

Impact of Prior Use or Recent Withdrawal of Oral Antiplatelet Agents on Acute Coronary Syndromes

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Background—Oral antiplatelet agents (OAAs) can prevent further vascular events in cardiovascular disease. How prior use or recent discontinuation of OAA affects clinical presentation of acute coronary syndromes (ACS) and clinical outcomes (death, myocardial infarction [MI]) is unclear.

Methods and Results—We studied and followed up for up to 30 days a cohort of 1358 consecutive patients admitted for a suspected ACS; of these, 930 were nonusers, 355 were prior users of OAA, and 73 had recently withdrawn OAA. Nonusers were at lower risk, more frequently presented with ST-elevation MI on admission, and more frequently had Q-wave MI at discharge than prior users (36.6% versus 17.5%, $P<0.001$; and 47.8% versus 28.2%, $P<0.001$, respectively). However, there was no difference regarding the incidence of death or MI at 30 days between nonusers and prior users (10.3% versus 12.4%, $P=NS$). In addition, prior users experienced more major bleeds within 30 days compared with nonusers (3.4% versus 1.4%, respectively; $P=0.04$). Recent withdrawers were admitted on average 11.9 ± 0.8 days after OAA withdrawal. Interruption was primarily a physician decision for scheduled surgery ($n=47$ of 73). Despite a similar cardiovascular risk profile, recent withdrawers had higher 30-day rates of death or MI (21.9% versus 12.4%, $P=0.04$) and bleedings (13.7% versus 5.9%, $P=0.03$) than prior users. After multivariate analysis, OAA withdrawal was found to be an independent predictor of both mortality and bleedings at 30 days.

Conclusions—Among ACS patients, prior users represent a higher-risk population and present more frequently with non-ST-elevation ACS than nonusers. Although patients with a recent interruption of OAA resemble those chronically treated by OAA, they display worse clinical outcomes. (*Circulation*. 2004;110:2361-2367.)

Key Words: acute coronary syndromes ■ aspirin ■ risk factors ■ thrombosis

Oral antiplatelet agents (OAAs), including aspirin (ASA) and thienopyridines, can prevent myocardial infarction (MI), stroke, and death in cardiovascular disease.¹ However, the impact of prior chronic OAA use on the severity of acute coronary syndromes (ACS) and their outcomes remains controversial. Previous studies have reported that prior ASA users have less severe presentation with reduced infarct size and less frequent Q waves than nonusers.²⁻⁴ In addition, subgroup analyses of randomized trials have shown that non-ST-elevation (NSTEMI) ACS patients previously on ASA therapy have worse short-term outcomes than those not previously on aspirin.^{5,6} Surprisingly, opposite results have also been reported in a large registry.⁷ In this registry, patients with coronary artery disease (CAD) had better outcomes if they were previously on ASA.

Among the confounding factors to explain these discrepancies is the recent withdrawal of OAA, a factor never evaluated prospectively. Despite indication for lifelong treatment,⁸ temporary interruption of OAA is commonplace, and

acute rebound effect with coronary thrombosis has been suspected as a consequence of the progressive recovery of the platelet cyclooxygenase activity.^{9,10} Epidemiological data on the potential deleterious effect of OAA withdrawal are clearly lacking. For these reasons, we investigated prospectively whether prior use or recent withdrawal of OAA influences the severity of ACS and short-term clinical outcomes (death, MI, bleedings).

Methods

Patient Population

We studied 1358 consecutive patients who were entered into the Pitié-Salpêtrière Registry of Ischemic Coronary Syndromes (PARIS registry) between November 1999 and June 2002. All were admitted with ACS; of the 1358, 417 had an evolving ST-elevation (STEMI) MI (<12 hours of symptom onset) or a recent Q-wave MI (<48 hours), and 941 had NSTEMI ACS. NSTEMI ACS was defined as ischemic symptoms lasting >10 minutes in the 24 hours before admittance with ECG changes and/or raised serum levels of cardiac markers, including creatinine kinase (CK) and troponin measurements. NSTEMI

