Original Paper

An Evaluation of the Effects of an Angiotensin Receptor Blocker on Health-Related Quality of Life in Patients With High-Normal Blood Pressure (Prehypertension) in the Trial of Preventing Hypertension (TROPHY)

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*The Trial of Preventing Hypertension (TROPHY) demonstrated the feasibility of possibly reducing the incidence of hypertension with the angiotensin receptor blocker candesartan compared with placebo. The long-term benefits of pharmacologic therapy in high-normal blood pressure, or prehypertension are not known, and the long-term effect on health-related quality of life (HRQL) has not been determined. An analysis of covariance model was used to assess treatment differences from baseline in the HRQL scores using Short Form (SF)–36, and component measures at subsequent visits. Of the 809 randomized patients, 734 had both baseline and ≥1 HRQL follow-up assessment: 95% (379 of 397) of patients receiving candesartan and 91% (355 of 388) of patients receiving placebo. There were no statistically significant between-group differences in least-squares mean physical component survey and mental component survey scores or the individual scales at each scheduled visit relative to baseline values (*P>.05*). In TROPHY, patients with prehypertension had relatively high baseline HRQL, and HRQL was maintained with the angiotensin receptor blocker candesartan over both the 2-year treatment period and a total 4-year trial period.* J Clin Hypertens (Greenwich). *2008;10:436–442.* ©*2008 Le Jacq*

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Clinical safety and efficacy data are necessary but insufficient for the comprehensive evaluation of new therapies, especially when the possible undesirable side effects of treatment on patients' overall well-being could lead to poor adherence and, consequently, lost opportunities to reduce morbidity and mortality.

Patient-reported outcome (PRO) refers to the assessment of subjective patient experience. Health-related quality of life (HRQL) is a particular type of PRO that provides a distinct contribution in determination of the impact of an illness and its treatment on overall patient well-being. Physiologic measures of drug effectiveness sometimes do not reflect how patients feel and function. In a study of antihypertensive therapies, for example, significant differences in HRQL scores between treatments were observed where the therapies had otherwise comparable clinical safety and efficacy.[1] Pharmacologic interventions may also

play an important role in maintaining and possibly improving patient HRQL. Several studies in patients with established hypertension have shown that patient symptoms and HRQL improve with control of blood pressure measures with diuretics and other medications.[2–4] However, to the best of our knowledge, no studies to date have evaluated this relationship in patients with prehypertension.

Although there is currently no standardized approach for the assessment of HRQL in hypertensive patients,[5] scientific methods for measuring such subjective outcomes are well developed, with psychometric evaluations providing evidence on each instrument's reliability and validity. Scientifically sound clinical trial designs and statistical analyses are required to capture changes in HRQL.

Prevention of hypertension is considered an important intervention in the prevention of cardiovascular disease by the World Health Organization and by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC). The Trial of Preventing Hypertension (TROPHY) reported the feasibility of reducing the incidence of hypertension in patients with high-normal blood pressure, or prehypertension, using the angiotensin receptor blocker (ARB) candesartan compared with placebo.[6] In TROPHY, during the 2-year period of active treatment and 4-year total trial duration, treatment with this ARB was associated with a safety and tolerability profile similar to placebo. However, hypertension and its pharmacotherapy have been associated with changes in HRQL,[7] potentially due to possible effects on patients' symptoms.[8] Although the many studies performed to evaluate HRQL in hypertensive patients have frequently demonstrated no change or an improvement in quality of life scores as blood pressure is lowered, no such evaluations have been made in patients with prehypertension.[9] This report will present the analysis of HRQL, a prespecified secondary end point, in TROPHY as well as an analysis of burden of illness (BOI) and a comparison of baseline characteristics relative to otherwise similar normotensive individuals and relative to those with uncomplicated clinical hypertension.

MATERIALS AND METHODS

Detailed information regarding the design of TROPHY is provided in a separate publication.[6] Briefly, TROPHY was a 4-year randomized, double-blind, placebo-controlled multicenter US study that enrolled patients aged 30 to 65 years who had prehypertension (average blood pressure values ≤139 mm Hg systolic/85–89 mm Hg diastolic or 130–139 mm Hg systolic/≤89 mm Hg diastolic) and had not received pharmacologic therapy in the preceding 6 months. Patients were randomized to once-daily double-blind treatment with candesartan 16 mg or matching placebo for 2 years, followed by a 2-year single-blind period during which all patients were treated with placebo.

