Survival in Primary Pulmonary Hypertension
The Impact of Epoprostenol Therapy

Vallerie V. McLaughlin, MD; Alicia Shillington, RN, MPH; Stuart Rich, MD

Background—Primary pulmonary hypertension (PPH) is a severe and progressive disease. Without treatment, the median survival is 2.8 years, with survival rates of 68%, 48%, and 34% at 1, 3, and 5 years, respectively. Intravenous epoprostenol was the first Food and Drug Administration–approved therapy for PPH. The long-term impact that epoprostenol has made on PPH remains to be defined.

Methods and Results—One hundred sixty-two consecutive patients diagnosed with PPH and treated with epoprostenol were followed for a mean of 36.3 months (median, 31 months). Data including functional class, exercise tolerance, and hemodynamics were recorded in a customized database. Vital status was verified in each patient. Observed survival with epoprostenol therapy at 1, 2, and 3 years was 87.8%, 76.3%, and 62.8% and was significantly greater than the expected survival of 58.9%, 46.3%, and 35.4% based on historical data. Baseline predictors of survival included exercise tolerance, functional class, right atrial pressure, and vasodilator response to adenosine. Predictors of survival after the first year of therapy included functional class and improvement in exercise tolerance, cardiac index, and mean pulmonary artery pressure.

Conclusions—Intravenous epoprostenol improves long-term survival in PPH. (Circulation. 2002;106:1477-1482.)

Key Words: pulmonary heart disease ■ prostaglandins ■ survival

In 1980, the National Institutes of Health (NIH) established a registry on primary pulmonary hypertension (PPH) that described the clinical characteristics of the disease and its natural history over a 5-year period. The median survival was 2.8 years, with survival rates of 68%, 48%, and 34% at 1, 3, and 5 years, respectively. Based on the data from this registry, an equation incorporating the pulmonary artery pressure, right atrial pressure, and cardiac index was developed to predict survival.

Ten years after the conclusion of the NIH Registry, intravenous epoprostenol (Flolan, Glaxo-SmithKline) became the first Food and Drug Administration (FDA)-approved treatment for advanced PPH. Epoprostenol has antithrombotic properties related to its effect on platelets, is a potent vasodilator of both the systemic and pulmonary arteries, and has positive inotropic properties. Early studies indicated that intravenous epoprostenol, when given over the short-term, produces vasodilatation more consistently than do calcium channel blockers. The first randomized clinical trial in PPH showed that epoprostenol improved quality of life, hemodynamics, exercise tolerance, and survival over a 12-week period. Epoprostenol has become the standard of care treatment for patients with advanced PPH.

The impact of epoprostenol on the natural history of PPH has not fully been characterized. It remains unknown whether epoprostenol affects the disease process or provides only temporary clinical improvement. The objective of this study was to evaluate long-term effects of epoprostenol on survival in PPH and to identify factors that may predict outcome.

Methods
The Rush Heart Institute, Center for Pulmonary Heart Disease, has developed a customized patient database to collect specific variables on every patient treated with epoprostenol. This study included consecutive patients with PPH treated with epoprostenol between November 1, 1991 and December 31, 2001. The diagnosis of PPH was established according to the criteria of the NIH Registry on PPH. All patients were New York Heart Association functional class (FC) III and IV despite optimal medical therapy. Clinical data, the results of exercise testing, and cardiac catheterizations that were performed for clinical assessment were extracted from the patients’ medical records. This registry was approved by the Institutional Review Board at Rush-Presbyterian-St Luke’s Medical Center.

Treadmill exercise testing was performed according to a Naughton-Balke protocol. Resting hemodynamics, systemic and pulmonary arterial oxygen saturation, and cardiac output were measured in all patients. In most cases, the hemodynamic response to intravenous adenosine challenge was measured by an established protocol. Patients who responded to adenosine with a fall in mean pulmonary artery pressure to <30 mm Hg were treated with calcium channel blockers. Patients included in this study were thus, by definition, either those who had been treated with calcium channel blockers previously and failed to improve or those in whom the acute
response to vasodilator challenge was limited to the extent it would predict failure of chronic calcium-blocker therapy.

