Long-Term Outcome of Adjunctive Celecoxib Treatment After Paclitaxel-Eluting Stent Implantation for the Complex Coronary Lesions

Two-Year Clinical Follow-Up of COREA-TAXUS Trial

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Background—In the COREA-TAXUS trial (“Effect of Celecoxib On REstenosis after coronary Angioplasty with a TAXUS stent”), celecoxib reduced late luminal loss and adverse cardiac events at follow-up around 6 months. The objective of this study was to assess the long-term outcome of short-term adjunctive celecoxib treatment after paclitaxel-eluting stent implantation.

Methods and Results—This is a 2-year clinical follow-up of the COREA-TAXUS trial, an open-label randomized controlled study. A total 274 patients were randomized to receive or not receive celecoxib (400 mg before the intervention and 200 mg twice daily for 6 months after the procedure), and 271 underwent successful paclitaxel-eluting stent implantation. All patients were given aspirin (100 mg daily indefinitely) and clopidogrel (75 mg daily for at least 6 months). Among the 271 patients, 267 (98.5%) completed the 2-year clinical follow-up. From the previous follow-up to 2 years, there was no difference in the rate of adverse cardiac events between the celecoxib and control groups (1.6% versus 4.3%, \(P = 0.27\)). Thus, at 2 years, the rate of adverse cardiac events was consistently lower in the celecoxib group (6.9% versus 19.7%, \(P = 0.002\)). A significant reduction in need for target lesion revascularization was observed (6.2% versus 18.2%, \(P = 0.003\)). The efficacy benefit in the celecoxib group was not undermined by an increased risk for cardiac death or myocardial infarction at 2 years (1.5% versus 1.4%).

Conclusions—Six-month adjunctive celecoxib treatment after paclitaxel-eluting stent implantation was associated with durable long-term efficacy up to 2 years. However, the inconclusive evidence for the long-term safety of this treatment warrants caution.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT 00292721.

Key Words: angioplasty ■ coronary disease ■ stents ■ restenosis ■ celecoxib

Drug-eluting stents (DES) are highly effective in reducing neointimal hyperplasia and need for repeat revascularization compared with bare-metal stents.\(^1\)\(^2\) However, restenosis is still a problem, especially in complex patients and lesions,\(^3\)\(^4\) leaving room for systemic adjunctive therapy after stent implantation.

Clinical Perspective on p 248

Celecoxib is a selective inhibitor of cyclooxygenase 2 (COX-2) that is commonly used as an anti-inflammatory agent. However, it also has antiproliferative, proapoptotic, and antitumor effects.\(^5\)\(^-\)\(^8\) We have shown that, through inhibition of the Akt-glycogen synthase kinase signaling axis, celecoxib inhibits proliferation of vascular smooth muscle cells and increases their apoptosis in vitro and that it inhibits neointimal hyperplasia after angioplasty in vivo.\(^9\) On the basis of these novel findings, we have further demonstrated that adjunctive celecoxib treatment for 6 months after paclitaxel-eluting stent (PES) implantation in patients with complex coronary lesions reduces late luminal loss and need for target lesion revascularization at 6 months in the COREA-TAXUS randomized clinical trial (“Effect of Celecoxib On REstenosis after coronary Angioplasty with a TAXUS stent”).\(^10\)

However, caution for COX-2 inhibitors was raised when rofecoxib was voluntarily withdrawn from the market by its manufacturer after the Adenomatous Polyp Prevention On
Vioxx study. Since the publication of that study, there has been much controversy and intense debate whether there is an increased risk for adverse cardiovascular events with celecoxib. In the COREA-TAXUS trial, adjunctive celecoxib treatment did not increase the risk for cardiac death or myocardial infarction at 6 months. This may be partly due to dual antiplatelet therapy with aspirin and clopidogrel for at least 6 months, which was routine for patients with drug-eluting stent implantation.

Despite the clinical benefit at 6 months, there can be possible long-term adverse effects after short-term celecoxib use. However, the long-term outcome of this treatment is unknown. We report 2-year clinical follow-up of the COREA-TAXUS trial to assess the long-term efficacy and safety of short-term adjunctive celecoxib treatment after PES implantation.

