Comparison of Triple Antiplatelet Therapy Including Triflusal and Conventional Dual Therapy in Patients Who Underwent Drug-Eluting Stent Implantation

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Summary

Triflusal is a derivative of acetylsalicylic acid but it exhibits different pharmacological and pharmacokinetic properties. The object of this study was to evaluate the efficacy of additional use of triflusal in patients who underwent drug-eluting stent implantation.

First, we prospectively tested platelet function with a rapid platelet function analyzer (VerifyNow®-Aspirin) in patients with stable angina (male, age, 61.6 ± 8.3, body weight, 69.3 ± 11.2 kg) who maintained dual (aspirin 100 mg and clopidogrel 75 mg per day, n = 23) or triple (aspirin 100 mg, clopidogrel 75 mg, and triflusal 300 mg per day, n = 23) therapy for more than one month. They were randomly assigned to a group. The triple group showed superior inhibition of arachidonic acid induced platelet aggregation compared to the dual group (420.2 ± 47.7 ARU versus 465.0 ± 71.2 ARU, P = 0.016). Second, we compared composite outcomes (death, myocardial infarction, and nonhemorrhagic stroke) after drug-eluting stent (DES) implantation between the dual (n = 1474) and triple (n = 433) groups in the prospective Seoul National University Hospital drug-eluting stent (SNUH-DES) cohort. The triple group had more current smokers, male patients, and patients with a previous history of revascularization. Also, the triple group underwent more complex interventions such as left main, chronic total occlusion, long lesion, and restenotic lesion than the dual group. In spite of their higher risk profiles, the triple group patients showed comparable composite outcomes (19 cases, 4.4%) to those of the dual group ones (41 cases, 2.8%) (P = 0.12).

The triflusal-based triple antiplatelet therapy achieved superior platelet inhibition compared to the dual therapy ex vivo and it could be applied after complex intervention with DES. (Int Heart J 2009; 50: 701-709)

Key words: Triflusal, Antiplatelet therapy, Thrombosis, Drug-eluting stent

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This study received sponsorship from the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (0412-CR02-0704-0001).

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Received for publication March 19, 2009.

Revised and accepted June 15, 2009.
Resistance to antiplatelet agents is an emerging issue in the drug-eluting stent era.\(^1\) It has been shown to be associated with more atherothrombotic events after acute coronary syndrome (ACS)\(^2,3\) and with more stent thrombosis after drug-eluting stent (DES) implantation.\(^4\) Aspirin resistance is defined as the failure of aspirin to inhibit platelet thromboxane A2 production or aggregability that is dependent on platelet thromboxane production.\(^5,6\) Previous studies have reported the prevalence of aspirin resistance varied from 5% to 45% of the population, depending on the type of study and the method of determining therapeutic failure. In addition, many possible mechanisms have also been suggested.\(^1\) Trials for overcoming aspirin resistance are actively being conducted. One of these is the addition of another antiplatelet agent on top of conventional dual therapy.

Triflusal (2-acetoxy-4-trifluoromethylbenzoic acid) is an antiplatelet drug that, despite its structural analogy to acetylsalicylic acid, exhibits different pharmacological and pharmacokinetic properties.\(^7\) The deacetylated and main metabolite of triflusal, 2-hydroxy-4-trifluoromethylbenzoic acid (HTB), also retains significant antiplatelet activity.\(^8\) Triflusal and HTB have been reported to have anti-inflammatory and vasodilatory effects in addition to the antiplatelet effect.\(^9-11\) Triflusal reduces serious vascular events, especially in high risk patients with a previous history of ischemic strokes, myocardial infarction, or peripheral artery disease.\(^12\) Also, it has been reported to show a better safety profile with respect to bleeding complications.\(^13,14\) These pleiotropic beneficial aspects of triflusal would lead to better laboratory and clinical outcomes in patients treated with DES.

The objective of this study was to determine whether the use of triflusal on top of aspirin and clopidogrel can augment the antiplatelet effect of aspirin assessed by the VerifyNow\textsuperscript{®}-Aspirin system and to validate the safety of this new regimen by comparing the atherothrombotic composite outcomes (death, myocardial infarction, and nonhemorrhagic stroke) with conventional dual regimen in patients treated with DES.

