Endogenous Erythropoietin and Outcome in Heart Failure

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Background—Endogenous erythropoietin is increased in patients with heart failure (HF). Previous small-scale data suggest that these erythropoietin levels are related to prognosis. This study aims to analyze the clinical and prognostic value of erythropoietin levels in relation to hemoglobin in a large cohort of HF patients.

Methods and Results—In patients hospitalized for HF, endogenous erythropoietin levels were measured at discharge and after 6 months. In anemic patients, the relation between erythropoietin and hemoglobin levels was determined by calculating the observed/predicted ratio of erythropoietin levels. We studied data from 605 patients with HF. Mean age was 71±11 years; 62% were male; and mean left ventricular ejection fraction was 0.33±0.14. Median erythropoietin levels were 9.6 U/L at baseline and 10.5 U/L at 6 months. Higher erythropoietin levels at baseline were independently related to an increased mortality at 18 months (hazard ratio, 2.06; 95% confidence interval, 1.40 to 3.04; P<0.01). In addition, persistently elevated erythropoietin levels (higher than median at baseline and at 6 months) were related to an increased mortality risk (hazard ratio, 2.24; 95% confidence interval, 1.02 to 4.90; P=0.044). The observed/predicted ratio was determined in a subset of anemic patients, 79% of whom had erythropoietin levels lower than expected and 9% had levels higher than expected on the basis of their hemoglobin. Multivariate Cox regression analysis revealed that a higher observed/predicted ratio was related to an increased mortality risk (hazard ratio, 3.52; 95% confidence interval, 1.53 to 8.12; P=0.003).

Conclusions—Erythropoietin levels predict mortality in HF patients, and persistently elevated levels have an independent prognostic value. In anemic HF patients, the majority had a low observed/predicted ratio. However, a higher observed/predicted ratio may be related to an independent increased mortality risk. (Circulation. 2010;121:245-251.)

Key Words: anemia ■ epidemiology ■ heart failure ■ inflammation ■ prognosis

The causes for higher erythropoietin levels in HF patients compared with normal subjects are multifactorial.4 One possible explanation is that the chronic inflammatory state in HF causes inhibition of erythropoiesis in the bone marrow.5 As a result, elevated erythropoietin levels may be caused by bone marrow resistance to endogenous erythropoietin. Recently, in a small cohort of anemic HF patients, our group demonstrated that higher-than-expected erythropoietin levels for a given hemoglobin value were associated with higher mortality.6 This suggests that anemic HF patients, who are hyporesponsive to the effects of endogenous erythropoietin on the bone marrow, seem to have a worse prognosis compared with patients with normal or lower-than-expected erythropoietin levels.

The aim of the present study is 2-fold. First, we investigated the prognostic role of both single and sequential erythropoietin measurements in a large cohort of HF patients. Second, we studied the prognostic role of higher-than-expected erythropoietin levels for a given hemoglobin in anemic HF patients.

Methods

Patients

The Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH) was a multicenter randomized trial to evaluate the effect of 2 interventions (basic support versus intensive support) compared with care as usual in HF patients. Participants were randomized during hospitalization for HF (New York Heart Association class II to IV). The background, rationale, and results of the main study are published elsewhere.7,8 In brief, inclusion in the main trial required a hospital admission for HF, and patients had to be at least 18 years of age with evidence of structural...
underlying heart disease. The primary outcome was a composite end point of hospitalization for HF or all-cause mortality. A total of 1023 patients were included in the main study, and follow-up was performed at 1, 6, 12, and 18 months after discharge. Hospitalization for HF was defined as an unplanned overnight stay in a hospital (different dates for admission and discharge) as a result of progression of HF or directly related to HF. All events were adjudicated by an independent end-point committee. Of the 17 participating centers, 16 centers agreed to collect additional blood samples. We did not apply specific criteria to select the included subjects. Baseline characteristics of the 1023 subjects in the main COACH cohort did not differ significantly from those of the 605 patients in whom blood samples were taken before discharge.

The study followed the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Medical Ethical Committee, and all subjects gave written informed consent.

Renal Function and Hemoglobin

The estimated glomerular filtration rate (eGFR) was measured with the abbreviated Modification of Diet in Renal Disease equation: 

\[ \text{eGFR} = 186.3 \times \text{creatinine}/(88.4)^{1.154} \times (\text{age}^{-0.203} \times \text{0.742 if female})^{9} \]

Anemia was defined according to the World Health Organization criteria as a hemoglobin level <13.0 g/dL in men and <12.0 g/dL in women.

