Efficacy and Safety of Tenecteplase in Combination With the Low-Molecular-Weight Heparin Enoxaparin or Unfractionated Heparin in the Prehospital Setting

The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS Randomized Trial in Acute Myocardial Infarction

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Background—The combination of a single-bolus fibrinolytic and a low-molecular-weight heparin may facilitate prehospital reperfusion and further improve clinical outcome in patients with ST-elevation myocardial infarction.

Methods and Results—In the prehospital setting, 1639 patients with ST-elevation myocardial infarction were randomly assigned to treatment with tenecteplase and either (1) intravenous bolus of 30 mg enoxaparin (ENOX) followed by 1 mg/kg subcutaneously BID for a maximum of 7 days or (2) weight-adjusted unfractionated heparin (UFH) for 48 hours. The median treatment delay was 115 minutes after symptom onset (53% within 2 hours). ENOX tended to reduce the composite of 30-day mortality or in-hospital reinfarction, or in-hospital refractory ischemia to 14.2% versus 17.4% for UFH (P=0.080), although there was no difference for this composite end point plus in-hospital intracranial hemorrhage or major bleeding (18.3% versus 20.3%, P=0.30). Correspondingly, there were reductions in in-hospital reinfarction (3.5% versus 5.8%, P=0.028) and refractory ischemia (4.4% versus 6.5%, P=0.067) but increases in total stroke (2.9% versus 1.3%, P=0.026) and intracranial hemorrhage (2.0% versus 0.97%, P=0.047). The increase in intracranial hemorrhage was seen in patients >75 years of age.

Conclusions—Prehospital fibrinolysis allows 53% of patients to receive reperfusion treatment within 2 hours after symptom onset. The combination of tenecteplase with ENOX reduces early ischemic events, but lower doses of ENOX need to be tested in elderly patients. At present, therefore, tenecteplase and UFH are recommended as the routine pharmacological reperfusion treatment in the prehospital setting. (Circulation. 2003;108:135-142.)

Key Words: myocardial infarction ■ fibrinolysis ■ hemorrhage ■ heparin ■ reperfusion

Time to reperfusion remains a key modifiable determinant of mortality in ST-elevation myocardial infarction (STEMI).1–4 Despite many years of medical advances, the time from symptom onset until the start of pharmacological reperfusion treatment remains largely unchanged, with a median of ≈2.5 to 3 hours.5 A prehospital treatment strategy has been shown to reduce time to treatment by 0.5 to 1.0 hour, to reduce mortality by ≈17% (relative reduction) in a recent meta-analysis,6–12 and even to compare favorably with primary angioplasty in a recent randomized study.13

Despite the development of a series of new fibrinolytic agents14–16 for the treatment of STEMI, there has been little improvement in survival rate over the past decade, which is perhaps partly related to limited improvement in coronary
perfusion, continued occurrence of reinfarction, and bleeding complications.\textsuperscript{17,18} The new single-bolus fibrinolytic drug tenecteplase has facilitated the treatment of acute myocardial infarction, with efficacy equivalent to alteplase for 30-day and 1-year mortality and with the added benefit of less systemic bleeding.\textsuperscript{16} Because of its simplicity, the bolus regimen is an attractive choice for the prehospital setting. However, few data are available concerning the efficacy and safety of this prehospital regimen.\textsuperscript{19}

In pilot studies, subcutaneous low-molecular-weight heparin (LMWH) combination of bolus fibrinolytics and LMWH in the prehospital setting. In the ASSENT-3 trial, tenecteplase with enoxaparin (ENOX) versus UFH reduced in-hospital reinfarction and refractory ischemia without any significant excess in hospital setting. In the ASSENT-3 trial, tenecteplase with enoxaparin (ENOX) versus UFH reduced in-hospital reinfarction and refractory ischemia without any significant excess in major bleeding or intracranial hemorrhage (ICH).\textsuperscript{25} As an extension of the ASSENT-3 trial, we performed the current randomized open-label trial in the prehospital setting. The objectives were to study the feasibility and treatment delays and compare efficacy and safety of the 2 antithrombin cotherapies with tenecteplase in the prehospital setting.

