Stroke Was Predicted by Dimensions of Quality of Life in Treated Hypertensive Men

Stefan Agewall, MD, PhD; John Wikstrand, MD, PhD; Björn Fagerberg, MD, PhD

Background and Purpose—Psychosocial factors have been suggested as risk factors for atherosclerotic disease. The purpose of the present study was to examine whether quality of life predicted strokes and acute coronary events in a prospective study.

Methods—The study included 412 treated hypertensive men, aged 50 to 72 years, with $1 of the following: serum cholesterol $6.5 mmol/L, smoking, or diabetes mellitus. The Minor Symptoms Evaluation Profile (MSEP) was used to estimate quality of life at entry. Incidences of stroke and acute coronary events were recorded during follow-up. The median follow-up time was 6.6 years.

Results—Sixty-four patients had an acute coronary event, and 37 had a stroke during the follow-up period. The Cox regression analyses revealed that the 3 dimensions of MSEP at entry were significant predictors of stroke. The relationship between low contentment at entry and the incidence of stroke during follow-up remained significant (relative risk = 1.04; 95% CI, 1.01 to 1.06; $P = 0.003$) even after adjustment for other potential cardiovascular risk factors. Vitality also remained an independent predictor for stroke after adjustment for these potential cardiovascular risk factors (relative risk = 1.04; 95% CI, 1.02 to 1.06; $P < 0.0001$). There was no relationship between MSEP score at entry and myocardial infarction during follow-up.

Conclusions—An independent and significant association between reduced well-being at entry and future stroke was observed in hypertensive men at high cardiovascular risk. The causal relationship is not known, however. (Stroke. 1998;29:2329-2333.)

Key Words: psychiatric status rating scales ■ quality of life ■ risk factors ■ social support ■ stroke

Psychosocial factors have been suggested as risk factors for atherosclerotic disease. Experimental studies of several animal species have shown that coronary pathology can result when animals are exposed to conditions that disrupt the social environment.1 Cynomolgus macaque monkeys in particular have been used to study the behavioral influences on atherosclerosis. Recently, in a study of female monkeys it was reported that subordinate animals developed significantly more atherosclerosis in the iliac artery than dominant monkeys.2

In humans, the type A personality has been found to be associated with an increased risk for myocardial infarction in some prospective studies.3,4 However, other studies have failed to find this association.5,6 Low socioeconomic status has been found to be associated with an increased incidence of coronary heart disease,7 and it has been reported that social support, which refers to emotional and informational aid obtained from an individual’s social ties or community resources, might have a protective effect8,9 against coronary heart disease. High workload, low status control, competitiveness, depression, feelings of anger, and a low level of social activities are examples of other factors that have been shown to be associated with atherosclerotic diseases.1,10-12

Most of the previous studies have examined the relationship between several psychosocial factors and coronary heart disease. However, a few studies also suggest a relationship between psychosocial factors and cerebrovascular disease. In a study of noninstitutionalized elderly men and women, depressive symptoms were associated with an increased stroke incidence during the follow-up period.13 In a cross-sectional study of patients with signs of atherosclerosis, a significant relationship was revealed between plaque status in the carotid artery, evaluated with high-resolution B-mode ultrasonography, and feelings of aggression and anger.10 We have previously reported that feelings of discontent in treated hypertensive men at high cardiovascular risk were significantly and independently associated with an increase in maximum intima-media thickness in the common carotid artery after 3 years of follow-up.14

Because these patients have been followed up for >6 years, we wanted to examine, in a hypothesis-seeking study, whether
quality of life, as measured by the Minor Symptoms Evaluation Profile (MSEP), predicted strokes and acute coronary events.

Subjects and Methods

Patients
Five hundred eight male patients with treated hypertension were included in a risk factor intervention study. The inclusion criteria for the patients in that study were, apart from treated hypertension and male sex, age between 50 and 72 years and ≤1 of the following: hypercholesterolemia (serum cholesterol ≥6.5 mmol/L), tobacco smoking (≥1 cigarette per day), or diabetes mellitus. The present study was a subset of a sample from this larger intervention study, since 412 of the 508 answered the MSEP questionnaire.

