Quality of Life Measured in a Practice-Based Hypertension Trial of an Angiotensin Receptor Blocker

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Effectiveness of antihypertensive treatment depends not only on drugs that avoid or minimize symptomatic side effects but also on therapy that has a positive effect on quality of life. This study assessed the effect on quality of life of a contemporary agent (an angiotensin receptor blocker) and evaluated the validity and practicality of using a quality-of-life instrument in the practice-based setting. A total of 2716 hypertensive patients, either untreated or on single-agent therapy, were started on or switched to 40 mg telmisartan for 6 weeks; in patients whose blood pressures remained above 130/85 mm Hg after 2 weeks, the dose was increased to 80 mg for the remaining 4 weeks of treatment. Quality of life was measured by patient self-administration of the Psychological General Well-Being Index (GWBI) at baseline and at the end of the study. Sixty-eight percent (n=1858) of patients treated with telmisartan fully completed both GWBI tests; the test score increased by 5.2±0.3 (p<0.0001) from 77.7±0.4. This improvement was observed across all six emotional and health subscales of the GWBI. White and black patients, those aged <65 or ≥65 years, and men and women had similar increases, though the baseline value in women was sharply lower (p<0.001) than in men. The GWBI rose more in patients whose blood pressure was controlled by treatment (<140/90 mm Hg) than in noncontrolled patients (6.1 vs. 4.1, p<0.0001); for all patients the decreases in systolic and diastolic blood pressures produced by telmisartan correlated significantly (p<0.001 for each) with the increases in the GWBI scores. Controlling blood pressure appears to be an important element in improving subjective health perceptions of hypertensive patients.
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Guidelines on antihypertensive therapy based on the results of major clinical outcomes trials urge achievement of lower blood pressure goals,[1] yet only one in four hypertensive patients in the United States has a blood pressures below the recommended target of 140/90 mm Hg.[2] Although a variety of clinical, social, and economic factors contribute to this poor result, side effects or poor tolerability of drugs can also be a limiting factor in optimizing treatment.

Symptomatic side effects alone are by no means the only factors that determine patient satisfaction with antihypertensive therapy. The concept of measuring quality of life during treatment of hypertension was first highlighted in a major trial in 1986 when a rigorous comparison was made among three drugs commonly used at that time:

the central α agonist methyldopa, the β blocker propranolol, and the angiotensin-converting enzyme (ACE) inhibitor captopril.[3] Despite the virtually identical blood pressure effects of these agents, the quality-of-life scores with captopril were significantly better than with the other two drugs. Since then, numerous other clinical trials have evaluated quality-of-life measures during antihypertensive trials.[4–8] The ability of instruments that measure quality of life to discriminate among drugs was demonstrated in one trial in which two members of the ACE inhibitor class, despite very similar blood pressure efficacy and side effect profiles, were shown to have different impacts on quality of life.[9]

The angiotensin receptor blockers are a relatively new class of antihypertensive agents that have already demonstrated clinical outcomes benefits like stroke prevention in hypertension[10] and renal protection in diabetic nephropathy.[11,12] These agents are now well accepted for antihypertensive treatment.[13] Telmisartan, a member of this class of drugs, has produced significant antihypertensive effects in formal clinical trials and has exhibited a tolerability profile that is not different from placebo.[14,15]

The purpose of this study was to evaluate the efficacy of telmisartan in a practice-based clinical trial and in particular to measure its effects on quality of life in patients being managed by primary care physicians. The Psychological General Well-Being Index (GWBI)[16] was the instrument selected for measuring quality of life in this study. A second objective of this research was to determine whether this type of measurement could be applied effectively in the offices and clinics of a large number of physicians with little or no formal research experience. Demonstrating successful use of such an instrument in this setting could create future opportunities for rigorously evaluating the true effectiveness of drugs in the hands of clinicians.

METHODS

Investigators

The study was performed by 703 community-based physicians who responded to invitations to participate in the trial. These physicians, most of whom had not previously participated in formal clinical research protocols, were instructed by the principal investigators of the study in conducting an observation of this type, including identification of patients, the need for rigorous and accurate completion of the case report forms, and the appropriate rules for obtaining informed consent from potential subjects. A central Institutional Review Board approved most of the participating physician sites, although a small number of investigators with academic or hospital affiliations obtained approval from their local Institutional Review Boards.

