Effects of Controlled-Release Metoprolol on Total Mortality, Hospitalizations, and Well-being in Patients With Heart Failure

The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)

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Context
Results from recent studies on the effects of β1-blockade in patients with heart failure demonstrated a 34% reduction in total mortality. However, the effect of β1-blockade on the frequency of hospitalizations, symptoms, and quality of life in patients with heart failure has not been fully explored.

Objective
To examine the effects of the β1-blocker controlled-release/extended-release metoprolol succinate (metoprolol CR/XL) on mortality, hospitalization, symptoms, and quality of life in patients with heart failure.

Design
Randomized, double-blind controlled trial, preceded by a 2-week single-blind placebo run-in period, conducted from February 14, 1997, to October 31, 1998, with a mean follow-up of 1 year.

Setting
Three hundred thirteen sites in 14 countries.

Participants
Patients (n = 3991) with chronic heart failure, New York Heart Association (NYHA) functional class II to IV, and ejection fraction of 0.40 or less who were stabilized with optimum standard therapy.

Interventions
Patients were randomized to metoprolol CR/XL, 25 mg once per day (NYHA class II), or 12.5 mg once per day (NYHA class III or IV), titrated for 6 to 8 weeks up to a target dosage of 200 mg once per day (n = 1990); or matching placebo (n = 2001).

Main Outcome Measures
Total mortality or any hospitalization (time to first event), number of hospitalizations for worsening heart failure, and change in NYHA class, by intervention group; quality of life was assessed in a substudy of 741 patients.

Results
The incidence of all predefined end points was lower in the metoprolol CR/XL group than in the placebo group, including total mortality or all-cause hospitalizations (the prespecified second primary end point; 641 vs 767 events; risk reduction, 19%; 95% confidence interval [CI], 10%-27%; P < .001); total mortality or hospitalizations due to worsening heart failure (311 vs 439 events; risk reduction, 31%; 95% CI, 20%-40%; P < .001), number of hospitalizations due to worsening heart failure (317 vs 451; P < .001); and number of days in hospital due to worsening heart failure (3401 vs 5303 days; P < .001).

NYHA functional class, assessed by physicians, and McMaster Overall Treatment Evaluation score, assessed by patients, both improved in the metoprolol CR/XL group compared with the placebo group (P = .003 and P = .009, respectively).

Conclusions
In this study of patients with symptomatic heart failure, metoprolol CR/XL improved survival, reduced the need for hospitalizations due to worsening heart failure, improved NYHA functional class, and had beneficial effects on patient well-being.

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tance of neuroendocrine activation in heart failure and the possibility of modifying such mechanisms of the disease process have greatly improved treatment in clinical practice. Thus, angiotensin-converting enzyme (ACE) inhibitors have been established as standard therapy for patients with chronic heart failure due to left ventricular systolic dysfunction, with proven effects on mortality and symptoms related to worsening heart failure. Despite the benefits of this mode of therapy, mortality and morbidity remain high for patients with heart failure.

The role of β-blocker treatment in the management of chronic heart failure has taken time to clarify. The results from meta-analyses of previous smaller studies of various β-blockers in heart failure, including the carvedilol studies, have indicated beneficial effects. Two studies on the survival effects of β-blockade published in 1999, the Cardiac Insufficiency Bisoprolol Study (CIBIS) II and the present Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), demonstrated that total mortality was reduced by 34%.

Although the survival benefit of β-blockade in chronic heart failure due to systolic dysfunction has been established, the need for hospital care, safety aspects, symptom alleviation, and improved quality of life are additional important aspects of treatment, for both the patient and the clinician. However, the impact of β-blockers on these outcomes has not been fully explored. Accordingly, the MERIT-HF was designed to study the effects of controlled-release/extended-release metoprolol succinate (metoprolol CR/XL) on mortality, as previously reported, as well as hospitalizations, symptoms, and quality of life.