**Methods**

**Study Population**

The COREA-TAXUS trial is an open-label randomized controlled study based at 2 referral centers in South Korea, the Seoul National University Hospital and the Seoul National University Bundang Hospital. Patients were enrolled between September 2004 and March 2006. The detailed descriptions of the study protocol and procedure were previously reported.19 Men and women were eligible if they were 18 to 75 years old, had angina pectoris or a positive stress test, and had native coronary lesions for which PES (Taxus, Boston Scientific, Mass) implantation was feasible. Complex lesions such as chronic total occlusion, long, calcified, type C, bifurcation, or small artery lesions were included because adjunctive medications to reduce restenosis is really needed for lesions with high restenosis rates. Exclusion criteria were acute ST-segment elevation myocardial infarction, definite intracoronary thrombus, renal dysfunction (serum creatinine ≥2.0 mg/dL), disease of the left main coronary artery, and severe left ventricular dysfunction (left ventricular ejection fraction ≤30%). All patients gave written informed consent, and the institutional review boards of both centers approved this study.

**Procedures**

All patients were given aspirin and clopidogrel before coronary intervention. Aspirin (100 mg daily) was taken indefinitely and clopidogrel (75 mg daily) was taken for at least 6 months. Patients who were randomly assigned to the celecoxib group were given 400 mg celecoxib before the coronary intervention and 200 mg twice daily for the next 6 months. This is an open-label study and a placebo was not used. To investigate the effect of celecoxib in a representative population, patients who had PES implantation in lesions other than the target vessel were included. For patients who had PES implants in several vessels, the operator declared the target lesion before the intervention and decided the order of treatment. Coronary intervention followed standard techniques. Predilatation, poststenotic adjunctive balloon inflation, and use of a glycoprotein IIb/IIIa inhibitor were all at the operators’ discretion. Clinical follow-up visits were scheduled for 1 month after coronary intervention and every 2 months thereafter. Medical records were reviewed by the investigators and by a study nurse; the nurse and physicians also asked patients about potential outcomes or adverse events at each visit.

**End Points and Definitions**

In the COREA-TAXUS trial, the clinical end points were adverse cardiac events, including cardiac death, nonfatal myocardial infarction, and target lesion revascularization at 6 months and yearly for 5 years after coronary intervention. Each event was counted in a nonhierarchical manner.

All deaths were regarded as cardiovascular unless there was a documented evidence of a clear noncardiovascular cause. Myocardial infarction was defined as the presence of at least 2 of the following: ischemic symptoms; increase in the levels of cardiac enzymes (creatine kinase [CK] muscle and brain isoenzymes [MB], CK-MB) to at least twice their upper normal limits; and new electrocardiographic changes compatible with myocardial infarction. Stent thrombosis included definite or probable cases as defined by the Academic Research Consortium.12 Stroke and acute decompen-sated heart failure were also analyzed to assess the global cardio-cerebrovascular adverse effect of adjunctive celecoxib treatment. Stroke was defined as the presence of focal neurological deficit not caused by trauma or tumor that persists more than 24 hours. Acute decompen-sated heart failure was defined as a development of New York Heart Association functional class ≥3 dyspnea not caused by acute coronary syndrome.

**Statistical Analysis**

We compared continuous variables using the Student t test, and we analyzed categorical variables using the \( \chi^2 \) test or Fisher exact test when appropriate. Cumulative incidence of adverse cardiac events was analyzed from the time of stent implantation to the first event according to the Kaplan-Meier method, and the difference was evaluated by log-rank test. Significance of all tests was defined at the \( P<0.05 \) level. All statistical analyses were performed using SPSS software, version 12 (SPSS Inc., Chicago, Ill). The investigators had direct access to the primary data.
Patients (Figure 1). Baseline clinical, angiographic, and procedural characteristics were comparable between the 2 groups (Table 1).

**Clinical Outcomes**

In the COREA-TAXUS trial, we planned follow-up angiography at 6 months, most of which was actually performed at 5 to 8 months. Our previous 6-month report thus included events within up to 8-month follow-up and this article included additional events afterward. Between the previous follow-up and 1 year, there were 3 target lesion revascularizations in the control group (0% versus 2.6%, P=0.99), of which were performed during the delayed follow-up angiography at 9 months. Clinical outcomes at 1 and 2 years are summarized in Table 2. Between 1 and 2 years, there was 1 nonfatal myocardial infarction and 1 target lesion revascularization in each group (1.6% versus 1.8%, P=0.99). The rate of adverse cardiac events was thus consistently lower in the celecoxib group at 2 years (6.9% versus 19.7%, P=0.002), mainly because of reduced need for target lesion revascularization (6.2% versus 18.2%, P=0.003). There were no differences between the celecoxib and control groups with regard to cardiac death (0% versus 0.7%, P=0.99) and nonfatal myocardial infarction (1.5% versus 0.7%, P=0.61) at 2 years.