### Methods

#### Study Populations

The inclusion criteria were identical to those in both the ASSENT-\textsuperscript{24} and ASSENT-3\textsuperscript{23} trials: age $\geq$ 18 years, onset of symptoms $\leq$ 6 hours before randomization, ST-segment elevation of $\geq 0.1$ mV in $\geq 2$ limb leads or $\geq 0.2$ mV in $\geq 2$ contiguous precordial leads, or left bundle-branch block. Exclusion criteria on arrival were systolic blood pressure $>180$ mm Hg and/or diastolic blood pressure $>110$ mm Hg; use of glycoprotein IIb/IIIa inhibitors within the preceding 7 days; major surgery, biopsy of a parenchymal organ, or substantial trauma within the preceding 2 months; any head or other trauma occurring after onset of current myocardial infarction; any known history of stroke, transient ischemic attack, or dementia; any known structural damage to the central nervous system; current therapy with oral anticoagulants; treatment with UFH $>5000$ U or a therapeutic subcutaneous dose of LMWH within the previous 6 hours; known thrombocytopenia ($< 100,000$ cells/\u00b5L); known renal insufficiency (serum creatinine $>2.5$ mg\% for men and $>2.0$ mg\% for women); sustained cardiopulmonary resuscitation ($> 10$ minutes) in the previous 2 weeks; pregnancy, lactation, or parturition in the previous 30 days; active participation in another investigative drug or device study in the previous 30 days; previous enrollment in this study; any other disorder that would place the patient at increased risk; and inability to follow the protocol and to comply with the follow-up requirements.

All patients were primarily evaluated in the prehospital setting by paramedics, nurses, or physicians, in accordance with the resources of the ambulance system at each center and in each country. The clinical history, physical examination, and occurrence of any complication were collected according to a structured form. A 12-lead ECG was obtained by mobile ECG equipment in the patient’s home or in the ambulance and evaluated by the emergency physician in the ambulance or after telephone communication to the emergency center or coronary care unit. If the physician, on the basis of clinical history, physical examination, and ECG, approved the indication for fibrinolytic treatment, the patient was eligible for entry in the trial. Each hospital’s institutional review board approved the protocols.

### Randomization and Study Treatments

After giving informed consent, patients were randomly assigned open-label treatment by means of sealed envelopes. Each ambulance carried 2 kits marked “A” and “B,” one of which contained tenecteplase and ENOX and one of which contained tenecteplase and UFH. By opening the envelopes in consecutive order, patients were randomly given treatment A or B according to a permuted block design. Tenecteplase was administered over 5 seconds according to body weight: 30 mg if body weight was $< 60$ kg; 35 mg if body weight was $60 < 70$ kg; 40 mg if body weight was $70 < 80$ kg; 45 mg if body weight was $80 < 90$ kg; and 50 mg if body weight was $90$ kg. Patients assigned to the intravenous UFH arm received a bolus of 60 U/kg (maximum of 4000 U) followed by an initial infusion of 12 U/kg per hour (maximum of 1000 U/h), which was to be begun in the prehospital setting. The first blood sample for activated partial thromboplastin time (aPTT) measurement was drawn after 3 hours. The UFH infusion rate was adjusted to maintain an aPTT of 50 to 70 seconds for 48 hours. Patients assigned ENOX cotherapy received an intravenous bolus of 30 mg immediately followed by the first subcutaneous dose of 1 mg/kg. This subcutaneous dose was repeated every 12 hours up to hospital discharge or revascularization, with a maximum of 7 days. The first 2 subcutaneous doses could not exceed 100 mg. An initial dose of aspirin (150 to 325 mg) was given to all patients and followed by a daily dose of 100 to 325 mg.