The impact of candesartan on HRQL was assessed using the self-administered Short Form (SF)–36 questionnaire. The SF-36 consists of 36 items that cover 8 domains (physical functioning [PF], role physical [RP], bodily pain [BP], general health [GH], vitality [VT], social functioning [SF], role emotional [RE], and mental health [MH]). Patients completed the SF-36 questionnaire at the randomization visit, at months 24 and 48 (or at the time of premature discontinuation), and at the time of the primary study end point of developing clinical hypertension as defined in TROPHY: blood pressure ≥140/90 mm Hg on any 3 visits or at the final visit, blood pressure ≥160/100 mm Hg on any one visit, or development of hypertension requiring treatment. Changes from baseline in subscale scores and physical and mental component summary scores of the SF-36 were also evaluated.

The 8 individual domains were used to derive the physical component summary (PCS) and mental component summary (MCS) scores. The PCS score was derived from the PF, RP, BP, and GH scales, while the MCS score was derived from the VT, SF, RE, and MH scales. Scoring of the scales and summary measures were based on algorithms defined in the SF-36 manual.[10]

Statistical Analysis

Our HRQL sample included all randomized patients who had both a baseline and at least one postbaseline HRQL assessment. For the HRQL analyses, patients were analyzed according to their randomized treatment (eg, intention-to-treat) using the last-observation-carried-forward (LOCF) approach. An analysis of covariance model was used in the comparison of treatment differences in the changes from baseline in HRQL scales and component scores at months 24 and 48. If <50% of the items in one scale were missing, the mean scores for the completed items in the same scale for that patient were used for imputation. If at least 50% of the items in one scale were missing, the subscale was considered missing for that patient. Data were not imputed if the entire scale was missing.

To further characterize the TROPHY population, regression methods were utilized to compare

Table I. Patient Characteristics at Baseline (N=734)	
DEMOGRAPHICS	
Age, y	48.7
Male	60.1
Female	39.9
Asian	4.5
Black	9.4
Caucasian	83.4
Hispanic	1.5
Other	1.2
CLINICAL CHARACTERISTICS	
Cardiovascular diseases	4.2
Type 2 diabetes	1.4
Other	16.1
Values are percentages unless otherwise noted.	

the BOI in patients with prehypertension to the US general population norms and to patients with uncomplicated hypertension (with no other chronic condition) from the Medical Outcome Study (MOS), statistically adjusting them to match the age and sex distributions of the TROPHY sample. Additional covariates included the presence of cardiovascular disease, type 2 diabetes, and any other chronic conditions. Significance tests were used to compare the means across samples.

The US general population norms were estimated from the responses to the 1998 National Survey of Functional Health Status (NSFHS), which included the SF-36 health survey. The overall response rate for the NSFHS was 67.8%. Sampling weights were applied to adjust the sample to match the age, sex, and age by sex distribution of the US population, according to 1998 US Census Bureau data. Detailed sampling and data collection methods of the NSFHS are described elsewhere.[11]

The MOS was a 4-year observational study of variations in practice styles and of health outcomes for chronically ill patients.[12] More than 20,000 patients participated in the MOS in 1986 from 523 randomly sampled clinicians in prepaid group practice HMOs, multispecialty groups, and solo and small single-specialty group practices in Boston, Chicago, and Los Angeles. Patients with 5 "tracer" conditions (hypertension, myocardial infarction, type 2 diabetes, congestive heart failure, and clinical depression) were selected for the study. The presence of 27 comorbid medical conditions was determined using a standardized medical history questionnaire completed at the baseline visit of the study. Patients completed a mailed questionnaire that included the SF-36. The MOS data were used for comparisons.

RESULTS

Baseline Characteristics

Of 809 randomized patients, 734 patients had both a baseline and at least one post baseline measurement: 95% (379 of 397) of patients receiving candesartan and 91% (355 of 388) of patients receiving placebo. Of these, 730 patients had evaluable data (one candesartan and three placebo patients had missing baseline PCS scores). The majority of study participants were male (60.1%) and Caucasian (83.4%), with a relatively low prevalence of chronic conditions including cardiovascular diseases, 4.2%; type 2 diabetes, 1.4%; and other conditions, 16.1% (Table I). A total of 51 patients (18 candesartan, 33 placebo) had their HRQL data imputed. There was no evidence that the missing data were systematic.