**Cumulative Incidence of Adverse Cardiac Events**

Cumulative incidence of adverse cardiac events (mean follow-up 27.7±9.5 months) was significantly lower in the celecoxib group for the duration of follow-up (8.4% versus 21.8%, P=0.002; Figure 2). Most events were target lesion revascularization at the time of the follow-up angiography.

**Stent Thrombosis**

In the celecoxib group, 1 patient who had experienced definite, subacute stent thrombosis during use of aspirin and clopidogrel repeatedly experienced definite, very late stent thrombosis of the same stent segment late at 20 months during use of aspirin, clopidogrel, and cilostazol. Otherwise, there was no late or very late stent thrombosis, resulting in a comparable rate of stent thrombosis at 2 years (0.8% versus 0.7%, P>0.99).

**Other Events**

No hospitalization as a result of stroke or acute decompensated heart failure was noticed in both treatment groups.

<table>
<thead>
<tr>
<th>Table 2. MACE at 1 and 2 Years</th>
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<tbody>
<tr>
<td>1 Year</td>
</tr>
<tr>
<td>Control (n=137)</td>
</tr>
<tr>
<td>Cardiac death</td>
</tr>
<tr>
<td>Nonfatal MI</td>
</tr>
<tr>
<td>TLR</td>
</tr>
<tr>
<td>Total MACE</td>
</tr>
<tr>
<td>Stent thrombosis*</td>
</tr>
</tbody>
</table>

| Data are presented as n (%) or mean±SD. | *Definite or probable stent thrombosis as defined by Academic Research Consortium.
patients (1.4%) in the control group died of definite noncardiac causes. One patient died of esophageal variceal bleeding at 17 months, and the other patient died of pneumonia combined with advanced lung cancer at 21 months.

Medical Treatment
Details of medication at 2 years could be obtained in 249 (93.3%) patients (Table 3). There was no significant difference in the prescription rate of aspirin, clopidogrel, statins, β-blockers, and rennin-angiotensin-aldosterone system blockers. Mean duration of dual antiplatelet therapy with aspirin and clopidogrel was $405\pm283$ days in the celecoxib group and $436\pm300$ days in the control group ($P=0.39$).

Discussion
We have demonstrated that the early efficacy benefit of 6-month adjunctive celecoxib treatment after PES implantation was maintained at 2-year follow-up without an increased risk for cardiac death or myocardial infarction.

Our study supports the long-term clinical efficacy of PES in complex lesions. Indeed, the rate of complex patient and lesion characteristics was high: 33% had diabetes, 49% had type C lesion, 11% had total occlusion, and 20% had moderate to heavy calcification; the mean stent length was almost 30 mm. The benefit of PES in reducing target lesion revascularization seems to be durable in low complexity de novo lesions for up to 4 years in the TAXUS I trial.\textsuperscript{13} However, data on long-term clinical efficacy of PES for complex lesions are limited. In the TAXUS VI trial, the efficacy benefit of PES was durable and proportionally consistent, compared with bare-metal stent, up to 2 years.\textsuperscript{14} Although there was no bare-metal stent arm in the COREA-TAXUS trial, the increase in the rate of target lesion revascularization between 1 and 2 years in the control group (0.7%) was as low as that in the TAXUS group of the TAXUS VI trial (1.4%).

We previously reported that adjuvant celecoxib treatment after PES implantation for complex coronary lesions was highly effective, resulting in a 65% reduction of target lesion revascularization from 15.4% in the control group to 5.4% in the celecoxib group at follow-up angiography around 6 months. This clinical benefit in the celecoxib group was durable versus the control group up to 2 years. At 2-year follow-up, there was a 66% reduction of target lesion revascularization from 18.2% in the control group to 6.2% in the celecoxib group. The rate of target lesion revascularization between follow-up angiography around 6 months and 2 years was only 1.6% in the celecoxib group versus 4.3% in the control group. This 2-year clinical follow-up suggests that adjunctive celecoxib treatment for 6 months after PES implantation is not associated with clinical late catch-up up to 2 years. Follow-up for 2 years may not be sufficient to evaluate the long-term effect of an antirestenotic therapy. Five-year follow-up of our cohort is ongoing to confirm the long-term efficacy of this therapy.