The serum cholesterol criterion was based on the mean of 2 measurements. The diagnosis of hypertension had been established according to previously reported routines. Exclusion criteria were unwillingness to participate and malignant or other serious chronic disease. The background population was representative of high-risk hypertensives in Gothenburg, Sweden, since the majority (>90%) were recruited earlier by screening a random third of all men in their respective age groups in Gothenburg.

In the risk factor intervention study, the patients were randomized either to an intervention program directed toward hypercholesterolemia, smoking, and diabetes mellitus or to conventional treatment. All subjects gave informed consent after written and oral information was received, and the study was approved by the Ethical Committee of the Faculty of Medicine, Göteborg University.

Examinations
At entry the patient history of cardiovascular or renal disease was carefully documented. Established criteria for stroke, intermittent claudication, myocardial infarction, and angina pectoris were used. Smoking habits were evaluated by means of a questionnaire. Patients' ongoing medication was recorded.

Blood pressure was measured by specially trained nurses with a mercury sphygmomanometer using a cuff of appropriate size. Diastolic blood pressure was determined as Korotkoff phase V. The patient rested in the recumbent position for 5 minutes, and the mean of 2 recordings was used. Body mass index was calculated as weight in kilograms/(height in meters)^2. Venous blood was drawn after an overnight fast and after 5 minutes of supine rest for determination of blood glucose and serum concentrations of total cholesterol, HDL cholesterol, and triglycerides according to established methods.

The patients were seen biannually during the follow-up. After an average of 6.2 years, the patients were examined in a manner similar to that at entry.

Intervention
For the intervention group, the aims were to obtain a serum concentration of total cholesterol <6.0 mmol/L, to help current smokers to quit, to prevent patients from starting to smoke, and to reduce the HbA1c level to <6.0% in diabetic patients. With respect to blood pressure, the treatment goal was a diastolic blood pressure <90 mmHg in both groups.

The results of the intervention program in the total study group (n=508) have previously been reported. In summary, the program was effective in reducing cardiovascular morbidity and mortality.

Minor Symptoms Evaluation Profile
Subjective experiences of the patients were evaluated with a standardized questionnaire at entry of the study. The MSEP is a self-administered questionnaire with 24 questions based on a visual analog scale, which has been shown to be valid, reproducible, and sensitive to the effects of pharmacological treatment. The internal consistency (Cronbach's α-coefficient) of the dimensions has previously been shown to be 0.81 for contentment, 0.81 for vitality, and 0.77 for sleep. Low values on the visual analog scale indicate positive feelings, and high values indicate negative feelings.

The MSEP has been shown to discriminate between symptoms induced by different classes of drugs, as well as differences in the subjective well-being of normotensive, borderline hypertensive, and hypertensive subjects. Thus, the present study used the MSEP as the measure of quality of life.

Instead of using the answers to the individual questions as effect variables, the questions that have similar factor loading in a principal component analysis are combined. Three dimensions are thus created from 15 of the 24 questions in the MSEP. These 3 dimensions are assumed to reflect the patient’s condition regarding contentment, vitality, and sleep: (1) contentment (7 items: happiness, tranquillity, self-control, decisiveness, self-confidence, mental fatigue, and general well-being); (2) vitality (5 items: enthusiasm, initiative, endurance, concentration, and responsiveness); and (3) sleep (3 items: nocturnal sleep, quality of sleep, and insomnia).

By using the 3 dimensions as primary variables instead of using the answers from each of the 24 questions for evaluating subjective symptoms, the variability in the answers can be reduced, and the problem of multiple significance is avoided.