Treatment Effect Analysis

Among patients included in the HRQL population, mean scores and standard deviations for the PCS and MCS at baseline were similar in the candesartan (51.85±7.17 and 52.98±7.25, respectively) and placebo (51.46±7.37 and 53.80±7.18, respectively) groups.

At each scheduled time point, scores for the PCS and MCS were relatively unchanged relative to baseline values in both treatment groups. At the LOCF visit, mean PCS and MCS scores averaged 50.91±8.01 and 53.04±7.98 in the candesartan group, respectively, and 51.19±7.38 and 53.90±7.48 in the placebo group, respectively (Table II). Similarly, there were no differences between the candesartan and placebo groups for any of the individual physical or mental scales at any time point ($P>.05$).

BOI Analysis

Initial comparison to the age- and sex- adjusted US general population norms (N=2031) demonstrated significantly better baseline scores for the TROPHY participants than the general population norms on all of the 8 scales and 2 summary measures, with the mean score differences between the groups ranging from 1.91 for the PF scale to 4.31 for the BP scale ($P<.0001$). Further adjustment for chronic conditions, however, revealed that TROPHY participants had significantly lower scores (worse HRQL) on all of the scales except the RP and RE scales and the MCS measure (mean range, 1.14–2.53; $P<.05$) (Table III).

When compared with the age- and sex-adjusted MOS patients with uncomplicated hypertension (n=1581), the TROPHY participants had a significantly higher score on 3 scales (RP, GH, and RE)

Table II. Treatment Group Effects and Pairwise Comparisons for Baseline, Month 24, Month 48, and Final Visit (LOCF) for SF-36 Component Summaries (Quality of Life Population)

	Candesartan		Placebo		Treatment Group Difference (Candesartan Minus Placebo)[a]		
Time Point/Scale	No.	LS Mean (SE)	No.	LS Mean (SE)	LS Mean (SE)	95% CI	*P* Value
Baseline[b]	378		352				
PCS		51.85±7.17		51.46±7.37			
MCS		52.98±7.25		53.80±7.18			
Month 24	316		202				
PCS		51.320 (0.376)		51.733 (0.471)	–0.413 (0.603)	–1.597 to 0.772	.494
MCS		53.030 (0.405)		53.673 (0.507)	–0.643 (0.650)	–1.921 to 0.634	.323
Month 48	139		94				
PCS		51.022 (0.560)		52.382 (0.681)	–1.360 (0.881)	–3.097 to 0.376	.124
MCS		54.465 (0.527)		54.766 (0.642)	–0.311 (0.834)	–1.954 to 1.331	.709
Final visit (LOCF)	375		347				
PCS		50.815 (0.347)		51.380 (0.361)	–0.565 (0.501)	–1.549 to 0.418	.260
MCS		53.242 (0.364)		53.647 (0.379)	–0.405 (0.526)	–1.438 to 0.628	.442

Abbreviations: CI, confidence interval; LOCF, last-observation-carried-forward; LS, least-squares; SE, standard error; [a]Pairwise comparisons performed using an analysis of covariance model with baseline as the covariate. [b]Baseline values include mean and standard deviations. Physical component summary (PCS) consists of the physical functioning, role physical, bodily pain, and general health concepts. Mental component summary (MCS) consists of the vitality, social functioning, role emotional, and mental health concepts.

Table III. Burden Comparison of the Baseline TROPHY Data to the US Norms

	TROPHY Sample (n=734)		General US Population Norms, Age- and Sex-Adjusted (N=2031)		General US Population Norms, Age-, Sex-, and Disease-Adjusted (N=2031)		TROPHY vs General Population, Age-, Sex-, and Disease-Adjusted	
	Mean	SE	Mean	SE	Mean	SE	Mean Difference	F
SF-36 scales								
Physical functioning	52.02	0.30	50.11	0.28	53.93	0.38	1.91	15.341[a]
Role physical	53.69	0.26	50.25	0.30	54.36	0.41	0.67	1.883
Bodily pain	53.99	0.31	49.68	0.31	55.85	0.40	2.53	13.216[b]
General health	53.54	0.25	49.90	0.31	55.48	0.40	1.94	16.662[a]
Vitality	54.53	0.30	50.69	0.31	55.67	0.42	1.14	4.832[c]
Social functioning	53.26	0.27	50.46	0.31	54.70	0.43	1.44	8.119[d]
Role emotional	52.94	0.26	50.52	0.31	53.56	0.44	0.62	1.472
Mental health	52.52	0.27	50.25	0.31	54.05	0.43	1.53	9.030[d]
SF-36 summary measures								
Physical summary	53.29	0.26	49.87	0.29	54.99	0.39	1.70	13.19[b]
Mental summary	53.07	0.27	50.56	0.31	53.94	0.43	0.87	2.872

