OBJECTIVES
We sought to determine whether aspirin withdrawal is an encountered situation in coronary disease patients who relapsed.

BACKGROUND
Despite the recognized benefits of aspirin in coronary disease, and because of the threat of bleeding or poor compliance, aspirin intake is sometimes stopped. It is not known whether withdrawal of aspirin can be harmful in coronary-disease patients.

METHODS
Between September 1999 and April 2002, a total of 1,236 patients hospitalized for acute coronary syndrome (ACS) were questioned in order to determine whether aspirin intake had been interrupted.

RESULTS
Fifty-one of these ACSs occurred within 1 month after aspirin withdrawal. This represents 4.1% of all coronary events but 13.3% of recurrences. Among those patients who relapsed, the incidence of ST-segment elevation ACS was higher in those who stopped aspirin when compared to the 332 patients who did not stop aspirin (39% vs. 18%; p = 0.001). Ten (20%) cases involved a thrombosis of an uncoated stent implanted on average 15.5 ± 6.5 months previously. Mean delay between aspirin withdrawal and the acute coronary event was 10 ± 1.9 days. Reasons for aspirin withdrawal included minor surgery in 7 cases, fibroscopy in 8 cases, dental treatment in 13 cases, bleeding in 3 cases, and patient non-compliance in 20 cases.

CONCLUSIONS
Our results support the hypothesis that aspirin withdrawal in coronary patients may represent a real risk for the occurrence of a new coronary event. Many cases involved late uncoated-stent thrombosis. Assessment of the exact incidence of coronary recurrences after aspirin withdrawal will need prospective studies. (J Am Coll Cardiol 2005;45:456–9) © 2005 by the American College of Cardiology Foundation.

Aspirin is a mandatory treatment for secondary prevention of coronary artery disease (CAD) and must be continued throughout life (1,2). It has not been established, however, whether withdrawal of aspirin can precipitate coronary events. We collected consecutive cases of coronary syndromes following aspirin withdrawal in patients with known coronary disease scheduled to be treated throughout life with aspirin.

METHODS
Between September 1999 and April 2002, patients hospitalized for acute coronary syndrome (ACS) were questioned to discover whether they had stopped any prescribed treatment for coronary disease, especially aspirin. Questions were asked on admission and then, to avoid errors, repeated twice during the patient’s hospital stay, with the assistance of the family when necessary.

If aspirin had been interrupted, the exact reason and the time since withdrawal were determined with the help of the practitioner who had advised the patient to do so. We also sought to discover whether a substitution therapy had been given. As the occurrence of subacute stent thrombosis has been well described in published reports, patients treated with coronary angioplasty and stent implantation during the previous month were excluded. Moreover, as coronary syndrome after major surgery is a multi-factorial phenomenon, those events occurring after major surgery were not included in the survey. Coronary angiography was performed in all patients as part of the diagnosis and treatment of the coronary syndrome. Patients who presented with a coronary recurrence were compared according to whether they had stopped aspirin or not.

Statistical analysis. Comparisons of variables between aspirin users and those who discontinued aspirin were made with a either a chi-square test or Fisher exact test for nominal variables and with a two-sample t test for continuous variables (Table 1). The type of ACS in patients with recurrence according to aspirin intake was compared using a chi-square test for a four-fold table (Table 2).

RESULTS
During the 32-month study-period, 1,236 patients with coronary syndrome (non-ST-segment elevation or ST-segment elevation) were hospitalized in our center. Among these, 383 (31%) were known coronary disease patients and, consequently, should have been taking aspirin regularly. Fifty-one new coronary events occurred <1 month after aspirin withdrawal. These 51 cases represent 4.1% (51 of 1,236) of all patients hospitalized for a coronary event, and 13.3% (51 of 383) of those who relapsed.

The coronary history that had required the prescription of
aspirin in these patients consisted of a previous myocardial infarction in 15 cases (29%) and stable angina in 36 cases (71%). Mean delay between diagnosis of the initial coronary disease requiring aspirin prescription and the recurrent coronary event after aspirin withdrawal was 4.1 ± 1.2 years. Coronary syndrome following aspirin withdrawal involved ST-segment elevation coronary syndrome in 19 cases (37%) and non-ST-segment elevation coronary syndrome in 32 cases (63%). Mean delay between aspirin withdrawal and the acute coronary event was 10 ± 1.9 days (range 4 to 17 days). Coronary angiography was performed systematically. Hence, the culprit lesion was identified in all cases. Furthermore, because all patients had been catheterized at least once, we were able to compare with the previous condition of the newly diseased artery segment.