Assessment of End Points
The underlying intervention study started in November 1987 and ended on June 1, 1995. The maximum follow-up time was 7.8 years, and the median follow-up time was 6.6 years. No patient was lost to end-point registration. The criteria for myocardial infarction were hospitalization for a clinically diagnosed infarction and fulfillment of ≥2 of the following: (1) central chest pain, shock, syncope, or pulmonary edema suggesting myocardial infarction; (2) typical changes in enzymes; and (3) typical ECG changes with occurrence of pathological Q waves and/or localized ST variations. Stroke was defined as hospitalization for this diagnosis, ie, clinical signs of sudden focal or global neurological deficit of presumed vascular origin. Both fatal and nonfatal events were recorded. All events were independently coded by 2 physicians without knowledge of the identity of the patients. The physicians had access to blinded copies of hospital records, autopsy records, and death certificates. In cases with multiple causes of death, previously established coding rules were used.

Statistical Analysis
Results are presented as means and SDs. Unpaired t test and Fisher’s exact test were used to compare continuous and categorical variables, respectively. Relative risk and 95% CI were calculated with the Cox regression model. Relative risk was calculated as the risk when the variable in focus was increased by 1 unit (x+1)/x and by 1 SD (x+SD)/x. Only 2-sided tests were performed. P<0.05 was regarded as statistically significant.

Results
At entry, 412 patients completed the MSEP questionnaire, and 96 patients did not. In the group with missing MSEP data, smoking was more prevalent than in the patients with available MSEP data (41% and 26%, respectively; P<0.05). Otherwise the group with available MSEP data did not differ from the group with missing MSEP data.

Clinical characteristics and drug treatment at entry for patients with and without stroke during the follow-up period are given in Table 1 (n=412). Patients who suffered from a stroke during follow-up had significantly higher values for contentment, vitality, and sleep, indicating more negative feelings, than those without stroke during the study period. The former group also had a higher prevalence of concomitant cardiovascular disease at entry and were more often treated with calcium channel blockers. No other significant differences were observed between those groups.

Patients with any other previous cardiovascular disease (myocardial infarction, angina pectoris, intermittent claudication, or stroke) at entry (n=111) had significantly higher values (indicating more negative feelings) of contentment,
vitality, and sleep than patients without additional concomitant cardiovascular disease \( (P < 0.01) \).

The most pronounced difference was observed when those with intermittent claudication \( (n = 37) \) were compared with the other patients. The MSEP value for contentment was 36 ± 17 for the group with intermittent claudication compared with 24 ± 12 for the other patients \( (P < 0.0001) \).

The corresponding values for vitality were 37 ± 20 and 26 ± 14, respectively \( (P < 0.0001) \), and the values for sleep were 40 ± 28 and 24 ± 21, respectively \( (P < 0.0001) \). Patients with concomitant cardiovascular disease at entry were more often treated with calcium channel blockers than patients without previous cardiovascular disease \( (22\% \text{ and } 12\%, \text{ respectively}; \ P < 0.05) \).

Serum creatinine was significantly associated with contentment at entry \( (r = 0.11; \ P < 0.05) \). Weight and HDL cholesterol were significantly associated with vitality at entry \( (r = 0.12 \text{ and } r = 0.10, \text{ respectively}; \ P < 0.05) \). Sleep was not associated with any of the measured variables at entry.

**Cardiovascular Events During Follow-Up**

No patient was lost to end-point registration. Sixty-four patients had an acute coronary event (38 nonfatal myocardial infarctions, 17 fatal myocardial infarctions, and 9 sudden coronary deaths), and 37 had a stroke (32 nonfatal and 5 fatal) during the follow-up period.