### Primary End Points, Data Handling, and Statistical Analysis

The trial was initially planned as a feasibility trial of 1000 patients. The primary end points were identical to those of the ASSENT-3 trial—ie, the composite of 30-day mortality or in-hospital reinfarction or in-hospital refractory ischemia (primary efficacy end point) and the composite of the above plus in-hospital ICH or in-hospital major bleeding other than intracranial (primary efficacy-plus-safety end point). Initially, no statistical hypothesis was prespecified. However, after the presentation of the significant benefit of enoxaparin in the ASSENT-3 trial, and with the availability to the preliminary outcome of the first 500 patients in the present trial, the Data and Safety Monitoring Board recommended an extension of the trial. Consequently, the steering committee formulated a primary exploratory hypothesis with the aim of detecting an absolute 5% benefit of ENOX compared with UFH for the primary efficacy end point. This hypothesis was based on the expected event rates in the ASSENT-3 PLUS trial as estimated from the background characteristics of the first 500 patients, which were entered into a logistic model for the efficacy composite end point derived from the ASSENT-3 database. The number of subjects to be randomized in the ASSENT-3 PLUS trial was therefore increased to 1600 patients because a sample size of 790 patients in each arm was required to detect an absolute 5% difference with 80% power at a 5% significance level.

Data were entered with the use of Oracle Clinical (version 3.1.1) and electronically transferred to the central database in Leuven, Belgium, with the same quality control as in ASSENT-3.\textsuperscript{23} Safety data were reported monthly to the Data and Safety Monitoring Board. All stroke cases were reviewed by the same stroke committee with the same quality control as in ASSENT-3.\textsuperscript{23} All statistical analyses of ASSENT-3 PLUS were performed according to intention-to-treat. Between-groups comparisons for each end point were done by presenting the relative risk with the 2-sided 95% CI. In addition, nonparametric, covariate-adjusted rates were calculated using Koch’s method.\textsuperscript{26} Covariates used were gender, age, weight, infarct location, previous infarct, Killip class, heart rate, time to tenecteplase, and systolic blood pressure. Because
the results of the adjusted and nonadjusted analyses were very similar, only nonadjusted results are presented. For the primary end points, Kaplan-Meier curves were constructed, and log-rank tests were done. In a multivariable analysis of the risk of ICH, the following variables were used: age, age category (≥75, >75 years), gender, diabetes mellitus, smoking, aspirin treatment, hypertension, systolic blood pressure, clopidogrel-ticlopidine treatment, glycoprotein IIb/IIIa treatment, nonprotocol UFH or ENOX treatment, randomized study treatment, and the interaction term between age category and randomized study treatment.

Results

We recruited 1639 patients in 88 centers located in 12 countries between July 25, 2000, and July 16, 2002. The details of treatments provided and follow-up are outlined in Figure 1. There were no significant differences in baseline characteristics between the groups (Table 1). However, there tended to be more elderly females in the ENOX group (38%) than in the UFH group (30%). Killip class at entry was not recorded in 21% of the cohort.

Almost all (98%) of the patients received tenecteplase before hospital arrival. Approximately 20% of patients received >105% of the correct tenecteplase dose as based on estimated weight in comparison to actual weight in hospital. In the UFH group, after the initial intravenous bolus injection, the UFH infusion was started before hospital arrival in only 61%. Furthermore, only 30% of the UFH patients were within 40% to 60% were below the target aPTT range at the different time points for aPTT measurements (Figure 2). In contrast, both the intravenous and subcutaneous ENOX dose was given according to schedule in 88% of patients. During the hospital stay, nonscheduled LMWH had been used in 33% of the ENOX and 47% of the UFH patients.

The median time from onset of pain to the call for an ambulance was 60 minutes; from call to arrival of the ambulance, 13 minutes; from arrival to randomization, 23 minutes; and from randomization to the bolus injection of tenecteplase, an additional 10 minutes (Table 2). Thus, the median delay from symptom onset to tenecteplase administration amounted to 115 minutes. Accordingly, 53% of patients were treated within the first 2 hours after onset of symptoms. There were no significant differences in delay times between the ENOX and UFH groups.