Erythropoietin Measurements

Blood samples for routine laboratory measurements, and erythropoietin were measured at baseline (hospital discharge) and at 6 months of follow-up. Blood samples were collected in pyrogen-free tubes containing EDTA (Becton Dickinson, San Jose, Calif) and were immediately centrifuged at 2000g for 30 minutes at 4°C. The platelet-poor plasma was separated and stored at −80°C until analysis. Plasma erythropoietin levels were measured with the IMMULITE EPO assay (Diagnostic Products Corp, Los Angeles, Calif), which was described previously.10 This assay consists of a ligand-labeled monoclonal anti-erythropoietin capture antibody, an alkaline phosphatase-labeled polyclonal conjugate antibody, and a solid-phase anti-ligand–coated polystyrene beads. The amount of plasma erythropoietin was quantified by chemiluminescence measurement in a luminometer. A reference range was provided with values ranging from 2.6 to 34 U/L.

Erythropoietin Responsiveness

We used a validated approach to determine the response of endogenous erythropoietin to the level of hemoglobin in anemic patients.11 To avoid interference with erythropoietin production or erythropoietin activity, a sample of anemic patients without renal or cardiac disease were excluded. Erythropoietin levels were divided at their median, and groups were compared by use of the log-rank test. For the anemic population, Kaplan–Meier plots were constructed for the different groups of O/P ratio of erythropoietin levels at baseline, and log-rank testing was performed. The association between parameters and all-cause mortality was assessed by Cox proportional-hazards regression. Because of the relatively small number of events, only a limited number of univariable parameters that are known predictors of mortality in HF (age, sex, eGFR, N-terminal pro-B-type natriuretic peptide [NT-proBNP], and hemoglobin) were used. Those univariable factors that had a value of \( P<0.10 \) were identified. Finally, these factors were entered into the multivariable model to assess the impact of baseline erythropoietin levels and of continuously elevated erythropoietin levels on all-cause mortality. Hazard ratios (HRs) with 95% CIs demonstrated the risk of death. The assumption of proportional hazards was checked by comparing the estimated log-minus-log survival curves for parallelism. No violations were found. All tests were 2 tailed, and a value of \( P<0.05 \) was considered statistically significant. All analyses were performed with SPSS for Windows version 16.0 (SPSS, Chicago, Ill).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Characteristics

Baseline characteristics of all 605 patients are presented in Table 1. Mean age was 71±11 years; 62% were male; and mean left ventricular ejection fraction was 0.33±0.14. The mean number of days from admission for acute HF to discharge was 13.3 days. During 18 months of follow-up, 9 patients were lost to follow-up, and 173 (29%) patients died. These patients were older and had significant lower hemoglobin values, worse renal function, and higher NT-proBNP and erythropoietin levels. In addition, more patients had diabetes mellitus type II and atrial fibrillation (Table 1). Prognostic Value of Erythropoietin

Median erythropoietin levels at baseline were 9.6 U/L (IQR, 5.1 to 16.0 U/L). Kaplan–Meier survival plots for all-cause mortality, cardiovascular mortality, and HF hospitalization demonstrated that higher erythropoietin levels at baseline predicted a worse prognosis (log-rank \( P<0.01 \), and \( P=0.066 \), respectively; Figure 1A through 1C). Furthermore, multivariate Cox regression analysis showed that higher log erythropoietin levels (HR, 2.06 per 1 U/L; 95% CI, 1.40 to 3.04; \( P<0.001 \)), lower eGFR (HR, 0.90 per 10 mL·min⁻¹·1.73 m⁻²; 95% CI, 0.82 to 0.99; \( P=0.025 \)), higher NT-proBNP (HR, 1.44 per 1000 pmol/L; 95% CI, 1.26 to 1.64; \( P<0.001 \)), and higher age (1.19 per 5 years; 95% CI, 1.09 to 1.30; \( P<0.001 \)) were independent predictors for mortality (Table 2).