Patients

The participants in the trial were patients aged 18 years or older. Men and women were enrolled, although women of childbearing potential were excluded from the study. To be eligible for the study patients were required to have stage 1 hypertension (i.e., systolic blood pressure 140–159 mm Hg, diastolic pressure 90–99 mm Hg, or both). Patients could either be untreated at the time of study entry or have stage 1 hypertension while on current therapy. This latter group was termed the "Treated but Uncontrolled" group, and probably included patients who had stage 2 or higher hypertension before starting treatment. Only those patients receiving single-agent therapy at the time of entering this study were eligible for enrollment. If at any time during the study a patient's systolic blood pressure was ≥180 mm Hg or diastolic blood pressure was ≥110 mm Hg, they were to be withdrawn from the trial and given additional or alternative therapy to bring their blood pressure under control.

Protocol

All patients started treatment with 40 mg telmisartan once daily. In the case of patients who were taking another antihypertensive agent at the start of the study, telmisartan was substituted for the other agent. There was no washout period. If after 2 weeks (visit 2) the systolic blood pressure was ≥130 mm Hg, the diastolic blood pressure was ≥85 mm Hg, or both, the dose of telmisartan was increased to 80 mg once daily for the 4-week treatment maintenance period. Patients controlled at visit 2 remained on the 40-mg dose. Patients taking medications for concomitant conditions continued those medications throughout the study. Details of these treatments are not reported here.

Measurements

At each visit blood pressure and heart rate were measured with patients in the seated position after 5 minutes rest. Blood pressure was taken as the average of two readings obtained 2 minutes apart. As part of the investigator training there was a description of correct measurement technique, although in the trial investigators used the instruments and methods that were customary in their offices or clinics. Clinical evaluations were done at each visit and documented both in the patient's medical chart and

Table I. Effects of Telmisartan on Quality of Life (General Well-Being Index) Composite Scores*

PATIENTS	BASELINE	TREATMENT	ADJUSTED DIFFERENCE**	*P* VALUE†
Previously untreated (n=1321)	77.5±17.3	83.2±15.4	5.6±10.8	<0.0001
Treated controlled (n=48)	79.8±16.4	81.9±18.1	2.7±10.4	0.0618
Treated uncontrolled (n=486)	78.2±16.9	82.7±15.4	4.6±11.2	<0.0001

*Values are mean±SD; an increase in score means an improvement in quality of life; **adjusted for baseline values; †values are for within-group changes, the adjusted mean differences within the groups were not significantly different from each other

in the Case Report Form. If at any time the investigator determined that continued study participation could jeopardize a patient's well-being or safety (primarily the onset of a serious medical event, although such events were not reported in detail), the patient was to be discontinued from the study.

Quality of Life

Quality of life was measured by GWBI[16] at the time of study initiation (when patients were either untreated or receiving single-drug therapy with an agent other than telmisartan) and again at the end of the study. GWBI is a composite of six different subjective emotional and well-being domains that are listed in the Results section. Each of these subscales is composed of three or four questions. Because the questions from the different subscales are intermingled, it is necessary for patients to complete virtually the entire instrument to provide valid results for any of the subscales. In this study, data are presented only if patients fully completed the baseline and treatment evaluations. The protocol required patients to answer the questions at their physician's office without knowing their blood pressure responses to treatment and without input from family members or the professional staff.

Statistics

All available data from all investigator sites were combined for analysis. For categorical variables, frequencies and percentages were calculated as appropriate. When applicable, comparisons among subgroups employed the Fisher exact test. For continuous variables, descriptive statistics were employed. Comparisons among subgroups were performed using analyses of variance (ANOVA) if the data were normally distributed. If the data were not normally distributed the Kruskal-Wallis test was used. A paired *t* test was used to compare data between baseline (visit 1) and the end of treatment (visit 3). Covariates such as the respective baseline values were evaluated for having an effect on the change in measurements. If any of these baseline values were found to significantly affect the results, they were included in the final model. Blood pressure control rates were evaluated using the Cochran-Mantel-Haenszel test. All tests were performed using a two-tailed test at a significance level of 0.05.