The primary efficacy end point tended to be lower with ENOX compared with UFH (14.2% versus 17.4%, \(P=0.080\)), and there was a smaller, nonsignificant trend for the primary efficacy and safety end point (18.3% versus 20.3%, \(P=0.297\)) (Table 3). Accordingly, the Kaplan-Meier curves showed a nonsignificant separation of the treatment groups.
Among the predefined subgroups, there was a significant reduction in the primary efficacy end point in ENOX patients 75 years of age (11.2% versus 15.2%, \( P = 0.033 \)). On the other hand, there was no significant difference between the treatment groups in either end point in those 75 years of age. With regard to the individual end points, there was a significant reduction in in-hospital reinfarction and a corresponding trend in in-hospital refractory ischemia (Table 3).

With regard to safety, there was a significant increase in total stroke (2.9% versus 1.3%, \( P = 0.026 \)) and in-hospital ICH (2.20% versus 0.97%, \( P = 0.047 \)) in the ENOX group (Table 4). The excess of ICH occurred mainly during the first and second days after treatment, with 8 versus 2 cases and 5 versus 1 case in the ENOX versus UFH group, respectively (Figure 4). The increased rates in stroke and ICH were explained by high rates of these events in the predefined subgroup of patients >75 years of age: total stroke, 9.4% versus 2.3%, \( P = 0.01 \); and ICH, 6.7% versus 0.8%, \( P = 0.01 \) (Figure 4). In the multivariable analysis, age category (\( P < 0.001 \)) and the interaction between age category and randomized study treatment (\( P = 0.011 \)) were the only factors that significantly influenced the risk of ICH. There was no relation between the ICH rate and the proportion of patients treated with the target dose of tenecteplase in the ENOX group—ie, 1 of 35 patients (2.86%) had ICH at <95% of the ideal tenecteplase dose, 13 of 615 patients (2.11%) had ICH at 95% to 105% of the ideal tenecteplase dose, and 4 of 152 patients (2.63%) had ICH at >105% of the ideal tenecteplase dose. In contrast, in the UFH group, overdosing of tenecteplase tended to be associated with an increased ICH rate ie, 0 of 31 patients (0.0%) had ICH at <95% of the ideal tenecteplase dose, 5 of 602 patients (0.83%) had ICH at 95% to 105% of the ideal tenecteplase dose, and 3 of 173 patients (1.73%) had ICH at >105% of the ideal tenecteplase dose. There was no difference in ICH rate between patients in whom the UFH infusion was started in the ambulance (3 of 113 patients [0.96%]) versus in the hospital (5 of 481 patients [1.04%]).

In the total cohort, there was a nonsignificant (\( P = 0.234 \)) higher mortality rate with ENOX (7.5% [61 deaths]) compared with UFH (6.0% [49 deaths]) (Table 3). From the overall excess of 12 deaths with ENOX, intracranial bleeding accounted for 9, whereas 3 were due to other, noncardiac causes. There were 45 cardiac deaths in both groups at 1 month.

Minor bleeding was somewhat more common with ENOX, whereas thrombocytopenia (\(<50 000 \text{ cells/\( \mu \)L}\)) was rare (0% to 0.2%) with both agents. In the total cohort, there was a 27% rate of urgent and 23% rate of nonurgent percutaneous TABLE 2. Percentiles of Time Delays (Minutes) in the Combined ENOX and UFH Groups

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>No. of Patients</th>
<th>Percentile of Time Delay, min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10th</td>
<td>25th</td>
</tr>
<tr>
<td>Symptom onset—calling ambulance</td>
<td>1580</td>
<td>12</td>
</tr>
<tr>
<td>Calling ambulance—arrival at scene</td>
<td>1568</td>
<td>5</td>
</tr>
<tr>
<td>Symptom onset—arrival at scene</td>
<td>1611</td>
<td>25</td>
</tr>
<tr>
<td>Arrival of ambulance—randomization</td>
<td>1599</td>
<td>9</td>
</tr>
<tr>
<td>Randomization—first injection</td>
<td>1594</td>
<td>1</td>
</tr>
<tr>
<td>Randomization—TNK-tPA injection</td>
<td>1598</td>
<td>4</td>
</tr>
<tr>
<td>Symptom onset—TNK-tPA injection</td>
<td>1633</td>
<td>55</td>
</tr>
<tr>
<td>Arrival at scene—arrival at hospital</td>
<td>1599</td>
<td>42</td>
</tr>
<tr>
<td>Symptom onset—arrival at hospital</td>
<td>1617</td>
<td>80</td>
</tr>
</tbody>
</table>

TNK-tPA indicates tenecteplase.