**METHODS**

**Organization**

The MERIT-HF was a randomized, double-blind placebo-controlled trial with a single-blind, 2-week placebo run-in period. Randomization was performed according to an optimal allocation procedure, which balanced the metoprolol CR/XL and placebo groups for investigational site, age, sex, race/ethnicity, cause of heart failure, previous acute myocardial infarction (AMI), and, within the previous AMI group, time since last AMI, diabetes mellitus, ejection fraction, and New York Heart Association (NYHA) functional class. An interactive voice recording system (Covance, Princeton, NJ) was used to provide investigators with the computer-generated study drug number based on the optimal allocation procedure.

A total of 3991 patients with symptomatic chronic heart failure and decreased ejection fraction who were stabilized with standard treatment were randomized (Figure 1) at 313 investigational sites in the United States and 13 European countries (Belgium, Czech Republic, Denmark, Finland, Germany, Hungary, Iceland, the Netherlands, Norway, Poland, Sweden, Switzerland, and the United Kingdom). The study was approved by the institutional review board of each hospital and all patients provided written informed consent.

The Independent Endpoint Committee, whose 5 members were unaware of treatment status, classified all events from copies of medical charts and other documents according to prespecified definitions. An Independent Safety Committee monitored safety issues during the study.

The stopping rule for efficacy was based on the total number of expected deaths, analyzed based on the intent-to-treat principle. The study used an asymmetrical group sequential procedure to monitor total mortality. A Peto-type boundary was used for monitoring a positive trend. This approach favors a large critical Z-value for all interim tests before the end of the trial. The cumulative α level was planned to be .0012, .0024, and .0036 at the first, second, and third interim analyses to take place when 25%, 50%, and 75%, respectively, of the total number of expected deaths had occurred. The cumulative probability of early stopping for harm was planned to be .005, .010, and .015 at the first, second, and third interim analyses, respectively.

**Outcome Measures**

There were 2 primary outcome measures: total mortality and the combined endpoint of total mortality or all-cause hospitalization (time to first event). The MERIT-HF was stopped early, on October 31, 1998, because the second preplanned interim analysis showed a significant 34% reduction in total mortality in the metoprolol CR/XL group. As previously reported, 145 patients died in the metoprolol CR/XL group compared with 217 in the placebo group.

The following combined end points (time to first event) were also predefined: total mortality or hospitalization due to worsening heart failure; death or heart transplantation; cardiac death or nonfatal AMI; and total mortality or hospitalization due to worsening heart failure or emergency department visit due to worsening heart failure. Other end points were number of hospitalizations due to heart failure and other cardiovascular causes, withdrawal of study drug due to worsening heart failure, and change in NYHA functional class. Effect on quality of life was assessed in a substudy that was conducted in the United States, United Kingdom, Sweden, Norway, and the Netherlands.

**Patients**

The major inclusion criteria were symptomatic heart failure for at least 3 months,
corresponding to NYHA class II to IV, and a left ventricular ejection fraction of 0.40 or less in men and women aged 40 to 80 years. For patients with an ejection fraction between 0.36 and 0.40, it was mandatory that a 6-minute walk test result did not exceed 500 yd (450 m). Resting heart rate had to be 68/min or more. Patients had to be receiving optimal treatment (defined as any combination of diuretics and an ACE inhibitor) for at least 2 weeks prior to randomization. If an ACE inhibitor was not tolerated, hydralazine, long-acting nitrate, or an angiotensin II blocker could be used. Digitalis also could be prescribed. In addition, the inclusion criteria included a stable clinical condition during the 2-week placebo run-in phase before randomization (Table 1).

The main exclusion criteria included AMI or unstable angina pectoris within 28 days before randomization, indication or contraindication for treatment with β1-blockade, severe decompensated heart failure (eg, pulmonary edema, hypoperfusion), or supine systolic blood pressure of less than 100 mm Hg. A more detailed description of the study protocol has been published previously.12

Treatment and Measurements

At the randomization visit, patients were allocated to treatment with metoprolol CR/XL or placebo administered once daily. The starting dosage was one 25-mg tablet once per day (half of a 25-mg tablet was recommended for patients with NYHA functional class III or IV). It was recommended to double the dosage after each 2-week period to reach the target dosage level of 200 mg/d of metoprolol CR/XL or placebo. This regimen could be modified according to the judgment of the investigator. If a patient did not tolerate increased titration of study drug, temporary reduction in dosage or increase in diuretic dosage was advocated. During follow-up, patient visits were scheduled every third month.