Epoprostenol therapy was initiated after insertion of a Hickman catheter into a subclavian or jugular vein and administered continuously with the use of a portable infusion pump (CADD 1 Model 5100HF, Pharmacia Deltec). Epoprostenol was started at a dose of 2 ng/kg per min and gradually increased to a maximum tolerated dose during the initial hospitalization. It was additionally increased on an outpatient basis, depending on the symptoms of pulmonary hypertension and side effects of epoprostenol. Patients treated between November 1991 and February 1996 received epoprostenol as part of an open-label compassionate use protocol. From February 1996 onward (after FDA approval), patients were treated after approval of the patient’s health insurance provider.

From 1991 until 1998, it was our strategy to continually increase the dose of epoprostenol to the maximum tolerated dose. In 1998, however, it became apparent that patients could have adverse consequences from too much epoprostenol. From that point onward, their epoprostenol dose was readjusted based on periodic heart catheterizations. Specifically, patients whose cardiac index at the time of a follow-up heart catheterization was below normal continued to have their dose increased. Patients whose cardiac index was in the normal range were kept at a constant dose from that point onward. Patients whose cardiac index was found to be above normal had their dose reduced. For the purposes of dose adjustment, we considered 2.5 to 4.0 L/min per m² to be the normal range.

Conventional therapies were also used in most patients. All patients without contraindications were given warfarin anticoagulation. Diuretics were freely prescribed and adjusted. Digoxin was prescribed in patients whose cardiac output was reduced. Patients with a resting arterial oxygen saturation below 90% were prescribed continuous nasal oxygen, and those with hypoxemia with exercise were recommended to wear nasal oxygen during activities. It is our practice to perform a clinical evaluation, including an exercise test and right heart catheterization, on a periodic basis on patients treated with epoprostenol. These results were recorded at each time point that they were performed. The mean time to the first follow-up period was 17±15 months; second follow-up period, 50±16 months; third follow-up period, 43±14 months; fourth follow-up period, 57±17 months; and fifth follow-up period, 68±19 months. Vital status was confirmed on every patient as of December 31, 2001.

Statistical Analysis

The date of initial catheterization was used as the index date for determining survival, which was calculated using Kaplan-Meier estimates. Patients were censored if they underwent lung transplantation or electively discontinued epoprostenol. Patients who died within the first 30 days of epoprostenol initiation were excluded from the survival analysis. Expected survival was calculated for each time point that they were performed. The mean time to the first follow-up period was 17±15 months; second follow-up period, 50±16 months; third follow-up period, 43±14 months; fourth follow-up period, 57±17 months; and fifth follow-up period, 68±19 months. Vital status was confirmed on every patient as of December 31, 2001.

TABLE 1. Hemodynamics at Baseline and With Adenosine Challenge

<table>
<thead>
<tr>
<th></th>
<th>A (n=162)</th>
<th>B (n=127)</th>
<th>Adenosine (n=127)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRAP, mm Hg</td>
<td>14±6</td>
<td>13±6</td>
<td>14±7</td>
<td>0.004</td>
</tr>
<tr>
<td>mPAP, mm Hg</td>
<td>61±13</td>
<td>61±12</td>
<td>62±14</td>
<td>NS</td>
</tr>
<tr>
<td>mPCWP, mm Hg</td>
<td>9±3</td>
<td>9±3</td>
<td>10±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>3.34±1.14</td>
<td>3.28±1.08</td>
<td>4.31±1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CI, L/min per m²</td>
<td>1.82±0.57</td>
<td>1.78±0.51</td>
<td>2.31±0.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PA Sat, %</td>
<td>53.0±11.3</td>
<td>52.2±10.7</td>
<td>62.6±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AO Sat, %</td>
<td>89.7±6.9</td>
<td>89.3±7.2</td>
<td>93.2±5.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVR, Wood units</td>
<td>17.5±8.1</td>
<td>17.8±8.3</td>
<td>14.0±7.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SVR, Wood Units</td>
<td>25.9±9.3</td>
<td>26.9±9.3</td>
<td>20.4±7.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Baseline data for all 162 patients (A). Paired data for the 127 patients who underwent adenosine challenge (B and Adenosine). P value refers to paired t test for B and adenosine. mRAP indicates mean right atrial pressure; mPAP, mean pulmonary artery pressure; mPCWP, mean pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; PA Sat, pulmonary artery saturation; AO Sat, systemic artery saturation; PVR, pulmonary vascular resistance; and SVR, systemic vascular resistance.