TABLE 3. Primary and Secondary End Points (Relative Risks and 95% CIs) in the ENOX and UFH Groups

<table>
<thead>
<tr>
<th>End Point</th>
<th>ENOX (n=818)</th>
<th>UFH (n=821)</th>
<th>Risk Ratio (UFH/ENOX)</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-Day mortality or in-hospital reinfarction or in-hospital refractory ischemia</td>
<td>116/817 (14.2)</td>
<td>142/818 (17.4)</td>
<td>1.22 (0.98, 1.53)</td>
<td>0.080</td>
<td></td>
</tr>
<tr>
<td>30-Day mortality or in-hospital reinfarction or in-hospital refractory ischemia or in-hospital ICH or in-hospital major bleeds</td>
<td>149/816 (18.3)</td>
<td>166/818 (20.3)</td>
<td>1.11 (0.91, 1.36)</td>
<td>0.297</td>
<td></td>
</tr>
<tr>
<td>Death at 30 days</td>
<td>61/817 (7.5)</td>
<td>49/818 (6.0)</td>
<td>0.80 (0.56, 1.15)</td>
<td>0.234</td>
<td></td>
</tr>
<tr>
<td>In-hospital reMI</td>
<td>29/818 (3.5)</td>
<td>48/821 (5.8)</td>
<td>1.65 (1.05, 2.59)</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>In-hospital refractory ischemia</td>
<td>36/818 (4.4)</td>
<td>53/821 (6.5)</td>
<td>1.47 (0.97, 2.22)</td>
<td>0.067</td>
<td></td>
</tr>
<tr>
<td>Total stroke</td>
<td>24/818 (2.9)</td>
<td>11/821 (1.3)</td>
<td>0.46 (0.23, 0.93)</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>In-hospital ICH</td>
<td>18/818 (2.20)</td>
<td>8/821 (0.97)</td>
<td>0.44 (0.19, 1.01)</td>
<td>0.047</td>
<td></td>
</tr>
<tr>
<td>In-hospital major bleeding</td>
<td>33/817 (4.0)</td>
<td>23/821 (2.8)</td>
<td>0.69 (0.41, 1.17)</td>
<td>0.168</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as n/N (%). reMI indicates reinfarction.
coronary intervention (PCI), without any significant differences between the treatment groups. There also were no differences in other major complications (Table 4).

### Discussion

ASSENT-3 PLUS is the first large, randomized study to evaluate the feasibility and efficacy of prehospital single-bolus fibrinolytic and adjunctive bolus antithrombin treatment in a multinational environment. As compared with the ASSENT-3 in-hospital trial, which used identical inclusion criteria, the median treatment delay was shorter by 47 minutes, which corresponds to previous time gains observed with a prehospital reperfusion strategy. The median delay from onset of symptoms until injection of tenecteplase was 115 minutes, and hence more than half of the patients were treated within 2 hours of symptom onset. Because the randomization procedure might have delayed treatment by 10 to 15 minutes, even more patients would have been treated within the first 2 hours in a real-life situation without the need for obtaining informed consent and the practicalities of treatment allocation. The only way to further reduce time to treatment will probably be through educational efforts in the community to obtain a reduction in patient delay. However, such efforts have most often been only temporarily successful with limited lasting effects.

