Volumetric Analysis of In-Stent Intimal Hyperplasia in Diabetic Patients Treated With or Without Abciximab

Results of the Diabetes Abciximab stEnt Evaluation (DANTE) Randomized Trial

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Background—In diabetic patients in the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial, abciximab reduced target vessel revascularization by ∼50% compared with placebo. Whether this is a result of a lower restenosis rate caused by inhibition of intimal hyperplasia remains to be defined.

Methods and Results—The purpose of this study was to determine whether abciximab at the time of stent implantation would reduce in-stent intimal hyperplasia measured by intravascular ultrasound at 6-month follow-up in type 2 diabetics. Ninety-six diabetic patients (96 lesions) who underwent elective stent implantation for a de novo lesion in a native coronary artery were randomly assigned to receive abciximab or no abciximab. In-stent intimal hyperplasia volume, expressed as percentage of stent volume, did not differ between groups: 41.3 ± 21.0% for those treated with abciximab versus 40.5 ± 18.3% for those treated without abciximab (P = 0.9). There were also no significant differences in angiographic minimal luminal diameter at follow-up (1.74 ± 0.69 versus 1.66 ± 0.63 mm; P = 0.5), late loss (1.03 ± 0.63 versus 1.07 ± 0.58 mm; P = 0.7), restenosis rate (17.8% versus 22.9%; P = 0.5), or cumulative incidence of major adverse cardiac events at 12 months (19.1% versus 20.4%; P = 0.9).

Conclusions—Six-month intravascular ultrasound volumetric analysis showed that abciximab, at the time of coronary stent implantation, was not associated with a reduction of in-stent intimal hyperplasia in diabetic patients. (Circulation. 2004;109:861-866.)

Key Words: diabetes mellitus ■ stents ■ glycoproteins ■ ultrasonics

Patients with diabetes mellitus have an increased risk of restenosis after conventional stent implantation.1–3 Abciximab, a IIb/IIIa glycoprotein inhibitor, decreases early ischemic complications4–6 and late death7 after percutaneous coronary intervention (PCI) in diabetics, but it is uncertain if it reduces in-stent restenosis. The EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting)8,9 study showed that abciximab halved the rate of target vessel revascularization among diabetic patients treated with stents (8.1% versus 16.6%, P = 0.02) and had a nonsignificant reduction in angiographic late loss (0.69 ± 0.63 versus 0.90 ± 0.67 mm, P = 0.098), leaving uncertain the role of abciximab in decreasing neointimal proliferation and angiographic restenosis. Therefore, we tested the hypothesis that abciximab might reduce neointimal hyperplasia after stenting in diabetic patients by measuring in-stent volume obstruction by 3-dimensional (3D) intravascular ultrasound (IVUS).

Methods

Study Design and Population

The Diabetes Abciximab Stent Evaluation (DANTE) trial was a prospective, randomized, open-label study that compared stenting with versus without abciximab in diabetic patients undergoing elective procedures at Instituto “Dante Pazzanese” de Cardiologia, São Paulo, Brazil. Patients were required to have documented type 2 diabetes mellitus and a symptomatic or ischemia-provoking de novo stenosis in a native coronary artery. Patients were excluded if they had myocardial infarction within <7 days, renal dysfunction (serum creatinine ≥2.0 mg/dL), or standard contraindications to abciximab. Angiographic exclusions included target vessel <2.5 mm or >4.0 mm in reference diameter, target lesion >18 mm in length, impaired left ventricular function (ejection fraction ≤30%), unprotected left main coronary lesion ≥50%, ostial lesion, total occlusion, or evidence of thrombus. Patients with multivessel disease had staged procedures. If more than one lesion met the required angiographic criteria, the lesion selected for inclusion in the study was chosen randomly. This study was performed according to the
principles of the Declaration of Helsinki and approved by the institutional ethics committee. Every patient provided written informed consent before random assignment.