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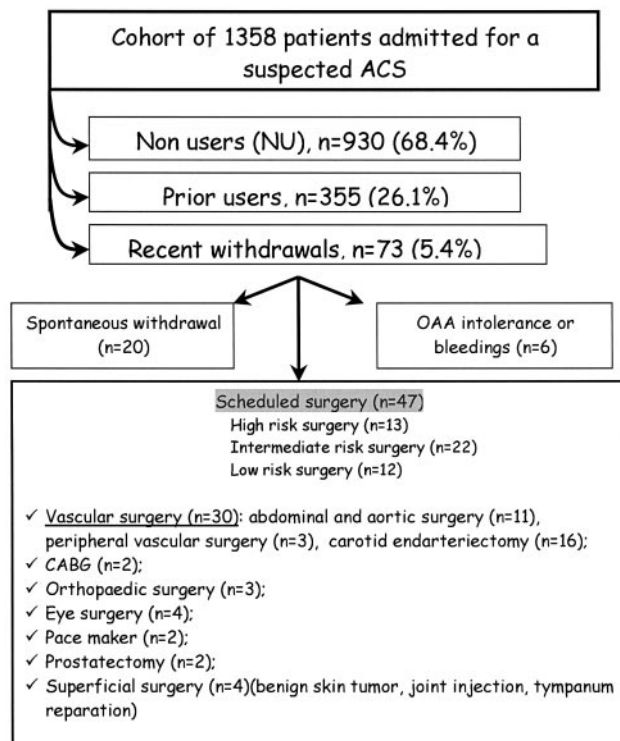


Figure 1. Flow of patients in PARIS registry, including definitions and number of patients in each category.

MI was considered present on admission if the initial troponin-I level was $>0.2 \mu\text{g/mL}$. All patients except those with a recent history of bleeding or an ongoing bleeding received an initial loading dose of aspirin (500 mg IV) followed by 75 to 250 mg/d, β -blockers, and intravenous nitrates unless contraindicated.

Our strategy was to perform primary percutaneous coronary intervention with the combination of stent and abciximab in patients with evolving STEMI as previously shown.¹¹ In patients with NSTEMI ACS, enoxaparin was given subcutaneously at a dose of 1 mg/kg (100 IU/kg) at 12-hour intervals. Patients recruited after the publication of the CURE results were given clopidogrel with a loading dose of 300 mg followed by 75 mg/d.¹² Glycoprotein IIb/IIIa receptor antagonists were given before catheterization only to patients with a troponin-I $\geq 0.2 \mu\text{g/mL}$ or with a recurrent ischemic episode. Catheterization was performed at the treating physician's discretion with immediate percutaneous coronary intervention if needed. Stent-implanted patients received ticlopidine (500 mg/d) or clopidogrel (300-mg loading dose followed by 75 mg/d) for at least 1 month. Heart failure was defined as Killip stage ≥ 3 . Renal failure was defined as a creatinine clearance $<30 \text{ mL/min}$.

Pattern of Use of Oral Antiplatelet Agents

The use of OAA was carefully examined in all patients who entered the study (Figure 1). Nonusers were defined as patients who had no prior history of vascular disease or those with prior vascular events who were not given an OAA as a chronic therapy during the 6 months before admission. Prior users of OAA were defined as patients who routinely took either aspirin or ADP receptor antagonists as chronic therapy to prevent acute vascular events without cessation within the 3 weeks before admission. Prior users taking aspirin in the setting of primary prevention were identified as those >50 years of age and with ≥ 2 risk factors for CAD and no history of vascular event. Patients who had withdrawn OAA within the 3 weeks before admission were identified as recent withdrawers.