Among patients presenting with ST-segment elevation coronary syndrome, stent thrombosis was the culprit in 10 cases (19%). All these stents were uncoated, and they had been implanted a mean 15.5 ± 6.5 months earlier. Among the remaining 41 cases, coronary angiogram performed on average 36 h after the coronary event showed that the culprit lesion had occurred in a previously angiographically normal segment in 23 cases and in a previously abnormal segment in 18 cases. In all, lesions were: total coronary obstruction in 19 cases (including the 10 cases of stent thrombosis) and non-occlusive lesions, mainly plaque disruption, in the remaining 32 cases.

Reasons for aspirin discontinuation included: minor surgery in 7 cases, fibroscopy in 8 cases, dental treatment in 13 cases, bleeding in 3 cases, and patient non-compliance in the remaining 20 cases. Aspirin was not replaced by another anti-platelet treatment in any of these cases. In four cases, other treatments (i.e., beta-blockers [n = 4], statins [n = 3], and angiotensin-converting enzyme inhibitors [n = 2]) were also stopped.

The 383 patients who experienced a recurrence were compared according to whether they had discontinued aspirin (n = 51) or not (n = 332). The main characteristics of the two groups of patients appear similar (Table 1). In contrast, one can note a higher incidence of ST-segment elevation coronary syndrome in the aspirin withdrawal group as compared to the group of patients who had a recurrence but were still taking aspirin (39% vs. 18%, p < 0.001) (Table 2).

**DISCUSSION**

Our main findings shows that coronary events occurring after aspirin withdrawal represent 4% of all coronary events hospitalized but 13.3% of coronary recurrences. Relapses were more often ST-segment elevation ACS in patients who had stopped taking aspirin (39% vs. 18%; p < 0.001). Finally, 10 of these involved non-coated stent occlusion occurring on average 15.5 ± 6.5 months after implantation. Unless there is an obvious contraindication, aspirin is mandatory treatment for patients with coronary disease (1,2).

In biological terms, the platelet inhibition achieved with aspirin, although irreversible for target platelets, lasts until a significant pool of new platelets is synthesized. However, complete recovery of platelet aggregation may occur in 50% of cases by day 3 and in 80% of cases by day 4 (3). Some investigators even suspect the existence of a biological platelet aggregation "rebound phenomenon." Beving et al. (4) found that rapid withdrawal of aspirin may cause abnormally high levels of blood markers reflecting an increase of thromboxane A₂ which may have possible hazardous effects in patients with cardiovascular disease. After aspirin discontinuation, the recovery of cyclooxygenase activity may occur rapidly, with a heterogeneous synthesis of thromboxane A₂ by fresh platelets (5).

### Table 1. Characteristics in Recurrent Patients According to Aspirin Intake

<table>
<thead>
<tr>
<th>Aspirin Withdrawal (n = 51)</th>
<th>No Aspirin Withdrawal (n = 332)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (64 ± 12)</td>
<td>63 ± 16</td>
<td>0.43</td>
</tr>
<tr>
<td>Women (n = 10)</td>
<td>n = 90</td>
<td>0.26</td>
</tr>
<tr>
<td>Diabetes mellitus (n = 14)</td>
<td>n = 100</td>
<td>0.70</td>
</tr>
<tr>
<td>Hypertension (n = 10)</td>
<td>19%</td>
<td>0.81</td>
</tr>
<tr>
<td>Creatinine &gt;2 mg/dl (n = 4)</td>
<td>n = 31</td>
<td>1</td>
</tr>
<tr>
<td>Tobacco use (n = 10)</td>
<td>9%</td>
<td>0.10</td>
</tr>
<tr>
<td>Beta-blockers (n = 50)</td>
<td>99%</td>
<td>0.51</td>
</tr>
<tr>
<td>Statins (n = 45)</td>
<td>99%</td>
<td>0.84</td>
</tr>
<tr>
<td>Calcium channel blockers (n = 4)</td>
<td>91%</td>
<td>0.35</td>
</tr>
<tr>
<td>ACE inhibitors (n = 38)</td>
<td>75%</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Data are presented as n (%). p = NS for all variables (continuous variables were compared by means of the Student t test and categorical variables by means of the chi-square test).

ACE = angiotensin-converting enzyme.