**Methods**

**Phase 1, Test of platelet function:** We prospectively tested platelet function with a rapid platelet function analyzer (VerifyNow\textsuperscript{®}-Aspirin) in patients with stable angina who maintained dual (\(n = 23\)) or triple (\(n = 23\)) antiplatelet therapy for more than one month. Patients were treated with aspirin 100 mg and clopidogrel 75 mg daily. The triple group also received triflusal (300 mg/day, Disgren\textsuperscript{®}, Myung-In Pharm, Seoul, Korea).

The VerifyNow\textsuperscript{®}-Aspirin system incorporates the agonist arachidonic acid
to activate platelets and is designed to measure platelet function based on the ability of activated platelets to bind fibrinogen.\textsuperscript{15-17} The sample result is interpreted based on the extent of platelet aggregation measured and is reported in Aspirin Reaction Units (ARU).\textsuperscript{15}

**Phase 2, Clinical outcomes in DES cohort study:** We analyzed patients ($n = 1907$) who were registered in our prospective cohort from February 2003 to April 2006, which was composed of all consecutive patients who received DES at Seoul National University (SNUH) and Seoul National University Bundang Hospital (SNUBH) as previously reported.\textsuperscript{18} In this cohort, a triple regimen was used in 433 patients (753 lesions) and a dual regimen in 1474 patients (2082 lesions) at least for 6 months after stent implantation.

The endpoint of the phase 2 study was a composite of atherothrombotic events (death, myocardial infarction, and nonhemorrhagic cerebral infarction) within 6 months after percutaneous coronary intervention. Myocardial infarction was defined as the presence of at least two of the following findings: ischemic symptoms; cardiac enzyme (CK-MB) concentration at least twice the upper limit of the normal range; or new electrocardiographic changes compatible with myocardial infarction. Nonhemorrhagic cerebral infarction was defined as a new focal neurologic deficit of vascular origin lasting at least 24 hours that was proven to be nonhemorrhagic by either CT or MRI scanning.

The follow-up protocol included a medical visit at the outpatient clinic at one month after stent placement and every two months thereafter. Clinical events were assessed on the basis of the information provided by hospital readmission records, the referring physician, or a phone interview with the patient. Observers of clinical events were blinded to the medication profile of patients when they made assessments.

Continuous variables are presented as the mean and standard deviation (SD). Student’s $t$ test was used to compare the degree of platelet inhibition between the two groups. Fisher’s exact test was used to compare the incidence of clinical endpoints between the two groups. A $P$ below 0.05 was considered statistically significant.

**Results**

**Phase 1, Additional inhibition of platelet by triflusal on top of dual agents:** The clinical characteristics of patients are summarized in Table I. There were no significant differences in characteristics between the dual and triple groups, except age ($59.7 \pm 8.9$ versus $64.7 \pm 7.4$, $P = 0.02$). Platelet function assessed using the VerifyNow\textsuperscript{®}-Aspirin system revealed that more potent inhibition of platelet aggregation was found in the triple group ($n = 23$, $420.2 \pm 47.7$ ARU) than in
the dual group \( (n = 23, 465.0 \pm 71.2 \text{ ARU}, P = 0.016, \text{Figure 1}) \). When we used \( \geq 550 \text{ ARUs} \) as a dichotomous indicator of aspirin resistance, \(^{15-17}\) one patient (4.3%) in the triple group and 3 patients (13.0%) in the dual group exhibited aspirin resistance \( (P = 0.61) \).
Phase 2: Clinical outcomes of triple versus dual agents in SNUH-DES cohort: The clinical and angiographic characteristics are summarized in Table II and Table III.

In the clinical characteristics, there were more current smokers (33.0% versus 22.9%, \( P < 0.001 \)), male patients (73.0% versus 63.2%, \( P < 0.001 \)), and patients with a previous history of revascularization (39.5% versus 23.9%, \( P < 0.001 \)) in the triple group. The triple group showed a lower level of total cholesterol compared to that of the dual group (169.3 ± 37.0 versus 177.4 ± 39.9 mg/dL, \( P < 0.001 \)).