Clinical Follow-Up

In-hospital follow-up was based on physical examination, ECG, and CK and troponin I levels. All patients in this study were followed up

at 1 month (100%). Death from any cause was evaluated at 30 days of follow-up. Recurrent MI was defined as recurrent chest pain and/or ECG changes with ≥ 1 of the following criteria: (1) CK >2 times the upper limit of normal with a rise of $>50\%$ of the prior value associated with a positive troponin I test and (2) the appearance of a new left bundle-branch block or new Q waves. We also evaluated the composite end point of all-cause mortality or recurrent MI at 30 days. Safety end point included 30-day major and minor bleeding events. Bleeding definitions were adapted from the TIMI 11B trial.¹³ Major hemorrhage corresponded to overt bleeding resulting in death; a bleed in a retroperitoneal, intracranial, or intraocular location; a hemoglobin drop of $\geq 3 \text{ g/dL}$; or the need for transfusion of $\geq 2 \text{ U}$ blood. Minor hemorrhage was any clinically important bleeding that did not qualify as major.

Statistical Analysis

Categorical variables are expressed as frequencies and percents, and continuous variables are given as mean \pm SEM. Potential associations between clinical and biological parameters were tested by univariate procedures through the use of Student *t* and χ^2 tests for continuous and categorical variables, respectively. Comparisons between groups of patients according to pattern of OAA use were performed by ANOVA for continuous variables and χ^2 or Fisher exact test for categorical variables with Bonferroni corrections. Independent predictors of either bleeding (all bleeds at 30 days) or ischemic events (death or nonfatal MI at 30 days) were identified through the use of a stepwise multivariate logistic analysis with SAS software, version 8.2 (SAS Institute). Variables included in the model were univariate predictors with $P < 0.15$. The α level was set at 0.05.

Results

Baseline Characteristics

The characteristics of our study population were those of all comers with ACS; therefore, this population had a higher risk profile than populations of randomized trials. A total of 449 patients had a prior history of CAD, of whom only 65% (289 of 449) were on long-term OAA. The vast majority of prior users (97%) were admitted with aspirin as long-term OAA therapy. Among patients who would have required OAA as primary prevention therapy before admission, only 20.3% (71 of 349) were appropriately treated. As expected, prior users were at higher risk than nonusers (Table 1), and recent withdrawers resembled prior users more closely and were older than both prior users and nonusers.

Characteristics of Recent Withdrawers

Recent withdrawers were admitted 11.9 ± 0.8 days after OAA cessation (aspirin, $n=70$; ticlopidine, $n=3$). OAA was discontinued as a result of patient decision or physician decision for scheduled surgery or for bleeding complications (Figure 1). All bleedings leading to OAA cessation were minor except 1. Scheduled surgery was vascular surgery in 62% of the patients. Two thirds of the patients who interrupted OAA for planned surgery were scheduled for intermediate-risk ($n=22$) or low-risk ($n=12$) surgery in terms of expected mortality or bleeding complications (Figure 1).¹⁴ None of the recent withdrawers had a recent coronary procedure (<2 months). A substitution therapy was initiated the day of OAA cessation in two thirds of the patients ($n=31$). This was performed either with 2 cycled injections ($n=10$) or with a single injection ($n=6$) of a low-molecular-weight heparin, with oral nonsteroidal antiinflammatory agents (flurbiprofen; $n=15$), or with both ($n=5$). The replacement therapy was

TABLE 1. Baseline Characteristics

| | Nonusers (n=930) | Prior Users (n=355) | Recent Withdrawers (n=73) |
|------------------------------------|---------------------|------------------------|------------------------------|
| Demographics | | | |
| Age, y | 65.9±0.5 | 66.9±0.7 | 70.3±1.7† |
| Female, % | 33.0‡ | 22.8 | 23.9 |
| >80 y of age | 17.0 | 16.3 | 27.4 |
| Risk factors | | | |
| Smoker, % | 46.3 | 45.1 | 44.2 |
| Dyslipidemia, % | 39.7‡ | 55.2* | 38.3 |
| Hypertension, % | 42.3‡ | 53.3 | 54.9 |
| Diabetes, % | 19.7‡ | 31.8 | 26.7 |
| Familial CAD, % | 17.3 | 15.2 | 8.5 |
| BMI, kg/m ² | 25.4±0.2 | 26.4±0.4 | 25.1±0.4 |
| Known CAD, % | 17.2 | 69.6 | 57.5 |
| Prior history of, % | | | |
| MI | 11.7‡ | 47.3 | 32.8† |
| CABG | 3.0‡ | 21.7 | 9.6† |
| PCI | 6.8‡ | 38.6 | 34.2† |
| Stroke | 4.9 | 7.9* | 17.8† |
| Risk profile (on admission) | | | |
| Creatinine clearance, mL/min | 72.6±1.2‡ | 66.2±2.0 | 61.6±3.5 |
| Creatinine clearance <30 mL/min, % | 6.4‡ | 16.0 | 8.2 |
| Heart failure, % | 24.2 | 24.8 | 31.5 |

