β-Adrenergic Blockade After Stroke. A Preliminary Closed Cohort Study

Gunilla Kinnander, Matti Viitanen, and Kjell Asplund

To collect background data for a prospective clinical trial of β-blocking agents in the prevention of deaths after stroke, the long-term prognosis in 60 patients discharged from a stroke unit on β-blocker therapy was compared with the outcome in 60 matched patients with stroke but without β-blockers. Matching included sex, age, type of stroke, and presence or absence of hypertension and cardiac failure. Thirteen patients (22%) in the β-blocker group died during a median followup of 41 months. Of the 60 patients not on β-blockade at discharge, 21 (35%) died during a median followup of 36 months. By life-table technique and log-rank test, the relative risk for death was 0.60:1.00 (p = 0.14). During followup, 12 recurrent strokes were observed in patients on β-blockers and 19 in patients without β-blockers (relative risk 0.57:1.00; p = 0.12). It appeared that the reduction in mortality could only marginally be ascribed to fewer deaths from myocardial infarction; other causes of death were also less frequent in β-blocker-treated patients. The results emphasize that supplementary information on the effect of β-blocking agents on mortality after stroke is needed before a larger trial of β-blocker therapy in patients with manifest cerebrovascular disease can be initiated. (Stroke 1987;18:240-243)

Most attempts to improve prognosis after stroke have been directed towards the cerebrovascular disease process itself. The benefits of such attempts are, at best, limited. The long-term case fatality rates in patients with cerebrovascular disease are, however, determined as much by death due to cardiac disorders as by recurrent strokes. Therefore, an alternative approach to reduce morbidity and mortality late after stroke could be to prevent new cardiac events in patients with cerebrovascular disease. Such a therapeutic strategy has previously been advocated for patients with transient ischemic attacks (TIA’s).

Several studies have demonstrated that β-adrenergic-blocking agents (β-blockers) reduce mortality after acute myocardial infarction (MI) (for reviews, see References 5 and 6), and β-blockers are now used extensively in the secondary prophylaxis of MI. We have therefore explored the feasibility of a randomized trial of β-blocking agents after stroke and the possible expected effects of such a treatment. The long-term outcome in patients discharged from our stroke unit on β-blockers has been compared with the outcome in matched patients without β-blockers.

Subjects and Methods

This is a "closed cohort" study, i.e., all probands and control patients have been obtained from the same well-defined cohort of stroke patients, all of whom have been investigated by a common structured program at the time of acute stroke and then followed prospectively. Within this database, cases have been identified retrospectively and matched with control patients from the same cohort.

The background cohort consisted of 522 patients with acute stroke (excluding subarachnoidal hemorrhage) admitted to the stroke unit of Umeå University Hospital between 1978 and 1983. Of the surviving patients, 60 were discharged with β-blockers. Of these, 33 were on selective (28 metoprolol, 5 atenolol) and 27 on nonselective drugs (15 propranolol, 7 alprenolol, 5 pindolol).

Each of the 60 patients on β-blocker therapy was matched with a control subject obtained from the same background cohort. Focal time (corresponding to time of entry in randomized trials) was defined as the day of discharge from the stroke unit. Matching at this point included sex, age (within 5 years), cerebrovascular diagnosis (TIA, embolic brain infarction, nonembolic infarction, and intracerebral hemorrhage), presence or absence of hypertension, and a previous history of congestive heart failure. This last cardiac variable was chosen because it has been found to be the single most powerful cardiac-related prognostic factor in this cohort (Viitanen et al, to be published). When a perfectly matching patient was not available, we made the best possible match using the hierarchy among the 5 items described above. Apart from cardiac failure (which was included in the matching), no obvious cardiovascular absolute or relative contraindications to β-blockers were found in the control patients in a retrospective surveillance of the medical records. All clinical data were obtained from our computer-based prospective stroke unit registry.

The possibility that any beneficial effects of β-blockers was restricted to the acute phase of stroke, limiting the brain lesion and thus creating a prognosti-
cally more favorable situation in treated patients, was considered. A subpopulation of patients on treatment with β-blockers at entry to the hospital and still on β-blockers at discharge were compared with their matched controls. In this comparison, only pairs in which both patients were fully lucid on admission to the hospital were included. After applying these criteria, 35 pairs remained for the subset analysis.