### Table 2. Type of Acute Coronary Syndrome in Patients With Recurrence According to Aspirin Intake

<table>
<thead>
<tr>
<th>Non–ST-segment elevation coronary syndrome</th>
<th>ST-segment elevation coronary syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin Withdrawal (n = 51)</td>
<td>No Aspirin Withdrawal (n = 332)</td>
</tr>
<tr>
<td>31 (61%)</td>
<td>271 (82%)</td>
</tr>
<tr>
<td>20 (39%)</td>
<td>61 (18%)</td>
</tr>
</tbody>
</table>

Data are presented as n (%). p < 0.001.
From a clinical point of view, Collet et al. (6) published 11 cases of coronary events after aspirin cessation. They also recently reported data very similar to ours. Indeed, in their center, patients had ceased taking antiplatelet agents (not only aspirin) in about 5% of all ACS cases treated. Like us, they found a greater incidence of ST-segment elevation ACS in those patients who relapsed after aspirin withdrawal. Finally, they reported higher mortality in those patients relapsing when aspirin was discontinued (7).

In addition, our study showed that aspirin withdrawal may involve a higher risk for late non-coated stent thrombosis. Indeed, ten of our cases involved non-coated stent occlusion occurring on average 15 ± 6.5 months after implantation. Although a late-occurring stent thrombosis has been described in published data (8,9), it remains a rare phenomenon. In our series, late stent thrombosis represents a high proportion (i.e., 20% [10 of 51]) of all coronary events occurring after aspirin withdrawal, but a very high proportion (i.e., 53% [10 of 19]) of coronary total occlusions. Our data should offset the very recent report concerning four cases of late coated-stent thromboses after antiplatelet withdrawal (10) and suggest that the coating may not be the culprit. A non-totally endothelialized coronary strut may trigger coronary thrombosis when the protective effect of aspirin treatment has worn off or whether the stent is coated or not.

Cessation of aspirin in various scheduled minor surgical procedures is beginning to arouse concern in published reports. An initial study from Kaluza et al. (11) clearly showed that non-cardiac surgery soon after stent placement (often requiring aspirin withdrawal) was linked to a very high rate of adverse events. Subsequent data seemed to provide reassurance in cases where non-cardiac surgery was performed two months after stent implantation. However, antiplatelets were stopped in fewer than 7% of these patients (12). The prospective Pulmonary Embolism Prevention (PEP) study (13) has shown that hip surgery procedures can be performed on patients taking aspirin, although the excess of six postoperative transfused bleeding episodes per 1,000 patients assigned aspirin must be placed in balance with the expected benefit. Finally, in the setting of bypass surgery, Mangano et al. (14) have shown that aspirin cessation is not only unnecessary but may even be harmful. The French Society of Anesthesiology and Intensive Care has published expert recommendations regarding antiplatelet agents during the perioperative period. As many questions remain unresolved, probably the main interest of these expert opinions is to raise the problem so as to avoid systematic withdrawal in low-risk bleeding circumstances. However, in “real life,” owing to the threat of bleeding, patients taking aspirin are often asked by their dentist or surgeon to stop antiplatelet medications before a procedure. This “recommendation” is often made without consulting the cardiologist or the general practitioner who prescribed the antiplatelet agents.

Our results support the hypothesis that aspirin withdrawal in coronary patients may represent a real risk for the occurrence of a new coronary event. We hypothesize that, in certain at-risk patients, discontinuation of aspirin increases platelet reactivity at a sufficient level to reach the platelet-aggregation threshold. It is then possible that, in certain conditions, events such as spontaneous coronary plaque rupture or plaque dissection, which we now know are more frequent than previously thought (15,16), aspirin cessation may lead to coronary thrombosis. We did not consider or compare hematologic parameters at presentation in either group of relapsing patients. Aspirin was discontinued because of bleeding in 3 cases and due to poor compliance in 20 cases. Hence, we cannot conclude whether aspirin withdrawals presented more often with anemia, which might have exacerbated outcomes, a hypothesis raised in recent published data.

Finally, the assessment of the exact incidence of coronary recurrences after aspirin withdrawal will need prospective studies. As aspirin withdrawal is obviously not harmful in all patients, we also need to specify which patients are at risk. While awaiting these data, we believe it is necessary to teach patients, as well as doctors, that aspirin withdrawal may have harmful consequences and should be discussed in each case. Furthermore, whenever possible, we need to improve aspirin-treatment compliance.

Reprint requests and correspondence: Dr. Emile Ferrari, Cardiology Department, Pasteur Hospital, 30, Avenue de la voie Romaine, Nice, Alpes Maritimes 06200. E-mail: ferrari.e@chu-nice.fr.

REFERENCES