BMI indicates body mass index; PCI, percutaneous coronary intervention.

*Significant difference between prior users and recent withdrawers using ANOVA or χ^2 with Bonferroni correction ($P<0.017$).

†Significant difference between recent withdrawers and nonusers using ANOVA or χ^2 with Bonferroni correction ($P<0.017$).

‡Significant difference between nonusers and prior users using ANOVA or χ^2 with Bonferroni correction ($P<0.017$).

withheld 12 hours before surgery, and OAA was usually reintroduced the day after surgery. We found no correlation between the time from OAA cessation to admission for ACS and the reason of OAA withdrawal, type of surgery, aspirin dosage, or type of replacement treatment.

Type of ACS According to Pattern of OAA Use

Prior users and recent withdrawers were less likely to show STE on the admission ECG and were less likely to have a final diagnosis of STEMI than nonusers (Figure 2). In addition, prior users were less likely to have an acute MI by enzyme tests than nonusers (60.0% versus 69.8%, $P=0.0008$) and recent withdrawers (60.0% versus 76.7%, $P=0.005$), whereas no significant difference was found between recent withdrawers and nonusers ($P=NS$). Among patients with elevated cardiac markers, nonusers more frequently had Q-wave MI than prior users (47.8% versus 28.2%, $P<0.0001$) and recent withdrawers (47.8% versus 26.8%, $P=0.0002$).

In-Hospital Management According to Pattern of OAA Use

Medical management and coronary revascularization did not differ significantly according to pattern of OAA use before

admission (Table 2). Pharmacological interventions, including aspirin therapy and anticoagulation, were similar in the 3 groups of patients. More than 97% of the patients with NSTEMI/ACS were given an association of aspirin and low-molecular-weight heparin, and 40% underwent elective revascularization, of whom 50% received a glycoprotein IIb/IIIa receptor antagonist. In-hospital urgent revascularization was more frequent in recent withdrawers than in nonusers or prior users (Table 2). Recent withdrawers who had withheld OAA for a

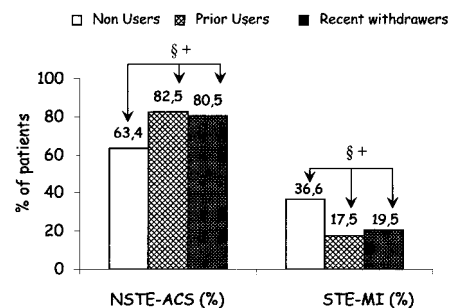


Figure 2. Type of ACS according to pattern of OAA use. § Indicates significant difference between nonusers and recent withdrawers; +, significant difference between prior users and nonusers, both using χ^2 with Bonferroni's correction ($P<0.017$).

TABLE 2. Pharmacological Interventions and Coronary Revascularization According to Pattern of OAA Use

| | Nonusers, % | Prior Users, % | Recent Withdrawers, % |
|--------------------------------------|----------------|-------------------|--------------------------|
| NSTE ACS (n=941) | | | |
| GP IIb/IIIa RA | 17.2 | 19.8 | 17.3 |
| LMWH or UH | 98.1 | 99.3 | 98.1 |
| Aspirin | 95.6 | 95.1 | 94.3 |
| Thienopyridines | 33.4 | 41.7 | 37.7 |
| Elective revascularization | 37.3 | 39.7 | 43.4 |
| In-hospital urgent revascularization | 1.1 | 3.7 | 7.5 |
| CABG | 7.2 | 9.2 | 15.1 |
| STEMI (n=417) | | | |
| Primary PCI | 68 | 75 | 88 |
| Rescue PCI | 6.0 | 4.8 | 0.0 |
| Thrombolysis | 12.4 | 9.7 | 0.0 |
| Aspirin | 92.0 | 91.7 | 94.1 |
| Thienopyridines | 55.9 | 61.2 | 58.8 |
| GP IIb/IIIa RA | 48.2* | 67.7 | 60.0 |