Results

Baseline Characteristics

Over the study period, there were 162 patients with PPH started on epoprostenol. Their mean age was 42.2 years, with a 3:1 female to male ratio. Twenty-two patients (13.6%) were identified as having familial PPH. Forty-six percent were FC II, 21% fall in pulmonary vascular resistance (range, 11.1 and 27.2 Wood units), whereas it was 8.3 Wood units in those initiated after 1998. The mean dose of epoprostenol in patients initiated from 1991 until November 1996 was 5100HF, Pharmacia Deltec). Epoprostenol was started at a dose of 2.5 to 4.0 L/min per m² to be the normal range.

Dosing of Epoprostenol

The dose of epoprostenol was increased to 34.5±30 ng/kg per min at period 1, 51.7±34.6 ng/kg per min at period 2, 55.4±42.0 ng/kg per min at period 3, 48.0±33.3 ng/kg per min at period 4, and 48.6±24.9 ng/kg per min at period 5. The mean dose of epoprostenol in patients initiated from 1991 to 1997 was higher at periods 1 and 2 (43.2±35.4 and 57.2±36.0 ng/kg per min, respectively), whereas it was 21.9±11.1 and 27.2±7.6 ng/kg per min in those initiated from 1998 to 2001 (P<0.001).
Outcome
As of December 31, 2001, 70 patients (43.2%) died and 11 patients (6.8%) underwent lung or heart-lung transplantation. Three patients electively discontinued epoprostenol. One patient improved for 3 years but eventually experienced refractory right ventricular failure and elected to discontinued epoprostenol to hasten her death, which was not censored for the purposes of this analysis. Epoprostenol was transiently interrupted in 1 patient, resulting in her death, which was not censored.

Influence of Epoprostenol Therapy on Functional Class, Exercise, Hemodynamics, and Survival
Paired comparisons were made between FC at baseline and period 1. Of the 115 patients who were evaluated at period 1, there was a significant improvement in FC from a mean of 3.50 to 2.50 (P<0.001). Of patients who were FC III at the time of presentation, 1.8% improved to FC II, 68.4% improved to FC III, and 27.6% remained FC III at period 1. Of those patients who were FC IV at the time of presentation, 15.5% improved to FC I, 56.9% improved to FC II, and 27.6% remained FC III at period 1. Those patients who were FC IV at the time of presentation, 19.3% improved to FC II, 68.4% improved to FC III, and 10.5% remained FC IV at period 1.

Paired exercise data were available in 87 patients at baseline and period 1. The exercise time improved from 311±92 seconds at baseline to 578±305 seconds at period 1 and to 658±265 seconds at period 2 (P<0.001) but remained unchanged at 620±279 seconds at period 3 (Figure 1).

One hundred fifteen patients underwent right heart catheterization at period 1 and showed a significant improvement in hemodynamics (Table 2). The hemodynamics from a subset of 61 patients who had assessments through period 3 showed similar improvements in between periods 1 and 2 but no additional changes over period 3 (Figure 2).