RESULTS

Of the 2716 patients enrolled in the trial, fully completed baseline and treatment scores for the GWBI were available in 1858 patients (68.4%). For patients for whom data were not included in the analysis, the principal reason was inadequate completion of either the baseline or the treatment test. The average age of the patients was 55 years in both men and women. The other clinical characteristics of these participants are shown in Tables I–IV. The average baseline blood pressure for patients as a whole was 153±12.2/93.6±7.7 mm Hg; the changes in systolic and diastolic blood pressures and in heart rate during the 6 weeks of treatment with telmisartan are summarized in Figure 1.

For the entire cohort, the baseline composite score for GWBI was 77.7±0.4, and it increased by 5.2±0.3 ($p<0.0001$) by the end of the study. The baseline and treatment values for GWBI in the three principal patient groups (previously untreated, previously treated but with uncontrolled blood pressure, and previously treated with controlled blood pressure) during the study are shown in Table I. There were highly significant increases in both the previously untreated and treated but uncontrolled groups; the increase in the small treated and controlled group was less than in the other groups and did not reach significance.

GWBI data subdivided according to major demographic subgroups are summarized in Table II.

Table II. Effect of Telmisartan on Quality of Life (General Well-Being Index) in Treatment Subgroups*

PATIENTS	BASELINE	TREATMENT	ADJUSTED DIFFERENCE**	*P* VALUE BETWEEN SUBGROUPS
Age				
<65 (n=1362)	77.1±17.5	82.9±15.5	5.6±0.3	<0.01
≥65 (n=494)	79.7±16.3	83.3±15.1	4.2±0.5	
Sex				
Male (n=926)	81.1±15.9	85.5±14.8	5.5±0.3	0.303
Female (n=930)	74.5±17.8	80.6±15.6	5.0±0.3	
Race				
White (n=1405)	77.9±17.2	82.8±18.5	5.0±0.3	0.1408†
Black (n=251)	77.7±17.6	83.4±15.5	5.7±0.6	

*Baseline and treatment values are mean±SD; **mean±SE based on least mean square with baseline values as covariant in model; for all values, $p<0.0001$; †based on overall analysis of covariance, white vs. black is not significant

Table III. Composite Quality-of-Life Score (General Well-Being Index) in the Telmisartan 40-mg and 80-mg Dose Groups and in Patients Controlled or Noncontrolled

GROUP	BASELINE	TREATMENT	ADJUSTED DIFFERENCE*	*P* VALUE BETWEEN SUBGROUPS**
Dose group				
40 mg (n=773)	77.8±16.7	83.7±14.7	5.9±0.4	0.0395
80 mg (n=1049)	77.6±17.6	82.6±15.9	4.9±0.3	
Blood pressure control (<140/90 mm Hg)				
Controlled (n=1064)	78.5±17.1	84.4±14.8	6.1±0.3	<0.0001
Noncontrolled (n=794)	76.8±17.3	81.2±16.1	4.1±0.4	

*Adjusted for baseline values; differences are based on least square means, $p<0.0001$ within each group; **based on least squares means with baseline values as covariant in model

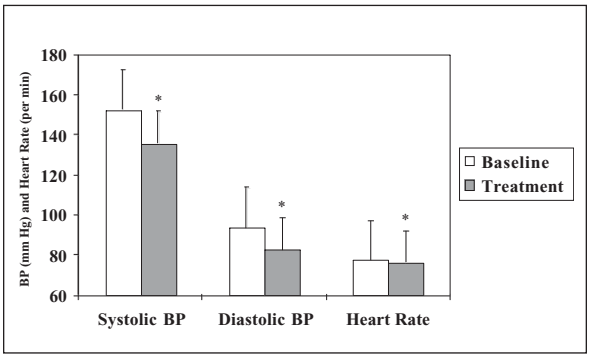

*Figure 1. Baseline and treatment values (mean±SD) for systolic and diastolic blood pressures (BPs) and heart rate in 1858 patients treated with telmisartan 40–80 mg daily for 6 weeks; *p<0.0001*

When patients were divided into those aged <65 years and those ≥65 years, there was a tendency for a greater increase in the quality-of-life score in the younger group. However, this may have been partly accounted for by the higher baseline value in the older group. There were virtually identical numbers of men and women in the study. There was a sharp difference between these two subgroups in their baseline scores, with men having significantly higher values than women. During the study there were similar increases in GWBI score for both subgroups. There were no differences either in baseline values or changes during treatment for GWBI between white and black patients.

