Brief Rapid Communication

Indobufen in the Prevention of Thromboembolic Complications in Patients With Heart Disease
A Randomized, Placebo-Controlled, Double-Blind Study

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Background. The purpose of this randomized, double-blind study was to evaluate the efficacy of indobufen, a reversible inhibitor of platelet cyclooxygenase, in the prevention of embolic events of cardiac origin.

Methods and Results. One hundred ninety-six patients with heart disease and at risk for cardiogenic embolism (90 with atrial fibrillation and 106 in sinus rhythm) were randomly assigned to receive indobufen (100 mg b.i.d.) or placebo. All patients were reexamined every 3 months for the duration of the study. The primary study end points were cerebral ischemic attack (stroke and transient ischemic attack), systemic embolism, pulmonary embolism, and fatal myocardial infarction. The median duration of treatment was 854 days in the indobufen group and 865 days in the placebo group. The frequencies of primary end points (fatal and nonfatal) were 6.1% and 17.3%, respectively, in the indobufen and placebo groups (p < 0.05) for a reduction of 65% in the risk of a primary event (indobufen/placebo relative risk, 0.35; 95% confidence limits, 0.14–0.89). Adverse drug reactions, mostly gastrointestinal or hemostasis disorders, occurred in 9.2% of indobufen-treated patients.

Conclusions. The results of the study indicate that indobufen may reduce the risk of ischemic events in patients with heart disease associated with an increased risk of embolism. (Circulation 1993;87:162–164)

KEY WORDS • atrial fibrillation • embolism • indobufen • platelet aggregation inhibitor

Many types of heart disease have been associated with an increased risk of systemic embolism, even though such events usually involve cerebral circulation. The present study was designed to assess the effect of treatment with indobufen, a reversible inhibitor of platelet cyclooxygenase, in preventing embolic events of cardiac origin. When the study was initiated, there were no published reports of prospective studies documenting the effectiveness of anticoagulants and antiaggregants in such a pathology.

Methods

The study was carried out between January 1986 and July 1991. Potential participants were identified from among outpatients or those hospitalized in the Cardiology Department of the Novara Hospital. Admitted to the trial were patients of either sex, between 18 and 80 years of age, and suffering from chronic nonvalvular atrial fibrillation or presenting in sinus rhythm and showing one of the following conditions known to be a potential source of embolism: idiopathic dilative cardiomyopathy without congestive heart failure, mitral valve prolapse, asymmetrical septal hypertrophy, or previous myocardial infarction (≥1 month) with residual ventricular dyskinesia. Exclusion criteria were a recent history of ischemic events (≤1 month), mitral stenosis by echocardiography, prosthetic heart valve, ejection fraction of <25%, treatment with anticoagulant or antiaggregant therapy during the past 6 months, and peptic ulcer or hemorrhagic diathesis.

All patients underwent a complete baseline evaluation consisting of a clinical examination, ECG, bidimensional echocardiography, and general hematological and clinical chemistry tests. All patients gave their informed consent to participation in the trial. At the time of recruitment, the patients were randomized to treatment with indobufen (100 mg b.i.d.) or placebo in a double-blind fashion. Randomization was carried out by the sequential use of medication packages according to a predetermined random order.

All patients were reexamined every 3 months for the duration of the study (3 years). The primary study end points were cerebral ischemic attack (stroke and transient ischemic attack), systemic embolism, pulmonary embolism, and fatal myocardial infarction.

The criteria for cerebrovascular events were clinical signs or a history of sudden onset of a neurological deficit lasting <24 hours (transient ischemic attack) or >24 hours (stroke). A computed tomography scan was

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always taken in the event of a cerebrovascular episode. Cerebrovascular episodes were validated by two neurological consultants who were unaware of treatment allocation. The diagnosis of systemic embolism was confirmed by a surgeon. In the case of suspected pulmonary embolism, a lung perfusion scintigraphy was carried out. Death certificates and postmortem examinations were obtained. Nonfatal myocardial infarction and death from causes other than those listed were regarded as secondary end points.