The observed survival was compared with the predicted survival based on the NIH registry equation. The observed survival at 1, 2, and 3 years was 87.8%, 76.3%, and 62.8% and was significantly greater than the expected survival of 58.9%, 46.3%, and 35.4% (P<0.001 at all time points, χ² analysis) (Figure 3). The observed survival at years 4 and 5 was 56% and 47%, respectively.

Influence of Epoprostenol Dose and Concurrent Medications on Survival
Using a Cox regression model of dose as a continuous variable, we found no significant relationship between survival and dose of epoprostenol (OR 0.998; 95% CI, 0.99 to 1.01; P=0.05). Because of the 2 dosing strategies that were used before and after 1998, we compared whether there was a difference in survival of patients treated from 1998 onward versus those treated since 1991. No difference was found (OR 1.4; P>0.05).

Concomitant medication was also examined independently to determine if there was any detectable influence on survival. There was no statistically significant difference in outcome in those patients who were on warfarin, digoxin, diuretics, or calcium channel blockers.

Baseline Predictors of Survival With Epoprostenol Therapy
Table 3 displays the results of the univariate analysis of clinical variables at baseline and follow-up period 1 that predicted survival. Baseline exercise time (P=0.03) and the change in pulmonary vascular resistance with adenosine challenge (P=0.023) were predictive. The only hemodynamic measurement that was predictive of survival was right atrial pressure (P=0.001). Kaplan-Meier analysis showed a significant difference between patients who were FC III and FC IV at the time of presentation (Figure 4, P=0.0001 by log-rank test). For patients who were FC III initially, there was an 81% and 70% survival after 3 and 5 years, respectively, which is substantially improved from the survival of patients in the NIH registry. For patients who presented as FC IV, 3 and 5 year survivals were 47%, and 27%, respectively.

Predictors of Survival at Follow-Up Period 1
Of patients who survived to follow-up period 1, those who were FC I or II had 3 and 5 year survival rates of 89% and 73%, respectively, compared with 62% and 35% for patients

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**Figure 1.** Serial exercise test results for a subgroup of 47 patients who underwent testing at baseline and periods 1, 2, and 3. *P<0.001 compared to baseline; †P<0.01 compared to period 1.

**Table 2.** Paired Hemodynamics at Baseline and First Follow-Up (n=115)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRAP, mm Hg</td>
<td>13±6</td>
<td>10±6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>mPAP, mm Hg</td>
<td>61±13</td>
<td>53±13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>mPCWP, mm Hg</td>
<td>9±3</td>
<td>10±3</td>
<td>NS</td>
</tr>
<tr>
<td>PA saturation, %</td>
<td>54±10</td>
<td>62±10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>3.41±1.15</td>
<td>5.05±2.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CI, L/min per m²</td>
<td>1.85±0.54</td>
<td>2.85±1.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PVR, Wood units</td>
<td>16.7±6.4</td>
<td>10.2±5.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Paired t test.

mRAP indicates mean right atrial pressure; mPAP, mean pulmonary artery pressure; mPCWP, mean pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; PA Sat, pulmonary artery saturation; PVR, pulmonary vascular resistance.
who were FC III. Patients who were FC IV at period 1 had a 42% survival at 2 years and a 0% survival at 3 years ($P<0.001$) (Figure 5). We also analyzed hemodynamic variables in patients who survived to period 1 that would predict subsequent survival. The change in cardiac index ($P=0.024$) and mean pulmonary artery pressure ($P=0.001$) were significantly associated with survival, as was the change in exercise time ($P=0.013$).

Morbidity of Epoprostenol Therapy
One of the major limitations of chronic epoprostenol therapy is the morbidity associated with a chronic indwelling catheter. Over the entire observation period, our patients had 119 local infections at the exit site (0.24 per person-year), 70 episodes of sepsis (0.14 per person-year), 10 tunnel infections (0.02 per person-year), and 72 instances where the catheter had to be replaced (0.15 per person-year). Four patients died of sepsis, which may have been related to the catheter, and 1 patient died after interruption of the epoprostenol infusion.