**Study Protocol**

Patients were randomly assigned, by use of sealed envelopes, to stenting with versus without abciximab. Abciximab was administered as a bolus of 0.25 mg/kg, followed by a 12-hour infusion (0.125 μg/kg per minute, maximum 10 μg/min). Patients received 200 mg of aspirin and 500 mg of ticlopidine started >24 hours before the procedure. Ticlopidine was maintained for 4 weeks and aspirin indefinitely. Patients assigned to abciximab received 70 IU/kg (maximum, 7000 IU) heparin with supplemental doses to achieve an activated clotting time >200 seconds; patients assigned to stent without abciximab received an initial bolus of 100 IU/kg (maximum, 10,000 IU) heparin with supplemental doses to achieve an activated clotting time >300 seconds. The stents used were the MultiLink Tristar, Tetra, or Penta (Guidant) available in diameters 2.5 to 4.0 mm and lengths 8 to 28 mm. Stents were implanted according to standard protocols, followed by high-pressure (≥12 atm) balloon postdilation. If clinically indicated, a second stent could be used. Angiograms were performed only after administration of 200 μg of nitroglycerin before and after the procedure as well as after the procedure as well as at follow-up. Follow-up clinical visits were scheduled at 1, 6, and 12 months.

**Follow-Up Angiographic and IVUS Procedures**

Patients underwent follow-up angiographic and IVUS studies at 6 months or earlier in the event of recurrent symptoms. Postprocedural angiography was performed in at least 2 orthogonal projections; the same orthogonal projections were repeated at follow-up studies. Stented vessel segments were examined with a 30- or a 40-MHz single-element mechanical transducer (ClearView, CVIS, Boston Scientific Corp). A constant pullback speed of 0.5 mm/s was used for IVUS image acquisitions. A complete IVUS run was recorded on s-VHS tape for off-line 3D reconstruction.

**Quantitative Angiographic and IVUS Analysis**

Quantitative coronary angiography and IVUS measurements were performed by two investigators blinded to the assigned treatment. Quantitative coronary angiography was carried out with the use of an automated edge-detection system (CMS, MEDIS). A contrast-filled, nontapered catheter tip was used for calibration. The minimum lumen diameter (MLD), reference diameter, percent diameter stenosis, and the diameter of the maximally inflated balloon were analyzed and measured. IVUS images were analyzed with the use of 3D reconstruction software (echoPlaque 2, Indec Systems Inc). With the use of computerized planimetry, stent and reference segments were measured every 1 mm. Reference segment external elastic membrane (EEM), lumen, and plaque and media (P+M=EEM−lumen) areas were measured over a 5-mm length adjacent to stent edge and averaged. Stent, lumen, and intimal hyperplasia (stent-lumen) areas were measured within the stented segment; volumes were calculated by means of Simpson’s rule. The in-stent percent volume obstruction was calculated as the ratio between the neointimal hyperplasia volume and the stent volume × 100.

**End Points and Definitions**

The primary end point was the in-stent percent volume obstruction as measured by IVUS at 6-month follow-up. Secondary angiographic end points included MLD, late loss, and binary restenosis. Secondary clinical end points were the composite major adverse cardiac events (MACE) of death of any cause, nonfatal myocardial infarction, and target lesion revascularization (TLR) within 30 days and 1 year after the procedure. Angiographic success was defined as a residual diameter stenosis <30% after successful stent implantation. Myocardial infarction was defined as new pathological Q waves in 2 or more contiguous leads or the elevation of creatine kinase (CK) or its MB isoenzyme ≥3 times the upper limit of normal during hospital admission or ≥2 times the upper limit of normal thereafter. CK and CK-MB were determined before and 8 to 12 and 18 to 24 hours after treatment and daily thereafter until discharge.

**Statistical Analysis**

According to published data in diabetic patients, calculation of sample size was based on the assumption of a percent volume obstruction of 49±14% in the control group. We designed the study to detect a 20% reduction of the percent volume obstruction by abciximab compared with control, with a 2-sided α-level of 0.05 and power of 90%. Therefore, a sample size of 43 patients in each group was required; to account for ineligibility or losses to follow-up angiography, we intended to include 95 patients. All data were analyzed on an intention-to-treat basis. Categorical variables were expressed as percent frequency and compared with the χ² test or Fisher’s exact test as appropriate. Continuous variables were presented as mean±1 SD and were analyzed by Student’s t test for unpaired samples. Event-free survival curves were constructed by the Kaplan Meier method, and survival probabilities were compared by the log-rank test. Statistical evaluation was performed with SPSS 11.0 software (SPSS Inc). Probability values of P<0.05 were considered significant.

**Results**

**Baseline Characteristics**

Study flow is shown in Figure 1. A total of 96 diabetic patients were randomly assigned between February 2001 and March 2002; 47 patients were assigned to stent plus abciximab and 49 assigned to stent without abciximab. Baseline clinical and angiographic characteristics are shown in Table 1. With the exception of a significantly higher percentage of previous myocardial infarctions in the stent-plus-abciximab group, the two groups were similar with regard to all evaluated variables.

