65.0 ± 24.1	119	68.6 ± 23.8	0.26	685	77.1 ± 23.0	629	72.9 ± 23.3	<0.001
	6 month	98	67.9 ± 24.7	117	64.9 ± 27.1	0.39	717	77.8 ± 22.6	606	73.2 ± 23.5	<0.001
	1 yr	96	66.0 ± 26.1	114	70.5 ± 27.0	0.22	682	75.6 ± 23.8	599	73.2 ± 23.4	0.07
	2 yrs	90	68.0 ± 23.8	97	71.3 ± 24.7	0.36	600	74.1 ± 24.3	551	71.4 ± 24.2	0.06
	3 yrs	64	65.1 ± 26.6	72	72.0 ± 26.0	0.13	474	74.8 ± 23.8	448	73.6 ± 23.4	0.43
Quality of life	Baseline	116	47.1 ± 23.3	151	51.1 ± 26.2	0.20	787	51.8 ± 24.9	702	51.6 ± 24.8	0.99
	1 month	108	67.4 ± 23.2	128	63.2 ± 24.0	0.17	707	67.8 ± 23.6	657	61.3 ± 24.1	<0.001
	3 month	110	71.9 ± 21.8	125	68.5 ± 22.7	0.25	701	73.1 ± 22.1	639	68.2 ± 23.1	<0.001
	6 month	104	71.6 ± 24.7	118	67.0 ± 24.7	0.14	729	75.1 ± 21.8	622	70.8 ± 22.6	<0.001
	1 yr	100	73.9 ± 22.3	121	75.8 ± 21.9	0.52	694	75.6 ± 20.9	608	71.7 ± 22.4	0.001
	2 yrs	91	93.1 ± 11.4	97	78.1 ± 20.9	0.53	616	76.5 ± 22.1	557	74.8 ± 22.3	0.20
	3 yrs	68	80.8 ± 18.5	75	79.1 ± 18.6	0.60	483	77.8 ± 20.3	454	76.9 ± 20.8	0.52
Treatment satisfaction	Baseline	116	88.2 ± 14.9	151	84.8 ± 17.7	0.10	789	87.6 ± 15.0	700	85.9 ± 16.6	0.04
	1 month	108	91.1 ± 11.6	129	85.6 ± 17.9	0.004	707	91.6 ± 12.0	656	89.0 ± 14.3	<0.001
	3 month	110	92.6 ± 11.8	125	87.2 ± 14.3	0.002	701	92.2 ± 12.2	640	90.1 ± 13.9	0.003
	6 month	104	91.3 ± 11.8	119	87.4 ± 14.6	0.03	726	91.6 ± 12.9	622	90.5 ± 13.6	0.15
	1 yr	100	91.9 ± 12.2	121	90.1 ± 14.8	0.34	693	92.1 ±11.7	610	89.9 ± 13.8	0.003
	2 yrs	91	93.1 ±11.4	97	92.1 ± 12.5	0.55	615	92.2 ± 12.9	558	91.8 ± 12.7	0.53
	3 yrs	68	91.3 ± 13.8	75	88.6 ± 14.7	0.29	483	91.6 ± 12.1	455	91.8 ± 11.0	0.79
Angina frequency	Baseline	116	65.9 ± 26.8	151	68.9 ± 26.8	0.37	788	69.5 ± 26.3	712	70.0 ± 25.5	0.25
	1 month	108	80.6 ± 21.3	129	76.1 ± 25.5	0.15	709	81.7 ± 22.9	657	61.3 ± 24.1	<0.001
	3 month	110	83.2 ± 22.7	125	79.8 ± 24.3	0.27	702	85.0 ± 21.9	640	81.0 ± 23.0	0.001
	6 month	104	83.9 ± 21.5	120	83.3 ± 22.1	0.83	730	87.0 ± 19.6	622	83.5 ± 21.2	0.002
	1 yr	100	83.9 ± 21.6	120	85.7 ± 20.7	0.54	695	87.8 ± 19.1	610	84.4 ± 20.6	0.002

Domain	Visit	CKD					No CKD				
		PCI Plus OMT		OMT Alone		p	PCI Plus OMT		OMT Alone		p
		n	Mean ± SD	n	Mean ± SD		n	Mean ± SD	n	Mean ± SD	
Angina stability	2 yrs	91	89.9 ± 16.2	99	88.6 ± 18.6	0.61	617	88.9 ± 17.9	560	85.9 ± 19.4	0.007
	3 yrs	68	91.2 ± 13.2	75	89.1 ± 16.5	0.40	480	88.2 ± 19.3	451	87.7 ± 18.5	0.68
	Baseline	114	50.7 ± 32.3	148	58.1 ± 32.0	0.58	774	54.6 ± 33.1	694	52.2 ±31.9	0.16
	1 month	108	80.3 ± 24.4	128	69.5 ±31.0	0.003	700	80.6 ± 26.8	649	73.2 ± 27.4	<0.001
	3 month	108	76.6 ± 27.0	124	72.6 ± 26.4	0.25	694	77.2 ± 27.9	630	73.2 ± 27.4	0.009
	6 month	103	76.5 ± 27.1	116	70.4 ± 30.0	0.12	717	75.6 ± 28.0	614	73.7 ± 28.1	0.22
	1 yr	97	69.8 ± 28.9	117	71.6 ± 29.3	0.66	679	74.0 ± 26.7	595	69.9 ± 27.9	0.008
	2 yrs	91	77.2 ± 24.1	97	70.9 ± 26.9	0.09	600	72.5 ± 27.4	551	69.5 ± 27.1	0.06
	3 yrs	67	72.0 ± 27.0	75	69.3 ± 27.4	0.56	474	71.2 ± 27.9	442	70.9 ± 28.2	0.88