Sample size was estimated on the basis of an event rate of 20% in 3 years in the placebo group and 10% in the indobufen group. Considering a test power of 50% (α=0.05) to be satisfactory for a pilot trial, 100 patients in each group were planned.

The incidence of events over time in the two arms of the trial was compared by means of Cox’s approach. To allow for the possible differential effect of prognostic factors, all clinical variables reported in Table 1 were inserted into the model. Relative risk (RR) and 95% confidence limits (CL) also were calculated.

Data were processed by the SAS version 5.18 computer software package (SAS Institute, Cary, N.C.). Statistical analyses were performed by the Biometry Section, Farmitalia Carlo Erba Italia, under the supervision of the Institute of Medical Statistics and Biometry, University of Milan.

### Results

A total of 196 patients was enrolled in 2 years of recruitment. Table 1 shows the main characteristics of patients randomized into two treatment groups. Mean age at entry was 62 years; 12% of the patients were ≥75 years old. Chronic atrial fibrillation was present in approximately 50% of cases, and a history of myocardial infarction was present in 41% of cases. Thirty-one percent of the patients were hypertensive.

The scheduled trimonthly visits were kept by the patients; only approximately 5% of the planned control examinations were missed. In these cases, the patient was contacted by telephone, and a new appointment was made. No patient was lost to follow-up. Patients with temporary discontinuation of the study medication (≤15 days) were included in the analysis.

The median duration of treatment was 854 days (range, 50–1,672 days) in the indobufen group and 865 days (range, 39–1,611 days) in the placebo group.

Table 2 shows the distribution of primary end points detected during the course of the study. Overall, there were six events (two of which were fatal) in the indobufen group (6.1%) and 17 events (seven of which were fatal) in the placebo group (17.3%).

The difference between groups in this respect was statistically significant (p<0.05), for a reduction of 64.7% in the risk of a primary event (indobufen/placebo RR, 0.35; 95% CL, 0.14–0.89). The RR adjusted for the variables reported in Table 1 was 0.31 with a 95% CL of 0.12–0.81.

Regarding secondary end points, there were three cases of nonfatal myocardial infarction in the placebo group and one in the indobufen group. There were five deaths in the indobufen group (three due to heart failure and two from unidentified causes) and two deaths (both due to heart failure) in the placebo group.

In patients ≥75 years old, the overall incidence of primary end points was 30.4% (two of 10 in the indobufen group and five of 13 in the placebo group). There was a higher incidence of ischemic events among patients with atrial fibrillation (17.6%) than among those with embolic heart disease and in sinus rhythm (5.3%).

Overall, the incidence of primary plus secondary end points was 12.2% (12 of 98) in the indobufen group and 22.4% (22 of 98) in the placebo group (RR, 0.54; 95% CL, 0.27–1.09) for a risk reduction of 45.5%. The RR adjusted for baseline variables was 0.51 with a 95% CL of 0.25–1.05.

Discontinuation of treatment for reasons unrelated to end point events occurred in 22 patients (13 on indobufen and nine on placebo). The study medication was withdrawn for adverse reactions in 13 cases, refusal to continue in six cases, and other reasons in three cases. Regarding adverse reactions (nine on indobufen and four on placebo), one patient receiving indobufen developed melena that was not severe enough to necessitate blood transfusion. In the other cases, discontinuation of indobufen treatment was due to hemostasis