At each visit, the investigators judged and documented the patient’s NYHA functional class. The Minnesota Living with Heart Failure questionnaire was completed by patients at randomization, after each 6-month treatment period, and at study closure.13 This questionnaire consists of 21 items; the total score ranges from 0 to 105, with lower scores indicating better quality of life. The McMaster Overall Treatment Evaluation questionnaire (OTE) was completed by the patients after each 6-month treatment period and at study closure.14 This questionnaire has 3 items that assess the overall effect according to whether a patient experienced any change in activity limitation, symptoms, or feelings since the treatment started, using 7-point scales. Any improvement or deterioration was subsequently scored by the patient in terms of magnitude and importance to the patient’s ability to carry out daily activities.

Hospizations were defined as care at an acute-care hospital lasting for 24 hours or more and had to be separated from other hospitalizations by separate dates for discharge and admission. Transfer from one ward to a different type of hospital ward was counted as 1 hospitalization. Hospitalization due to heart failure was defined as documentation in the medical charts indicating worsening heart failure as the reason for hospitalization. If competing reasons were judged to be of equal importance, the heart failure diagnosis took preference. Emergency department visit was defined as care in an urgent fashion with urgent-care treatment such as intravenous medication.

Statistical Analyses

The power calculation showed that the mean follow-up time had to be 2.4 years if 1600 patients were randomized to each treatment group over 14 months. This was based on a significance level of α = .04 (2-sided) for the first primary end point of total mortality and α = .01 for the second primary end point of total mortality or any hospitalization (time to first event), a power of at least 80% (β = .2), and the following assumptions: a 9.4% mean annual mortality in the placebo group, a mean risk-reducing effect of metoprolol CR/XL of 30% (with treatment), and a withdrawal rate from study drug of 20% the first year and 5% annually thereafter.12 Because patient recruitment proceeded faster than planned, 3991 patients were randomized during the recruitment period, thereby increasing the power of the study.

The analysis was by intent to treat. The main analyses used the log-rank test for the comparison of the 2 randomized groups and the Cox proportional hazards model to calculate relative risk and 95% confidence intervals (CIs). Additional Cox proportional hazards regression analyses of the combined end points of total mortality or all-cause hospitalizations (time to first event) and total mortality or hospitalizations due to heart failure (time to first event) were performed to explore any unfavorable outcome in prespecified risk groups, defined by entry characteristics as previously described.10,12 For ejection fraction, systolic and diastolic blood pressure, and heart rate, patients in the lowest tertile were compared with those in the middle and upper tertiles. Regarding age, the upper tertile was compared with the middle and lower tertiles. New York Heart Association class, etiology of heart failure, smoke-
ing status, sex, previous AMI, diabetes mellitus, and hypertension were also pre-
specified as risk groups. Ischemic and nonischemic heart disease have been de-
defined as the 2 major causes of heart fail-
ure. Hypertension was defined as phar-
macologically treated high blood pres-
sure, and diabetes mellitus was defined as a clinical diagnosis made by the in-
vestigator. More than 180 events in any
such subgroup would yield a power of
at least 70% to detect a 30% increase in
risk. Data on complementary subgroups
having less than 180 events have also
been depicted.

The sample size calculation for the
quality of life substudy showed that with
419 patients in each group, it would be
possible to detect a difference of 3 units
on total Living with Heart Failure score
between the treatment groups based on the
following assumptions: SD for
change = 16, α = .05, and β = .20. A net
difference of 3 units was judged to be a
clinically meaningful change. The
changes in NYHA class and OTE score
were tested by means of a permutation
test using raw data scores. Changes in
Living with Heart Failure score were
analyzed using an analysis of covari-
ance model with adjustment for the
baseline Living with Heart Failure score.
A 2-sided P<.05 was regarded as statis-
tically significant.