The relationships between the treatment-induced changes in quality of life and in blood pressure were evaluated three different ways. First, univariate regression analysis (Pearson's correlation coefficient) for the change in systolic blood pressure and change in GWBI was -0.12 ($p<0.0001$, two-tailed test), and for the change in diastolic blood pressure and GWBI it was -0.11 ($p<0.0001$). The second approach (Table III) was to compare quality-of-life results in those patients whose blood pressures were controlled on the initial 40-mg telmisartan dose and those who required titration to the higher 80-mg

Table IV. Changes in Quality-of-Life Scores in Each of the Six Subscales of the General Well-Being Index*

	Anxiety Subscale	Depressed Mood Subscale	Positive Well-Being Subscale	Self-Control Subscale	General Health Subscale	Vitality Subscale
Blood pressure controlled?						
Yes (n=1064)	1.7±0.1**	0.7±0.1**	1.0±0.1**	0.5±0.1**	0.8±0.1**	1.3±0.1**
No (n=796)	1.0±0.1	0.4±0.1	0.7±0.1	0.2±0.1	0.5±0.1	0.9±0.1
Age						
<65 (n=1362)	1.5±0.1	0.7±0.04**	0.9±0.1††	0.4±0.04	0.7±0.05**	1.2±0.1
≥65 (n=494)	1.3±0.1	0.4±0.1	0.7±0.1	0.3±0.1	0.5±0.1	1.0±0.1
Ethnicity						
White (n=1405)	1.4±0.1	0.5±0.04	0.8±0.1†	0.3±0.04	0.6±0.05	1.1±0.1
Black (n=251)	1.5±0.2	0.6±0.1	1.2±0.2	0.3±0.1	0.8±0.1	1.3±0.2
Sex						
Men (n=926)	1.5±0.1	0.7±0.05†	0.9±0.1	0.4±0.05	0.8±0.1**	1.2±0.1
Women (n=930)	1.3±0.1	0.5±0.05	0.9±0.1	0.3±0.05	0.5±0.1	1.1±0.1

*Values are mean±SE; **p<0.01; †p<0.05; ††p<0.1

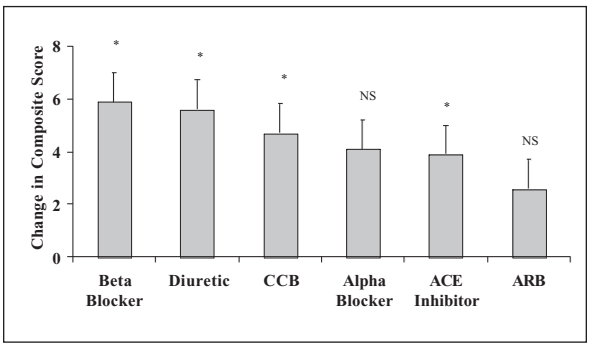

Figure 2. Changes (mean±SD) in the composite Psychological General Well-Being Index scale in hypertensive patients divided according to their hypertensive treatment before being switched to telmisartan 40–80 mg daily. CCB=calcium channel blocker; ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker

dose. There was a trend for the more easy-to-control 40-mg group to have a slightly greater increase in GWBI score during the trial, but this difference, although significant, was modest. Finally, there was a comparison between patients whose blood pressures were controlled (<140/90 mm Hg) by the end of the study and those whose blood pressures were not controlled (Table III). The adjusted difference between these groups (taking into account their baseline differences) indicated a significantly greater increase in GWBI score in the patients who achieved blood pressure control.