GP indicates glycoprotein; RA, receptor antagonists; LMWH, low-molecular-weight heparin; UH, unfractionated heparin; and PCI, percutaneous coronary intervention.

*Significant difference between nonusers and prior users using Fisher exact test with Bonferroni correction ($P<0.017$).

recent history of bleeding ($n=6$) or for high-risk scheduled surgery ($n=13$) were not given glycoprotein IIb/IIIa receptor antagonists. However, all recent withdrawers except 1 received OAA.

Clinical Outcomes

Prior users tended to have a worse short-term outcome than nonusers, although the difference did not reach statistical significance ($P=0.3$) (Figure 3). Unexpectedly, recent withdrawers had a 2-fold increase in the rates of both death and death/MI compared with prior users and nonusers. The rates of MI at 30 days were 1.4%, 2.5%, and 2.7% in nonusers, prior users, and recent withdrawers, respectively ($P=0.2$). Bleeding events were also found to be more frequent in recent withdrawers than in prior users and nonusers (Figure 4). Of interest, recent withdrawers who died or had an MI within 30 days had also a significantly higher incidence of bleeding

complications compared with recent withdrawers without ischemic events at 30 days (15.9% versus 7.0%, $P=0.004$). There was no significant correlation between bleeding rates and reason for withdrawal. In particular, there was no excess bleeding in patients who underwent planned surgery compared with those who had withdrawn spontaneously or because of bleeding events (13.0% versus 15.0% versus 16.7%, respectively; $P=NS$).

As expected, there was a higher incidence of death at 30 days in patients taking OAA for secondary prevention ($n=503$) compared with those given OAA for primary prevention ($n=349$) (12.3% versus 7.7%, $P=0.03$). We also found that OAA withdrawal was associated with an excess of death at 30 days compared with prior users in whom OAA were maintained regardless of the indication for antiplatelet use (13.3% versus 8.9%, $P=0.6$ for primary prevention; 20.4% versus 10.8%, $P=0.06$ for secondary prevention). Similarly, there was a trend for a higher incidence of bleedings in patients who had withdrawn OAA compared

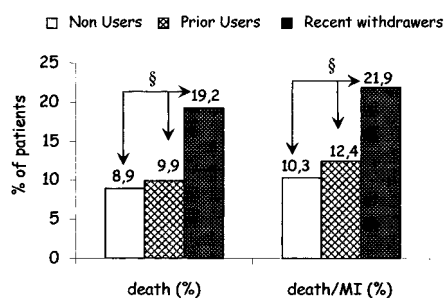


Figure 3. Ischemic events at 30 days according to pattern of OAA use before admission. § Indicates significant difference between nonusers and recent withdrawers using χ^2 with Bonferroni's correction ($P<0.017$). There was no significant difference between prior users and nonusers.

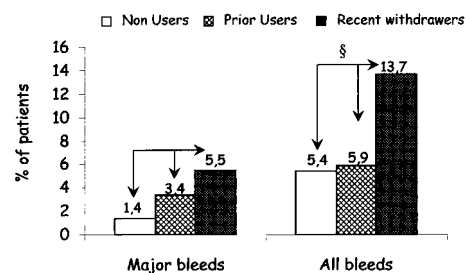


Figure 4. Bleeding events at 30 days according to pattern of OAA use before admission. § Indicates significant difference between nonusers and recent withdrawers using χ^2 with Bonferroni's correction ($P<0.017$).