RESULTS

Randomization began on February 14,
1997, and the last patient was random-
ized on April 14, 1998. The Interna-
tional Steering Committee stopped the
study on October 31, 1998, on recom-
mandation from the Independent Safety
Committee. The second preplanned in-
terim analysis (at the halfway point) had
shown that the predefined criterion for
termination of the study was met and ex-
ceeded. In total, 2004 patient-years were
accumulated in the metoprolol CR/XL
group and 1977 in the placebo group (to-
tal mortality). The corresponding patient-
years for the combined end point of to-
tal mortality or all-cause hospitalization
were 1650 vs 1600 patient-years, and for
total mortality or hospitalization for
worsening heart failure were 1880 vs
1840 patient-years, respectively. The
mean follow-up time was 1 year.

The 2 groups were similar at entry
(Table 1). Furosemide daily dosage at
baseline and during follow-up was 66
mg/d and 70 mg/d in the metoprolol
CR/XL group and 65 mg/d and 73 mg/d
in the placebo group, respectively. The
ACE inhibitor daily dosage was also
similar at baseline and during fol-
low-up in both randomization groups.
For enalapril, it was 14 mg/d at base-
line and 15 mg/d at follow-up in both
groups; corresponding dosages at base-
line and follow-up, respectively, for cap-
Metoprolol were 68 mg/d vs 70 mg/d in the metoprolol CR/XL group and 60 mg/d vs 64 mg/d in the placebo group, and for lisinopril were 17 mg/d vs 17 mg/d in the metoprolol CR/XL group and 16 mg/d vs 16 mg/d in the placebo group.

The patients who participated in the quality of life substudy (n = 741) had characteristics similar to those of the entire group (mean age, 64.4 years; female sex, 28%; NYHA class II, 39%; NYHA class III, 56%; NYHA class IV, 5%; mean ejection fraction, 0.27; previous AMI, 51%; and treatment with ACE inhibitor or angiotensin II blocker, 96%).

**Combined End Points**

Metoprolol CR/XL significantly reduced all combined end points (time to first event) compared with placebo (Table 2, Figure 2, and Figure 3). Total mortality or all-cause hospitalizations (the prespecified second primary end point) was reduced by 19% (Figure 2), total mortality or hospitalization for worsening heart failure by 31% (Figure 3), death or heart transplantation by 32%, cardiac death or nonfatal AMI by 39% (Figure 3), and total mortality or hospitalization due to worsening heart failure or emergency department visit due to worsening heart failure by 32%. No significant increase in total mortality or all-cause hospitalizations (time to first event) or in total mortality or hospitalizations due to worsening heart failure (time to first event) were observed in any of the predefined subgroups analyzed for safety reasons (Figure 4).

**Hospitalizations**

Compared with placebo, metoprolol CR/XL reduced the number of patients with any hospitalization, the total number of hospitalizations, and the total number of days in the hospital due to all causes (Figure 5, Table 3). This was mainly explained by a reduction in the number of patients who were hospitalized for worsening heart failure, accompanied by decreases in the total number of hospitalizations and total number of days in the hospital due to heart failure (Table 3, Figure 5). To account for the improved survival with metoprolol CR/XL, the proportion of days spent alive outside the hospital was also calculated as 93% in the metoprolol CR/XL group and 93% in the placebo group (P < .001).
the study. Improvement was recorded in 28.6% vs 25.8% of the metoprolol CR/XL and placebo groups, respectively (26.0% vs 24.3% improved 1 class; 2.6% vs 1.5% improved 2 classes); 65.4% vs 66.7% were unchanged; 6.0% vs 7.5% deteriorated (5.7% vs 6.8% deteriorated 1 class, 0.3% vs 0.7% deteriorated 2 classes). These data show a more favorable change in NYHA class in the metoprolol CR/XL group compared with the placebo group (P = .003).

There was a statistically significant improvement in the OTE score in the metoprolol CR/XL group compared with placebo (P = .009; Figure 6). In the metoprolol CR/XL group, 185 patients (50%) reported improvement, and patients' evaluations of the importance of this change were available for 184 patients, showing that 132 patients (72%) judged this improvement as important, very important, or extremely important to carry out daily activities. In the placebo group, 148 patients (40%) reported improvement that was judged to be important, very important, or extremely important by 72% of these patients.