Abbreviations: SE, standard error; SF, Short Form; TROPHY, Trial of Preventing Hypertension. [a]*P*<.0001; [b]*P*<.001; [c]*P*<.05; [d]*P*<.01.

as well as the PCS (mean difference, 1.92–5.34; *P*<.01). Further adjustment for chronic conditions, however, demonstrated that the prehypertensive patients had a significantly lower BP score (mean difference, 1.81; *P*<.05) and significantly higher GH (mean difference, 3.82; *P*<.0001) and RE (mean difference, 1.57; *P*<.05) (Table IV).

When compared with the US general-population healthy subsample (n=589), approximately 8% more TROPHY participants reported having at least some level of BP; approximately 4 times more TROPHY participants reported that at least "a little bit" of BP interfered with normal work (81.4% vs 20.7%). Approximately 18% more TROPHY

Table IV. Burden Comparison of the Baseline TROPHY Data With the MOS Uncomplicated Hypertension Group

	TROPHY Sample (n=734)		MOS Uncomplicated Hypertension Group, Age- and Sex-Adjusted (n=1581)		MOS Uncomplicated Hypertension Group, Age-, Sex-, and Disease-Adjusted (n=1581)		TROPHY vs Uncomplicated Hypertension Group, Age-, Sex-, and Disease-Adjusted	
	Mean	SE	Mean	SE	Mean	SE	Mean Difference	F
SF-36 scales								
Physical functioning	52.02	0.30	52.32	0.59	53.35	0.64	1.33	3.56
Role physical	53.69	0.26	50.44	0.64	52.25	0.69	–1.44	3.756
Bodily pain	53.99	0.31	53.84	0.60	55.80	0.65	1.81	6.254[a]
General health	53.54	0.25	48.20	0.54	49.72	0.58	–3.82	36.725[b]
Vitality	54.53	0.30	53.49	0.59	55.05	0.63	0.52	0.555
Social functioning	53.26	0.27	53.35	0.48	54.09	0.53	0.83	1.998
Role emotional	52.94	0.26	50.67	0.66	51.37	0.72	–1.57	4.200[a]
Mental health	52.52	0.27	52.48	0.56	52.89	0.61	0.37	0.307
SF-36 summary measures								
Physical summary	53.29	0.26	51.37	0.60	53.37	0.65	0.08	0.012
Mental summary	53.07	0.27	52.28	0.56	52.72	0.61	–0.35	0.282

Abbreviations: MOS, Medical Outcome Study; SE, standard error; SF, Short Form; TROPHY, Trial of Preventing Hypertension.
[a]$P<.05$; [b]$P<.0001$.

participants reported that at least "a little bit" of BP interfered with normal work than in the healthy subsample (n=751) of the uncomplicated hypertension group who did not have any other comorbidity (81.4% vs 63.7%).

The responses to the individual GH items of the TROPHY participants were largely comparable to those of the healthy subsample of the US general population. The perception of the GH of the healthy subsample of the uncomplicated hypertension group with no comorbidity appeared to be worse than that of the TROPHY participants. For example, approximately 70% of the TROPHY participants did not expect their health to get worse, but only 50% of the uncomplicated hypertension group with no comorbidity perceived that it might.

DISCUSSION

In the current study, we evaluated the impact of the ARB candesartan on HRQL in the TROPHY trial. Patient self-reports of HRQL were relatively unchanged throughout the 4-year study following treatment with both candesartan and placebo. The current study is the first to report the effect of antihypertensive therapy on HRQL in prehypertensive patients.

The current analysis is confirmatory of previously reported data on the tolerability of candesartan in the TROPHY population, in which the proportion of patients who discontinued study medication prematurely due to an adverse event was comparable in the medication and placebo groups during the 4-year study period (7.3% vs 5.9%) and during the 2-year double-blind treatment period (5.6% vs 5.4%). A factor in selecting an ARB for use in this trial compared with placebo was the expected safety and tolerability profile based on treatment of patients with hypertension.