The composite GWBI is composed of six subscales (Anxiety, Depressed Mood, Positive Well-Being, Self Control, General Health, and Vitality). The results for these individual subscales are shown separately for each of the blood pressure control and demographic patient subgroups in Table IV. Patients whose blood pressures were controlled during the study had significantly better scores in all six of the individual subscales than patients whose blood pressures were not controlled. Differences between the other subgroups were less consistent, but both younger patients and men seem to have better outcomes in the General Health subscale whereas black patients appeared to do better than whites in the Positive Well-Being subscale.

Patients who entered the study with blood pressure uncontrolled on previous single-agent antihypertensive therapy were immediately switched to treatment with telmisartan. Thus, the baseline values in these patients reflected their scores on previous treatment whereas the end-of-study scores reflected the values on telmisartan. Figure 2 shows the changes in the composite GWBI scores produced by telmisartan according to the previous classes of agents. There were significant increases in

the composite scores when patients were switched from β blockers (baseline value 79.1±17.3), diuretics (baseline value 74.0±19.0), calcium channel blockers (baseline value 78.6±16.2), and ACE inhibitors (baseline value 79.4±16.3). The changes from α blockers (baseline value 86.9±13.2) and angiotensin receptor blockers (baseline value 76.5±17.1) were not significant. The drug was well tolerated. Headache caused withdrawal in 0.5% of patients, asthenia in 0.2%, chest pain in 0.2%, other complaints listed as body as a whole in 0.2%, cardiovascular complaints in 0.5%, digestive complaints in 0.6%, and dizziness in 0.4%.

DISCUSSION

The angiotensin receptor blockers are known to be effective antihypertensive agents,[13,17] and it is not surprising that single-agent treatment with telmisartan reduced blood pressure by an average of 16/11 mm Hg in hypertensive patients studied in this practice-based trial. Blood pressure was controlled (<140/90 mm Hg) in 54% of these patients. This was achieved with the starting dose of 40 mg in just over half of the controlled patients, whereas the higher 80-mg dose was required in the others. Consistent with previous experiences with this agent and other angiotensin receptor blockers,[13–15,17] the incidence of adverse events in this study was very low.

The principal objective of this study was to measure the effect of this type of antihypertensive treatment on quality of life as measure by the GWBI.[16] For patients as a whole, there was a highly significant increase of 5.2 from the baseline value of 77.7 in the composite score. This result compares favorably with increases of 2.2–4.2 reported in the principal subgroups of the Hypertension Optimal Treatment (HOT) trial[18] in which the same quality-of-life instrument was used in patients receiving antihypertensive treatment regimens designed to achieve aggressive blood pressure targets. It is possible that the greater increase in GWBI score in our study reflects the use of a single, well-tolerated agent compared with more complex multidrug therapy. Moreover, the duration of treatment in the HOT trial was far longer than in this study, again requiring caution in making comparisons.

In another antihypertensive trial that also used GWBI, comparisons among a calcium channel blocker, an ACE inhibitor, and a low-dose fixed combination of a diuretic and β blocker demonstrated benefits for both the calcium channel blocker and the combination therapy,[19] although of lesser amplitude than in our study. However, one caveat in interpreting the results of this study is that data were not obtained (due to inadequate or absent documentation) for about 30% of patients; we cannot fully exclude the possibility of some selection bias such that patients who were dissatisfied with the treatment experience might have declined to fill out the test documents.

Role of Blood Pressure Control

In this study effective blood pressure reduction with telmisartan was a meaningful contributor to improved GWBI scores. Not only was there a significant statistical correlation between the reductions in blood pressure and the increases in the quality-of-life scores, but also the mean increase in the GWBI in patients whose blood pressures were controlled was significantly greater than in those whose blood pressures were not. Moreover, those patients whose blood pressures responded rapidly to the 40-mg starting dose of telmisartan had greater increases than those who required titration to the 80-mg dose. These findings are consistent with those from the HOT study in which patients allocated to the most aggressively treated group had greater improvements in quality of life than those patients whose blood pressures were reduced to a lesser extent.[18] Our findings may also help explain the report cited earlier[19] in which GWBI scores in patients treated with an ACE inhibitor rose significantly less than in patients treated with a calcium channel blocker or a diuretic-β blocker combination. In that study the reduction in blood pressure with the ACE inhibitor was significantly less than with the other therapies.