Living with Heart Failure forms completed at randomization and at the last visit were available for 670 patients. Scores were similar at randomization in the 2 study groups. The total Living with Heart Failure score, adjusted for the score at baseline, decreased (improved) by 0.7 in the metoprolol CR/XL group (n = 331) and increased (deteriorated) by 0.2 in the placebo group (n = 339) (mean difference, −0.9; 95% CI, −3.4 to 1.6; P = .20).

Withdrawal of Study Drug

The most frequent adverse events necessitating withdrawal of study drug were worsening heart failure, atrial fibrillation, and angina pectoris, and these events were less frequent in the metoprolol CR/XL group than in the placebo group (Table 4). Dizziness, bradycardia, and hypotension occurred slightly more frequently in the metoprolol CR/XL group.

Permanent withdrawal of study drug due to any cause during the study is shown in Figure 2 and occurred in 279 patients in the metoprolol CR/XL group and 310 patients in the placebo group (risk reduction for withdrawal decreased by 10% in the metoprolol CR/XL group; 95% CI, −5% to 24%; P = .18). Permanent withdrawal of study drug due to any adverse event occurred in 196 patients in the metoprolol CR/XL group and 234 patients in the placebo group (risk reduction, 17%; 95% CI, −1% to 31%; P = .06). Worsening heart failure was the main reason for withdrawal in 64 patients (3.2%) in the metoprolol CR/XL group and 85 (4.2%) in the placebo group (risk reduction, 23%; 95% CI, −4% to 46%; P = .08).

**COMMENT**

This study demonstrated that metoprolol CR/XL, a β1-blocker given once per day in addition to conventional therapy to patients with chronic heart failure, improved survival as previously reported, reduced the need for hospital admissions due to worsening heart failure, and improved symptoms and well-being.

In the MERIT-HF, there were no differences between the study groups in underlying pharmacological treatment for heart failure at baseline or during follow-up. All-cause mortality or hospitalizations (the prespecified second primary end point, time to first event) was significantly reduced by 19% in the metoprolol CR/XL group. Correspondingly, total deaths or hospitalizations due to worsening heart failure were reduced by 31%. The annual mortality in the placebo group was 11.2% and total mortality was reduced by 34% in the metoprolol CR/XL group. Despite this improved survival and more patients at risk for hospital admissions, fewer patients were hospitalized due to any cause...
in the metoprolol CR/XL group, mainly due to a 35% reduction in the number of patients hospitalized for worsening heart failure. The total number of days in the hospital due to heart failure was reduced to a similar degree in the metoprolol CR/XL group, with no increase in hospitalizations for other reasons. Conversely, the number of days alive without need for hospital care was higher in the metoprolol CR/XL group than in the placebo group. Given the comparatively low cost of β-blocker therapy and the high cost of hospitalizations, the 36% reduction in days spent in the hospital for worsening heart failure suggests a positive effect on health care costs with metoprolol CR/XL treatment in patients with chronic heart failure. It is noteworthy that there was considerable comorbidity among these patients because hospitalizations due to noncardiovascular causes accounted for 30% of all days spent in the hospital and one quarter of all days was due to cardiovascular causes other than worsening heart failure (Table 3, placebo group).

Our results are consistent with data from the CIBIS-II study, in which treatment with the β1-blocker bisoprolol also reduced hospital admissions due to any cause and due to worsening heart failure. The previously published documentation of the effect of β-blockade on the Living with Heart Failure score in patients with heart failure relates mainly to nonselective β-blockade with carvedilol therapy, showing no statistically significant effect.