Discussion
Primary pulmonary hypertension represents a progressive pulmonary vasculopathy. Its natural history in an era where there was no effective therapy has been well defined by the NIH Registry on PPH. Patient survival seems to be related to the ability of the right ventricle to adapt to the chronically elevated pulmonary artery pressure. This is reflected in the right atrial pressure (a measure of right ventricular diastolic function) and the cardiac index (a measure of right ventricular systolic function), hemodynamic parameters that were shown to be the strongest predictors of outcome.$^2$ In addition, FC was also strongly predictive of outcome, as has been seen in studies of congestive heart failure. A quantitative measure of exercise was not done in the NIH registry but was done in the initial clinical trial evaluating epoprostenol in PPH and was also found to predict survival.$^4$

Our study shows that chronic intravenous epoprostenol therapy significantly prolongs survival in patients with PPH. Although our observation was not based on a randomized clinical trial, a long-term randomized clinical trial with
epoprostenol is no longer ethically possible given the high mortality of the patients with advanced PPH. However, using the NIH registry as a surrogate of the natural history of PPH has been validated as an acceptable comparison. Our study also confirms the short-term observations of the impact of epoprostenol on improving quality of life, exercise performance, and hemodynamics. Interestingly, most of the exercise and hemodynamic improvements occur over the first 12 to 18 months, with little improvement thereafter.

This study also addressed the dose titration of epoprostenol. In the early 1990s, it was believed that tolerance to epoprostenol requires constant dose escalation. Our data refute that perception. We demonstrate that dose titration to a cardiac index in the normal range allows for continued clinical and hemodynamic benefit.

An exercise test using a Naughton-Balke protocol was found also to predict survival. Of the baseline hemodynamic parameters found to be predictive of survival in the NIH registry, only the right atrial pressure was predictive in patients treated with epoprostenol. As in the NIH registry, survival was related to FC at the time of epoprostenol initiation, an important point to consider given other therapies that have recently become available. The acute response to intravenous adenosine also predicted the chronic effects of epoprostenol. Because adenosine has similar properties to epoprostenol, it was anticipated that it would reflect the hemodynamic effects one may anticipate from chronic therapy. Adenosine testing may provide insight into the long-term response to epoprostenol in a given patient. It is likely that more responsive patients have less advanced disease.

The benefit of epoprostenol was most apparent at period 1, with little incremental improvements thereafter. However, clinical deterioration was slowed, suggesting that there was continued benefit given the progressive nature of the disease. The improvement in exercise tolerance and hemodynamics yielded important prognostic information. Additionally, survival was highly correlated with FC at follow-up period 1. These observations have influenced our recommendations regarding lung transplantation. Based on our data, if a patient demonstrates a substantial improvement in exercise tolerance and hemodynamics and is FC I or II at the first follow-up, we recommend that