**Procedural Characteristics**

Angiographic stent implantation was successful in all patients. Equal numbers of patients were predilated with balloon angioplasty (40.4% versus 37.5%, P=0.8). Patients received 1 stent per lesion in the abciximab group and 1.06 stents per lesion in the control group. Three patients required an additional stent to treat residual dissections. All assigned patients completed the study drug protocol with the exception of one patient, who had the infusion of abciximab stopped after 6 hours because of gastrointestinal bleeding. There was no crossover to abciximab from the control group.
Adverse Events

One-year clinical follow-up was available in 100% of the patients (Table 2). No stent thrombosis was observed; no death, myocardial infarction, or additional revascularization occurred in the first month, yielding a 30-day MACE rate of 0. Two patients in the abciximab-stent group had hemorrhagic complications: One had limited gastrointestinal bleeding that required no blood product transfusion, and the other had a surgically treated femoral pseudoaneurysm.

During the 1-year follow-up period, 4 patients in the abciximab-stent group (8.5%) died: One died suddenly 62 days after stent implantation, and the other 3 died on the 9th, 10th, and 11th months of follow-up. These late deaths occurred in patients with patent target lesions at 6-month angiographic follow-up (the first 2 died after myocardial infarction and the last died of heart failure). One patient in the control group (2.0%) also had sudden death 104 days after stent implantation. Two patients in the control group had nonfatal myocardial infarction at follow-up, one related to brachytherapy failure of the target lesion and the other caused by late occlusion of a previously treated non-target vessel.

Percutaneous revascularization of the target lesion was performed in 5 patients (10.6%) of the abciximab-stent group and 8 patients (16.3%) of the control group (P=0.4). Reintervention without documented ischemia occurred in 62% (8 of 13) of these patients. No patient required coronary bypass surgery for TLR.

Event-free survival curve for major cardiac events is shown in Figure 2. At 1 year, event-free survival for MACE showed no difference between groups (80.9% versus 79.6%, P=0.8).

Quantitative Angiographic Analysis

Angiographic data at 6 months were available for 93 of 96 patients (96.9%) (Table 3). The target vessel reference vessel diameter, lesion length at baseline, preintervention MLD, postintervention MLD, follow-up MLD, late loss, and loss indexes were similar in the two groups. At 6-month follow-up, MLD had decreased significantly compared with before intervention in both groups (Figure 3). The binary restenosis rate was likewise similar in the two groups (17.8% versus 22.9%, P=0.5). No episode of occlusive stent restenosis was detected.

IVUS Analysis

IVUS analysis at follow-up was not possible in 2 patients: The IVUS catheter could not reach the stented segment in one
patient, and in the other patient, imaging was considered not suitable for analysis because of artifacts (nonuniform rotational distortion). Therefore, the 6-month follow-up IVUS data were available in 91 of 96 patients (94.8%). In-stent percent volume obstruction was similar between the two groups (41\% versus 40.5\%; stent-abciximab versus stent, \(P=0.9\); Figure 4). In addition, there were no significant differences in stent length, stent volume, lumen volume, absolute in-stent neointimal volume, or reference segment measurements (Table 4).

Because of interest in insulin-requiring patients, we performed a post hoc analysis of the primary end point results according to treatment regimen. In the non–insulin-requiring diabetics, the percent volume obstruction was similar between patients treated with or without abciximab (42.4\% versus 37.8\%; \(P=0.3\)). However, in the insulin-requiring group, there was a trend toward a reduced percent volume obstruction in patients treated with abciximab (36.7\% versus 35.5\%; \(P=0.075\)).

Discussion

The DANTE trial was a randomized study designed to investigate the effect of abciximab on neointimal hyperplasia, as measured by IVUS, in type 2 diabetic patients. Our results showed that abciximab given at the time of coronary stenting did not reduce the 6-month IVUS-determined percent volume obstruction compared with the reference treatment. Angiography, none of the indexes of restenosis suggested an advantage of abciximab, and the frequency of clinical events was similar in both groups.