Metoprolol CR/XL was well tolerated. Withdrawal of study drug from all causes was 10% lower and withdrawal due to worsening heart failure was 25% lower in the metoprolol CR/XL group compared with the placebo group. These findings are of interest, especially against the background that no metoprolol CR/XL test dose had been given prior to initiating double-blind treatment. For the most frequent adverse reactions leading to withdrawal of study drug, including worsening heart failure, atrial fibrillation, and angina pectoris, withdrawal was more common in the placebo group. Fewer than 1 of 100 patients treated for 1 year

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**Table 4. Cause-Specific Adverse Events Leading to Withdrawal of Study Drug According to Absolute Value for Net Difference Between the Randomization Groups**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Metoprolol CR/XL, No. (%)</th>
<th>Placebo, No. (%)</th>
<th>Net Difference, % per First Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>78 (3.9)</td>
<td>117 (5.8)</td>
<td>−2.2</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (0.1)</td>
<td>17 (0.8)</td>
<td>−0.8</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>9 (0.5)</td>
<td>20 (1.0)</td>
<td>−0.6</td>
</tr>
<tr>
<td>Bradycardia‡</td>
<td>16 (0.8)</td>
<td>5 (0.2)</td>
<td>0.6</td>
</tr>
<tr>
<td>Hypotension‡</td>
<td>12 (0.6)</td>
<td>5 (0.2)</td>
<td>0.4</td>
</tr>
<tr>
<td>Dizziness‡</td>
<td>12 (0.6)</td>
<td>6 (0.3)</td>
<td>0.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (0.7)</td>
<td>9 (0.4)</td>
<td>0.3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15 (0.8)</td>
<td>12 (0.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Myocardial infarction§</td>
<td>11 (0.6)</td>
<td>15 (0.7)</td>
<td>−0.2</td>
</tr>
<tr>
<td>All patients with any adverse event</td>
<td>196 (9.8)</td>
<td>234 (11.7)</td>
<td>−2.2</td>
</tr>
</tbody>
</table>

*CR/XL indicates controlled release/extended release. Adverse events that led to withdrawal of study drug are specified if the frequency of the cause-specific adverse event was greater than 0.5% in either group. The net difference (metoprolol CR/XL − placebo) refers to the percentage of patients treated during the first year of treatment (1386 vs 1819 patient-years of follow-up until withdrawal of study medicine or death in the metoprolol CR/XL group and placebo group, respectively).

†Patients may have had more than 1 reason for withdrawal.
‡The cumulative net difference for bradycardia, dizziness, and hypotension in the metoprolol CR/XL group was 0.9%.
§The total number of patients who had a myocardial infarction during follow-up was 35 vs 41 in the metoprolol CR/XL and placebo groups, respectively.

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withdrew from metoprolol CR/XL treatment because of bradycardia, dizziness, or hypotension. There were no specific safety concerns observed in any of the preidentified risk groups.

In this study, controlled-release/extended-release metoprolol succinate once per day was used. This formulation led to a more pronounced and even β-blockade over 24 hours compared with conventional immediate-release metoprolol tartrate tablets, 50 mg 3 times per day.27 In patients with chronic heart failure, the dosing schedule can be simplified with metoprolol CR/XL and the target dosage also can be increased to 200 mg once per day compared with 50 mg 3 times per day with the conventional formulation, without increasing the peak plasma concentration of the drug.24 The titration schedule started with a low once-daily dosage, 25 mg/day for those in NYHA class II and 12.5 mg/day for those in NYHA class III or IV, with increased titration every 2 weeks. The target dosage, 200 mg/day, was reached by 64% of the patients, and 87% received 100 mg/day or more.10 The mean dosage was 159 mg/day.10

The combined results from MERIT-HF and CIBIS II demonstrate that it is safe to treat patients with heart failure with β-blockers by using a low starting dosage and gradual increased titration.

This study has several limitations. Several categories of patients were not included (eg, patients with severe heart failure who were confined to bed, patients with heart failure and an ejection fraction of more than 0.40, and patients with heart failure early after AMI). The group of patients in NYHA functional class IV was small, resulting in wide 95% CIs overlapping those in NYHA functional classes II and III.15 However, results from a recent meta-analysis of several studies indicate that treatment with β-blockers confers significant beneficial effects on the clinical outcome in patients in NYHA class IV.25

In conclusion, the MERIT-HF study demonstrates that treatment with metoprolol CR/XL once daily added to standard therapy for patients with mild to severe heart failure due to left ventricular systolic dysfunction improves survival, reduces the need for hospital admission due to worsening heart failure, improves symptoms of heart failure, and increases well-being.

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