All comparisons of event rates between the prehospital ASSENT-3 PLUS and the in-hospital ASSENT-3 trials need to be interpreted with caution in spite of identical inclusion criteria and study treatments. These trials recruited patients in different settings, at different times, and from different countries and used different concomitant treatments. Compared with the in-hospital population, the prehospital

### Table 4: Bleeding Complications, Thrombocypenia, Major Cardiac Complications, and Invasive Cardiac Procedures in the ENOX Compared With the UFH Groups

<table>
<thead>
<tr>
<th></th>
<th>ENOX (n=818)</th>
<th>UFH (n=821)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bleeding episodes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>271/818 (33.1)</td>
<td>221/821 (26.9)</td>
<td>0.007</td>
</tr>
<tr>
<td>Major</td>
<td>33/817 (4.0)</td>
<td>23/821 (2.8)</td>
<td>0.176</td>
</tr>
<tr>
<td>Minor</td>
<td>237/817 (29.0)</td>
<td>198/821 (24.1)</td>
<td>0.025</td>
</tr>
<tr>
<td>Transfusion</td>
<td>34/818 (4.2)</td>
<td>25/821 (3.0)</td>
<td>0.236</td>
</tr>
<tr>
<td>Any thrombocytopenia</td>
<td>9/818 (1.10)</td>
<td>6/821 (0.73)</td>
<td>0.452</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
<td>0.611</td>
</tr>
<tr>
<td>&lt;20 000 cells/μL</td>
<td>0/818 (0.0)</td>
<td>0/821 (0.0)</td>
<td></td>
</tr>
<tr>
<td>20 000 to 50 000 cells/μL</td>
<td>2/818 (0.24)</td>
<td>1/821 (0.12)</td>
<td></td>
</tr>
<tr>
<td>50 000 to &lt;100 000 cells/μL</td>
<td>7/818 (0.86)</td>
<td>5/821 (0.61)</td>
<td></td>
</tr>
<tr>
<td><strong>Major cardiac complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained hypotension</td>
<td>16/818 (2.0)</td>
<td>25/821 (3.0)</td>
<td>0.205</td>
</tr>
<tr>
<td>Pulmonary edema and/or cardiogenic shock</td>
<td>43/818 (5.3)</td>
<td>52/821 (6.3)</td>
<td>0.398</td>
</tr>
<tr>
<td>Major arrhythmias</td>
<td>71/818 (8.7)</td>
<td>81/821 (9.9)</td>
<td>0.444</td>
</tr>
<tr>
<td><strong>Invasive cardiac procedures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>413/815 (50.7)</td>
<td>446/813 (54.9)</td>
<td>0.092</td>
</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td>13/815 (1.6)</td>
<td>19/813 (2.3)</td>
<td>0.291</td>
</tr>
<tr>
<td>Urgent CABG</td>
<td>8/815 (1.0)</td>
<td>15/813 (1.8)</td>
<td>0.148</td>
</tr>
<tr>
<td>Nonurgent CABG</td>
<td>19/815 (2.3)</td>
<td>21/813 (2.6)</td>
<td>0.752</td>
</tr>
<tr>
<td>Urgent PCI</td>
<td>204/815 (25.0)</td>
<td>239/813 (29.4)</td>
<td>0.051</td>
</tr>
<tr>
<td>Nonurgent PCI</td>
<td>190/814 (23.3)</td>
<td>183/813 (22.5)</td>
<td>0.723</td>
</tr>
</tbody>
</table>

Values are n/N (%). CABG indicates coronary artery bypass grafting.
than walk-in patients, the 6.0% 30-day mortality rate in ambulance patients constitute a higher-risk group ever, considering the higher risk profile at baseline and the adjusted comparison of outcome between the 2 trials. However, the time saving in ASSENT-3 PLUS was likely accompanied by similar benefits, as would be expected on the basis of previous randomized prehospital trials.

Conclusions

Prehospital reperfusion therapy with tenecteplase and ENOX or UFH allowed treatment within 2 hours of symptom onset in >50% of the patients with STEMI. Prehospital as well as in-hospital adjunctive therapy with ENOX reduced the incidence of ischemic complications. However, in the prehospital setting, tenecteplase with ENOX was associated with an increased risk of major bleeding and ICH in patients >75 years of age. Additional large-scale clinical trials are needed and are in progress to further study the efficacy and safety with reduced ENOX doses in combination with fibrinolytics in the elderly. At present, the combination of tenecteplase and UFH is therefore recommended as the routine pharmacological reperfusion treatment in the prehospital setting.
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Appendix

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References


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