It is well known that diabetes mellitus is associated with increased restenosis after stenting, usually ranging between 25\% and 37.5\%.1,3,11 Serial IVUS observations have demon-

### Table 3. Technical and Quantitative Angiographic Data

<table>
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<th>Abciximab</th>
<th>Control</th>
<th>(P)</th>
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<tr>
<td>Follow-up angiography, mo</td>
<td>6.67±0.50</td>
<td>6.51±0.95</td>
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<tr>
<td>Vessel size, mm</td>
<td>2.99±0.49</td>
<td>2.89±0.47</td>
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**Before stenting**

<table>
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<tbody>
<tr>
<td>MLD, mm</td>
<td>0.96±0.46</td>
<td>0.85±0.35</td>
<td>0.19</td>
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<tr>
<td>Diameter stenosis</td>
<td>64±15</td>
<td>66±12</td>
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<tr>
<td>Balloon-to-vessel ratio</td>
<td>1.11±0.13</td>
<td>1.16±0.13</td>
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<tr>
<td>Inflation pressure, atm</td>
<td>14.9±1.7</td>
<td>15.4±2.6</td>
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<tr>
<td>Lesion length, mm</td>
<td>11.5±4.7</td>
<td>11.0±3.5</td>
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</table>

**After stenting**

<table>
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<tr>
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<tbody>
<tr>
<td>MLD, mm</td>
<td>2.77±0.40</td>
<td>2.73±0.42</td>
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<tr>
<td>Diameter stenosis</td>
<td>10±6</td>
<td>10±5</td>
<td>0.9</td>
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**At follow-up**

<table>
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<tr>
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<tbody>
<tr>
<td>MLD, mm</td>
<td>1.74±0.69</td>
<td>1.66±0.63</td>
<td>0.5</td>
</tr>
<tr>
<td>Diameter stenosis</td>
<td>32±18</td>
<td>35±19</td>
<td>0.4</td>
</tr>
<tr>
<td>In-stent restenosis</td>
<td>17.8</td>
<td>22.9</td>
<td>0.5</td>
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<tr>
<td>Acute gain, mm</td>
<td>1.82±0.42</td>
<td>1.88±0.47</td>
<td>0.5</td>
</tr>
<tr>
<td>Late loss, mm</td>
<td>1.03±0.63</td>
<td>1.07±0.58</td>
<td>0.7</td>
</tr>
<tr>
<td>Net gain, mm</td>
<td>0.77±0.68</td>
<td>0.82±0.59</td>
<td>0.7</td>
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<tr>
<td>Loss index</td>
<td>0.59±0.38</td>
<td>0.57±0.30</td>
<td>0.8</td>
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</table>

### Table 4. IVUS Measurements

<table>
<thead>
<tr>
<th></th>
<th>Abciximab</th>
<th>Control</th>
<th>(P)</th>
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<tbody>
<tr>
<td>Proximal reference (mean CSA analysis)</td>
<td></td>
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<tr>
<td>EEM area, mm(^2)</td>
<td>15.0±4.5</td>
<td>14.2±4.4</td>
<td>0.4</td>
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<tr>
<td>Lumen area, mm(^2)</td>
<td>6.4±3.0</td>
<td>6.0±2.2</td>
<td>0.5</td>
</tr>
<tr>
<td>P+M area, mm(^2)</td>
<td>8.6±3.1</td>
<td>8.1±3.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Stented segment (volumetric analysis)</td>
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<tr>
<td>Stent length, mm</td>
<td>18.1±4.0</td>
<td>19.8±5.6</td>
<td>0.10</td>
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<tr>
<td>Stent volume, mm(^3)</td>
<td>137.1±44.0</td>
<td>147.4±54.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Lumen volume, mm(^3)</td>
<td>83.4±44.7</td>
<td>86.7±36.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Intimal hyperplasia volume, mm(^3)</td>
<td>53.6±28.5</td>
<td>60.7±40.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Volume obstruction, %</td>
<td>41.3±21.0</td>
<td>40.5±18.3</td>
<td>0.9</td>
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<tr>
<td>Distal reference (mean CSA analysis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEM area, mm(^2)</td>
<td>11.5±6.0</td>
<td>11.7±4.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Lumen area, mm(^2)</td>
<td>5.4±3.6</td>
<td>5.5±3.1</td>
<td>0.9</td>
</tr>
<tr>
<td>P+M area, mm(^2)</td>
<td>6.1±3.6</td>
<td>6.2±3.2</td>
<td>0.9</td>
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CSA indicates cross-sectional analysis.
strated that the increased in-stent restenosis in diabetics is explained by an exaggerated intimal hyperplasia compared with nondiabetic patients.

IVUS measurement of in-stent neointimal hyperplasia volume has been validated against ex vivo histomorphometry. The use of IVUS-determined percent neointimal hyperplasia volume obstruction as a primary end point allows studies with a lower sample size with adequate power to detect a reasonable biological difference between groups. Previous studies with newer-generation bare metal stents have shown percent in-stent volume obstructions usually ranging between 29% and 31.5% in unselected patients. Our results, among others, confirm the concept that diabetic patients constitute a high-risk subgroup for exaggerated intimal hyperplasia, with an IVUS-determined percent volume obstruction of 41%.