The individuals were followed for 17–89 months or until death; median followup among survivors was 41 months in patients on β-blockade and 36 months in control patients. Causes of death were based on autopsy in 8 of the 13 deceased patients (62%) in the β-blocker group and in 12 of 21 cases (62%) in the non-β-blocker group; otherwise they were all based on clinical examination in the hospital before death. Data were analyzed with the life-table technique and log-rank test.9,10

**Results**

**Matching**

Table 1 shows that the matching procedure resulted in closely similar baseline characteristics in patients with and without β-blockade at discharge from the stroke unit. The distributions of gender and stroke diagnoses were identical. Mean ages were closely similar. A slightly higher proportion of control patients had a history of cardiac failure, whereas hypertension was somewhat more common in patients on β-blockers. One important difference between the two groups emerged, however: On admission to the hospital, 2 of the patients in the β-blocker-treated group had presented with drowsiness, the corresponding figure for the control patients being 9. At discharge from the stroke unit, all patients were lucid.

**Mortality**

During followup, 13 of the patients on β-blockers and 21 of the control patients died (Figure 1). When analyzed with the life-table technique and log-rank test, the relative risk was 0.60:1.00 and *p* was 0.14. There was no major difference in mortality between patients with selective vs. nonselective β-blockers. Thus, 6 of 33 (18%) patients with selective drugs and 7 of 27 (26%) with nonselective drugs died during followup.

Forty-nine patients were on treatment with β-blockers on admission to the hospital (45 in the β-blocker-treated group and 4 in the control group). When analyzing only patients already on β-blockade treatment at admission for stroke and excluding pairs in which not both patients were fully lucid on admission, 35 pairs remained for analysis. In these 35 pairs, 10 of the patients on β-blocker therapy and 13 without β-blockers died during followup.

**Fatal and Nonfatal Circulatory Events**

During followup, 12 patients treated with β-blockers had a recurrent stroke; 2 of these were fatal. The corresponding figures for patients without β-blockers were 19 and 3, respectively. By the life-table technique, the relative risk of recurrent stroke in pa-

<table>
<thead>
<tr>
<th>Table 1. Characteristics of 60 Patients Discharged from the Hospital With β-Blockade and 60 Matched Patients Discharged Without β-Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
</tr>
<tr>
<td><strong>Items included in matching</strong></td>
</tr>
<tr>
<td>Sex (males : females)</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
</tr>
<tr>
<td>Type of stroke</td>
</tr>
<tr>
<td>Nonembolic brain infarction</td>
</tr>
<tr>
<td>Embolic brain infarction</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
</tr>
<tr>
<td>Medical history</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Cardiac failure</td>
</tr>
<tr>
<td><strong>Items not included in matching</strong></td>
</tr>
<tr>
<td>Medical history</td>
</tr>
<tr>
<td>Previous stroke</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Level of consciousness on admission</td>
</tr>
<tr>
<td>Awake</td>
</tr>
<tr>
<td>Drowsy</td>
</tr>
</tbody>
</table>
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242

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the life-table technique in 60 stroke patients discharged from a stroke unit with \(\beta\)-blocking drugs (—) and 60 matched stroke patients without \(\beta\)-blockade (---).

![Life table product](image)

Figure 1. Probability of survival calculated by the life-table technique in 60 stroke patients discharged from a stroke unit with \(\beta\)-blocking drugs (—) and 60 matched stroke patients without \(\beta\)-blockade (---).

Discussion

The matching procedure resulted in two groups of patients, with and without \(\beta\)-blockers, respectively, that were closely similar at discharge from the stroke unit in several important prognostic variables such as age, diagnostic category, history of hypertension, and cardiac failure. Other cardiovascular disorders not included in the matching had similar prevalences in the \(\beta\)-blocker-treated group and the control group. It appeared that the outcome *quo ad vitam* was better in patients treated with \(\beta\)-adrenergic-blocking drugs than in matched control patients during a long-term followup, but the difference did not reach statistical significance.