### Table 1. Baseline Characteristics of Patients Receiving Indobufen or Placebo

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Indobufen</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>98</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>55/43</td>
<td>45/53</td>
<td></td>
</tr>
<tr>
<td>Age (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤64 Years</td>
<td>53.1</td>
<td>54.1</td>
<td></td>
</tr>
<tr>
<td>65–74 Years</td>
<td>36.7</td>
<td>32.7</td>
<td></td>
</tr>
<tr>
<td>≥75 Years</td>
<td>10.2</td>
<td>13.2</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>50.0</td>
<td>54.1</td>
<td></td>
</tr>
<tr>
<td>Mitral valve prolapse (%)</td>
<td>21.4</td>
<td>18.4</td>
<td></td>
</tr>
<tr>
<td>Dilative cardiomyopathy (%)</td>
<td>10.2</td>
<td>9.2</td>
<td></td>
</tr>
<tr>
<td>Septal hypertrophy (%)</td>
<td>4.0</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>44.9</td>
<td>36.7</td>
<td></td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>9.2</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>33.7</td>
<td>27.6</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>10.2</td>
<td>14.3</td>
<td></td>
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<tr>
<td>Current smoker (%)</td>
<td>32.7</td>
<td>28.6</td>
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</table>

### Table 2. Frequency of Primary End Points in Groups Receiving Indobufen or Placebo

<table>
<thead>
<tr>
<th>Event</th>
<th>Indobufen</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>98</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Fatal events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Nonfatal events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Total                          | 6 (6.1%)  | 17 (17.3%) | *p<0.05; relative risk, 0.35; 95% confidence limits, 0.14–0.89.*
disorders (two cases of epistaxis, one hematuria, one ecchymosis, and one hemorrhoidal bleeding) and mild gastrointestinal disturbances (two cases of abdominal pain and one heartburn). In all cases, the adverse reactions abated after treatment discontinuation.

**Discussion**

The study was designed to explore the effectiveness of treatment with an inhibitor of platelet aggregation (indobufen) in preventing thromboembolic events in patients with heart disease associated with an increased risk of systemic embolization. Because the purpose of the research was to assess a potential pharmacodynamical effect rather than to identify particular factors of prognostic significance, we recruited patients with diversified heart conditions who shared a risk of embolic complications. The results appear to show that indobufen can reduce the incidence of ischemic events presumably due to cardioembolic disorders. In particular, treatment with the active drug reduced the risk of triggering a primary end point event by 64.7% and the risk of overall (primary and secondary) end points by 45.5%.

Although the varying definition of primary end points precludes a homogeneous comparison, the effect of indobufen was inferior to that obtained with warfarin in the Stroke Prevention in Atrial Fibrillation (SPAF) and the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) studies (risk reduction, 81.6% and 86.6%, respectively) yet superior to that seen with aspirin in the same SPAF study (risk reduction, 48.9%). Nevertheless, a more homogeneous comparison in terms of risk reduction in primary end points as defined in the SPAF (i.e., stroke, systemic embolism, and death from any cause) gave values very close to those obtained with aspirin (32% versus 35.7% with indobufen).

The results of this study appear to confirm that age is an important risk factor for embolic events. Although the antiaggregant treatment appeared to retain its validity in the elderly group (age, ≥75 years), the number of such patients in our series was too small to warrant definite conclusions.

Throughout the study there was only one instance of a major adverse reaction—a case of melena not severe enough to require specific treatment, and it abated spontaneously after drug withdrawal.

**Conclusions**

Three large-scale, prospective, randomized trials showed that warfarin reduces the incidence of thromboembolic events in patients with nonvalvular atrial fibrillation. This favorable effect is accompanied by a low incidence of severe hemorrhagic episodes. Aspirin, for which a favorable effect was demonstrated at the dosage of 325 mg/daily and no effect at the dosage of 75 mg/daily, may be used as an alternative to warfarin in low-risk patients or in those in whom oral anticoagulant treatment is contraindicated.

The results of this trial show that indobufen may also reduce the risk of ischemic events in patients with heart disease with an increased risk of embolism. To define the relative value of indobufen in this pathology, a large-scale, prospective, randomized trial versus warfarin was started in January 1991 and is expected to be completed in December 1994.

**Acknowledgment**

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**References**

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