It has been suggested that the satisfaction associated with achieving a good blood pressure result might, of itself, contribute to a perceived improvement in quality of life.[20] Although this possibility cannot be ruled out, patients in our study, as in the previous experiences,[18,19] supposedly were not aware of their responses to treatment at the time they underwent their final GWBI testing. A further explanation for the improvement in the quality-of-life score for patients in this study could be related to more frequent visits to their doctor's office. The detailed care and attention that patients received from the clinical staff may also have contributed to an improved quality of life.

Major Subgroups

Similar increases in quality of life were observed in each of the major subgroups: men and women, patients aged under 65 years and 65 years or older, and in white patients and black patients. For the two ethnic groups, the baseline values and the changes

during treatment were virtually identical. Younger patients had a greater increase in GWBI score during the study, but because the older group had a slightly higher baseline value, the end scores for the two subgroups were similar. Although the effects of treatment on quality of life did not differ between men and women, it was noteworthy that the baseline values in women were significantly lower than in men. Although a difference of this magnitude clearly is meaningful, the explanation is not obvious. Possible reasons could include the fact that women, when compared with men, have a more realistic understanding of the cardiovascular implications of a condition like hypertension. It is also possible that in a cohort with an average age of 55 years a relatively large proportion of female patients may have been affected by menopausal symptoms.

Consistency Across Domains

GWBI is composed of six separate domains representing separate emotional states that, taken together, provide an accurate and reproducible subjective assessment of well-being or distress.[16] Treatment with telmisartan in this study was effective in increasing the scores in each of these subscales (as listed in Table IV).

Differences between the various demographic subgroups or those patients regarded as controlled or noncontrolled tended to be small. Men had a slightly greater improvement than women in the general health subscale as did younger patients compared with older patients. Black patients seem to get a greater benefit than white patients in the Positive Well-Being subscale but other differences based on age, ethnicity, or gender were modest. Control of blood pressure appeared to provide a consistent advantage across all six subscales, again emphasizing that a successful treatment outcome appears to provide broad-based emotional benefits.

Comparison With Previous Treatment

In the subset of patients who were switched to telmisartan at the start of the study after their blood pressure had not been controlled on previous single-agent therapy, the greatest increases in quality of life were observed in patients originally treated with β blockers or diuretics. The large improvement observed in quality of life in patients previously receiving diuretics is not particularly surprising, for the baseline GWBI scores in that group were clearly lower than in patients taking other types of drugs. The improvement of quality of life in patients who had previously taken β blockers could have been predicted by the results of the first major quality-of-life studies in hypertension, in which the ACE inhibitor captopril was found to be significantly superior to the β blocker propranolol.[3] Appropriately, the least improvement in quality of life was observed in those patients who were switched to telmisartan from other angiotensin receptor blockers, confirming the validity of the differences between telmisartan and the other antihypertensive drug classes. Although these findings are of some interest, it should be noted that in clinical practice it is more common to add drugs rather than substitute when treatment responses are inadequate.

Implications for Practice

This study has shown that clinicians without experience as clinical investigators are able to assess quality of life utilizing GWBI in their practices. This instrument is robust and carefully interweaves its six principal domains among the questions that patients are asked. Previous studies have shown that there is no carryover effect of previous treatments when the GWBI is measured,[19] so changes resulting from new treatment or interventions probably are meaningful. The validity of this tool was further established in our study by the observation that the greatest improvements in quality of life occurred, as in previous studies,[18,19] in those patients who experienced the greatest reductions in blood pressure during antihypertensive therapy. In addition, the observation that quality of life increased far more in patients switched from previous therapy with either diuretics or β blockers, which are known to be associated with lower quality-of-life scores than other drug classes,[3,21] whereas there was not a significant change in patients previously treated with angiotensin receptor blockers, provides further confidence in the instrument. It is also evident that drugs like telmisartan are well tolerated and are associated with greater long-term adherence to therapy than other drug classes.[21–23]

Because this type of quality-of-life testing is simple to apply, requires little time, and is convenient and inexpensive, consideration should be given to employing it more frequently to evaluate the well-being of patients in clinical practice and to assess their overall responses to treatment.

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