The present approach to recruit probands as well as controls from a closed cohort that has been subjected to identical structured investigations has been forwarded as an improvement on the conventional retrospective study. Only identification of probands has been made retrospectively, whereas all data have been collected and registered prospectively. Since the hypothesis of a protective effect of \(\beta\)-blockers following stroke was formulated after the data had been obtained, no bias could be involved at this point of the investigation. However, it is possible that some bias may have been introduced at other stages. Matching included no less than 5 variables, and the two groups were also similar in most of the clinical variables not used in the matching procedure. Nevertheless, it cannot be excluded that the groups were so different in some other (unknown) variable that the control patients had, in fact, a worse prognostic profile than the \(\beta\)-blocker-treated probands at focal time. The fact that more patients in the control group died from malignancies during followup points in this direction. Another obvious limitation of the present study is that the relatively small number of patients available for analysis precluded meaningful statistical analyses. It is quite apparent that the present methodological approach does not obviate the need for a large randomized controlled study. Our investigation may rather be used to guide in the decision on whether to embark on such a laborious trial or not.

When designing the present study, we assumed that a primary effect of long-term treatment with \(\beta\)-blockers after stroke would be to reduce fatal cardiac events. The prevalence of ischemic heart disease (acute MI and/or angina pectoris) was closely similar in the two groups at entry. The number of cardiac deaths during followup was limited, and the difference in cardiac mortality between the two groups was small. Therefore, the present data do not permit us to decide whether or not \(\beta\)-blockers can prevent death by coronary heart disease after stroke.

It seemed, however, that there was a reduction in mortality from causes other than cardiac disease and that the number of nonfatal recurrent strokes was lower among patients on \(\beta\)-blockade. This could have been due to chance or to an inadvertent imbalance between the two groups in prognostic factors. But it should also be considered that \(\beta\)-blockers exert long-term beneficial effects other than those related to cardiac death.

In experimental studies, propranolol has been shown to be significantly more effective than hydralazine in preventing diet-induced atherosclerosis of the neck vessels, despite similar blood pressure levels during treatment. In a prospective study of long-term effects of metoprolol after MI, a significant reduction of stroke occurrence was observed. Direct beneficial effects of ongoing treatment with a \(\beta\)-blocker when stroke occurs could also be considered. There are several lines of circumstantial and direct evidence that \(\beta\)-blockers may be beneficial in brain ischemia. Catecholamines may act as uncouplers of oxidative phosphorylation, thereby enhancing oxygen demands, and \(\alpha\)-as well as \(\beta\)-adrenergic-blocking agents have been shown to reduce cerebral oxygen requirements in patients with ischemic stroke. Depletion of cerebral norepinephrine content enhances recovery after experimental brain ischemia. In other

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With (\beta)-blocker</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>2</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>6</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
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<tr>
<td>Bronchopneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0</td>
</tr>
<tr>
<td>Other causes</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2. Causes of Death
tissues, β-blockade preserves mitochondrial function and reduces enzyme leakage during anoxia.15,16 At high doses, β-blockers may also shift the oxygen dissociation to the right, making more oxygen available to the tissues.17

Many patients with stroke have very high circulating levels of catecholamines, and these high levels are associated with a poor outcome in patients with ischemic stroke18 and subarachnoid hemorrhage.19 Beneficial effects of propranolol given during the acute phase of subarachnoid hemorrhage have been observed.20 In experimental studies, propranolol has been reported to reduce hypoxia-induced mortality21 and focal brain infarction size.22,23 Lack of protective effects has also been reported,24 but this may be explained by inappropriate methodology (cf. Reference 23). In a retrospective study of general stroke patients, it was observed that subjects on β-blockers in the acute phase had a better short-term outcome than matched patients without β-blockers.25 In line with such findings, we observed that, when compared with patients without β-blockers, fewer of those on β-blockers had presented with drowsiness at entry to the hospital. A specific long-term effect of β-blockade on the cerebrovascular system may also be considered, since the relative risk for recurrent stroke (most of them nonfatal) was considerably lower in patients treated with β-blocking agents.

In conclusion: The present results do not refute the possibility that long-term treatment with β-adrenergic-blocking drugs are of benefit after stroke. However, supplementary information on the possible effects of long-term β-blockade on total mortality and causes of death after stroke is needed before a randomized trial that decides whether this is a sound therapeutic concept or not can be initiated.

References

Key Words • β-adrenergic blocking agents • mortality after stroke • case fatality rate • causes of death
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