TABLE 3. Univariate and Multivariate Analyses of Predictors of Death at 30 Days

| | Dead at 30 d (n=132) | Alive at 30 d (n=1226) | P, Univariate Analysis | P, Multivariate Analysis | OR (95% CI) |
|------------------------------|-------------------------|---------------------------|---------------------------|-----------------------------|------------------|
| Age, y | 75.7 (12.0) | 65.42 (13.8) | <0.0001 | 0.003 | 1.03 (1.01–1.05) |
| Creatinine clearance, mL/min | 45.23 (29.25) | 72.99 (35.9) | <0.0001 | <0.0001 | 0.98 (0.97–0.99) |
| Smoking, % | 31.06 | 47.31 | 0.0004 | NS | |
| Male, % | 59.85 | 71.29 | 0.006 | NS | |
| Hypercholesterolemia, % | 33.33 | 44.78 | 0.01 | NS | |
| OAA withdrawal, % | 10.61 | 4.81 | 0.02 | 0.03 | 2.05 (1.08–3.89) |
| History of MI, % | 29.55 | 21.37 | 0.03 | NS | |
| Diabetes, % | 30.30 | 22.43 | 0.04 | NS | |

with prior users in whom OAA was maintained regardless of the indication for antiplatelet use.

Independent Predictors of Outcomes

Multivariate regression analyses were performed to evaluate the association between the pattern of prior OAA use and the type of ACS on admission and the association between the pattern of prior OAA use and 1-month outcomes. Prior users and recent withdrawers were less likely to have STEMI (OR, 0.65; 95% CI, 0.47 to 0.89) than nonusers. Similarly, prior users and recent withdrawers were less likely to have Q-wave MI than non-Q-wave MI (OR, 0.64; 95% CI, 0.43 to 0.86).

Compared with all other patterns of OAA use, OAA withdrawal was found to be a strong independent predictor of mortality and of death/MI at 30 days, along with age and creatinine clearance (Table 3). Aspirin withdrawal compared with all other patterns of OAA use was also a significant predictor of bleedings at 30 days, along with age and the use of glycoprotein IIb/IIIa receptor antagonist (Table 4).

Discussion

The most important finding of the present study is that 5% of the patients admitted with an ACS had withdrawn OAA within 3 weeks before admission. It is the first time that this variable (OAA withdrawal) was systematically and prospectively collected in a large cohort of patients. Subsequently, we report the largest series of patients presenting with ACS linked to recent interruption of OAA. To date, only case reports of recent withdrawers and small series of patients without control groups have been reported.^{9,10} Our study not only allows us to give an accurate incidence of recent withdrawers in ACS patients but also provides a plausible explanation for the discrepancies observed in the literature

concerning the prognosis of prior users versus nonusers. Indeed, the relation of prior use of OAA and clinical outcome remains controversial. Some randomized studies have reported prior use of OAA to be an independent predictor of adverse outcome both short term and long term.^{5,6} In contrast, another study⁷ failed to show a relation between prior use of OAA and clinical outcomes, probably because of differences in types of population, statistical methods, and study design.^{3,15}

In the present study and as previously reported,^{2–7} prior users of OAA have apparently less severe clinical presentation than nonusers, although they carry a much higher risk profile than nonusers. However, we found little difference in 1-month outcome between prior users and nonusers, with a trend for worse short-term outcomes in prior users compared with nonusers. We suspect that the higher risk profile of prior users may be neutralized by a less severe presentation of the ACS in our patients, explaining the lack of difference in outcome with nonusers. Recent withdrawers obviously make up an important subgroup of patients. Indeed, if unidentified, recent withdrawers would have been classified as prior users; consequently, prior users would have had a significantly poorer outcome than nonusers in our study (30-day death or MI rate of 10.3% versus 14.1% for nonusers and prior users, respectively; $P=0.04$), thereby resembling findings of randomized studies.^{5,6} On the other hand, considering the specific GRACE definitions, recent withdrawers would have been classified as nonusers, which may explain why the nonusers had a worse outcome than prior users in this registry.