### TABLE 3. Univariate Predictors of Survival at Baseline, First Follow-Up, and Delta

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Odds Ratio (95% CI)</th>
<th>First Follow-Up Odds Ratio (95% CI)</th>
<th>Delta Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic and historical data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (0.98 to 1.02)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Sex (men: women)</td>
<td>0.78 (0.43 to 1.42)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>2.95 (1.66 to 5.25)*</td>
<td>3.28 (1.84 to 5.83)*</td>
<td>1.72 (0.89 to 3.31)</td>
</tr>
<tr>
<td>Exercise test duration</td>
<td>0.998 (0.996 to 0.999)*</td>
<td>0.997 (0.995 to 0.998)*</td>
<td>0.997 (0.996 to 0.999)*</td>
</tr>
<tr>
<td><strong>Hemodynamic parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right atrial pressure</td>
<td>1.06 (1.02 to 1.11)*</td>
<td>1.11 (1.05 to 1.17)*</td>
<td>1.05 (0.995 to 1.11)</td>
</tr>
<tr>
<td>Pulmonary artery pressure</td>
<td>0.98 (0.96 to 1.01)</td>
<td>1.02 (0.99 to 1.05)</td>
<td>1.03 (1.01 to 1.06)*</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>0.73 (0.43 to 1.23)</td>
<td>0.57 (0.40 to 0.79)*</td>
<td>0.47 (0.29 to 0.76)*</td>
</tr>
<tr>
<td>Pulmonary vascular resistance</td>
<td>1.0 (0.97 to 1.04)</td>
<td>1.08 (1.02 to 1.15)*</td>
<td>1.07 (1.02 to 1.15)*</td>
</tr>
<tr>
<td>Change in PVR with adenosine challenge</td>
<td>0.13 (0.03 to 0.69)*</td>
<td>. . .</td>
<td>. . .</td>
</tr>
</tbody>
</table>

*P < 0.01.
they be placed on inactive status for lung transplantation. Patients who are FC IV at first follow-up should be transplanted as soon as organs are available. Recommendations for patients who are FC III at first follow-up must be individualized.

Epoprostenol has several pharmacologic properties that should favorably affect PPH. It is a potent vasodilator of the systemic and pulmonary vascular beds and in that regard would be expected to lower the pulmonary artery pressure acutely and chronically. However, epoprostenol is used only in patients who are considered to be resistant to vasodilatation, and thus it would be surprising to see a large effect on pulmonary artery pressure. In our series, the initial mean fall in pulmonary artery pressure was 8 mm Hg (13%) and did not increase over time. Epoprostenol also has potent antithrombotic properties primarily by its action on platelet aggregation. However, virtually all patients treated with epoprostenol receive warfarin, a treatment that has been associated with a survival advantage. Thus, it is unlikely that epoprostenol has a significant impact on the disease process through this mechanism.

The impact on cardiac output, however, is quite marked and correlates with long-term survival. As patients with PPH typically have a low cardiac output, an improvement in cardiac output likely contributes to the improved outcome. This inotropic effect, however, is in variance with inotropic therapies in trials of congestive heart failure and needs additional understanding as to a unique mechanism of action of epoprostenol on the failing right ventricle. Epoprostenol also has a dramatic effect on exercise performance. Because hemodynamics are only representative of the resting state, we believe it is also essential to do an exercise assessment of these patients. Lastly, the concept of vascular remodeling has been described in many vascular diseases. Because epoprostenol and its analogues have been shown to have inhibitory properties on smooth muscle cell growth in culture, it remains possible that this is another potential mechanism of action.

Besides being costly, the major morbidity associated with epoprostenol therapy has been Hickman catheter-based infections. Our center’s experience on the rate of infection is less than previously published studies, but it is still a major source of morbidity. Of note is that there has been no chronic morbidity noted on any organ system (eg, brain, liver, kidney, or bone marrow).

There are several limitations to this observational study. In comparison with the NIH registry cohort, our group was much more ill. Twenty-nine percent of patients in the NIH registry were FC II, whereas none of our patients were. We adjusted for this by using the NIH equation to predict the survival of each patient rather than using the overall survival data from the NIH registry. Patients underwent testing (exercise and right heart catheterizations) for clinical indications, and there was some variability in the frequency of this testing. For some, testing was limited because of logistical issues (insurance coverage or residence remote from our center). Only patients who survived underwent follow-up testing, which may bias the results favorably. Additionally, our practices have evolved over the 10-year time period of this study. In the first 5 years we did not obtain the exercise testing or hemodynamics as consistently as in the second 5 years. Our dosing strategy also changed over the observation period.

In summary, chronic intravenous epoprostenol is an effective therapy to improve long-term quality of life and survival in patients with PPH. Whether newer prostacyclin analogues given through alternative delivery systems or new classes of therapies to treat PPH will have a similar beneficial effect remains to be evaluated.

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References

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