Regarding the angiographic characteristics, more cases of ACC/AHA type B2 or C lesions (74.9% versus 66.6%, \( P < 0.001 \)) were found in the triple group. The triple group underwent more high risk interventions such as left main (7.0% versus 2.9%, \( P < 0.001 \)), bifurcation (32.5% versus 21.6%, \( P < 0.001 \)), chronic total occlusion (7.3% versus 4.3%, \( P = 0.002 \)), and restenotic lesion (9.2% versus 6.2%, \( P = 0.004 \)). In the procedural characteristics, the triple group was

### Table II. Clinical Characteristics of Patients With Dual or Triple Antiplatelet Agents in SNUH-DES Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dual agents ((n = 1474))</th>
<th>Triple agents ((n = 433))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>64.2 ± 9.7</td>
<td>63.3 ± 9.6</td>
<td>0.096</td>
</tr>
<tr>
<td>Male, %</td>
<td>63.2</td>
<td>73.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Acute coronary syndrome, %</td>
<td>50.5</td>
<td>46.4</td>
<td>0.14</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>39.3</td>
<td>39.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>66.3</td>
<td>62.6</td>
<td>0.17</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>22.9</td>
<td>33.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Previous revascularization, %</td>
<td>23.9</td>
<td>39.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>EF, baseline</td>
<td>57.5 ± 10.8</td>
<td>56.1 ± 11.8</td>
<td>0.078</td>
</tr>
<tr>
<td>Baseline Cr, mg/dL</td>
<td>1.38 ± 1.47</td>
<td>1.25 ± 1.13</td>
<td>0.10</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>177.4 ± 39.9</td>
<td>169.3 ± 37.0</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

AMI, indicates acute myocardial infarction; EF, ejection fraction; and Cr, serum creatinine.

### Table III. Lesion Characteristics of Patients With Dual or Triple Antiplatelet Agents in SNUH-DES Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dual agents ((lesion n = 2082))</th>
<th>Triple agents ((lesion n = 753))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC class B2/C type, %</td>
<td>66.6</td>
<td>74.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Left main disease, %</td>
<td>2.7</td>
<td>7.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Chronic total occlusion, %</td>
<td>4.3</td>
<td>7.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Restenotic lesion, %</td>
<td>6.0</td>
<td>9.2</td>
<td>0.004</td>
</tr>
<tr>
<td>Bifurcation lesion, %</td>
<td>21.6</td>
<td>32.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stent length, mm</td>
<td>29.1 ± 13.4</td>
<td>34.3 ± 17.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stent number</td>
<td>1.13 ± 0.51</td>
<td>1.22 ± 0.67</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stent diameter</td>
<td>2.98 ± 0.35</td>
<td>3.07 ± 0.36</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
treated with the implantation of longer, larger, and more stents than the dual group; there were significant differences in total stent length (34.3 ± 17.6 versus 29.1 ± 13.4 mm, $P < 0.001$), stent diameter (3.07 ± 0.36 versus 2.98 ± 0.35 mm, $P < 0.001$), and stent number per lesion (1.22 ± 0.67 versus 1.13 ± 0.51, $P < 0.001$) between the two groups.

The 6-month long clinical follow-up was completed in both groups. Mortality within 6 months after the procedure was 2.8% ($n = 12$) in the triple group and 2.0% ($n = 30$) in the dual group ($P = 0.35$). The incidence of nonfatal myocardial infarction was 1.4% ($n = 6$) in the triple group and 0.7% ($n = 10$) in the dual group ($P = 0.23$). Each group had one case of nonhemorrhagic stroke and it was not statistically significant ($P = 0.40$). Finally, composite outcomes were not different between the two groups (4.4% versus 2.8%, $P = 0.12$, Table IV).

**DISCUSSION**

In the first half of this study to assess the platelet function test, we provided evidence that the additional use of triflusal on top of conventional dual antiplatelet therapy may potentiate the antiplatelet action of dual agents in the *ex vivo* platelet function test. In the second half of study using an SNUH-DES cohort, such an augmentation of the antiplatelet effect by triflusal may lead to a benefit to high risk patients with DES implantation, considering the comparable clinical outcomes of the triple-agent group as those of the dual-agent one, even though the triple group had higher risk profiles and underwent more tough interventions.

In each phase of this study, we administered 300 mg/day of triflusal to patients in the triple group. This was a relatively small dose compared to a conventional dose for patients with cerebrovascular disease.\(^{15,19}\) Thus, adding a small dose of triflusal increased the antiplatelet effect of aspirin in patients with coronary artery disease and this could be used effectively in patients who underwent high risk coronary interventions.