At 6 months, erythropoietin levels were available in 330 patients. The median baseline value of these patients was 8.3 U/L (IQR, 4.6 to 14.7 U/L), and at 6 months, the median erythropoietin level was slightly increased to 10.5 U/L (IQR, 7.2 to 15.5 U/L). Kaplan–Meier survival analysis showed that patients with persistently high (ie, above the median) erythropoietin levels at both baseline and 6 months were at the highest risk compared with patients with low (ie, below the median) erythropoietin levels either at baseline or at 6 months (log-rank \( P=0.01 \); Figure 1D). Comparison between groups revealed that patients with persistently high erythropoietin analysis was done in which all events before 6 months of follow-up were excluded. Erythropoietin levels were divided at their median, and groups were compared by use of the log-rank test. For the anemic population, Kaplan–Meier plots were constructed for the different groups of O/P ratio of erythropoietin levels at baseline, and log-rank testing was performed. The association between parameters and all-cause mortality was assessed by Cox proportional-hazards regression. Because of the relatively small number of events, only a limited number of univariable parameters that are known predictors of mortality in HF (age, sex, eGFR, N-terminal pro-B-type natriuretic peptide [NT-proBNP], and hemoglobin) were used. Those univariable factors that had a value of \( P<0.10 \) were identified. Finally, these factors were entered into the multivariable model to assess the impact of baseline erythropoietin levels and of continuously elevated erythropoietin levels on all-cause mortality. Hazard ratios (HRs) with 95% CIs demonstrated the risk of death. The assumption of proportional hazards was checked by comparing the estimated log-minus-log survival curves for parallelism. No violations were found. All tests were 2 tailed, and a value of \( P<0.05 \) was considered statistically significant. All analyses were performed with SPSS for Windows version 16.0 (SPSS, Chicago, Ill).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.
levels had significant lower hemoglobin (P<0.001), higher age (P<0.001), and higher NT-proBNP levels (P=0.022; Table 3). Cox regression analyses showed that not only age but also baseline hemoglobin, NT-proBNP, and eGFR were independent predictors of mortality. After adjustment for these variables in the multivariable analysis, repetitive erythropoietin levels above the median remained an independent predictor of mortality (HR, 2.24; 95% CI, 1.02 to 4.90; P=0.044; Table 4).

**Erythropoietin Responsiveness**

An O/P ratio was determined in a subset of 135 anemic patients. In this population, the median erythropoietin value was 12.8 U/L (IQR, 9.0 to 19.5 U/L). On the basis of their O/P ratio, patients were divided into 3 groups: erythropoietin levels lower than expected (107 patients), erythropoietin levels as expected (16 patients), and erythropoietin levels higher than expected (12 patients; Table 5). Kaplan–Meier survival analysis showed that patients with higher-than-expected erythropoietin levels had a higher mortality risk (log-rank P=0.033; Figure 2). Cox regression analysis demonstrated that in the anemic cohort, mortality was independently predicted by higher age (HR, 1.07 per 1 year; 95% CI, 1.03 to 1.11; P<0.01), higher NT-proBNP (HR, 1.44 per 1000 pmol/L; 95% CI, 1.12 to 1.85; P=0.005), and higher-than-expected erythropoietin levels (HR, 3.52; 95% CI, 1.53 to 8.12; P=0.003).

**Discussion**

The present study investigated the prognostic role of erythropoietin in a large cohort of HF patients. The results showed that both elevated erythropoietin levels at baseline and, in particular, persistently elevated erythropoietin levels predicted impaired survival. Second, in most anemic HF patients, erythropoietin levels did not correspond well with the level of hemoglobin. The majority of patients had lower-than-expected erythropoietin levels. Interestingly, anemic patients with erythropoietin levels that were higher than expected given the hemoglobin value had a worse prognosis compared with patients with normal or lower-than-expected erythropoietin levels.

A few studies by our group and others have demonstrated that elevated erythropoietin levels in HF patients independently predicted impaired outcome.1–3,6 In the present study, we confirmed these findings in a larger cohort of HF patients. These patients were included after stabilization of acute decompensated HF; therefore, they are at a much higher risk of future events compared with patients with stable chronic HF.12

A novel finding of the present study is that a higher mortality risk is predicted not only by single high erythropoietin levels but also by erythropoietin levels that remained high at sequential measurements during follow-up. This may indicate that HF patients who show consistently high erythropoietin levels are doing worse clinically and have a more advanced state of the disease, which is also indicated by the higher NT-proBNP levels found in this group.

Interestingly, only a minority of patients in the anemic cohort had erythropoietin at levels that could be expected on the basis of their hemoglobin levels. Only 12% of anemic patients had erythropoietin levels as expected, and 9% had erythropoietin levels higher than expected given their hemoglobin values. An important observation of the present study was that in the majority of patients, erythropoietin levels were lower than expected on the basis of their hemoglobin levels. There might be 2 explanations for this finding. First, many acute HF patients are fluid overloaded and may have dilu-
tional anemia. Of note, blood samples of included patients were obtained before discharge, so patients were already stabilized. Hemodilution therefore does not seem to play a dominant role but still might have contributed to this finding. Second, renal dysfunction is frequently present in HF and may explain the relatively lower erythropoietin levels. In our study, patients with a low O/P ratio showed more renal dysfunction compared with the other O/P ratio groups, although this difference did not reach statistical significance.