Despite the black box warning on celecoxib in the United States, it has not been fully determined whether celecoxib increases the risk for adverse cardiovascular events. This is not a simple question, and several confounding factors, such as dose and duration of celecoxib, concomitant antiplatelet therapy, and concomitant treatment with angioplasty, should not be neglected.

Table 3. Details of Medications at 2 Years

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib (n=121)</th>
<th>Control (n=128)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>118 (97.5)</td>
<td>121 (94.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>29 (24)</td>
<td>43 (33.6)</td>
<td>0.09</td>
</tr>
<tr>
<td>Statins</td>
<td>100 (82.6)</td>
<td>106 (82.8)</td>
<td>0.97</td>
</tr>
<tr>
<td>β-blockers</td>
<td>81 (66.9)</td>
<td>74 (57.8)</td>
<td>0.14</td>
</tr>
<tr>
<td>RAAS blockers</td>
<td>60 (49.6)</td>
<td>72 (56.3)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Data are presented as n (%). RAAS indicates rennin-angiotensin-aldosterone system.
vascular risk of celecoxib was reduced to a nonsignificant events regardless of baseline aspirin use and that the dose-related risk of celecoxib (400 mg twice daily >200 mg twice daily >400 mg once daily) was more pronounced in patients at higher risk. According to this analysis, patients in the celecoxib group of the COREA-TAXUS trial (mostly at high risk taking 200-mg twice daily celecoxib) should have had a 2-fold increased risk for adverse cardiovascular events compared with patients in the control group. However, in this 2-year follow-up, adjunctive celecoxib treatment did not increase the risk for adverse cardiovascular events during its use and after its discontinuation. There can be some possible explanations for these contradictory results. Dual antiplatelet therapy with aspirin and clopidogrel for >6 months after stenting fully covered the period of celecoxib treatment, which may have negated the potential thrombotic cardiovascular risk of celecoxib. In the Adenoma Prevention With Celecoxib (APC) study and the Prevention of Colorectal Sporadic Adenomatous Polyp (PreSAP) study, the cardiovascular risk of celecoxib was reduced to a nonsignificant level in patients who were taking aspirin. Moreover, Borgdorff et al reported that increased platelet activity by COX-2 inhibitors in the presence of arterial stenosis could be prevented by low-dose clopidogrel. Relatively short-term use of celecoxib may also have reduced the adverse cardiovascular events. In the Adenomatous Polyp Prevention On Vioxx study using rofecoxib, which is several times more COX-2 selective than celecoxib, the cardiovascular risk difference between rofecoxib and placebo was noticed only after 18 months from the start of the study drugs. In the APC trial, there was no cardiovascular risk difference at 6 months among 3 regimens: 400 mg twice daily celecoxib, 200 mg twice daily celecoxib, and placebo.

This study has several limitations. First, the sample size is too small to make conclusions on the safety of celecoxib because the study was primarily designed for evaluating its efficacy (The primary end point of the COREA-TAXUS trial was the in-stent late luminal loss at 6 months). Second, it was performed with PES and results could have been different with other DES. Third, this study was not intended to validate the safety of COX-2 inhibitor administration in patients with or without DES who are on no or single antiplatelet therapy. Finally, it was an open-label study, thus there could be possible biases in treating restenotic lesions.

In conclusion, 6-month adjunctive celecoxib treatment after PES implantation under coverage of dual antiplatelet agents was associated with durable long-term efficacy up to 2 years, without an increased risk for cardiac death or myocardial infarction. However, the sample size was too small to make firm conclusions on the safety of this treatment, warranting larger trials.

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Disclosures
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References
Celecoxib, a cyclooxygenase-2 inhibitor, is a commonly used anti-inflammatory drug that also has antiproliferative and antitumor effects. The concept of the COREA-TAXUS trial was that celecoxib might augment the ability of drug-eluting stents to reduce the risk of lesion recurrence and consequently the need for repeat revascularization procedures. We administered 400 mg of celecoxib preprocedure and 200 mg daily for 6 months in an open-label randomized trial of patients receiving paclitaxel-eluting stents. We observed a beneficial effect at 2-years of follow-up, with patients treated with celecoxib requiring substantially less target lesion revascularization in comparison with patients who were treated with conventional care alone. Importantly, patients treated with celecoxib did not experience any excess of untoward thrombotic events.
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