**Additional action mechanisms of triflusal beyond aspirin:** Triflusal was also reported to increase nitric oxide production by neutrophil and endothelial nitric

<table>
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<tr>
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<th>Triple agents ($n = 433$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, $n$ (%)</td>
<td>30 (2.0)</td>
<td>12 (2.8)</td>
<td>0.35</td>
</tr>
<tr>
<td>Non-fatal MI, $n$ (%)</td>
<td>10 (0.7)</td>
<td>6 (1.4)</td>
<td>0.23</td>
</tr>
<tr>
<td>Stroke, $n$ (%)</td>
<td>1 (0.1)</td>
<td>1 (0.2)</td>
<td>0.40</td>
</tr>
<tr>
<td>Composite events, $n$ (%)</td>
<td>41 (2.8)</td>
<td>19 (4.4)</td>
<td>0.12</td>
</tr>
</tbody>
</table>
oxide synthase (eNOS) protein expression in neutrophils. After triflusal treatment, the neutrophils demonstrated a higher ability to prevent ADP-induced platelet aggregation.

The antithrombotic properties of triflusal in inhibiting thromboxane synthesis and in increasing cAMP and nitric oxide contributed greatly to the prevention of serious vascular events in people at high risk. It reduced the incidence of nonfatal myocardial infarction in patients with unstable angina. The antithrombotic properties have been also demonstrated in patients with aortocoronary vein grafting, peripheral arteriopathy, and cerebrovascular disease. Moreover, it has a protective effect against retinal microangiopathy, improves renal flow, and reduces proteinuria in diabetic patients.

Both triflusal and its main metabolite, HTB, were more potent than aspirin or salicylate as inhibitors of NF-kB. They had beneficial effects on the process where de novo COX-2 expression is involved or in pathological situations where genes under NF-kB control are upregulated. COX-2 from monocytes, macrophages, and endothelial cells can activate platelets and this was not sufficiently blocked by aspirin. Recently, a neuroprotective effect of triflusal was suggested and it has been attributed to the antioxidant and anti-inflammatory effects of triflusal.

The balloon injury in the process of percutaneous coronary intervention elicits inflammatory cascades such as nuclear translocation of nuclear factor-kappaB (NF-kB) and cyclooxygenase-2 (COX-2). They potently stimulate platelets through interaction with monocytes, macrophages, neutrophils, and endothelial cells. The additional use of triflusal may inhibit platelet activation by the regulation of COX-1 and nitric oxide and may exert anti-inflammatory effects in the progression of atherosclerosis.

**Clinical implication, a possible option for patients with high risks or aspirin resistance:** There have been concerns that aspirin and triflusal may competitively interact and that triflusal may decrease the efficacy of aspirin due to their structural similarity.

In the phase 1 study of the platelet function test, there was a significant difference in the values of ARU between the dual and triple groups. The frequency of ‘aspirin resistance’ defined as ARU ≥ 550 units, was 4.3% in the triple group whereas it was 13.0% in the dual group. This suggests that triflusal showed an additive effect on top of aspirin without a competitive drug-interaction and may be a potential candidate which compensates for a resistance to aspirin.

The phase 2 study was a prospective DES cohort study which compared the composite outcomes (death, nonfatal myocardial infarction, and nonhemorrhagic stroke) of patients who underwent DES implantation by the type of antiplatelet therapy. Despite the unfavorable clinical and angiographic charac-
teristics of the triple group, there were no significant differences in the endpoint. This showed that the triflusal-based triple antiplatelet therapy could be applied to patients who underwent high-risk and complex interventions.

To the best of our knowledge, this is the first report on triflusal-based triple antiplatelet therapy in patients who underwent drug-eluting stent implantation. The addition of triflusal on top of conventional dual therapy offered an additive antiplatelet effect *ex vivo* and may be a potential candidate regimen in patients who underwent complex percutaneous coronary intervention in the era of DES.

**Study limitations:** In phase 1, the small number of patients is a limitation of this study. The phase 2 study was a prospective cohort study and the use of triflusal was left to the discretion of the physician. The difference in baseline characteristics between the two groups is another limitation of this study. Further large-scale, prospective, and randomized studies are needed to prove the efficacy of additional triflusal therapy in patients who receive DES.

**Acknowledgment**

This study was supported by a grant from the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (0412-CR02-0704-0001). We did not receive any industry support for the design, conduct, analysis, or publication of the study, and there were no other real or potential conflicts of interest on behalf of those involved.

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