In the Cox regression analyses, all 3 dimensions of MSEP at entry were predictors of stroke (Table 2). In the following Cox regression analyses, group assignment in the underlying risk factor intervention study and all variables significantly associated with the respective dimension of MSEP at entry were entered into the analyses (Table 3). The relationship between low contentment at entry and the incidence of stroke during follow-up remained significant \( (\text{relative risk} = 1.04; \ 95\% \text{ CI, 1.01 to 1.06}; \ P = 0.003) \) even after adjustment for serum creatinine at entry, group assignment in the underlying risk factor intervention study, and previous cardiovascular disease at entry (myocardial infarction, angina pectoris, intermittent claudication, and stroke). Vitality remained an

<table>
<thead>
<tr>
<th>TABLE 1. Patient Characteristics at Entry for Patients Without and With Stroke During the Follow-Up Period (n=412)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Without Stroke During Follow-Up</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
</tr>
<tr>
<td>Systolic</td>
</tr>
<tr>
<td>Diastolic</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/L</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
</tr>
<tr>
<td>Any cardiovascular disease at entry, n (%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
</tr>
<tr>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Intermittent claudication</td>
</tr>
<tr>
<td>Previous stroke</td>
</tr>
<tr>
<td>Drug treatment, n (%)</td>
</tr>
<tr>
<td>Thiazides</td>
</tr>
<tr>
<td>β-blocker</td>
</tr>
<tr>
<td>Calcium antagonist</td>
</tr>
<tr>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>Hydralazine</td>
</tr>
</tbody>
</table>

Values are mean (SD), unless otherwise is stated. ACE indicates angiotensin-converting enzyme.

*P < 0.05, †P < 0.01.

**TABLE 2. Relative Risks for Stroke in Treated Hypertensive Men (n=412)**

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>95% CI</th>
<th>β-Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contentment</td>
<td>1.037</td>
<td>1.014–1.061</td>
<td>0.037</td>
</tr>
<tr>
<td>Vitality</td>
<td>1.042</td>
<td>1.022–1.062</td>
<td>0.041</td>
</tr>
<tr>
<td>Sleep</td>
<td>1.014</td>
<td>1.001–1.027</td>
<td>0.014</td>
</tr>
</tbody>
</table>
TABLE 3. Relative Risks for Stroke in Treated Hypertensive Men After Adjustments for Group Assignment in the Underlying Risk Factor Intervention Study and All Variables Significantly Associated with the Respective Dimension of MSEP at Entry (n=412)

<table>
<thead>
<tr>
<th>Dimension of MSEP at Entry</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>β-Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contentment (after adjustment for CVD at entry, group assignment, creatinine)</td>
<td>1.036</td>
<td>1.012–1.061</td>
<td>0.035</td>
<td>0.003</td>
</tr>
<tr>
<td>Vitality (after adjustment for CVD at entry, group assignment, HDL, weight)</td>
<td>1.043</td>
<td>1.022–1.064</td>
<td>0.042</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep (after adjustment for CVD at entry and group assignment)</td>
<td>1.011</td>
<td>0.998–1.024</td>
<td>0.010</td>
<td>0.096</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease.

Discussion

The major finding of this study was that a low self-estimated measure of quality of life was an independent predictor for stroke after >6 years of follow-up in treated hypertensive men.

To estimate quality of life is very difficult, and there is no gold standard method to measure this dimension. The method used in the present study, the MSEP, is based on a questionnaire for self-assessment in which a visual analog scale is used. This instrument has been evaluated by assessing the effects of different drugs on well-known symptom profiles. In addition, construct validity has been established by calculating the correlation coefficients between dimensions of MSEP and those of other questionnaires, eg, the Nottingham Health Profile. Compared with equivalent dimensions of other questionnaires for measurement of health-related quality of life, the dimensions of the MSEP were found to be relevant. Furthermore, a fundamental requirement is that the used instrument produces the same results in repeated use. This matter has previously been evaluated by test/retest reliability and has been shown to be acceptable.

In the present study, all 3 MSEP dimensions were found to differ significantly between patients with and without other cardiovascular disease. This was an expected finding that supports the validity of the MSE profile to estimate the quality of life. Hence, all these observations taken together lead us to believe that the MSEP is a valuable tool to estimate aspects of quality of life that are of clinical importance.