A small number of patients had erythropoietin levels that were higher than expected. This number is lower than recently reported in a smaller group of HF patients from an

Figure 1. Kaplan–Meier survival curves for all-cause mortality (A), cardiovascular mortality (B), and hospitalization for HF (C) with baseline erythropoietin (Epo) levels divided into quartiles. (D), Kaplan–Meier survival curve for patients divided into groups defined by their median erythropoietin levels at baseline and at 6 months. Low-Low indicates erythropoietin levels below the median at both baseline and 6 months; Low-High, erythropoietin levels below the median at baseline and above the median at 6 months; High-Low, erythropoietin levels above the median at baseline and below the median at 6 months; and High-High, erythropoietin levels above the median at both baseline and 6 months.

Table 2. Cox Regression for All-Cause Mortality in the Total Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, 5 y</td>
<td>1.21 (1.12–1.31)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>eGFR, 10 mL·min⁻¹·1.73m⁻²</td>
<td>0.79 (0.74–0.84)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>NT-proBNP, 1000 pmol/L</td>
<td>1.50 (1.35–1.68)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Hb, 1 g/dL</td>
<td>0.85 (0.79–0.92)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Log Epo, U/L</td>
<td>2.50 (1.78–3.54)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1. *P<0.05.
can be explained by a difference in volume status because patients in our study were included while hospitalized for HF. However, impairment of renal function may have played a significant role as well. Several mechanisms may be responsible for these higher-than-expected erythropoietin levels. First, in HF, increased erythropoietin production by the kidney may be a response to a reduction in renal perfusion caused by a decreased cardiac output, not a response to lower hemoglobin levels. In our analysis, patients with a high O/P ratio tended to have lower left ventricular ejection fraction and higher NT-proBNP levels. Second, an altered metabolic state, causing the oxygen-hemoglobin dissociation curve to shift to the right, may influence erythropoietin production. Third, angiotensin is increased in HF, even in the presence of an active proinflammatory state, vitamin deficiencies, and blood loss. Currently, a large randomized, controlled clinical trial is ongoing with darbepoetin alfa treatment in anemic HF patients. Not only might potential beneficial effects of exogenous erythropoietin administration in HF patients be related to correcting anemia, but experimental studies have demonstrated that erythropoietin also improves cardiac function by stimulating neovascularization and reducing apoptosis. These effects are seen even when erythropoietin is administered in low doses that do not increase hematocrit. These extrahematopoietic effects may be useful in HF and may prevent cardiac function loss after myocardial infarction. Presently, a randomized multicenter trial is evaluating the effect of a single bolus of erythropoietin administered after a first acute myocardial infarction on left ventricular function.

Several limitations of this study should be acknowledged. Although we analyzed data from a large cohort of HF patients, erythropoietin levels at 6 months were not measured in all patients for logistical reasons. The reference equation for defining O/P ratios for erythropoietin was constructed for patients in our study were included while hospitalized for HF. However, impairment of renal function may have played a significant role as well. Several mechanisms may be responsible for these higher-than-expected erythropoietin levels. First, in HF, increased erythropoietin production by the kidney may be a response to a reduction in renal perfusion caused by a decreased cardiac output, not a response to lower hemoglobin levels. In our analysis, patients with a high O/P ratio tended to have lower left ventricular ejection fraction and higher NT-proBNP levels. Second, an altered metabolic state, causing the oxygen-hemoglobin dissociation curve to shift to the right, may influence erythropoietin production. Third, angiotensin is increased in HF, even in the presence of an active proinflammatory state, vitamin deficiencies, and blood loss. Currently, a large randomized, controlled clinical trial is ongoing with darbepoetin alfa treatment in anemic HF patients. Not only might potential beneficial effects of exogenous erythropoietin administration in HF patients be related to correcting anemia, but experimental studies have demonstrated that erythropoietin also improves cardiac function by stimulating neovascularization and reducing apoptosis. These effects are seen even when erythropoietin is administered in low doses that do not increase hematocrit. These extrahematopoietic effects may be useful in HF and may prevent cardiac function loss after myocardial infarction. Presently, a randomized multicenter trial is evaluating the effect of a single bolus of erythropoietin administered after a first acute myocardial infarction on left ventricular function.