In addition to being relatively healthy, TROPHY participants were from a highly functioning population. Regardless, some limitations, such as bodily pain, might have interfered with normal life when compared with the healthy US population. The observed increase in BP in TROPHY participants may be to some extent related to the higher average body mass index (BMI) in this population (30 kg/m^2) ,compared with the US norm (27 kg/m^2), as BMI and BP are highly correlated.[13,14]

The findings from this study further reinforce the impression that hypertension is a relatively but not completely "silent" disease. The BOI analysis indicates that hypertension alone, particularly when in an early stage, does not have a great impact on functional status and psychological well-being. The comparison against disease-adjusted norms, however, suggests that there is some impact, but the impact is relatively small. Recent data suggest that patients

with established hypertension receiving pharmacotherapy may feel better as blood pressure is lowered because of symptom improvement, regardless of the type of medication given.[2,15] Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists may offer some advantage with regard to effects on cognitive function and sexual activity[16]; one study has also suggested that a calcium channel blocker–based treatment regimen lowered the incidence of dementia.

The current results are consistent with previous studies evaluating the effect of candesartan on HRQL. A previous study demonstrated that in a placebo-controlled trial of hypertensive African Americans, lower diastolic and systolic blood pressure levels were achieved in patients treated with candesartan 16 to 32 mg once daily, with no change in their HRQL as assessed by SF-36, during the 12-week study.[17] Another study that evaluated the effect of candesartan on the HRQL of elderly hypertensives (Study on Cognition and Prognosis in the Elderly [SCOPE])[18] reported similar findings. Adverse effects are commonly a cause of therapy discontinuation in many conditions including hypertension. A treatment regimen that maintains patients' HRQL is more likely to be taken regularly, with potential additional benefits. Pharmacologic interventions in patients with established hypertension with many medications, including ARBs, suggest a great impact on HRQL in treated patients compared with placebo.[4]

Study Limitations

The current study results have to be considered in the context of several limitations. First, HRQL was assessed using a generic instrument. Disease-specific PRO measures are relevant to a particular group of patients and are developed to assess specific populations and evaluate the impact of a particular medical condition and/or treatment and may be more appropriate to use.[19,20] However, there are currently no disease-specific PRO measures for prehypertension or hypertension. Generic measures may be used to characterize healthy samples without a particular medical condition, and since TROPHY was a trial in relatively healthy patients, the use of a generic measure was appropriate.[21]

Lipid abnormalities were defined using medical history codes 272.0, 272.1, and 272.9. National Cholesterol Education Program Adult Treatment Panel III guidelines for identifying patients with dyslipidemia were not utilized. This may have underestimated or overestimated the prevalence of dyslipidemia in the TROPHY population; however, any misclassification due to this definition is nondifferential between the treatment groups and should not alter the study conclusions.

Another limitation is that the relatively healthy TROPHY patients with high baseline HRQL may be healthier than patients with similar blood pressure levels who may not be willing or eligible to participate in a clinical trial due to the implementation of the inclusion and exclusion criteria. To that end, the study findings may underestimate the BOI of prehypertension.

The study design did not allow for a responder analysis, which would further evaluate whether individuals who developed clinical hypertension had a lower HRQL compared with those who remained disease-free. Moreover, since we did not collect data on circadian blood pressure, we could not further evaluate the relationship between changes in blood pressure levels and changes in HRQL over time. Last, while the study cohort included 9% blacks and 8% other races, there were too few nonwhites for a post hoc subgroup analyses.

The current study also has several strengths. It was the first study to evaluate the BOI in prehypertension and the impact of treatment on HRQL in this population. Further, previous studies evaluating the impact of HRQL in hypertension generally focused on a smaller sample of patients and provided short-term (eg, 12 weeks) assessments.[5] Unlike those studies, the current analysis included a longer-term assessment (up to 4 years) and a relatively large sample size.

CONCLUSIONS

In TROPHY, patients with prehypertension had relatively high baseline HRQL. HRQL were maintained with the ARB candesartan over the 2-year treatment period and an additional 2-year period when all patients were on placebo follow-up. Future research should consider the development of standardized methods for assessing HRQL in hypertension and prehypertension in order for comparisons to be made more easily across various studies and patient populations. Additional studies on how prehypertension can impact HRQL in patients outside of trial settings would further help to characterize the impact of disease on everyday functions. Given the fact that HRQL in hypertension may be affected by the lack of adherence to treatment regimens,[22] it is important to provide programs and/or services to improve adherence, which would ultimately maximize therapeutic benefits. Last, the observed higher BMI in this patient population suggests the importance of early screening and identification of patients at risk for hypertension

and the effective management of comorbidities that may affect the development of hypertension and its consequences, as well as HRQL.

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