All 3 dimensions of the MSE profile were predictors of stroke. However, there were obviously confounding factors. The intervention program was found to improve survival, an important finding that has been reported previously; in addition, as mentioned, cardiovascular disease at entry was associated with MSEP. When these and other variables associated with the dimensions of MSEP were included as covariates in the Cox regression analyses, the dimensions of contentment and vitality were independently and significantly associated with the incidence of stroke during the follow-up period.

Few studies have evaluated the importance of psychosocial factors in relation to stroke incidence. A prospective study by Colantonio et al reported that symptoms of depression predicted stroke in elderly noninstitutionalized subjects. In a cross-sectional study, socioeconomic status was related to the intima-media thickness of the carotid artery, evaluated with ultrasound, in a population-based sample. In a smaller cross-sectional study, feelings of anger were associated with atherosclerotic plaque score in the carotid artery. We have previously observed that feelings of discontent predicted progression of intima-media thickness of the common carotid artery in a subgroup of patients in the present study. Recently, Everson et al reported that psychological stress increased the progression of intima-media thickness of the common carotid artery. In the latter study, subjects with signs of atherosclerotic plaques in the carotid artery combined with feelings of psychological stress had a particularly pronounced increase of intima-media thickness during follow-up compared with low-stress subjects.

Thus, several previous reports support a relationship between psychosocial factors and cerebrovascular atherosclerosis; however, most previous studies have reported a relationship between psychosocial factors and coronary heart disease.

In the present study we found no relationship between MSEP score at entry and major coronary events during follow-up. The underlying mechanism behind the observation that a low self-estimated measure of quality of life was an independent predictor for stroke, but not for coronary disease, is not obvious. However, it is important to keep in mind that several previous studies have failed to find an association between psychosocial factors and coronary heart disease; and there certainly is a publication bias; a positive finding is more likely to be published than a negative observation. The relationship between psychosocial factors and coronary heart disease is not completely established. Furthermore, our study group was unique in that it involved mostly elderly, treated hypertensive men with additional cardiovascular risk factors and with a high prevalence of...
other coexisting cardiovascular diseases, whereas most previous studies have been population-based studies.

Because of the selection criteria of the study group, we cannot generalize our conclusions to the entire hypertensive population, even though most of the patients originally were recruited by screening a random third of all men in their respective age groups in Gothenburg.27

Both feelings associated with a high sympathetic activity3,4,10 and feelings associated with low socioeconomic status, depression, and, as in the present study, low quality of life9,11,13,22,24 have been observed to be associated with atherosclerotic manifestations. Since such different emotions lead to the same result, there probably are different pathophysiological pathways between different psychosocial factors and cardiovascular disease. Knowledge about this potentially causal relationship is limited. It has been suggested that increased sympathetic nervous activity is associated with atherosclerotic disease. Acute stress produced by anesthesia in rabbits28 and psychosocial stress in monkeys28 have been shown to injure the vascular endothelium. Interestingly, blockade of β-adrenergic receptors has been shown to inhibit the atherogenic effects of chronic stress, suggesting that high chronic sympathetic activity may contribute to the pathogenesis of atherosclerosis during chronic stress.27 Others have suggested that the link between emotional states and cardiovascular disease is mediated by a neuroendocrinological activation. The renin-angiotensin system is activated by emotional arousal,28 and this results in an increased production of angiotensin II, which might accelerate atherosclerosis.29 There are also indications that the fibrinolytic system is activated during mental stress, which may have the potential to increase the risk for cardiovascular events.29 Altogether, the link between psychosocial factors and cardiovascular disease is not clear.

In conclusion, an independent and significant association between reduced well-being at entry and future stroke was observed in hypertensive men at high cardiovascular risk. The causal relationship, however, is not known. Our results must be confirmed in other studies. If these studies yield similar results, further research is needed to understand the underlying mechanisms. This might lead to the development of novel treatment strategies in patients at high risk of cardiovascular disease.

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