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### Table 3. Baseline Characteristics Between Groups of High Versus Low Erythropoietin Levels During Follow-Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low-Low (n=120)</th>
<th>Low-High (n=66)</th>
<th>High-Low (n=51)</th>
<th>High-High (n=93)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67 ± 11*</td>
<td>71 ± 12</td>
<td>67 ± 14†</td>
<td>73 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>71 (59)</td>
<td>42 (64)</td>
<td>26 (51)</td>
<td>61 (66)</td>
<td>0.349</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>32 ± 14</td>
<td>28 ± 14</td>
<td>33 ± 13</td>
<td>34 ± 13</td>
<td>0.680</td>
</tr>
<tr>
<td>eGFR, mL · min⁻¹ · 1.73 m⁻²</td>
<td>59 (46–72)</td>
<td>58 (41–69)</td>
<td>57 (19–68)</td>
<td>52 (38–67)</td>
<td>0.276</td>
</tr>
<tr>
<td>Epo, U/L</td>
<td>4.5 (2.4–6.5)*</td>
<td>5.6 (3.8–8.0)*</td>
<td>14.9 (12–18.4)</td>
<td>16.1 (12.4–25.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>14.0 ± 1.6*</td>
<td>14.1 ± 2.4*</td>
<td>13.1 ± 1.9</td>
<td>12.7 ± 1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NTproBNP, pmol/L</td>
<td>1791 (835–3145)†</td>
<td>2070 (1046–4659)</td>
<td>2597 (1574–5103)</td>
<td>2785 (1442–4347)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1, plus Low-Low indicates erythropoietin levels below the median at both baseline and 6 months; Low-High, erythropoietin levels below the median at baseline and above the median at 6 months; High-Low, erythropoietin levels above the median at baseline and below the median at 6 months; and High-High, erythropoietin levels above the median at both baseline and 6 months. P values were calculated with ANOVA.

*P<0.001, †P<0.05 versus high-high.

### Table 4. Cox Regression Analysis for All Cause Mortality With Erythropoietin Levels Higher Than Median at Baseline and 6 Months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age, 5 y</td>
<td>1.21 (1.12–1.31)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>eGFR, 10 mL · min⁻¹ · 1.73 m⁻²</td>
<td>0.80 (0.73–0.87)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>logNT-proBNP, pmol/L</td>
<td>1.41 (1.15–1.76)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>0.87 (0.78–0.97)</td>
<td>0.012*</td>
</tr>
<tr>
<td>Hb change</td>
<td>0.95 (0.71–1.26)</td>
<td>0.701</td>
</tr>
<tr>
<td>Epo low-low</td>
<td>1.00</td>
<td>. . .</td>
</tr>
<tr>
<td>Epo high-low</td>
<td>0.77 (0.20–2.57)</td>
<td>0.599</td>
</tr>
<tr>
<td>Epo low-high</td>
<td>1.54 (0.61–3.90)</td>
<td>0.363</td>
</tr>
<tr>
<td>Epo high-high</td>
<td>3.32 (1.58–6.98)</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

*P<0.05.
using a sample size of 20 patients. However, based on a small number of patients, the reference equation was previously constructed by our group, so it was also used in the present analyses. Furthermore, the number of anemic HF patients in whom an O/P ratio could be assessed was small, as was the final number of patients with higher-than-expected erythropoietin levels. Therefore, these data should be interpreted with caution. Finally, no hematinic parameters were measured to assess the true nature of anemia.

### Conclusions

Both elevated baseline erythropoietin levels and persistently elevated erythropoietin levels were independently related to increased mortality. Furthermore, the majority of patients had erythropoietin levels that were lower than expected. Patients with a high O/P ratio showed an increased mortality risk compared with patients with normal or lower-than-expected erythropoietin levels.

### Acknowledgment

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### Disclosures

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Amgen and is a member of the Executive Committee of the Darbepoetin Morbidity/Mortality Heart Failure Trial (RED-HF).

**References**


**CLINICAL PERSPECTIVE**

Small-scale studies in patients with heart failure (HF) have suggested that a single measurement of erythropoietin levels has prognostic value. In the present study, we sequentially measured erythropoietin levels in a large cohort of HF patients. We confirmed that elevated erythropoietin levels were independently related to a poor prognosis. Furthermore, patients in whom erythropoietin levels remained high at a second measurement had an even worse prognosis compared with patients with only 1 elevated erythropoietin measurement. Moreover, we showed that anemic HF patients with erythropoietin levels higher than expected, ie, suggesting erythropoietin resistance, have an increased mortality risk. Although erythropoietin might be used in everyday clinical practice as a prognostic marker in HF; we believe that these results may be potentially interesting for additional reasons. First, evaluation of erythropoietin levels in HF may help us better understand the pathophysiology of HF. Second, erythropoiesis-stimulating agents are currently studied as a possible novel therapy in HF; therefore, insight into the natural course of erythropoietin in HF is essential. In this respect, a certain group of patients appear to be erythropoietin resistant, and it may be speculated that this resistance might also be associated with the response to exogenous erythropoietin.
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