One of the mechanisms potentially involved in neointima formation is platelet deposition and aggregation at the site of vessel injury. In experimental models, antibody-induced thrombocytopenia inhibits neointimal thickening after arterial injury. Abciximab is a potent glycoprotein IIb/IIIa platelet inhibitor that has additional distinctive properties, such as the inhibition of vascular cell vitronectin and leukocyte Mac-1 receptors. Vitronectin receptors appear to be implicated in vascular repair processes, promoting the adhesion of activated platelets to the endothelium, platelet-mediated thrombin generation, interactions between endothelial and white blood cells, smooth muscle cell migration/proliferation, and vascular cell apoptosis. Leukocyte Mac-1 receptors appear to modulate inflammation, coagulation, and cell proliferation after arterial injury. These multiple abciximab actions would be beneficial in reducing neointima formation, especially in diabetic patients, in whom various mechanisms combine to promote the restenosis phenomenon. Diabetics usually have endothelial dysfunction, increased size of platelets with enhanced adhesiveness and hyperaggregability, overexpressed growth factors, and increased extracellular matrix production.

The inability of abciximab to reduce in-stent neointimal formation either in unselected patient populations or those with thrombus-containing lesions has been demonstrated. In the diabetic subgroup, however, the effect with regard to target vessel revascularization (TVR), the clinical surrogate for restenosis, has been controversial. Abciximab was not successful in reducing TVR rates for diabetics treated with balloon angioplasty but decreased by 50% TVR rates for those treated with stents, suggesting a reduction in angiographic restenosis. The evoked benefit of vitronectin and Mac-1 receptors inhibition by abciximab in reducing neointimal proliferation among diabetic patients, however, was challenged by the results of the head-to-head comparison of abciximab and tirofiban, which did not show benefit for abciximab in reducing TVR rates with abciximab versus 8.8% with tirofiban, \( P = 0.257 \). Our results clarify the findings of abciximab in diabetics, demonstrating the failure of abciximab to reduce in-stent neointimal formation in this subgroup of patients.

Unlike the angiographic findings from the EPIS gaze study that showed a significant increase in net gain and a decrease in the late loss index for stent-abciximab cases, none of the luminal change in the current analysis showed differences between abciximab-treated and control patients. The late loss of 1.0 mm was similar to the 0.77- to 1.27-mm late loss usually found for the diabetic subgroups in various stent studies. The somewhat lower-than-expected in-stent restenosis rate for diabetic patients in the present study (20.4%) is close to the 24% restenosis rate reported by Van Belle et al. for diabetics with relatively large native vessels (mean reference diameter of 3.06 mm) and short lesions (9 mm in length) that were mostly covered with a single stent. In addition, all of our patients were treated with the corrugated ring design MultiLink stent, which may reduce tissue proliferation at the 6-month follow-up angiographic evaluation compared with tubular slotted design stents.

Although the present study did not have statistical power to detect differences in clinical outcomes, it is noteworthy that none of our patients had 30-day clinical events. We speculate that the good angiographic results and the antiplatelet protection provided by >24 hours of ticlopidine and aspirin pretreatment could have contributed to the favorable results. The benefits of the long-term (1-year) dual antiplatelet therapy after elective PCI have been demonstrated recently, and, if implemented, may have prevented some of the late follow-up thrombotic events.

**Study Limitations**

One limitation of the study is related to the unblinded nature of the trial. Although the assignment to abciximab versus control was not blinded, the primary end point (percent volume obstruction) was assessed in the core laboratory by two investigators unaware of assigned treatments. The study did not have the power to identify differences in clinical events or to assess effectiveness in more complex angiographic subgroups. The restrictive character of the angiographic inclusion and exclusion criteria of this investigation must be kept in mind, and thus the results may or may not be extrapolated to other diabetic patients. Information about the adequacy of glycemic control during follow-up is lacking; thus, the analysis of its relation to neointimal tissue proliferation could not be performed. Finally, the post hoc analysis of the insulin-treated diabetics is, at best, exploratory, given the small number of patients in each group.

**Conclusions**

In the DANTE randomized study, IVUS volumetric analysis obtained at 6-month follow-up showed that the administration of abciximab at the time of coronary stent implantation was not associated with a reduction of in-stent neointimal hyperplasia in diabetic patients.

**Acknowledgments**

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**References**


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