Recent withdrawers are characterized by catastrophic outcomes with a 2-fold increase in the rate of death compared with prior users or nonusers. In addition, bleeding complica-

TABLE 4. Univariate and Multivariate Analyses of Predictors of Bleedings (Minor and Major) at 30 Days

| | Bleed (n=81) | No Bleed (n=1277) | P, Univariate Analysis | P, Multivariate Analysis | OR (95% CI) |
|------------------------------|-----------------|----------------------|---------------------------|-----------------------------|------------------|
| Creatinine clearance, mL/min | 56.06 (30.2) | 71.21 (36.4) | <0.0001 | <0.0001 | 0.98 (0.97–0.99) |
| GP IIb/IIIa, % | 41.98 | 27.41 | 0.005 | 0.0005 | 2.32 (1.45–3.72) |
| Age, mean (SD), y | 70.90 (12) | 66.13 (14) | 0.003 | NS | |
| OAA withdrawal, % | 4.94 | 1.72 | 0.034 | 0.0096 | 2.58 (1.26–5.30) |
| Male, % | 60.49 | 70.79 | 0.06 | NS | |

GP indicates glycoprotein. For age, OR is per year. For creatinine clearance, it is for each 1-mL increment.

tions in this subgroup were unusually high and were significantly linked to ischemic events, although medical management and revascularization strategies did not differ between recent withdrawers and either prior users or nonusers. It is likely that the excess bleeding reported in these patients may reflect their individual high-risk profile. After multivariate analysis, OAA cessation per se was found to be an independent predictor of death and major ischemic events. This finding supports the hypothesis of a rebound effect after OAA interruption, leading to acute coronary thrombosis that might have been triggered in some cases by the surgical stress. This superimposed thrombotic tendency is certainly critical in these patients, who also are known to exhibit enhanced generation of thrombin, a potent agonist of platelet aggregation and a marker of subsequent coronary events.^{16,17} The average delay between OAA withdrawal and MI is consistent with the rebound in platelet activity after aspirin cessation,^{10,18} the mean platelet life span being ≈ 10 days.¹⁹

The need for temporary interruption of OAA is frequently encountered in stable CAD patients, particularly before planned surgery to reduce the risk of perioperative bleeding. The present study suggests that interruption of OAA even in stable CAD patients could be harmful. Moreover, it is likely that OAA interruption is not justified in all cases, and clear recommendations for the management of OAA in perioperative situation are needed.²⁰ Although none of our patients underwent percutaneous coronary intervention before admission, our study follows previous reports suggesting that elective noncardiac surgery should be postponed for at least 2 to 4 weeks after coronary stent placement, given the proven high risk of both stent thrombosis and bleeding complications during this critical period.²¹

When OAA interruption is justified, substituting a reversible antithrombotic treatment is an option. However, there is no scientific demonstration to validate strategies using short-acting drugs such as flurbiprofen, indobufen, or low-molecular-weight heparin in place of OAA.²² In the present study, half of the recent withdrawers underwent various types of substitution therapy, which did not protect the patients. However, this does not tell us the potential preventive effect of these replacement strategies in patients requiring OAA interruption. Only an adequately sized randomized study could answer this question.

Appropriate use of OAA is of critical importance, given their proven efficacy to prevent many vascular events. It has recently been shown that aspirin resistance in stable CAD patients was associated with a significant increase in the risk of major adverse ischemic events.^{23–25} Similarly, defective compliance has been shown to be associated with a 4-fold increase in the rate of death compared with those appropriately treated.²⁶ Obviously, OAA withdrawal is another potential important issue that has become even more critical with the new recommendations for the chronic use of 2 antiplatelet agents after ACS.^{12,27,28} The present study does not demonstrate that the incidence of ACS is higher after recent discontinuation of OAA than in other populations. Indeed, the lack of patients who had withdrawn OAA without any clinical consequences and the nonrandomized nature of the present investigation are major limitations.

Further randomized large-scale studies are needed to clearly establish whether OAA withdrawal can be harmful and to determine the best strategies to prevent death and bleeding in these CAD patients requiring surgery. In addition, extending the potential deleterious effect of OAA withdrawal to other groups of patients such as primary prevention is another important unsolved issue.

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